Inhibitory and Disinhibitory Effects on I-Wave Facilitation in Motor Cortex

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Cash RFH, Ziemann U, Thickbroom GW. Inhibitory and disinhibitory effects on I-wave facilitation in motor cortex. J Neurophysiol 105: 100–106, 2011. First published October 13, 2010; doi:10.1152/jn.00650.2010. A suprathreshold pulse of transcranial magnetic stimulation (TMS) delivered to human motor cortex results in a period of long-interval intracortical inhibition (LICI) followed by a briefer period of disinhibition (late cortical disinhibition [LCD]). Short-interval intracortical facilitation (SICF) is mediated by excitatory networks in the motor cortex responsible for the generation of the indirect (I-) wave volleys that are evoked by TMS at a periodicity of about 1.5 ms. Because the excitatory synaptic network responsible for SICF undergoes inhibitory regulation, we hypothesized that SICF will be modulated during periods of inhibition and disinhibition. In particular we were interested to know whether SICF was up-regulated during disinhibition, implying an increase in excitatory synaptic efficacy. We measured SICF, at a paired-pulse interval of 1.5 ms, at various times (100–300 ms) after a suprathreshold priming stimulus (PS) of sufficient strength to evoke LICI and LCD. We found that the strength of SICF was normal during LICI, but was increased during LCD by an average of 64%. SICF onset latency was reduced by one I-wave interval during LCD and was delayed by one I-wave interval during LICI. We conclude that disinhibition, rather than inhibition, modulates the excitatory neuronal networks that underlie SICF, whereas the I-wave targeted is modified by the presence of both inhibition and disinhibition and that there is therefore a dissociation between the strength and site of SICF interaction. The increase in SICF during disinhibition further indicates that this is a promising period to investigate or modulate excitatory synaptic networks while they are less constrained by ongoing levels of inhibition.

INTRODUCTION

A brief suprathreshold transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) can generate multiple descending volleys (typically three to four) at a periodicity of about 1.5 ms, possibly by recurrent firing of principal cells, recurrent activation of reciprocal excitatory interneuronal connections, or activation of interneurons in separate networks (Ziemann and Rothwell 2000). Although the generators remain uncertain, it is widely accepted that these volleys (I-waves) arise from transynaptic (indirect) activation of principal cells through excitatory interneuronal connections (Amassian et al. 1987; Patton and Amassian 1954). One approach to investigate these volleys is to deliver paired-pulse TMS (test–conditioning stimulus [TS.CS]) at an I-wave interval, with pulse strength at or above resting motor threshold (Lilic et al. 2002; Tokimura et al. 1996; Ziemann et al. 1998a). This leads to a facilitatory interaction (short-interval intracortical facilitation [SICF]) between the I-waves generated by the test and conditioning stimuli. Peaks occur around 1.1–1.5 ms (the strongest peak), 2.3–2.9 ms and 4.1–4.4 ms interpulse intervals (IPIs) (Ziemann et al. 1998a), and the magnitude of these peaks may reflect the strength of excitatory synaptic interactions in M1.

Single-pulse TMS activates multiple excitatory and inhibitory networks and the motor-evoked potential (MEP) arising from M1 stimulation will reflect the balance of these effects. One of the strongest of the inhibitory effects is long-interval intracortical inhibition (LICI), first described by Valls-Sole et al. (1992), in which a suprathreshold stimulus attenuates the amplitude of the MEP to a subsequent stimulus for up to about 200 ms. LICI is thought to be mediated through activation of postsynaptic metabotropic γ-aminobutyric acid type B (GABAB) receptors that lead to a long-lasting inhibitory postsynaptic potential (IPSP) (McDonnell et al. 2006; Werhahn et al. 1999). The same stimulus that causes sufficient GABA release to activate these receptors can also activate their counterparts on the presynaptic membrane, leading to attenuation of GABA release and correspondingly presynaptic disinhibition (Chu et al. 2008; Muller-Dahlhaus et al. 2008; Sanger et al. 2001). We have recently provided evidence that disinhibition runs in parallel with postsynaptic inhibition during the course of LICI, but that disinhibition is more persisting, outlasting LICI and leading to a period of about 50 ms post-LICI during which disinhibition predominates (Cash et al. 2010).

