

## Bilateral vs. unilateral repetitive transcranial magnetic stimulation to treat neuropathic orofacial pain: A pilot study

To the Editor

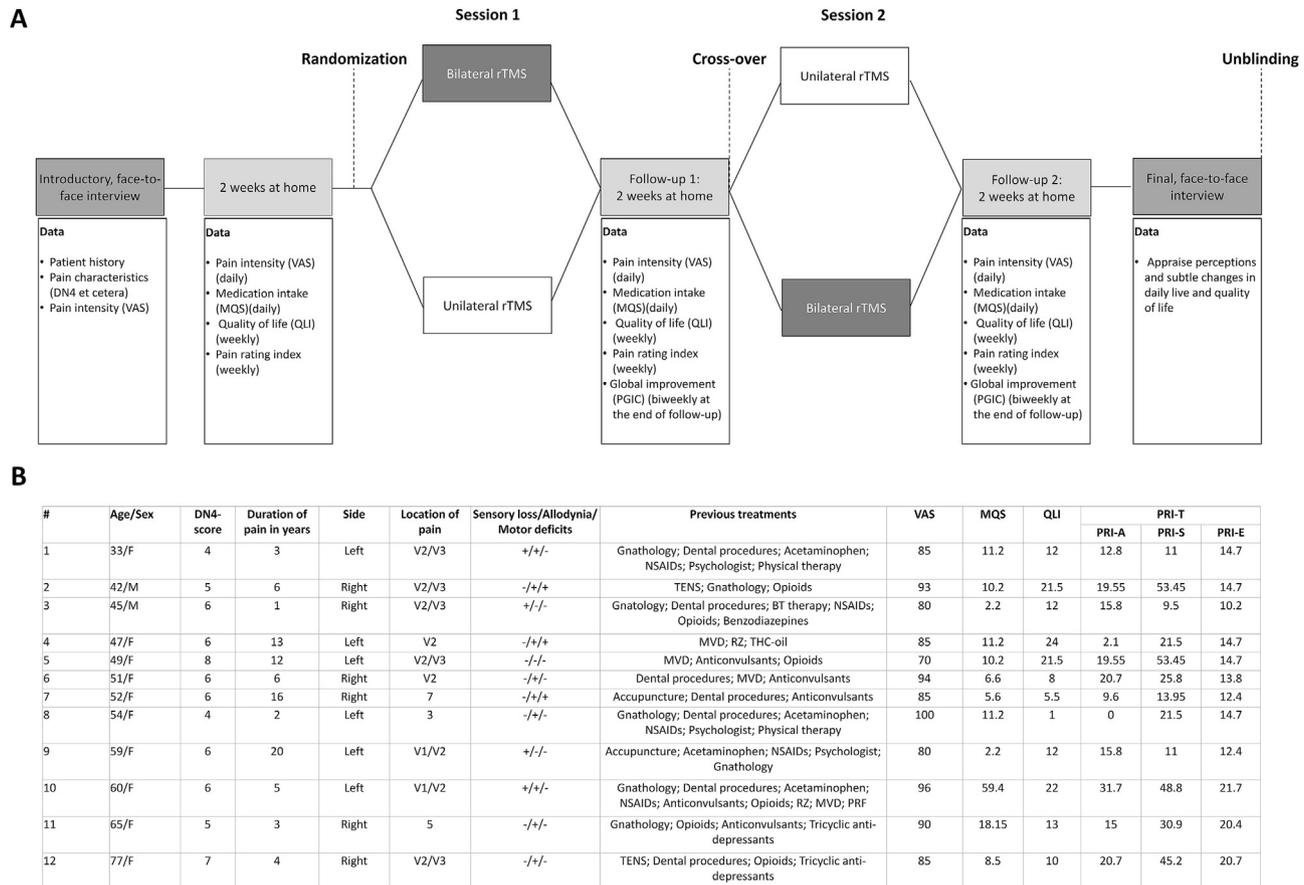
Neuropathic orofacial pain can be caused by various disorders that originate in the central- or peripheral nervous system [1]. One of these disorders includes painful trigeminal neuropathy for which an effective management can be difficult to establish, when pharmacotherapy fails. This has led to the search for new treatment options, e.g., transcranial magnetic stimulation of the primary motor cortex (TMS). TMS uses electromagnetic induction to influence cortical excitability [2,3]. Orientation of the coil and stimulation intensity were found to influence neurons in a different fashion [4]. TMS pulses can be applied singly, but for therapeutic use, multiple pulses are rapidly applied (repetitive TMS (rTMS)). In general, rTMS as a treatment for pain is delivered over the contralateral hemisphere with regard to the pain site with an anteroposterior orientation of the coil [3]. Nevertheless, a bilateral activation pattern of the trigeminal nociceptive system has recently been observed and explained anatomically [5,6], leading to the hypothesis that bilateral rTMS could possibly be more effective than unilateral rTMS for painful trigeminal neuropathy.

