

## Case report

## Non-invasive therapeutic brain stimulation for treatment of resistant focal epilepsy in a teenager

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## ABSTRACT

**Aims:** A 13-year-old boy with symptomatic focal epilepsy due to a right parietal dysembryoplastic neuroepithelial tumor (DNET) presented pre- and post-operatively fluctuating tinnitus and sensory symptoms which became persistent after incomplete tumor resection. He received low-frequency rTMS treatment and cathodal tDCS treatment.

**Methods:** Case report with clinical details and pictures from rTMS and tDCS stimulation targets.

**Results:** The patient became symptom free with an initial low-frequency rTMS treatment series targeted to the EEG-verified epileptic zone followed by maintenance therapy at the same region with cathodal tDCS at home.

**Conclusions:** Both rTMS and tDCS could be more often used in adolescents when drug treatment and surgery do not cease focal epilepsy, here with fluctuating tinnitus.

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## 1. Introduction

The incidence of seizures in patients with brain tumor is 12% at the time of diagnosis and 14% on long-term follow-up (Ullrich et al., 2015). Dysembryoplastic neuroepithelial tumors (DNET) of the brain present with seizures almost 100% of the time. Resection of the tumor yields seizure freedom in 86% of the cases in children (Ranger and Diosy, 2015).

An evaluation of possible benefits of invasive neuromodulation treatments (e.g. vagus nerve stimulation and deep brain stimulation) should be conducted when epilepsy surgery is not feasible or successful (Kwan et al., 2011; Engel, 2016). Invasive stimulation techniques carry a risk of serious complications which has raised interest in the potential of novel, non-invasive brain stimulation techniques for treatment-resistant epilepsy.

Repetitive transcranial magnetic stimulation (rTMS) is a safe and effective non-invasive brain stimulation method that is frequently clinically used for treating depression and neuropathic pain (Lefaucheur et al., 2020; Cruccu et al., 2016). The potential efficacy of rTMS for the treatment of epilepsy has been investigated in a few studies with promising results especially in cortical focal epilepsy. A recent review and meta-analysis of 12 small studies using low-

frequency rTMS for the treatment of drug-resistant epilepsy confirmed a mean 30% reduction in seizure frequency, with better results in patients younger than 21 years (Cooper et al., 2017). Low-frequency rTMS applies frequencies at  $\leq 1$  Hz, most often 0.3–0.5 Hz, inhibiting the synaptic activity in the underlying cortex and the networks connected to it (Hsu et al., 2011). One study (Sun et al., 2011) of patients with a mean age of 21.3 years (range 14–42 years) showed that low-frequency rTMS at an intensity of 90% of resting motor threshold (RMT) decreased the number of seizures and inter-ictal spikes in the EEG compared to the baseline, while very low intensity (20% RMT) had no effect. Neocortical epilepsy, especially epilepsy due to cortical dysplasia, has been found to respond best to rTMS treatment, with a marked decrease in seizure frequency (Hsu et al., 2011). Therapeutic neuromodulation with rTMS has also been shown effective in patients with persistent seizures after epilepsy surgery (Sun et al., 2011). According to current guidelines, rTMS has a possible antiepileptic effect by focal low-frequency stimulation of the epileptic focus (Lefaucheur et al., 2020).

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique utilizing weak (1–3 mA) direct currents applied to the scalp via surface electrodes. tDCS with the cathode placed over the epileptic focus has been shown to have favorable effects in children with refractory focal epilepsy (Auvichayapat et al., 2013) and Lennox-Gastaut syndrome (Auvichayapat et al., 2016).

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So far, tDCS has not been recommended for use in epilepsy, (Lefaucheur et al., 2017), despite promising preliminary reports, because only a few studies with small numbers of patients have been carried out. Both rTMS and tDCS methods have been shown to be safe in children (Frye et al., 2008; Bikson et al., 2016, Antal et al., 2017, Woods et al., 2016), with no serious adverse effects when current safety guidelines are followed (Rossi et al., 2009).

