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A comparative study of the effects of repetitive paired transcranial magnetic stimulation on motor cortical excitability

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Abstract

Objectives: Various methods of application of repetitive transcranial magnetic stimulation (TMS) have been evaluated for their potential capacity to alter motor cortical excitability. Initial research suggests that the repetitive application of paired TMS pulses (repetitive paired pulse TMS (rppTMS)) may have greater effects on cortical excitability, perhaps through the facilitation of I-wave interaction. We aimed to compare the post-train effects of 15 min trains of rppTMS to investigate the potential therapeutic application of this technique as well as to compare it to a standard high frequency repetitive TMS paradigm.
Methods: Ten normal subjects received three 15 min sessions of rppTMS, 5 Hz high frequency rTMS and sham TMS in randomised order. rppTMS consisted of a single train of 180 pulse pairs (0.2 Hz, 1.5 ms inter-stimulus interval, supra-threshold intensity) administered over 15 min. The rTMS condition involved 750 pulses provided in 5 s 5 Hz trains with a 25 s inter-train interval at 90% of the RMT. Motor evoked potential size and cortical silent period duration were assessed before and after each session.
Results: There were no significant changes in cortical excitability produced by any of the stimulation conditions. Five hertz rTMS produced an increase in cortical silent period duration ($p = 0.004$) which was not affected by rppTMS.
Conclusions: Fifteen minutes trains of 1.5 ms rppTMS do not substantially increase post train cortical excitability. Repetitive brief trains of 5 Hz rTMS also do not alter excitability but appear to effect cortical inhibition.
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Keywords: Repetitive transcranial magnetic stimulation; Cortical excitability; Paired pulse; Motor cortex

1. Introduction

A considerable number of studies have investigated the effects of repetitive transcranial magnetic stimulation (rTMS) trains at various frequencies on the excitability of the motor cortex (Fitzgerald et al., 2006a). Generally, high frequency trains have been shown to produce transiently increased cortical excitability, as assessed by a post-train increase in evoked motor potential (MEP) size (Fitzgerald et al., 2006a). In contrast, low frequency trains (usually ∼1 Hz) have been shown to reduce MEP size (Fitzgerald et al., 2006a). These forms of stimulation are being widely assessed for use in the treatment of a number of psychiatric and neurological disorders (for example (Fitzgerald et al., 2003; George et al., 1995; Hoffman et al., 2003)). More recently a number of novel forms of TMS have been developed for the purpose of enhancing stimulation effects. One of these approaches has been the repetitive application of pairs of pulses (repetitive paired pulse TMS (rppTMS)). This involves the application of the pairs at very low frequency (for example 0.2 Hz). The first rppTMS study involved pulses at a 3 ms interval that were shown to produce a substantial decrease in cortical excitability (Khedr et al., 2004; Sommer et al., 2002). More recently, Thickbroom et al. have shown that pairs at a 1.5 ms interval and frequency of 0.2 Hz produce an increase in motor cortical excitability that appears to be substantially greater than that previously seen with high frequency rTMS

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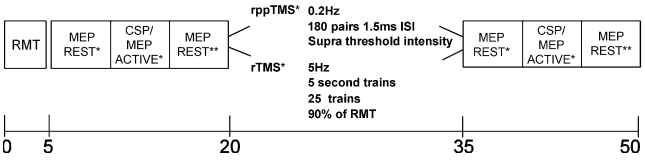

Fig. 1. Experimental timeline. RMT = resting motor threshold, MEP = motor evoked potential, CSP = cortical silent period, rTMS = repetitive transcranial magnetic stimulation, rppTMS = repetitive paired pulse transcranial magnetic stimulation, ISI = interstimulus interval. (*) Procedures conducted with Magstim 200/Bistim equipment and (**) procedures conducted with Magstim Super-Rapid.

protocols (Thickbroom et al., 2006). In particular, this study reported increases in MEP size of the order of 400% during the train and of similar magnitude in the 10 min post-train. However, this study did not directly compare the effects of rppTMS to a standard high frequency condition.

