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The unusual case of dental pain with sham repetitive transcranial magnetic stimulation: A benign idiosyncrasy or diagnostic opportunity?

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Repetitive transcranial magnetic stimulation (rTMS) is a promising treatment for major depressive disorder [1]. Recently, we investigated 10 sessions of high-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) in chronic stroke survivors with depression (randomised controlled trial; ACTRN12619001303134; institutional ethics approval 200697). Stimulation was delivered at 110% resting motor threshold at 10 Hz for a total of 3000 pulses. Here we report the experience of a 51-year-old male with mild upper-limb impairment (Fugl-Meyer 49/66; structural imaging Fig. 1), who experienced anatomically confined stimulus-evoked dental pain in response to sham stimulation.

Prior to inclusion, the participant was screened for brain stimulation safety [2]. There were no contraindications and no noteworthy medical history beyond a stroke three years prior. Current medications were anti-depressants and anti-coagulants with dosage stable for more than 6-months. The participant had previously participated in transcranial direct current stimulation research more than two months prior with no adverse events beyond standard transient symptoms documented in the literature [3]. Therefore, the participant was deemed safe for rTMS, included in the trial and was progressed to full initial assessment.

After initial assessment, the participant was informed that there was an active and sham condition in this trial and that he would be blinded to allocation. He was randomised to receive sham rTMS. The session began at 10:30am. Threshold of the left motor cortex was 52% maximal stimulator (Magstim Super Rapid) output using a Magstim 70mm Fig. 8 air film coil (part-number 3910-23-00). Sham rTMS was delivered with a Magstim 70 mm Fig. 8 air film placebo coil (part-number 3950-23-00) to the left DLPFC at 57% maximal stimulator output. Immediately upon delivery of sham rTMS, he recoiled his head away from the stimulation coil and reported strong pain on the left side of his face. Stimulation was immediately stopped. Pain resolved almost instantly. On further questioning, the participant described the discomfort as a strong stabbing pain in his upper and lower teeth, posterior to his left incisors, and extending into and along his mandible. Several attempts were made to optimise coil position or adjust stimulation intensity (down to 50%). However, the same pain occurred with each stimulation and resolved immediately. That is, the pain appeared to be directly evoked by sham rTMS over the left DLPFC. No other sensory or motor symptoms were reported; no motor signs were observed. On further questioning, the participant recalled that two weeks earlier he had undergone a dental procedure that included a filling to a left upper molar. He had not raised this earlier because it did not appear relevant and it had not been associated with symptoms then or since.

There are very few published reports of adverse events during or following sham rTMS. One study reported a toothache in a participant with depression following sham rTMS, but the time course, distribution and type of pain was not clear [1]. There was also no mention of dental procedures, oral and maxillofacial pathology, nor additional neurological pathologies. There are reports of face pain in response to active rTMS. For example, one study reported that a patient experienced tooth pain (location not specified) following active rTMS to the left DLPFC [4]. The treatment was ceased to alleviate the pain. Another patient report, again involving left DLPFC high-frequency rTMS, described a local 'dental twinge' near the upper left jaw that disappeared during the inter-train interval and diminished over the course of treatment [5]. The authors attributed the pain to "local irritation of the superficial temporal portion of the trigeminal nerve by the pulsating magnetic fields and projection via the N. buccalis into the dental region" [5]. Although the location of stimulation is consistent between those rTMS cases and the current sham rTMS case, raising the possibility that similar mechanisms are involved, we suspect that sensitisation within, or upstream, from the trigeminal (sub-caudate) nucleus is a more likely explanation and raises interesting possibilities for future investigation outside of the neuromodulation field.

