

## Letter to the Editors

### Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations?

Dear Editors,

The majority of auditory verbal hallucinations (AVH) are responsive to antipsychotic medication, but in 25–30% hallucinations persist despite adequate pharmacotherapy (Shergill et al., 1998). Low frequency repetitive Transcranial Magnetic Stimulation (rTMS) offers an alternative treatment for this medication-resistant group (Hoffman et al., 2005). A recent meta-analysis concluded that rTMS is an effective treatment for AVH, with an effect size of 0.76 (Aleman et al., 2007). So far, rTMS was mostly applied to the left temporo-parietal area. However, functional Magnetic Resonance Imaging (fMRI) studies show that in approximately 50% of patients hallucinatory activation mainly involves the right hemisphere (Sommer et al., 2003). The effect of rTMS may therefore be increased when the treatment is applied exactly over the cortical area that is active in hallucinations. In this study we used individual fMRI scans of hallucinatory activation to stereotactically guide TMS treatment to the cerebral area with maximal hallucinatory activation.

15 male schizophrenia patients with medication-resistant AVH were included in an open-label study. Comorbidity, such as current depression or substance abuse, was an exclusion criterion. Patients were maintained on medication at steady dosages from 4 weeks before treatment until the last follow-up ten weeks after treatment. Symptoms were assessed three days before treatment started (baseline), at the end of each treatment week and at two follow-up measurements at 6 and 13 weeks after baseline. Primary outcome measure was the frequency of hallucinations measured with the Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003). Secondary outcome measure was the total score on the positive items of the Positive and Negative Symptom Scale (PANSS).

Functional scans were obtained in three sessions of 15 min. Patients indicated the presence of AVH by

squeezing an air-mediated button and holding it until the AVH subsided. We used a BOLD sensitive, 20-slice gradient EPI sequence (TR/TE 1200/35 ms, flip angle: 35°, FOV: 256 × 10 × 204.80 mm, voxel size 4 × 4 × 4 mm, scan-time per fMRI volume 1.2 s, 750 scans per session) on a Philips Achieva 3 T scanner. An anatomical scan was obtained for detailed localisation (TR/TE: 25/1.68 ms, voxel size 1 × 1 × 1 mm, flip angle: 30°, FOV: 256 × 180 × 208, 200 slices). fMRI data were analysed using SPM2. After realignment and co-registration, a model of expected hallucination-related BOLD signal change, was created using a box-car signal, with button squeezes as hallucination onsets and the time between squeezes and releases as the duration of the hallucinations, which was convolved with the standard hemodynamic response function from SPM2 to mimic the delayed BOLD response. These hallucination periods were compared to scans during non-hallucinatory episodes. Beta values were tested against zero in a 2nd level *T*-test (threshold  $p < 0.01$ , cluster size > 10 voxels). The cerebral area with the largest number of continuous activated voxels was used as rTMS focus. Image-guided stereotaxy was performed with a Neural Navigator (Negggers et al., 2004), in which the activation map was projected upon the brain's anatomy. The anatomical scan was transformed to a skin rendering, which was co-registered to the patients' head using 3D craniotopic coordinates marked in the software on the skin rendering, mapped onto the same craniotopic landmarks measured directly on the patients head with a 3D digitizer pen (MiniBIRD position tracker system, Acension Technologies). The point on the scalp exactly overlying the largest activated area was marked by a surgical skinmarker.

When no adequate activation maps could be acquired (no activation of > 10 continuous voxels below  $p = 0.01$ ) or when hallucinatory activity was inaccessible to rTMS, patients were assigned to the unguided treatment group. In the unguided condition stimulation was focussed on the left temporo-parietal cortex, midway between positions T3 and P3 on a 10–20 EEG electrode cap (Hoffman et al., 2005). rTMS was administered for 20 min at 1 Hz at 90% of the patients' motor threshold

