BRIEF REPORT

Examining Frontotemporal Connectivity and rTMS in Healthy Controls: Implications for Auditory Hallucinations in Schizophrenia

Paula M. Gromann
King's College London and VU University Amsterdam

Derek K. Tracy, Vincent Giampietro, and Michael J. Brammer
King's College London

Lydia Krabbendam
VU University Amsterdam

Sukhwinder S. Shergill
King's College London

Objective: Repetitive transcranial magnetic stimulation (rTMS) has been shown to have clinically beneficial effects in altering the perception of auditory hallucinations (AH) in patients with schizophrenia. However, the mode of action is not clear. Recent neuroimaging findings indicate that rTMS has the potential to induce not only local effects but also changes in remote, functionally connected brain regions. Frontotemporal dysconnectivity has been proposed as a mechanism leading to psychotic symptoms in schizophrenia. The current study examines functional connectivity between temporal and frontal brain regions after rTMS and the implications for AH in schizophrenia. ***Method:*** A connectivity analysis was conducted on the fMRI data of 11 healthy controls receiving rTMS, compared with 11 matched subjects receiving sham TMS, to the temporoparietal junction, before engaging in a task associated with robust frontotemporal activation. ***Results:*** Compared to the control group, the rTMS group showed an altered frontotemporal connectivity with stronger connectivity between the right temporoparietal cortex and the dorsolateral prefrontal cortex and the angular gyrus. ***Conclusion:*** This finding provides preliminary evidence for the hypothesis that normalizing the functional connectivity between the temporoparietal and frontal brain regions may underlie the therapeutic effect of rTMS on AH in schizophrenia.

Keywords: transcranial magnetic stimulation, functional MRI, auditory hallucinations, connectivity

Auditory hallucinations (AH) are a common and disturbing feature of schizophrenia. In approximately 25% of patients with schizophrenia, symptoms are resistant to standard treatment (Shergill, Murray, & McGuire, 1998). Repetitive transcranial magnetic stimulation (rTMS) has recently emerged as a clinical intervention for various neurological deficits. AH are associated with increased activation within the temporoparietal cortices (Shergill, Brammer, & Williams, 2000). The rTMS might work by suppressing this increased activation in the temporoparietal cortex, thereby reducing AH. Several studies have shown that 1Hz rTMS to the temporoparietal cortex results in reduced AH (Brunelin et al., 2006; Hoffman et al., 2003, 2005; Lee et al., 2005; Poulet et al., 2005; Sommer et al., 2007). In spite of these promising findings, it is clear that rTMS does not work equally well for all patients; a recent large scale study failed to find a beneficial effect of rTMS on the severity and frequency of AH (Slotema et al., 2011). Thus, it is important to examine possible mechanisms underpinning the effects of rTMS in patients.

Interestingly, rTMS has the potential to induce not only local effects but also changes in remote, functionally connected brain regions (Tracy et al., 2010). Functional dysconnectivity may constitute a core pathological feature in schizophrenia (Friston, 1998; Friston, Frith, Fletcher, Liddle, & Frackowiak, 1996; Stephan, Baldeweg, & Friston, 2006). Previous research suggests that the functional interactions between temporal and prefrontal areas are disturbed in schizophrenia, both in the right and in the left hemispheres (Shergill, Bullmore, Simmons, Murray, & McGuire, 2000; Shergill et al., 2007). Reduced frontotemporal functional connectivity has been linked to AH in schizophrenia but not to delusions (Lawrie et al., 2002).

Although there is considerable evidence for the clinical relevance of rTMS and disturbed functional connectivity in AH, the therapeutic effect of rTMS is not yet well understood.

The purpose of this study was to investigate whether functional connectivity between temporal and frontal brain regions changes after rTMS administration. To accomplish this, a connectivity analysis was conducted on a previously acquired fMRI data set on a group of healthy subjects receiving rTMS and a control group receiving sham TMS during a language task associated with robust frontotemporal activation (Tracy et al., 2010). Understanding the neural effects in healthy controls is an essential prerequisite in examining the mechanism of any therapeutic effects in a patient cohort. Considering the prominent role of the right temporoparietal cortex in the etiology of AH (Shergill, Brammer, et al., 2000), we decided to use this side for application of the rTMS. This region has been linked to prosodic processing (Ross & Mesulam, 1979; Shah, Baum, & Dwivedi, 2006). Abnormal prosodic processing has been demonstrated in schizophrenia (Frith & Done, 1988), and it is correlated specifically with AH (Matusmoto et al., 2006).

The rationale of our study was to find out whether altered functional connectivity between temporal and frontal brain regions constitutes a potential mechanism underlying the therapeutic efficacy of rTMS on auditory hallucinations. We expected that the rTMS group would show a potentiated connectivity network compared to the control group, with enhanced connectivity between frontotemporal brain regions.