As the excitatory motor cortical synaptic network responsible for SICF undergoes inhibitory regulation (Lilic et al. 2002; Wagle-Shukla et al. 2009; Ziemann et al. 1998b), we hypothesized that SICF will be modulated during these periods of inhibition and disinhibition. In particular we were interested to know whether SICF is up-regulated during disinhibition, implying an increase in excitatory synaptic efficacy. We therefore measured SICF, at a paired-pulse interval of 1.5 ms, to explore excitatory synaptic interactions in M1 during periods of inhibition and disinhibition that were evoked by a preceding priming pulse.

METHODS

The study had the approval of the ethics committee of the hospital of the Goethe-University of Frankfurt am Main and conformed to the latest revision of the declaration of Helsinki. Seven neurologically healthy individuals (three female; 20–38 yr of age) without acute or chronic medication or a family history of epilepsy participated in the studies. All were right-handed according to the Edinburgh Inventory (Oldfield 1971). Participants gave informed written consent and completed a safety questionnaire prior to the study. Subjects were seated in a comfortable armchair and measurements were taken at rest.

MEPs were recorded from surface electrodes placed in a belly-tendon arrangement over the first dorsal interosseous (FDI) muscle of the right hand. The electromyographic (EMG) signal was amplified and filtered (20 Hz to 2 kHz), digitized (sample rate 4 kHz) using a
Measurements of PS.

Second, the intensity was adjusted for TS.CS (unprimed, 12 stimuli each) were delivered after every IPI. PS.TS and PS.TS.CS were delivered at each IPI and, as well, TS and 1.25-s intervals to reduced nonspecific anticipatory effects). First, stimulus combination, at each IPI, 12 stimuli were delivered (at 5 ms were used. The IPI sequence was pseudorandomized. For each individual's baseline value and averaged across the group. Statistical analysis was performed on these data as described in the following paragraph. In the unadjusted-intensity condition, the MEP arising from PS.TS at the shorter IPIs was strongly attenuated as a result of the inhibitory effects of PS, making the normal SICF calculation from PS.TS.CS divided by PS.TS unstable and unreliable. For data presentation purposes only, we calculated the difference between PS.TS.CS and PS.TS as an alternative indication of the effect of the conditioning stimulus and compared this to the equivalent difference for the adjusted-intensity condition.

The curves for corticomotor excitability and SICF as a function of IPI were subjected to a linear mixed-model analysis to determine the effects of fixed factor(s) on each response variable and allowing for a random-effects factor for the individual (subjects). Where the model assumptions were not met, a square root transformation of the response variable and allowing for a random-effects factor for the individual (subjects). The curves for corticomotor excitability and SICF as a function of IPI were subjected to a linear mixed-model analysis to determine the effects of fixed factor(s) on each response variable and allowing for a random-effects factor for the individual (subjects). Where the model assumptions were not met, a square root transformation of the response variable and allowing for a random-effects factor for the individual (subjects). Where the model assumptions were not met, a square root transformation of the response variable and allowing for a random-effects factor for the individual (subjects). Where the model assumptions were not met, a square root transformation of the response variable and allowing for a random-effects factor for the individual (subjects).

TMS protocols

Figure 1 outlines the experimental protocol. We assessed corticospinal excitability by the amplitude of the MEP arising from the delivery of a test stimulus (TS) at an intensity set to generate a MEP of just over 1 mV in amplitude (peak–peak) at baseline. We delivered the TS after a priming stimulus (PS) of strength 1.3RMT, at IPIs between 100 and 300 ms (this protocol is referred to as PS.TS). We measured SICF using a paired test-conditioning stimulus (TS.CS) at an IPI of 1.5 ms. The strength of the conditioning stimulus (CS) was about 0.9RMT, adjusted for each individual to give roughly 150% facilitation of the TS MEP to avoid floor and ceiling effects and keep the SICF measurement sensitive to change (Peurala et al. 2008). TS.CS was applied after PS at IPIs of between 100 and 300 ms (referred to as PS.TS.CS). Finally, the strength of TS, with coapplication of PS, was adjusted separately at each IPI to maintain MEP amplitude at just over 1 mV (the adjusted test stimulus is referred to as TS and this measurement as PS.TS). Measurement of the conditioned TS was made at each IPI following PS (i.e., PS.TS.CS). IPIs (PS to TS) of 100, 150, 175, 190, 200, 210, 220, 250, and 300 ms were used. The IPI sequence was pseudorandomized. For each stimulus combination, at each IPI, 12 stimuli were delivered (at 5 ± 1.25-s intervals to reduced nonspecific anticipatory effects). First, PS.TS and PS.TS.CS were delivered at each IPI and, as well, TS and TS.CS (unprimed, 12 stimuli each) were delivered after every IPI. Second, the intensity was adjusted for TS at each IPI and 12 measurements of PS.TS and PS.TS.CS were made for each IPI.

