Reproducibility of brain activation during auditory verbal hallucinations

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ARTICLE INFO

ABSTRACT

Previous studies investigated fMRI-guided repetitive Transcranial Magnetic Stimulation (rTMS) as an alternative treatment for auditory verbal hallucinations (AVH). This tailor-made treatment focuses at directing the rTMS coil to the location where hallucinatory activation is maximal, as identified with fMRI scans of individual patients. For the effective use of such treatment it is important to determine whether brain activation during AVH can be reliably detected using fMRI. Thirty-three psychotic patients indicated the presence of AVH during two subsequent scans. Reproducibility was measured by calculating 1) the distance between local maxima of significantly activated clusters and 2) percentage overlap of activation patterns over the two scans. These measurements were obtained both in single subjects and on group-level in five regions of interest (ROIs). ROIs consisted of the areas that were most frequently activated during AVH. Scans were considered reproducible if the distance between local maxima was smaller than 2 cm, as rTMS-treatment may target an area of approximately 2–4 cm. The median distance between local maxima was smaller than 2 cm for all ROIs on single-subject level, as well as on group-level. In addition, on single-subject level median percentage overlap varied between 14 and 38% for the different ROIs. On group-level, this was substantially higher with percentages overlap varying between 34 and 98%. Based on these results, AVH-scans may be considered sufficiently reproducible to be suitable for fMRI-guided rTMS treatment.

1. Introduction

The development of functional imaging techniques capable of "symptom-capturing" (i.e., capturing brain activation related to a symptom) has enabled the start of individual tailor-made treatments of psychiatric or neurological symptoms. An example of this strategy is the focal treatment of auditory verbal hallucinations (AVH) with repetitive Transcranial Magnetic Stimulation (rTMS) or experimental treatment such as invasive electrocortical stimulation. A major advantage of these tailor-made treatments is that they have the potential to treat medication-resistant symptoms such as AVH, tics, tremor or obsessions.

At present, the primary treatment for AVH consists of antipsychotic medication which is often combined with cognitive behavioral therapy. Although antipsychotic medication is largely effective in treating hallucinations, AVH do not respond to antipsychotic medication in 25–30% of schizophrenia patients. Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive method for altering activation of cortical neurons by rapidly changing magnetic fields. RTMS is a safe treatment method with only mild side effects such as transient headache and

scalp discomfort during stimulation (Slotema et al., 2012) which may be a treatment option for AVH in patients with insufficient response to pharmacotherapy. Most studies, thus far, have applied low frequency rTMS for the treatment of hallucinations. Although the exact mechanism by which low frequency rTMS may improve AVH remains elusive, it is thought that when stimulation with rTMS is applied repeatedly, the targeted area becomes less active for a longer period, i.e., decreasing hallucinatory hyperactivation.

Although three large RCTs published recently failed to show a significant effect of rTMS in comparison to placebo-controlled treatment (Vercammen et al., 2009; Loo et al., 2010; Slotema et al., 2010), meta-analyses reported a significant effect of rTMS as compared to placebo on the treatment of AVH with mean weighted effect sizes ranging from 0.33 to 1.0 (Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010, 2012).

Most studies applying rTMS in the treatment of AVH targeted a fixed position on the skull corresponding to the left temporoparietal area (Slotema et al., 2012). The rationale for selecting this area is that it overlies speech perception areas, hyperactivation of which has been hypothesized to be involved in the occurrence of AVH. While treatment of this area seems to result in a decrease in the severity of AVH, a number of fMRI studies showed that activation patterns during AVH tend to vary significantly among individual patients as in approximately one-half of the patients activation during AVH can be observed in right-hemispheric

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areas, i.e., the right temporoparietal and inferior frontal area, homologous to Broca's area of language production (Sommer et al., 2007; Sommer et al., 2008). Initial reports from studies targeting other areas than the left temporoparietal region do, however, not show superior or even comparable effects. While Lee et al. (2005) reported reductions in severity of AVH after rTMS directed at the right temporoparietal region, this was not replicated by others (Jandl et al., 2006; Loo et al., 2010). In addition, repetitive TMS treatment of the bilateral temporoparietal regions revealed no significant differences in comparison with placebo treatment (Vercammen et al., 2009; van Lutterveld et al., 2012). Finally, stimulation of Broca's area or the left superior temporal gyrus (Schonfeldt-Lecuona et al., 2004) was no more effective than sham treatment. It should, however, be noted that the lack of efficacy of rTMS directed at more frontally located areas, such as Broca's area, might be due to the facial musculature overlying the skull in this area. Because rTMS can only reach a depth of 1–2 cm, additional muscle layers might prevent the rTMS pulse from affecting Broca's area (Hoffman et al., 2007; Slotema et al., 2012). Moreover, only few studies targeted other areas than the left temporoparietal area and the superior effects of this area as compared to other areas may result mainly from lacking power to support efficacy of rTMS targeted at other areas.