The local ethical review board approved the protocol and all participants gave written informed consent prior to inclusion. Twelve patients (mean age:  $52.9 \pm 11.5$  years; two males/ten females) with a median pain duration of 5.5 years (1–20 years) were included for this study. All patients received a bilateral and unilateral rTMS-session in a random order (Fig. 1A). The effects of both sessions were evaluated with 1) the pain intensity visual analogue scale (VAS); 2) subsets of the McGill pain questionnaires (i.e., the quality of life index (QLI) and pain rating index (PRI)); 3) the medication quantification scale (MQS) and; 4) the patient global impression of change (PGIC). All evaluations took place twice before the rTMS-sessions, and twice after each rTMS-session. At the end of the study, individual, semi-structured, face-to-face interviews were conducted by D.H. in order to appraise perceptions and subtle changes in quality of daily live. rTMS was delivered with a biphasic pulse configuration using a MagVenture C-B60 Butterfly coil (70mm) connected to a MagPro-X100 stimulator (MagVenture®, Farum, Denmark) with a tangential position to the scalp in a posterior-anterior direction,  $45^\circ$  from the midline to align it perpendicular to the primary motor cortex. The position of the hand notch on the primary motor cortex was mapped using exploratory single pulses and its location was saved using neuronavigation software (Brainsight, Rogue Resolutions Ltd, Cardiff CF10 1AF, United Kingdom). Resting motor threshold was determined and defined as the lowest intensity eliciting a visual motor response of the contralateral interosseous muscles after delivering a single pulse.

Stimulation intensity was set at 80% of the resting motor threshold to prevent involuntary muscle responses during the intervention and because stimulation performed above the motor threshold is not associated with better outcome [7,8]. Furthermore, strict somatotopic targeting of the facial region on the primary motor strip of rTMS has not shown to be critical for improving neuropathic orofacial pain [9]. Patients received ten 10s-trains of 10Hz with an inter-train interval of 50 seconds, totalling in 1000 pulses per hemisphere. The position of the coil was secured online using the neuronavigation. Sham rTMS was performed by using the same stimulation parameters, tilting the coil away from the patients' scalp in a 90-degree angle.

Fig. 1B provides the characteristics and scores at baseline. Mean VAS-scores after bilateral- ( $49.9 \pm 21.9$  points) and unilateral rTMS ( $67.0 \pm 22.0$  points) were significantly different ( $p = 0.014$ , 95%-CI 4.1–29.0 points) in favour of bilateral rTMS. QLI scores after bilateral- ( $10.9 \pm 5.1$  points) and unilateral rTMS ( $13.2 \pm 16.1$  points) were not significantly different ( $p = 0.634$ , 95%-CI -8.0–12.8 points). MQS-scores obtained after bilateral rTMS ( $8.9 \pm 9.8$  points) did not differ ( $p = 0.279$ , 95%-CI -2.1–6.7 points) from scores acquired after unilateral rTMS ( $11.1 \pm 15.9$  points). Mean scores of PRI-T after bilateral- ( $46.5 \pm 27.4$ ) and unilateral rTMS ( $55.5 \pm 27.9$ ) were not significantly different ( $p = 0.171$ , 95%-CI -4.6–22.5 points). This was also the case for all different descriptors included in the PRI-T. Bilateral- and unilateral rTMS elicited mean PGIC-scores of  $5.5 \pm 1.0$  points and  $3.0 \pm 1.2$  points, which were found to be significantly different ( $p < 0.0001$ , 95%-CI -1.5–3.4 points). Qualitative assessment suggested a notable positive change in daily quality of life after the bilateral session for eleven patients, whereas this was not reported after unilateral rTMS. Patients reported changes on social-, physical-, emotional- and material well-being. For example, patients reported to experience favorable changes regarding their daily mood, whereas others reported to be more at ease during the day.

