



The EEG correlates of the TMS-induced EMG silent period in humans



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ABSTRACT

Application of magnetic or electrical stimulation to the motor cortex can result in a period of electromyography (EMG) silence in a tonically active peripheral muscle. This period of EMG silence is referred to as the silent period (SP). The duration of SP shows intersubject variability and reflects the integrity of cortical and corticospinal pathways. A non-invasive technique for assessing the duration of SP is the combination of Transcranial Magnetic Stimulation (TMS) with EMG. Utilizing TMS–EMG, several studies have reported on the shortening or lengthening of SP in neuropsychiatric disorders such as schizophrenia, bipolar disorder, depression, obsessive compulsive disorder, epilepsy, Parkinson's disease, and stroke. However, cortical, corticospinal and peripheral components are difficult to disentangle from EMG alone. Here, we use the multimodal neuroimaging technique of TMS–EMG combined with concurrent electroencephalography (EEG) recording to further examine the cortical origin of SP and the cortical oscillatory activity that underlies SP genesis. We demonstrate that the duration of SP is related to the temporal characteristics of the cortical reactivity and the power of delta to alpha oscillations in both local and remote areas ipsilateral and contralateral to the stimulation site, and beta oscillations locally. We illustrate that, compared to EMG, the EEG indices of the SP provide additional information about the brain dynamics and propose that the EEG measures of SP may be used in future clinical and research investigations to more precisely delineate the mechanisms underlying inhibitory impairments.

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Introduction

Cortical inhibition in non-human species was originally identified through direct electrical stimulation of the cortical surface and it was indexed by assessing the time period during which the probability of neuronal firing was significantly diminished (Krnjevic et al., 1966). Through such methods, the latency, duration and spatial distribution of cortical inhibition were examined across brain regions in several non-human species (Krnjevic et al., 1966). Since it is introduced by Barker in the 1980s (Barker et al., 1985), the non-invasive activation of the human cortex through transcranial magnetic stimulation (TMS) has provided an invaluable means for investigating cortical

inhibitory processes in humans across the life span, in health and disease, and without the need for invasive recordings. Several TMS protocols have been formulated to evaluate the integrity of the inhibitory, excitatory, and plasticity processes in the human motor cortex, by capitalizing on the coupling of TMS with peripheral electromyography (EMG) recording and monitoring the modulation of TMS-induced motor evoked potentials (MEPs). One such TMS protocol suggested to assess cortical inhibition is the cortical silent period (CSP) (Fuhr et al., 1991; Inghilleri et al., 1993). In CSP, suprathreshold stimulation of the contralateral motor cortex during voluntary contraction of a target muscle results in a period of EMG silence for up to several hundred milliseconds.

Converging lines of evidence suggest that the TMS-induced silent period (SP) has both a peripheral and a cortical origin. The first demonstration of cortical stimulation leading to a period of muscle activity cessation was in the 1980s, when Marsden et al. demonstrated that transcranial electrical stimulation (TES) applied to the intact scalp over the motor cortex resulted in an MEP followed by a transient period of EMG silence in a tonically active muscle (Marsden et al., 1983). A decade later, application of TMS to the motor cortex was shown to induce a similar suppression of background EMG in the activated target

