Effect of Low-Frequency rTMS on Electromagnetic Tomography (LORETA) and Regional Brain Metabolism (PET) in Schizophrenia Patients with Auditory Hallucinations

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\section*{Key Words}
Low-frequency rTMS \cdot Schizophrenia \cdot Auditory hallucinations \cdot Brain metabolism \cdot Lateralization

\section*{Abstract}
\textbf{Background:} Auditory hallucinations are characteristic symptoms of schizophrenia with high clinical importance. It was repeatedly reported that low frequency (\(\leq 1\)Hz) repetitive transcranial magnetic stimulation (rTMS) diminishes treatment-resistant auditory hallucinations. A neuroimaging study elucidating the effect of rTMS in auditory hallucinations has yet to be published. \textbf{Objective:} To evaluate the distribution of neuronal electrical activity and the brain metabolism changes after low-frequency rTMS in patients with auditory hallucinations. \textbf{Methods:} Low-frequency rTMS (0.9 Hz, 100\% of motor threshold, 20 min) applied to the left temporoparietal cortex was used for 10 days in the treatment of medication-resistant auditory hallucinations in schizophrenia (\(n = 12\)). The effect of rTMS on the low-resolution brain electromagnetic tomography (LORETA) and brain metabolism (\(^{18}\)FDG PET) was measured before and after 2 weeks of treatment. \textbf{Results:} We found a significant improvement in the total and positive symptoms (PANSS), and on the hallucination scales (HCS, AHRS). The rTMS decreased the brain metabolism in the left superior temporal gyrus and in interconnected regions, and effected increases in the contralateral cortex and in the frontal lobes. We detected a decrease in current densities (LORETA) for the beta-1 and beta-3 bands in the left temporal lobe whereas an increase was found for beta-2 band contralaterally. \textbf{Conclusion:} Our findings implicate that the effect is connected with decreased metabolism in the cortex underlying the rTMS site, while facilitation of metabolism is propagated by transcallosal and intrahemispheric connections. The LORETA indicates that the neuroplastic changes affect the functional laterality and provide the substrate for a metabolic effect.

\section*{Introduction}

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that induces the depolarization of neuron membranes and subsequent functional changes in a discrete area of the cerebral cortex [1]. The effect
of rTMS depends on the power of the magnetic field, the localization of the stimuli, and the frequency [2]. Low-frequency rTMS (≤1 Hz) inhibits the cortical excitability and leads to a weakening of the transfer at the synapses [3, 4].

Neuroimaging studies indicate that auditory hallucinations are associated with the overactivity of the auditory-linguistic cortex [5], specifically the left [6] and right [7, 8] superior temporal gyrus, and Broca's area [9, 10]. These results are congruent with the finding of abnormal activation of the primary linguistic cortex in hallucinations which competes with auditory stimuli [11]. In the same regions structural abnormalities were also detected [12–13]. The pathology of the auditory-linguistic cortex in auditory hallucinations is a part of a distributed cortical-subcortical network dysfunction [14] which includes the hippocampal and parahippocampal regions [15].

With respect to the supposed overactivation of the left temporoparietal auditory-linguistic cortex Hoffman et al. [16] published the first report indicating the efficacy of a subthreshold intensity of 1 Hz rTMS in the treatment of auditory hallucinations in schizophrenia. Promising results were replicated with an extended duration of stimulation for 2 weeks [17] and with a higher intensity of magnetic field [18–21]. Conversely, the effect was not replicated by studies with a treatment period only up to 5 days [22, 23] or when the magnetic field was administered in the subthreshold intensity [24, 25].

A neuroimaging study elucidating the effect and mechanism of low-frequency rTMS in auditory hallucinations has yet to be published. The general aim of our study was to detect the changes in the intracerebral distribution of neuronal electrical activity and regional brain metabolic changes after a series of low-frequency rTMS treatments in patients with auditory hallucinations.

