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Local immediate versus long-range delayed changes in functional connectivity following rTMS on the visual attention network

Lorella Battelli[1,2,*], **Emily D. Grossman**[3,*], and **Ela B. Plow**[4]

[1]Center for Neuroscience and Cognitive Systems@UniTn, Istituto Italiano di Tecnologia, Via Bettini 31, 38068 Rovereto (TN)

[2]Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School. Boston, MA 02215, USA

[3]Department of Cognitive Sciences, University of California Irvine, Irvine, California 92697

[4]Department of Biomedical Engineering and Department of Physical Medicine and Rehabilitation, Cleveland Clinic. Cleveland, OH 44195, USA

Abstract

Background—The interhemispheric competition hypothesis attributes the distribution of selective attention to a balance of mutual inhibition between homotopic, interhemispheric connections in parietal cortex [1,2]. In support of this hypothesis, repetitive inhibitory TMS over right parietal cortex in healthy individuals rapidly induces interhemispheric imbalance in cortical activity that spreads beyond the site of stimulation [3]. Behaviorally, the impacts of inhibitory rTMS may be long delayed from the onset of stimulation, as much as 30 minutes [4,5].

Objective—In this study, we examine the temporal dynamics of inhibitory rTMS on cortical network integrity that supports sustained visual attention.

Methods—Healthy individuals received 15 min of 1Hz offline, inhibitory rTMS (or sham) over left parietal cortex, and then immediately engaged in a bilateral visual tracking task while we recorded brain activity with fMRI. We computed functional connectivity (FC) between three nodes of the attention network engaged by visual tracking: the intraparietal sulcus (IPS), frontal eye fields (FEF) and human MT+ (hMT+).

Results—FC immediately and significantly decreased between the stimulation site (left IPS) and all other regions, then recovered to normal levels within 30 minutes. rTMS increased FC between left and right FEF at approximately 36 min following stimulation, and between sites in the unstimulated hemisphere approximately 48 min after stimulation.

Corresponding author: Lorella Battelli: Lorella.Battelli@iit.it.

*L.B. and E.D.G. contributed equally to this work

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Conclusions—These findings demonstrate large-scale changes in cortical organization following inhibitory rTMS. The immediate impact of rTMS on connectivity to the stimulation site dovetails with the putative role of interhemispheric balance for bilateral visual sustained attention. The delayed, compensatory increases in functional connectivity have implications for models of dynamic reorganization in networks supporting spatial and nonspatial selective attention, and compensatory mechanisms within these networks that may be stabilized in chronic stroke.

Keywords

visual attention; functional connectivity; intraparietal sulcus; rTMS; fMRI

Introduction

The interhemispheric competition hypothesis is the leading proposal for cortical control of visual spatial attention. This hypothesis attributes the spatial distribution of selective attention to a balance of mutual inhibition between homotopic, interhemispheric connections in parietal cortex [6,7,1]. Disruptions in interhemispheric balance are increasingly linked to impaired visual attention in patients, such as hemispatial neglect and extinction [8]. Indeed, more severe hemispatial neglect is correlated with increased interhemispheric imbalances in cortical activity and decreased interhemispheric functional connectivity in the parietal components of the dorsal attention network [9–11]. In healthy individuals, asymmetric mutual inhibition is believed to underlie pseudoneglect and pseudoextinction [12–14].

Interhemispheric imbalance is implicated specifically in the ability to attend to rapidly changing competing sensory inputs, such as in visual tracking. Bilateral visual tracking is a task that requires the coordination of spatiotemporal attention to selected targets while suppressing signals for irrelevant distractors in both visual fields [15,2,4]. In healthy individuals, the load and spatial attention demands imposed by visual tracking are correlated with neural activity in the superior parietal lobule (specifically in the intraparietal sulcus, IPS) and the frontal eye fields (FEF) [16,17], the same neural circuits implicated by the interhemispheric competition hypothesis [1,8,18].

