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## Characterising the optimal pulse number and frequency for inducing analgesic effects with motor cortex rTMS

High- ( $\geq 5$ Hz), but not low-frequency ( $\leq 1$ Hz) rTMS (repetitive Transcranial Magnetic Stimulation) of the contralateral primary motor cortex (M1) can induce transient analgesic effects [5]. However, the impact of TMS frequency and pulse number remains poorly understood and may present an opportunity to optimise analgesic efficacy and promote long-term effects. Prior work indicated that a single session consisting of 2,000, but not 500 pulses of 10Hz rTMS, was necessary to induce a significant alleviation of neuropathic pain relative to sham stimulation [7]. At least 1000 pulses per session is recommended by the European Academy of Neurology, with the suggestion that increasing the pulse number may increase analgesic efficacy [2]. The most common dosage for chronic pain is 1000–2000 pulses per session, although up to 3000 pulses per session is cleared by the Food and Drug Administration (FDA) for treating major depression disorders. Regarding stimulation frequency, while 10Hz is most commonly employed in pain management, 20Hz M1-rTMS has also been demonstrated to be effective [4]. However, no direct comparison has been made between 10 and 20Hz rTMS.

Here we performed a single-blind, sham-controlled, crossover study to investigate the influence of pulse number and frequency on rTMS analgesia in a single session. Using cold pain threshold, we directly compared the analgesic efficacy of 3000 pulses with 1500 pulses of 10Hz rTMS over the M1 region. We also explored the analgesic influence of 3000 pulses of 20Hz rTMS. As session duration can affect rTMS analgesia [3], this third condition of 3000 pulses at 20Hz additionally balances pulse number and session duration. Before and after rTMS, we also assessed motor-evoked potential (MEP) amplitude for single pulse stimulation and long-interval cortical inhibition (LICI), to assess the impact of the differing rTMS doses on corticospinal excitability and GABA<sub>B</sub> mediated cortical inhibition. We hypothesised that 3000 pulses at 10Hz and 20Hz would achieve a better pain relief than 1500 pulses.