The effect of rTMS on regional brain metabolism was measured by 18fluoro-deoxyglucose (18FDG) positron emission tomography (PET) in the resting state before and after 2 weeks of rTMS treatment. Because the EEG signals reflect the currents associated with the excitatory and inhibitory postsynaptic potentials [26], a link with brain metabolism (PET) is expected and the information obtained by both methods is expected to be complementary. In contrast to PET, the quantitative EEG has a high temporal resolution (milliseconds), but a spatial resolution limited to the area of the electrode sites. The low-resolution brain electromagnetic tomography (LORETA) represents a new approach to address this problem and permits truly 3-D tomography of electrical brain activity (current density) with no predetermined knowledge about the putative number of discernible source regions [27–29]. We used LORETA to detect the electrophysiological effect on regional functional activity subsequent to the rTMS treatment separately for the different EEG frequency bands with specific functional interpretations.

Due to the expected long-lasting neuroplastic changes induced by the rTMS treatment, we hypothesized that the clinical effect of low-frequency rTMS on hallucinations may be linked to a decrease in glucose metabolism in the left auditory-linguistic cortex (coil position) and corresponding changes in the distribution of cortical neuronal electrical activity with propagation via inter- and intra-hemispheric pathways.

**Methods**

**Subjects**

Our sample consisted of 12 right-handed patients (5 females and 7 males) with a mean age of 34.4 years (SD = 9.1) and a mean duration of schizophrenia of 76.3 months (SD = 47.0). One additional patient was excluded due to newly diagnosed temporal epilepsy and her case was published separately [30]. All 12 patients met the diagnostic criteria for paranoid schizophrenia according to the DSM-IV. The main inclusion criteria were medication-resistant auditory hallucinations for at least 1 conventional and 1 classical antipsychotic and at least 5 episodes of auditory hallucinations per day during the past month [18]. All patients were on stable antipsychotic medication for at least 3 weeks before and throughout the rTMS treatment period. Six patients were on monotherapy (olanzapine 15 and 20 mg, levomepromazine 50 mg, quetiapine 600 mg, amisulpride 900 mg, and ziprasidone 160 mg), 3 patients were on 2 antipsychotics (risperidone 4 mg with amisulpride 500 mg or clozapine 100 mg, and olanzapine 5 mg with haloperidol 4 mg). The last 3 patients were on a combination with mood stabilizers (lithium carbonicum 1350 mg with sulpiride 500 mg and levomepromazine 25 mg, carbamazepine 900 mg with risperidone 3 mg and ziprasidone 160 mg, and carbamazepine 900 mg with quetiapine 800 mg and fluphenazine decanoate 40 mg every 2 weeks).

The standard physical examination, medical history evaluation, biochemistry, ECG and EEG were performed to exclude neurological or medical illness, and drug or alcohol abuse. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, written informed consent was obtained from all subjects, and the local ethics committee approved the study.

**rTMS and the Study Protocol**

The psychometric assessments were conducted at baseline (before the first stimulation) and after the 1st and 2nd week of the rTMS treatment. The PET and qEEG were investigated in the resting state within 4 days before and after rTMS treatment. 0.9 Hz of
low-frequency rTMS at 100% of MT was administered over the left temporoparietal region defined as the midway between the T3 and P3 sites according to the international 10/20 EEG electrode system, as described in previous reports [16, 18–21]. In our study, we chose the frequency of 0.9 Hz instead of 1 Hz to ensure an inhibitory effect on the brain cortex. The inhibitory effect of 0.9 Hz rTMS on cortical connectivity or functional coupling has been clearly documented by EEG and a continuous relationship between the frequency and the cortical excitability has been illustrated [31, 32]. The motor threshold was assessed as the lowest strength of TMS needed to elicit 5 or more electromyographic responses (EMG, Neurosign 400) \( \geq 50 \mu \text{V} \) within 10 trials [33]. A Magstim Super Rapid stimulator (Magstim, Whitland, UK) with an air-cooled, figure-eight 70-mm coil was used for 20 min daily in 10 consecutive working days over 2 weeks with a total number of 10,800 pulses in the study.