This article presents a 13-year-old boy with a treatment-resistant symptomatic focal epilepsy due to DNET and nearly persistent tinnitus as a residual epileptic symptom after non-complete resection of the tumor. He became seizure free with an initial low-frequency rTMS treatment series followed by maintenance therapy with cathodal tDCS at home.

## 2. Case description

A 9-year-old boy presented with two epileptic seizures with a one month interval. His first seizure started with nausea followed by a high-pitch tinnitus and directly after the aura sound he lost consciousness and started seizing. In subsequent seizures his symptoms were an aura in the form of high-pitch tinnitus, with following numbness of the left hand that could at times proceed to a generalized tonic-clonic convulsion during the day, and nocturnal myoclonias. The tinnitus sound was intermittent, lasting up to a few minutes when the epileptic seizures first started. EEG showed epileptiform spikes over the right parieto-temporal cortex (between P4 and T6 electrodes according to the International 10/20 EEG electrode placement system; maximum negativity at the T6 electrode location). A 3-Tesla brain MRI revealed a tumor (3–4 cm diameter), which subsequently was confirmed by biopsy to be a DNET. The tumor was located on the right side posterior to the posterior central sulcus (Fig. 1). The last EEG before surgery was done two months after the first seizure, showing slowing within the right temporo-parietal area but no signs of epileptiform activity. After the resection, no ictal EEG-changes were noted during the tinnitus.

Prior to the surgery, brain mapping of the motor cortex using an E-field navigated NBS-TMS device (Navigated Brain Stimulation, Nexstim Ltd, Helsinki, Finland) was performed to identify the area of the left-hand motor representation. It was observed to be located anteriorly to the tumor, indicating practically no risk for perioperative damage. In contrast, the fMRI indicated that the left-hand motor area was partially located in the tumor area, frontally and medially.

Resection of the DNET-tumor was carried out two months later, at 9 years and 7 months of age. During the surgery, the tumor was partially resected, but a small (8 mm diameter) residual tumor

remained within the postcentral gyrus (S1/M1) close to the hand representation area in postoperative MR-imaging. The neurosurgeon left the resection incomplete due to lack of demarcation of tumor tissue and the close proximity of deeper tracts (Fig. 1).

Postoperatively, the patient had no new neurological or neuropsychological deficits.

Most of the symptoms were alleviated and controlled with medication after the surgery, but tinnitus remained, sometimes followed by left hand numbness, in line with residual focal epileptic symptoms. Although he had infrequent epileptic seizures and almost daily auditory sensory symptoms, he was developing normally and had a normal curriculum in school apart from being taught in a small 2-pupils group. Repeated awake EEG recordings were done, showing neither focal slowing nor epileptiform activity.

Due to severe and daily subjective discomfort caused by the almost continuous high-pitch tinnitus sound, rTMS-treatment was started at the age of 13 years and 1 month. The E-field-navigated NBS-TMS device (Navigated Brain Stimulation, Nexstim Ltd, Helsinki, Finland) was used for rTMS treatment; during the first session, the TMS-EEG (Navigated Brain Stimulation and eXimia EEG system, Nexstim Ltd, Helsinki, Finland) was applied to record EEG simultaneously during stimulation. The protocol was started with 11 sessions (intensive period), one session per day. The RMT was measured giving single TMS stimuli to the left M1 cortex and recording from the right hand thenar muscles with surface ENMG electrodes, as has previously been described in detail (Valmunen et al., 2009). RMT was 61% of the maximum output of the device. The target for rTMS was located between P4 and T6 electrodes, corresponding to the site of the strongest epileptiform activity in preoperative EEG-studies. This area was located about 1–2 cm posterior and lateral to the resection area. Fig. 2 shows the location of the treatment target area and the direction of the electric field induced by the rTMS.