If repetitive paired stimulation is able to be used to markedly enhance cortical excitability, it would have some significant advantages over high frequency stimulation. This method would result in considerably less stress on equipment used and should be substantially more comfortable for individual subjects. However, further confirmation of the strengths of these effects is required prior to the conduct of therapeutically oriented trials. In addition, the 30 min of rppTMS utilised in the study of Thickbroom et al. is considerably longer than the duration of rTMS provided in most previous rTMS trials. Although the 'in train' data provided by Thickbroom et al. suggest that cortical excitability is markedly increased after only 15 min (Thickbroom et al., 2006; see Fig. 1), it is not clear if these changes would be apparent if post-train effects were measured at this time. Therefore, we conducted a study to assess the post-train effects of a shorter duration of rppTMS (15 min) on cortical excitability to investigate if this is potentially useful as a therapeutic intervention. We also included a high frequency (5 s trains of 5 Hz rTMS) comparator condition as well as a sham stimulation condition. This was chosen as it is a commonly used application of rTMS used in treatment trials (for example Fitzgerald et al., 2006b; George et al., 2000; Rumi et al., 2005). The conditions were not fully matched in pulse number or intensity but chosen to be matched in time and be provided as approximate potential treatment protocols, for example as may be used in TMS treatment of depression.

2. Methods

2.1. Subjects

Ten normal subjects were studied (mean age 27.3 ± 3.97 years, six females, four males). The Human Subject and Ethics Committee of Bayside Health, The Alfred Hospital approved the study and all subjects gave written informed consent. All subjects were screened with a brief clinical interview for current or past psychiatric or neurological disorders and were free of any psychoactive drugs or medication. Menstrual cycle stage was not controlled in the female subjects.

2.2. Study procedure

All subjects were studied on three randomly ordered occasions, at least one week apart. One testing session involved a 5 Hz rTMS condition, one session an rppTMS condition and one a sham condition which was a 'mock' 5 Hz condition. In each experiment, cortical excitability and inhibition was measured before and immediately after the conditioning train in the same order. In all subjects, for all sessions, we initially measured resting and active MEP size and cortical silent period (CSP) duration with a Magstim 200 (used in the rppTMS condition) to ensure our primary variable of interest was assessed within the window (10 min) that post train effects were found previously (Thickbroom et al., 2006). As there is evidence that the effects of rTMS trains are specific to the stimulator used to induce them (Lang et al., 2006), resting MEP size was measured primarily with a Magstim 200 (used in the rppTMS condition) but also subsequently with a Magstim SuperRapid (used for rTMS). Active MEP size and CSP duration were measured with the Magstim 200 only.

2.3. Electromyographic (EMG) recordings

EMG was recorded from the right abductor pollicis brevis (APB) muscle using self-adhesive electrodes (Medtronic). One electrode was placed over the muscle belly and another on the dorsal aspect of the interphalangeal joint of the thumb. An earth electrode was placed on the mid-forearm. All EMG signals were amplified and filtered (low pass 2.4 kHz, high pass 10 Hz). They were sampled (rate 10 kHz) using a Digidata 1320A Data Acquisition board and pCLAMP 8.0 software (Axon Technologies) run on a standard PC. EMG recordings were made at rest and during sustained contraction with visual display feedback.

2.4. Transcranial magnetic stimulation

Subjects were seated in a reclining chair with a headrest for stabilisation of the head. Single and paired pulse stimulation was administered with a figure-of-8 coil (70 mm diameter, peak magnetic field 2.2 T) using two Magstim 200 magnetic stimulators (Magstim, UK) linked with a Bistim module (Magstim, UK). rTMS was administered with a Magstim SuperRapid (Magstim, UK). The stimulators were triggered through the pCLAMP software and Digidata 1320A Data Acquisition board. At the start of the procedure, the optimal site for stimulation of the APB muscle was established. The coil was placed on the scalp at the estimated position of the left motor cortex (5 cm lateral to and 2 cm anterior to the vertex). The coil was moved until the position that produced the largest motor evoked potential (MEP) response at supra-threshold intensity was located. This position was marked on the scalp and used throughout the experiment. The coils were held tangential to the scalp with the handle pointing back and away from the midline at 45°. The induced current flow was posterior to anterior in the cortex perpendicular to the central sulcus. The coil orientation was identical to that used for single and paired pulse stimulation. The resting motor threshold was measured with EMG methods at the site of optimal

