



## Brief report

# Theta burst transcranial magnetic stimulation for the treatment of auditory verbal hallucinations: Results of a randomized controlled study



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## ABSTRACT

One Hertz (1 Hz) repetitive transcranial magnetic stimulation (rTMS) is an effective therapy for auditory verbal hallucinations (AVH). Theta burst protocols (TBS) show longer after-effects. This single-blind, randomized controlled study compared continuous TBS with 1 Hz rTMS in a 10-day treatment. Patients were diagnosed with schizophrenia or schizoaffective disorder. TBS demonstrated equal clinical effects compared to 1 Hz TMS.

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## 1. Introduction

In patients with medication-resistant auditory verbal hallucinations (AVH), repetitive transcranial magnetic stimulation (rTMS) has been demonstrated as an effective therapy (Hoffman et al., 2003). A meta-analysis of 10 placebo-controlled TMS studies yielded a mean effect size of  $d=0.76$  for AVH (Aleman et al., 2007). In the 2009 schizophrenia PORT guidelines (Buchanan et al., 2010), 1-Hz TMS is recommended as treatment for patients with AVH that have not responded to pharmacological treatments.

Even though there are several reports that question the effectiveness of rTMS for treatment of AVH (Slotema et al., 2011), a recent meta-analysis, controlling for publication bias, confirmed a reduced but significant effect size (Hedge index 0.41) (Demeulemeester et al., 2011).

A rTMS protocol that has recently been introduced into clinical research is theta burst stimulation (TBS) (Huang et al., 2005). TBS seems to induce plastic changes in cortical synapses in a long-term potentiation or long-term depression-like fashion. It was shown that continuous TBS (cTBS) over the contralesional hemisphere reduces neglect in stroke patients for several hours (Nyffeler et al., 2009). Furthermore, the cTBS protocol has proven to be effective in language research (Kindler et al., 2012).

So far, there are three case reports applying cTBS in AVH (Eberle et al., 2010; Poulet et al., 2009; Sidhoumi et al., 2010), with one of

them demonstrating a full response in a patient with chronic AVH after a 9-week bilateral continuous theta burst TMS treatment (Eberle et al., 2010). A larger clinical trial has not been published yet.

From a clinical point of view, cTBS has the advantage of a very short application duration (44 s), as compared to the often-used 1-Hz stimulation protocol (15 min) for the same number of pulses.

In conventional TMS studies, the left temporoparietal cortex (TP3 of the 10–20 international EEG system) served as the target region for TMS stimulation. Area Spt (Sylvian parietotemporal), located in the Sylvian fissure at the parietotemporal boundary, is a sensorimotor interface between the sensory and motor speech systems (Hickok and Poeppel, 2007). Recently we demonstrated that the functionally defined Area Spt is close to the conventionally targeted area TP3 (Kindler et al., 2013).

Here, we present a single-blind, controlled clinical trial comparing 1 Hz with cTBS treatment regarding clinical outcome variables.

## 2. Methods

### 2.1. Patients and clinical investigation

Participants comprised 24 patients (Table 1), with 12 patients receiving 1-Hz rTMS and 12 receiving cTBS. Inclusion criteria were diagnosis of schizophrenia or schizoaffective disorder (ICD-10), medication resistant AVH, age between 18 and 65 years, and right-handedness (assessed with the Edinburgh Handedness Scale (Oldfield, 1971)). Exclusion criteria were history of epileptic seizures, signs of elevated neuronal activity in electroencephalography (EEG), MR contraindications

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**Table 1**  
Demographics and ratings of psychopathology.

	1 Hz, n = 12 Mean	S.D.	cTBS, n = 12 Mean	Statistical test	Test	t-value	d.f.	p-value
<b>Demographics</b>								
Age	43.1	9.2	40.7	14.0	t-test	0.71	22	0.48
Sex	7f		7f		Fisher's		n.a.	1.00
Diagnosis (F20/F25)	11/1		10/2		Fisher's		n.a.	0.67
Cpx	536.5	170.0	563.8	325.0	t-test	0.34	22	0.83
<b>Psychopathology scores before treatment</b>								
PANSS	66.4	9.1	81.7	18.11	t-test	2.61	22	0.02*
PsyRats	33.8	9.3	42.7	12.7	t-test	1.94	22	0.07
AHRS	32.0	5.7	36.4	6.1	t-test	1.83	22	0.08
<b>Psychopathology difference values (<math>\Delta</math>=pre vs. post treatment)</b>								
$\Delta$ PANSS	4.3	5.5	7.5	7.1	t-test	1.22	22	0.23
$\Delta$ PsyRats	4.1	6.1	7.1	6.2	t-test	1.20	22	0.24
$\Delta$ AHRS	7.1	8.9	10.9	11.0	t-test	0.94	22	0.36
$\Delta$ HCS	3.2	3.9	3.2	3.2	t-test	0.00	22	1
Response	4		5		Fisher's		n.a.	0.77

S.D.=Standard deviation, Sex f=female, Fisher's=Fisher's exact test, Cpx=chlorpromazine equivalents, PANSS=Positive and Negative Syndrome Scale, AHRS=Auditory Hallucination Rating Scale, PsyRats=Psychotic Symptom Rating Scale, HCS=Hallucination Change Score, Diagnosis F20=schizophrenia, F25=schizoaffective disorder, d.f.=degrees of freedom, t-value=test value.

