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Low-frequency rTMS is better tolerated than high-frequency rTMS in healthy people: Empirical evidence from a single session study

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ABSTRACT

Low-frequency and high-frequency repetitive transcranial magnetic stimulation (rTMS) are similarly efficacious for treatment-resistant depression. Low-frequency is posited to be better tolerated than high-frequency rTMS, however, this is not supported by empirical evidence to date. This study aimed to quantify and compare the tolerability of low-versus high-frequency rTMS. Twenty healthy participants (mean age 38.6 ± 13.9 years) underwent low- and high-frequency rTMS administered on left frontal, fronto-central and central sites at 100% resting motor threshold. For the low-frequency protocol, 60 s of 1 Hz stimulation was applied at each site and for the high-frequency protocol, 3 × 5 s trains of 10 Hz stimulation with a 30 s inter-train interval were applied at each site. Tolerance for each stimulation type was assessed immediately after stimulation through participant ratings of overall intensity of scalp sensations, pain, muscle twitching, discomfort and any other sensation. Low-frequency rTMS was significantly less intense than high-frequency rTMS in overall intensity, pain, muscle twitching (all $p < .01$) and discomfort ($p < .001$). Limitations of this study include the healthy participant sample and administration of a single session of rTMS. While further work is needed in clinical samples using typical rTMS treatment protocols, these data provide the first evidence that low-frequency is better tolerated than high-frequency. These findings may inform clinical practice of rTMS treatment for depression (and other illnesses) by supporting the application of low-frequency protocols.

1. Introduction

Low-frequency right sided repetitive transcranial magnetic stimulation (rTMS) and high-frequency left sided rTMS treatments are similarly efficacious for medication resistant depression (Cao et al., 2018; Chen et al., 2013). While rTMS is generally extremely well tolerated with a low rate of side effects or adverse events (Rossi et al., 2009), there is a general consensus that low-frequency is better tolerated than high-frequency. However, to our knowledge, there is no empirical evidence to date for differences in tolerability between these rTMS modalities.

The evidence that low-frequency is better tolerated than high-frequency has been reported through clinical observation (Fitzgerald and Daskalakis, 2013; Loo et al., 2008). Additionally, a meta-analysis characterised the frequency of side-effects (including headache, scalp discomfort, facial twitching, tearfulness, erythema and drowsiness) of low- and high-frequency rTMS and showed an increased occurrence of all side-effects with high-frequency, except for facial twitching which occurred more frequently with low-frequency (Slotema et al., 2010). This suggests that generally, low-frequency is more tolerable, however, differences were not statistically tested. The only study that has statistically compared tolerability between low- or high-frequency rTMS found no significant differences in spontaneously reported side-effects or drop-out rates (in depressed participants randomised to either low- or high-frequency protocols) (Dell'Osso et al., 2015). Furthermore, meta-analyses have not found differences in drop-out rates between these rTMS types, albeit only two clinical trials reported drop-out rates (Cao et al., 2018; Chen et al., 2013).

Accordingly, the aim of the current study was to conduct a preliminary investigation on the tolerability of low-versus high-frequency rTMS in the same group of individuals by comparing subjectively reported ratings of overall sensation, and sensations commonly reported during rTMS (i.e. pain, discomfort and muscle twitching).

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2. Materials and methods

2.1. Sample and procedure

Twenty healthy participants aged between 18 and 65 years (range = 20–62; mean = 38.6 ± 13.9) were recruited via flyers displayed in Melbourne, Australia at the Monash Alfred Psychiatry Research Centre, Alfred Hospital, Monash University, public notice boards and on social media. Four participants were University students and 3 participants had a prior experience or some knowledge of TMS. Participants were screened for psychopathology with the M.I.N.I International Neuropsychiatric Interview (Sheehan et al., 1998). Exclusion criteria were contraindication to TMS (including but not limited to the presence of metal inside the head excluding dental work, being a professional driver (to reduce the risk of any serious adverse event occurring whilst driving), pregnancy or currently breast-feeding and history of any neurological disorder) and history of or current cardiac abnormalities. Participants were asked to refrain from nicotine, caffeine and alcohol consumption prior to study assessment for at least 3 h, 2 h and 12 h, respectively.

