



Add-on accelerated continuous theta burst stimulation (a-CTBS) over the left temporoparietal junction for the management of persistent auditory hallucinations in schizophrenia: A case series



Dear Editor,

Auditory verbal hallucinations (AVH) form one of the cardinal symptoms of schizophrenia with about 65–75% reporting them [1]. Antipsychotics proclaimed to be effective for positive symptoms, fail to bring remission in about 30–40% of individuals reporting auditory hallucinations [1]. Transcranial magnetic stimulation (TMS) owing to its targeted modulation of neural activity has the potential for the treatment of these symptoms. However, the use of conventional TMS protocols has been limited by studies showing small effects, requiring longer time and larger numbers needed to treat (NNT) to demonstrate responses, and having the pragmatic burden of daily hospital visits for availing treatment facilities [2]. Accelerated TMS protocols could address some of these by shortening the treatment duration and thereby increasing the efficiency of standard TMS. Furthermore, studies have demonstrated that higher doses of TMS pulses can be tolerated with no significant side effects [3,4].

In schizophrenia, cTBS has been examined as an add-on treatment in the management of persistent auditory hallucinations in controlled trials [5]. While accelerated protocols having more than two sessions per day have been described for depression [3] and OCD [6], it has not been studied in schizophrenia. We report the clinical effects of MRI-guided neuronavigation-based add-on accelerated cTBS (five per day sessions) to the left temporoparietal junction (TPJ) for persistent AVH in schizophrenia.

Three patients (right-handed, males) with DSM-5 (Diagnostic and Statistical Manual, 5th edition) diagnosis of schizophrenia, having persistent auditory hallucinations (a score >3 in the global rating of auditory hallucinations on the SAPS scale) despite treatment with at least one adequate antipsychotic trial were offered accelerated cTBS after screening with the TMS adult safety screen. There was no history of significant delusions, substance use, neurological or medical disorder, or intellectual disability. Patients were on stable doses of medications for the preceding four weeks. Informed consent was obtained after explaining the procedure using a video aid. The accelerated cTBS protocol was administered using standard equipment [MagProX100 (case z) or PowerMag TMS system (case x & y)] ensuring stringent safety measures. The left temporoparietal junction was localized using anatomical landmarks. Brainsight® and visor2™ neuronavigation systems were used to position the TMS coil over the individualised stimulation target [7]. Sessions were delivered using the figure-of-8 cooled coil. Each participant received five treatment sessions per day, 1 h apart, for five

consecutive days. Each session consisted of 1800 pulses delivered over 2 min, (total of 600 bursts at 5 bursts/second with each burst consisting of three pulses at 200 ms interpulse interval) administered continuously at 120% RMT or maximum tolerable dose, whichever was smaller, with a total of 90,000 pulses per day. A structured questionnaire was used to assess for any treatment-related side effects at the end of each session and before the start of the new session on a subsequent day [8]. Patients were assessed using the Hoffman's Auditory Hallucination Rating Scale (AHRS), Scale for Assessment of Positive Symptoms and Scale for Assessment of Negative Symptoms, and the Clinical Global Impression-Severity at baseline and at the end of the intervention.

Mild tingling at the scalp and muscle contraction at the stimulation site was reported during most of the sessions, as assessed by the structured questionnaire [8]. None of the sessions were discontinued due to side effects. Significant improvement in auditory hallucinations was noted in two (x and z) of the three patients (AHRS score change 41.3% and 29.6%), which was associated with improvement in positive (SAPS score change 67.5% and 31.3%) and negative symptoms (SANS score change 35% and 53.6%) (Table 1). Incidentally, both the responders had one failed antipsychotic trial, whereas, the non-responder had two failed antipsychotic trials and was on clozapine.

Discussion

Accelerated protocols of 2–10 sessions per day have been reported for a variety of psychiatric and neurological disorders [9]. Accelerated protocol using twice-daily sessions has been described in the past for AVH in schizophrenia [9]. To our knowledge, this is the first report of an attempt to shorten the duration of a month-long therapeutic TMS protocol to 5-days in patients with persistent AVH. All patients tolerated the sessions well and had no major adverse effects. We could complete the protocol for all the patients. Thus, accelerated cTBS is a feasible option for persisting auditory hallucinations in schizophrenia.

