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Neurocognitive Brain Response to Transient Impairment of Wernicke's Area

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This study examined how the brain system adapts and reconfigures its information processing capabilities to maintain cognitive performance after a key cortical center [left posterior superior temporal gyrus (LSTGp)] is temporarily impaired during the performance of a language comprehension task. By applying repetitive transcranial magnetic stimulation (rTMS) to LSTGp and concurrently assessing the brain response with functional magnetic resonance imaging, we found that adaptation consisted of 1) increased synchronization between compensating regions coupled with a decrease in synchronization within the primary language network and 2) a decrease in activation at the rTMS site as well as in distal regions, followed by their recovery. The compensatory synchronization included 3 centers: The contralateral homolog (RSTGp) of the area receiving rTMS, areas adjacent to the rTMS site, and a region involved in discourse monitoring (medial frontal gyrus). This approach reveals some principles of network-level adaptation to trauma with potential application to traumatic brain injury, stroke, and seizure.

Keywords: brain adaptation, brain trauma, functional magnetic resonance imaging, language, repetitive transcranial magnetic stimulation

Introduction

Adaptation is a hallmark of human brain function in several contexts, one of which is the adaptive change following brain injury. Investigations of cognitive function after brain damage arising from focal lesions have allowed scientists to gain key insights into the roles of specific regions in the variety of tasks to which each contributes. However, these investigations have primarily relied on human behavioral studies in which the level of prior functioning was often unknown, damage was typically not limited to a single functional region, and uniformity of lesions across participants was difficult to achieve. Recently, repetitive transcranial magnetic stimulation (rTMS) has made it possible to temporarily downregulate the activity of a single brain region of modest volume (e.g., slightly larger than 1 cm^3; Bestmann et al. 2008) by applying a rapidly fluctuating strong magnetic field to the scalp (Bohning et al. 1997, 1999; Bestmann et al. 2008).

The nature of rTMS depression of function is that it generally decreases the excitability of the targeted region to delay a cognitive process, not completely disrupt it (Robertson et al. 2003). As a consequence, the targeted region is temporarily less available for cognitive processing, often leading to increased behavioral response times (RTs) in a task that would normally involve that region (Day et al. 1989). Here, we provide evidence that rTMS, applied during the performance of a language comprehension task, not only has these local effects, but also brings about an adaptive reconfiguration of a network of cortical regions to maintain comprehension performance despite the decreased availability of a critical region.

Although language is typically considered a left-lateralized process, brain imaging findings have repeatedly found a much more nuanced division of labor between the hemispheres for language processing. Of particular relevance to our study are the many findings of right-hemisphere activation during sentence comprehension in cases where Broca's or Wernicke's areas become damaged or overloaded with processing (Just et al. 1996; Keller et al. 2001; Röder et al. 2002). Consistent with decades of neuropsychological data, which indicated that lexical semantics was a left temporal function and sentence production a left inferior frontal function, neuroimaging studies have repeatedly found both left temporal and left frontal activations associated with the sentence level processing (Just et al. 1996; Friederici et al. 2003) as well as for an extended text (Xu et al. 2005; Lerner et al. 2011). Right-hemisphere language areas become activated during sentence comprehension under 2 types of circumstances: 1) damage to left hemisphere (LH) language areas (Weiller et al. 1995; Karbe et al. 1998; Thulborn et al. 1999) or processing demands that outstrip the available resources (Mason et al. 2003; Prat et al. 2012) tend to evoke right hemisphere (RH) activation (in addition to evoking extra LH activation); and 2) higher level and figurative text comprehension processes (e.g., inferences, metaphor, irony, theory of mind [ToM]) tend to evoke RH activation (in addition to evoking extra LH activation; see Mason and Just 2006; Ferstl 2007 for reviews). These 2 types of circumstances, which evoke RH language-related activation, suggest that the RH areas have 2 types of roles: As ancillary or back-up resources for LH language areas and as processes that perform suprasentence-level analyses.

Most relevant to the current study is the evidence of the recruitment of right-hemisphere homologs as texts increase in difficulty (Just et al. 1996; Mason et al. 2003; Prat et al. 2012). The explanation offered for this phenomenon is that when the processing resources of the LH language areas (Broca's and Wernicke's) approach exhaustion during sentence comprehension, the contralateral RH areas become recruited and processing appears to spill over into the RH. This spillover theory of cortical plasticity in language function provides the basis for examining plasticity as primary language regions become less available following the application of rTMS.

Prior to the development of rTMS, the plasticity of cortical networks in humans was studied in investigations of healthy controls performing a learning task (Draganski et al. 2004), in patients with brain tumors (Thiel et al. 2006), and in patients with brain lesions following stroke (Mimura et al. 1998; Thulborn et al. 1999; Winhuisen et al. 2005), indicating both peri- and contralesional recoveries (for a review see Cappa and

Vallar 1992). More recently, rTMS has been used to examine cortical reorganization and the recovery of processing in patients with brain damage (Oliveri et al. 1999; Turkeltaub et al. 2012). Subsequently, functional magnetic resonance imaging (fMRI) studies of rTMS in nonimpaired populations have been applied in perceptual tasks and have reported both focal and nonfocal consequences (Ruff et al. 2006, 2008, 2009; Sack et al. 2007). However, previous taxonomies of neural plasticity have not focused on network-level phenomena, such as changes in synchronization between activating regions (Grafman 2000). An enriched understanding of adaptive brain processes can be attained by using fMRI to examine how the brain activation of neurotypical participants changes following a transient virtual lesion caused by rTMS. This combination of methods enables the examination of both peri- and contralesional regions as well as the synchronization (coordination) among the activated regions of the cortex.

Studies that have investigated the impact of rTMS on language-processing performance have reported both facilitating effects (e.g., faster word recognition with LSTGp stimulation; Andoh et al. 2006) and inhibitory effects (e.g., slower lexical decision times for abstract words with LSTGp stimulation; Papagno et al. 2009); speech arrest following high-frequency stimulation over the prefrontal cortex results (Pascual-Leone et al. 1991; for a review see Flöel and Cohen 2007; Flöel 2012). Whether the impacts of rTMS are positive or negative can vary with stimulation strength, rTMS stimulation site, and cognitive task.

It is possible to apply rTMS and then to assess its impact not only on behavioral performance, but also on brain activation and connectivity across the network. For example, TMS applied over the prefrontal cortex during a N-back working memory task has been shown to decrease activation in not only the stimulated frontal site, but also in parietal areas that were part of the functional network (Mottaghy et al. 2000). More recently, it has become possible to apply rTMS in an MRI scanner during fMRI to study the dynamic mechanisms that respond to focal disruptions. One such study examined rTMS effects in action selection tasks (O'Shea et al. 2007). Even though concurrent rTMS and fMRI enable research into dynamic processing across a broad network, it has not yet been applied to reading comprehension, the consummate task for studying network configuration. Because reading relies on a broadly distributed cortical network, rTMS provides the capability to assess changes in network activity on a moment-to-moment basis.