The aims of the current study were to assess participants' experience of each type of rTMS and were explained within the participant information and consent form of a broader study (Kaur et al., unpublished data). Note: the rTMS protocols were designed as part of the broader study which provided the opportunity to undertake the current preliminary investigation on the tolerability of low- and high-frequency rTMS. Prior to commencing the session, participants were told that they would receive low- and high-frequency rTMS and they would be asked about their experience after each type but they were not told which order they would receive each type or which sensations they were to rate. Participants first underwent resting motor threshold (RMT) assessment. Low-frequency and high-frequency rTMS were then administered, with the order of frequency type counter-balanced across participants. Participants completed a visual analogue scale immediately after each rTMS protocol. This study was approved by the Alfred Hospital and Monash University Human Research Ethics Committees and written informed consent was provided by all participants, in keeping with the declaration of Helsinki.

2.2. Repetitive transcranial magnetic stimulation

Stimulation was be applied using a Medtronic MagPro stimulator and a 70-mm diameter figure-of-8 coil. The TMS coil was positioned with the centre of the coil in contact with the head and at a 45° angle from the midline, with the coil handle facing backwards and away from the midline. Single-pulse TMS was applied to the left motor cortex to measure the RMT (mean RMT = 49.8% ± 5.6) using electromyography using standard published methods (Fitzgerald et al., 2002). The low- and high-frequency rTMS protocols were applied to the 10–20 EEG system left hemisphere sites F3, FC3 and C3 (in accordance with the protocol of a broader study; Kaur et al. unpublished data). Custom made EEG caps with marked 10–20 sites were used to navigate to each stimulation site. The low-frequency protocol was a single 60 s train of 1 Hz at 100% of RMT applied at each site, with a 30 s interval between sites (180 pulses in total over 4 min and 30 s with 3 min of stimulation). The high-frequency rTMS protocol was three, 5 s trains of 10 Hz at 100% of RMT at each site, with a 30 s inter-train interval (450 pulses in total over 5 min and 15 s with 2 min and 15 s of stimulation).

2.3. Visual analogue scale

The visual analogue scale quantified tolerability of rTMS protocols immediately after each rTMS type. On a scale of 0–10 (0 representing no sensations and 10 representing extremely strong sensations), participants rated: i) overall intensity of any scalp sensations and, intensity of ii) pain, iii) muscle twitching, iv) discomfort and v) any other sensation to be specified.

Table 1
Descriptives, paired-sample *t* statistics and p values for visual analogue scale ratings of overall intensity, pain, discomfort and muscle twitching for high-frequency and low-frequency repetitive transcranial magnetic stimulation. *Note*: SD = standard deviation; HF = high-frequency; LF = low-frequency.

	Mean ± SD	Paired samples *t*-test [p]
HF overall intensity	5.9 ± 1.9	*t* (19) = 3.9 [.001]
LF overall intensity	4.1 ± 2.1	
HF pain	2.6 ± 2.3	*t* (19) = 4.1 [.001]
LF pain	1.0 ± 1.3	
HF discomfort	3.9 ± 2.7	*t* (19) = 4.4 [< .001]
LF discomfort	2.0 ± 2.1	
HF muscle twitching	4.0 ± 1.8	*t* (19) = 2.9 [.009]
LF muscle twitching	2.5 ± 2.2	

2.4. Statistical analyses

SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) for Windows was used to perform statistical analyses. Data were assessed for normality with the Kolmogorov-Smirnov test and non-normal data were transformed via square root. Paired samples t-tests determined significant differences between rTMS types on each scale item. Alpha was adjusted to 0.013 using Bonferroni correction to control for multiple comparisons.

3. Results

Low-frequency rTMS was rated significantly less intense than high-frequency rTMS across all variables: that is, overall intensity, pain, muscle twitching (all $p < .01$) and discomfort ($p < .001$), as shown in Table 1 and Fig. 1. Pain behind the eye (n = 1) and headache (n = 1) were reported with high-frequency stimulation. Jaw discomfort (n = 1) and tingling sensation in the hand (n = 1) were reported with low-frequency stimulation.

4. Discussion

The current study is the first to show that low-frequency is more tolerable than high-frequency rTMS as it is significantly less intense to experience and, is associated with significantly less pain, muscle twitching and discomfort. These findings are in keeping with documented clinical observations (Fitzgerald and Daskalakis, 2013; Loo et al., 2008) and the frequency of side effects previously reported for the rTMS types (Slotema et al., 2010). Coupled with the lack of evidence that high-frequency is therapeutically superior to low-frequency rTMS (Cao et al., 2018; Chen et al., 2013), this research encourages greater consideration for low-frequency protocols in the treatment of depression (and other illnesses). In addition, low-frequency rTMS is purportedly associated with a lower seizure occurrence (Rossi et al., 2009) and has even been suggested lower seizure risk (Fregni et al., 2006), although further study to confirm this is required.