APB stimulation as the lowest stimulation intensity at which 5 MEPs of greater than 50 μV were recorded out of 10 stimuli with stimulation provided at 0.2 Hz.

2.5. Measurement procedure

Measures of MEP size and CSP duration were made before and after the rTMS or rppTMS conditioning train in the same order (see Fig. 1). For all subjects, testing of the measures of corticospinal excitability was completed within 15 min of the completion of the rTMS train. As we were modulating the activity of the motor cortex with two different TMS systems with differing pulse characteristics (i.e. Magstim 200 with the square wave pulse and the SuperRapid with a sine wave pulse) and it is possible that these could affect differing aspects of motor cortical activity, we chose to measure cortical excitability with both systems. We measured MEP size at rest and during a sustained tonic contraction with the Magstim 200 connected to the Bistim module and we measured MEP size at rest with the SuperRapid device. For measurement using each condition (rest with the two devices and tonic contraction with the Magstim 200), we collected 10 sweeps of data during stimulation at 120% of the RMT. We monitored the degree of tonic contraction to ensure consistencies of 5% of maximum. The peak-to-peak MEP amplitude and the CSP duration were measured on individual sweeps off-line and the results averaged manually. CSP duration was calculated from the time of stimulation to the return of spontaneous EMG activity. An investigator blinded to the type of conditioning stimulation made all off-line measurements.

2.6. Conditioning trains

The rTMS condition consisted of 750 pulses provided in 5 s 5 Hz trains with a 25 s inter-train interval at 90% of the RMT (taking 15 min). The rppTMS condition consisted of a single train of 180 pulse pairs also administered over 15 min. A pair was provided every 5 s and there was a 1.5 ms inter-stimulus interval within each pair. The stimulation intensity for the pulse pairs was determined as the intensity that would produce an MEP of between 500 and 1000 μV. These stimulation conditions have been shown to produce a facilitation of descending I-wave activity (Ziemann et al., 1998). Prior to each rppTMS condition, a brief series of pairs and single pulses were applied to ensure I-wave facilitation was achieved. This was clearly apparent in all subjects with at least a 50% increase in MEP size in the paired compared to the single pulse condition. The sham stimulation condition was identical to the 5 Hz condition but with the coil angled away from the scalp at 45° from the side wing of the coil.

Following the main experiment, four of the same subjects were tested with the rppTMS condition applied on a single occasion for a duration of 30 min.

2.7. Statistical analysis

Changes in each of the dependent variables (MEP size measured with the Magstim 200, MEP size measured with SuperRapid, Active MEP size and CSP duration) were analysed with separate two-way ANOVA models with time (before and after the conditioning stimulation train) and TMS type (5 Hz, rppTMS or sham) as the two within factors. Significant effects were explored with post hoc paired t tests with a significant p value considered to be <0.01. Significance was otherwise set at $p < 0.05$. All statistical analysis was conducted in SPSS 14.0 (SPSS for Windows, Chicago: SPSS; 2005).

3. Results

All participants completed each phase of the study and there were no adverse events. The CSP data from one subject was not able to be analysed due to technical problems with the data collection.