The impact of an rTMS-induced virtual lesion on brain activation and coordination in a network of cortical areas during the performance of a cognitive task can be assessed using fMRI data that are acquired concurrently with the application of rTMS. This project assesses the adaptive reorganization of a large-scale cortical network after rTMS has been applied to one of its central nodes during the performance of a language comprehension task. We propose that the response to rTMS is not only physiological/anatomical in nature (downregulation of the focal, targeted region), but also involves a neurocognitive response in that compensatory mechanisms are evoked, and regions that had been collaborating with the downregulated area also become downregulated. A dynamic cognitive neuroarchitecture, 4CAPS, postulates a specific mechanism through which the computations involved in performing a complex task become dynamically allocated to appropriate cortical areas as a function of areas' computational specializations and their availability (Just and Varma 2007). If a cortical area becomes unavailable for some reasons (lesion damage was the cause of unavailability of a LH language area in a previous 4CAPS model), the processing spills over into RH areas with the most appropriate computational specializations.

The study below examined brain function (fMRI-measured activation and synchronization of cortical regions) and cognitive performance (RTs to comprehension probes) in a sentence comprehension task before, during, and after the application of rTMS to a cortical area (LSTGp, posterior superior temporal gyrus, or Wernicke's area) that is ubiquitously activated in such tasks. In the current experiment, healthy participants read a set of cognitively demanding sentences containing an embedded clause that described an interaction between 2 characters (e.g. The hippie that the drummer visited poured the wine). The primary interest was the cortical response to the transient unavailability of a primary language region during the language task.

We hypothesized that the lowered availability of LSTG due to rTMS during the performance of a language comprehension task would evoke dynamic cortical reorganization similar to that found in brain damage (Thulborn et al. 1999), or in cases where the demands of the task exceed individual working memory capacity (Prat et al. 2012). In contrast to brain lesions and working memory capacity, rTMS places the unavailability under experimental control. Moreover, we hypothesized that as the rTMS is applied, the patterns of synchronization among brain areas would change dynamically to reflect the lowered functioning of the pre-rTMS network and increased synchronization of a new dynamically evoked by the lowered availability of LSTG brought about by rTMS. In particular, we expected to observe a change in the synchronization between the area receiving the rTMS and the areas with which it was synchronized prior to rTMS. Areas whose synchronizations might be expected to increase after rTMS include regions adjacent to or contralateral to the stimulated area, and other areas occasionally, but not centrally, involved in language processing.

Materials and Methods

Participants

Data were analyzed from 26 right-handed, native English speaking participants (17 males and 10 females, aged 18–33 years) who were paid volunteers recruited through Carnegie Mellon University. Of these, 16 (10 males) received rTMS to the left hemisphere, and a secondary, smaller control group, 10 (7 males) received rTMS to the right hemisphere. An additional 12 participants were tested, but excluded from analysis, either because of head motion (9 participants), or because they were run using reduced thresholds due to self-reported sensitivity to mechanical vibrations. The large number of excluded participants because of excessive head motion was due to the physical consequences of applying rTMS in the scanner. When applied in the scanner, TMS pulses were assessed by some participants to cause some level of discomfort, which may have resulted in moving their head away from the stimulation site. It was also possible that a large mechanical vibration brought about by the pulses could, over time, cause a participant's head to move away from the coil. The use of human participants was approved by the Carnegie Mellon University IRB. All participants gave informed consent prior to participation.

Materials

The materials consisted of 54 two-clause sentences. Half of the sentences were subject-relative clauses (e.g., The parent that interrupted the teacher asked a question), and half were object-relative clauses

(The parent that the teacher interrupted asked a question). All sentences were constructed such that pre-existing semantic relations did not more readily pair subjects to verbs or objects (i.e., parent and teacher are relatively equally associated with interrupted and asked). No subjects, verbs, or objects were repeated across the experiment. An equal number of subject- and object-relative clause sentences appeared in each portion of the experiment (pre-, during-, and post-TMS), thus equating the temporal regions on difficulty.

Each sentence was followed by a true/false comprehension probe (e.g., The parent interrupted the teacher). Half of the comprehension probes were true, and half were false. Half of the probes tested recognition of information presented in the first clause of the sentence, and half tested recognition of information presented in the second half of the sentence. False probes were constructed by creating a mismatch between the actors and actions mentioned in the sentence, rather than introducing new entities. Sentences and comprehension probes were presented in a pseudorandom order that was the same for all participants. All sentences (9 words) and probes (5 words) were equated for word length.

Procedure

Prescan

To introduce them to the sensation of rTMS, and to the experimental paradigm, all participants underwent a practice behavioral rTMS session several days prior to their scan. During this session, participants were given a sentence comprehension task similar to the experimental paradigm used in the scanner, but consisting of different stimuli. Participants initially read 20 sentences and responded to comprehension probes as quickly and accurately as possible. They also received a series of 300 low-frequency (1 Hz) rTMS pulses, read another 20 sentences, and responded to the comprehension probes with 1 of the 2 possible button presses as quickly and accurately as possible (2 participants of the control group were dropped from a post hoc behavioral test due to missing practice session data). They were acclimated in a scanning simulator with the rTMS coil to ensure that they could comfortably fit. Participants received the Reading Span (RSPAN) Test (Daneman and Carpenter 1980), the Nelson Denny Reading Test (Brown 1960), the Edinburgh Handedness Inventory (Oldfield 1971), and the Raven Progressive Matrices (Raven 2000) during the practice session.

rTMS Parameters

A temporary depression of function was created in the targeted region (Wernicke's area, defined as area CP5 using the International 10-20 system; Chatrian et al. 1988) using a stimulation rate of 1 Hz for 300 pulses, or 5 min, at 110% of the established motor threshold. Resting motor thresholds were assessed during the practice session as the lowest stimulation intensity capable of evoking a motor-evoked potential in 5 of 10 stimulations. Biphasic rTMS pulses were applied using a Magstim Rapid^2 stimulator and an MRI compatible (model 3812-00) 70-mm figure-of-eight coil in the scanner. All participants received stimulation of either Wernicke's area or, for the secondary, smaller control group, the contralateral right-hemisphere homolog. To reduce mechanical vibrations and maximize subject comfort, the TMS coil was held in place in the scanner by a brace fashioned to fit to the MRI head coil. In the practice session, participants received contralateral stimulation to what was received in the scanner during the experiment using a 70-mm figure-of-eight coil.

fMRI Scanning and Data Analysis Parameters

Imaging was done on a Siemens Verio 3-T scanner at the Scientific Imaging & Brain Research Center (SIBR) at Carnegie Mellon University. An echo-planar pulse acquisition sequence was used where the acquisition parameters for the 14 oblique axial slices were time repetition = 1000 ms (a specialized pulse sequence was designed with a 100-ms gap during which the rTMS pulse occurred, resulting in 900 ms for the 14 slice acquisition), time echo = 30 ms, 64 × 64 acquisition matrix, 5-mm thickness, 1-mm gap, flip angle 60°, and transmit–receive CP head coil. Images were corrected for slice acquisition timing, motion-corrected, normalized to the Montreal Neurological Institute (MNI) template, resampled to $2 \times 2 \times 2$ mm^3 voxels, and the images were smoothed with an 8-mm Gaussian kernel to decrease spatial noise. The fMRI data acquired in conjunction with the first sentence presented at the onset of rTMS were discarded because of excessive noise. A general linear model analysis was performed with regressors for each sentence and probe pair before, during, or after rTMS was applied. Activation was correlated with the RSPAN administered during the practice session (Daneman and Carpenter 1980).