**Psychometric Measurement**

The clinical effect was assessed by the Positive and Negative Syndrome Scale (PANSS) [34], Hallucination Change Scale (HCS) and the Auditory Hallucination Rating Scale (AQRS). The HCS was scored by requesting the patient to generate a narrative description of the hallucinations and these follow-up scores ranged from 0 to 20 using 10 as the baseline comparison. We used AHIRS as an objective composite scale consisting of 7 items (table 1) for a more detailed quantification of the auditory hallucination [18, 20]. The sample was part of a larger study focused on neurobiology and different treatment modalities, the raters were blind to the current treatment.

**PET Investigation and Analysis**

The patients were fasted for at least 6 h before the investigation. In a dimly lit and quiet room, 3 MBq/kg of \(^{18}\)FDG was administered via a peripheral vein catheter. The patients rested for 30 min

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The patients were fasted for at least 6 h before the investigation. In a dimly lit and quiet room, 3 MBq/kg of \(^{18}\)FDG was administered via a peripheral vein catheter. The patients rested for 30 min in a specified condition that is described as random episodic silent thinking (REST). The REST produced favorable reliability in PET findings for a schizophrenic population [35]. The data were acquired using the ECAT EXACT 922 (CTI/Siemens, Knoxville, Tenn., USA) PET scanner. The 2-D ‘hot’ transmission scans were immediately followed by 3-D emission scanning which lasted 15 min. The data were reconstructed by an iterative OS-EM algorithm (matrix: 1,282, brain mode, 47 slices, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) and implemented using ECAT 7.2 software. The data analysis was performed using Statistical Parametric Mapping, SPM99 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (MathWorks, Natick, Mass., USA). The PET scans were normalized into standard stereotactic space and smoothed with an isotropic Gaussian filter (full width at half maximum of 12 mm). The global intensity differences were corrected by proportional scaling (global mean to 50, analysis threshold 0.8), and global calculation was performed by the mean voxel value. The paired t test was used to determine the influence of rTMS on the regional brain metabolism. The association between brain metabolism and the severity of auditory hallucinations and clinical improvement was evaluated by the use of total AHIRS score and the change of AHIRS as the covariance. The p values at a voxel level of \( p \leq 0.001 \) with a minimum of 10 voxels per cluster (extent threshold) were considered statistically significant for the regions involved in the a priori hypothesis (the left auditory-linguistic cortex and directly interconnected regions). We tested the

**EEG Investigation and LORETA Analysis**

The EEG data for the LORETA analysis were analyzed in a subgroup of 9 patients (5 males and 4 females, mean age = 32.4, SD = 7.4, mean schizophrenia duration = 104.3 months, SD = 52.7). The EEG data from the remaining 3 patients were not analyzed due to the inability of the patients to perform either one of the two EEG examinations. Studies were performed using the BrainScope amplifier system (Unimedis, Prague, Czech Republic) with 19 electrodes placed according to the International 10–20 system. Subjects were resting in an alert state with their eyes closed in a sound-attenuated room with subdued lighting. During the recording, the alertness was controlled. If the patterns of drowsiness appeared in the EEG, the subjects were aroused by acoustic stimuli. All signals were sampled with a frequency of 250 Hz and a 0.5- to 70-Hz filter. Before analysis, artifact detection was performed visually with the exclusion of all EEG segments that contained obvious eye and head movements, muscle artifacts or a decrease in alertness. After recomputation to the average reference, spectral analysis was performed for at least six artifact-free 5-second epochs with the data digitally filtered according to Kubicki et al. [36] into 7 frequency bands: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz) and beta-3 (21.5–30 Hz). Subsequently, the 3-D, intracerebral current density distribution was estimated by LORETA [27–29, 37]. Localization of the differences in electrical activity was assessed by voxel-by-voxel paired t tests of the LORETA images, based on the log-transformed power of the estimated electric current density. To visualize the global distributions of the voxel-by-voxel paired t test differences, we computed the mean center of gravity location of all voxels with positive and negative t values for each band. To correct for multiple comparisons, a nonparametric single-threshold test was applied on the basis of the theory for randomization and permutation tests [38]. The omnibus null hypothesis of no activation anywhere in the brain was rejected if at least one t value (i.e. voxel, \( t_{\text{max}} \)) was above the critical threshold (\( t_{\text{crit}} \)) for \( p = 0.05 \), determined by 5,000 randomizations.

