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Network mechanisms of responsiveness to continuous theta-burst stimulation

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Abstract

Continuous theta-burst stimulation (cTBS) can modify behavior, but effects are inconsistent and their mechanisms insufficiently understood. Since coherence in resting-state networks influences human behavior, we hypothesized that cTBS may act via modulation of neural oscillation coherence. This study used electroencephalography (EEG) to investigate whether behavioral effects of cTBS on visuospatial attention are associated with coherence changes in the attention network.

In healthy human subjects, cTBS of the right posterior parietal cortex (PPC) was compared to sham and frontal eye field (FEF) stimulation. Effects on visuospatial attention were quantified with a visual exploration task, and network effects were assessed from surface EEG with inverse solutions and source coherence analyses.

Before stimulation, left visual exploration was linearly correlated with alpha-band coherence between the right PPC and the rest of the brain. PPC stimulation reduced alpha-band coherence at the stimulation site but also enhanced it in the contralateral left temporo-parietal cortex. The contralateral increase correlated with the induced reduction in left visual attention. The behavioral response of individual participants to cTBS could be predicted by coherence in the right temporo-parietal junction before stimulation.

Behavioral effects of cTBS therefore depend on network states before stimulation and are linearly associated with changes in network interactions. In particular, cTBS equilibrates an interhemispheric competition in alpha-band coherence. EEG network imaging might help optimize therapeutic cTBS in the future.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is one of the most promising tools for modulation of brain activity and behavior in healthy subjects as well as in patients with brain disease (Bolognini *et al.*, 2009; Song *et al.*, 2011; Tanaka *et al.*, 2011). It can modify behavior in healthy subjects (Nyffeler *et al.*, 2006; Nyffeler *et al.*, 2008) and induce therapeutic effects in patients with brain disease. For instance, it can enhance brain plasticity and improve recovery in patients with motor, language, or spatial attention deficits due to acquired lesions (Di Lazzaro *et al.*, 2005; Hamilton *et al.*, 2011; Cazzoli *et al.*, 2012; Koch *et al.*, 2012). The so-called theta-burst stimulation (TBS) protocol is particularly attractive, because it can induce long-lasting behavioral effects while requiring only short stimulation times of < 1 min (Huang *et al.*, 2005; Nyffeler *et al.*, 2006). Yet, the effects of rTMS are inconsistent and some brain stimulation studies have even reported harmful effects (Ackerley *et al.*, 2010; Iezzi *et al.*, 2010). The reason for this inconsistency is largely unknown.

The brain is a network of massively interconnected processing elements (Sporns *et al.*, 2004) showing synchronous fluctuations at rest which are correlated with behavior (He *et al.*, 2007; Carter *et al.*, 2010; Wang *et al.*, 2010). Specifically, the magnitude of coherence in the alpha frequency band (7 to 13 Hz) between a brain area responsible for a given function and the rest of the brain was significantly associated with individual performance in this function (Dubovik *et al.*, 2012; Dubovik *et al.*, 2013). Given this network basis of human behavior, we expect rTMS to have not only local effects on the stimulated cortex but influences on an entire network. Previous fMRI studies have indeed shown that rTMS influences not only stimulated areas but also other nodes from the same functional network (Hubl *et al.*, 2008; Grefkes *et al.*, 2010; Eldaief *et al.*, 2011). However, it is unknown whether rTMS affects network communication. Insights into the effects of rTMS on neural communication might be crucial to understand and predict the variable behavioral responses across subjects (Hampson & Hoffman, 2010; Vanneste *et al.*, 2011).

We hypothesized that (i) rTMS influences network coherence at specific neural oscillation frequencies, and (ii) that at least some of these changes in network communication, in particular alpha-band coherence, are linearly related to behavioral effects of TMS. In order to test this, we specifically focused on a continuous theta-burst stimulation (cTBS) protocol (Nyffeler *et al.*, 2008; Goldsworthy *et al.*, 2012) which was expected to exert an inhibition of the underlying cortex. It was chosen because it is currently the most appealing protocol for clinical applications with low risk of inducing seizures compared to excitatory protocols. We targeted a network responsible for spatial attention in healthy volunteers to induce a mild transitory reduction in attention for the left visual field (Nyffeler *et al.*, 2008), qualitatively similar as it can be observed in patients with hemispatial neglect due to right hemispheric damage.