Functional Connectivity Analysis

Functional connectivity was evaluated by correlating the average time course of signal intensity of all the voxels in each member of a pair of a priori defined regions of interest. The functional connectivity was a correlation between the average time course of signal intensity of all the voxels in each member of a pair of regions of interest (fROIs). Twenty-five fROIs were defined (see Table 1 for size and anatomical location). For 23 of these ROIs, a sphere was defined (with a radius ranging from 5 to 12 mm) that best captured the cluster of activation in the map using data from a pilot version of the experiment that was performed on different participants. An additional 2 fROIs were designed to match the regions that correlated with the individual differences variables (RSPAN and RT improvement) as these regions fell outside of our predefined fROIs. The functional connectivity was computed (separately for each participant) in the following steps: First, the average time courses were extracted from each participant over all voxels within each fROI during task performance, excluding the fixation conditions. Secondly, the correlations were computed on the extracted time courses among ROI pairs. Thirdly, Fisher's r-to-z transformation was applied to the correlation coefficients for each participant. Fourthly, for each participant, the mean functional connectivities were statistically compared. A term that has been used in neuroimaging for this measure is functional connectivity, but we favor the term synchronization and use the 2 terms interchangeably.

Stimulus Presentation

During the fMRI scan, passages were projected onto a plastic screen attached to the bore of the scanner. Participants viewed the sentences through a pair of mirrors above the head coil, subtending a visual angle of approximately 30°. Each sentence appeared on the screen for

Table 1
List of fROI metrics (label, location, and size)

Anatomical location	fROI	MNI coordinate of centroid			Radius
		x	*y*	*z*	
Left fusiform	LFus	−54	−46	2	12
Left hippocampus	LHIP	−22	−30	−2	6
Left inferior frontal gyrus (inferior portion)	LIFGi	−48	30	−10	12
Left inferior frontal gyrus (middle portion)	LIFGm	−48	18	18	12
Left inferior frontal gyrus (superior portion)	LIFGs	−40	2	52	12
Left inferior parietal lobe	LIPL	−32	−50	48	10
Left middle frontal gyrus	LMFG	−32	0	35	8
Left occipital gyrus	LOcc	−18	−94	−4	12
Left superior temporal gyrus (anterior portion)	LSTGa	−50	10	−26	12
Left superior temporal gyrus (middle portion)	LSTGm	−56	−22	−12	12
Left superior temporal gyrus (posterior portion)	LSTGp	−54	−46	2	12
Medial frontal gyrus (inferior)	MFGi	−6	56	40	12
Medial frontal gyrus (superior)	MFGs	−2	10	50	12
Right fusiform	RFus	40	−56	−22	12
Right hippocampus	RHIP	24	−28	−6	6
Right inferior frontal gyrus (inferior portion)	RIFGi	52	30	−14	10
Right inferior frontal gyrus (superior portion)	RIFGm	48	22	26	12
Right inferior frontal gyrus (middle portion)	RIFGs	40	2	52	12
Right occipital gyrus	ROcc	22	−90	−6	12
Right superior parietal lobe	RSPL	34	−58	48	10
Right superior temporal gyrus (anterior portion)	RSTGa	54	10	−28	10
Right superior temporal gyrus (middle portion)	RSTGm	60	−32	−4	12
Right superior temporal gyrus (posterior portion)	RSTGp	58	−56	14	12
Right temporo-parietal junction (small)	RTPJ	46	−52	34	4
Left inferior frontal gyrus (anterior portion)	LIFGa	−46	42	−10	4

7 s. It was replaced by the probe with the true/false options presented on the screen. Participants were given 5 s to respond to the probe. Each probe was followed by a rest X on the screen for 8 s before the next sentence appeared. There were 20 pairs (8 min) presented both before and after rTMS, and 14 pairs presented during the rTMS application period (5 min). Fixation baseline periods occurred at the beginning and end of the pre-TMS and post-TMS sections for 25 s each and for 18 s in the during TMS interval. During these periods, participants viewed an X on the center of the screen and were instructed to relax and clear their minds.

Results

Overview

Following initial downregulation of a network of regions caused by rTMS of LSTGp during the performance of a language comprehension task, there were 2 outstanding facets of the subsequent brain adaption: Synchronization changes in compensating contralateral RH, medial frontal and perilesional regions, and recovery processes in downregulated regions. The compensatory adaptation consisted of increased coordination between the right-hemisphere homolog of the stimulation site (contralesional) and a medial frontal region, as well as between regions close to the stimulation site (perilesional) and the same frontal region of cortex. The recovery processes consisted of the initially downregulated regions' activation gradually returning to their original levels. Despite the previously downregulated regions returning to their original levels, the compensating regions did not all phase out their activity, resulting in coactivity in the recovered and compensating networks, together supporting the unimpaired and perhaps enhanced behavioral performance during and after rTMS. Furthermore, the degree of compensation and recovery in an individual was related to the individual's working memory capacity for language (measured as reading span).

Compensation Through Altered Cortical Partnerships

After rTMS applied to LSTGp caused downregulation locally as well as in several other distal regions that had been activated in the sentence comprehension task (particularly left inferior frontal gyrus (LIFG), as described below), the main adaptive response was an increase in synchronization in 2 pairs of regions. One pair that showed an increase in synchronization following rTMS included the right-hemisphere homolog of the stimulation site (RSTGp) and the medial frontal gyrus (MedFG), as shown by the dotted line in Figure 1. This pair's synchronization increased from $z' = 0.38$ (z' is a Fisher's r-to-z transformation) before rTMS to 0.46 post-TMS ($t_{(15)} = 2.16$, $P < 0.05$). The second pair consisted of an area just anterior to the stimulation site (left superior temporal gyrus (middle portion) [LSTGm]) and the MedFG, an area associated with executive and monitoring processes. The synchronization of these 2 regions reliably increased from 0.46 (z') before rTMS to 0.56 after rTMS ($t_{(15)} = 3.57$, $P < 0.005$). (It is notable that in a control group, which received rTMS to the right-hemisphere homolog, there were no regions whose synchronization increased, presumably because no primary region was downregulated, and hence there was no need to establish compensating partnerships.) The 2 pairs of regions described here were the only pairs showing a reliable increase in synchronization following rTMS (Table 2A lists these pairs and the full set of synchronization results). It is likely that these new cortical partnerships were centrally involved in computing the agent–patient information that the comprehension task probed in the face of LSTGp/LIFG-diminished capabilities.