**Statistical Analyses**

We used the mean and standard deviation for descriptive statistics. Due to non-normally distributed variables in the psychometric scales (Shapiro-Wilk test \( p \leq 0.05 \)), the results and percentage change from the baseline are reported as medians with an interquartile range. Friedman’s test with the Wilcoxon signed rank post-hoc test and a Bonferroni correction for multiple comparisons were performed in the analysis of hallucination ratings and PANSS. A p value of less than 0.05 for the Friedman and Wilcoxon signed rank tests was regarded as significant and the criterion alpha (two-tailed) after a Bonferroni correction for multiple comparisons was set at 0.016. We performed all statistical computations with Statsoft Statistica 7.0.
Results

Clinical Effect of rTMS

With the exception of mild headaches, the rTMS treatment was well tolerated. The effect of rTMS on the psychometric measurements is presented in Table 1. After 2 weeks of treatment, we found a significant decrease in the Hallucination item as well as in the positive and total PANSS score. We did not find an effect on the negative or the global PANSS subscale. We detected significant decreases in both the total AHRS and HCS after the 1st and 2nd week of treatment. The analysis for the separate AHRS items showed a significant effect on the loudness of voices and distress levels after the 1st week. At the end of the rTMS treatment, the effect on distress levels was more pronounced and a significant decrease was found for attentional salience (p ≤ 0.05).

Effect of rTMS on Brain Metabolism (PET)

Decreases in regional brain metabolism after 2 weeks of rTMS treatment were found in the regions corresponding to the coil position, such as the left superior and inferior temporal gyri and insula (Table 2). The metabolism also decreased in the left cerebellum, cuneus and bilaterally in the hippocampus (Fig. 1a). The $^{18}$FDG uptake increased (Fig. 1b) bilaterally in the middle frontal gyrus and contralaterally to the site of stimulation in the temporal and occipital cortex (t = 4.02, p ≤ 0.001).

Due to the lateralized metabolic effect, we supposed that the series of rTMS affects the functional connectivity of left superior temporal gyrus. To evaluate this hypothesis we used the mean $^{18}$FDG uptake in the left superior temporal gyrus as a covariate of the entire brain volume metabolism. Before rTMS, we found a robust positive covariation with a large cluster consisting of the bilateral, lateral and medial temporal cortices. After rTMS, the positive covariation generally decreased and remained significant for the left temporal cortex in particular. In addition, the negative covariation decreased after rTMS for the pre- and postcentral gyri and parietal regions. However, the new negative covariation was detected for the right superior frontal gyrus. For exact locations and coordinates, see figure 2.

To identify the association between regional brain metabolism and the severity of auditory hallucinations, we used the AHRS score as the covariate. Before rTMS treatment, the total AHRS score positively correlated with regional brain metabolism in the left interior temporal gyrus (54 voxels) and to a lesser extent in the right middle temporal gyrus (13 voxels). After treatment, the AHRS score positively correlated with the right middle temporal gyrus (145 voxels). To detect the association between the pretreatment regional brain metabolism and clinical effect of rTMS, we used the change of AHRS during the study as the covariate for the $^{18}$FDG uptake before treatment. The AHRS change was positively predicted by the

Table 1. Clinical effect of rTMS on auditory hallucinations in schizophrenia (n = 12) assessed by HCS, AHRS (total and individual items), positive, negative symptoms and the total PANSS score