Data analysis

For convenience of reference, the MEP amplitude associated with each stimulation combination is referred to by the combination itself (e.g., TS MEP amplitude is referred to as TS amplitude, or just TS if the context is unambiguous). TS amplitude (mean of the 10 measurements taken after each IPI) was assessed for change over IPI, with a one-way repeated-measures (rm)ANOVA, and then averaged across IPI to form the baseline (unprimed) value for TS. At each IPI, the mean TS amplitude was expressed as a percentage of the individual’s baseline value and averaged across the group. This formed the measure of corticomotor excitability as a function of IPI. Baseline SICF was taken from the ratio of the mean unprimed TS.CS divided by the mean TS values that were delivered after each IPI and averaged across IPI (after confirming no change of TS.CS with IPI with a test-conditioning stimulus (TS.CS) at an IPI of 1.5 ms. The strength of the conditioning stimulus (CS) was about 0.9RMT, adjusted for each individual to give roughly 150% facilitation of the TS MEP to avoid floor and ceiling effects and keep the SICF measurement sensitive to change (Peurala et al. 2008). TS.CS was applied after PS at IPIs of between 100 and 300 ms (referred to as PS.TS.CS). Finally, the strength of TS, with coapplication of PS, was adjusted separately at each IPI to maintain MEP amplitude at just over 1 mV (the adjusted test stimulus is referred to as TS and this measurement as PS.TS). Measurement of the conditioned TS was made at each IPI following PS (i.e., PS.TS.CS). IPIs (PS to TS) of 100, 150, 175, 190, 200, 210, 220, 250, and 300 ms were used. The IPI sequence was pseudorandomized. For each stimulus combination, at each IPI, 12 stimuli were delivered (at 5 ± 1.25-s intervals to reduced nonspecific anticipatory effects). First, PS.TS and PS.TS.CS were delivered at each IPI and, as well, TS and TS.CS (unprimed, 12 stimuli each) were delivered after every IPI. Second, the intensity was adjusted for TS at each IPI and 12 measurements of PS.TS and PS.TS.CS were made for each IPI.

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The amplitude match between TS and PS.TS was tested using an independent samples t-test. The effect of PS on SICF was calculated in the adjusted-intensity condition from the ratio of PS.TS.CS to PS.TS at each IPI, expressed as a percentage of the baseline SICF (unprimed SICF) as described previously, computed for each individual and averaged across the group. Statistical analysis was performed on these data as described in the following paragraph. In the unadjusted-intensity condition, the MEP arising from PS.TS at the shorter IPIs was strongly attenuated as a result of the inhibitory effects of PS, making the normal SICF calculation from PS.TS.CS divided by PS.TS unstable and unreliable. For data presentation purposes only, we calculated the difference between PS.TS.CS and PS.TS as an alternative indication of the effect of the conditioning stimulus and compared this to the equivalent difference for the adjusted-intensity condition.

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a subtraction analysis on the MEP waveforms. We calculated\(\frac{(TS.CS)}{H11002}\)\(\frac{TS}{H11001}\)\(\frac{CS}{TS.H11002}\), which reduces to \(\frac{TS.CS}{H11002}\) because the CS did not generate a MEP. This calculation was repeated for the adjusted-intensity condition in the presence of PS (i.e., \(\frac{PS.TS}{H11002}\)). This subtraction was carried out individually and averaged across the group. The onset of interaction was determined by cursoring of the first deviation of the subtraction waveforms from baseline and compared with and without PS (referred to as the primed and unprimed TS.CS interaction latency).