Compensation Correlated with Working Memory Capacity

There were systematic individual differences in the degree of compensation for the rTMS-induced downregulation, reminiscent of previous findings of differential cortical adaptability to cognitive workload being correlated with working memory capacity (Prat et al. 2007; Prat and Just 2011). Specifically, adaptability (increased activation following rTMS when compared with before rTMS) in the posterior RH area was positively correlated with individual participants' working memory span (mean RSPAN = 3.1, standard deviation = 0.66), in a region slightly superior to the homolog of the rTMS site, namely right temporo-parietal junction (RTPJ; MNI centroid 48, −58, 34; $r_{(16)} = 0.61$, $P < 0.001$ uncorrected). There was also an area in the left anterior inferior frontal gyrus (MNI centroid −48, 44, 8) whose activation increase was correlated with RSPAN ($r_{(15)} = 0.601$, $P < 0.001$ uncorrected). These regions were more involved after rTMS regardless of the response during the rTMS period. Thus, the adaptability exemplified by the RSPAN-modulated compensatory activation in RTPJ constitutes an individually-tuned dynamic cognitive

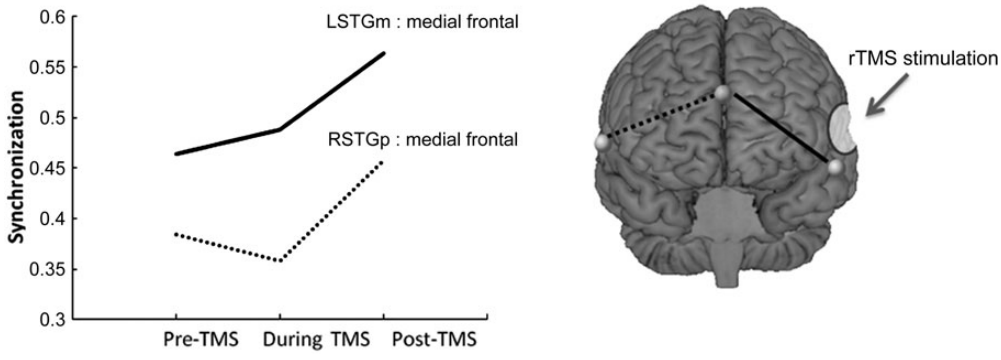

Figure 1. Increased synchronization of the 3 compensatory regions. The left panel shows the increase in synchronization following rTMS for 2 pairs of fROIs. The contralateral right posterior temporal gyrus (RSTGp) increased in synchronization with the MedFG, a key region in monitoring of coherence. The second pair included the region of cortex anterior to the rTMS targeted site (LSTGm) and the same MedFG.

Table 2
Extended results from the functional connectivity (synchronization) analyses

ROI	Pre	During	Post	*t* post > pre	*P*-value	*t* pre > during	*P*-value	Network
Left hemisphere rTMS:								
A. Compensatory increased synchronization (correlation of the time courses of activation between the fROI pairs) following rTMS								
LSTGm:MFGi	0.46	0.49	0.56	3.567	0.001	0.642	n.s.	LH-Lang: ToM
RSTGp:MFGi	0.38	0.36	0.46	2.161	0.039	0.551	n.s.	RH-Lang: ToM
B. Decreased synchronization during rTMS accompanied by increased synchronization (recovery) following rTMS								
ROI	Pre	During	Post	*t* pre > during	*P*-value	*t* post > during	*P*-value	Network
LHIP:LSTGa	0.54	0.45	0.50	2.089	0.045	2.123	0.042	LH-Lang within
LIFGs:LSTGp	0.97	0.83	0.96	3.470	0.002	2.461	0.020	LH-Lang within
LHIP:RHIP	0.69	0.60	0.69	2.365	0.025	2.764	0.010	LH-Lang: RH-Lang
LIFGs:RSTGp	0.30	0.19	0.29	3.117	0.004	2.134	0.041	LH-Lang: RH-Lang
LSTGa:RSTGa	0.67	0.55	0.65	3.045	0.005	2.279	0.030	LH-Lang: RH-Lang
LSTGm:RHIP	0.58	0.46	0.56	3.619	0.001	2.333	0.027	LH-Lang: RH-Lang
RHIP:RSTGp	0.40	0.26	0.40	4.368	<0.001	3.065	0.005	RH-Lang within
C. Additional pairs with decreased synchronization during rTMS without significant (recovery) following rTMS								
ROI	Pre	During	Post	*t* Pre >Dur	*P*	*t* Post > Dur	*P*	Network
LIFGm:RSPL	0.87	0.82	0.80	2.793	0.009	0.267	n.s.	LH-Lang: Parietal
LSTGa:RSPL	0.39	0.33	0.34	2.722	0.011	0.256	n.s.	LH-Lang: Parietal
LSTGm:RSPL	0.58	0.46	0.45	3.619	0.001	0.180	n.s.	LH-Lang: Parietal
LSTGp:RSPL	0.86	0.70	0.75	4.948	0.000	1.083	n.s.	LH-Lang: Parietal
LFus:RIFGi	0.52	0.42	0.44	2.404	0.023	0.488	n.s.	LH-Lang: RH-Lang
LFus:RIFGm	0.72	0.55	0.59	3.486	0.002	0.741	n.s.	LH-Lang: RH-Lang
LFus:RSTGm	0.57	0.48	0.50	2.630	0.013	0.604	n.s.	LH-Lang: RH-Lang
LIFGi:RIFGm	0.69	0.52	0.61	2.721	0.011	1.397	n.s.	LH-Lang: RH-Lang
LIFGm:RIFGm	0.84	0.71	0.73	2.627	0.013	0.426	n.s.	LH-Lang: RH-Lang
LIFGm:RSTGp	0.32	0.22	0.29	2.605	0.014	1.863	n.s.	LH-Lang: RH-Lang
LIFGs:RIFGm	0.77	0.60	0.65	3.515	0.001	0.839	n.s.	LH-Lang: RH-Lang
LSTGp:RIFGm	0.76	0.58	0.66	3.094	0.004	1.230	n.s.	LH-Lang: RH-Lang
LSTGp:RIFGs	0.84	0.74	0.83	2.783	0.009	1.444	n.s.	LH-Lang: RH-Lang
LSTGa:MFGs	0.56	0.47	0.51	2.399	0.023	0.987	n.s.	LH-Lang: ToM
LSTGm:MFGs	0.60	0.50	0.58	2.375	0.024	1.631	n.s.	LH-Lang: ToM
LIFGi:LIPL	0.68	0.58	0.63	3.076	0.004	1.387	n.s.	LH-Lang within
LIFGm:LSTGa	0.47	0.40	0.41	2.385	0.024	0.214	n.s.	LH-Lang within
LIPL:LSTGm	0.51	0.43	0.45	2.960	0.006	0.402	n.s.	LH-Lang within
LIPL:LSTGp	0.85	0.72	0.76	3.448	0.002	0.753	n.s.	LH-Lang within
RIFGi:RSPL	0.43	0.34	0.35	2.603	0.014	0.211	n.s.	RH-Lang: Parietal
RIFGm:RSPL	0.82	0.71	0.79	4.440	0.000	1.795	n.s.	RH-Lang: Parietal
RSPL:RSTGm	0.48	0.39	0.39	3.461	0.002	0.172	n.s.	RH-Lang: Parietal
RSPL:RSTGp	0.31	0.23	0.29	3.552	0.001	1.561	n.s.	RH-Lang: Parietal
MFGs:RIFGi	0.52	0.41	0.43	2.566	0.016	0.750	n.s.	RH-Lang: ToM
MFGs:RIFGm	0.71	0.53	0.59	3.198	0.003	1.001	n.s.	RH-Lang: ToM
MFGs:RSTGm	0.56	0.46	0.49	2.429	0.021	0.682	n.s.	RH-Lang: ToM
MFGs:RSTGp	0.41	0.27	0.37	3.686	0.001	1.883	n.s.	RH-Lang: ToM
LOcc:RIFGm	0.60	0.45	0.49	2.622	0.014	0.848	n.s.	RH-Lang: Visual
LOcc:RSTGm	0.39	0.28	0.33	2.460	0.020	1.357	n.s.	RH-Lang: Visual
RIFGi:ROcc	0.44	0.33	0.32	2.613	0.014	0.194	n.s.	RH-Lang: Visual
RIFGm:ROcc	0.60	0.44	0.47	2.704	0.011	0.758	n.s.	RH-Lang: Visual
RHIP:RIFGm	0.53	0.40	0.44	3.218	0.003	0.749	n.s.	RH-Lang within
RHIP:RSTGm	0.52	0.44	0.52	2.460	0.020	1.759	n.s.	RH-Lang within
RIFGi:RIFGm	0.61	0.48	0.53	2.574	0.015	1.073	n.s.	RH-Lang within
RIFGi:RIFGs	0.57	0.47	0.49	2.629	0.013	0.429	n.s.	RH-Lang within
RIFGm:RIFGs	0.91	0.74	0.84	2.991	0.006	1.470	n.s.	RH-Lang within
RIFGm:RSTGm	0.68	0.57	0.55	2.527	0.017	0.511	n.s.	RH-Lang within
RIFGs:RSTGp	0.45	0.34	0.44	3.297	0.003	2.011	n.s.	RH-Lang within
D. Regions showing significantly increased synchronization following rTMS but without downregulation during rTMS								
ROI	Pre	During	Post	*t* pre > during	*P*-value	*t* post > during	*P*-value	Network
RSTGp:LMFG	0.17	0.09	0.17	1.938	n.s.	2.628	0.013	Frontal: RH-Lang
LSTGm:RSTGp	0.50	0.45	0.55	1.893	n.s.	2.654	0.013	LH-Lang: RH-Lang
MFGi:LSTGp	0.38	0.36	0.46	0.551	n.s.	2.211	0.035	LH-Lang: ToM
MFGs:LSTGa	0.44	0.38	0.49	1.314	n.s.	2.363	0.025	LH-Lang: ToM
LIFGi:LIFGm	0.86	0.75	0.85	2.006	n.s.	2.337	0.026	LH-Lang within
LIFGi:LIFGs	0.81	0.73	0.81	1.546	n.s.	2.178	0.037	LH-Lang within
Right-hemisphere rTMS[a]								
E. Pairs with decreased synchronization during rTMS without significant (recovery) following rTMS								
ROI	Pre	During	Post	*t* pre > during	*P*-value	*t* post > during	*P*-value	Network
LFus:RIFGi	0.64	0.49	0.45	2.315	0.033	0.565	n.s.	LH-Lang: RH-Lang
LFus:RSTGm	0.69	0.49	0.52	2.240	0.038	0.497	n.s.	LH-Lang: RH-Lang
LSTGa:RIFGi	0.65	0.54	0.55	2.268	0.036	0.263	n.s.	LH-Lang: RH-Lang
LSTGa:MFGs	0.52	0.35	0.44	2.153	0.045	1.576	n.s.	LH-Lang: ToM
LIFGi:LOcc	0.73	0.55	0.53	2.454	0.025	0.368	n.s.	LH-Lang: Visual
LIFGi:ROcc	0.78	0.60	0.57	2.182	0.043	0.426	n.s.	LH-Lang: Visual
LIFGm:LOcc	0.85	0.65	0.67	2.595	0.018	0.231	n.s.	LH-Lang: Visual
LIFGm:ROcc	0.91	0.70	0.71	2.614	0.018	0.196	n.s.	LH-Lang: Visual
LIPL:LOcc	0.84	0.67	0.63	2.158	0.045	0.431	n.s.	LH-Lang: Visual