Materials and Methods

Participants

Nine healthy volunteers (five females) aged between 22 and 32 years (mean age 25.8, SD 3.5 years) participated in this study. Exclusion criteria were a history of brain injury, the presence of major medical illness, neurological or psychiatric clinical antecedents and intake of medication during the study. All participants gave their written informed consent for the experiment and were remunerated for participation. Handedness was assessed with the Edinburgh inventory (Oldfield, 1971). One of the participants was left-handed and one ambidextrous. The study was approved by the University Hospital of Geneva Ethics Committee and conducted according to the Declaration of Helsinki.

Study design

In three sessions separated by at least 1 week, continuous theta burst stimulation (cTBS) of either the right intraparietal sulcus (IPS) or the right frontal eye field (FEF), or sham stimulation over the right IPS was delivered in counterbalanced order in each subject. In each session, ten-minutes of high-density resting-state EEG were recorded prior to, immediately after, and 30 min after stimulation. Moreover, visual exploration was assessed immediately before and 15 minutes after stimulation with an eye tracking device (Figure 1).

Recordings

Resting-state EEG data was recorded with a TMS compatible, 64-channel BrainAmp DC system (Brain Products GmbH, Gilching, Germany), using a sampling rate of 500 Hz. The participants were asked to keep their eyes closed, but to stay awake. Artifacts like eye movements and muscular contractions, as well as periods with excessive sleepiness were excluded by visual inspection of the data. Five minutes of artifact-free data were then recalculated against the average reference.

Visual exploration task and behavioral data analysis

Behavioral effects of TMS were evaluated with a visual exploration task. Twenty-five symmetrical naturalistic color photographs were displayed in a dark room on a computer screen with a size of 40x30 cm, a resolution of 1280x1024 pixels, 32 bit color depth, and a refresh rate of 85 Hz. Subjects were instructed to fixate a central cross and to freely explore images when they appeared on the screen. Each photograph was presented for 5.5 s. Different picture sets were used before and after stimulation to avoid familiarity effects and left-right flipped versions were randomly presented across subjects to further maximize the symmetry. Gaze direction was recorded with an eye tracking device (HighSpeed, SMI GmbH, Teltow, Germany). The system has a spatial resolution better than .3°, and a sampling rate of 240 Hz. During the experiment the head of the participant was fixed to prevent movements. The viewing distance was set at 65 cm.

Fixations were extracted from the eye tracking data by removing eye blinks and saccades. An eye movement was considered as a saccade when velocity exceeded 35°⁄s or the movement distance 0.1°. Fixations had to last at least 80 msec. Nyffeler et al. (2008) have demonstrated that cTBS over the right PPC induces a reduction of cumulative fixation duration, mean fixation duration, and number of fixations in the left visual field, while it increased them in the right visual field. Here, we focus on cumulative fixation duration in the left visual hemifield as behavioral measure of left visual exploration; the other measures showed similar results. Values were compared across stimulation conditions with a repeated-measures analysis of variance (ANOVA).

TMS procedure

Continuous theta-burst stimulation (cTBS) intended to exert an inhibition at the stimulation site was carried out with a MagPro X100 system (MagVenture A/S, Farum, Denmark). In each of three conditions different coils were used to deliver repetitive magnetic pulses in order to follow respective recommendations of the literature. We used a round coil (MC-125), with an outer diameter of 120 mm for the stimulation of right PPC (Nyffeler *et al.*, 2008), an eight-shaped coil (MCF-B65) with an outer diameter of 2x90 mm for the stimulation of right FEF (Nyffeler *et al.*, 2006) and eight-shaped sham coil (MCF-P-B65) of the same diameter in the sham condition. Stimulation of the right PPC was performed with the posterior segment of the round coil placed tangentially over electrode P4 (according to the international 10-20

EEG system) with the current flowing in a clockwise direction as viewed from above. Stimulation intensity was set to 90% of the individual resting motor threshold (Nyffeler *et al.*, 2008). For the sham condition, the center of the eight-shaped placebo coil was accordingly placed over P4. The stimulation site for the FEF condition was determined individually in each subject as described previously and intensity was set to 80% of the individual resting motor threshold (Nyffeler *et al.*, 2006). The theta-burst protocol was the same in all conditions and implied 267 bursts, each consisting of three pulses applied at 30 Hz. Bursts were repeated at 6 Hz corresponding to an inter-burst interval of 167 ms (Nyffeler *et al.*, 2008).