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muscle (Fuhr et al., 1991; Inghilleri et al., 1993). The SP produced by TES and TMS was suggested to be different from the SP that can be observed following peripheral nerve stimulation (Marsden et al., 1983). The duration of SP was longer in response to TMS with an average of 300 ms, compared to 200 ms in TES and 100 ms following peripheral nerve stimulation (Inghilleri et al., 1993). To further examine the contribution of spinal versus cortical mechanisms to SP genesis, the amplitude of spinal reflexes (e.g., H-reflex) and descending volleys was examined at different time points during SP. H-reflex, or Hoffmann's reflex, is a muscle reaction in response to the electrical stimulation of the nerve innervating a particular muscle. The H-reflex has a latency of 25 to 35 ms with respect to electrical nerve stimulation onset. Changes in spinal reflexes provide a means by which the modulation of spinal inhibitory and excitatory mechanisms could be systematically studied (Knikou, 2008). In these investigations, a change in H-reflexes would be indicative of a spinal mechanism, and a change in descending volleys is reflective of the contribution of supraspinal mechanisms. H-reflexes were found to be suppressed only during the initial part of SP and recovered after 75 ms (Fuhr et al., 1991). Corticospinal volleys during SP were recorded in a limited number of studies in which participants had epidural electrodes implanted for various clinical purposes (Chen et al., 1999). Previously, similar studies in patients at rest or during anesthesia had been conducted to examine the effect of a TMS pulse on the corticospinal pathway. Through these studies, it was postulated that a TMS pulse activates pyramidal neurons trans-synaptically and through activation of excitatory interneurons as evident by the TMS-induced generation of multiple indirect descending volleys referred to as I-waves (Ziemann and Rothwell, 2000). When descending volleys were recorded during SP, the TMS-induced I-waves were unchanged during the early phase and suppressed in the late part of SP. Collectively, the recovery of H-reflexes and the suppression of cortically evoked I-waves during the late part of SP support the involvement of segmental inhibition in the early phase and cortical mechanisms in the late phase of SP.

The results of pharmacological interventions and the comparison between TMS markers of inhibition suggest that SP is, in part, related to the activity of the gamma-aminobutyric acid (GABA)ergic neurotransmitter system. In this regard, Siebner et al. reported a significant prolongation of the SP_{dur} following the continuous intrathecal administration of baclofen, a GABA_B agonist, in a patient with generalized dystonia (Siebner et al., 1998). Baclofen was shown to prolong the TMS-induced SP, while it did not affect the cutaneous SP, which is a spinal inhibitory reflex (Stetkarova and Kofler, 2013). Similarly, tiagabine, a GABA re-uptake inhibitor, was shown to prolong SP duration (Werhahn et al., 1999). Furthermore, the duration of SP is consistent with the peak of GABA_B receptor activation that is reported by *in vitro* studies to be 100 to 300 ms (McCormick, 1989). While SP is postulated to reflect the duration of GABA_B mediated intracortical inhibition, the paired pulse TMS paradigm long interval cortical inhibition (LICI) is suggested to reflect the magnitude of GABA_B mediated intracortical inhibition (Kapogiannis and Wassermann, 2008; McDonnell et al., 2006; Sanger et al., 2001). In LICI, a suprathreshold conditioning stimulus delivered within 50 to 200 ms prior to a suprathreshold test stimulus, suppresses the response to the test stimulus (Valls-Sole et al., 1992). Although previous studies have often failed to find a direct association between SP and LICI (Benwell et al., 2007; Inghilleri et al., 1996; McDonnell et al., 2006), we have recently demonstrated that SP_{dur} correlates with the magnitude of EMG suppression in LICI (Farzan et al., 2010c). Epidural recordings have demonstrated that LICI suppresses the late I-waves at interstimulus interval of 100 to 200 ms (Chen et al., 1999; Di Lazzaro et al., 2002; Nakamura et al., 1997), consistent with the peak activity of GABA_B receptors.

Paralleling the above-mentioned proof-of-concept studies, several investigators have utilized TMS–EMG techniques to examine the integrity of SP_{dur} in patients with neurological or psychiatric disorders. The results