Unlike in previous investigations (Dell'Osso et al., 2015; Slotema et al., 2010), a significant strength of this study is that low- and high-frequency protocols were administered on the same hemisphere (i.e. left) and in the same individuals. Therefore, the findings cannot be attributed to differences in stimulation intensities, pain thresholds, psychological factors that might influence the experience of pain (Linton and Shaw, 2011) or the subjective experience of stimulation across individuals.

Nevertheless, there are some limitations in the applicability the current findings for clinical practice, including the absence of a clinical sample. While there is no published data on the experience of rTMS in healthy compared with clinical samples, there is some evidence suggesting altered pain perception in depression (Thompson et al., 2016).

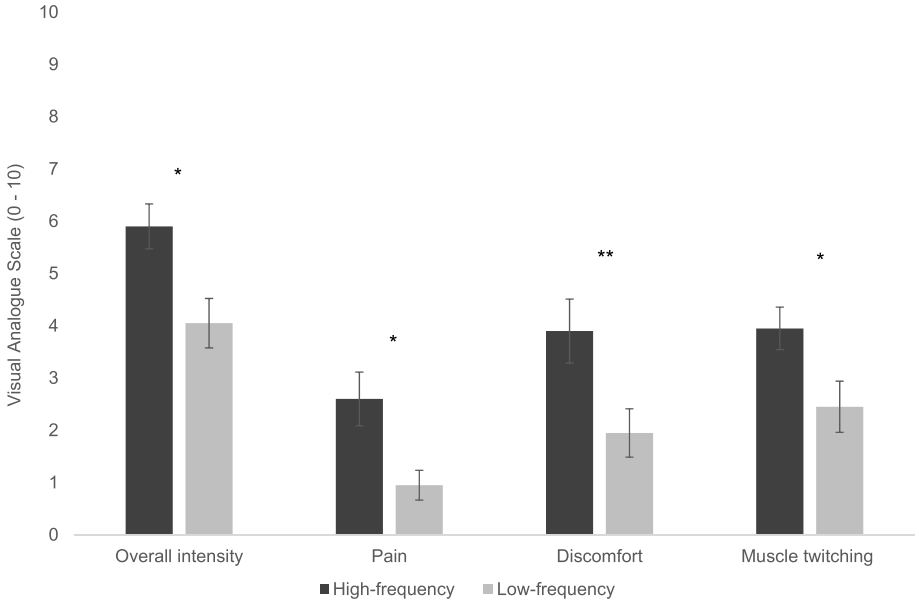

Fig. 1. Visual analogue scale mean ratings of overall intensity, pain, discomfort and muscle twitching for high-frequency (black) and low-frequency (grey) repetitive transcranial magnetic stimulation, where 0 represents no sensation and 10 represents extremely strong sensations. Error bars represent standard error of the mean. *Note*: ** denotes *t*-test significance at $p < .001$; *denotes *t*-test significance at $p < .01$.

Other limitations relate to differences between the rTMS protocol used here and the typical rTMS protocol used in clinical practice. Firstly, tolerability of rTMS was quantified from one rTMS session which was shorter (~10 min of stimulation) than the average session (~20 min of stimulation). This may have limited the current study given that stimulation may become more tolerable over time and with subsequent sessions. Notwithstanding, the initial experience of rTMS is relevant since it is likely to influence treatment compliance. Three sites (frontal, fronto-central and central) were stimulated and while this was consistent for both rTMS types evaluated in this study, this experience is likely to have varied from a typical rTMS treatment session for depression where one frontal site would be stimulated. In addition, the high-frequency protocol had a greater total number of pulses and shorter time of active stimulation (450 pulses and ~2 min, respectively) compared with the low-frequency protocol (180 pulses and ~3 min, respectively). While this may have affected the results, it is very difficult to compare high- and low-frequency rTMS protocols in this manner because their application is inherently disparate, with similar differences between high- and low-frequency rTMS parameters in clinical practice. Lastly, a power calculation was not undertaken to determine the sample size of this study as there are no empirical data to base a power calculation on; this should be considered in further research.

In summary, the current study provides the first empirical evidence that low-frequency rTMS is better tolerated, in terms of overall intensity of scalp sensations, pain, muscle twitching and discomfort, compared to high-frequency rTMS. While further research on clinical samples and using typical rTMS treatment parameters are required to replicate the current findings, this work advocates greater consideration of low-frequency rTMS in clinical practice in order to provide patients receiving rTMS with the most efficacious and tolerable protocols.

Conflicts of interest

PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Neuronetics and Brainsway Ltd and funding for research from Neuronetics. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. We have no other conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.03.015.

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