Effects of low frequency rTMS treatment on brain networks for inner speech in patients with schizophrenia and auditory verbal hallucinations

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\textbf{ABSTRACT}

\textbf{Introduction:} Efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) targeting the temporo-parietal junction (TPJ) for the treatment of auditory verbal hallucinations (AVH) remains under debate. We assessed the influence of a 1 Hz rTMS treatment on neural networks involved in a cognitive mechanism proposed to subserve AVH.

\textbf{Methods:} Patients with schizophrenia (N = 24) experiencing medication-resistant AVH completed a 10-day 1 Hz rTMS treatment. Participants were randomized to active stimulation of the left or bilateral TPJ, or sham stimulation. The effects of rTMS on neural networks were investigated with an inner speech task during fMRI. Changes within and between neural networks were analyzed using Independent Component Analysis.

\textbf{Results:} rTMS of the left and bilateral TPJ areas resulted in a weaker network contribution of the left supramarginal gyrus to the bilateral fronto-temporal network. Left-sided rTMS resulted in stronger network contributions of the right superior temporal gyrus to the auditory-sensorimotor network, right inferior gyrus to the left fronto-parietal network, and left middle frontal gyrus to the default mode network. Bilateral rTMS was associated with a predominant inhibitory effect on network contribution. Sham stimulation showed different patterns of change compared to active rTMS.

\textbf{Conclusion:} rTMS of the left temporo-parietal region decreased the contribution of the left supramarginal gyrus to the bilateral fronto-temporal network, which may reduce the likelihood of speech intrusions. On the other hand, left rTMS appeared to increase the contribution of functionally connected regions involved in perception, cognitive control and self-referential processing. These findings hint to potential neural mechanisms underlying rTMS for hallucinations but need corroboration in larger samples.

\section{1. Introduction}

Auditory verbal hallucinations (AVH) are a common symptom of schizophrenia, associated with significant distress and dysfunction. They can be defined as perceptual experiences occurring in the absence of corresponding external stimuli, and may appear like real voices (Aleman and Larøi, 2008). AVH are typically treated with a combination of antipsychotic medication and psychological interventions (NICE, n.d.), but in 25–30% of the patients with schizophrenia AVH appear to be refractory to these interventions (Kane et al., 1988; Shergill et al., 1998). Therefore, other treatment options are being explored, among which the non-invasive neuromodulation technique repetitive Transcranial Magnetic Stimulation (rTMS). rTMS in a low frequency mode of 1 Hz can decrease excitability of underlying brain tissue (Di Lazzaro et al., 2002; Pascual-Leone et al., 2002; Fitzgerald et al., 2006a). Given that the left temporo-parietal junction (TPJ) area has been shown to be over-active during the experience of AVH (Jardri et al., 2011), it appears the most optimal target region for rTMS treatment. Over the past years, this set-up has been applied to investigate treatment efficacy. In the vast majority of studies, only the left TPJ area was stimulated (McIntosh et al., 2004; Hoffman et al., 2005; Fitzgerald et al., 2007; Brunelin et al., 2006; Saba et al., 2006; Rosa et al., 2007; de...
Jesús et al., 2011; Slotema et al., 2011). However, some trials have also evaluated the effect of right-hemispheric (Lee et al., 2005; Jandl et al., 2006; Loo et al., 2010) or bilateral stimulation (Vercammen et al., 2009; Bais et al., 2014), based on the more recent finding that the right hemisphere may also contribute to the genesis of AVH (Lennox et al., 2000; Shergill et al., 2000a). While results of early studies were promising (Aleman et al., 2007), the effect sizes reported in meta-analyses decreased with the increasing number of published trials (Tranulis et al., 2008; Slotema et al., 2010; Slotema et al., 2012; Zhang et al., 2013; Slotema et al., 2014; Otani et al., 2014). In order to make an informed decision about whether to further explore rTMS as a treatment for AVH, a better understanding of the underlying neural substrate is paramount. The findings of functional imaging studies that assessed brain activation during AVH suggest engagement of a distributed network involved in language processing and verbal memory, including the inferior frontal gyrus, middle/superior temporal gyrus and medial regions such as the hippocampus and insula, when comparing AVH periods to rest (Jardri et al., 2011; Kuhn and Gallinat, 2012). Another method to study the mechanisms of AVH in patients with schizophrenia is the use of tasks that evoke cognitive processes thought to be involved in AVH. One well-supported theory states that AVH arise through misattribution of self-generated mental events (e.g. inner speech) due to defective source monitoring (Dittman and Kuperberg, 2005; Johns and McGuire, 1999). Cognitive imaging studies using speech processing paradigms have revealed reduced involvement of temporal regions, cingulate cortex, supplementary motor area, hippocampal complex, cerebellar, and subcortical areas (Shergill et al., 2000b; Woodruff et al., 1997; McGuire et al., 1995) in patients with AVH. The reduced brain response to external stimulation has been taken to suggest that AVH and speech processing compete for the same neural resources (Woodruff et al., 1997). Interestingly, advances in neuroimaging analysis techniques now allow us to not only investigate differential responses in isolated brain areas, but also within synchronous networks, and to assess connectivity between these task-activated networks. This approach has the capacity to be especially insightful for studying schizophrenia, as the disorder has been considered a disconnectivity syndrome (Priston, 1998; Stephán et al., 2006). Aberrant connectivity between brain areas and networks has been associated with the diagnosis of schizophrenia in general (Jafri et al., 2008), but also with AVH specifically (Alderson-Day et al., 2015).