Functional connectivity analysis

Connectivity analysis was performed in Matlab with NUTMEG (http://nutmeg.berkeley.edu) (Dalal *et al.*, 2011) and its FCM toolbox (Guggisberg *et al.*, 2011), as described previously (Guggisberg *et al.*, 2008; Guggisberg *et al.*, 2011). In short, the lead-potentials were calculated by using a spherical head model with anatomical constraints (Spinelli *et al.*, 2000) based on the segmented grey matter of the individual T1 weighted MRI. The EEG was bandpass-filtered between 1 and 40 Hz and projected to grey matter voxels with an adaptive spatial filter (scalar minimum variance beamformer) (Sekihara *et al.*, 2004). The connectivity was inferred by calculating the absolute imaginary component of coherence (IC) (Nolte *et al.*, 2004) between all pairs of gray matter voxels. In contrast to magnitude squared coherence, IC has the advantage of being robust to overestimations and distortions of cortical connectivity due to spatial leakage of the inverse solutions (Guggisberg *et al.*, 2008; Sekihara *et al.*, 2011). A disadvantage of IC is that, unlike other measures of FC, it does not only depend on the magnitude of coupling but is additionally influenced by the phase lag. However, previous direct comparisons of IC to other measures of FC have shown that this difference does not lead to systematic differences in the reconstruction of functional networks and that the magnitude of IC is behaviorally meaningful (Guggisberg *et al.*, 2011; Dubovik *et al.*, 2012).

IC maps of the participants with individual structural images were spatially normalized to the canonical MNI brain space with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).

We then used a two-step approach to examine the multidimensional data array (Dubovik *et al.*, 2012; Dubovik *et al.*, 2013). First, we calculated the global FC of each voxel as the average absolute IC across its connections with all other voxels. This provided maps of the overall connectivity of each voxel with all other voxels during the entire resting state recording. Second, we defined anatomical regions showing largest overall connectivity changes in the first step as seed regions of interest (ROIs) and computed the IC between these seed nodes and all other voxels.

ROIs belonging to the spatial attention network were defined *a priori* based on coordinates described in the literature (Fox *et al.*, 2005; He *et al.*, 2007). Stimulation-induced changes in the ROIs were tested for significance with paired t-tests. IC magnitudes and IC changes at all frequency bins were subjected to a Pearson correlation analysis. Based on previous findings (Guggisberg *et al.*, 2008; Dubovik *et al.*, 2012) we *a priori* expected effects in alpha frequencies which were therefore considered significant without correction. Conversely, all other frequency bins were required to remain significant after correction for multiple tests with a false discovery rate (FDR) of 5%. In order to demonstrate the spatial specificity of network changes, we additionally performed voxel-wise analyses with statistical non-parametric mapping (SnPM) (Singh *et al.*, 2003). Voxel maps are reproduced without correction for multiple testing to visualize the full spatial extent of network changes.

Results

Baseline

Before stimulation, subjects spent on average more time fixating the left half of the photographs (Figure 2a). However, the difference between left and right fixations was not significant (t_8=0.88, p=0.40) and there was a large inter-individual variability across subjects. This behavioral variability was associated with corresponding differences in alpha-band IC in the right temporo-parietal cortex. Subjects with a preference for the left visual field had large alpha-band IC between the right temporo-parietal cortex and the rest of the brain (Figure 2b, example marked with filled arrow) whereas in subjects with a preference for the right visual hemifield, the alpha-band connectivity between the temporo-parietal cortex and the rest of the brain was relatively low (Figure 2b, example marked with empty arrow). In consequence, left-sided visual exploration was linearly correlated with the level of alpha-band IC between the right temporo-parietal cortex and the rest of the brain (Figure 2c) and in particular between the right IPS and the right middle frontal gyrus (Figure 2d). In other words, the more these regions were coherent in the alpha-band, the more subjects fixated the left half of the photographs.

Effects of cTBS

Figure 3a shows changes in leftward visual exploration induced by the different stimulation conditions. Stimulation of the right PPC induced the expected *reduction* in left visual exploration in most participants. Yet, 2 participants showed the inverse effect: cTBS over the right IPS *increased* their left visual exploration. In consequence, when statistical analysis was performed across all 9 subjects, no significant difference between of stimulation conditions could be observed (but see next section).

The effects of right PPC stimulation on alpha-band IC are shown in Figure 3b. Continuous TBS induced significant changes in oscillation coherence between nodes of the attention network and the rest of the brain. Specifically, a decrease of alpha-band IC was observed in the stimulated right IPS and in the left FEF, whereas an increase was found in the homologous contralateral left IPS and right FEF. The spectrograms in Figure 3c illustrate the oscillation frequencies at which cTBS had significant impact on IC. In addition to the effects on the alpha-band, we observed decreases of IC at 30 Hz between the right IPS and the rest of the brain. Figure 3d visualizes stimulation effects at 10Hz and 30Hz in four ROIs directly after and 30 min after stimulation. Effects on the FC were specific for stimulation of the right PPC and lasted for at least 30 to 40 minutes. Most importantly, the cTBS-induced changes of FC in the left temporo-parietal cortex at 10 and 21 Hz correlated positively with the induced neglect-like effect on visual exploration: the more cTBS was able to increase IC between the left temporo-parietal cortex and the rest of the brain, the more participants shifted their attention to the right (Figure 3e).