Sensitisation within the trigeminal nucleus, most obviously via non-associative learning and activation of neuroinflammatory and vasoactive cells, will decrease the activation threshold of second order nociceptors. This has long been the primary aetiological model for trigeminal neuralgia [6,7]. The central changes are often attributed to injury, pathogenic invasion, compression or dystrophy of the trigeminal nerve [8]. The bioresonance theory suggests that certain frequency non-noxious peripheral input can trigger second order nociceptors [9]. Upstream, altered thalamo-cortical connectivity and default mode network changes have been identified in those with trigeminal neuralgia and proposed as possible causes

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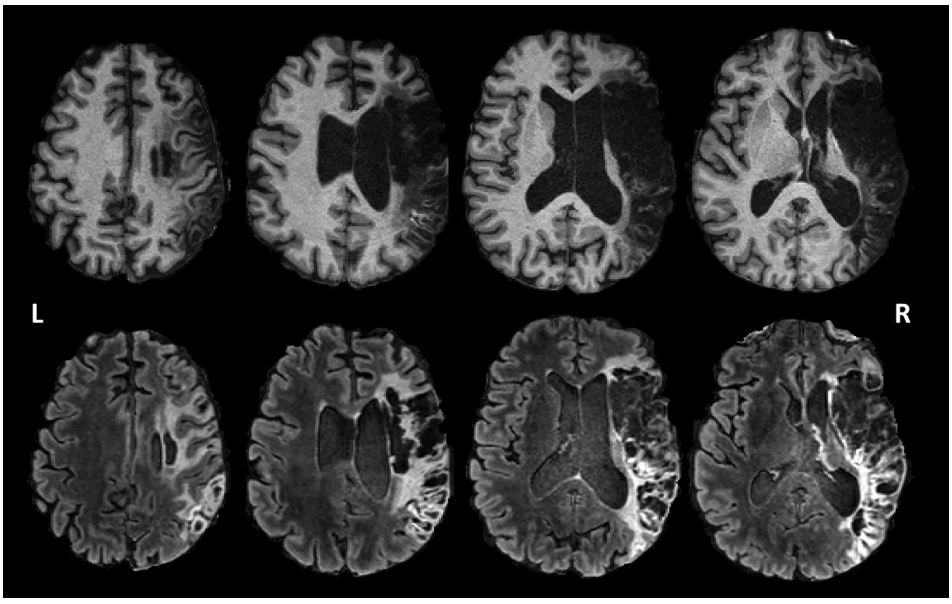

Fig. 1. Structural magnetic resonance imaging in the axial plan demonstrating a significant right hemispheric lesion. Top row, T1 weighted images (MPRAGE, voxel 1 mm × 1 mm × 1mm, repetition time 2300 ms, echo time 2.98 ms, flip angle 9°). Bottom row, T2 fluid-attenuated inversion recovery images (voxel 0.5 mm × 0.5 mm × 0.5mm, repetition time 5000 ms, echo time 393 ms).

of the condition [10]. In each case, a non-physiological stimulation of one branch of the trigeminal nerve may be sufficient to evoke pain in the distribution of another.

According to Magstim, its sham rTMS coil (part-number 3950-23-00) produces an electromagnetic field strength of <0.3T. This is much lower than that produced by the active rTMS coil (0.8T, part-number 3910-23-00) and thought insufficient to stimulate the cortex, but may well be sufficient to activate trigeminal efferents under the coil. That this appeared to trigger trigeminal neuralgia-like pain in our participant raises an interesting opportunity: could we have identified a pre-clinical sign of trigeminal neuralgia? The participant did report dental work two weeks earlier which, although without symptoms, may have initiated local irritation. Alternatively, perhaps the recognised causes of trigeminal neuralgia – dystrophy, compression or disease of the peripheral nerve – were underway in this participant but not yet causing spontaneous symptoms. Of course, we cannot ignore the fact that this participant had sustained a stroke, but we can see no clear mechanisms by which his stroke would impart this effect.

We have reported this adverse event for three reasons: our experience clearly shows that ipsilateral face pain is possible with sham rTMS and other researchers should be aware of this possibility; it may be prudent for future studies targeting the DLPFC to carefully question participants about recent dental pathologies or procedures; the potential of non-physiological stimulation such as that involved in sham or real TMS to identify pre-clinical trigeminal neuralgia seems worthy of exploration.

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