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 1 week</th>
<th>After 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive PANSS</td>
<td>17.5 (14.5–20.0)</td>
<td>14.5 (13.0–18.0)*</td>
<td>14.0 (13.0–16.0)*</td>
</tr>
<tr>
<td>PANSS P-3</td>
<td>4.5 (4.0–5.0)</td>
<td>4.0 (3.0–4.5)</td>
<td>3.0 (3.0–4.0)*</td>
</tr>
<tr>
<td>Negative PANSS</td>
<td>20.0 (16.0–23.5)</td>
<td>20.0 (16.5–22.5)</td>
<td>20.0 (16.5–21)</td>
</tr>
<tr>
<td>Total PANSS</td>
<td>70.0 (60.5–85.0)</td>
<td>70.5 (58.5–77.5)</td>
<td>66.0 (58.0–70.0)*</td>
</tr>
<tr>
<td>HCS</td>
<td>10 (10–10)</td>
<td>7.5 (6.5–9.0)*</td>
<td>7.5 (4.5–9.5)*</td>
</tr>
<tr>
<td>Total AHRS</td>
<td>25.0 (23.0–32.0)</td>
<td>21.0 (19.5–24.5)*</td>
<td>17.0 (14.0–23.0)*</td>
</tr>
<tr>
<td>AHRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>4.0 (2.0–6.5)</td>
<td>3.5 (2.5–4.0)</td>
<td>2.5 (1.0–4.0)</td>
</tr>
<tr>
<td>Reality</td>
<td>4.0 (4.0–5.0)</td>
<td>4.0 (4.0–4.0)</td>
<td>3.5 (1.5–4.0)</td>
</tr>
<tr>
<td>Loudness</td>
<td>3.0 (3.0–4.0)</td>
<td>2.0 (2.0–3.0)*</td>
<td>2.5 (1.5–3.0)</td>
</tr>
<tr>
<td>Number of voices</td>
<td>2.0 (1.0–3.5)</td>
<td>1.5 (1.0–2.0)</td>
<td>2.0 (1.0–2.5)</td>
</tr>
<tr>
<td>Length</td>
<td>3.0 (3.0–4.0)</td>
<td>3.0 (2.5–3.5)</td>
<td>2.5 (1.5–3.0)</td>
</tr>
<tr>
<td>Attentional salience</td>
<td>5.0 (4.5–5.0)</td>
<td>4.0 (3.0–4.5)</td>
<td>3.0 (2.0–4.5)*</td>
</tr>
<tr>
<td>Distress level</td>
<td>4.0 (3.5–5.0)</td>
<td>3.0 (3.0–4.0)*</td>
<td>2.5 (1.5–3.5)*</td>
</tr>
</tbody>
</table>

Data are presented in medians (interquartile range). The differences between the baseline and values after 1 and 2 weeks of rTMS were determined by the Friedman test followed by the post-hoc Wilcoxon paired test. The p values are ≤0.05 with a Bonferroni correction for the 2 time points (marked by an asterisk).

rTMS, LORETA and PET in Hallucinations

Fig. 1. The influence of low frequency rTMS on regional brain metabolism. a The most pronounced decrease in \(^{18}\)FDG PET uptake was found in the left temporal cortex and in the cerebellum. b \(^{18}\)FDG PET uptake following low-frequency rTMS increased in the middle frontal gyrus bilaterally and in the right temporoparietal cortex. For a list of all significant changes and technical details, see table 2. R = Right hemisphere; L = left hemisphere.

Table 2. Comparison of \(^{18}\)FDG uptake PET measured before and after 0.9-Hz rTMS treatment

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Hemi-sphere</th>
<th>Brain region</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in (^{18})FDG uptake after rTMS</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>252</td>
<td>–46</td>
<td>14</td>
<td>–26</td>
<td>L</td>
<td>superior temporal gyrus</td>
<td>38</td>
</tr>
<tr>
<td>–</td>
<td>–52</td>
<td>12</td>
<td>–16</td>
<td>L</td>
<td>superior temporal gyrus</td>
<td>38</td>
</tr>
<tr>
<td>167</td>
<td>–22</td>
<td>–64</td>
<td>–24</td>
<td>L</td>
<td>cerebellum-hemisphere, lobule 6</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>–42</td>
<td>–20</td>
<td>–28</td>
<td>R</td>
<td>inferior temporal gyrus</td>
<td>20</td>
</tr>
<tr>
<td>54</td>
<td>–50</td>
<td>–72</td>
<td>–32</td>
<td>L</td>
<td>cerebellum-hemisphere, lobule crus2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>–30</td>
<td>–28</td>
<td>24</td>
<td>L</td>
<td>insula</td>
<td>13</td>
</tr>
<tr>
<td>33</td>
<td>–12</td>
<td>–94</td>
<td>34</td>
<td>L</td>
<td>cuneus</td>
<td>19</td>
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<tr>
<td>78</td>
<td>–32</td>
<td>–2</td>
<td>–40</td>
<td>L</td>
<td>inferior temporal gyrus</td>
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<td>–</td>
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<td>19</td>
<td>–28</td>
<td>–20</td>
<td>–6</td>
<td>L</td>
<td>hippocampus</td>
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<tr>
<td>15</td>
<td>30</td>
<td>–10</td>
<td>–34</td>
<td>R</td>
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<tr>
<td>Increase in (^{18})FDG uptake after rTMS</td>
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<td>35</td>
<td>32</td>
<td>20</td>
<td>64</td>
<td>R</td>
<td>middle frontal gyrus</td>
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<tr>
<td>382</td>
<td>44</td>
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<td>34</td>
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<td>R</td>
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<td>79</td>
<td>–26</td>
<td>58</td>
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<td>237</td>
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<td>R</td>
<td>middle frontal gyrus</td>
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<td>36</td>
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<td>–48</td>
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<td>R</td>
<td>precuneus</td>
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<tr>
<td>19</td>
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<td>–50</td>
<td>36</td>
<td>R</td>
<td>supramarginal gyrus</td>
<td>40</td>
</tr>
</tbody>
</table>