of these endeavors have shown pathological prolongation or reduction of SP_{dur} in a variety of neurological and psychiatric conditions. For example, reduction of SP_{dur} has been reported in schizophrenia (Daskalakis et al., 2002; Fitzgerald et al., 2002, 2004), bipolar disorder (Levinson et al., 2007), unipolar major depression (Bajbouj et al., 2006b; Levinson et al., 2010), obsessive compulsive disorder (Richter et al., 2012), Alzheimer's Disease (Alagona et al., 2001), borderline personality disorder (Barnow et al., 2009), Parkinson's disease (Nakashima et al., 1995; Priori et al., 1994a), fibromyalgia (Salerno et al., 2000), and chronic neuropathic pain (Lefaucheur et al., 2006). Pathological prolongation of SP has been reported in conditions such as stroke (Braune and Fritz, 1995; Classen et al., 1997), cerebellar ataxia (Oechsner and Zangemeister, 1999; Tamburin et al., 2004; Teo et al., 2008), sport related concussion (De Beaumont et al., 2007, 2009; Tremblay et al., 2011), Huntington's disease (Priori et al., 1994b), generalized seizure (Macdonnell et al., 2001), partial seizure during periods with high chance of relapse (Cincotta et al., 2002), unilateral cerebellar stroke with damage of dentate nucleus (Battaglia et al., 2006), abstinence cocaine-dependence (Gjini et al., 2012), and agenesis of corpus callosum (Fecteau et al., 2006). In addition to these efforts, several studies have further examined the effect of rehabilitation, neuro-modulation and pharmacological interventions on restoration of SP_{dur}. As examples, in Parkinson's disease, repetitive TMS (Siebner et al., 2000), eight weeks of intense exercise (Fisher et al., 2008), and dopaminergic (Lefaucheur, 2005) treatment resulted in prolongation of SP. In depression, ten sessions of unilateral ECT prolonged SP (Bajbouj et al., 2006a). In schizophrenia, patients who were treated with clozapine had longer SP_{dur} compared to unmedicated patients (Daskalakis et al., 2008a). Cognitive behavioral therapy prolonged SP in problematic perfectionists (Radhu et al., 2012). Finally, low frequency TMS over premotor cortex but not motor cortex prolonged SP and improved the hand writing score in focal dystonia (Murase et al., 2005).

Reviewing the wealth of experimental evidence on the neurophysiology of SP and the long list of pathological states that lead to SP impairments, as well as the potential therapeutic strategies that may restore such impairments, several questions remain: first, with the duration of the EMG silence as the primary outcome measure, the exact origin of SP (spinal versus cortical) remains unclear. Second, the degree to which local versus remote cortical processes contribute to SP_{dur} remains elusive as it appears that brain areas that are not directly stimulated have significant impacts on SP_{dur} (e.g., prolongation of SP in cerebellar stroke and corpus callosum agenesis). Consequently, it remains unclear whether SP merely reflects the impairment of the inhibitory processes of the stimulated motor cortex, or whether deficits in the other motor-related areas and non-motor regions contribute significantly to SP_{dur}. Thus, more sensitive neurophysiological techniques and markers are desirable through which future clinical studies could further classify and more selectively restore inhibitory impairments based on the exact origin and neurophysiology of the underlying mechanisms.

The combination of concurrent electroencephalography (EEG) with TMS has provided a new way to study the effects of non-invasive brain stimulation and appears particularly suited to address these questions. TMS–EEG complements the H-reflexes and the invasive epidural recordings and permits revisiting the classical TMS–EMG paradigms and delineating, with more precision, neural processes that underlie the MEP modification at the periphery. Thus, a growing number of TMS–EEG studies have begun to document the EEG correlates of single and paired pulse TMS paradigms in the motor cortex at rest (Farzan et al., 2010a, 2010b, 2010c; Ferreri et al., 2011; Ilmoniemi et al., 1997; Komssi and Kahkonen, 2006; Nikulin et al., 2003; Paus et al., 2001; reviewed in Farzan et al., 2011). However, the EEG correlates of the TMS-induced SP have not been described. In this study, we combine TMS–EMG with concurrent EEG to further explore the features and characteristics of local as well as remote cortical reactivity during the period of EMG silence in healthy subjects.