RESULTS

Primed TS

The PS.TS curve is presented in Fig. 2. Two effects of PS on TS were observed, in keeping with our previous report (Cash et al. 2010). For IPIs ≤175 ms PS.TS was reduced below the baseline (TS), whereas for IPIs from 200 to 220 ms PS.TS was increased. The amplitude reduction was greatest at an IPI of 100 ms (20 ± 6% of baseline; \(P < 0.01\)) and remained significantly reduced at 150 ms (35 ± 8%; \(P < 0.01\)) and 175 ms (61 ± 17%; \(P < 0.01\)). Facilitation was significant at IPIs of 200, 210, and 220 ms (171 ± 25, 196 ± 20, and 191 ± 19%, respectively; \(P < 0.01\)). PS.TS returned to baseline by 250 ms. At the IPI of greatest attenuation (100 ms) PS.TS amplitude was 0.25 ± 0.06 mV and, at the point of greatest facilitation (210 ms), this was 2.33 ± 0.34 mV. Baseline TS amplitude was 1.29 ± 0.05 mV.

Primed conditioned TS

Figure 3A illustrates the effect of PS on the MEP amplitude (mV) of TS.CS, as well as the unprimed TS.CS and TS MEPs. In the absence of a PS there was no dependence on IPI for TS or TS.CS and the figure illustrates that these measurements, taken interspersed with the primed measurements, were consistent throughout the recording session. Mean TS amplitude was 1.29 ± 0.05 mV and mean TS.CS amplitude 2.05 ± 0.03 mV, giving 159% SICF. The addition of a PS modulated TS.CS amplitude as a function of IPI, with peak PS.TS.CS being 3.92 ± 0.58 mV at an IPI of 210 ms, representing a near doubling from TS.CS amplitude alone. At the IPI where attenuation of PS.TS was greatest (0.25 mV at 100 ms) PS.TS.CS was 1.56 ± 0.15 mV, indicating that the inclusion of CS substantially reversed the attenuating effect of PS on TS at this IPI.

Figure 3B presents corresponding data for PS.TS and PS.TS.CS. The figure shows that the TS adjustment was
effectiveness in maintaining PS.TS amplitude near to TS alone (cf. Fig. 3A), and mean PS.TS was 1.34 ± 0.03 mV and was not significantly different from the value for TS. The addition of CS in the PS.TS.CS combination resulted in PS.TS.CS being increased over PS.TS across IPI, with PS.TS.CS greatest for IPIs around 200 ms, peaking at 3.83 ± 0.72 mV.

Figure 3C presents the difference plots in the unadjusted (PS.TS.CS minus PS.TS) and adjusted (PS.TS.CS minus PS.TS) conditions. These curves indicate the magnitude of increase in MEP amplitude brought about by the conditioning stimulus, again demonstrating a period of increased facilitation centered around an IPI of 200 ms.

**Primed SICF**

In the adjusted condition, primed SICF (PS.TS.CS/PS.TS) expressed as a percentage of baseline SICF (TS.CS/TS) is illustrated in Fig. 4, together with PS.TS.CS MEP waveforms for one subject. Primed SICF was significantly greater than baseline at IPIs of 190–220 ms (*P < 0.05), but at other IPIs, including shorter IPIs, there was no difference from baseline. The percentage increase in SICF at IPIs of 190, 200, 210, and 220 ms was 185 ± 28, 152 ± 15, 170 ± 24, and 150 ± 19%, respectively (mean 164%).

**Primed TS.CS interaction**

Waveform subtraction analysis was carried out at the IPIs for which LICI was greatest (100 ms; cf. Fig. 2) and at which LCD was greatest (210 ms; cf. Fig. 2). At 100 ms, the primed interaction latency was 1.5 ms later than the unprimed interaction latency (Fig. 5A). At 210 ms IPI this pattern was reversed and the primed interaction was 1.75 ms earlier than the unprimed interaction (Fig. 5B). As a consequence, MEP latency was earlier during LCD than that during LICI and this is illustrated for one subject in Fig. 4 (inset).

