CASE REPORT

Long-term repetitive transcranial magnetic stimulation therapy: new research questions arising from one tinnitus case?

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SUMMARY

Tinnitus may become refractory to treatment and disabling. Brain transcranial magnetic stimulation (TMS) has shown promise as a therapy, but has been employed primarily short-term. We treated a patient with 5 weeks of weekly repetitive TMS (rTMS), followed by 6 months of monthly rTMS. He was a 75-year-old dentist with chronic tinnitus from occupational noise exposure. Physical examination and MRIs of the auditory canals and brain had revealed no lesions. The patient showed a general gradual, progressive improvement on per cent of severe tinnitus diary days (from baseline 100% to 33%), tinnitus handicap inventory (from baseline score 70 to 18), and mini-tinnitus questionnaire (from baseline score 17 to 6). No changes occurred in serial audiograms. Transient adverse events were a headache during stimulation, and dizziness 30 min after treatment. Implications and questions for future non-invasive neuromodulation clinical research raised by our case are discussed.

BACKGROUND

Chronic tinnitus may become lifelong and disabling. Treatment options are few, but repetitive transcranial magnetic stimulation (rTMS) over auditory cortex has shown promise.[1] Most protocols use short-term courses of aggregated rTMS treatment, typically daily for 5 or 10 consecutive working days; in some patients, persistent benefits for up to several years were seen.[2] A regularly scheduled, longer term course of treatment may be more beneficial, and more convenient for the patient, in this chronic illness. We report treating a tinnitus patient over a 7-month course on a structured, intermittent distributed weekly or monthly treatment schedule, with excellent results. Implications and questions for future non-invasive neuromodulation clinical research raised by our case are discussed.

CASE PRESENTATION

Our patient was a 75-year-old dentist with chronic refractory tinnitus from occupational noise exposure. Physical and neurological examinations were unremarkable. The patient's medical, surgical and family history were non-contributory.

INVESTIGATIONS

MRIs of the auditory canals and brain revealed no lesions. His baseline audiogram demonstrated mild sensorineural high-frequency hearing loss bilaterally.

TREATMENT

Our protocol schedule was: 5 weeks of baseline observation before the first rTMS to assess stability of the outcome measures (weeks −5 to 1); 5 weeks of weekly rTMS (weeks 1 to 5); 6 months of monthly rTMS (weeks 5 to 26) and 1 month of follow-up with no rTMS (weeks 26 to 30). During baseline and study phases, the patient completed a daily diary rating tinnitus as mild, moderate or severe,[3] and completed tinnitus questionnaires at the study assessment visits. rTMS was delivered half way between C3 and T5 (10–20 system; contralateral to most affected ear). Each 30 min session comprised 1800 pulses at 1 Hz at 100% of the resting motor threshold (RMT). Outcome measures were: the per cent of days since the last assessment visit with tinnitus rated as severe on the diary; tinnitus handicap inventory (THI);[4] tinnitus severity scale (TSS)[5] and mini-tinnitus questionnaire (MTQ).[6] The protocol was approved by the Burke Institutional Review Board.

OUTCOME AND FOLLOW-UP

Results are in table 1. THI, TSS and MTQ were stable over the baseline period (weeks −5 to 1). The patient showed a general gradual, progressive improvement on per cent of severe tinnitus diary days (from 100% to 33%), THI (from 70 to 18) and MTQ (from 17 to 6). The TSS did not change. No changes occurred in serial audiograms. Transient adverse events were a headache during stimulation, lasting 10 min, and dizziness 30 min after treatment, lasting for 30 min.

DISCUSSION

It seems unlikely that our patient improved this dramatically spontaneously, coincident with, but unrelated to, rTMS, at this point in his illness, but we cannot rule out this possibility. Placebo effect also cannot be excluded; however, the patient improved on only three of four outcome measures.