Two causal studies link the interhemispheric balance in parietal cortex to tracking abilities. Chronic right parietal patients with impaired visual tracking can improve their tracking scores following 1Hz offline inhibitory rTMS to the healthy left parietal cortex [4]. And in healthy individuals, rTMS over left IPS impairs tracking, with the severity of impaired performance correlated with the impact of rTMS on BOLD activity [3]. In addition to changes in performance overall, both of these studies reported a delay in the peak rTMS impact on behavior and cortical activity. In the right parietal patients, the peak improvement in tracking performance was observed 30 minutes after stimulation. In the healthy individuals, the correlation between individual subject performance and the magnitude of the univariate BOLD response emerged 25 minutes following stimulation. Delayed impact of rTMS is difficult to explain with current models of TMS intervention but is not without precedent, and has been linked to long-term depression/potentiation mechanisms [19,20].

In this study, we investigate changes in functional connectivity during visual tracking, specifically measuring the influence of rTMS interventions on interhemispheric

relationships. Functional connectivity is a metric of network integrity that reveals the structure of neural pathways independent of the magnitude of BOLD activity levels [21,22]. Using the protocol of Plow et al. [3], we examine the time dependent changes in cortico-cortical functional connectivity altered by rTMS, and compare its impact to visual tracking scores in healthy individuals. In this analysis we examine connectivity in a simplified model of three brain regions in the dorsal attention network engaged by visual tracking: the intraparietal sulcus (IPS), frontal eye fields (FEF) and human MT+ (hMT+). These three brain regions were selected because they are linked to tracking abilities in healthy individuals [2,17,3] and the interhemispheric weights within these regions predicts individual bias in spatial allocation of attention [23]. Importantly, understanding the dynamic nature of connectivity within these mechanisms, and how their dynamic interplay changes across time when disrupted, could help determine the extent to which these neural circuits may be amenable to therapeutic interventions to promote long-term plasticity.

Methods

Participants

Nine healthy subjects (mean age ± SD 27.72 ± 5.99 years, 7 males) participated in the experiment. Two subjects were excluded from analysis due to gradient artifacts in the MR data. All subjects had normal or corrected-to-normal vision. All participants met all TMS [24] and MRI screening criteria and provided written informed consent in accordance with the Institutional Review Board of the Beth Israel Deaconess Medical Center, Boston, MA.

Stimuli & Procedure

Data used in this analysis was previously published in Plow et al. [3]. Briefly, subjects participated in a total of two experimental sessions in which they engaged in a visual tracking task following offline, inhibitory rTMS or sham (conducted on 2 separate days in a counterbalanced order). In this task, subjects monitored high-contrast pairs of four-spokes-pinwheels displayed on either side of a central fixation. At the beginning of each trial two spokes, one for each pinwheel, were flickered briefly, indicating the targets. Both pinwheels then rotated at a fixed rate for 3 seconds. At the end of the trial all spokes on the target pinwheel appeared as probes and subjects were asked to indicate on a four alternative forced choice procedure which spoke was the target (top, bottom, right or left, Figure 1) [2,25]. Subjects were briefly tested before each fMRI session where we psychophysically measured the speed threshold at which they could report the target spoke at 85% accuracy, using a staircase procedure. We then used that same individually estimated threshold speed throughout the entire fMRI session.

Stimuli were generated in MATLAB using the Psychophysics Toolbox [26,27] and displayed on a PC laptop with a 17″ monitor screen projected with a rear-view mirror attached to the head coil in the scanner. Subjects completed a total of 48 trials of tracking over four scans (twelve per scan) with the trials randomly and evenly split across the two hemifields. Data for tracking in the left and right hemifields were pooled in the subsequent functional connectivity analysis.

rTMS

Transcranial magnetic stimulation was applied using a MagStim device (MagStim, Whitland, Wales, UK) with a 70-mm figure-of-eight coil guided by neuronavigation (BrainsightTM, Rogue Research Inc., Montreal, QC, Canada). Low-frequency 1 Hz rTMS was applied for 15-min at 75% of the maximum stimulator output, targeting the left intraparietal sulcus (IPS), identified using frameless stereotaxic image guidance co-registered with the individual subject's anatomical images [2]. Specifically, all subjects participated in a previous TMS experiment where we anatomically and functionally defined the left posterior IPS individually (average Talairach (mean ± SD): X = −23.37 ± 5.24; Y = −67.60 ± 4.25 and Z = 52.88 ± 2.47 mm) [2]. The TMS coil was held with the handle pointing posteriorly at an angle of 45° to the inter-hemispheric fissure, at an orientation that aligned it perpendicular to the left IPS. For the sham condition we placed the edge of the coil at an angle perpendicular to the head, while stimulation was delivered at the same intensity as in the rTMS session. The fMRI data collection was initiated within four minutes from completion of rTMS/sham.