All study data is presented in Table 1. With regards to MEP size, we found no changes produced by either 5 Hz or the paired stimulation condition. For MEP size measured with the Magstim 200 system, there was no significant difference produced by the two active conditions over time: there was no effect of TIME ($F(2,8) = 0.83$, $p = 0.47$) and no TIME by TMS interaction ($F(2,8) = 0.97$, $p = 0.42$). A similar result was seen for MEP size measure with the SuperRapid: no effect of TIME ($F(2,8) = 3.3$, $p = 0.09$) and no TIME by TMS interaction ($F(2,8) = 1.3$, $p = 0.33$). The same result was seen for active MEP size: no effect of TIME ($F(2,8) = 1.2$, $p = 0.37$) and no TIME by TMS interaction ($F(2,8) = 1.1$, $p = 0.38$).

When change in MEP size was examined for the two active groups as measured with the same device used to condition the motor cortex, we also saw no effect on MEP size of 5 Hz stimulation ($t(9) = -1.1$, $p = 0.31$) or paired stimulation ($t(9) = 1.1$, $p = 0.28$).

Table 1
Motor evoked potential (MEP) and cortical silent period (CSP) data for before and after stimulation

Intervention group	Before		After	
	Mean	S.D.	Mean	S.D.
MEP size (Magstim 200 (μV))				
5 Hz rTMS	680.14	334.45	874.59	712.545
rppTMS	749.15	518.10	888.91	531.92
sham	623.45	251.42	622.91	247.27
MEP size (SuperRapid (μV))				
5 Hz rTMS	876.02	883.02	1042.16	595.83
rppTMS	760.94	579.23	1009.42	771.40
sham	810.77	328.39	603.95	271.27
Active MEP size (μV)				
5 Hz rTMS	3538.3	1656.2	3792.8	1975.9
rppTMS	3365.2	1460.7	3380.2	1853.6
sham	2891.8	1558.9	2848.0	1121.3
CSP duration (ms)				
5 Hz rTMS*	182.12	27.60	191.98	26.27
rppTMS	177.97	32.10	173.28	36.13
sham	155.54	37.54	174.34	38.92

rTMS = repetitive transcranial magnetic stimulation, rppTMS = repetitive paired pulse TMS, MEP = motor evoked potential, CSP = cortical silent period duration. All effects were non significant except post hoc comparison for CSP duration in the 5 Hz rTMS group (*$p = 0.004$).

In regards to CSP duration, there was a significant overall effect of TIME ($F(1,8) = 24.9$, $p = 0.001$) and a significant TIME by TMS interaction ($F(2,7) = 4.8$, $p = 0.04$). There was a significant increase produced in CSP duration in the 5 Hz group ($p = 0.004$) but no significant change in the other two groups.

In the four subjects tested on a second occasion with 30 min of paired stimulation, there was also no effect of stimulation on MEP size (pre-TMS MEP size = 1652.1 ± 700.9 μV, post-TMS = 1107.3 ± 426.3 μV, $t(3) = 1.5$, $p = 0.22$).

4. Discussion

In this randomised comparison study, we did not find any significant effects of 15 min of rppTMS on cortical excitability or cortical inhibition as measured by MEP size and CSP duration. A number of TMS methods have been described which may be used to alter the excitability of motor cortex and potentially other cortical regions. These paradigms require exploration and replication prior to the testing their therapeutic potential in neuropsychiatric diseases such as depression and schizophrenia. Unfortunately, our study does not provide support for the use of 15 min of rppTMS at this stage. Further research, especially ongoing testing of longer stimulation protocols, is required before this technique may be more widely utilised.

