Modulation of I-wave generating pathways by theta-burst stimulation: a model of plasticity induction

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Key points

- Mechanisms underlying plasticity induction by repetitive transcranial magnetic stimulation protocols such as intermittent theta-burst stimulation (iTBS) remain poorly understood.
- Individual response to iTBS is associated with recruitment of late indirect wave (I-wave) generating pathways that can be probed by the onset latency of transcranial magnetic stimulation applied to primary motor cortex (M1) at different coil orientations.
- We found an association between late I-wave recruitment (reflected by anterior–posterior (AP)-lateromedial (LM) latency; i.e. the excess latency of motor-evoked potentials generated by transcranial magnetic stimulation with an AP orientation over the latency of motor-evoked potentials evoked by direct activation of corticospinal axons using LM stimulation) and changes in cortical excitability following iTBS, confirming previous studies.
- AP-LM latency significantly decreased following iTBS, and this decrease correlated with the iTBS-induced increase in cortical excitability across subjects.
- Plasticity in the motor network may in part derive from a modulation of excitability and the recruitment of late I-wave generating cortical pathways.

Abstract Plasticity-induction following theta burst transcranial stimulation (TBS) varies considerably across subjects, and the underlying neurophysiological mechanisms remain poorly understood, representing a challenge for scientific and clinical applications. In human motor cortex (M1), recruitment of indirect waves (I-waves) can be probed by the excess latency of motor-evoked potentials elicited by transcranial magnetic stimulation with an anterior–posterior

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(AP) orientation over the latency of motor-evoked potentials evoked by direct activation of corticospinal axons using lateromedial (LM) stimulation, referred to as the ‘AP-LM latency’ difference. Importantly, AP-LM latency has been shown to predict individual responses to TBS across subjects. We, therefore, hypothesized that the plastic changes in corticospinal excitability induced by TBS are the result, at least in part, of changes in excitability of these same I-wave generating pathways. In 20 healthy subjects, we investigated whether intermittent TBS (iTBS) modulates I-wave recruitment as reflected by changes in the AP-LM latency. As expected, we found that AP-LM latencies before iTBS were associated with iTBS-induced excitability changes. A novel finding was that iTBS reduced AP-LM latency, and that this reduction significantly correlated with changes in cortical excitability observed following iTBS: subjects with larger reductions in AP-LM latencies featured larger increases in cortical excitability following iTBS. Our findings suggest that plasticity-induction by iTBS may derive from the modulation of I-wave generating pathways projecting onto M1, accounting for the predictive potential of I-wave recruitment. The excitability of I-wave generating pathways may serve a critical role in modulating motor cortical excitability and hence represent a promising target for novel repetitive transcranial magnetic stimulation protocols.

Introduction

Theta burst stimulation (TBS) can transiently change the excitability of human motor cortex by inducing early-stage long-term potentiation/depression, such as effects at cortical synapses. However, the after-effects of TBS vary considerably between subjects (Hamada et al. 2013; Hinder et al. 2014; López-Alonso et al. 2014; Nettekoven et al. 2015). Many factors contribute to these inter-individual differences, such as age, time of day or circulating hormones (Suppa et al. 2016; Guerra et al. 2018). Hamada et al. (2013) reported that individual responses to TBS can be predicted by the differential recruitment of cortical pathways by the transcranial magnetic stimulation (TMS) pulse. These pathways generate different indirect waves (I-waves) of neural activity descending the corticospinal tract after a TMS pulse has been applied to the primary motor cortex (Day et al. 1989; Di Lazzaro et al. 1998). I-wave recruitment can be non-invasively assessed via the onset latencies of motor-evoked potentials (MEPs) elicited by TMS pulses with different current orientations: posterior–anterior (PA) currents preferentially result in short-latency responses, whereas anterior–posterior (AP) currents evoke MEPs with longer latencies, and lateromedial (LM) directed currents at high intensities evoke direct waves featuring the shortest latencies (Day et al. 1989; Sakai et al. 1997; Di Lazzaro et al. 1998; Hamada et al. 2013). We refer to the excess latency of MEPs produced by AP-TMS over the latency of MEPs evoked by LM-TMS as the ‘AP-LM latency’ difference and the the excess latency of PA-TMS over LM-TMS as the ‘PA-LM latency’ difference. AP-LM latencies, reflecting late (i.e. long onset latency) I-wave recruitment, have been shown to strongly correlate with the plasticity effect induced by TBS across subjects (Hamada et al. 2013). Because the biphasic (i.e. PA–AP) TMS pulse applied during TBS preferentially activates neurons during the reverse stimulation phase (AP) (Maccabee et al. 1998; Di Lazzaro et al. 2001), the MEPs evoked by AP stimulation might represent activation of the same elements as those stimulated with TBS (Hamada et al. 2013). This leads to the question whether plasticity induction by TBS may partially derive from selective changes in the elements activated by AP stimulation (i.e. cortical pathways underlying late I-wave generation). Support for this hypothesis was provided by Di Lazzaro et al. (2008), who showed that excitability enhancing intermittent TBS (iTBS) enhances late but not early I-waves in spinal recordings of descending activity (Di Lazzaro et al. 2008). Moreover, we recently observed that AP-LM latencies are closely associated with the functional connectivity between primary motor cortex (M1) and a network of premotor areas as assessed via functional magnetic resonance imaging (fMRI): Subjects featuring late I-waves (i.e. long AP-LM latency) showed weaker premotor–M1 connectivity (Volz et al. 2015). Importantly, functional M1 connectivity has previously been shown to be readily increased by iTBS, especially in responders to iTBS (Nettekoven et al. 2014, 2015). Thus, iTBS-induced increases in M1 connectivity may reflect decreased recruitment of late I-wave generating pathways following iTBS.