fMRI procedure and analysis

Brain imaging was conducted with a whole-body 3T Phillips scanner equipped a standard birdcage headcoil. We acquired high-resolution T1-weighted MPRAGE images for each subject that reconstructed the individual structural brain anatomy (1 × 1 × 1.2 mm saggital images with no gap between slices, 170 slices). Subjects participated in four gradient-echo planar imaging (EPI) scans (TR = 2 s, TE = 55 ms, flip angle = 90°, TE = 30 ms, FOV = 23 cm and 96 × 96 matrix, final voxel size of 2.4 × 2.4 × 4 mm and a gap of 0.5mm, 20 axial slices acquired interleaved) in which 366 volumes were collected in each 12:12 min scan.

fMRI data collection was initiated within four minutes following the rTMS/sham. The first three EPI scans were collected successively, and the fourth and final scan was completed following a twelve minute interval during which subjects relaxed and viewed a popular cinema movie.

All functional scans were corrected for slice acquisition timing and for movement within and across the volumes. We removed the linear trends and slow temporal fluctuations (3 cycles per scan high pass filter) from each voxel. Functional data was then registered to standardized Talaraich space [28] and minimally spatially smoothed with a 3 mm FWHM filter.

We computed functional connectivity between the left and right corresponding regions for three bilateral regions of interest (ROIs): the intraparietal sulcus (IPS), human middle temporal complex (hMT+) and the frontal eye fields (FEF). These regions were identified in individual subjects, using a contrast of visual tracking versus fixation, and included only voxels significantly correlated with visual tracking with a Bonferroni family-wise error correction of $p < .0001$). Scans that were collected following TMS and sham conditions were included in the localization mapping. The ROIs were further localized in individual subjects using the following anatomical landmarks: the dorsal ridge of the intraparietal sulcus (IPS), the fundus of the descending branch of the inferior occipital sulcus, and the

anterior wall and fundus of the precentral sulcus (FEF). All ROIs were constructed as a sphere with 10mm radius centered on the peak voxels of activation and anatomical landmark. The group mean Talairach coordinates for the centroid of each region (right and left hemispheres) are shown in Table 1.

Functional connectivity was computed as the Pearson's r correlation coefficient for the z-score normalized timeseries of BOLD activity from each ROI. The ROI timeseries were constructed from the normalized (z-scored) BOLD for the entire 12 minute scans, which included intervals of visual tracking interspersed with fixation (rest). Correlation coefficients were Fisher-z transformed and the effect of rTMS on functional connectivity was estimated as $FC = FC_{TMS} - FC_{SHAM}$. This was computed separately for each 12 min scan then averaged across subjects.

Statistical significance was assessed by a bootstrap Monte Carlo procedure that computed the expected difference in correlation coefficients expected by chance. Bootstrap timeseries were constructed from timelocked pairs of timepoints selected from two ROIs, sampled with replacement from the TMS and sham conditions. This process was repeated 1,000 times to generate a distribution of samples that test the null hypothesis that the TMS and sham functional connectivity scores originate from the same population distribution. Those correlation coefficients with scores that exceeded two standard deviations of the simulated null population distribution were deemed statistically significant.

The recovery from the impact of TMS on functional connectivity was estimated by computing the slope of a linear fit to the FC scores from the first three sequential scans. The slope and intercept of those fits gives an estimate of the impact of the rTMS on the individual subjects. We also compared these metrics of rTMS impact to individual subject tracking scores to determine the strength of the relationship between the rTMS induced reorganization of cortical connectivity and behavior.