Next, we specifically examined connections of nodes belonging to the spatial attention network. The assessments of global connectivity above suggested that cTBS-induced FC changes in the left temporo-parietal cortex are linearly associated with behavioral effects (Figure 3e). We therefore examined the connections of the left IPS more closely and observed that changes in its functional connections with the precuneus, the orbito-frontal cortex (OFC), and the left angular gyrus were correlated with cTBS-induced shifts in visual exploration (Figure 4). No significant correlations were found for interactions between the left IPS and other nodes belonging to the spatial attention network (the right IPS and the FEF).

Network predictors of cTBS effects

We then examined whether we could explain the opposite behavioral effects on leftward visual exploration observed in 2 participants by differences in their network states before cTBS. All subjects with average or high alpha-band FC in the right temporo-parietal junction (TPJ) prior to stimulation of the right PPC displayed the expected neglect-like effect. Conversely, cTBS applied to the 2 subjects whose right TPJ was already poorly connected at baseline induced the inverse effect of more left-sided exploration (Figure 5a). In an analysis across all subjects, the magnitude of alpha-band IC in the right TPJ before stimulation was significantly correlated with the magnitude of the behavioral rightward shift in visual exploration induced by subsequent cTBS ($r=.74$, $p=.022$) (Figure 5b). This correlation was specific for interactions in alpha frequencies (Figure 5c).

Hence, the effect of PPC stimulation on visual exploration behavior could be predicted by the alpha-band IC in the right TPJ prior to stimulation. When the behavioral analysis was limited to the 7 subjects in whom the right TPJ was not already poorly connected at baseline, a one-way repeated measures ANOVA revealed a significant effect of stimulation condition ($F_{2,18}=4.6$, $p=0.025$). Paired *t*-tests showed a significant difference between PPC and sham stimulation ($t_6=-2.8$, $p=0.030$) and a trend for a difference between PPC and FEF stimulation ($t_6=-2.25$, $p=0.065$).

Discussion

This study demonstrates for the first time the impact of cTBS on interregional interactions in neural resting-state networks. This impact is spatially specific in that it affects communication within and across networks at nodes belonging to the stimulated network. The effect is also specific with regards to the frequency of modulated oscillations. Coherence changes were observed especially in the alpha frequency band corresponding to the human idling rhythm. Importantly, alpha-band coherence changes were linearly correlated with behavioral changes, hence suggesting that effects on network communication translate linearly into behavioral effects. Moreover, our data show that the effect of cTBS on behavior can be predicted before stimulation by individual endogenous patterns of network-level oscillations. Our findings therefore provide new insights into the mechanisms of stimulation-induced brain plasticity by demonstrating that network communication at rest shapes the brain reorganization induced by TMS therapy.

We have previously demonstrated in patients with stroke lesions (Dubovik *et al.*, 2012) and Alzheimer's disease as well as in elderly healthy subjects (Dubovik *et al.*, 2013) that the more a brain region is coherent with the rest of the brain in the alpha band, the better subjects perform in tasks mediated by this area. Here we reproduce a linear association between leftward visual exploration and alpha-band coherence in regions that have been described previously as belonging to a spatial attention network (Corbetta *et al.*, 2005; Ptak, 2012) and the dorsal fronto-parietal pathway (Ptak & Schnider, 2010). This confirms alpha-band IC as predictor of behavior also in the context of this study. Alpha coherence seems to be associated with a resting-state integration of activity in specialized brain areas, which translates linearly to behavioral performance.