The cluster size is presented as the number of voxels over the statistical threshold \(t = 4.02\) corresponding to a \(p\) value of 0.001. Dashes in the cluster size column indicate that the peak belongs to the same cluster as above. R = Right hemisphere; L = left hemisphere; xyz = coordinates of the MNI space for each maximum; BA = Brodmann area.
pretreatment metabolism in the left inferior temporal gyrus (34 voxels) and parahippocampal gyrus (13 voxels) and the right precentral gyrus (478 voxels). The higher metabolism in the left inferior frontal gyrus (16 voxels) was the negative predictor of clinical improvement (t = 4.14, p < 0.001 for all covariation analyses).

**Effect of rTMS on LORETA**

For a list of all significant changes and the coordinates for each maximum, see figure 3. In the anterior cingulate, we found a bilateral increase in current densities in the delta band (fig. 3a). The current densities decreased in the beta-1 and beta-3 bands in the temporal lobe ipsilateral to the site of stimulation (fig. 3b, d). In the beta-2 band (fig. 3c), we found an increase in the current densities in the middle temporal and in the inferior parietal lobule on the right side. The significant changes were not detected for the theta, alpha-1, and alpha-2 bands.

**Discussion**

Our data confirm that low-frequency rTMS is effective in the treatment of auditory hallucinations [16–21]. With respect to the previous studies with negative results [22–25] our results are in favor of rTMS application of a longer duration (20 min per day for 10 days) with a higher intensity of magnetic field up to 100% MT. The similar trend for rTMS therapeutic efficacy in relation to the higher number of pulses and magnetic field intensity is documented for depression [39]. However, our study was focused on the detection of neuroimaging changes and hence this clinical presumption may be confirmed by a sham-controlled study.

The decrease in brain metabolism in the temporal cortical region ipsilateral to the coil position is congruent with the inhibitory effect of the low-frequency rTMS [40, 41] and with the a priori formulated hypothesis. Resting $^{18}$FDG PET primarily reflects the regional glutamate turnover at the synaptic (particularly, presynaptic) level
and provides a probe for relative synaptic strength and consequent metabolic activity [42, 43]. Therefore, our observation is in accordance with the supposed long-term depression phenomenon induced by low-frequency rTMS as the most probable mechanism responsible for the inhibitory effect [3, 4]. Considering the focus of the coil position estimated to be over the posterior part of the superior temporal gyrus, the anatomical location of the prominent decrease in \(^{18}\)FDG uptake was shifted rostrally (anterior part of the superior temporal gyrus) and medially (insula). A similar effect of anteriomedially shifted metabolic decrease in relation to the coil position was detected for low-frequency rTMS over the left prefrontal cortex [41]. This mild shift in the inhibitory changes may result from the induced spread of the physiologic effect in the temporal cortex to the lower stages of auditory information processing in the anterior part [44]. The decreased metabolism in this region is congruent with the clinical effect that is most pronounced in the loudness and attentional salience of AHRS and less so on the more complex...
PET analysis. The conventional separation of the beta cordance with a lateralized metabolic effect obtained by distribution found in our study by LORETA were in accordance with the temporoparietal region of coil positioning and so it was not involved in the a priori hypothesis on metabolic changes under the coil and directly interconnected regions. Hence, in the case of cerebellum the PET results presented at p ≤ 0.001 without correction for multiple comparisons should be interpreted cautiously considering the risk of false-positive results. Nevertheless, tracer studies in primates have confirmed the cerebellum is interconnected with areas 9 and 46 of the prefrontal cortex [48, 49]. Thus the changes induced by rTMS in the prefrontal region might be responsible for the indirect modulatory effect in the cerebellum.