Results

Figures 2 and 3 show how functional connectivity evolved in the approximately one hour following stimulation over the left IPS, with connectivity scores normalized by connectivity following sham. Positive scores that exceed the dashed line indicate significantly stronger functional connectivity following rTMS as compared to sham, while negative scores (below the dashed line) indicate rTMS significantly reduced functional connectivity. Significance was assessed via a bootstrap procedure (see methods).

Figure 2 shows functional connectivity between the right and left regions of interest (interhemispheric homotopic connections). Functional connectivity between the stimulation site and the homologous right IPS decreased significantly immediately following stimulation (scan 1), and recovered to within normal levels by approximately 30 minutes following the rTMS (scan 3). This timecourse of normalized functional connectivity is consistent with the duration over which rTMS influences behavioral performance in healthy individuals as reported in a wide range of cognitive and attention tasks [29,30].

We also examined functional connectivity in two regions distal and functionally connected to the stimulation site. The influence of rTMS on the functional connectivity between left and right FEF was delayed and brief, with increased connectivity approximately 36 min following stimulation that returned to levels consistent with sham within 60 min. The late increase in functional connectivity in the FEF was unexpected, however it is consistent with a previous report of delayed impact of rTMS on the bilateral FEF BOLD activity following theta burst stimulation over right FEF [31] and may relate to potential compensatory effects observed in Plow et al. [3] rTMS had no impact on interhemispheric connectivity between the left and right hMT+.

We next looked at the impact of rTMS on inter-regional functional connectivity, and found that the influence depended on hemisphere and time. In the stimulated left hemisphere, FEF and hMT+ connectivity to the stimulation site (left IPS) decreased immediately following rTMS, then recovered to normal levels (Figure 3a). This pattern of connectivity has the same timing as the IPS interhemispheric connections.

In the unstimulated right hemisphere, FEF and hMT+ connectivity increased only in the fourth and final scan, approximately 50 minutes following stimulation and after a period of free-viewing the movie. These delayed and remote effects of rTMS on functional connectivity in the unstimulated hemisphere were unanticipated.

In previous reports using the same paradigm, the extent to which rTMS shifts the cortical imbalance in neural activity between homotopic regions in parietal cortex is linked to individual subject tracking scores [3]. We therefore investigated a possible brain-behavior link in functional connectivity changes over time by examining the correlation between recovery in functional connectivity and visual tracking.

To quantify the temporal dynamics of functional connectivity recovery following rTMS, we modeled the functional connectivity scores using linear regression for the first 40 min following stimulation. Whereas the initial impact of rTMS (as indicated by the intercept) had a marginal relationship with functional connectivity to the stimulation site ($r = .54$, $p>.05$), it was the recovery of the functional connectivity that most strongly correlated with tracking performance (Table 2 and Figure 4). Dynamic changes in the left and right IPS functional connectivity, the left and right hMT+ connectivity, and the connections between the stimulated IPS and hMT+ were all significantly correlated with tracking scores ($r = -.78$, $r = -.87$, and $r = -.74$, respectively; all $p < .05$; Table 2). Those subjects that experienced the greatest impact of rTMS on functional connectivity also made the most tracking errors. We found no relationship between the impact of rTMS on functional connectivity in the unstimulated hemisphere.

Discussion

In a normally functioning system, visual orienting is controlled by bilateral cortical mechanisms that direct attention to contralateral space, and the functional integrity of this attention network is critical for healthy visual attention. In this study, we measured the temporal dynamics of functional connectivity for 50 minutes during a visual tracking task,

with and without 1 Hz repetitive TMS. This study is motivated by the observation that inhibitory TMS over the IPS impairs bilateral visual tracking in healthy individuals [2] and improves bilateral tracking when applied to the healthy (left) parietal cortex in right parietal patients [4]. Both of these findings are consistent with the interhemispheric competition hypothesis for bilateral control of visual orienting.