The main finding of our study was that we did not demonstrate a substantial increase in MEP size with 15 min of rppTMS. There are several significant differences between our protocol and that of Thickbroom et al. (2006). The main difference between our two studies is that in our full sample we only applied the repetitive stimulation for a period of 15 min whereas in the initial study the conditioning train was applied to a total of 30 min (Thickbroom et al., 2006). As described above, we chose a shorter time duration initially as we were interested in the clinical utility and comparability of this technique and as there seemed to be a substantial effect on MEP size by 15 min in the original study (Thickbroom et al., 2006). However, it is important to note that this effect at 15 min was within train and may not be translated to post train effects that are likely to be more relevant to therapeutic applications. Interestingly, in the four subjects who we did study on a second occasion with the rppTMS applied for 30 min, we did not find any increase in MEP size to suggest that effects would be produced with longer trains or perhaps more likely, that the sample was simply too small. In the full sample, there was an actual (non-significant) increase in MEP size in the rppTMS group (and the 5 Hz group). It is possible that this could reach significance in a larger sample, but given the variance figures, a substantially larger sample would be required. Most importantly, the degree of increase is markedly lower than that found in the original report (Thickbroom et al., 2006). The other notable difference was in our assessment of MEP size. Unlike Thickbroom et al. (2006), we did not measure a MEP recruitment curve but chose instead the more limited method of assessing MEP size at a single stimulation intensity only. Given that assessment of MEP size alone showed clear differences in the original study, and our desire to measure MEP size in several ways, we believed that this was a reasonable compromise. As there was a lack of a significant trend in regards to the MEP size post-rppTMS, it is unlikely that the more sensitive recruitment curve methods (or a method controlling the size of baseline MEP size) would have yielded differing results in our study. The final difference is the choice of coil. Thickbroom et al. used a more focal 50 mm diameter coil which may have produced different effects than the 70 mm coil we applied. Based on our overall aim in this study, this was chosen as it is a more commonly used coil in therapeutic settings.

Five hertz rTMS was included in the study as a comparison condition as high frequency rTMS is the 'standard' application used for increasing cortical excitability in many treatment studies and 5 Hz is commonly used, sometimes at the same stimulation intensity we applied (for example Rumi et al., 2005). Interestingly, we did not find an effect of 5 Hz rTMS on MEP size as measured with any of the stimulation conditions. However, despite the widespread use of high frequency rTMS, relatively few studies have investigated the effects on cortical excitability following stimulation with multiple stimulation trains (Fitzgerald et al., 2006a). Of the studies that have investigated the effects of 5 Hz stimulation, Siebner et al. reported no effect on RMT level (Siebner et al., 2000) and there is one report of an increase in MEP size following 1800 but not 150 5 Hz pulses (Peinemann et al., 2004). In the later study, the rTMS condition involved considerably longer 5 Hz stimulation trains (30 s) than we have used or which are applied in most therapeutic applications of high frequency stimulation. Studies at higher frequencies (10 and 20 Hz) have also not consistently demonstrated an increase in excitability induced by multiple stimulation trains. Studies have reported an increase in MEP size with 20 Hz but not 10 Hz (Maeda et al., 2000b) and with 1600 but not 240 pulses (Maeda et al., 2000a) but this has not been supported by more recent work (Daskalakis et al., 2006). At this stage it does not appear that we can confidently assume that multiple short trains of high frequency stimulation do produce an increase in local cortical excitability that persists following the end of stimulation. Further research is required to explore differences between short and long high frequency stimulation trains: to optimise parameters for altering excitability without substantially increasing seizure risk. In addition, given that the number of pulses influences whether rTMS affects cortical and/or spinal activity (Quartarone et al., 2005), the mechanism of action of rTMS and rppTMS requires further exploration.

In contrast to the lack of effect we have found on MEP size, we did find that 5 Hz stimulation produced an increase in cortical inhibition as assessed by CSP duration. CSP duration appears in part to be dependent on the functioning of cortical $GABA_B$ receptors as suggested by the modulation of the CSP by drugs active at this receptor and the time course of the effect (Siebner et al., 1998). Initial reports of the effects of 5 Hz stimulation on the CSP suggested that it was not altered (Peinemann et al., 2004; Siebner et al., 2000) but at least another study recently has reported an increase in CSP duration with high frequency stimulation (10 and 20 Hz) (Daskalakis et al., 2006). There is also more consistent evidence that high frequency stimulation alters other forms of cortical inhibition, in particular inhibition assessed with paired pulse TMS, although this effect is most consistently a reduction in magnitude (Fitzgerald et al., 2006a).