As maximum activation during AVH varies over patients a more suitable approach might be to identify areas where hallucinatory activation is maximal on a single subject-level and use these foci as the target for rTMS treatment (Sommer et al., 2007). While this tailor-made approach has proved to be feasible, only three studies have thus far investigated fMRI-guided rTMS in multiple patients of which just two studies directly compared guided to non-guided rTMS. Hoffman et al. (2007) used a design in which the first five patients were treated with rTMS targeted at three sites where hallucinatory activation was maximal or brain areas that showed significant correlation with the timecourse in Wernicke's area during AVH. In the remaining patients up to six active sites could be targeted with rTMS. Statistically greater rates of improvements in AVH were observed when rTMS was directed to left temporoparietal sites compared to anterior temporal sites and sham stimulation. Enabling a direct comparison between guided and non-guided rTMS Sommer et al. (2007) treated seven patients with guided rTMS while six patients received non-guided rTMS. Although no significant difference could be observed upon the frequency of AVH, fMRI-guided rTMS appeared superior at trend level to non-guided rTMS in decreasing severity of general psychosis. While this argues for the use of fMRI guided rTMS treatment the largest study to date revealed that the effects of fMRI-guided rTMS (and left temporoparietal rTMS) on the severity of AVH were comparable to those of sham treatment (Slotema et al., 2010). Although these results should be treated with caution, a reason for these negative findings might be that brain activation during AVH cannot be reliably detected using fMRI. This is crucial for optimal treatment as scans that are unreliable may not reflect the true substrate of interest and will therefore be less effective when used as the main source for treatment guidance. The aim of the present study was therefore to investigate spatial reproducibility of AVH-related brain activation both at the individual and at the group level. To circumvent the influence of factors that are difficult to keep constant with increased time between measurements, such as arousal, medication and caffeine-intake, reproducibility was investigated between two AVH-sessions acquired within the same visit.

2. Materials and methods

2.1. Subjects

Thirty-three psychotic patients with medication-resistant AVH were recruited from the University Medical Center Utrecht and the Parnassia Bavo Group in The Hague, The Netherlands. Patients were selected for participation from a larger group of patients with chronic hallucinations (Slotema et al., 2011) if they met the following criteria: (1) the presence of two subsequent AVH scans in which (2) intermittent AVH were

experienced (i.e., AVH alternated with non-AVH state), (3) at least three AVH-episodes were present per scan (4) and AVH were indicated correctly (i.e., AVH-onsets were followed by clear offsets). Patients were diagnosed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) interview according to DSM-IV criteria by an independent psychiatrist. Demographic and clinical data of the participants is provided in Table 1.

2.2. Data acquisition

Participants indicated the presence of AVH by balloon-squeezes while scans were acquired continuously. Data acquisition was similar for all AVH-scans and took 8 min per scan. Images were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner. An AVH scan consisted of a series of blood-oxygenation-level-dependent T2* weighted images over time. PRESTO-SENSE was used to acquire the T2* weighted fMRI images, optimally using parallel imaging and echo shifting to reduce acquisition time of up to 609 ms/volume (Neggers et al., 2008). Eight hundred PRESTO-SENSE images were acquired per session (40 slices, TR/TE 21.75/32.4 ms, flip angle 10°, field of view $224 \times 256 \times 160$, matrix $64 \times 64 \times 40$, voxelsize 4 mm isotropic, acquisition time 609 ms/volume). To improve localization of functional data, a high-resolution anatomical scan was conducted in addition to the AVH-scans (TR/TE: 9.86/4.6 ms, $1 \times 1 \times 1$ voxels, flip angle 8°, FOV $224 \times 160 \times 168.00$, 160 slices).

2.3. Data analysis

Preprocessing and analysis were conducted with Statistical Parametric Mapping (SPM5; Welcome Department of Cognitive Neurology, London, UK) and included the following steps: realignment, coregistration, spatial normalization and smoothing, using an 8-mm full width at half maximum Gaussian kernel. Scans were analyzed on a voxel by voxel basis using multiple regression analysis with

Table 1
Demographic data of the participants.

	Group 1: reliability analyses (N = 33)	Group 2: to define ROIs (N = 30)
	Mean	Mean
Age (years)	39.28 (SD = 10.15)	39.6 (SD = 10.01)
Age (years) at onset AVH	19 (SD = 19)	21 (SD = 11)
Gender		
Females	19	14
Males	14	16
Handedness		
Right-handed	26	26
Not right-handed	6	4
Diagnosis		
Schizophrenia	22	23
Schizo-affective disorder	3	1
Psychosis NOS	6	4
Personality disorder and psychosis NOS	1	0
Borderline personality disorder and psychosis NOS	1	1
One-time depressive period	0	1
Medication		
Antipsychotic		
No antipsychotics	4	6
Typical antipsychotics	10	7
Atypical antipsychotics	18	15
Combi typical & atypical antipsychotics	1	1
PANSS scores		
Total	67 (SD = 15)	70 (SD = 15)
Positive subscale	16 (SD = 4)	18 (SD = 4)
Negative subscale	18 (SD = 5)	18 (SD = 6)

Abbreviations: AVH, auditory verbal hallucinations; N, number; SD, standard deviation; NOS, not otherwise specified; and PANSS, Positive and Negative Syndrome Scale.