Target stimulation was guided by individual neuroimaging-based neuronavigational system. It ensured consistent and unifocal stimulation. Two of the three patients demonstrated clinically meaningful improvement to this briefer 5-day protocol. Nevertheless, both these patients had only one antipsychotic failure and the non-responder in this series was resistant to clozapine after failing 3 other antipsychotics. It is known that the degree of treatment resistance is an important determinant of response to TBS in

Table 1
Clinical details of the three cases at baseline and change with accelerated cTBS.

Subjects	Age		Duration of untreated illness (in Months)	Treatment duration (in Months)	Current Treatment	Failed prior antipsychotic trials (n)	AHRS		CGI-S		SAPS		SANS	
	(in Years)	(in Years)					PRE	POST	PRE	POST	PRE	POST	PRE	POST
x	37	14	3	269	Clozapine 550mg/day Lamotrigine 100mg/day Escitalopram 10mg/day	4	33	30	6	6	51	52	55	53
y	30	26	24	43	Olanzapine 25 mg/day	1	27	19	6	5	51	35	95	44
z	34	16	1	216	Risperidone 6mg/day	1	29	17	6	4	37	12	40	26

AHRS = Auditory Hallucinations Rating Scale; CGI-S=Clinical Global Impression Severity scale; SAPS=Scale for Assessment of Positive symptoms; SANS= Scale for assessment of Negative Symptoms.

depression [10]. Future studies need to consider this aspect of the degree of treatment resistance while allocating participants in RCTs.

Our results provide preliminary evidence that five days of accelerated (five sessions per day) MRI-guided cTBS application to the left TPJ is feasible, safe and tolerable. The effectiveness of this intervention needs to be systematically assessed in randomised control trials. These studies should account for the degree of antipsychotic resistance, which may moderate response to treatment.

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Declaration of competing interest

The authors declare no conflict of interest.

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References

- Li W, Zhang Q, Tang Y, Park SC, Park Y, Yang SY, et al. Network analysis of psychiatric symptoms in schizophrenia: findings from the research on asian psychotropic prescription patterns for antipsychotics (REAP-AP). *Asian J Psychiatr* 2022;75:103200.
- Mehta UM, Naik SS, Thanki MV, Thirthalli J. Investigational and therapeutic applications of transcranial magnetic stimulation in schizophrenia. *Curr Psychiatr Rep* 2019;21(9):89.
- Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatr* 2022;179(2):132–41.
- Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, et al. Accelerated TMS for Depression: a systematic review and meta-analysis. *Psychiatr Res* 2019;273:770–81.
- Nathou C, Etard O, Dollfus S. Auditory verbal hallucinations in schizophrenia: current perspectives in brain stimulation treatments. *Neuropsychiatric Dis Treat* 2019;15:2105–17.
- Williams NR, Sudheimer KD, Cole EJ, Varias AD, Goldstein-Piekarski AN, Stetz P, et al. Accelerated neuromodulation therapy for obsessive-compulsive disorder. *Brain Stimul* 2021;14(2):435–7.
- Dollfus S, Jaafari N, Guillin O, Trojak B, Plaze M, Saba G, et al. High-frequency neuronavigated rTMS in auditory verbal hallucinations: a pilot double-blind controlled study in patients with schizophrenia. *Schizophr Bull* 2018;44(3):505–14.
- Giustiniani A, Vallesi A, Oliveri M, Tarantino V, Ambrosini E, Bortoletto M, et al. A questionnaire to collect unintended effects of transcranial magnetic stimulation: a consensus based approach. *Clin Neurophysiol* 2022;141:101–8.
- Vercammen A, Knegtering H, Liemburg EJ, den Boer JA, Aleman A. Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS treatment of auditory hallucinations. *J Psychiatr Res* 2010;44(11):725–31.

- Baliga SP, Mehta UM. A review of studies leveraging multimodal TMS-fMRI applications in the pathophysiology and treatment of schizophrenia. *Front Hum Neurosci* 2021;15:662976.

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