This study shows that alpha-band coherence can be modulated with brain stimulation. Healthy subjects usually have a right-hemispheric dominance for spatial attention with a slight preference for attending to visual stimuli in the left hemifield over right stimuli (Okada *et al.*, 2006). Application of cTBS over the right IPS reverses the right-hemispheric dominance (Nyffeler *et al.*, 2008) and induces a visual exploration behavior qualitatively similar as described in patients with right hemispheric lesions (Sprenger *et al.*, 2002). Previous studies have demonstrated that this effect is due to a stimulation-induced suppression of the dominant right parietal region which in turn leads to disinhibition and hence increased excitation in the left parietal homologue (Koch *et al.*, 2008). Our findings show that a similar interhemispheric competition exists also for alpha-band coherence. cTBS induced a disruption of alpha-band IC at the stimulated cortex which went in parallel with an *increase* in the homologous contralateral cortex. Importantly, the contralateral increase was linearly correlated with the behavioral effect of cTBS, meaning that the disinhibition of alpha-band coherence could explain the changes in behavior. These findings in the alpha frequency band are in line with previous reports of TMS-induced changes in endogenous alpha oscillations (Klimesch *et al.*, 2003; Hamidi *et al.*, 2009) and extend them to network interactions.

Stimulation of the right IPS also induced FC changes at 30 Hz, although this effect did not survive correction for testing multiple frequency bands. As this corresponds to the frequency of the applied intra-burst pulse frequency, we can speculate that cTBS alters network communication specifically at the pulse frequency even beyond the duration of the stimulation. However, this needs to be confirmed in future studies comparing the effects of different pulse and burst frequencies on network interactions. In any case, the selective effects at certain frequencies only may explain why TMS stimulation frequencies seem to be critical for the induced effect on the behavioral (Romei *et al.*, 2011; Goldsworthy *et al.*, 2012) as well as network level (Eldaief *et al.*, 2011).

Interestingly, stimulation of the right PPC specifically modulated functional connections between the left IPS and regions belonging to the so-called default mode network (DMN). The DMN is defined as a group of regions that increase their activity during resting state, and decrease their activity during external tasks (Raichle *et al.*, 2001). Here, the precuneus, left angular gyrus and the OFG increased their coherence with the left IPS after cTBS, and this increase was positively correlated with the behavioral effect of cTBS. In contrast, coherence changes within the spatial attention network, i.e., between the left IPS and the right IPS and both FEF, were not correlated with behavioral changes (Figure 4). This suggests that neural adaptation and plasticity induced by cTBS depends on a recruitment of the DMN and less on changes in neural interactions within the stimulated spatial attention network. An implication of the DMN in network plasticity has been observed previously both in patients as well as in healthy subjects (Voss *et al.*, 2010; Sharp *et al.*, 2011; Wang *et al.*, 2012). The fact that functional interactions between the default mode and the spatial attention networks are frequency-bound might make them difficult to detect with fMRI.

This study targeted two different nodes of the spatial attention network. It found consistent behavioral and network effects only after stimulation of the right PPC but not after stimulation of the right FEF. The right PPC is the most central part of the attention network since it receives multisensory inputs and contains a priority map of the environment whereas the FEF is mainly involved in visual behavior (Ptak & Schnider, 2010). Only stimulation of this main node but not of connected nodes seems to lead to robust effects on visual exploration. Note that we used more focal and slightly weaker magnetic pulses for stimulation of the FEF than for the IPS. Yet, our stimulation parameters were based on previous studies describing behavioral effects on saccade latency after FEF stimulation with this protocol (Nyffeler *et al.*, 2006), which argues against the possibility that stimulation may have been too weak.

One of the main problems for application of rTMS protocols in clinical practice is the inconsistency of the effects across subjects, which we indeed also observe in the present study. Our findings suggest that EEG network imaging before stimulation might predict individual responses and hence enable a selective application to patients who are likely to benefit. All participants who had a low level of alpha-band IC in the right TPJ prior to cTBS responded with an inverse behavioral change to cTBS with increased leftward visual exploration. These findings suggest that electrophysiological and behavioral effects of cTBS result from an interaction between the stimulation signal and individual patterns of network interactions. Hence, by shaping brain reorganization, network communication at rest seems to predetermine not only current but also future behavior.

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Conflict of interest

The authors declare no competing financial interests.

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Figure Captions

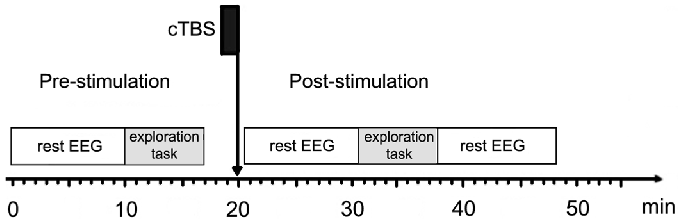

Figure 1. Study sessions. Each participant underwent 3 sessions separated by at least one week with PPC, FEF, or sham stimulation in counterbalanced order. The exploration task consisted in recording visual fixations during free exploration of symmetrical photographs.

