

rTMS parameters and that subjects should have clearly defined pain conditions suitable for motor cortex rTMS. Although we agree for the need to standardise all assessment tools, condition-specific instruments, and consensus-recommended metrics, we believe that it is too early to standardise rTMS parameters or to limit treatment option to groups amenable to motor cortex stimulation and that a degree of innovation is still required.

As noted by Klein et al., the best methods for using rTMS in the treatment of pain are yet to be established and more trials are needed to optimize design. Although current analyses suggest that targeting the motor cortex and treatment courses of at least 10 days of acute stimulation are “best,” neither have been definitively explored through direct comparison of stimulation site, protocol length, and their application across heterogeneous pain groups. Existing meta-analyses exploring the clinical efficacy of rTMS for pain all report a clear bias in the number of motor cortex investigations vs other brain sites (eg, dorsolateral prefrontal cortex and parietal cortex).<sup>5,7</sup> The importance of alternative brain targets may differ depending on the pain syndrome and the resulting therapeutic outcomes (eg, sensory, affective, or cognitive modulation). This may be critical for disorders of diffuse pain experience such as fibromyalgia in which a clear motor cortex target site or laterality is not definable.

In addition, length of stimulation in relation to best treatment outcomes has not been determined. There is therefore no consensus whether a 10-day induction treatment course followed by intermittent maintenance sessions (used in several rTMS for pain investigations [eg, Ref. 6]) provides better treatment efficacy than a 4- or 6-week daily treatment course, the latter of which is standard for treatment-resistant depression. It is possible that a 10-day acute protocol may be limiting the degree of response, and possibly even the number of responders considering symptomatic relief is generally not observed until 2 to 3 weeks after treatment in depression.<sup>3</sup>

In short, we are in no doubt that the proposed guidelines for pain treatment research will improve future research; however, we believe that it is too soon to standardise rTMS parameters and protocols (see emerging positive findings on Theta Burst Stimulation in depression<sup>1,2</sup>). We support the execution of more well-designed clinical trials and encourage the inclusion of exploration within this space.

### Conflict of interest statement

The authors have no conflicts of interest to declare.

B. M. Fitzgibbon is supported by a National Health and Medical Research Council (NHMRC, Australia) Early Career Fellowship [1070073]. K. E. Hoy is supported by a NHMRC Career Development Fellowship [1082894]. P. B. Fitzgerald is supported by an NHMRC Practitioner Fellowship [606907]. P. B. Fitzgerald has received equipment for research from MagVenture A/S, Medtronic Ltd, Cervel Neurotech, Neuronetics Inc, and Brainsway Ltd and funding for research from Cervel Neurotech and Neuronetics Inc.

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<http://dx.doi.org/10.1097/j.pain.0000000000000503>

### Reply

#### Letter To Editor:

We thank Fitzgibbon et al. for their thoughtful comments, and we agree that more research is needed to confirm the “best” parameters for treating chronic pain with repetitive Transcranial Magnetic Stimulation (rTMS). The goal of our article<sup>1</sup> was to identify the key elements that should be reported in all publications to permit replication and to facilitate meta-analysis, and also to recommend that treatment variables be consolidated toward those demonstrated as most effective for pain targets. Furthermore, our suggestions applied only to clinical trials intended to support applications for regulatory approval of rTMS for treating chronic pain. Given the huge personal, societal, and economic costs of undertreated chronic pain, the path from basic research to clinical availability must be as direct as possible.

### Conflict of interest statement

A. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab, Neuroelectrics, Axilum Robotics, Magstim, and Neosync and is listed as an inventor on several issued and pending patents on the real-time integration of TMS with EEG and MRI. None of these patents is currently licensed or generating any license fees. M. Hallett may accrue revenue on U.S. Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil), and he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. M. Fox is listed as an

inventor in issued patents or patent applications on functional connectivity and guidance of TMS. The remaining authors have no conflicts of interest to declare.

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