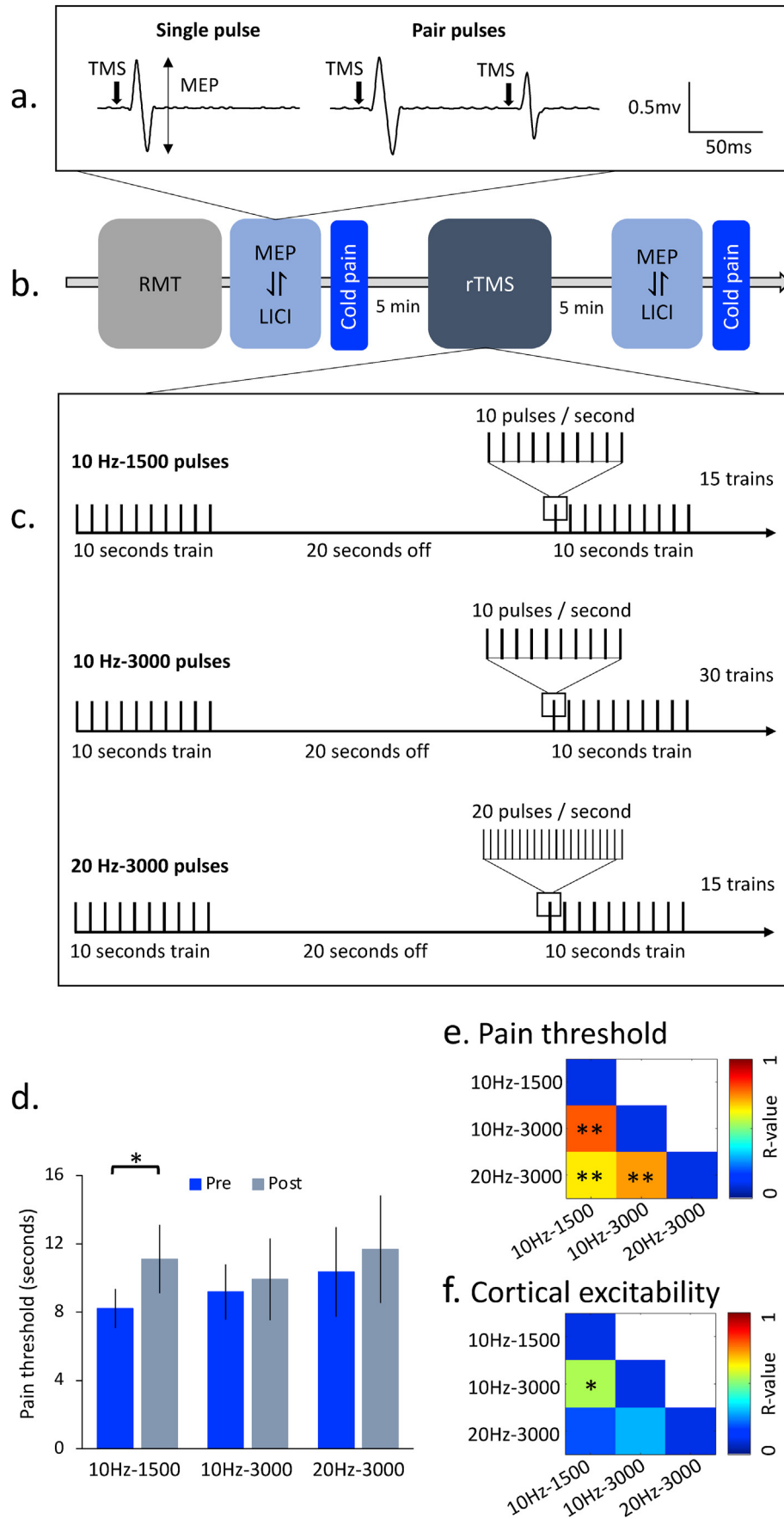
An a priori sample size calculation ( $\alpha = 0.05$ ,  $\beta = 0.8$ , effect size = 0.3), indicated a minimum of 24 participants for the study to be sufficiently powered. The effect size of 0.3 was estimated based on studies using the same stimulation protocol and cold pain assessment (e.g. Ref. [8]). A group of 29 healthy, right-handed, TMS eligible [9] participants were recruited to account for potential dropouts (ethical approval: 20201217). Three participants withdrew after the first session, data from 26 participants (age range: 18–28 years, mean  $\pm$  SD: 20  $\pm$  2.35, 10 males) were analysed.

Participants visited the lab three times, receiving one of 1500 pulses at 10Hz, 3000 pulses at 10Hz, or 3000 pulses at 20Hz at each session ( $\geq 72$  hours between sessions) (Fig. 1c). A sham condition was not included as 1500 pulses at 10Hz has been repeatedly

shown to reduce pain in sham-controlled studies [5]. Each session started with the assessment of resting motor threshold (RMT), using a figure-eight coil connected to a Magstim Rapid<sup>2</sup> system (Magstim Company Ltd., UK) delivering single pulses to the hand region of the left M1 at 5s  $\pm$  10% jitter intervals (Fig. 1b). RMT was determined by the minimum intensity to evoke MEPs  $>0.05$  mV in 5/10 trials and re-examined in each session. MEP and LICI were then assessed with single and paired pulse (100 ms) paradigms at 120% RMT (45° to the midline, handle pointing backward), with the sequence being randomised across participants (Fig. 1a). Coil position was measured relative to the nasion andinion to facilitate consistent re-positioning of the coil between sessions. Participants were then subjected to cold pain at 5 °C using circulating cold water with the right hand. Baseline temperature of the right hand was initially controlled by immersing it into water at room temperature for 30 seconds. Pain threshold was recorded as the time (in seconds) at which participants first reported cold pain. As pain can affect corticospinal excitability, participants then took a break for 5 min during which they inserted the right hand into a hand warmer ( $\sim 40$  °C) to recover from cold pain. rTMS was then delivered to the left M1 (80% RMT, parallel to the midline, handle pointing back), dependent on the stimulation protocols which were randomised within participants. Corticospinal excitability and cold pain were re-evaluated following a 5-min interval.