Methods

Subjects

We studied 18 right-handed healthy subjects (age range = 21–41 years; 13 males and 5 females, age = 31.1 ± 7.0 years, please note that throughout the manuscript descriptive values are reported as mean \pm standard deviation, unless indicated otherwise). Subjects were recruited through advertisement and psychopathology was ruled out through the personality assessment screener (Psychological Assessment Resources, Inc). Exclusion criteria also included a self-reported medical illness or a history of drug or alcohol abuse. In all subjects, handedness was confirmed using the Oldfield Handedness Inventory (Oldfield, 1971). All participants gave their written informed consent and the protocol was approved by the local ethics committee at the Centre for Addiction and Mental Health in accordance with the Declaration of Helsinki.

Data recording

Transcranial magnetic stimulation

Monophasic TMS pulses were administered using a Magstim 7 cm figure-of-eight coil and one Magstim 200 stimulator (Magstim Company Ltd, UK). At the beginning of each experiment, resting motor threshold was determined by applying single pulses of TMS to the left motor cortex while the coil was placed at the optimal position for eliciting MEPs from the right abductor pollicis brevis (APB) muscle. Resting motor threshold was defined as the minimum stimulus intensity that elicited an MEP of more than 50 μ V in at least five out of ten trials (Rossini et al., 1994). We determined resting motor threshold once prior to positioning the EEG cap on the head, and once after. This intensity corresponded to an average of $42.2 \pm 8.0\%$ of maximum stimulator output without the EEG cap, and $56.6 \pm 10.0\%$ with the EEG cap across 18 subjects. The optimal position was marked on the EEG cap with a felt pen to ensure identical placement of the coil throughout the experiment, and the handle of the coil pointed backward, perpendicular to the presumed direction of the central sulcus, approximately 45° to the midsagittal line. The direction of the TMS-induced current in the brain tissue was posterior–anterior.

Electromyography

Throughout the experiment, the subjects were seated in a comfortable armchair with their hands positioned on a pillow placed over their laps, and they were asked to maintain relaxation as EMG was monitored on a computer screen, unless instructed to contract their muscle. Two disposable surface disc electrodes were placed in a tendon–belly arrangement over the right APB muscle, a ground electrode was placed over the right forearm, and EMG activity was acquired through Signal software (Cambridge Electronics Design, UK). The EMG signals were amplified (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), filtered (band-pass 2 Hz to 5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, UK), and stored in a laboratory computer for offline analysis.

Silent period. The SP was recorded during voluntary contraction of the right APB muscle by stimulation of the left motor cortex at 140% of resting motor threshold. This corresponded to $79.2 \pm 14.0\%$ of stimulator output. A total of fifty stimuli were delivered with an interstimulus interval of 10 s, while the APB muscle was contracted at 20% of maximum muscle contraction measured by a strain gage meter. It should be noted that, while in our previous reports we delivered 80–100 pulses (Daskalakis et al., 2008b), in this study we administered 50 pulses to minimize the possibility of inducing muscle fatigue associated with repetitive muscle contraction.

Electroencephalography

EEG signals were acquired through a 64-channel Synamps2 EEG system (Neuroscan, Compumedics, USA). A 64-channel EEG cap was positioned on subjects' head and for all electrodes impedance was lowered to ≤ 5 K Ω . The 64-channel EEG cap included 62 electrodes, one ground electrode, and one reference electrode. Four additional electrodes were placed on the outer side of each eye, and above and below the left eye to monitor eye movement artifacts. All electrodes were referenced to an electrode placed over the vertex posterior to the CZ electrode. EEG signals were recorded with filters set at DC to 200 Hz at 20 kHz sampling rate, which was shown to avoid saturation of amplifiers and minimize the TMS-related artifact (Daskalakis et al., 2008b). It should be noted while this amplifier setting was effective in this setup, it is recommended that the use of online filters be avoided if possible (Ilmoniemi and Kicic, 2009). Throughout the experiments, EEG and EMG were recorded simultaneously.

Data analysis

EMG measures of silent period

Peripheral motor activity. EMG trials were reviewed and trials contaminated with physiological and TMS artifact were deleted using the commercially available software Signal (Cambridge Electronics Design, UK). All trials were also imported into MATLAB (The MathWorks, Inc. Natick, MA, USA) for further analysis as well as visual representation of the data (Fig. 1A).

