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RESEARCH ARTICLE

Neuromodulation by paired-pulse TMS at an I-wave interval facilitates multiple I-waves

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Abstract Corticospinal excitability can be increased by a transcranial magnetic stimulation (TMS) intervention that delivers repeated paired TMS pulses at an I (indirect)-wave interval of 1.5 ms. This is thought to target excitatory synaptic events by reinforcing facilitatory I-wave interaction, however, it remains to be determined what effect this intervention has on the various I-wave components. In the present study we compared I-wave facilitation curves over a range of inter-pulse intervals (IPIs) encompassing the first three I-waves, before and after 15 min of a paired-pulse TMS intervention with an IPI of 1.5 ms. The three peaks in the I-wave facilitation curves occurred at the same IPIs pre- and post-intervention (1.3, 2.5 and 4.3 ms). The facilitation curves were increased in amplitude for all three I-wave peaks post-intervention (mean increase 33%), and the mean increase across all IPIs correlated with the post-intervention increase in single-pulse MEP amplitude ($r = 0.77$). Modelling showed that the changes in the post-intervention curves were consistent with an increase in amplitude and broadening of the individual I-wave peaks. We conclude that an iTMS intervention with an IPI of 1.5 ms is able to target multiple I-waves. The findings are consistent with existing models of I-wave generation and suggest that the intervention increases the efficacy of synaptic events associated with the generation of descending I-wave volleys.

Keywords Transcranial magnetic stimulation · Motor cortex · I-wave · iTMS · Facilitation

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Introduction

For more than a decade, transcranial magnetic stimulation (TMS) has been explored as a means of modulating cortical plasticity and improving function in a range of neurological and psychiatric disorders. Originally employing rate-dependent repetitive TMS (rTMS) protocols that could increase (Pascual-Leone et al. 1994) or decrease (Wassermann et al. 1996) corticospinal excitability, there are now a number of newer approaches that encompass both rate-dependent and time-dependent plasticity mechanisms, incorporating sensorimotor aspects [paired-associative stimulation (PAS)], naturally occurring rhythms [theta-burst stimulation (TBS)] and interneuronal networks (for reviews, see Fitzgerald et al. 2006; Thickbroom 2007).

This last aspect is the basis for an excitatory repetitive paired-pulse TMS intervention designed to directly target the network of interneurones involved in the generation of the brief train of high-frequency descending volleys known as indirect (I)-waves. These I-waves have a periodicity of ~1.5 ms, and are thought to result from trans-synaptic activation of corticospinal neurons via excitatory cortical interneurones or via recurrent activation (Ziemann and Rothwell 2000). Paired-pulse TMS at I-wave periodicity can lead to a facilitatory interaction between the second pulse and the I-waves generated by the first pulse (Tokimura et al. 1996; Ziemann et al. 1998; Hanajima et al. 2002) leading to an

increase in the amplitude of the motor evoked potential (MEP) compared to that with paired pulses at non-I-wave intervals.

Consequently, the rationale for designing a TMS intervention around I-wave periodicity is that persistently activating facilitatory I-wave interactions might be a means for increasing the efficacy of trans-synaptic events involved in their generation. It has been shown that corticospinal excitability (as determined by MEP amplitude) can be increased by steadily delivering pairs of TMS at an inter-pulse interval (IPI) of 1.5 ms every 5 s for 15–30 min (iTMS; Benwell et al. 2006; Thickbroom et al. 2006; Di Lazzaro et al. 2007; Hamada et al. 2007) and it has been argued that this approach may be an analogue of spike-timing dependent models of synaptic plasticity (Thickbroom 2007).

However, it remains to be determined whether I-wave effects do underlie the increase in MEP amplitude associated with this intervention. There is evidence from spinal epidural recordings and I-wave facilitation curve measurements that activity of I-wave networks is modulated in some rTMS and PAS protocols (Ridding and Taylor 2001; Di Lazzaro et al. 2002; Quartarone et al. 2005). A recent iTMS study combined with epidural I-wave recording suggested that networks other than those responsible for I-wave generation may be activated by the intervention, although observations were limited to a single-case experiencing chronic pain (Di Lazzaro et al. 2007). Therefore, in the present study we compared I-wave facilitation curves, encompassing the first three I-waves, before and after a period of iTMS. Our aim was to determine whether the increase in MEP amplitude post-intervention could be explained by an increase in I-wave facilitation, and whether the intervention affected all I-wave components similarly.