Method

Participants

A group of 22 healthy participants were recruited and randomly separated into two groups of 11 subjects. The first group of participants received sham rTMS, and they were scanned while performing a prosody discrimination task associated with frontotemporal activation. The second group received low frequency rTMS, and they were scanned while performing the same task. The recruitment took place via newspaper advertisement. Volunteers were included only if they were right-handed males between 18 and 55 with English as a first language. Volunteers were excluded when one of the following applied: previous psychiatric or neurological illness, hearing or speech impairment, illicit drug use in previous six months, and contradictions to MRI scanning. This study was approved by the ethics committee of South London and the Maudsley NHS Foundation Trust, in accordance with the standards of the 1964 Declaration of Helsinki. All participants gave informed consent before inclusion in this study.

rTMS Protocol

The rTMS was applied for 16 min using the Magstim Super Rapid stimulator (Magstim Co. Ltd, UK) with a figure-of-eight coil. Participants were comfortably seated, and motor thresholds (MT) in the abductor pollicis brevis muscle of the left hand were established by visual inspection for all (both the active and sham groups) by the application of rTMS to the right motor cortex. AMT is a synchronous muscle response evoked by a TMS pulse stimulating the motor cortex, and the lowest magnetic field required to induce this is known as the motor threshold (Haraldsson, Ferra-

relli, Kalin, & Tononi, 2004). MT are reasonably stable within individuals (Mills & Nithi, 1997). Following the protocol previously used by Hoffman et al. (2000), either active (at 90% of MT) at 1 Hz or sham rTMS was applied to the temporoparietal junction, deemed to be 5 cm posterior and 2 cm inferior to the abductor pollicis brevis site. Sham rTMS utilized a purpose-built coil (Magstim Co. Ltd, UK) that looked identical to the real coil but which did not deliver a magnetic field.

Experimental Design

A modified English version of the music and prosody discrimination task designed by Patel, Peretz, Tramo, and Labreque (1998) was used in this study. The stimuli consisted of lexically matched sentence pairs. The only prosodic changes in stimuli utilized in this experiment were in internal pitch pattern (emphasis shift), as our previous work (Tracy et al., 2010) had found internal pitch changes to be the most sensitive to subtle neurological deficits. Each trial consisted of a pair of stimuli separated by a 1-s interval. The pair of stimuli differed in the pitch of an internal component in 50% of the trials. Stimuli pairs had an average length of 5,036 ms. Following a visual cue at the end of each trial, participants indicated whether the paired stimuli were the same or different by using their right index finger and a button press. Pilot work suggested that participants experienced greater difficulty in same paired stimuli compared with different pairs, as they reported actively having to attend to the entire length of the sequence during the same pairs' comparison.

fMRI Acquisition

Participants were scanned within 10 min of the application of the real or sham rTMS. Gradient echo echoplanar imaging (EPI) data were acquired on a neuro-optimized GE Signa 1.5 Tesla system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital in London. A quadrature birdcage headcoil was used for radio frequency transmission and reception. In order to minimize head movement, foam padding was placed around the subject's head in the coil. The acquired EPI dataset provided complete brain coverage. One hundred and forty-four $T2^*$-weighted whole-brain volumes depicting blood oxygen level–dependent (BOLD) contrast were acquired at each of 24 near-axial noncontiguous planes parallel to the intercommissural (AC-PC) line (slice thickness = 5 mm; slice gap = 0.5 mm; repetition time (TR) = 2.1 s; echo time (TE) = 40 ms; flip angle = 90°; matrix size = 64 × 64). A high-resolution gradient echo image of the whole brain was acquired in the intercommissural plane consisting of 43 slices (slice thickness = 3 mm; gap = 0.3 mm; TR = 3 s; flip angle = 90°; matrix size = 128 × 128) during the same scanning session. Scanner noise during stimuli presentation was minimized by using a partially silent acquisition (Amaro et al., 2002) during the stimuli presentation lasting 6.3 s after which the fMRI data (associated with prominent scanner noise) were collected during 2.1 s (TR).

Statistical Analysis

The imaging data were analyzed with the XBAM software, version 4 (cf. http://brainmap.it). This software uses a nonparametric permutation-based strategy to minimize assumptions. First,

an overlap map was created by means of a conjunction analysis (Nichols, Brett, Andersson, Wager, & Poline, 2005) of active task versus control, across both sham and rTMS groups, based on fMRI data of an earlier study collected during the prosody task (Tracy et al., 2010). One region in the right temporoparietal cortex (Talairach Coordinates: X = 39.72, Y = −55.56, Z = 36.85) was activated in the overlap map and was selected as the seed region for the subsequent analysis. Using the seed region as a mask, the average time series was extracted for each subject. This extracted time series was then used as a model for a whole brain correlational analysis, resulting in a network of brain regions showing a similar profile of temporal activation. The data were then normalized to Talairach space, and the analysis was extended from subject to group level by creating a cluster level group correlation map after the spatial normalization. Finally, an ANOVA Brain Activation Map (ABAM) was created in order to compare the connectivity network of sham controls with that of the group receiving rTMS. Results were analyzed at the clusterwise p value which was associated with less than one cluster by chance, that is, less than one false positive cluster for the whole brain.