(*continued*)

Table 2
Continued

ROI	Pre	During	Post	*t* post > pre	*P*-value	*t* pre > during	*P*-value	Network
LIPL:ROcc	0.89	0.71	0.68	2.110	0.049	0.418	n.s.	LH-Lang: Visual
LOcc:LSTGm	0.60	0.43	0.40	2.301	0.034	0.611	n.s.	LH-Lang: Visual
LOcc:LSTGp	0.84	0.63	0.70	2.903	0.009	1.037	n.s.	LH-Lang: Visual
LSTGm:ROcc	0.66	0.45	0.46	2.538	0.021	0.116	n.s.	LH-Lang: Visual
LSTGp:ROcc	0.91	0.68	0.78	3.432	0.003	1.796	n.s.	LH-Lang: Visual
LIFGi:LIFGs	0.86	0.67	0.79	2.105	0.050	1.598	n.s.	LH-Lang within
LIFGi:LSTGp	0.87	0.67	0.73	2.136	0.047	0.877	n.s.	LH-Lang within
LIPL:LSTGp	0.83	0.63	0.66	2.193	0.042	0.387	n.s.	LH-Lang within
MFGi:RSTGa	0.45	0.31	0.35	2.231	0.039	0.617	n.s.	RH-Lang: ToM
LOcc:RIFGm	0.65	0.44	0.44	2.683	0.015	0.055	n.s.	RH-Lang: Visual
LOcc:RSPL	0.81	0.64	0.58	2.198	0.041	0.747	n.s.	RH-Lang: Visual
LOcc:RSTGa	0.45	0.30	0.29	2.348	0.031	0.247	n.s.	RH-Lang: Visual
LOcc:RSTGm	0.45	0.27	0.26	2.717	0.014	0.169	n.s.	RH-Lang: Visual
LOcc:RSTGp	0.30	0.09	0.19	3.100	0.006	1.618	n.s.	RH-Lang: Visual
RIFGi:ROcc	0.54	0.38	0.33	2.173	0.043	0.502	n.s.	RH-Lang: Visual
RIFGm:ROcc	0.71	0.49	0.49	2.726	0.014	0.018	n.s.	RH-Lang: Visual
ROcc:RSPL	0.86	0.69	0.63	2.272	0.036	0.704	n.s.	RH-Lang: Visual
ROcc:RSTGa	0.48	0.33	0.32	2.539	0.021	0.119	n.s.	RH-Lang: Visual
ROcc:RSTGm	0.52	0.31	0.31	3.040	0.007	0.128	n.s.	RH-Lang: Visual
ROcc:RSTGp	0.36	0.12	0.25	2.807	0.012	1.618	n.s.	RH-Lang: Visual
F. Regions showing significantly increased synchronization following rTMS but without downregulation during rTMS								
ROI	Pre	During	Post	*t* pre > during	*P*-value	*t* post > during	*P*-value	Network
LHIP:RSTGp	0.43	0.25	0.41	1.76	n.s.	2.111	0.05	LH-Lang: RH-Lang

[a]There are no pairs demonstrating compensatory (increased synchronization following rTMS) nor recovery (decreased synchronization during accompanied by increased synchronization following rTMS) function following RH-TMS.

reorganization of the system, focused in the area contralateral to the rTMS site.