Duration of silent period. The SP_{dur} was measured from the onset of MEP to the reoccurrence of any background EMG activity according to previously described methods (Farzan et al., 2010c; Saisanen et al., 2008). We also measured the onset of the absolute SP defined as the onset of the period with no EMG activity after the TMS-induced MEP (Fig. 1A).

Amplitude of motor evoked potentials. For each subject, the mean peak-to-peak amplitude of MEPs and the maximum amplitude of the rectified MEPs were measured.

EEG measures of silent period

TMS-evoked potentials. The EEG recordings were first processed offline by the commercially available software (Neuroscan, Compumedics, USA). The EEG data were down sampled to 1 kHz sampling frequency and segmented with respect to the TMS stimulus such that each epoch included 1000 ms pre-stimulus baseline and a 1000 ms post-stimulus activity. Epochs were baseline corrected with respect to the TMS-free pre-stimulus interval (-1000 ms to -110 ms). EEG waveforms were then imported into MATLAB R2012a (The MathWorks, Inc. Natick, MA, USA) and further analyses were carried out by the open source signal processing functions available in the EEGLAB toolbox version 11b (Delorme and Makeig, 2004). Using EEGLAB 'scroll' function, each epoch was manually reviewed and trials and electrodes contaminated with muscle activity, EOG artifact, and TMS-related artifacts (amplitude >50 μ V) contaminating more than 60 ms of post TMS stimulus were excluded from further analysis. Approximately $13.0 \pm 15.0\%$ of trials were excluded in each subject, and the average number of clean trials per subject was 43 ± 9 trials. The TMS-related artifacts might have been due to short-lived high voltage TMS-induced artifact (Ives et al., 2006), TMS-induced activation of the peripheral nerves and cranial muscles near the coil (Korhonen et al., 2011; Maki and Ilmoniemi, 2011; Mutanen et al., 2012), the movement of the EEG sensors due to the electromotive forces (Sekiguchi et al., 2011) or the TMS-induced nerve and muscle activation, the TMS-induced accumulation of charges and their slow decay at every interface with capacitive properties such as the skin-electrodes interface (Veniero et al., 2009) or

even the interface between several deeper epithelial layers of the skin (Julkunen et al., 2008). The time window contaminated by the large-amplitude TMS-related artifacts (36 ± 10 ms) was replaced by interpolating the last artifact-free data point from the pre-stimulus period and the first artifact-free post-stimulus data point using cubic interpolation. It should be noted that although the duration of the TMS artifact is relatively long, this does not affect our study since we have chosen not to include the early brain response. A notch filter (band-stop: 55–65 Hz) was used to remove the 60 Hz noise. EEG signals were band passed filtered for the frequency range of 1–50 Hz to further minimize contamination by muscle artifact. The infinite impulse response (IIR) Butterworth filter of second order was employed

and both forward and backward filtering was applied (MATLAB function 'filtfilt') to maintain a zero phase shift. The data was then average re-referenced. To examine the EEG–EMG correlation across subjects, all clean trials were averaged for each channel (Fig. 1B). The average of cleaned trials for each channel is referred to as TMS-evoked potentials (TEPs) throughout the manuscript (Figs. 1C and 2A).