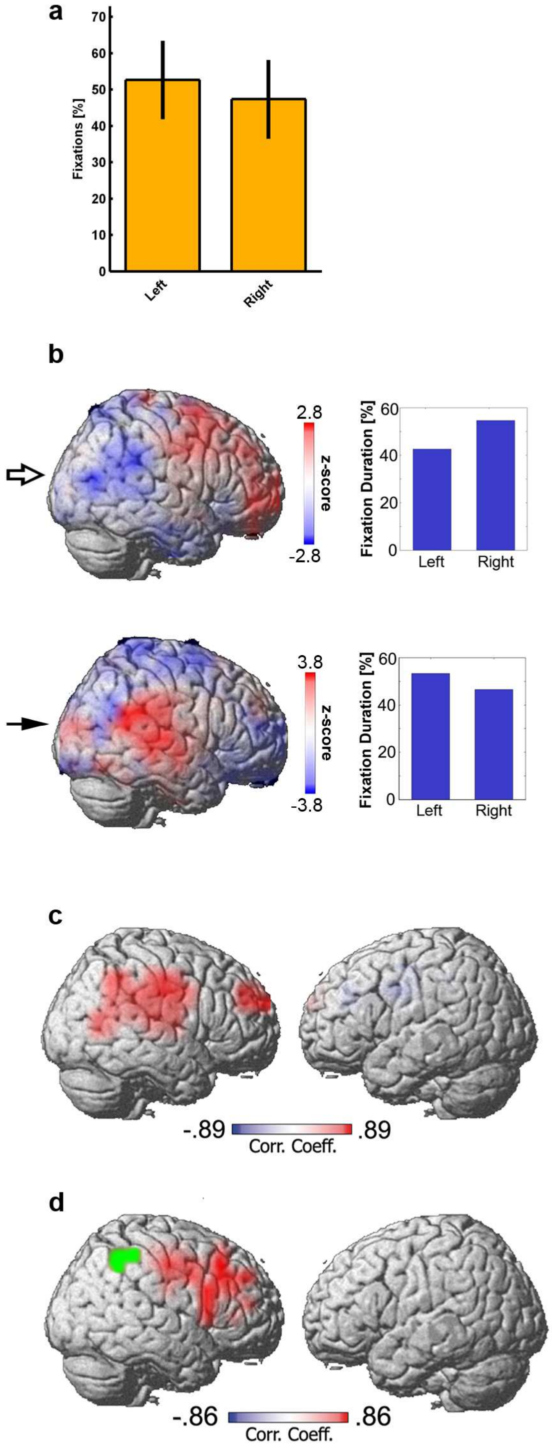

Figure 2. Visual exploration and network states before stimulation. a Mean (± standard error) cumulative fixation duration in the left and right visual hemifields before PPC stimulation. **b** Baseline IC maps and behavior of two extreme subjects in our sample. The participant marked with a filled arrow had high alpha-band IC in the right TPJ and a preference for left visual features at baseline. In contrast, the subject marked with an empty

arrow had low alpha-band IC in the right TPJ and a corresponding preference for right visual features. **c** Pearson correlation between mean alpha-band IC of each voxel with the rest of the brain and left exploration ($p<.05$, uncorrected). **d** Alpha-band IC between the right IPS (seed ROI marked in green) and the right middle frontal gyrus was linearly correlated with leftward exploration prior to stimulation ($p<.05$, uncorrected).