Very few studies have reported on the impact of rTMS treatment for AVH on brain function. In a first small study (Fitzgerald et al., 2007), increased task-related brain activation in speech generation and speech reception areas was observed after rTMS treatment. In a PET and low-resolution brain electromagnetic tomography (LORETA) study, rTMS treatment was linked to reduced brain metabolism in the left TPJ area and connected regions, as well as increased metabolism in the contralateral cortex and frontal lobes (Horacek et al., 2007). A seed-based resting state analysis (Vercammen et al., 2010), demonstrated that rTMS on the left TPJ area was associated with an increase in functional connectivity between the left TPJ and the right insula. These results indicate that rTMS over the left TPJ area may affect neural activation and functional connectivity in relevant regions, but targeted assessments of functional network connectivity are lacking.

The current study aimed to assess inner speech (Aleman et al., 2005) during fMRI in patients with schizophrenia and AVH, before and after they underwent 10 sessions of 1 Hz rTMS treatment, with a total of 14400 pulses. In comparison with earlier rTMS trials for AVH, we increased the number of pulses and sessions. The rationale for this modification was based on the finding that more and longer rTMS treatment sessions might be related to higher efficacy, as was observed in patients with depression (Gross et al., 2007). We performed an independent component analysis (ICA) to evaluate the effect of rTMS treatment on task-related activity within networks and the connectivity between networks (Jafri et al., 2008), as well as the spatial contribution of brain areas to networks. These patients were randomly assigned to three different treatment arms: stimulation of the left or bilateral TPJ area, or sham stimulation of the left TPJ area. In a previous study by our group, we observed reduced deactivation of the default mode network in patients with AVH, as compared to patients without AVH and control subjects, during the performance of the same word evaluation task (Bais et al., n.d.). Moreover, patients with AVH showed more activation within the auditory-sensorimotor network, and increased involvement of the left angular gyrus. Finally, the analyses demonstrated some indications of deviant connectivity between networks. Therefore, we hypothesized that rTMS would reduce activation of the auditory-sensorimotor network, including posterior language regions.

2. Materials and methods

2.1. Participants

The sample consisted of patients that participated in an rTMS trial previously described by Vercammen et al. (Vercammen et al., 2009) and Bais et al. (Bais et al., 2014). Patients were referred to the study by clinicians from the University Medical Center Groningen and regional mental health care institutions (Lentis, GGz Drenthe, GGz Friesland). A total of 47 patients received rTMS treatment in this trial. The first 36 patients were requested to undergo an fMRI scan before and after rTMS treatment. All patients met DSM-IV criteria for the diagnosis of schizophrenia, which was confirmed by a trained interviewer, using a SCAN interview (Schedules for Clinical Assessment in Neuropsychiatry (Giel and Nienhuys, 1996)). Patients were included in the trial if they experienced medication resistant auditory verbal hallucinations (AVH), defined as daily occurring AVH despite at least two adequate trials of antipsychotic medication for at least four weeks prior to study inclusion. Exclusion criteria were fMRI and TMS contra-indications. Antipsychotic dose was stable for the duration of the trial. Detailed demographical and clinical data are presented in Table 1.