Additional Evidence of the Compensatory Role of the Posterior Right Hemisphere (RSTSp and RTPJ)

There were 4 indicators of the centrality of the posterior right hemisphere in the brain system's adaptive response to the rTMS in 4 proximal RTPJ areas. First, as noted above, RSTGp increased its synchronization with MedFG (shown by yellow region in Fig. 2). Secondly, the degree of RTPJ activation was correlated with working memory capacity for language (RSPAN) as described above (shown by green regions). Thirdly, RTPJ (MNI centroid 46, −58, 34) was one of the few areas showing an increase in activation ($t_{(24)} = 3.47$, $P < 0.001$ uncorrected) in response to rTMS, indicated by the red region in Figure 2. (This increase was assessed with the contrast to the RH-rTMS control group.) Fourthly, the activation in a superior RTPJ location was correlated with the speed-up in successful completion of the task as measured by faster comprehension probe RTs following rTMS than before ($r_{(16)} = 0.606$, $P < 0.001$ uncorrected; blue regions in Fig. 2; MNI centroids 40, −62, 42 and 50, −44, 39). These 4 indicators of the posterior right hemisphere centrality in compensation all occur proximally to each other, having a mean distance 7.7 mm to the centroid of their centroids. The posterior right-hemisphere region supports the dynamically constructed compensatory network (whose nodes include perilesional and MedFG areas) to provide an alternative neurocognitive mechanism for comprehending sentences during the transient impairment of the primary regions. The recruitment of RSTGp and the slightly more superior RTPJ to the compensation process illustrates the more general principle of a secondary (less effective, for a given task) cortical region being automatically recruited to perform the task when the primary region is less available. In computational terms, the secondary areas are automatically evoked when their conditions of applications arise and the primary area fails to adequately respond (Just and Varma 2007).

Focal and Distributed Downregulation and Recovery Response

Even though rTMS was applied focally to LSTGp (indicated by the blue circle in Fig. 3), the resulting downregulation extended to several additional noncontiguous language areas in both the stimulated LH and, to a lesser degree, RH, as indicated by red regions in Figure 3. (The counts of downregulated voxels in primary language regions are shown in the bottom panel of Fig. 3.) The finding that regions that were activated in this ongoing task but distal from the rTMS site were nevertheless downregulated is indicative of a clear neurocognitive response to rTMS (in additional to other possible responses governed by anatomy and physiology). As noted in the Materials and Methods section, downregulation as a result of the rTMS occurred rapidly, reaching asymptote within about 40 s of the onset of the 1-Hz stimulation.

The activation gradually returned to near-normal level minutes after the rTMS, although never quite reaching pre-TMS levels during the duration of the study. (The control RH-rTMS group displayed an analogous right-lateralized neurocognitive response affecting RH language areas.) Recovery began to occur relatively quickly and was likely gradual (for a discussion of durations of rTMS effects see Robertson et al. 2003). Recovery occurred in a subset of the downregulated regions during the period of the study, although all of them presumably recovered eventually. Thus, the cortical response to the localized virtual lesion appears to have a neurocognitive basis, appearing in the primary language regions and their right-hemisphere homologs with recovery beginning in

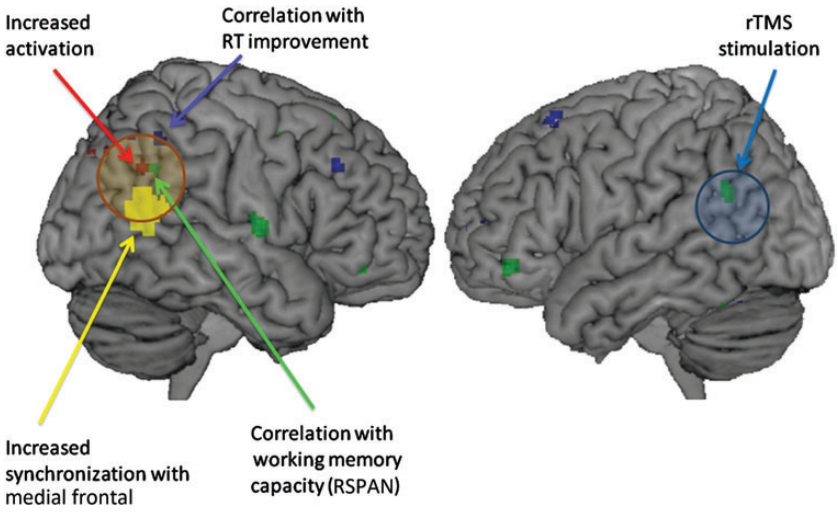

Figure 2. Four indicators of posterior RH (RSTSp and RTPJ) compensatory activity contralateral to the rTMS site. The highlighted region (brown circle) indicates a convergence of several measures including an increase in synchronization with the medial frontal compensatory region, a greater activation following rTMS and correlations with RSPAN and behavioral improvement following rTMS.

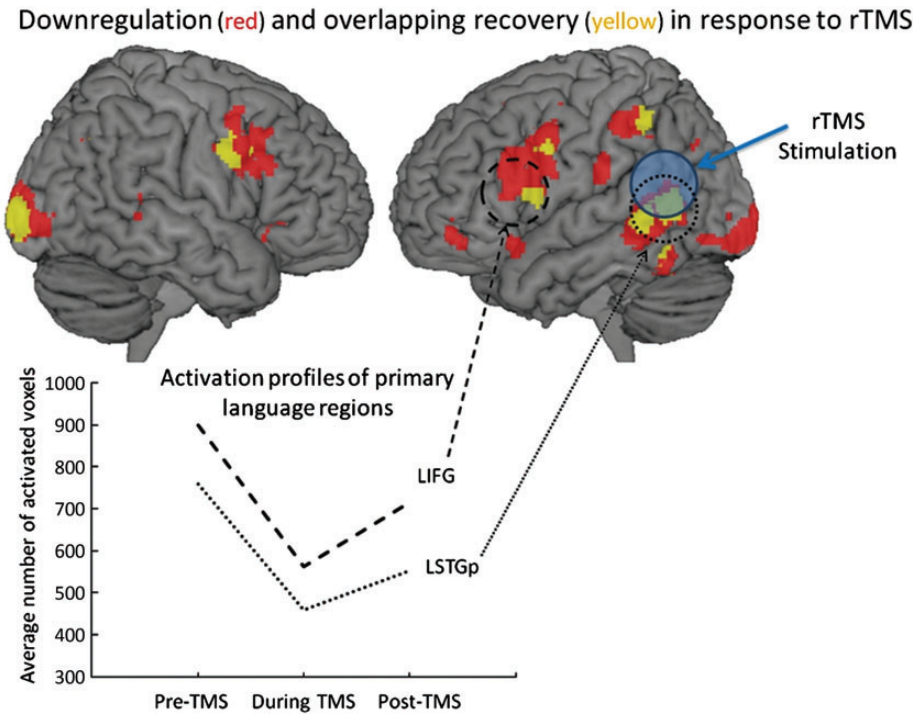

Figure 3. Downregulation and overlapping recovery in response to rTMS. The application of rTMS to Wernicke's area (semantic processing, indicated by blue circle) resulted in downregulation in language-processing regions (e.g., left temporal, left inferior frontal, left inferior parietal), a right-hemisphere homologous region (right inferior frontal) as well as primary visual (bilateral occipital) as shown in the top panel. The reduction of activated voxels during rTMS and subsequent partial recovery for the primary language regions are shown in the bottom panel.

those same regions (shown by yellow in Fig. 3), a pattern that occurred in the synchronization of the language regions as well (the full set of activated and recovered regions are listed in Table 3).