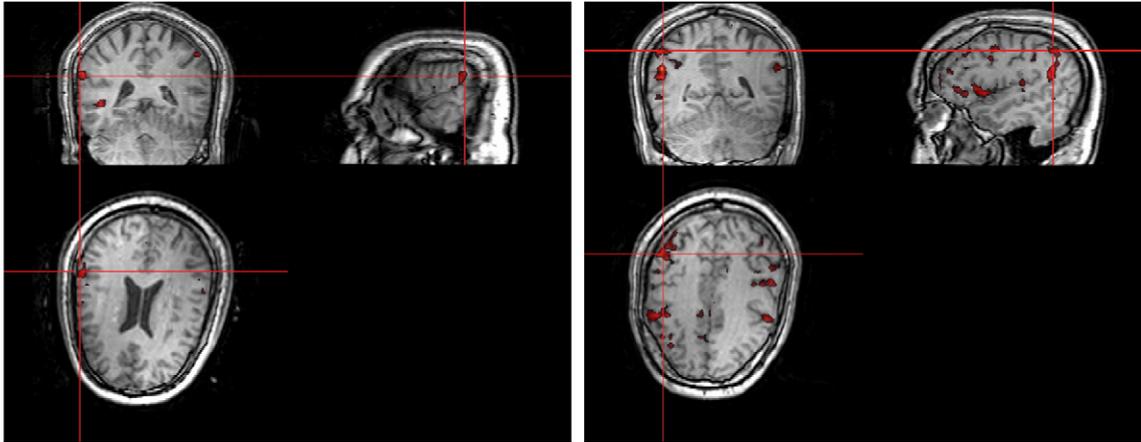


Fig. 1. Examples of hallucinatory activity in two patients (right=left in the figure).

using a Magstim Rapid2 with an air-cooled 70 mm figure-of-eight coil. Patients received daily treatments, except for the weekends, for three weeks.

The effect of treatment in the two groups was analysed with a GLM using the factors time (baseline, three ratings during treatment and two follow-ups) and treatment type (fMRI-guided versus non-guided).

From 15 participating patients, valid hallucination-related activation maps were obtained in 12 cases. The three patients with unsuccessful scans did not experience enough hallucinations while inside the scanner. From the 12 patients with successful scans, four had hallucinatory activation predominately within the left temporo-parietal areas, five mainly in the right-sided temporo-parietal areas and three patients showed hallucination-related activation located deep within the contralateral homologue of Broca's area. As this latter location is out of reach for rTMS, these three patients received non-guided rTMS treatment. The other nine patients were treated with fMRI-guided rTMS.

Two patients wished to abort the study at the second and eighth day of treatment, respectively, because they experienced anxiety and suspicion (Fig. 1). Both patients received fMRI-guided rTMS treatment to left temporo-parietal areas. Thirteen patients completed the study, from whom seven received fMRI-guided rTMS treatment.

At baseline, there were no differences in severity of AVH, severity of psychotic symptoms or any other clinical characteristic between the two groups (see Table 1).

The frequency of AVH showed a significant main effect for time ( $F=4.2$ ,  $p=0.02$ ), indicating decreasing severity of AVH in both groups. The time by type of

treatment interaction was not significant ( $F=0.8$ ,  $p=0.5$ ). Ten weeks after the last treatment severity of AVH was still lower than at baseline ( $t=2.6$ ,  $p=0.03$ ).

The severity of psychosis increased during the first week of treatment, possibly as a result of moving to a new ward. In the second and third week of treatment severity of psychosis decreased. Overall the severity of psychosis did not improve significantly (main effect for time:  $F=0.8$ , n.s.), while the time by type of treatment interaction showed a trend towards more improvement in the fMRI-guided group ( $F=2.3$ ,  $p=0.10$ ).

The results of this study suggest that fMRI-guidance for rTMS treatment of AVH is feasible in the majority of patients with frequent AVH. Interestingly, most patients (eight out of 12) had predominantly right-sided hallucinatory activity. rTMS treatment guided by individual hallucination-activation maps was compared to rTMS treatment at a fixed position (left temporo-parietal), rendering no significant difference upon the frequency of AVH. This may well be a result of the limited power of our study. In contrast to the findings for frequency of AVH, fMRI-guided rTMS appeared superior to non-

Table 1  
Clinical characteristics of the patients that completed the study

Characteristic	fMRI-guided ( $n=7$ )	Non-guided ( $n=6$ )
Age	36 (sd 9)	38 (sd 5)
Handedness	6 right, 1 left	6 right, 0 left
AVH for ..years	14 (sd 11)	14 (sd 8)
Years after diagnosis of schizophrenia	12 (sd 7)	12 (sd 5)
Baseline severity of AVH	29 (sd 5)	29 (sd 5)
Baseline severity of psychosis	18 (sd 6)	19 (sd 3)

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