Inhibitory rTMS over left IPS induced widespread changes in the functional integrity of the dorsal attention network. These changes occurred both inter- and intra-hemispherically, with immediate and delayed timing, respectively. The immediate changes manifested as a decreased connectivity between the homotopic regions at the IPS stimulation site, and decreased inter-regional connectivity in stimulated hemisphere (FEF and hMT+ to the stimulation site). These changes in connectivity normalized within 36 minutes following stimulation. Delayed effects of the rTMS included increasing connectivity between homologous regions of the FEF approximately 36 min following stimulation, and increased interregional connectivity very late in the unstimulated hemisphere.

That rTMS can induce rapid changes in cortical activity directly under the site of stimulation and downstream from the stimulation site is well known [32]. Low frequency inhibitory rTMS decreases metabolic activity local to the stimulation site as measured by PET, and is often accompanied by compensatory increases in neural activity in functionally connected regions in the normal population [3,33–36].

Whereas at least four studies have documented large-scale shifts in interhemispheric balance within the dorsal attention network following rTMS to the parietal cortex [4,3,23,37], ours is the first to consider changes in functional connectivity during a sustained attention task. Functional connectivity measures are dominated by low frequency fluctuations on the order of .1 Hz or slower [38,39], reflecting phase-locked covariations of functionally connected regions. Our study demonstrates rTMS will disrupt the spontaneous connections between these regions for time extending beyond the period of stimulation, creating a wave of compensatory activity that alters neural coupling for extended durations remote from the region of stimulation.

The timing of recovery we observed for connectivity to the stimulation site, approximately 36 minutes, is consistent with the observed interval of impaired behavior on a wide range of attention tasks following rTMS [29]. We were also able to link the impact and recovery of functional connectivity to the stimulation site with individual subject tracking errors, establishing a causal relationship between the impact of rTMS on functional connectivity and the ability of individual subjects to engage in visual tracking.

The rTMS stimulation also induced delayed increases in functional connectivity distal to the stimulation site. We observed an increase in connectivity in the unstimulated right hemisphere, between the right IPS and right FEF, and right IPS and right hMT+. These findings were unpredicted, but not without precedent. Agosta et al., [4] observed peak improvement in tracking performance 20–30 minutes following inhibitory rTMS applied to the healthy, contralesional parietal cortex in stroke patients. Likewise, Nyffler et al. [40] observed delayed peak impact of theta burst rTMS over FEF on saccadic latency. A

subsequent study using the same paradigm documented delayed (20–35 min) peak decrease BOLD activity in the stimulated FEF and, to a lesser extent, in functionally connected regions [31]. The timescale of these changes is consistent with that of long-term depression/potentiation [19,41] and there is some evidence that the magnitude of these delayed effects may depend on the level of exertion engaged during stimulation [42].

That downstream changes in functional connectivity would be observed within the dorsal attention network is not surprising. The intraparietal sulcus and frontal eye field are strongly interconnected via the superior longitudinal fasciculi [43–45] and both are important for the implementation of voluntary directed attention to task-relevant features [see 46 for a recent review]. Focal TMS over IPS and FEF both disrupt selective attention in visual search tasks, albeit with different timing, in which targets are defined by conjunctions of features and thus require feature binding [47–49].

Posterior parietal cortex and the FEF are also linked to sustained awareness of sensory events, and to maintaining sustained cortical modulations in sensory cortex during encoding of task-relevant events [50–52]. Single pulses of TMS over posterior parietal cortex decreases the perceptual sensitivity for targets that are being monitored in the contralateral visual field [53] and shortens dominance intervals during binocular rivalry [54]. Patients with damage to posterior parietal cortex experience the perceptual fading of visual events more quickly that typical individuals [55]. The implication is that connectivity between posterior parietal cortex, frontal eye fields and sensory cortex are essential for sustained salience of attended features [56]. Our study demonstrates that acute disruptions to connectivity between these regions are followed by an interval dynamic stabilization within this highly connected network.

These findings also have implications for stroke models that implicate imbalanced network activity, as damage to one hemisphere leads to *disinhibition* in the competing, *unaffected* hemisphere [57]. This up-regulated activity in the unaffected hemisphere thus leads to excessive *inhibition* in the affected hemisphere. That is, not only does the lesioned hemisphere suffer the frank damage from the stroke, it is also further suppressed by “unabated” inhibition from the unaffected hemisphere. The improvement seen in the patients specifically implicates the ability of rTMS to restructure the balance of cortical activity through functional connectivity. In our study we found that it is the interplay and strength of inter- and intra-hemispheric connections among the cortical areas within the dorsal attention network that determine the efficiency of the sustained attention system [58].