After full description of the procedures of the study, written

<table>
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<th>Table 1</th>
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<td>Demographic and clinical characteristics, and task performance of the three subgroups at baseline.</td>
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Data are mean (± SD) or number of patients; M: male; F: female; PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987); AHRIS: Auditory Hallucination Rating Scale (Hoffman et al., 2003). a Some data is missing.
informed consent was obtained prior to participation. The study was conducted in accordance with the latest version of the Declaration of Helsinki and with approval of a licensed local medical ethical committee (University Medical Center Groningen, The Netherlands; METc protocol number: 2006.052).

2.2. Clinical outcome measure

Current hallucination severity and other positive, negative and general symptomatology were assessed with the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987)), which is a semi-structured interview. In addition, patients completed the Auditory Hallucinations Rating Scale (AHRS), which is a seven-item self-report scale developed by Hoffman et al. (Hoffman et al., 2003). Both the PANSS and AHRS were administered before rTMS treatment and within two days after treatment, by trained raters who were blind to the treatment condition. We chose Hallucination item P3 of the PANSS, and the AHRS total score as the primary clinical outcome measures. Although Hallucination item P3 represents the severity of hallucinations in all modalities, in the majority of patients these are AVH, and indeed patients were selected for the current trial on the basis of AVH.

2.3. rTMS procedure

Patients were randomly assigned to one of three treatment arms: active rTMS of the left TPJ area, active rTMS of the bilateral TPJ area, or sham rTMS of the left TPJ area. We used a Magstim Rapid System (Magstim Company Ltd., Whitland, Wales) with a 70 mm figure-of-eight coil. In patients who were enrolled in the left or bilateral treatment condition, resting motor threshold was determined (Schutter and van Honk, 2006). For the localization of the TPJ area, we used an EEG cap with electrode positions according to the 10–20 International System. Stimulation of the left TPJ area was administered halfway between T3 and P3 electrode positions (Hoffman et al., 2005). For bilateral treatment, first the left TPJ area was stimulated for 10 min. Subsequently, for the following 10 min, the coil position was switched to the right TPJ area, halfway between T4 and P4 electrode positions. Sham stimulation was administered using a TMS coil that produced a clicking sound, without delivering a measurable magnetic field. Patients received rTMS treatment during six consecutive working-days, twice daily, for 20 min on 1 Hz on 90% of resting motor threshold, resulting in a total of 14400 pulses.

2.4. fMRI procedure

Participants performed a word evaluation task, adapted from Aleman et al. (Aleman et al., 2005), consisting of two experimental conditions in which bisyllabic words were visually presented. In the inner speech condition, participants had to determine which syllable carried the metrical stress by using their inner speech (e.g. in the word ‘chapter’ the first syllable carries the stress: CHAP-ter and not chap-TER). In the emotional valence condition, participants had to rate the words as positive or negative (for example the word ‘summer’ has a positive emotional content and the word ‘cancer’ a negative emotional content). The two conditions were identical with respect to the stimuli and the two-choice task configuration. Each stimulus was presented for 2000 ms, and was followed by a fixation cross that appeared for 3000 ms. For both conditions, the stimuli were presented in four blocks, thus a total of eight blocks were alternately presented in a fixed order. Each block consisted of 12 trials with stimuli presented in random order, resulting in a total of 96 trials. Active task blocks were followed by 30 s rest blocks, such that the BOLD response could return to baseline. Participants were instructed to lie still during scanning, respond as quickly as possible, and fixate on a central cross on the screen during rest blocks.

2.5. fMRI data acquisition

For MRI-scanning, a 3T Philips Intera scanner (Best, The Netherlands) with a standard SENSE 8-channel head coil was used, located at the University Medical Center Groningen. A 3-D T1-weighted anatomical image was acquired, covering the whole brain (TR = 25 ms; TE = 4.6 ms; flip angle = 30°; field-of-view = 256 mm²; slice thickness = 1 mm; 160 transverse slices; no gap). Functional images were acquired using a T2*-weighted gradient echo EPI sequence (TR = 2500 ms; TE = 30 ms; flip angle = 80°; number of slices = 39; field of view = 224.0 × 136.5 × 224.0 mm³; slice thickness = 3.5 mm, matrix = 64 × 64; voxel size = 3.5 × 3.5 × 3.5 mm³; 322 slices).