Methods

Subjects

Eighteen healthy individuals participated in the study (right-handed, 18–28 years of age, $M = 3$). All subjects gave informed written consent to the study which had the approval of the Sir Charles Gairdner Hospital Human Research Ethics Committee. Subjects were seated comfortably, their arms resting on a cushion and were asked to remain relaxed but alert with open eyes for the duration of the experiment (~75 min). None of the subjects reported any discomfort during the studies.

TMS and EMG collection

Motor evoked potentials were recorded from surface electrodes placed in a belly-tendon arrangement over the first dorsal interosseous (FDI) muscle of the right hand (amplification 1,000, band pass 2–20 kHz). All recordings were made at rest. TMS was performed using a 7-cm figure-of-eight coil connected to a dual pulse stimulator (Bistim 2002, Magstim Co., UK) and placed over the motor 'hot-spot' for FDI and orientated ~45° to the sagittal plane.

TMS intervention (iTMS)

The iTMS intervention comprised paired-pulse TMS at 1.5 ms IPI, delivered every 5 s for 15 min (180 stimuli). Stimulus intensity was the same for each pulse in the pair, and set so that paired stimulation generated a MEP of 1–2 mV peak–peak amplitude. The change in paired-pulse MEP amplitude during the intervention was calculated by comparing the mean MEP amplitude in the first and the last minute of the intervention (12 MEPs averaged for each minute).

I-wave facilitation curves

I-wave facilitation curves were measured with paired-pulse TMS across a range of IPIs before and after the iTMS intervention in two experimental protocols (see below). Stimulus intensity was kept the same for each pulse, and adjusted so as to generate a MEP of 1–2 mV when delivered singly, and no more than 4 mV when delivered as a 1.5 ms pulse pair. This combination has been shown previously to generate well-defined facilitatory peaks (Ziemann et al. 1998). We first conducted a pilot study which confirmed that this stimulus intensity generates distinct facilitatory peaks (as opposed to broader peaks observed at lower intensities), and that three peaks in the facilitation curve could be recorded (corresponding to I1, I2 and I3). In each subject we also confirmed that a MEP of 2–4 mV was not a ceiling value, and that MEPs of an amplitude greater than this could be generated at higher stimulus intensity. Single-pulse control stimuli were delivered at the same intensity as pulses in the paired stimulation.

Experiment 1

I-wave facilitation curves were generated prior to iTMS and commencing 3 min post-intervention, using paired-pulse TMS at IPIs ranging from 0.8 to 4.8 ms in 0.2–0.3 ms steps, a total of 17 intervals. At these IPIs, the MEP waveform was biphasic, and MEP amplitude was measured peak–peak. We also explored IPIs up to 7.5 ms, however, the MEP began to separate into two components at IPIs ~5 ms. Each run was divided into four blocks, and in every block each IPI was presented once in a pseudo-randomised order. Three groups of four single-pulse control MEPs (12 in total) were collected at the beginning (before IPI block

1), middle (between IPI blocks 2 and 3) and at the end of each run (Fig. 1). The total acquisition time for the facilitation curve was ~7 min. We commenced the post-collection at 3 min post-intervention, to give subjects a short break after the 15 min of iTMS. The collection was completed by 10 min post-intervention, which is within the previously reported duration of the increased cortical excitability after iTMS (Thickbroom et al. 2006).

Experiment 2

In order to determine whether the I-wave facilitation curve is affected for a longer period post-intervention we conducted a second study in a subset of eight subjects, and measured two I-wave curves, commencing 3 and 15 min post-intervention (Post 2_a and Post 2_b, Fig. 1). These measurements were shortened to encompass only the first two I-waves, with 11 IPIs from 0.8 to 3.3 ms in 0.2–0.3 ms steps, and could be recorded in ~5 min.

Data analysis

For each subject, normalized pre-intervention curves were calculated by expressing mean MEP amplitude at each IPI as a percentage of the 12 control MEP amplitudes in that run. The percentage values at each IPI were then averaged across subjects. A similar analysis was performed on the post-intervention data, with the IPI data expressed as a percentage of the pre-intervention mean control value for each subject. A measure of overall change in facilitation curves pre- to post-intervention, was derived from the mean of the normalized curve data across IPI.