**DISCUSSION**

A suprathreshold PS elicited a period of reduced corticomotor excitability (as reflected by reduced TS amplitude) followed by a period (~200 ms post-PS) in which the TS amplitude was increased. The first period corresponds to LICI (Valls-Sole et al. 1992), an inhibition likely mediated by postsynaptic metabotropic GABA<sub>B</sub> receptors that lead to a long-lasting IPSP in principal cells of the motor cortex (McDonnell et al. 2006; Werhahn et al. 1999). Disinhibition of inhibitory interneurons targeting principal cells can also occur contemporaneously with LICI, likely mediated by presynaptic GABA<sub>B</sub> receptors on these interneurons (Cash et al. 2010; Chu et al. 2008; Muller-Dahlhaus et al. 2008; Sanger et al. 2001). During this first period, the effect of postsynaptic inhibition predominates and TS amplitude is reduced (LICI). The second period, during which TS amplitude was increased, has only recently been explored in detail and is associated with a prolongation of presynaptic disinhibition relative to LICI, leading to a period in which disinhibition predominates, which we have referred to as late cortical disinhibition (LCD) (Cash et al. 2010). In the present study we have explored how synaptic transmission in excitatory motor cortical networks, as assessed by SICF (Di Lazzaro et al. 1999; Tokimura et al. 1996; Ziemann and Rothwell 2000; Ziemann et al. 1998a), is modulated during LICI and LCD. We find that the strength of SICF is enhanced during LCD, but is relatively unaffected during LICI. Priming delayed the onset of SICF by an I-wave interval (~1.5 ms) during LICI but shortened it by a similar amount during LCD. The results suggest that SICF is increased in the presence of disinhibition, but that the I-wave targeted is modified by the presence of both inhibition and disinhibition.

**SICF during LICI**

With TS intensity not adjusted and at the IPI for which LICI was strongest (100 ms), the effect of incorporating a conditioning stimulus (CS) was disproportionate to its intensity, increasing PS.TS amplitude from barely 0.25 mV to >1.5 mV.
for PS.TS.CS. Unprimed TS.CS was just over 2 mV; thus although there was some attenuation by PS, this was relatively small compared with the substantial increase of PS.TS.CS over PS.TS. This suggests that LICI has only a minimal effect on the strength of SICF in the present results is at first sight somewhat unexpected.

One possibility is that the contemporaneous disinhibition associated with LICI (Muller-Dahlhaus et al. 2001) is at least equivalently important to SICF networks compared with LICI and this is supported by the facilitation in SICF during LCD. As well, pharmacological studies indicate that the GABA_B agonist baclofen has no effect on SICF for any of the I-wave peaks (Ziemann et al. 1998b). Because baclofen will activate both pre- and postsynaptic GABA_B receptors, this is a reasonable analogy to what should be the case 100 ms after PS when LICI and presynaptic disinhibition are both active. Another mutually nonexclusive possibility is that, in the nonadjusted situation, CS interacts with inhibited, small MEPs elicited by PS.TS. According to Ilic et al. (2002) a decrease in MEP amplitude, which in that study was achieved by decreasing TS intensity, would result in enhanced SICF (cf. Figs. 1A and 2D in that article). This counteracts inhibition of SICF during LICI and, if both effects were of approximately the same strength, then the magnitude of SICF during LICI would not change. Recently it has been shown that SICI, rather unexpectedly, also does not reduce SICF at 1.5 ms and, in fact, enhances SICF for later I-wave peaks (Wagle-Shukla et al. 2009). Taken together, whereas some commonality (such as the targeting of late I-waves) is anticipated in the circuits generating LICI, SICI, and SICF, there appear to be differences in how they interact. These differences may involve a shift in the I-waves targeted by SICF, as suggested by the interaction latency data discussed in further detail later whereas the magnitude of SICF may remain unchanged.

SICF during LCD

During the LCD phase (~200 ms IPI), PS.TS.CS amplitude peaked (Fig. 3a,c), indicating that the conditioning stimulus may have a stronger effect during LCD, although PS.TS amplitude was also increased during this period. However in the adjusted TS condition, in which PS.TS amplitude was constant across IPI, PS.TS.CS amplitude and SICF peaked at this time (Figs. 3b,c and 4), demonstrating an interaction between disinhibition and the networks responsible for SICF. Disinhibition has also been invoked to explain the increase in the later SICF peaks during the action of SICI, although in this case a form of disynaptic disinhibition has been proposed (Wagle-Shukla et al. 2009), rather than presynaptic disinhibition as in the present case. Here we provide more direct evidence for an interaction between disinhibition and the networks responsible for SICF. It is also known from experimental studies that GABA_B-mediated disinhibition facilitates excitatory postsynaptic potentials (EPSPs) (Mott and Lewis 1991; Otis et al. 1993), consistent with a modulatory role for disinhibition in the strength of SICF.