2.6. Data analysis demographic and clinical variables

Given the limited group size, all tests were performed non-parametrically with SPSS (version 22, SPSS inc. Chicago II. USA). Baseline group differences in age, education, clinical measures, accuracy, and reaction time were tested with Kruskal-Wallis tests. Chi-square tests were applied to test for differences in distribution of the nominal variables sex, handedness, and antipsychotic medication use. Change scores (post treatment – pre treatment) of the PANSS Hallucination item P3, AHRS total score, reaction time and accuracy were calculated, and Kruskal-Wallis tests were used to calculate differences between the groups with respect to treatment effect. For exploratory purposes, Wilcoxon’s signed rank tests were applied to test for within group treatment effects on the AVH measures. The alpha level of significance was set at 0.05, two-tailed.

2.7. Preprocessing of fMRI data

SPM8 (Statistical Parametric Mapping, version 8; The Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm) was used to preprocess fMRI data. Functional images were slice time corrected, realigned, and then coregistered to the anatomical T1 image. Images were spatially normalized to standard stereotactic space (MN1 T1 template) and smoothed with a 3D isotropic Gaussian kernel (FWHM 8 mm) to increase signal-to-noise ratio. Data were excluded from further analysis if participants moved more than voxel size (3.5 mm) in any direction.

2.8. ICA

Independent Component Analysis (ICA) was performed with the Group ICA of fMRI Toolbox (GIFT; version 3.0a, MIALAB Software) (Calhoun et al., 2001), which was implemented in Matlab version 7.8.0. Using Maximum Description Length (MDL) and Akaike’s criteria, the number of independent components was estimated. A principal component analysis (PCA) was done for data reduction at subject and group level. Next, a group level ICA was run using the Infomax algorithm, which was repeated 20 times with the ICASSO approach to establish independent component stability. Spatial-temporal regression was applied for back-reconstruction to subject-specific independent components.

In line with the limited sample size, we chose to restrict further analyses to the equivalents of six components that demonstrated the highest fit with a similar task in a previous study performed by our group, in a large sample of 84 subjects (Bais et al., n.d.). These six components and their correlations with the task in the previous study (Bais et al., n.d.) were the default mode network (r = 0.18), auditory-sensorimotor network (r = 0.19), salience network (r = 0.17), left fronto-parietal network (r = 0.22), right fronto-parietal network (r = 0.13), and bilateral fronto-temporal network (r = 0.17).
2.9. Network modulation

In a design matrix, both the inner speech and emotional valence conditions, and instructions were modeled as a boxcar function convolved with the hemodynamic response function in SPM8. To calculate task-relatedness, the temporal sorting option in GIFT was applied. The resulting beta weights represented the amount of task-related activation or deactivation per independent component per condition for every subject. These beta weights were exported to SPSS, after which change scores (post treatment – pre treatment) were calculated. These change scores were used to calculate group differences in network activation or deactivation by using the Kruskal Wallis test. Results were investigated at an uncorrected p-value of 0.05, and a Bonferroni corrected p-value of 0.0083 (0.05 divided by six, which is the number of tests; one for each component). Test results were further explored with post-hoc tests in case of significant results.

2.10. Spatial contribution within components

For each individual and each component, spatial maps before treatment were substracted from the spatial map after treatment. The resulting spatial maps represented the change in spatial contribution to each independent component over time. Group differences in these changes were tested using the between-group ANOVA option in SnPM (Statistical non-Parametric Mapping (Nichols and Holmes, 2002)). Group differences were subsequently reported at p < 0.001, T > 10, and an extent threshold of k = 20.

2.11. Functional network connectivity

Using in-house scripts, between-network functional connectivity during the two task conditions and scan sessions was determined by calculating the correlations between the six independent components’ time-courses, resulting in 15 correlations per condition. These correlation values were transformed into Fisher’s Z values, after which change scores were calculated (post treatment – pre treatment). The resulting values were exported into SPSS (version 22, SPSS inc. Chicago IL USA). For each between-network correlation and each condition, Kruskal-Wallis tests were performed to compare the three groups. Results were investigated at an uncorrected p-value of 0.05, and Bonferroni corrected p-value of 0.0017 (0.05 divided by 30, which is the number of tests; 15 for each condition). Test results were further explored with post-hoc tests in case of significant results.

3. Results

3.1. Patient characteristics

Of the 36 participants that underwent fMRI-scanning, 31 participants completed the task in both fMRI sessions. Due to excessive head movement, and/or low task performance, data of seven patients had to be excluded, leaving seven patients in the left treatment group, nine in the bilateral group and eight in the sham group. Group comparison showed no significant differences between the three patient groups in age of onset, illness duration, number of hospitalizations, baseline symptom scores, and task performance (Table 1).