We therefore hypothesized that iTBS reduces I-wave latency especially for subjects in whom iTBS induces cortical plasticity, as reflected by increased cortical excitability. In effect, we can imagine that AP-TMS
The assessment of MEP amplitudes and latencies was performed using a Magstim 200\(^2\) stimulator (The Magstim Co. Ltd, Whitland, UK) equipped with a 70 mm figure-of-eight coil eliciting monophasic pulses. A Magstim SuperRapid\(^2\) stimulator (The Magstim Co. Ltd) with a figure-of-eight coil (70 mm standard coil; The Magstim Co. Ltd) generating biphasic pulses was used to apply iTBS. The position of the TMS coil was monitored and recorded throughout the experiment using a Brainsight\(^2\) computerized frameless stereotactic system (Rogue Research Inc., Montreal, QC, Canada).

Ag/AgCl surface electrodes (Tyco Healthcare, Neustadt, Germany) placed in a belly-to-tendon montage were used to record the electromyograph (EMG) signals from the right first dorsal interosseous (FDI) muscle. The EMG signal was filtered (0.5 Hz high-pass and 30–300 Hz bandpass), amplified and digitized using a Power-Lab 26T and the LabChart software package (ADInstruments Ltd, Dunedin, New Zealand).

The resting motor threshold (RMT) was defined as the lowest stimulator intensity resulting in a MEP with a minimum amplitude of 50 \(\mu\text{V}\) in at least five out of 10 trials (Rossi et al. 2009). The active motor threshold (AMT) was defined as the lowest stimulator intensity resulting in a MEP with a minimum amplitude of 200 \(\mu\text{V}\) in at least five out of 10 trials while subjects performed constant contraction of the FDI muscle at ~10% of maximum strength (monitored by a force transducer; ADInstruments Ltd, Sydney, NSW, Australia). Of note, motor thresholds were assessed using monophasic pulses at different coil orientations (RMTpa, AMTpa, AMT\(\text{amplitude}\) (AMT\(\text{amplitude}\))) to individualize respective stimulation intensities for TMS applied with currents oriented in the AP, PA or LM direction. Stimulation intensities used to record MEPs for orientation-dependent latency assessment were individualized using the respective AMT. Cortical excitability before and after iTBS was probed via 20 MEPs evoked by monophasic PA-TMS applied at 120% of the individual RMTpa. The AMT was also assessed with biphasic pulses generated by the Magstim SuperRapid\(^2\) (in ‘standard’ PA orientation) to individualize iTBS intensity (80% of biphasic AMT).

To determine maximum grip force and monitor contraction during MEP recordings, a grip force sensor was placed between the bases of the thumb and index finger in pronation position of the hand, which results in effective recruitment of the FDI muscle during thumb–index abduction. Maximum contraction force was estimated by averaging over three repetitions performed by the subjects with breaks of several seconds between repetitions to prevent fatigue.