Linear mixed models (with random effect of individual) were used to examine the effects of the fixed factors IPI and time (pre- vs. post-intervention), and the interaction of IPI and time, on the MEP response. Due to the repeated nature of the data appropriate correlation structures were examined and specified. Restricted maximum likelihood estimation was used in all modelling. Analysis was carried out on log transformed data. Significance was tested using pairwise comparisons (one tail, testing for an increase in MEP amplitude due to the intervention).

To check the stability of MEP amplitude during a run, a linear mixed models analysis (with random effect of individual accounted for) was performed with factor time (beginning, middle, end of run; corresponding to the three sets of four control MEPs; mean MEP amplitude for each set) and dependent variables (pre and post-intervention control MEP).

In order to investigate whether there had been any time-shift in the I-wave facilitation curve post-intervention, the Pearson's correlation co-efficient between pre- and post-intervention curves was calculated by shifting the post-curve 0.1 and 0.2 ms to the left or right along the *x*-axis (i.e. ±0.1, 0.2 ms IPI), calculating five correlations in total.

We performed regression analysis on the pre- versus post-intervention facilitation curves to determine the relative scaling or translation of these curves. To explore the factors that might underlie a change in curve amplitude, each I-wave facilitation curve was modelled as three overlapping Gaussian curves each positioned in the *x*-axis (time axis) at times corresponding to I1, I2 and I3 latencies, and with amplitudes and widths mimicking the amplitude and spread of each of the I-wave peaks. The effect of the intervention on the facilitation curves was explored by manipulating the amplitude and half-width of the Gaussians.

Results

Experiment 1

There were three peaks in the I-wave facilitation curves. These occurred at the same IPIs pre- and post-intervention (1.3, 2.5 and 4.3 ms), and were consistent with I1, I2 and I3 wave intervals (Fig. 2). Before intervention, the normalised value of the facilitation curve at these intervals was 162 ± 14, 144 ± 11 and 148 ± 12%. After the intervention, these values increased significantly for all three I-waves, to 205 ± 24, 177 ± 23 and 173 ± 16%, respectively ($P < 0.05$). There was no relationship between the magnitude of the increase in MEP amplitude post-intervention, and IPI ($P = 0.97$, linear mixed models analysis). The mean normalized curve value (percentage values averaged across all IPIs) was increased after the intervention (137.4 ± 3.08

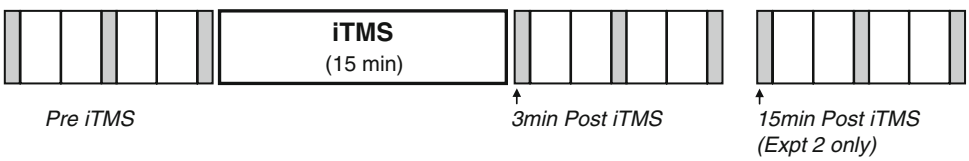

Fig. 1 Outline of experimental protocol. Prior to intervention, a set of four IPI runs were collected (*white boxes*), and in each run IPIs encompassing the first three I-waves (0.8–4.8 ms) were presented once pseudo-randomly. IPI runs were interspersed with single-pulse control runs (*grey boxes*; 4 stimuli in each) delivered at the beginning, middle and end of the set of IPIs. In Experiment 1, this was repeated after 15 min of iTMS, starting 3 min post-intervention. In Experiment 2, IPI runs were shortened to encompass just the first two I-waves (IPIs 0.8–3.3 ms) and a second set was collected commencing 15 min post-intervention

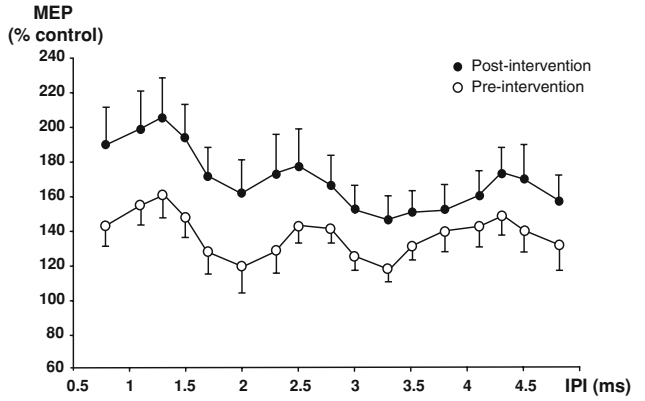

Fig. 2 I-wave facilitation curves pre- and post-intervention, showing facilitation peaks at 1.3, 2.5 and 4.3 ms for both curves, and an increase in MEP amplitude (normalized to pre-intervention) for all IPIs