3.2. Treatment effect on clinical measures

The results of the larger trial (47 patients), without neuroimaging measures, were published elsewhere (Bais et al., 2014). Comparison of the PANSS P3 change scores between the three groups in this subsample with pre- and post fMRI measures showed no significant group differences ($\chi^2(2) = 1.68$, p = 0.431). Exploratory within-group testing for treatment effect showed a trend towards a decrease in PANSS P3 scores in the left rTMS group (Z = −1.89; p = 0.059). In both the bilateral (Z = −1.00; p = 0.317) and sham rTMS group (Z = −0.707; p = 0.480) no significant effects were present. There were no group differences in AHRS total change scores ($\chi^2(2) = 0.23$, p = 0.892).

Analyses of the change scores on the PANSS positive, negative and general psychopathology subscales did not demonstrate between group differences ($\chi^2(2) = 1.73$, p = 0.421; $\chi^2(2) = 0.76$, p = 0.684, $\chi^2(2) = 1.71$, p = 0.426, respectively).

3.3. Treatment effect on task performance

Analysis of the change scores on accuracy did not reveal group differences in the inner speech and emotional semantics conditions ($\chi^2(2) = 0.16$, p = 0.925; $\chi^2(2) = 4.10$, p = 0.129, respectively). The groups did not show differential changes in reaction times either ($\chi^2(2) = 4.31$, p = 0.116; $\chi^2(2) = 1.40$, p = 0.496, respectively).

3.4. Independent component analysis

The equivalents of six independent components that were selected in a previous study (Bais et al., n.d.) — because they demonstrated the highest fit with the word evaluation task — were also selected for the present network analysis. Fig. 1 displays the six independent components. They resemble components that have been identified in resting state studies (Raichle et al., 2001; Damoiseaux et al., 2006; Smith et al., 2009; Allen et al., 2011). The composition of the networks and their correlations with the task in the present study were as follows. Component A (default mode network (DMN), r = 0.13) was composed of cortical midline structures, the bilateral angular gyri and inferior frontal areas. Component B (auditory-sensorimotor network, r = 0.26) demonstrated a bilateral network of superior temporal gyrus (including Heschl's gyrus), insula, pre- and post-central gyri, and parietal areas. Component C (salience network, r = 0.10) showed a pattern of bilateral insula, superior frontal regions, as well as the anterior cingulate cortex. Component D (left fronto-parietal network, r = 0.09) revealed primarily left middle and inferior frontal regions, as well as inferior and superior parietal gyri, the supramarginal and angular gyri. Component E (right fronto-parietal network, r = 0.10) included right middle and inferior frontal regions, as well as superior and inferior parietal gyri, the supramarginal and angular gyri. Component F (bilateral fronto-temporal network, r = 0.11) demonstrated a bilateral network of primarily the inferior frontal areas, including the insula, as well as superior and middle temporal gyri (see also Supplementary Table 1).

3.5. Treatment effect on network modulation

None of the networks demonstrated group effects, effects of task condition, or interaction effects with respect to changes in within-network activation.

3.6. Spatial contribution within components

Group comparisons of the changes in spatial contribution of brain areas to each network revealed several clusters (Table 2). After both left and bilateral rTMS, the left supramarginal gyrus contributed less to the bilateral fronto-temporal network. After left rTMS, increased network contributions were observed for the right superior temporal gyrus to the auditory-sensorimotor network, the right inferior gyrus to the left fronto-parietal network, and the left middle frontal gyrus to the default mode network. Conversely, these three regions showed decreased contributions to the respective networks after bilateral rTMS. After sham, both the left and right precentral gyri demonstrated increased involvement in the auditory-sensorimotor network, whereas there was no change in involvement after left-sided rTMS and an increased contribution after bilateral rTMS (Fig. 2).
Fig. 1. The spatial maps of (A) the default mode network (DMN; 0, -46, 25), (B) the auditory-sensorimotor networks (0, -22, 52), (C) salience network (0, 20, -6), (D) left fronto-parietal network (-46, -58, 48), (E) right fronto-parietal network (47, -50, 45), and (F) bilateral fronto-temporal network (0, 23, -6).
3.7. Between-network connectivity

Analyses of changes in between-network correlations did not reveal a main effect of group, condition, or interaction effect between group and condition.