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Highlights

- Offline inhibitory rTMS over the left intraparietal sulcus has a local, immediate and brief impact on the network integrity to functionally connected cortical regions in the dorsal attention network
- Those individuals with more disruptions in local functional connectivity are most impaired on sustained visual attention tasks, which dovetails with the hypothesized role of interhemispheric balance for bilateral visual sustained attention
- rTMS over left intraparietal sulcus creates remote and delayed increases in interregional functional connectivity in distal brain sites, which may have implications for models of compensatory mechanisms that may be stabilized in chronic stroke

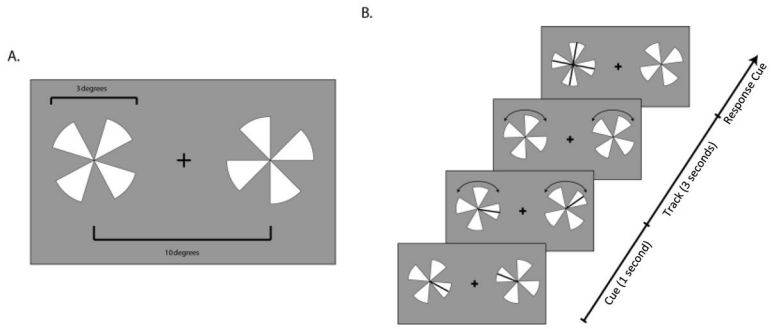

Figure 1. Bilateral Visual Tracking Task

A. Two pinwheels were presented. Cartoon of one frame of the task, where sizes of the pinwheels and distances are reported. B. One spoke for each pinwheel was cued (a black line flashed briefly). Once the black lines disappeared, the pinwheels began to rotate in randomly different directions. Once they stopped, one pinwheel was highlighted, and using a four-alternative forced-choice procedure, subjects indicated which spoke was the one cued at the beginning of the trial. The side of the target was unpredictable across trials.

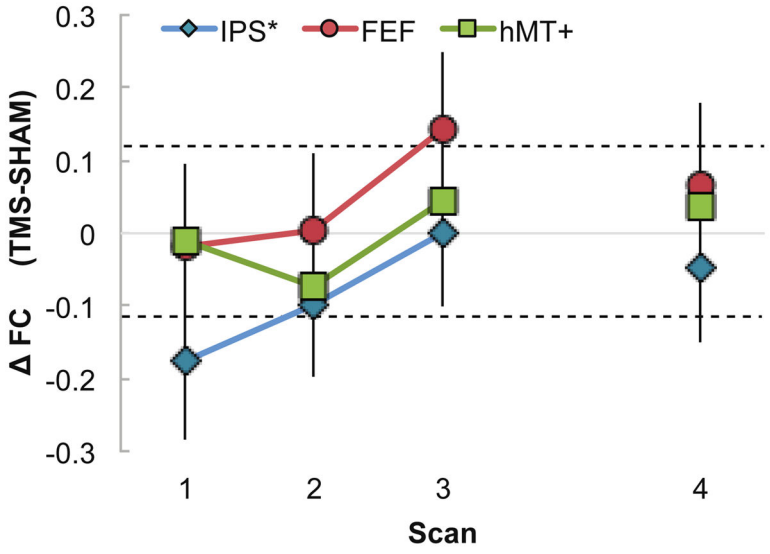

Figure 2. Interhemispheric FC across time

Functional connectivity difference between homotopic areas in the left (stimulated) and right hemisphere (Sham FC was subtracted from TMS FC). Colored symbols indicate the three areas: IPS (Intraparietal Sulcus, blue diamonds), FEF (Frontal Eye Field, red circles) and hMT+ (human Middle Temporal Area, green squares). While the first three runs were collected in close succession (Scans 1, 2 and 3 on the x-axis), scan 4 was collected approximately 48 minutes from the end of stimulation, following an intermediate run during which subjects rested while watching a video clip of a popular movie. Values above the dashed lines indicate statistically significant difference (between Sham and TMS), determined using a the bootstrap Monte Carlo procedure. FC between left and right IPS significantly decreased during Scan 1 and slowly recovered in Scan 2. FC between left and right FEF significantly increased during Scan 3, over 30 minutes after the end of stimulation.