To inhibit neuronal activity that produced the tinnitus (Shore et al., 2016), we applied an rTMS protocol of 0.75 Hz and 71% RMT during the first session, using a TMS-EEG cap to record simultaneous EEG during rTMS. The treatment did not evoke any epileptiform activity during the first session, so EEG recording was not used in the following treatment sessions that used 0.8 Hz, 80% RMT, and 1500–2000 pulses. The patient was asked before and after each rTMS session about the intensity and discomfort caused by the tinnitus using the Visual Analogue Scale (VAS, 0–100 mm), in which 0 was no tinnitus at all and 100 the highest intensity/discomfort imaginable. The patient reported in a symptom diary about the presence and intensity of tinnitus between sessions and how persistent it was as well as about the presence of other symptoms, such as hand numbness.

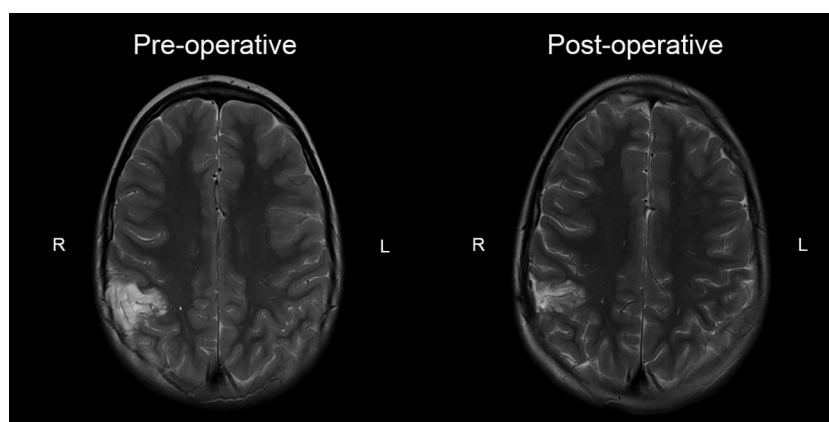
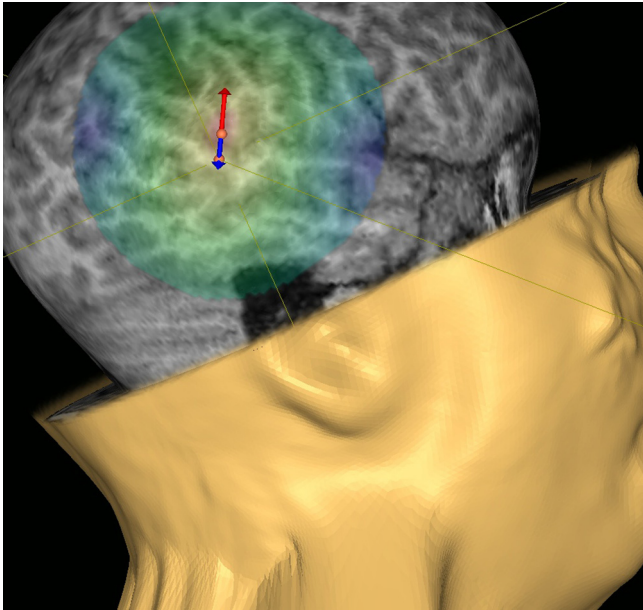


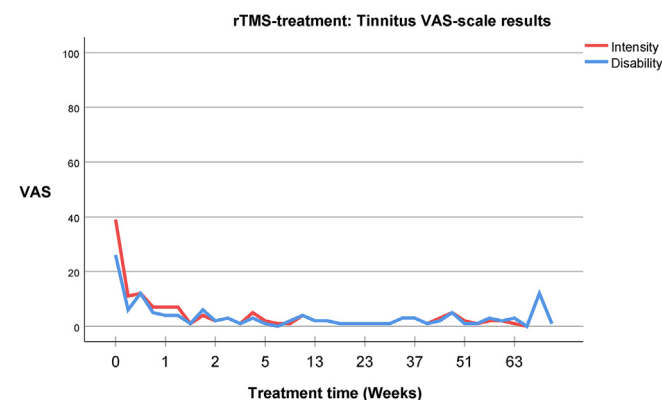
Fig. 1. Preoperative and postoperative MRI T2-sequence of the tumor.