The Language Network Becomes Decoupled During rTMS and Then Resynchronizes Post-TMS

rTMS produced decreases in synchronization among language areas, followed by the recovery of synchronization to pre-TMS levels, indicating that the teams of regions that functioned together prior to rTMS not only reactivate following rTMS, but also re-establish their previous partnerships. These pairs of activation areas did not show evidence of shifting partnerships. The pattern of decoupling followed by recovery was similar regardless of the locations of the 2 areas in the pair (both areas lying within the LH, both within the RH, and LH to RH), as shown in Figure 4. The general finding is that as soon as the rTMS effects subside, the main language

partnerships re-emerge. Thus, there was a downregulation in synchronization affecting a variety of regions with rTMS, initially producing a temporary dissolution of the usual language-processing partnerships followed by a re-establishment of their typical functioning following the rTMS period.

rTMS-induced desynchronization also occurred between the rTMS target site and primary visual regions (left occipital gyrus [LOcc] and right occipital gyrus [ROcc]), indicating a decoupling between the language network and the visual information supply chain. The activation time courses within the occipital regions were not much affected by the rTMS, suggesting that the decreased synchronization with LSTGp was primarily due to a change in the activity in the stimulated LSTGp area. (Such desynchronization between the rTMS site and visual regions [ROcc and LOcc] also occurred in the RH-rTMS control condition.) These findings suggest that the stimulated site becomes temporarily less capable of processing input from sensory areas.

Table 3
Areas of activation for the downregulation and recovery contrasts

Cortical region	Cluster size	Peak *t*-value	MNI coordinates		
			x	*y*	*z*
Downregulation (pre-TMS–during TMS)					
Left postcentral	57	4.83	−62	−20	24
Left middle temporal	884	7.57	−58	−46	−2
Left inferior parietal	359	6.1	−56	−30	46
Left inferior frontal (pars opercularis)	14	4.06	−56	12	12
Left orbital frontal	74	6.37	−46	50	−12
Left inferior temporal/fusiform	172	5.24	−46	−50	−22
Left inferior frontal	853	6.38	−34	14	24
Left occipital	7	3.98	−34	−70	34
Left occipital	341	6.05	−28	−88	−12
Left caudate/pallidum/putamen	169	4.79	−22	2	6
Bilateral supplementary motor area	468	7.22	−4	6	62
Right caudate	208	5.74	8	6	2
Right thalamus	25	5.25	12	−28	−2
Right occipital/calcarine/cuneus	669	8.4	18	−100	2
Right orbital frontal/insula	37	4.45	32	26	−8
Right inferior parietal	85	5.05	34	−44	42
Right angular/occipital	14	4.2	36	−66	36
Right inferior frontal/precentral	532	6.19	44	10	28
Right inferior frontal (pars triangularis)	9	4.19	56	22	24
Recovery (post-TMS–during TMS)					
Left inferior frontal	85	5.28	−58	14	8
Left middle temporal	73	4.59	−56	−40	−2
Left middle temporal	138	5.79	−54	−54	6
Left inferior parietal	313	5.48	−48	−46	52
Left inferior temporal/fusiform	75	4.52	−46	−50	−12
Left putamen/pallidum	372	5.3	−22	12	−6
Right occipital/calcarine/cuneus	197	5.01	18	−98	−4
Right pallidum	6	4.04	20	12	0
Right putamen	15	3.95	20	0	4
Right angular/occipital	24	4.23	34	−64	34
Right inferior frontal/precentral	176	4.32	48	2	40

Maintenance of Behavioral Performance Supported by Compensation

Behavioral responses indicated that most participants (15 of 16) adapted and recovered from rTMS. There was no negative impact on the RTs to the comprehension probes due to rTMS, even during its application. In fact, there were continuing decreases in RT, as shown in Figure 5. The RT speed-up of 332 ms following rTMS (pre-rTMS = 2229, post-rTMS = 1897) was significant ($F_{1,15} = 15.58$, $P = 0.001$). This performance indicates a successful cortical adaptation to rTMS, such that the complex sentences were still comprehensible during the lowered availability of key language-processing regions. The continuation of behavioral performance improvement during rTMS suggests that the complex language task was being performed using alternative mechanisms that compensated for the decreased availability of the downregulated regions. Although the monotonic decrease in RT could have been partially due to participants becoming faster at the task with increasing experience, the presence of a complementary monotonic increase in synchronization and activation in the compensatory regions (e.g., the LSTGm:medial frontal pair in Fig. 1) suggests that a compensatory mechanism underpinned the continuation of the behavioral improvement.

To ensure that the main speed-up due to experience would not occur during the fMRI scanning, all participants had previously performed the task on at least 40 unique sentences in the training session before the experiment began; this technique to level out RT's has been used in previous rTMS designs (Knecht et al. 2002) and was successful here. Two sources of evidence support the conclusion that the in-scanner behavioral improvement was due to an rTMS effect and not simply becoming faster with experience. First, the

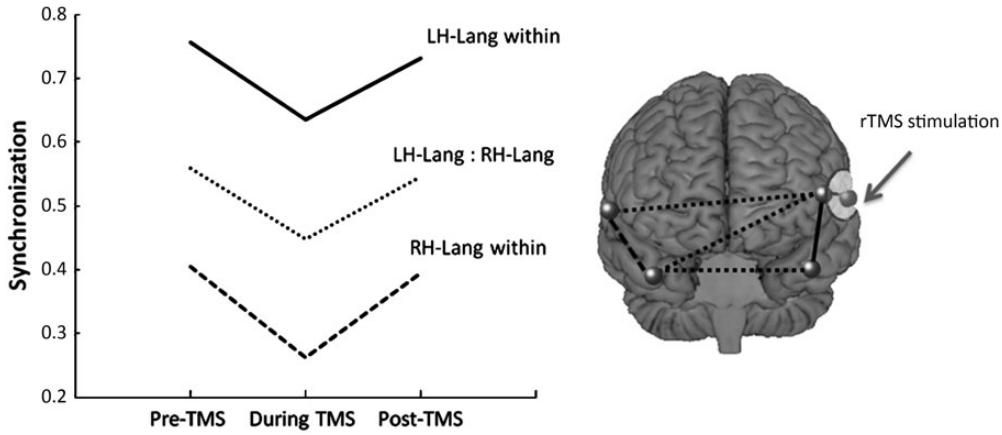

Figure 4. Downregulation and recovery of network partnerships in response to rTMS. The downregulation and recovery of the language network are indicated by the U-shaped function showing synchronization decreases during rTMS and recovery after, the lines represent synchronization as averaged over pairs of fROIs either within the LH, between the LH and RH, or within the RH. The right panel shows a schematic diagram of the location and connections of the 5 nodes (LSTGp, LIFG, LSTGa, RSTGp, and RSTGa) within the 3 networks.