Global Mean Field Amplitude. The Global Mean Field Amplitude (GMFA) was calculated for each subject using Eq. (1) adapted from Lehmann and Skrandies (1980). GMFA represents the root of the mean of the squared TEP differences at all K electrodes (i.e., $V_i(t)$) from the mean of instantaneous TEP across electrodes (i.e., $V_{mean}(t)$) (Lehmann and Skrandies, 1980). GMFA identifies the maximum amplitude of the evoked field (Lehmann and Skrandies, 1980) and has been used in previous TMS–EEG literature (Komssi et al., 2004) to measure the global brain response to TMS. For each subject, the amplitude and latency of peaks in GMFA (i.e., local maxima) were obtained (Fig. 2B).

$$GMFA = \sqrt{\left(\frac{\sum_i^K (V_i(t) - V_{mean}(t))^2}{K} \right)} \quad (1)$$

Amplitude of TMS-evoked potentials. The maximum amplitude of local (i.e., TEP_{amp} at each electrode) and global (i.e., $GMFA_{amp}$) TEPs was obtained by measuring the maximum amplitude of cortical activity during the absolute SP (Fig. 1C). To more closely approximate the time window during which cortical activity may correspond to SP generation at the periphery the following method was employed. For each subject, the MEP latency (19.21 ± 2.6 ms) was used as an estimate of transmission time to approximate the time it takes for the cortical activity to reach the APB muscle. The onset and offset of absolute SP were used and the offset of SP was leftward shifted by the MEP latency. We employed the onset of absolute SP to minimize the confounding contribution of cortical activity corresponding to the TMS-induced MEP generation. While we leftward shifted the SP offset by MEP latency, we did not leftward shift the absolute SP onset (latency ~ 67.1 ms) by MEP latency as TMS artifact contaminates the early brain response (average 36 ± 10 ms post TMS) and, therefore,