4. Conclusions

In this study, we evaluated the effect of a 1 Hz rTMS treatment of AVH on underlying brain circuitry, using an fMRI task that required the use of inner speech. Using independent component analysis, we aimed to investigate whether treatment would affect task-related network activity and within- and between-network connectivity. We observed that changes in within-network functional connectivity were dependent on treatment condition. Whereas left-sided rTMS was associated with stronger contributions of distant brain areas relative to the stimulated region, it resulted in decreased contributions of the left supramarginal gyrus, which is in proximity to the left-hemispheric stimulation target. In our sample, only the group receiving left-sided rTMS showed a trend for reduction of hallucination severity. Recent meta-analyses, based on larger samples, support a statistically significant effect of rTMS over the left temporoparietal cortex (Slotema et al., 2012; Slotema et al., 2014). Our results shed more light on putative underlying mechanisms of such rTMS effects. More specifically, low frequency rTMS of the left TPJ area could contribute to the amelioration of AVH severity by decreasing localized involvement of targeted brain regions while increasing the involvement of more distant brain areas to the networks they are operating in. The reduced contribution of left supramarginal gyrus to the bilateral fronto-temporal network after left-sided rTMS, may reduce the likelihood of speech intrusions, as the left supramarginal gyrus is

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<th>Component</th>
<th>Region</th>
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<th>Pseudo-t</th>
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Table 2. Clusters that showed group differences in changes of spatial contribution within networks. p-values are significant at T > 10, p = 0.001, k > 20, uncorrected for family wise error.

Fig. 2. Clusters that showed differences in network contribution. Bars represent median change score, and error bars indicate the 25th and 75th percentiles. A: left middle frontal gyrus (−26,28,52); B: right superior temporal gyrus (50, −20,12); C: left precenral gyrus (−42,0,56); D: right precentral gyrus (50, −2,52); E: right inferior frontal gyrus (48,20,4); F: left supramarginal gyrus (−46, −32,34).
crucially involved in speech perception (Bernstein et al., 2008). On the other hand, left rTMS appeared to increase the contribution of functionally connected regions involved in perception, self-referential processing and cognitive control. Bilateral rTMS however, did not show symptom alleviation, and appeared to reduce the contribution of discrete brain areas to within-network connectivity. Sham rTMS led to increases in the left and right precentral gyrus, possibly related to learning effects after repeated exposure to the word evaluation task.

The effects in the left rTMS treatment group corroborate to a large extent with results from a study by Horacek et al. (Horacek et al., 2007), in which they assessed resting-state brain metabolism after rTMS to the left TPJ area. Decreases in brain metabolism were observed in the left superior temporal gyrus, the left inferior temporal gyrus and the left insula after low frequency rTMS treatment, which could be explained by the immediate inhibitory effect of 1 Hz rTMS on brain function (Chen et al., 1997; Mottaghy et al., 2003). Conversely, brain metabolism was increased in connected regions: the bilateral inferior frontal cortex and the right superior temporal gyrus. As such, rTMS appears to affect functional connectivity within the auditory-verbal processing network even during rest. Also, cerebral blood flow in left hemispheric language regions was decreased in a group of patients with schizophrenia that clinically improved after ten days of either 1 Hz rTMS or theta burst stimulation to the left hemisphere (Kindler et al., 2013). In the present study, we took a different approach, by setting out to investigate changes in the neural networks involved in a cognitive mechanism proposed to subserve AVH, inner speech. In a previous study of our group, using the same inner speech task, patients with AVH demonstrated more activation within the auditory-sensorimotor network compared to patients without AVH and control subjects (Bais et al., n.d.). In that respect, it might be concluded that left rTMS treatment ‘normalized’ the involvement of the left supramarginal gyrus and engaged neural resources in remotely connected areas. One other study administered a word generation task during fMRI in a small sample of patients with schizophrenia that received rTMS treatment for AVH (Fitzgerald et al., 2007). They found increases in task-related activity in the left temporo-parietal cortex after rTMS, in addition to increases in the left inferior frontal area, which forms part of an integrated network of language processing and inner speech generation. It is conceivable that the spatial extent of the network shown to be favorably affected by rTMS treatment and AVH reduction will depend on the nature of the task employed to assess auditory-verbal processing, as well as on the techniques that are used for data analysis.

