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High frequency rTMS; a more effective treatment for auditory verbal hallucinations?

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ABSTRACT

The great majority of studies on repetitive transcranial magnetic stimulation (rTMS) as a therapeutic tool for auditory verbal hallucinations (AVH) have used 1-Hz stimulation with inconsistent results. Recently, it has been suggested that 20-Hz rTMS has strong therapeutic effects. It is conceivable that this 20-Hz stimulation is more effective than 1-Hz stimulation. The aim of this preliminary study is to investigate the efficacy of 20-Hz rTMS compared with 1-Hz rTMS as a treatment for AVH. Eighteen schizophrenia patients with medication-resistant AVH were randomized over two treatment groups. Each group received either 20 min of 1-Hz rTMS or 13 trains of 20-Hz rTMS daily over 1 week. After week 1, patients received a follow-up treatment once a week for 3 weeks. Stimulation location was based on individual AVH-related activation patterns identified with functional magnetic resonance imaging. Severity of AVH was monitored with the Auditory Hallucination Rating Scale (AHRS). Both groups showed a decrease in AVH after week 1 of rTMS. This decrease was significant for the 20-Hz group and the 1-Hz group. When the two treatment types were compared, no treatment type was superior. Based on these results we cannot conclude whether high frequency rTMS is more effective against AVH than is traditional 1-Hz rTMS. More research is needed to optimize stimulation parameters and to investigate potential target locations for stimulation.

1. Introduction

Auditory verbal hallucinations (AVH) are a common and stressful symptom of schizophrenia. In about 25–30% of patients these AVH are resistant to antipsychotic medication (Shergill et al., 1998). The level of resistance has stimulated the search for means of treatment augmentation. Repetitive transcranial magnetic stimulation (rTMS) could be such an additional therapeutic tool for AVH in schizophrenia. With rTMS, a magnetic field is generated by an electromagnetic coil. When placed on the scalp, this magnetic field induces a small electrical current in the brain. Depending on the characteristics of stimulation (e.g., intensity, timing and pulse shape), rTMS can induce neuronal inhibition or facilitation or even the release of neurotransmitters, which can result in transsynaptic action (Wagner et al., 2007). The first study that applied rTMS as a therapeutic instrument for AVH was performed by Hoffman et al. (1999). In this study a 1-Hz rTMS stimulation protocol was applied. The 1-Hz stimulation is based on the idea that cortical excitability could be reduced (Chen et al., 1998; Maeda et al., 2000a) by applying low frequency TMS, comparable to effects in long-term depression (LTD) as reported in electrophysiological studies. In addition, LTD-like and also long-term potentiation (LTP)-like mechanisms have been observed after rTMS (Ziemann et al., 1998), suggesting that the main effects of rTMS may be induced by altered synaptic plasticity. A recent review (Carson and Kennedy, 2013) on human studies also found evidence that these mechanisms underlie the therapeutic effects of rTMS. Over the last decade several studies have used rTMS as a therapeutic tool in schizophrenia with mixed results. There are reports of a positive effect in decreasing AVH (Chibbaro et al., 2005; Hoffman et al., 2005; Jandl, 2010; Lee et al., 2005; Poulet et al., 2005; Brunelin et al., 2006; Vercammen et al., 2009), but also studies revealing hardly any difference between active TMS and sham TMS (Schönfeldt-Lecuona et al., 2004; Fitzgerald et al., 2005; Saba et al., 2006; Rosa et al., 2007; Slotema et al., 2011). Two recently published randomized control trials (RCTs) with large sample sizes reported contrary results regarding the effectiveness of 1-Hz rTMS against AVHs. In the first, which included 62 patients, no difference between

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active 1-Hz rTMS and placebo was found (Slotema et al., 2011). The most recent, by Hoffman et al. (2013), which included 83 patients, reported an improvement on the Hallucination Change Score (HCS) when only patients ($n=69$) in whom a reliable motor threshold could be consistently detected were considered.