A number of ways of modulating cortical activity have been developed and suggested as alternative therapeutic tools for use in neuropsychiatric disorders. However, we continue to lack a sophisticated understanding of even the most basic of rTMS techniques and many of our conclusions to date have been sourced from un-replicated studies. In this study we failed to find effects of 15 min of rppTMS on motor cortical excitability. Although we had a relatively small sample size, positive rTMS effects have frequently been reported with similar sample sizes (for example eight subjects in the study of Thickbroom et al., 2006). In addition, although our study may have been improved by using more sensitive methods of measurement of MEP size, given the lack of a trend of any sort, it is unlikely that these would have revealed a positive effect of rppTMS on MEP size. In addition, although we did not formally analyse the data as it was not relevant to our primary objective, visual inspection of the intrain MEP size during the rppTMS condition did not reveal any dramatic increase in MEP size across the 15 min period. In fact we noticed no real pattern of change within or between subjects in MEP size within train. It is also not possible from our study to conclude whether or not rppTMS has any effects on other parameters of cortical excitability and inhibition such as short interval cortical inhibition or cortical facilitation. Finally, as the study included a number of female subjects and we did not control for menstrual cycle phase, this may have been a confounding factor. Further research is required to explore the potential for the rppTMS before it is applied in direct treatment studies as well as to better refine our understanding of the effects of rTMS in general.

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References

Daskalakis ZJ, Moller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. Exp Brain Res 2006;174:403–12.

Fitzgerald PB, Brown T, Marston NAU, Daskalakis ZJ, Kulkarni J. A double-blind placebo controlled trial of transcranial magnetic stimulation in the treatment of depression. Arch Gen Psychiat 2003;60:1002–8.

Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rtms on motor cortical excitability and inhibition. Clin Neurophysiol 2006a;117:2584–96.

Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharm 2006b;9:655–66.

George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li XB, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiat 2000;48:962–70.

George MS, Wassermann EM, Williams WA. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6:1853–6.

Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K, et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. Arch Gen Psychiat 2003;60:49–56.

Khedr EM, Gilio F, Rothwell J. Effects of low frequency and low intensity repetitive paired pulse stimulation of the primary motor cortex. Clin Neurophysiol 2004;115:1259–63.

Lang N, Harms J, Weyh T, Lemon RN, Paulus W, Rothwell JC, et al. Stimulus intensity and coil characteristics influence the efficacy of rTMS to suppress cortical excitability. Clin Neurophysiol 2006;117:2292–301.

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 2000a;133:425–30.

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000b;111:800–5.

Peinemann A, Reimer B, Loer C, Quartarone A, Munchau A, Conrad B, et al. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. Clin Neurophysiol 2004;115:1519–26.

Quartarone A, Bagnato S, Rizzo V, Morgante F, Sant'angelo A, Battaglia F, et al. Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. Exp Brain Res 2005;161:114–24.

Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. Biol Psychiat 2005;57:162–6.

Siebner HR, Dressnandt J, Auer C, Conrad B. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 1998;21:1209–12.

Siebner HR, Mentschel C, Auer C, Lehner C, Conrad B. Repetitive transcranial magnetic stimulation causes a short-term increase in the duration of the cortical silent period in patients with Parkinson's disease. Neurosci Lett 2000;284:147–50.

Sommer M, Kamm T, Tergau F, Ulm G, Paulus W. Repetitive paired-pulse transcranial magnetic stimulation affects corticospinal excitability and finger tapping in Parkinson's disease. Clin Neurophysiol 2002;113:944–50.

Thickbroom GW, Byrnes ML, Edwards DJ, Mastaglia FL. Repetitive paired-pulse TMS at I-wave periodicity markedly increases corticospinal excitability: a new technique for modulating synaptic plasticity. Clin Neurophysiol 2006;117:61–6.

Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W. Demonstration of facilitatory I-wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol (London) 1998;511:181–90.