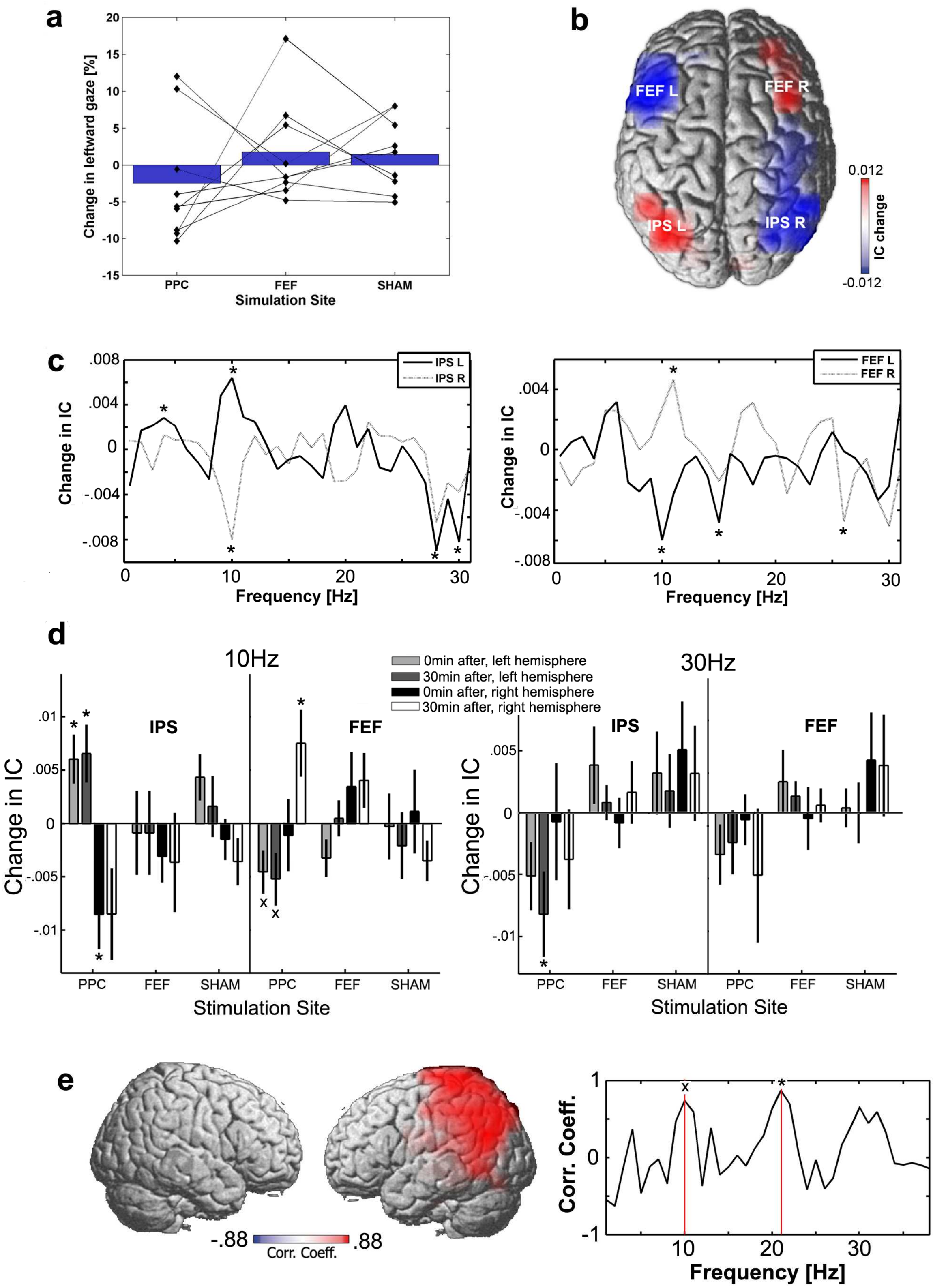

Figure 3. cTBS effects on networks and behavior. **a** Individual TMS-induced changes in leftward exploration. Only stimulation of the right PPC decreased leftward exploration in most subjects. Yet, in two subjects it showed the inverse behavioral effect. **b** Changes in

alpha-band IC after stimulation over the right PPC ($p<0.05$, uncorrected). **c** Spectrogram of IC changes in four ROIs of the spatial attention network (*$p<.05$, uncorrected). **d** Comparison of IC changes at 10Hz and 30Hz in ROIs of the spatial attention network in the 3 different stimulation conditions. Changes in each ROI are shown immediately after and 30 min after stimulation (*$p<.05$; x $p<0.07$). **e** Pearson correlation analysis between IC changes and behavioral effects induced by cTBS over the right PPC. The maps to the left show voxel-wise correlations at 20Hz ($p<0.05$, uncorrected), the spectrogram to the right the ROI correlation at the right IPS (* $p<0.05$, FDR corrected; x $p<0.05$, uncorrected).