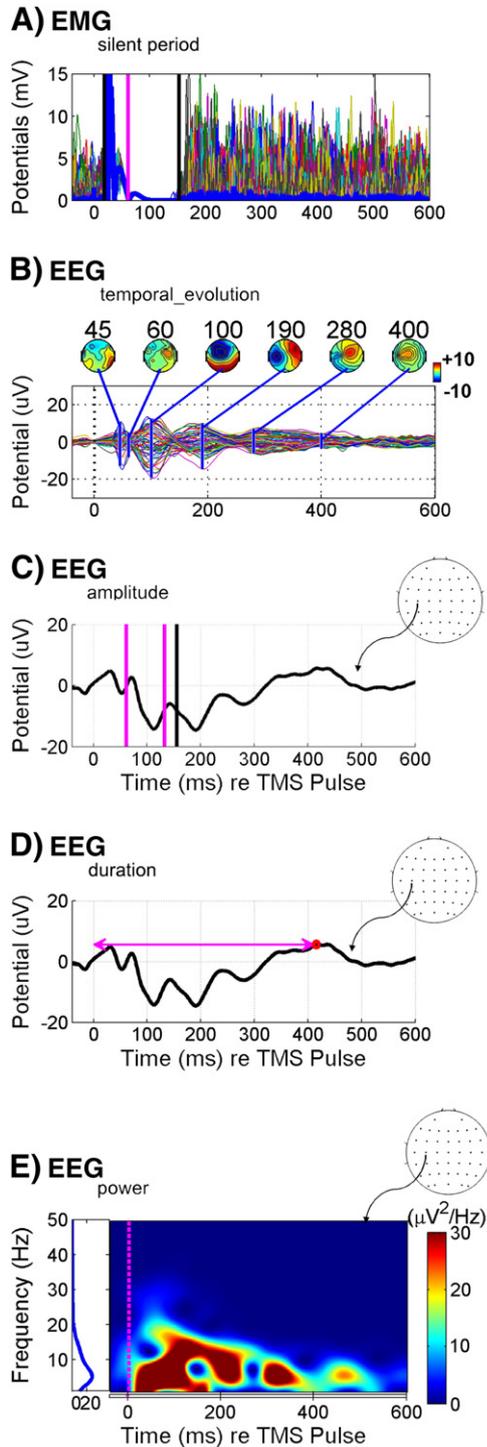


Fig. 1. Illustration of peripheral and cortical components of silent period in a representative subject. In all figures, the x-axes represent time relative to the onset of TMS administration. The data presented in all panels are taken from the same subject. A) Waveforms represent the rectified EMG recording from the abductor pollicis brevis (APB) muscle for all trials (colored waveforms) and averaged across the trials in one subject (the blue bold waveform). The y-axis represents EMG potential in mV. The first solid vertical black line represents the onset of MEP (MEP latency) which is often marked as the onset of silent period in previous TMS literature. The second vertical black line marks the emergence of background EMG activity and the end of the silent period. The first solid vertical pink line represents the onset of absolute silent period defined as the beginning of cessation of muscle activity. In B to D, y-axes represent EEG potential in μV . B) Waveforms represent the average TMS-evoked potentials (TEPs) for each channel. The head plots are the topographic representation of TEPs at several time points corresponding to previously published peaks identified in TMS–EEG studies (N45, P60, N100, P190, N280) and also 400 ms following TMS delivery, illustrating the temporal evolution of TEPs. In C–D, the waveform represents the average TEP from one electrode (i.e., C3). C) This panel illustrates TEP amplitude (TEP_{amp}) defined as the maximum amplitude of TEP during SP for each channel. The pink lines illustrate the time interval during which TEP_{amp} was obtained. The first pink line demonstrates the onset of absolute silent period the second pink line represents the offset of absolute silent period (black line) shifted by the MEP latency (about 20 ms). D) This panel illustrates TEP duration (TEP_{dur}) for each channel. The red circle illustrates the last peak of TEP that had an amplitude at least six standard deviation larger than the maximum potential in the pre-stimulus interval (-600 ms to -100 ms) of the global mean field amplitude (GMFA) in each subject. The arrow illustrates the duration of TEP, defined as the latency of this last peak with respect to the TMS onset. E) This figure shows the time–frequency representation of TEP in one electrode. The y-axis represents frequency in Hz. The colors represent absolute power in $\mu V^2/Hz$. Time–frequency representations were obtained by Fast Fourier Transform (FFT) and a sliding window size of 200 ms. FFT was carried out by EEGLAB toolbox (Delorme and Makeig, 2004) and through the function 'newtimef' using hanning FFT tapering.