There is one other report of a tinnitus case treated long-term with rTMS by Mennemeier *et al*.[7] Their stimulation parameters were nearly the same as ours (1800 pulses at 1 Hz delivered to right anterior superior temporal gyrus at 110% RMT). However, Mennemeier *et al*[7] used a treatment schedule that differed from ours. Their initial rTMS was aggregated daily for 5 days, and then they followed with a 6-month period with no stimulation. Subsequently, they added blocks of rTMS for several aggregated sequential days in the

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Table 1 Tinnitus ratings at assessment visits over the course of the study

Study week, assessment visits	rTMS treatment?	Percentage of days diary rated tinnitus 'severe'	Tinnitus handicap inventory	Mini-tinnitus questionnaire	Tinnitus severity scale
−5	Start of baseline, no rTMS	Not applicable, start of baseline	70	17	12
1	End of baseline, start rTMS	100	70	19	13
5	rTMS	59	46	15	11
10	rTMS	64	44	11	13
18	rTMS	46	34	10	8
30	Follow-up only, no rTMS	33	18	6	11

Declining scores indicate improvement.
rTMS, repetitive transcranial magnetic stimulation.

event of a tinnitus relapse, until the patient improved. Three separate blocks, of 1, 3 or 3 treatment days, were needed. Four months with good tinnitus control then followed. Initially Mennemeier *et al*[7] used an aggregated daily 5-day treatment schedule for their first five treatments, while we used a distributed once-per-week schedule for our first five treatments. Subsequently, Mennemeier *et al*[7] employed an as needed treatment approach for their next seven sessions (aggregated into several daily treatment blocks), while we employed a regularly scheduled distributed monthly single session treatment approach for our next five sessions. Both of these long-term schedules appeared successful. As rTMS gains greater acceptance as a potential treatment for chronic functional disturbances of the brain, such as depression, is it now time for various potentially optimal long-term therapeutic strategies to be compared and assessed, in terms of mechanisms, efficacy, tolerability, patient compliance and cost?

Virtually all studies of rTMS for depression also use an aggregated treatment schedule. An example is the long-term study reported by Janicak *et al*.[8] After 6–12 weeks of five times per week rTMS over the left dorsolateral prefrontal cortex, patients could enrol subsequently in a 24-week naturalistic durability continuation trial. Scheduled rTMS stopped. In the event of symptom recurrence during those 24 weeks, rTMS was reintroduced on a schedule of twice-per-week for 2 weeks, then five times per week for up to 4 weeks. In those 24 follow-up weeks, rTMS was reintroduced once in 38% of patients, twice in 15% of patients and three times in 5% of patients. Would distributed scheduled maintenance rTMS for depressed patients prevent a symptom-worsening relapse after the initial course of acute rTMS therapy is completed? Who might be the best candidates for this distributed treatment approach, and can they be identified in advance?

Our patient's gradual improvement over the course of the study is of interest. In general, these data show a relatively steady, progressive but protracted nature to this response. This suggests that with successive treatment sessions, the incremental brain modulatory effects we produced may have contributed to an additive, step-wise, neural reorganisation in the auditory cortex over time. In advance, we did not specifically hypothesise that we would observe this pattern. As alternatives, we may have seen no improvement initially, and then late improvement (a threshold effect); or we may have seen an initial improvement, with no later improvement (a plateau effect). Similarly, in a study of weekly supplementary motor area rTMS for Parkinson's disease, Hamada *et al*[9] described gradual improvement on the Unified Parkinson's Disease Rating Scale over 12 weeks. Monthly treatments, as we used for weeks 5–26, were not tested. Can details of the brain plasticity mechanisms underlying the time course of these changes with rTMS in a variety of neuropsychiatric illnesses be elucidated, so that we may leverage our understanding in order to obtain better outcome for our patients? In conclusion, we believe important research questions still may arise from a single case such as ours.

Learning points

- Non-invasive brain stimulation has been used to treat depression, and now extending its use to include tinnitus and Parkinson's disease is under investigation.
- Moving a therapy from a research to a clinical setting requires assessing practice items such as patients' schedules compliance, but also may allow additional scientific investigation of underlying mechanisms, such as the time course of the response.
- While the outcome from treating just one case with a novel intervention alone proves neither efficacy nor tolerability, a case study such as ours may raise significant further research questions.

Contributors DRL conceived the work, acquired and analysed the data, and drafted the work; and DE and MC collaborated to conceiving and drafting the work. All authors approve the work.

Competing interests None.

Patient consent Obtained.

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