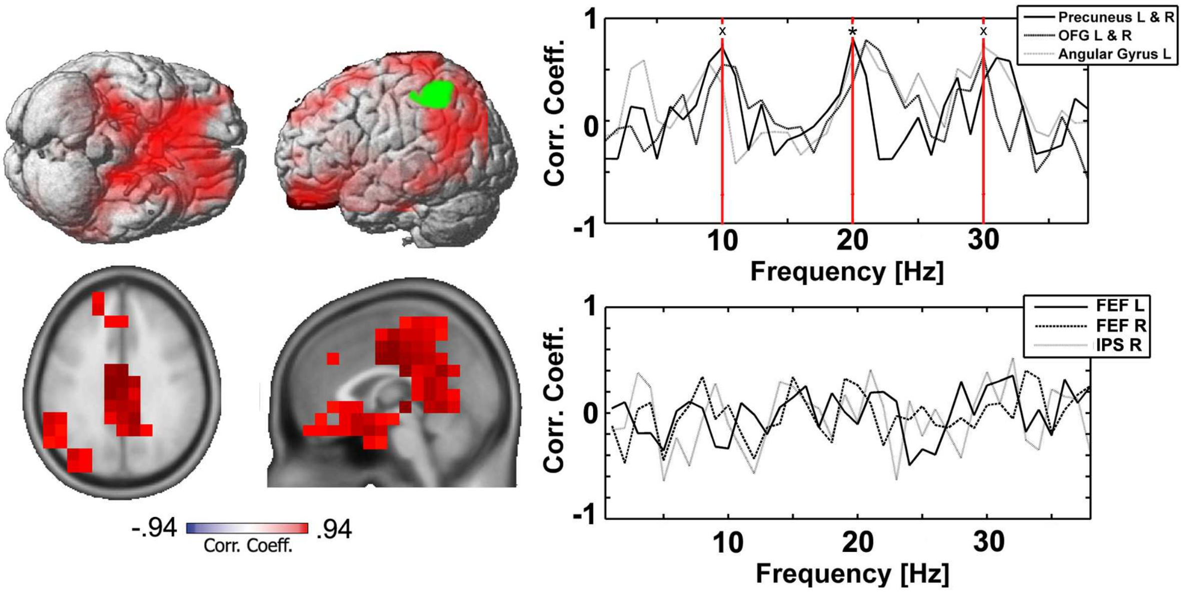

Figure 4. Connections of the spatial attention network. cTBS of the right PPC induced IC changes between the left IPS (seed region in green) and a group of regions belonging to the default mode network (in red), which correlated positively with the cTBS-induced decrease of left visual attention. Conversely, no linear relationship with behavioral changes was found for connections within the spatial attention network. The maps show voxel-wise correlations ($p<0.05$, uncorrected), the spectrograms correlations at anatomical ROIs (* $p<0.05$, FDR corrected; x $p<0.05$, uncorrected).

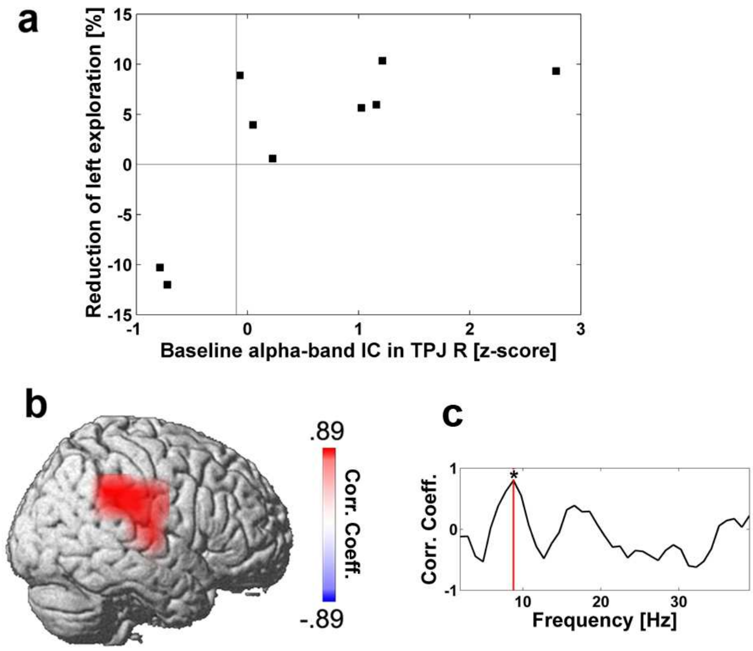

Figure 5. Prediction of stimulation outcome. a Scatter plot illustrating the association between baseline alpha-band IC in the right TPJ and effect on leftward attention of the participants induced by cTBS over the right PPC. All subjects with average or high alpha-band IC between the right TPJ and the rest of the brain at baseline showed the expected decrease of left visual exploration. Conversely, in subjects with deconnected right TPJ at baseline, cTBS did not further decrease left visual attention, but increased it. **b** Voxel-wise Pearson correlation across subjects between alpha-band IC before stimulation and behavioral effect of cTBS over the right PPC ($p<0.05$, uncorrected). **c** Spectrogram of the same correlation for the right TPJ (* $p<0.05$, FDR corrected).