We used iTBS as introduced by Huang and colleagues (Huang et al. 2005). iTBS was applied either over the left M1 (i.e. the ‘hotspot’) or over the parieto-occipital vertex as control stimulation (Herwig et al. 2007, 2010). Stimulation intensity was individualized to 80% AMT, as determined using the Magstim SuperRapid\(^2\).
AP oriented currents typically result in I-waves with longer onset latencies and LM oriented currents applied at high stimulation intensities result in shortest latency responses (i.e. direct waves; D-waves) (Day et al. 1989; Di Lazzaro et al. 1998; Hamada et al. 2013). Although latencies evoked by PA currents are relatively consistent, the latencies of MEPs elicited by AP-TMS are typically more variable across subjects (Hamada et al. 2013). Similar to previous studies (Hamada et al. 2013; Volz et al. 2015), we used the latency difference between LM and AP or PA evoked MEP onsets as a measure of I-wave recruitment. This latency difference reflects the excess time caused by the activation of cortical pathways relative to D-waves proposedly resulting from direct axonal stimulation of corticospinal pyramidal cells (Hamada et al. 2013).

The TMS coil was oriented in specific ways to evoke distinctly oriented currents. PA-TMS: the coil was positioned posterolaterally forming an angle of ~45° with the midline. AP-TMS: the coil was held at 180° relative to PA-TMS. LM-TMS: the coil was held with the handle pointing to the left, forming a 90° angle to the midline (Fig. 1). The coil position eliciting MEPs with maximal amplitudes following PA-TMS at minimum stimulation intensities was defined as the ‘TMS hotspot’. The same hotspot was used for all coil orientations and iTBS application.

MEP onset latencies were determined during constant contraction of the FDI muscle (~10% of the maximum contraction, with online feedback visualizing the generated force). Stimuli were applied at following intensities: PA-TMS: 110% AMTpa; AP-TMS: 110% AMTap; and LM-TMS: 150% AMTlm. In subjects whose 150% AMTlm did not reach 50% of maximum stimulator output (MSO), 50% MSO was used as the stimulation intensity to assure D-wave recruitment by LM-TMS (Werhahn et al. 1994). To ensure methodological validity of the results, the stimulation parameters applied in the present study were identical to those previously used to empirically assess distinct I-wave generating circuits (Hamada et al. 2013).

Twenty MEPs were recorded for PA- and AP-TMS and 10 MEPs were elicited by LM-TMS. After each block of 10 stimuli, subjects were instructed to relax their hand muscles to avoid fatigue. Recording latency measurements took 10–15 min. Importantly, all subjects successfully performed constant FDI-contraction at the given intensity throughout MEP recordings without significant fluctuations in grip strength as a result of the low force level.

### Statistical analysis

MEP onset latencies were determined by an automated method to minimize a potential observer bias, using a custom-made MATLAB script (MATLAB 2016b; The MathWorks, Inc., Natick, MA, USA). For each trial, the MEP onset was defined as the earliest time point following stimulation where EMG signals exceeded the average level plus 2 SDs of the pre-stimulus EMG signal (~100 to 0 ms of TMS). Of note, this analysis was performed after data collection (‘offline’) rather than in real time during data collection to prevent the induction of a potential bias of the investigator performing the TMS assessment.

Changes in both TMS-latencies and MEP amplitudes were analysed using two-factorial repeated-measures analyses of variance (rm-ANOVA) including the factors: STIMULATION (‘M1’, ‘control’) and TIME (pre iTBS, post iTBS) using the ezANOVA-package for R (Lawrence, 2015). In case of significant main or interaction effects, post hoc t tests were performed.