Results

Behavioral Data

All participants successfully completed both the rTMS and fMRI parts of the study. No side effects were reported from the rTMS. When exploring response time and accuracy, using a repeated measure ANOVA, we did not find any significant effects between the two groups, indicating a comparable behavioral performance on the prosody task.

Neuroimaging Data

The between-groups analysis of this study revealed that there are significant differences in functional connectivity between the two groups. The rTMS > controls activation map of the correlational ANOVA analysis (see Figure 1) shows that the activation in the seed region, that is, the right parietal cortex, is significantly more strongly correlated with activation in the dorsolateral prefrontal cortex and the angular gyrus (see Table 1) in the group who received rTMS. The effect of rTMS on these two regions is shown in Figure 2. The controls > rTMS activation map did not yield any significant differences, that is, the controls did not show a significantly higher correlation of brain activation with the seed region

than the rTMS group. Only the rTMS group showed a potentiated frontotemporal connectivity network during the prosody discrimination task.

Discussion

This study was aimed at examining whether altered functional connectivity between temporal and frontal brain regions constitutes a potential mechanism underlying the therapeutic efficacy of rTMS on AH. In line with our hypothesis, we found that the rTMS group showed a potentiated connectivity network with respect to the control group, with stronger connectivity between the right temporoparietal cortex and the dorsolateral prefrontal cortex as well as the angular gyrus. This suggests that rTMS may facilitate functional integration between temporoparietal and frontal brain regions.

While the original premise of using focal rTMS, applied over the temporoparietal cortex, was to treat AH by reducing underlying hallucination-related activity in temporoparietal cortex (Shergill, Brammer, et al., 2000), more recent data has suggested that there are secondary changes in distal connected regions (Tracy et al., 2010). These changes could also contribute by enhancing connectivity between these regions; addressing the dysconnectivity observed in schizophrenia between frontal and temporoparietal cortices (Friston et al., 1996; Friston, 1998; Ford, Mathalon, Whitfield, Faustman, & Roth, 2002).

Several theories suggest that schizophrenia results from a maladaptive integration of the neural transmission between different brain areas (Liang et al., 2006; Stephan et al., 2006). This is mainly based on findings of reduced functional connectivity between temporal, speech production areas, and (pre)frontal regions concerned with higher cognitive functions. Of note, rTMS has the potential to induce not only local effects but also changes in remote, functionally connected brain regions (Tracy et al., 2010). There is ample evidence for the beneficial inhibitory effects of rTMS on AH in schizophrenia (e.g., Brunelin et al., 2006; Hoffman et al., 1999, 2003, 2005; Poulet et al., 2005), which usually manifest themselves in terms of less severe or less frequent AH. Our findings indicate that rTMS increases the functional integration between temporal and frontal regions in healthy subjects during a prosody discrimination task, which demands high cognitive load of the area shown to be involved in the etiology of AH, that is, the temporoparietal cortex (Shergill, Brammer, et al., 2000). If there is dysfunctional frontotemporal connectivity in patients, then rTMS may have an impact through increased func-

Figure 1. Connectivity map of the right parietal cortex. The areas labeled black indicate regions that correlate more strongly with the seed region in the rTMS-treated group compared to the control group.

Table 1
Areas of Correlated Activation Shown in Figure 1

Size	Talairach Coordinates X, Y, Z			Hemisphere	BA	*p* value	Cerebral region
28	43	33	31	Right	9	0.000485	dorsolateral prefrontal cortex
52	36	−48	31	Right	39	0.000121	angular gyrus

Note. BA = Brodmann's Area.

tional integration between the temporal and frontal cortexes. This fits with the original source-monitoring account of schizophrenia (Frith, Friston, Liddle, & Frackowiak, 1992) and with related imaging findings (Shergill, Bullmore, et al., 2000; Simons et al., 2010), suggesting that self-generated speech is misattributed to an external agent, which results in the experience of hearing voices. If rTMS does indeed work by facilitating connectivity, the neural transmission of the temporal–frontal circuit would be improved. As a result, the frontal lobe would interpret the signals of the temporal lobe more accurately, resulting in better distinction between inner speech and external voices. This premise could be tested in a future study by applying rTMS over the prefrontal cortex in a control experiment. Reaching the required therapeutic threshold, inner speech should be less likely to be misinterpreted as external voices. This is a testable hypothesis, indeed an earlier study demonstrated a correlation between improved source monitoring and improvements in hallucinations following rTMS (Brunelin et al., 2006).