MEP amplitude was measured from peak-to-peak. LICI was calculated with formula  $[1 - (\text{MEP}_{\text{conditioned}}/\text{MEP}_{\text{unconditioned}}) \times 100]$ . Three (Condition) by two (Time) repeated measures ANOVAs revealed a significant condition  $\times$  time interaction effect on pain threshold ( $F_{1,83, 45.84} = 4.81$ ,  $P = 0.01$ ,  $\eta_p^2 = 0.16$ ) (Fig. 1d). Pairwise comparisons (Bonferroni corrected at 0.05) indicated that pain threshold was increased only in the 10Hz 1500 pulse condition ( $P_{\text{Bonf}} = 0.01$ ) from Pre- (mean = 8.21) to Post-stimulation (mean = 11.11). No main or interaction effect was found in MEP or LICI (see *Supplementary Material*). Changes in pain threshold were positively correlated across all rTMS conditions (all  $P_{\text{Bonf}} < 0.01$ ) (Fig. 1e). There was also a positive correlation in cortical excitability changes following 10Hz conditions ( $P_{\text{Bonf}} = 0.012$ ), but not between 10 and 20Hz conditions (Fig. 1f). With regard to side effects, two participants reported mild headache (scored 3 in 0–10 ratings) when receiving 3000 pulses at 10Hz, but this resolved by the end of the session.

Our data indicate that only 10Hz rTMS with 1500 pulses induced analgesic effects in healthy individuals subjected to cold pain, whereas 10 and 20 Hz stimulation with 3000 pulses had no effect. These results are surprising given the common expectation that a greater pulse number would induce stronger pain relief [2]. It is



**Fig. 1.** Study protocol and results. A) single pulse and paired-pulse protocols. B) Study protocol. C) The three stimulation protocols are indicated. D) shows the results of pain perception. Only 1500 pulses at 10Hz were able to increase pain threshold. E) Changes in pain threshold (Post - Pre) in the three stimulation conditions were positively correlated with each other (all  $P_{Bonf} < 0.01$ ). F) Change in single-pulse cortical excitability (Post - Pre) was significantly correlated in the 10Hz conditions ( $P_{Bonf} = 0.012$ ), but not between 10 and 20Hz conditions. \* denotes  $P < 0.05$ , \*\* denotes  $P < 0.01$ , Bonferroni corrected.

worth noting that our TMS protocol (80% RMT, 10-s trains) is similar, if not identical, to that employed in prior work (e.g. Ref. [8]). The present findings suggest that there may be no benefit of delivering more than 1500 rTMS (10Hz) pulses per session to achieve analgesic effects in healthy volunteers, warranting investigation in individuals with chronic pain. If these findings generalise, then a potential mechanism pertains to the homeostatic effect of pulse number on neuromodulatory effects. For example, cellular studies indicate that the neuromodulatory effects of 20–30 5 Hz bursts can be abolished by increasing this number to 70–100 bursts [10]. Similarly, recent work indicates unanticipated homeostatic effects of pulse number on the effects of theta burst stimulation [6].

Interestingly, individual-level changes in cortical excitability following rTMS were positively correlated between 10Hz conditions, but showed no relation to the changes elicited by 20Hz stimulation. This intriguing finding raises questions around the inherent assumption that plastic effects might generalise across different rTMS frequencies. Findings from this study revealed no group-level changes in MEP following 10Hz M1-rTMS delivered at 80% RMT. This is consistent with the literature in which rTMS analgesia over the M1 was not associated with corticospinal excitability measured by MEP [1], and typically stronger intensities are required to evoke changes in cortical excitability. Lastly, our data provide novel evidence that LIC1, a potential indicator of GABA<sub>B</sub> mediated cortical inhibition, is not associated with rTMS analgesia in the stimulation of the M1.

#### Declaration of competing interest

None declared.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.06.015>.

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