### Results

#### Motor thresholds

Motor thresholds evaluated with different current orientations and monophasic pulses did not differ between
sessions (all $P > 0.1$: RMTpa: $P = 0.11$; AMTpa: $P = 0.38$; AMTap: $P = 0.65$; AMTlm: $P = 0.18$, two-sided Student’s $t$-tests). Furthermore, significant intercorrelation coefficients indicated a high re-test reliability of motor thresholds (RMTpa: $r = 0.932$, $P < 0.001$; AMTpa: $r = 0.923$, $P < 0.001$; AMTap: $r = 0.805$, $P < 0.001$; AMTlm: $r = 0.860$, $P < 0.001$). Similarly, the AMT values determined by biphasic pulses for determination of iTBS intensity were similar ($P = 0.57$) and highly correlated between the two sessions ($r = 0.856$, $P < 0.001$). Hence, MEP recordings and iTBS application were performed at comparable intensities for each subject in both sessions rendering a potential bias of diverging threshold-adapted stimulation intensities improbable.

Cortical excitability

Cortical excitability before and after iTBS was assessed via monophasic PA-TMS applied at 120% of the individual RMTpa. iTBS aftereffects on cortical excitability were assessed via normalized MEP amplitudes relative to the baseline (post/pre stimulation) (Huang et al. 2005; Hamada et al. 2013; Nettekoven et al. 2014).

Although normalized MEP amplitudes significantly increased after M1-stimulation ($P = 0.035$, one-sample two-sided $t$ test) but not after control stimulation ($P = 0.463$), no significant difference was found when comparing normalized MEP amplitudes for control and M1 stimulation directly ($P = 0.181$, two-sided $t$ test) (Fig. 2A). Thus, in line with previous negative findings (Hamada et al. 2013), iTBS did not significantly modulate cortical excitability across all subjects.

In summary, although we found evidence that iTBS effectively modulated cortical excitability compared to baseline, the effect was not sufficiently strong compared to control stimulation, probably as a result of inter-individual differences in the responsiveness to M1-iTBS across subjects, as reported by previous studies (Hamada et al. 2013; Cárdenas-Morales et al. 2014; Nettekoven et al. 2015).

TMS latencies

For PA-LM latencies, a two-factorial rm-ANOVA showed no significant effects (STIMULATION: $F_{1,19} = 0.071$, $P = 0.792$; TIME: $F_{1,19} = 2.062$, $P = 0.167$; STIMULATION $\times$ TIME: $F_{1,19} = 0.097$, $P = 0.758$) indicating that PA-LM latencies did not differ between sessions or before and after iTBS. By contrast, for AP-LM latencies, we observed a significant interaction STIMULATION $\times$ TIME ($F_{1,19} = 10.090$, $P = 0.005$), without significant main effects (STIMULATION: $F_{1,19} = 0.243$, $P = 0.628$; TIME: $F_{1,19} = 2.234$, $P = 0.151$) (Fig. 2B). Post hoc tests showed that the significant interaction was driven by a significant decrease in AP-LM latency after M1- compared to control stimulation ($P = 0.005$). Hence, iTBS applied over M1 selectively reduced AP-LM but not PA-LM latencies compared to control stimulation (for a depiction of individual AP-LM and PA-LM latencies before and after iTBS (see Supporting information, Fig. S1). Stimulation effects on direction-dependent latencies may in principle be influenced by concurrent changes in the amplitudes of MEPs evoked by TMS with differential current directions. Importantly, MEP amplitudes evoked with

![Figure 2. iTBS effects on cortical excitability and I-wave recruitment](image)

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AP, PA or LM stimulation did not change significantly after stimulation (all $P > 0.1$, uncorrected). Moreover, changes in amplitudes elicited with different current directions did not correlate with latency changes observed following iTBS. Therefore, the observed effects on directionality-dependent latencies were not biased by changes in MEP amplitudes induced by iTBS.

**Cortical excitability and I-wave recruitment**

Pre-stimulation AP-LM latency significantly correlated with the relative increase in MEP amplitudes ($r = 0.467$, $P = 0.038$). Hence, subjects featuring longer AP-LM latencies showed greater increases in MEP amplitudes following iTBS to M1, but not following control stimulation ($r = 0.188$, $P = 0.428$) (Fig. 3A), replicating earlier findings by Hamada and colleagues (Hamada et al. 2013).

AP-LM latencies at baseline demonstrated a significant negative correlation with iTBS-induced decreases in AP-LM latencies ($r = -0.507$, $P = 0.022$) (Fig. 3B). Hence, subjects featuring long AP-LM latencies showed the strongest decreases in AP-LM latencies. Furthermore, these subjects also showed a more pronounced increase in MEP amplitudes as indicated by a significant negative correlation between the iTBS-induced change in AP-LM latencies and MEP amplitudes ($r = -0.596$, $P = 0.006$) (Fig. 3C).