\* Significant at  $p < 0.05$ .

and medical disorders other than schizophrenia or schizoaffective disorder. None of the patients reported substance misuse in the 4 weeks before or during the study.

Therapy refractoriness was defined as non-response to at least two antipsychotic treatments in recommended dosages, each for at least 8 weeks. Patients were randomly assigned to one of the TMS groups (see below). There was no sham control group. Diagnostic procedure was conducted based on clinical interviews and psychiatric history. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988), the Psychotic Symptom Rating Scale (PsyRats) (Haddock et al., 1999) and the Auditory Verbal Hallucination Rating Scale (AHRS) (Hoffman et al., 2003) before the first and after the last treatment session by a blinded rater. Hallucination Change Score (HCS) (Hoffman et al., 2003) was requested from the patient. Antipsychotic medication dosage was converted to chlorpromazine equivalents (Andreasen et al., 2010). The investigation was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Patients provided informed written consent to participate in the study.

## 2.2. Coil navigation

A frameless, ultrasound-based, stereotactic system was used for neuronavigation (Brainvoyager™ TMS Neuronavigator System, Brain Innovation®, B.V. 2006). Details on the functional magnetic resonance imaging task for localization of Area Spt and the neuronavigation procedure are published elsewhere (Kindler et al., 2013, Supplemental material).

## 2.3. TMS stimulation

A custom TMS stimulator (MagPro R 100, Medtronic Functional Diagnostics, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. Magnetic pulses were delivered with a figure-eight coil (Magnetic Coil Transducer MC-B70, Medtronic). Individual resting motor thresholds were identified by stimulating the motor cortex with single TMS pulses until a movement of the contralateral thumb was detected. The center of the coil was held tangentially to the skull. During the experiment, rTMS pulse intensity was adjusted to 90% of the motor threshold. Patients were randomly assigned to a 1-Hz ( $n=12$ ) or cTBS TMS protocol ( $n=12$ ).

In both treatment groups, the target area was stimulated for 10 consecutive days. Stimulation at 1 Hz was applied once a day, according to the protocol used by Hoffman et al. (2003).

The cTBS paradigm consisted of 267 bursts of three pulses at 30 Hz, repeated with an interburst interval of 100 ms (according to Nyffeler et al., 2009), delivering a total of 801 pulses within a total duration of 44 s. cTBS was applied in double trains with a 15-min intertrain interval. On the first 3 days, two double trains (total 3204 pulses) of cTBS were applied, whereas on days 4–10, one double (1602 pulses) cTBS train was applied (Supplemental material).

Safety protocols were in accordance with international safety standards of rTMS experimentation (Rossi et al., 2009). To minimize the risk of seizures, we conducted clinical EEGs before inclusion and during the TMS therapy. The rationale for the chosen rTMS (1 Hz, TBS) protocols was a combination of safety and efficiency parameters published for the respective protocol.

## 2.4. Statistics

Age, baseline psychopathology (PANSS, PsyRats, AHRS), and medication have been compared in two-sided, two-sample *t*-tests or Fisher's exact test between groups. Response was defined as improvement of AVH of  $\geq 50\%$  in HCS (hallucination change scale). Differences of PANSS, PsyRats, AHRS and response rates between the two TMS protocols ( $\Delta$ =difference pre vs. post) have been compared between the treatment groups (1Hz vs. cTBS) in two-sample *t*-tests. Throughout the manuscript mean and standard deviation (S.D.) are reported. Statistical significance was set at  $p < 0.05$ , two sided. Statistics was carried out in SPSS 19.0<sup>®</sup>.

## 3. Results

In the collapsed group, mean age was 41.88 ( $\pm 11.82$ ) years, gender 14f (10m), PANSS 74.0 ( $\pm 16.0$ ), PsyRats 38.3 ( $\pm 11.8$ ), and AHRS 34.2 ( $\pm 6.2$ ). Three of the patients were diagnosed with schizoaffective disorder, 21 with schizophrenia. Nine (38%) patients fulfilled criteria of response.

The cTBS group showed a significantly higher PANSS score at baseline, whereas all other scores or variables did not differ significantly. Further, no difference was detected when evaluating improvement in AVH scores (Table 1) between the two TMS treatment protocols.

### 3.1. Safety

All patients that entered the TMS study finished the treatment protocol. No seizures occurred, and no increased cerebral excitability was observed in any EEG. Twenty-five percent of TMS patients felt minor headaches at the beginning of the treatment period, which subsided within several days and did not need to be treated with analgesic medication. No differences regarding the different TMS protocols were observed.

## 4. Discussion

This is the first randomized control, single-blind study comparing the classical 1-Hz and the cTBS protocol with respect to clinical outcome. The advantage of cTBS is the shorter application time and previously described longer duration of the effects compared with 1-Hz protocols (Nyffeler et al., 2009). However, in our sample we did not find significant differences between 1-Hz and cTBS

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