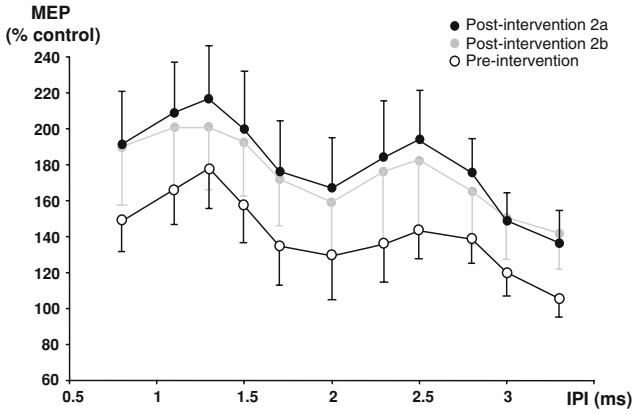

Fig. 3 Comparison of I-wave facilitation curves incorporating the first two I-waves for two time periods after intervention, Post 2a and Post 2b, commencing at 3 and 15 min, respectively, in relation to the baseline curve, showing the facilitation curves are elevated across both periods

pre- vs. $170.5 \pm 4.34\%$ post-intervention; $P < 0.001$). Correlation between pre- and post-intervention curves was maximal ($r = 0.88$) when there was no shift along the x-axis (IPI), indicating that there had been no relative time-shift in the overall curve post-intervention.

The mean control values during the 7 min pre- and post I-wave facilitation curve collections were 1.47 ± 0.26 and 2.11 ± 0.54 mV, respectively; a 144% increase. A linear mixed model analysis demonstrated that mean control values did not change during the course of the pre- and post-intervention facilitation curve collections themselves ($P = 0.454$ and $P = 0.913$, respectively), indicating stability in the excitability changes over these periods. During the iTMS intervention itself, MEP amplitude changed from 1.49 ± 0.2 to $2.81 + 0.5$ mV (first compared to last minute of intervention; $P < 0.005$).

Experiment 2

I-wave facilitation curves at Post 2_a and Post 2_b were significantly increased compared to the pre-intervention curve ($P < 0.001$), by an amount similar to Experiment 1. Post 2_a and Post 2_b were not significantly different to each other ($P = 0.996$; linear mixed models analysis; Fig. 3). The average control MEP amplitude at Post 2_a and Post 2_b was 2.62 ± 0.64 and 2.67 ± 0.69 mV, respectively, corresponding to increases of 35.2 ± 17.9 and $35.7 \pm 20.6\%$. In keeping with Experiment 1, the I-wave facilitation curve displayed peaks at 1.3 and 2.5 ms IPI. During the iTMS intervention itself, MEP amplitude increased from 1.76 ± 0.23 to 2.9 ± 0.58 mV ($P < 0.05$).

Regression and modelling

The average (across IPI) post-intervention increase in I-wave facilitation curve correlated with the post-intervention increase in single-pulse MEP amplitude ($r = 0.76$; $P < 0.05$; Fig. 4). When the change in single-pulse MEP amplitude after iTMS was accounted for by re-normalising the post-intervention I-wave curve to the post-intervention single-pulse control MEP amplitude, there was no significant difference in the degree of facilitation of I-wave peaks pre- to post-intervention ($P > 0.05$).

Regression analysis on the pre- and post-intervention curves revealed a linear relationship ($r = 0.77$; $P < 0.05$; Fig. 5) with a regression line described by the equation $y = 1.09x + 29.7$, where y corresponds to the post-intervention value of the curve as a function of IPI, and x to the associated pre-intervention value for that IPI. The equation indicates that the post-intervention curve can be described

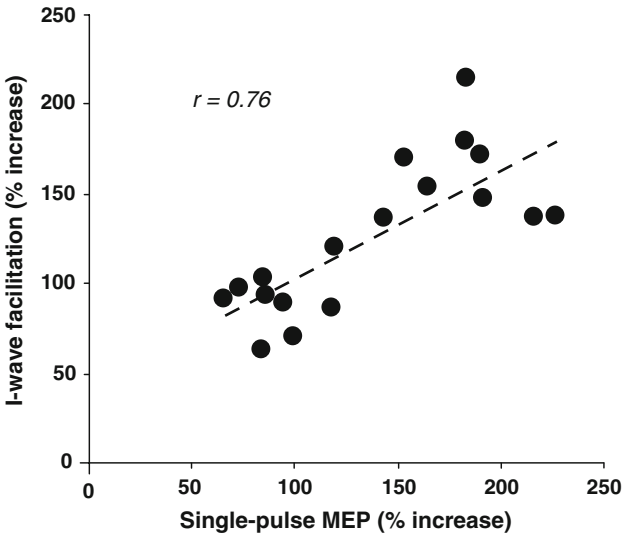

Fig. 4 Correlation of the mean (across IPI) increase in I-wave facilitation curve amplitude against the increase in single-pulse MEP amplitude post-intervention for each individual