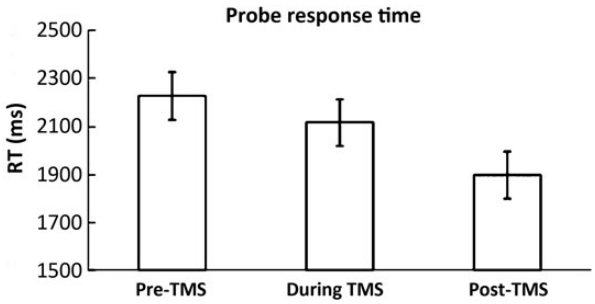

Figure 5. Faster probe RTs following rTMS. Mean response time to answering the probe question reflecting faster response following rTMS than before rTMS. Error bars indicate standard error of the mean.

309-ms speed-up in RT (from pre-rTMS to post-rTMS) was even greater than the 66-ms speed-up that occurred in the training session (first half of the session RT minus second half RT); this interaction approached significance ($F_{1,22} = 3.50$, $P = 0.07$). Secondly, there was no speed-up from the training session to the fMRI session, suggesting that the RTs had leveled off; that is, the RT for the second half of the training session was similar to the pre-rTMS RT in the fMRI session (no significant difference in the mixed group design or in either the LH-TMS or RH-TMS groups; all P's > 0.25). This suggests that most or all of the initial speed-up due to experience was complete when the scan began. Due to high accuracy rates in all conditions (range of group means 0.89–0.95), there were no significant differences in error rates (all F's < 1).

Many rTMS studies have similarly reported improvements in task performance following rTMS during picture naming (Schuhmann et al. 2009) and visuospatial attention (Kim et al. 2005; for a review see Sandrini et al. 2011), an enigmatic outcome of disrupting normal brain activity. The findings here suggest an explanation namely that the preserved or enhanced performance may be due to the compensating network remaining coactive with the recovering network. That is, the compensating regions continue increasing their coordination levels in the post-TMS period concurrently with the recovery of the targeted area and its partners, providing a dual cortical basis for continual improvement in performance.

Discussion

The Compensatory Network (Perilesional LSTG, MedFG, and the Posterior RH)

One of the central issues in this research concerns the instantaneous, dynamic way in which a compensatory network comes to be activated in the face of local perturbations, and how it operates. Our interpretation is that a set of compensating areas have some of the same computational capacities (though in less efficient forms) as the LH language areas that were downregulated. This capability is not usually exploited because the downregulated regions are specialized for this particular function and can perform it more efficiently. However, after rTMS, when the required output is no longer available from the typically used network, the processing may automatically shift to the corresponding RH area, based on its similar capabilities. This homologous region may have been occasionally providing some of the required information on an as needed basis all along (Just et al. 1996; Jung-Beeman 2005).

Under the post-rTMS regimen, the contralesional RSTGp and the perilesional LSTGm may have collectively performed the computations normally performed by the transiently less available Wernicke's area (LSTGp) and its downgraded collaborators. The involvement of the contralateral RSTGp is readily predicted by the Spillover hypothesis, whereby highly demanding language processing spills over from LH to RH areas; as the structural complexity of sentences increases, activation in the right-hemisphere homolog of Wernicke's area (RSTGp) increases (Just et al. 1996; Prat et al. 2011). Over a longer time scale, a focal lesion in a LH language area similarly results in spillover of processing to its RH homolog (Just and Varma 2007).

The increased synchronization of the key posterior RH region and the medial frontal region suggests an executive monitoring function being added as part of the compensatory process. The medial frontal area, which has been associated with protagonist monitoring and ToM processing during the comprehension of narrative text (Vogeley et al. 2001; Gallagher and Frith 2003; Saxe et al. 2004; Mason et al. 2008), becomes more activated when text is less coherent (Ferstl et al. 2002; Prat et al. 2011). Although the perilesional RH and the contralesional LSTGm may act as a temporary substitute for the downregulated language regions (LSTGp and LIFG), the rTMS presumably produces a momentary incoherence in comprehension resulting in the activation of the MedFG. Compensation then involves an increased synchronization between this monitoring region and the compensatory posterior RH. Thus, the shifting partnerships of the activated regions indicates a rapid compensatory process involving the automatically compensating spillover region (RSTGp), a perilesional secondary semantic region (LSTGm), and a coherence monitoring region (MedFG). The increase in synchronization in these 3 diverse and distal regions is indicative of a cognitive response to rTMS beyond any that would be predicted by physiological or anatomical factors.

Individual Differences

The greater activation in the posterior RH and the left anterior frontal region for participants with higher reading spans is indicative of their greater adaptability in response to the demands of the task (Prat and Just 2011; Prat et al. 2011). Not surprisingly, this evidence of greater adaptability appears in the primary compensation region (posterior RH). The activation in anterior frontal regions associated with the maintenance of language information has been shown to be correlated with working memory capacity in language tasks (Prat and Just 2011) and memory tasks (Rypma and Prabhakaran 2009). This increase in activation in frontal regions correlated with working memory capacity during complex tasks is hypothesized to have resulted in better binding and faster and more efficient retrieval at a later stage of processing. The additional recruitment of a region adjacent to the downregulated LIFG could have functioned as a secondary binding area for semantic information (agent–verb pairings), further evidence for the greater adaptability of high capacity individuals.

Summary and Conclusion

Concurrent rTMS and fMRI revealed dynamic reorganization of brain networks. The specific adaptation to a virtual lesion in

a primary language region entailed increased synchronization (collaboration) of function between contra- and perilesional regions and the MedFG in this language comprehension task as well as the recovery of function in the downregulated area and its other language network members.

This powerful new combination of fMRI of brain activity before, during, and after rTMS reveals some of the cortical mechanisms of adaption and recovery in real time, from impairment due to a transient virtual lesion. The brain system's ability to maintain intellectual function in the face of localized physical incapacitation has always seemed remarkable, but the precise immediate mechanisms have not been well understood. What can be loosely termed "rewiring" or "neuroplasticity" can be now more precisely described as a temporary change in neurocognitive cortical partnerships, including the substitution of new partners, to compensate for the lowered ability of a disabled region and its partners to perform their usual function. At the same time, activity of the partners of the disabled region is temporarily decreased. In addition, the coordination between the disabled area and the stream of perceptual input is decreased. People with greater working memory capacity have a greater ability to adapt in the face of reduced input from the disabled region, recruiting compensatory regions to a greater extent than individuals with lower working memory capacity. The temporary recruitment of compensatory mechanisms operating in conjunction with recovering mechanisms likely resulted in not only maintenance of the cognitive performance level, but also improved ability to perform the task. In the most general terms, the adaptation can be seen as a dynamic self-organization of brain centers into new coalitions of regions that can perform the task using alternative computational resources during the temporary incapacitation of a central network resource.

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