The increased metabolism in the bilateral middle frontal gyrus is analogous to findings from the low-frequency prefrontal rTMS study by Speer et al. [40] that proved decreased prefrontal perfusion with simultaneous intensity-dependent increases in distant interconnected areas. The authors explained these phenomena by the projections from the site of stimulation to the inhibitory interneurons. The primary changes induced by rTMS in the temporal cortex may cause a marked metabolic increase in the prefrontal cortex (and vice versa) via long intrahemispheric fascicules that highly interconnected both parts. The facilitation of metabolism in the frontal lobes implicates that low-frequency rTMS in the temporal location may improve the symptoms derived from the hypofrontality and induce the reintegration of frontotemporal disconnection documented in schizophrenia [50, 51].

The surprising finding is the increase in 18FDG uptake in the right temporoparietal cortex. The decrease in metabolism in the left temporal cortex correlates with the pretreatment intensity of hallucinations and represents the positive predictor of the clinical effect of rTMS.

We also found the metabolic decrease in cerebellum and hippocampus. The decrease in metabolism in the hippocampus could be mediated through well-established connections from both the temporal [45] and prefrontal cortices [46, 47]. Cerebellum is not directly interconnected with the temporoparietal region of coil positioning and so it was not involved in the a priori hypothesis on metabolic changes under the coil and directly interconnected regions. Hence, in the case of cerebellum the PET results presented at p ≤ 0.001 without correction for multiple comparisons should be interpreted cautiously considering the risk of false-positive results. Nevertheless, tracer studies in primates have confirmed that the cerebellum is interconnected with areas 9 and 46 of the prefrontal cortex [48, 49]. Thus the changes induced by rTMS in the prefrontal region might be responsible for the indirect modulatory effect in the cerebellum.

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The increase in current density in the delta band in the anterior cingulate indicates an increase in inhibitory processes in this region [60, 61] subsequent to the rTMS. The overactivity in this region was previously detected in positive schizophrenia symptoms [62, 63] and the increase in delta may reflect their improvement. These changes in the cingulate may result from indirect stimulation of the prefrontal cortex which has dense inhibitory connections to cingulate [64]. The lack of corresponding findings in the cingulate in our PET data is explained by the higher temporal sensitivity in EEG which enables the detection of the increased inhibitory oscillation in the delta band. The low correlation of the delta band with PET and the higher correlation for the beta frequency increase were documented in a concurrent FDG PET and LORETA neuroimaging study [55].

It is necessary to emphasize that the metabolic and EEG effect in our study was induced by long-term stimulation applied over 2 weeks. The 18FDG uptake in resting condition directly correlates with the synaptophysin level and should be accepted as the marker of synaptic density [43]. The EEG spectral distribution is stable over time in individual subjects [65, 66] and exerts heritability for all bands with the highest heritability for beta [67]. Therefore, in contrast to previous studies focused on acute perfusion or excitability changes [68, 69] the differences in both methods during rTMS treatment confirm the long-lasting neuroplastic remodeling of synaptic architecture and cortical integration in our experiment.

Conclusion

Our findings confirm the effect of rTMS on auditory hallucinations, and a decreased metabolism in the cortex underlying the rTMS site. We detected the metabolic influence propagated by transcallosal and intrahemispheric connections. The LORETA analysis corresponds to the PET data in the beta bands and indicates that the neuroplastic changes serve as the substrate for the metabolic effect.

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