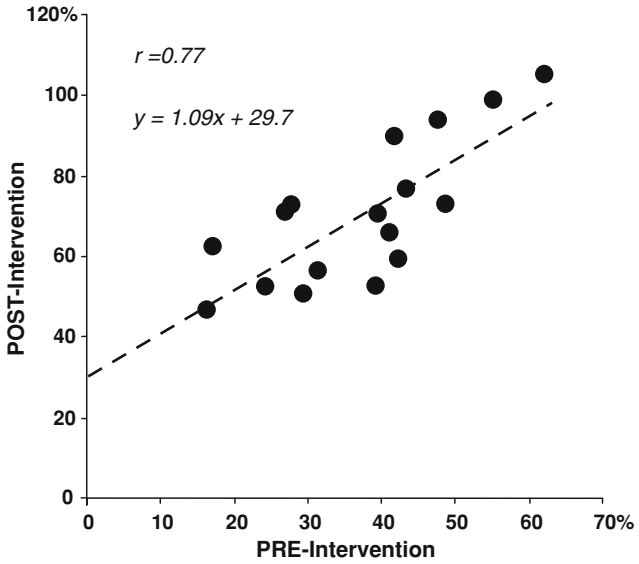

Fig. 5 Scatter-plot of pre- versus post-intervention MEP amplitude for all IPIs (% increase above baseline single-pulse MEP amplitude), showing a linear relationship ($r = 0.77$) described by $y = 1.09x + 29.7$

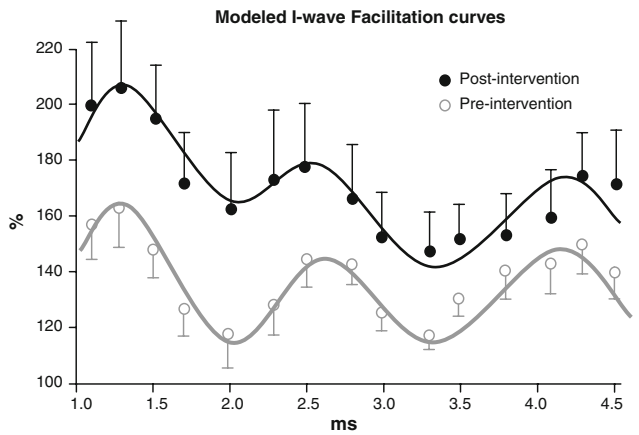

Fig. 6 Overlay of the Gaussian model plots onto the pre- and post I-wave facilitation curves from Fig. 2. The model is generated from the sum of three Gaussian curves centred on the I-wave peaks. The post-intervention curve has been derived from the pre-intervention curve, by a scaling in amplitude of each of the Gaussians (by a mean of 26%), and a broadening in time (by a mean of 10%)

by a translation (along the *y*-axis) of the pre-intervention curve (by 29.7%) and a modest and non-significant multiplicative component (1.09). This effect could be simulated by the Gaussian model of the facilitation curve by scaling (26%) and broadening (10%) the individual post-intervention Gaussian components (Fig. 6).

Discussion

We have confirmed that repeated I-wave facilitation by paired-pulse TMS at I-wave intervals (iTMS) leads to a sustained increase in corticospinal excitability, and have further shown that this is reflected in an amplification of the I-wave facilitation curve after the intervention. While the intervention itself involved only a single IPI (1.5 ms) the effect of the intervention was to increase the peaks in the facilitation curve across I-waves. The data modelling is consistent with an increase in the amplitude and a broadening of the peaks in the I-wave facilitation curve for the first three I-waves. The implication is that the intervention has increased the excitability of inter-neuronal networks involved in the generation of the first three I-waves, and has broadened the temporal-tuning of these networks.