This is the first study to show that bilateral rTMS yields significantly greater pain relief as measured by VAS scores as compared to unilateral rTMS in patients with painful trigeminal neuropathy. This observation is supported by the PGIC scores and the subjective changes suggested during the qualitative assessments. The effects of rTMS on the specific brain networks involved in nociceptive processing and modulation remain largely elusive. Possibly, the presence of a bilateral system, as described by others before [5,6], could play an important role in painful trigeminal neuropathy, especially for conditions which affect the trigeminal nerve and its branches. Several studies found that rTMS is capable of relieving pain by modulating various parts of the pain network, including



**Fig. 1. A Study-design.** DN4: douleur neuropathique 4 questions; MQS: medication quantification scale; PGIC: patient's global impression of change; QLI: quality of life index; VAS: visual analogue scale.

**B Patient demographics and characteristics at baseline.** A: affective component; BT therapy: botulinum toxin therapy; DN4: douleur neuropathique 4 questions; E: evaluative component; F: female; M: male; MVD: microvascular decompression; MQS: medication quantification scale; NSAIDs: non-steroidal anti-inflammatory drugs; NWC-T: number of words chosen-total; PRF: pulsed radiofrequency thermocoagulation; PRI-T: pain rating index total score = PRI-A + PRI-S + PRI-E; QLI: quality of life index; RZ: rhizotomy of the trigeminal root; S: somatosensory component; TENS: transcutaneous electrical neurostimulation; V1: ophthalmic dermatome; V2: maxillary dermatome; V3: mandibular dermatome; VAS: visual analogue scale.

the thalamus (for a review see Ref. [10]). Since only the ipsilateral thalamus has been described to be influenced by rTMS over the primary motor cortex and both thalami are activated by unilateral trigeminal stimuli [5], this could explain the diminished effectiveness of unilateral rTMS in comparison with bilateral rTMS, as shown here. Limitations of this study concern its limited sample size and the difficulty of blinding patients; subjects may still notice differences in the intensity of the sensory input after tilting the coil [3]. Also, the limited sample size makes it difficult to draw firm conclusions. Nevertheless, these preliminary findings underline the need for future studies investigating the effects of bilateral rTMS in painful trigeminal neuropathy failing conventional treatment.

### Conflicts of interest

The authors declare that they have had no conflict of interest in the conduction of this research.

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D.J.H.A. Henssen\*

*Department of Anatomy, Radboud University Medical Center,  
Nijmegen, the Netherlands*

*Donders Institute for Brain, Cognition & Behavior, Radboud University  
Medical Center, Nijmegen, the Netherlands*

*Department of Neurosurgery, Radboud University Medical Center,  
Nijmegen, the Netherlands*

W. Hoefsloot

*Department of Anatomy, Radboud University Medical Center,  
Nijmegen, the Netherlands*

P.S.M. Groenen

*Department of Anatomy, Radboud University Medical Center,  
Nijmegen, the Netherlands*

A.M. Van Cappellen van Walsum

*Department of Anatomy, Radboud University Medical Center,  
Nijmegen, the Netherlands*

E. Kurt

*Department of Neurosurgery, Radboud University Medical Center,  
Nijmegen, the Netherlands*

T. Kozicz

*Department of Anatomy, Radboud University Medical Center,  
Nijmegen, the Netherlands*

*Department of Clinical Genomics and Biochemistry and Molecular  
Biology, Mayo Clinic, Rochester, USA*

R. van Dongen

*Department of Anesthesiology, Pain and Palliative Care, Radboud  
University Medical Center, Nijmegen, the Netherlands*

D.J.L.G. Schutter

*Donders Institute for Brain, Cognition & Behavior, Radboud University  
Medical Center, Nijmegen, the Netherlands*

R.H.M.A. Bartels

*Department of Neurosurgery, Radboud University Medical Center,  
Nijmegen, the Netherlands*

\* Corresponding author. Department of Anatomy, Radboud  
University Medical Center, Nijmegen, the Netherlands.

*E-mail address:* [dylan.henssen@radboudumc.nl](mailto:dylan.henssen@radboudumc.nl) (D.J.H.A. Henssen).

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