**Fig. 2.** Brain target for rTMS treatment. The target was at the right parieto-temporal junction, between P4 and T6 EEG electrode locations. The red arrow represents the E-field orientation of the induced active TMS pulses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We additionally used the Global Impression of Change (GIC) scale, ranging from  $-3$  (the treatment severely worsens the symptoms) to  $+3$  (very significant benefit from the treatment),  $0$  meaning no change from the baseline, to evaluate the response to treatment. Sodium valproate 300 mg b.i.d. and lamotrigine 100 mg once a day were used, as before the rTMS. According to the VAS-scale, the intensity of the tinnitus was 39/100 and the discomfort 26/100 immediately before the first session; after treatment they decreased to 14/100 and 8/100, respectively. High-pitch ringing changed to low-pitch noise. After the 10th session, the intensity and the discomfort of the tinnitus were 2/100 and GIC was  $+3$ , both indicating a good response.

rTMS-treatment was continued with a maintenance protocol. We tried to maintain the good treatment response by a step-wise decrease in the frequency of the rTMS-sessions. The patient received one rTMS session every 3 weeks during the steady maintenance therapy. The tinnitus had almost totally gone away during this time, with an intensity of 1/100 and discomfort of 0–1/100 and GIC  $+3$ . We tried to further decrease the frequency of sessions to



**Fig. 3.** Evaluation of tinnitus intensity and discomfort during rTMS treatment.

once a month after 5 months. Both the intensity and the discomfort of the tinnitus were around 1–3/100 during this time (Fig. 3). The tinnitus disappeared immediately after each rTMS-session, but it sometimes reappeared during the evenings, and the patient considered the 1-month interval between two sessions too long and insufficient. Consequently, we continued with one session every 3 weeks, and the patient reported that this treatment frequency was appropriate. The EEG remained normal. The rTMS treatment lasted for 1 year and 5 months, with a total of 35 sessions (10 during intensive series, 25 during maintenance), for a total of 33 h.

We offered the patient the opportunity to continue maintenance therapy at home with a tDCS device because of the good response achieved with therapeutic rTMS. The patient would not need to come frequently to the hospital for the tDCS; instead, he could use the device himself under his parents' supervision at home. The follow-up would be taken care of by phone calls by the nurse, with a few yearly visits to hospital to see the doctor and to check the device and its batteries. The patient was given a tDCS device (Sooma Ltd, Helsinki) with a protocol of 2 mA, 20 min per session, once a week. At the start of the tDCS-treatment the patient was 13 years and 6 months old. The anode (red) was located on the left forehead, the cathode (black) at the right temporo-parietal region (Fig. 4), the same area that was used in the rTMS treatment as the target. Sooma ComfoTodes with ComfoPads were used with the tDCS device. The ComfoPads were soaked in saline before each use. The treatment was given at the hospital for the first 2 sessions with the tDCS, and both the patient and his parents were taught to use the device at that time. He used the tDCS-device at home from the 3rd session onwards. The intensity and discomfort of tinnitus were evaluated using an eleven-step Numeric Rating Scale (NRS) that asked the patient to rate the intensity and discomfort from 0 to 10/10. We used NRS instead of VAS, as the follow-up was done mostly with a phone call once a week. Dissimilarities between the measurement tools may explain the slightly higher NRS values compared to the VAS values.

After 4 tDCS sessions, GIC was  $+1.5$ , tinnitus intensity 2/10 and discomfort 1–2/10. tDCS treatment was continued but the number of sessions per week decreased, according to the maintenance protocol. With one session per week, there was a symptom peak with discomfort and intensity of 4/10 after 3 weeks, due to a two weeks' pause in the treatments, when the patient had first influenza and then a norovirus infection. Later, the symptom intensity fell back to 1–2/10, discomfort to 1/10 and with GIC  $+3$  after the 4th week, also with improvement in sleep quality. The patient used the tDCS-



**Fig. 4.** Placement of the tDCS electrodes, cathode (black, inhibition) and anode (red activation). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