While the majority of studies have applied left-sided rTMS in treating AH, and the data on the efficacy of right-sided rTMS has been limited, our own data in hallucinating patients has suggested a more prominent role of the right temporoparietal cortex (Shergill, Brammer, et al., 2000), supported by other neuroimaging data (Dierks et al., 1999; Sommer, Ramsey, & Kahn, 2001; Weiss et al., 2006; Woodruff et al., 1997), which guided our choice for application of the rTMS. This region has been implicated in prosodic

Figure 2. The effect of rTMS on the two clusters of activation correlating with the seed region. Activation is represented by the median sum of squares (SSQ) group statistics shown on the y-axis, with the mean of the cluster shown on the x-axis. Cluster 1 = dorsolateral prefrontal cortex; cluster 2 = angular gyrus.

processing (Borod et al., 1992; Pell, 1999; Ross & Mesulam, 1979; Shah et al., 2006; Wunderlich, Ziegler, & Geigenberger, 2003), which is a key component of AH. Recent neuroimaging data has also shown that there is prominent activation of the right inferior frontal cortex in hallucinating patients (Sommer et al., 2008). It is interesting that the strength of frontotemporol connectivity of the right frontal cortex was enhanced in response to rTMS. Considering these findings, rTMS may play a role in influencing this region by normalizing its connectivity with temporal cortices, thereby improving the feedback network between these frontotemporal cortices.

From a neuroanatomical perspective, the observed pattern of activation points to regions that are all interconnected by the superior longitudinal fasciculus (SLF; Koch et al., 2010; Makris et al., 2004). This is particularly interesting considering that the SLF seems to be altered in patients with schizophrenia (Rotarska-Jagiela et al., 2009; Shergill et al., 2007).

Our findings are clinically relevant by offering a potential explanation for the therapeutic effect of rTMS on auditory hallucinations in schizophrenia. However, a few limitations deserve to be mentioned. First, only right-handed males were included in the original study, which restricts the generalizability of the findings. The rationale was to avoid potential confounding, since handedness and gender may have potentially confounding effects on the brain areas involved in language processing. Second, the findings of this connectivity analysis are further limited by the small sample size. However, due to its nonparametric permutation-based strategy, the implemented XBAM software is very powerful in detecting robust effects in spite of small sample size. Third, rTMS was applied 5 cm posterior and 2 cm inferior to the abductor pollicis brevis site. Although this approach has been used in previous studies, making use of a navigational system for accurately locating the TMS coil might be a more adequate approach for future research. Also, subjects were scanned within 10 min of rTMS administration. Future studies could usefully clarify the factors influencing the duration of the TMS effects, for example, by varying the interval between applying rTMS and fMRI. Moreover, one has to bear in mind that our analyses are based on a single, specific approach, and alternative methods of generating functional connectivity map have also been utilized (Hoffman et al., 2010). Overall, it is strongly advisable to regard the current results as preliminary evidence which require replication in a larger sample. Future research should also include a clinical sample consisting of patients suffering from recurrent AH.
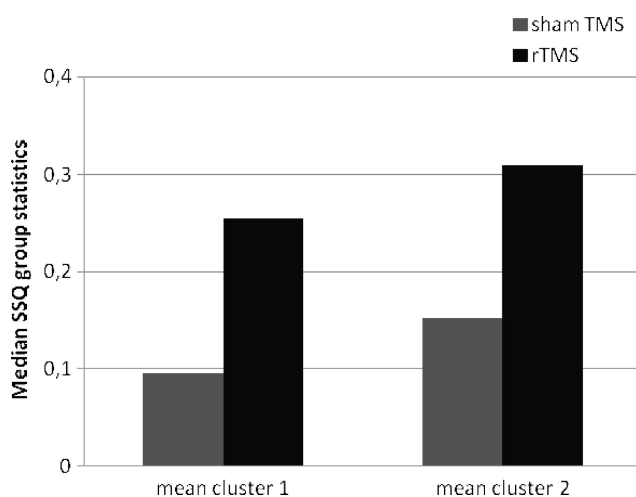
Conclusion

Up to now, rTMS in patients has been given on the basis that it reduces activation in the temporal cortices, thus reducing the hyperactivity related to hallucinations. However, our findings

yield preliminary support for a potentially complementary mechanism by which rTMS may be effective. In addition to reducing the hyperactivity in temporal cortices during hallucinations, rTMS may also extert its beneficial effects on AH by facilitating the functional connectivity between the temporoparietal and frontal cortexes. Changes in frontal cortical activation have recently been demonstrated to covary with positive symptoms over time (Krabbendam et al., 2009; Michalopoulou et al., 2010; Smee et al., 2011). These two different mechanisms of action may underlie change in different patients, perhaps explaining some of the variability in results of rTMS treatment of AH.

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