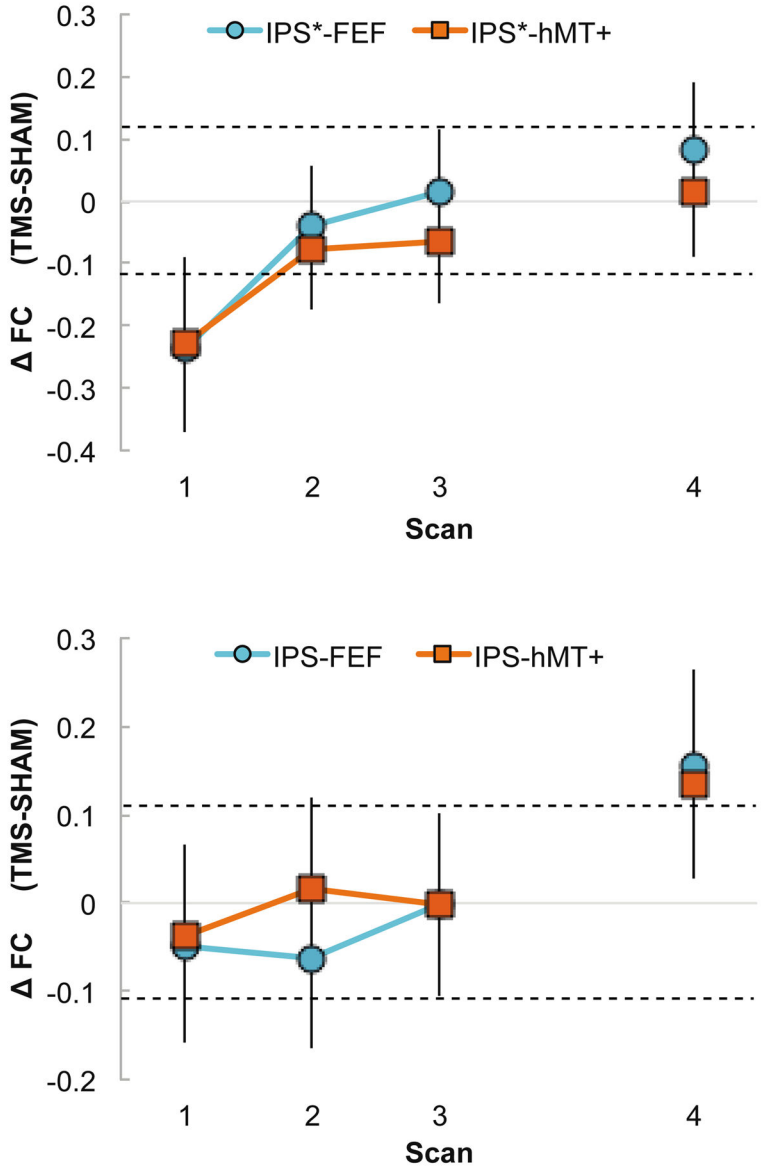

Figure 3. Intrahemispheric FC across time

Intrahemispheric impact of rTMS on FC within the left hemisphere (a. stimulated) and the right hemisphere (b. unstimulated). FC scores reflect the change in functional connectivity in the TMS condition as compared to Sham. A) FC between the left IPS and the left FEF (blue circles) and between the left IPS and left hMT+ (red squares) immediately and significantly *decreased* during Scan 1 (dotted line indicates significant difference) and recovered starting from Scan 2, 3 and 4. B) FC between the right IPS and the right FEF (blue circles) as well as between the right IPS and right hMT+ (red squares) significantly *increased* around 48 minutes after the end of stimulation, during Scan 4.