The largest RCT so far failed to find any difference between active 1-Hz rTMS and placebo (Slotema et al., 2011). Four meta-analyses revealed effect sizes between 0.52 and 1.05 (Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010), indicating moderate to large effects, but recent negative studies were not included. Two recent meta-analyses (Demeulemeester et al., 2012; Slotema et al., 2012) did include negative studies, and revealed effect sizes of 0.43 and 0.33 for the direct effects of rTMS. After 1 month, however, the effect of AVH was no longer significant (Slotema et al., 2012).

Several suggestions have been made that might improve the efficacy of rTMS treatment. Vercammen et al. (2009) applied rTMS bilaterally, but bilateral administration has not heretofore been shown to be more efficient in reducing AVH severity than 1-Hz rTMS. Freitas et al. (2009) urged the need for functional magnetic resonance imaging (fMRI) guidance, as at least this would provide us a location that is involved in the experience of AVH. Also longer durations of 1-Hz stimulation rTMS seem more effective (Maeda et al., 2000b). This could indicate a dose effect of rTMS. However, it is unknown if the number of repetitions or the total amount of pulses delivered yields better results. Increasing the frequency would be a straightforward and efficient way to obtain more stimulation even when safety regulations (Wassermann, 1998; Rossi et al., 2009) are taken into consideration. Therefore, high frequency rTMS is very suitable for intensifying stimulation within practical time limits, because the duration of the rTMS treatment can be reduced. However, contrary to the traditionally assumed inhibitory effects of low frequency and the excitatory effects of high frequency rTMS, several studies do report good clinical effects in suppressing symptoms by using high frequency rTMS. An open label study using 20-Hz rTMS (Montagne-Larmurier et al., 2009) observed a large effect of rTMS on AVH, but no control condition was used. Comparable effects have been reported with the use of high frequency rTMS as an instrument against tinnitus (Ridding and Rothwell, 2007; Khedr et al., 2008). A recent study investigated the long-term effects of rTMS on neuroplasticity in the rat brain (Gersner et al., 2011). Only for 20-Hz rTMS, however, was a long-term effect on markers of neuroplasticity found, whereas the effect was not present for 1-Hz rTMS. Eberle et al. (2010) found remarkable results in a single subject, using theta burst stimulation (Huang et al., 2005), in which a high number of pulses were delivered. However, none of these studies included a comparison condition and they did not apply double-blind randomized methods. Recently, Kindler et al. (2013a, 2013b), applied a similar theta burst protocol in comparison with a 1-Hz treatment group, but both treatments appeared to be equivalently effective. Both treatment groups did show a decreased activity in the primary auditory cortex of the treated hemisphere (Kindler et al., 2013b).

The question remains if a more intense stimulation protocol, such as 20-Hz rTMS, is indeed more effective as a treatment against AVH than traditional 1-Hz rTMS. This preliminary study investigates if an increased intensity of rTMS might improve efficacy of rTMS for the treatment of AVH. We compared the therapeutic effects of 5 days of stimulation with either 1-Hz or 20-Hz rTMS. Therefore, we did not include a sham TMS group, but instead the conventional 1-Hz rTMS was considered as a control condition. In a previous 1-Hz trial (Sommer et al., 2007), we noticed that after the first week of treatment (5 sessions), already a large decrease in AVH was reported, which improved only slightly in the last 2 treatment weeks. However, the trial consisted of a total of 3 weeks of daily treatment (15 sessions), which was quite demanding for the patients, as it meant many travel hours or a clinical admission. To reduce the burden for the patient, we tested the efficacy of a 1-week protocol, when accompanied by a weekly follow-up treatment. We evaluated the effect of rTMS on AVH duration after the first treatment session (direct effect), and the effects after five treatment sessions and after 3 weeks of follow-up treatment (maintenance effect).