In summary, we here observed for the first time that iTBS lead to a selective reduction in AP-LM latencies. This reduction was strongest in subjects who demonstrated pronounced increases in MEP amplitudes after iTBS. Of note, such a relationship was missing for baseline AP-LM values in the control session with both changes in MEP amplitudes ($r = 0.188$, $P = 0.428$) and in AP-LM latencies ($r = -0.374$, $P = 0.105$) following control stimulation, thus corroborating the specificity of this finding.

**Discussion**

Application of iTBS to M1 significantly reduced AP-LM latency. The amount of latency change correlated with the effect of iTBS: participants with the largest MEP increases after iTBS showed the greatest reduction in AP-LM latency. We hypothesize that iTBS modulates I-wave recruitment potentially by strengthening synapses in the I-wave pathway activated by AP pulses. This increases the amplitude of MEPs, whereas the resulting increased efficiency of synaptic transmission reduces the AP-LM latency.

**Plasticity induction and I-wave generating pathways**

Repetitive TMS (rTMS) after-effects on cortical excitability of the human brain are considered to derive from the induction of long-term potentiation-like or long-term depression-like effects at synapses in the stimulated tissue (Huang et al. 2005). However, it remains unknown whether plasticity induction primarily occurs via changes in synaptic transmission in specific pathways or subtypes of neurons, or whether all stimulated neurons are affected. The present study addressed this question using the iTBS protocol. Previous work by Hamada et al. (2013) showed that an individual’s response to iTBS can be predicted from measurement of the latency of MEPs evoked by AP-TMS. Because this direction of TMS primarily evokes late I-wave inputs to corticospinal neurons, the suggestion was that the synapses between neurons in this pathway might be the locus of the plastic changes induced by iTBS. That is, the more efficiently iTBS targeted the AP-pathway, the greater the chance of producing plastic changes in its synaptic connections. Indeed, work by Di Lazzaro et al. (2008) showed that iTBS enhances late but not early I-waves in spinal recordings of descending activity.

The present findings add to this work by showing that following iTBS there is a small, but significant reduction in the AP-LM latency (Fig. 2B), which was related to the amount of plasticity observed: Individuals who showed the largest increases in MEP amplitude had the greatest reduction in AP-LM latency (Fig. 3C). This was not a result of the increase in size of MEPs because latency measures were made using a constant response amplitude of $\approx 1$ mV. The reduction of AP-LM latency by iTBS was also inversely correlated with baseline AP-LM latency determined before stimulation (Fig. 3B). Hence, subjects with long AP-LM latencies (i.e. ‘canonical’ responders to iTBS) (Hamada et al. 2013), not only showed the strongest increases in cortical excitability (Fig. 3A), but also the most pronounced decreases in AP-LM latency (Fig. 3B).

In summary, we found that the response to iTBS may not only be predicted by probing I-wave recruitment, but application of iTBS appears to specifically modulate the cortical circuitry generating late I-waves. Alternatively, iTBS-induced plasticity may result from modulation of I-wave generating pathways primarily activated by PA stimulation. However, no significant change was observed in the excess latency of MEPs produced by PA-TMS over the latency of MEPs evoked by LM-TMS (i.e. PA-LM latency) following iTBS, nor did PA-LM latencies correlate with iTBS-induced changes in cortical excitability. Taken together, this renders a key role of I-wave generating pathways primarily recruited by PA stimulation rather improbable. Conversely, iTBS primarily induced plasticity in subjects prone to recruiting late I-waves following AP-TMS, which decreased in onset-latency after iTBS application. Of note, the notion that cortical pathways distinctly recruited by AP- and PA-TMS may contribute to motor plasticity is supported by a recent study showing that PA- and AP-inputs participate in the induction of cortical plasticity after
different paired associative stimulation protocols (PAS, Hamada et al., 2014). Our finding not only offers an explanation of the capacity of AP-LM latency to predict the susceptibility to plasticity-inducing rTMS protocols, but also grants novel insights into the putative neurobiological mechanisms underlying the effects of non-invasive brain stimulation in general (Grefkes & Fink, 2012). Of note, late I-wave recruitment has not only been associated with plasticity-induction by TBS, but also has been reported to predict plastic changes observed after anodal transcranial direct current stimulation (Wiethoff et al., 2014; McCambridge et al., 2015). This convergence of findings points to a general mechanism involving the modulation of activation properties of late I-wave generating pathways, which is not limited to TBS but potentially has implications for the modulation of human cortical excitability in a more general fashion.