Our results, as well as previous findings suggest that rTMS might induce local changes at the site of stimulation, but that rTMS-induced changes in AVH severity are likely reflected in a much broader network of connected regions. For instance, the contralateral increase in activity in the right STG in the study of Horacek et al. (Horacek et al., 2007) and the enhanced contribution of the right STG and IFG in our study might be explained by the release of these regions from transcallosal inhibition (TCI) (Chiarello and Maxfield, 1996; Cook, 1986). As low frequency rTMS is thought to inhibit cortical excitability (Di Lazzaro et al., 2002; Pascual-Leone et al., 2002; Fitzgerald et al., 2006a), a decreased contribution of the left TPJ area, as observed in the left supramarginal gyrus, could have led to a decrease of the TCI over contralateral regions. Moreover, disinhibition can also occur through long-range intra-hemispheric fasciculi (Speer et al., 2003), which might explain the elevated contribution of the left middle frontal gyrus. Consequently, these processes possibly increased the capacity of the right temporal and bilateral frontal regions to respond to (auditory-) verbal processing demands.

As opposed to the beneficial effects of left-sided rTMS, bilateral stimulation was followed by decreased network contributions. This might again be explained by the process of transcallosal inhibition (Chiarello and Maxfield, 1996). In our trial, we stimulated both hemispheres consecutively in one session. It is plausible that the effects induced by left-hemispheric stimulation were nullified or even worsened by right-sided stimulation. This idea is strengthened by the fact that bilateral stimulation was not associated by clinical improvement in this sample. Lack of treatment effect has also been reported in a treatment study for depression that applied rTMS in similar frequencies to the bilateral DLPFC (Loo et al., 2003). In theory, a combination of low frequency rTMS of the left TPJ area, and high frequency rTMS of the right TPJ area, might induce beneficial effects. This approach has shown positive results in depression (Fitzgerald et al., 2006b; Blumberger et al., 2012), but has, as yet, not been investigated for the treatment of AVH.

An interesting pattern was also observed in both the left and right precentral gyrri. After sham rTMS, the contribution of these regions was increased, whereas it was decreased after bilateral rTMS and no effect was observed in the group that received left-sided rTMS. Although speculative, this may be the result of a learning effect in the task itself. As the premotor cortex plays a role in the corollary discharge system associated with recognising inner speech (Christensen et al., 2007), repeated exposure to the inner speech task may have enhanced its involvement. Stimulation with low frequency rTMS on the other hand, might have inhibited this type of long term potentiation, which yielded in a weaker network contribution. Obviously, this hypothesis should be tested in future studies.

Although symptom improvement after left rTMS treatment was accompanied by changes within brain networks, favorable effects on AVH were relatively weak. Moreover, the changes in network contributions were not reflected by any changes in task performance, as one would expect if additional neurophysiological resources were available for task performance. It should be noted though that the task was designed to be sensitive to regional brain activation and not to be sensitive to behavioral change. A possible explanation for the limited rTMS effects on symptom severity and behavioral performance may be suboptimal stimulation parameters (length, intensity, frequency) for the rTMS. A high degree of inter-individual variation in a relatively small sample may also mean that our study may have been underpowered to detect relatively small effect sizes. Larger trials that may be able to categorize responders and non-responders to treatment will be necessary to elucidate the exact underlying neural substrates and cognitive mechanisms of AVH, and their alterations following successful treatment. It is also possible that such behavioral or cognitive effects may lag behind the first signs of clinical improvement. It is conceivable that stronger effects could be elicited by optimizing, or perhaps individualizing rTMS treatment parameters.

In summary, this study demonstrated that rTMS treatment of the left TPJ area is associated with decreased involvement of the stimulated region during auditory-verbal processing. This may consequently inhibit spontaneous verbalizations and thereby reduce the likelihood of such intrusions (Brebin et al., 2009) to be experienced as externally presented voices. Remotely located regions, on the other hand, appeared to become more involved, potentially leading to a normalization of functional associations between brain regions for verbal processing, which may have contributed to an improved attention and cognitive control. The selection of stimulation parameters and locations is crucial, given our observation that bilateral stimulation may have had counteracting effects on brain regions’ contributions to neural network activity. Further research should evaluate whether rTMS treatment of AVH could benefit from alternative configurations that optimize cross-network functionality, such as low frequency stimulation of the left hemisphere and high frequency stimulation of the right hemisphere.

Declaration of interest

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Appendix A. Supplementary data

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References