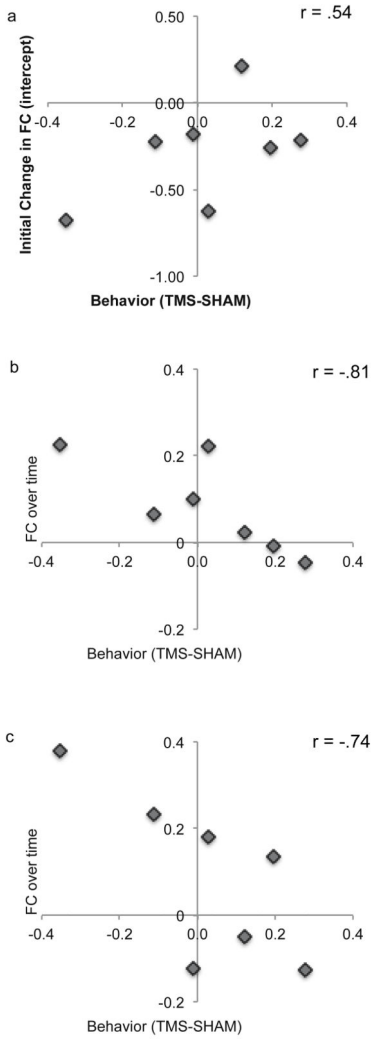

Figure 4. Relationship between tracking performance and impact of rTMS

(A) Change in tracking accuracy vs the initial impact of rTMS on homotopic IPS connectivity. Behavioral scores reflect the change in visual tracking following rTMS as compared to sham. Initial impact of rTMS on functional connectivity is computed as the intercept of the best linear fit for functional connectivity following rTMS vs sham (see methods). Those subjects most impacted by rTMS (on this connection, and many others) also have the most recovery in FC over time. **(B)** Change in tracking accuracy vs recovery (slope) of the homotopic IPS functional connectivity. These are the subjects where the rTMS really changed FC. **(C)** Change in tracking accuracy vs recovery (slope) of the left (stimulated) hemisphere IPS-hMT+ functional connectivity.

Table 1

Group mean Talairach X, Y and Z coordinates for the centroid of each region (left and right hemispheres).

	Left hemisphere			Right hemisphere		
	X	Y	Z	X	Y	Z
Intraparietal sulcus	−25.6 (6.2)	−60.9 (4.0)	53.9 (5.1)	22.3 (4.8)	−62.6 (2.1)	52.4 (2.4)
human MT+	−46.7 (2.1)	−66.7 (3.6)	3.7 (1.8)	43.7 (2.4)	−65.6 (0.5)	5.1 (3.3)
Frontal eye field	−28.9 (3.4)	−10.1 (3.0)	52.0 (2.7)	31.3 (2.5)	−11.1 (4.6)	53.1 (2.9)

Table 2

Brain-behavior correlation scores

Correlations between rTMS induced changes in visual tracking in each visual field (contra-stimulation, ipsi-stimulation, and overall performance) and dynamics of functional connectivity, broken down by initial impact (intercept) and dynamic recovery (slope).

		Intercepts			Slopes		
		Contra	**Ipsi**	**Overall**	**Contra**	**Ipsi**	**Overall**
Homotopic	IPS*-IPS	r=.38	r=.64	r=.54	r=−.67	r=−.81†	r=−.78†
	FEF-FEF	r=.30	r=.00	r=.16	r=−.53	r=−.35	r=−.46
	hMT+-hMT+	r=.72	r=.57	r=.66	r=−.87†	r=−.78†	r=−.87†
Stimulated Hemisphere	IPS*-FEF	r=.44	r=.36	r=.42	r=−.56	r=−.50	r=−.55
	IPS*-hMT+	r=.61	r=.57	r=.62	r=−.74†	r=−.67	r=−.74†
Unstimulated Hemisphere	IPS-FEF	r=−.12	r=−.36	r=−.25	r=−.24	r=−.08	r=−.17
	IPS-hMT+	r=−.10	r=.14	r=.02	r=−.68	r=−.63	r=−.65

†Significance at $p < .05$ (two-tailed).