Modulation of I-wave generating circuitry by iTBS

The neural mechanisms underlying the generation of different I-waves remain unknown, and several competing models have been introduced, ranging from oscillating properties of the corticospinal cells to distinct circuits of excitatory and inhibitory interneurons impacting on corticospinal target cells or the activation of synaptic inputs at different distances to the cell soma in layer 5 of M1 (Esser et al., 2005; Di Lazzaro & Ziemann, 2013; Rusu et al., 2014; Triesch et al., 2015). One popular model of I-wave generation hypothesizes that different pathways feature distinct numbers of interneurons and intercalated synapses from the first neuron onto the corticospinal neuron, with less synapses (monosynaptic) resulting in shorter latencies (i.e. early I-waves) and more synapses (oligosynaptic) leading to long-latency (i.e. late I-waves) (Lemon, 2008; Di Lazzaro et al., 2012; Di Lazzaro & Ziemann, 2013). Because subjects predominantly exhibiting late I-waves upon M1 stimulation showed an inter-related increase in cortical excitability and shortening of AP-LM latencies (Fig. 3), the late I-wave pathway appears to be modulated by iTBS. According to the oligo-synaptic I-wave model, iTBS-induced changes may occur in the late I-wave generating pathway projecting from premotor areas onto the corticospinal neurons located in or close to M1 (Shimazu et al., 2004; Lemon, 2008; Volz et al., 2015). A lack of increases in excitability in subjects for whom AP-TMS primarily recruits early I-waves may derive from the fact that the same oligo-synaptic I-wave pathway is already pre-activated and hence cannot be further optimized for rapid signal transmission (resulting in low latencies). Support for this hypothesis stems from a recent study reporting that responders to iTBS demonstrated both lower functional connectivity before stimulation and stronger stimulation induced increases in connectivity, in line with a ceiling on iTBS after-effects (Nettekoven et al., 2015). Of note, the observed reduction in AP-LM latency after iTBS was <1 ms and hence is sufficiently small to principally stem from reduced EPSP rise times (Sayer et al., 1990). An alternative mechanism underlying late
I-wave generation may lie in the preferential activation of GABAergic interneurons, specifically of the neurogliaform cell type (Di Lazzaro et al. 2018). TBS may modulate the activity and excitability of such GABAergic interneurons, thereby altering the response to AP-LM stimulation and potentially contributing to changes in cortical excitability and plasticity induction. Support for this hypothesis stems from animal studies showing differential TBS effects on the activity of distinct subtypes of inhibitory GABAergic interneurons (Benali et al. 2011; Funke & Benali, 2011; Volz et al. 2013). Future studies are needed to further clarify the cortical mechanisms of late I-wave recruitment and their role in induction of motor plasticity.

Conclusions

AP-LM latencies decreased in subjects who demonstrated long AP-LM latencies and showed pronounced increases in cortical excitability after iTBS. These findings are in line with the notion that iTBS-induced increases in cortical excitability may partly result from the modulation of late I-wave generating circuitry. Our current findings thus explain the predictive power of AP-LM latencies for the response to iTBS and constitute a mechanism of plasticity induction by TBS in the human cortex. These insights might help to develop novel stimulation protocols aiming to modulate the excitability of I-wave generating pathways to increase the efficiency of plasticity-induction via rTMS across subjects.

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Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

Experiments were performed at the Department of Neurology, University of Cologne, Germany. LJV, HM, JCR and CGH designed the study. All authors were involved in the acquisition, analysis or interpretation of the data and all authors contributed to the manuscript. All authors approved the final version of the manuscript submitted for publication.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Individual AP-LM (A) and PA-LM (B) latencies before (pre) and after (post) iTBS applied to M1 or the parieto-occipital vertex (control). AP-LM latency significantly decreased following M1 but not control-stimulation (*P = 0.005), although no significant changes were observed for PA-LM latencies.