As our aim was to obtain a measure of the increase in excitability induced by the intervention, the same stimulus parameters were maintained to compare the pre- and post-intervention facilitation curves. We chose not to adjust stimulus intensity (downwards) to compensate for the increase in excitability after the intervention, as this would have underestimated the change in excitability of the networks responsible for generating I-waves. The correlation between the mean increase in the amplitude of the facilitation curve and the increase in the single-pulse MEP amplitude as a result of the intervention would mean that adjusting stimulus intensity based on the change in single-pulse MEP amplitude would have obscured a change in the amplitude of the facilitation curves. Likewise, using the post-intervention single-pulse MEP as the control value for the facilitation curve post-intervention cancelled the increase in the I-wave peaks, consistent with the correlation between these measures.

What might underlie the observed amplification of the facilitation curve? The I-wave volley is known to be fairly regular, with intervals between successive I-waves of ~1.5 ms, which is compatible with the average synaptic delay. A number of models have been proposed for the generators of this volley (for reviews, see Rothwell et al. 1991; Ziemann and Rothwell 2000; Rothwell 2005). One possibility is that a chain of interneurones targeting a pyramidal tract neuron (PTN) is activated, in which case increasing the efficacy of the last element in this chain synapsing onto the output cell would increase the effectiveness of successive inputs via this element. If on the other hand, the network is more complex, and involves multiple connections but not in a chain arrangement, then paired pulses with a ~1.5 ms IPI could target each of these connections and lead to an overall increase in responsiveness of the network and enhanced PTN activation. Alternatively, inputs from different cortical layers, with a different latency of activation, may generate successive I-waves. The present findings are also consistent with this model if some change in intrinsic excitability of the PTN has occurred. Finally, if the PTN undergoes some form of recurrent monosynaptic or oligosynaptic activation, then again, targeting the synaptic delay

interval would be expected to increase the amplitude of successive I-waves. The present results are therefore consistent with the current models proposed for I-wave generation.

The overall effect of the intervention on the facilitation curve appeared to be a translation of the curve along the amplitude axis. This is apparent in the regression data that indicates almost all of the difference pre- and post-intervention is equivalent to a translation, with only a small scaling contribution. However, this result has to be interpreted with caution, as the modelling data indicates that a scaling in parallel with a broadening of the peaks can manifest as an apparent translation. With this interpretation, scaling would equate to an increase in the efficacy of the synapses involved in I-wave facilitation, and broadening is consistent with a widening in the temporal-tuning of networks, perhaps as a result of an increased recruitment of more excitable interneurones that are less closely coupled to the main I-wave facilitation event.

In this study we used a supra-threshold intensity for S2. This protocol was influenced by the data of Ziemann et al. (1998) who showed good I-wave peaks at this intensity, although it is perhaps more common to use an intensity nearer threshold. One possibility arising from a supra-threshold S2 is that there may be some interaction at the spinal level. However, Ziemann et al. (1998) conclude that even with a supra-threshold S2, the interaction occurs in the structures where I-waves are generated. This was based in part on the fact that there was no latency-shift in the peaks with increasing S2 intensity, and we also show, by cross-correlation analysis of the pre- and post-intervention curves, that there was no relative latency-shift post-intervention. In addition, F-wave recordings and stimulation at the cervico-medullary junction are consistent with a cortical effect of the intervention (Thickbroom et al. 2006; Di Lazzaro et al. 2007; Hamada et al. 2007).

The facilitatory effect of the 15 min intervention on single-pulse MEP amplitude was found to last longer than in our original iTMS study in which we used a 30 min intervention (Thickbroom et al. 2006). We carried out an experiment to determine whether the facilitation curves were elevated and stable over this longer time period, and confirmed that this was the case. We also demonstrated the stability of single-pulse MEP amplitude over this period. While the mechanisms responsible for limiting the time-course of the excitability changes following interventional TMS protocols have yet to be investigated, it is likely that plasticity-regulating mechanisms such as homeostatic plasticity are involved (see Thickbroom 2007). Thus while it may seem paradoxical, a shorter period of iTMS which is less effective in terms of increasing excitability may have allowed a longer lasting post-intervention effect because it is less likely to activate these compensatory mechanisms as strongly.

In conclusion, we have shown that a TMS intervention targeting I-wave facilitation can be effective in increasing corticospinal excitability, and that the effect extends to multiple I-waves. The findings are consistent with current models of I-wave generation, and suggest that the intervention increases the efficacy of the synaptic events associated with the generation of multiple descending volleys.

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