2. Methods

2.1. Subjects

Twenty-eight schizophrenia patients with frequent AVH were included. All patients were recruited from the psychiatry department of the University Medical Center Utrecht. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used for the assessment of symptoms on the day of the MRI scan. Although all patients used antipsychotic medication, they still suffered from severe AVH, occurring at least once an hour. All patients used typical or atypical antipsychotic medication in conventional dosages. Exclusion criteria were history of epileptic seizures in first degree relatives, metal objects inside or around the body (e.g., cochlear implant, surgical clips, piercings and cardiac pacemaker), cannabis or other drug abuse during the study, and the use of benzodiazepines and anti-epileptic medication. After inclusion, subjects were randomly assigned by a computer script to receive one of two treatment conditions, 1-Hz or 20-Hz rTMS. The treatment type was unknown to patients until the first day of stimulation. It was explained to the patients that two active types of treatment would be compared, but no information was provided about which dosage was the conventional and which dosage was the new treatment type. So they had no expectancy the efficacy of high versus low rTMS. Patients were maintained on medication at steady dosage from 4 weeks before treatment until the last follow-up 4 weeks after treatment. They also had no knowledge about the stimulation protocol of the other group. From all patients handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the medical ethical committee of the University Medical Center; after explanation to the participants, written informed consent was obtained.

2.2. MRI acquisition

Functional scans were obtained in one or two sessions of 8 min using a Philips Achieva 3-Tesla Clinical MRI scanner. Patients indicated the presence of AVH by squeezing an air-mediated button with their right hand and releasing it when the AVH subsided. These PRESTO SENSE fMRI scans were obtained with a repetition time (TR)/echo time (TE) of 21.75/32.4 ms (flip angle=10, field of view (FOV)=$224\times256\times160$ (ap, fh, rl), voxel size=4 mm isotropic, matrix=$64\times64\times40$, 40 slices, 800 scans scan time/volume 0.607 s). Note that PRESTO-SENSE fMRI is a 3D echo-planar imaging technique that is accelerated in two phase-encoding directions using parallel imaging (Neggers et al., 2008). Hence the short TR of 21.75 ms and fast acquisition time per volume of 607 ms which increases sensitivity to blood oxygen level dependent (BOLD) signal changes. Because for correct coregistration of the functional scans and the T1-weighted scan of one isolated PRESTO-SENSE volume, the 'reference' or FA 27 scan, was acquired with a flip angle of 27° instead of 10°, leading to more T1 weighting and hence anatomical contrast. It is otherwise identical to the fMRI scans. The T1-weighted anatomical scan was acquired with parameters TR/TE=9.87/4.6 ms, flip angle=8°, FOV $224\times160\times168$, matrix=256×256, slice thickness 1 mm (no gap) and voxel size 0.875 isotropic.

2.3. fMRI analysis

All functional MRI data were analyzed using SPM5. First, all functional scans were realigned with the FA27 scan; the T1 scan was then co-registered with this FA27 scan. Finally, functional scans were smoothed with an $8\times8\times8$ full-width at half-maximum Gaussian kernel.

A General Linear Model analysis of expected hallucination-related BOLD signal change was created using a regressor consisting of 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 SPM5 to mimic the delayed BOLD response. These hallucination periods were compared with scans during non-hallucinatory episodes. Regression coefficients for this regressor were tested against zero in a *T*-test (threshold $p=0.01$, cluster size 5 voxels). A mask was made according to the Automated Anatomical Labeling (AAL) (Tzourio-Mazoyer et al., 2002) with WFU Pickatlas (Maldjian et al., 2003) containing the bilateral angular gyrus (AG), bilateral supramarginal gyrus (SMG) and bilateral Heschl's gyrus (HG). This mask was warped to each individual's native space according to the inverse normalization parameters, which were acquired by segmentation of the corresponding T1 scan. Statistical tests were corrected for multiple comparisons for voxels within this mask (FWE $p=0.05$).

The selected areas are commonly associated with AVH (Shergill et al., 2000; Sommer et al., 2008; Diederen et al., 2013). Besides these regions, the insula and