Onset of interaction between CS and TS

We found that LICI delayed the effect of the CS by 1.5 ms (an I-wave interval). In contrast, during LCD, when disinhibition predominated, SICF advanced by one I-wave interval. These observations suggest a differential effect on I-waves targeted by the CS during inhibition and disinhibition.

One possibility is that it is unaffected by inhibition and disinhibition, which would be in keeping with the available evidence that this I-wave is relatively unaffected across multiple experimental protocols (Di Lazzaro et al. 2008). II may not be sufficient (at rest) to activate alpha-motoneu-
rons, but could raise the excitability of the motoneuron pool to a level that makes motoneurons susceptible to activation by later I-waves (Thickbroom 2010). In this case the latency of a MEP will depend on the relative magnitude of the I2 and I3 volleys under the influence of inhibition and disinhibition. The first-order interneuron responsible for the I2 volley is strongly controlled by inhibition (Ilic et al. 2002); thus during LICI the facilitatory effect of CS may be confined to I3 of TS and thus MEP latency set back one I-wave interval. During LCD, in which the presence of inhibition is reduced and excitability is increased as a result of disinhibition, the site of interaction jumps up (advances) by an I-wave interval. This is in keeping with Ilic et al. (2002) who showed the site of TS-CS interaction “jumped up” to an earlier I-wave, with increased excitability arising from voluntary contraction or with stronger stimulus strength. Taken together, the observations during LICI and LCD suggest that the magnitude and site of I-wave interaction by SICF can be differentially modulated by inhibition and disinhibition and that the site of interaction can be dissociated from changes in the strength of SICF.

Intensity adjustment

We made observations in the presence of PS by keeping TS intensity constant across IPI, and also by adjusting intensity (FS) at each IPI to keep the test MEP amplitude constant. In both cases the results were in agreement and followed a similar pattern, although a direct calculation of SICF was only possible from the FS data. While there is evidence supporting a constant-intensity approach in some situations (Garry and Thomson 2009), the constant-amplitude approach in the present situation enabled the effect of the conditioning pulse to be investigated without confounds surrounding the modulation of the test stimulus amplitude by PS. The intensity of the conditioning stimulus was not adjusted so that the perturbation applied to the networks was constant. This is in keeping with previous triple-pulse studies (Cash et al. 2010; Chu et al. 2008; Sanger et al. 2001; Wagle-Shukla et al. 2009), one of which (Sanger et al. 2001) showed that adjusting CS had no effect. The similarity in the pattern of the results when adjusting or not adjusting test intensity increases confidence in the conclusion that the strength of SICF is influenced by disinhibition rather than inhibition.

Physiological roles

We have previously suggested that the longer time course of disinhibition relative to inhibition may be relevant for regulating cortical rhythms because circuits that are initially inhibited through postsynaptic GABA\(_B\)-ergic processes are subsequently disinhibited (Cash et al. 2010). We suggest that this could be an active process to reactivate excitatory interneuronal circuits after they have been inhibited. The results for SICF, which targets excitatory interneuronal networks, support the up-regulation of excitatory transmission in the presence of disinhibition, both increasing the magnitude and reducing the latency of interaction. Further, disinhibition may have a permissive role in some forms of plasticity (Davies et al. 1991; Rose and Dunwiddie 1986) and thus potentially have a role in either adaptive or maladaptive plasticity in neurological disorders. The link between disinhibition and excitatory transmission suggests that TMS interventions targeting LTP of excitatory networks could prove more effective if delivered during disinhibition evoked by a priming pulse.

Conclusion

The interneuronal networks responsible for SICF are more excitable in the presence of disinhibition, but less influenced by inhibition in the form of LICI. The results support a role for disinhibition in the regulation of excitatory neuronal networks, such as those underlying SICF, and suggest that the identification of LCD in human motor cortex may provide an opportunity to investigate excitatory synaptic networks when they are less constrained by ongoing levels of inhibition and this period may be a promising target for interventional TMS protocols.

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Disclosures

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