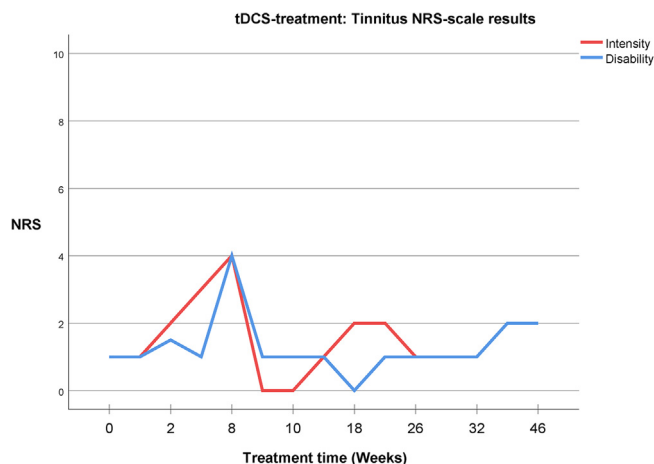


Fig. 5. Evaluation of tinnitus intensity and discomfort during tDCS treatment.

device 1–2 times per week, depending on symptom severity, over the next 4 months, for a total of 21 h. The tinnitus intensity was 1–2/10, discomfort was 0–1/10 during this time (Fig. 5). As of when this report was written, the tDCS-treatment had lasted 8 months, and the treatment with non-invasive neuromodulation was still successful. No adverse effects occurred during the rTMS or tDCS treatments.

### 3. Discussion

Before the operation, epileptic phenomena were observed in the EEG as an interictal spike focus with maximum negativity fluctuating at P4 and T6 derivations (parietal and posterior temporal area on the right side). From the beginning, tinnitus was a sensory symptom, an auditory aura, starting the seizure, and accompanied with nausea and following numbness in the left hand as other sensory symptoms. These sensory symptoms could proceed via secondary generalization to a generalized tonic-clonic convulsion. Every seizure had the same, typical ictal semiology. Before the surgery, the sensory symptoms occurred almost daily but not always with convulsions.

After the surgical tumor resection, the patient had no seizures and nor other symptoms for 9 months. Thereafter, daily sensory symptoms started to reappear in the form of a fluctuating tinnitus with exacerbations lasting around 10 s. He had also a few seizures with the habitual ictal semiology. The clinical picture resembled a focal auditory status epilepticus but the EEG did not show any spike-bursting nor continuous discharges. However, epileptiform activity may not necessarily be recognizable by routine 10–20 scalp electrode recordings if the epileptogenic zone is located within the parietal area (Asadollahi et al., 2017). Another explanation could simply be an iatrogenic induced auditory tinnitus due to the intervention itself. We consider the latter explanation less probable because the postoperative clinical symptoms were identical to the preoperative, stepwise progressing symptoms that were shown to be epileptic in nature. Considering that tinnitus is a frequent (25%) complication of unilateral temporal lobe resection (Paquette et al., 2017), and typically appears in the contralateral ear of the epileptic hemisphere (Florindo et al., 2006), we cannot fully ascertain the epileptic nature of the postoperative tinnitus symptomatology of our patient.

### 4. Conclusions

Treatment of a refractory, nearly persistent tinnitus four years after its initial manifestation is difficult and has a low chance of

success. Abolishing this disabling symptom after unsuccessful treatments with medications and a neurosurgical resection with non-invasive therapeutic neuromodulation techniques that are virtually side-effect free, is remarkable. This patient case report illustrates the potential of rTMS and tDCS in a teenager, for treatment-resistant tinnitus, presumably a symptom of focal sensory epilepsy, and how to manage the maintenance phase successfully with a patient-operated tDCS device at home. Non-invasive and safe brain stimulation methods with very few and mild adverse effects could be used more often when drug treatment and surgery do not cease all the epileptic symptoms and epileptiform EEG activity, particularly in adolescents, as an alternative to more invasive neuromodulation techniques. rTMS and tDCS are safe in adolescents, and tDCS can easily be administered at home with parental assistance.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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