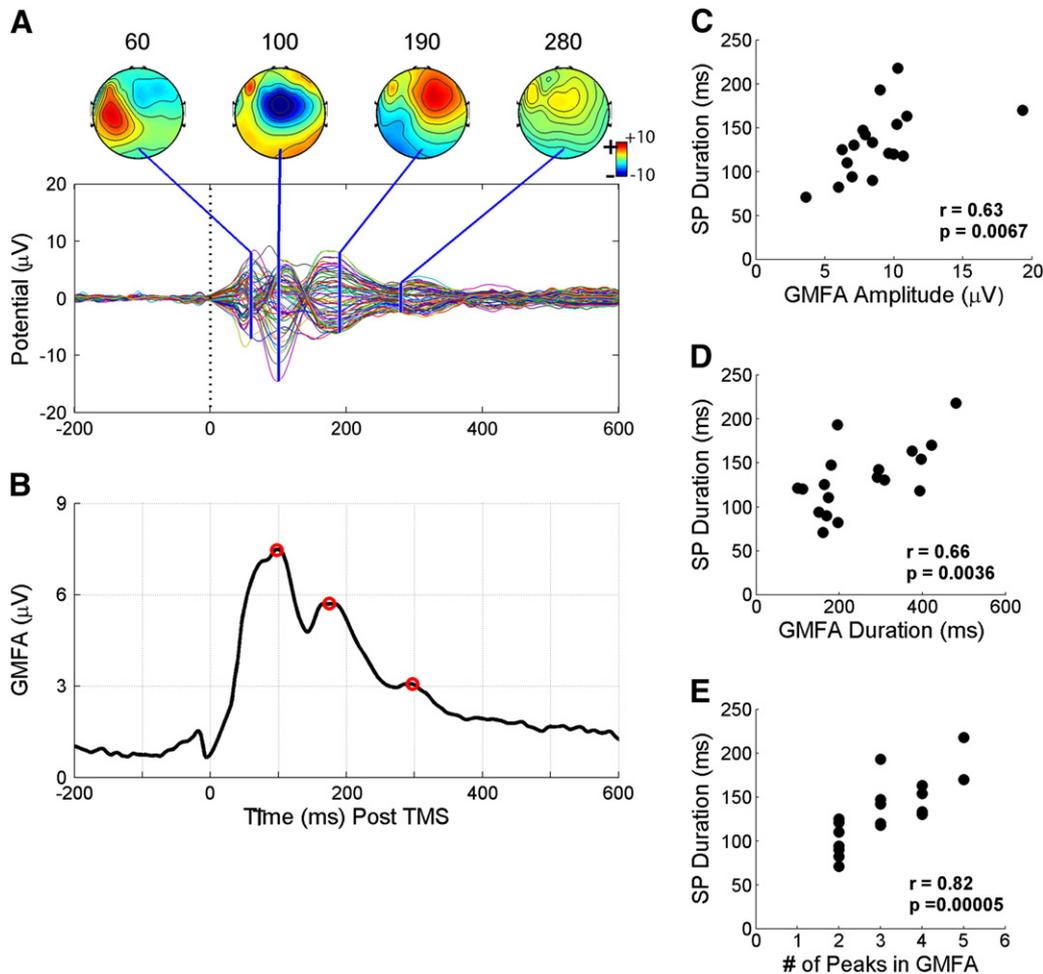


Fig. 2. Mean temporal characteristics of cortical activity across subjects. A, B) In both figures, x-axes represent time in milliseconds with respect to TMS delivery, and y-axes represent EEG potential in μV . A) Waveforms represent mean TMS-evoked potentials (TEPs) for each electrode averaged across subjects. Head plots are topographic illustration of TEPs amplitude at 60, 100, 190, and 280 ms time points following TMS, which correspond to components reported in previous TMS-EEG literature. B) The waveform demonstrates the Global Mean Field Amplitude (GMFA) averaged across subjects. The red circles mark the peaks. In C–E, points represent data from individual subjects, and the y-axes represent the silent period (SP) duration in millisecond. C) The x-axis represents the maximum GMFA amplitude during SP in μV . This figure illustrates the correlation between the SP duration and the maximum GMFA amplitude during SP. D) The x-axis represents the GMFA duration measured as the latency of last peak that had an amplitude at least six standard deviation larger than the maximum potential in the pre-stimulus interval (-600 ms to -100 ms) of the GMFA of each subject. This figure illustrates the correlation between the SP and GMFA duration. E) The x-axis represents the number of GMFA peaks. This figure illustrates the correlation between the number of GMFA peaks and SP duration.

the TEP response within the first 50 ms are not reliably recorded for all subjects. Although not our intention, this procedure may also in part reduce the confounding contribution of the afferent somatosensory potentials due to proprioceptive feedback related to the TMS-induced MEP. In addition, the mean latency of TEP_{amp} was calculated for each electrode.

Finally, we investigated the presence, amplitude, and the latency of TEP components P60, N100, P190 and N280 which have been previously reported in single pulse TMS-EEG studies and which we could identify across several channels in this dataset. The P60 component was defined as a positive deflection that occurred within a time window of 50 to 70 ms post TMS pulse. Similarly, N100, P190, and N280 components were defined as negative, positive, and negative deflections that occurred within a time window of 75 to 130 ms, 150 to 230 ms, and 250 to 350 ms post TMS pulse, respectively.

Duration of TMS-evoked potentials. The duration of local (i.e., TEP_{dur} at each electrode) and global (i.e. GMFA_{dur}) cortical responses were identified for each subject. In each subject, the duration of TEP and GMFA were defined as the latency of the last peak of the cortical response, within the time interval of 50 to 500 ms post TMS, that had an amplitude at least six standard deviation larger than the peak amplitude in the pre-stimulus interval (-600 ms to -100 ms) of

each subject's GMFA. In addition, for each subject we also identified the total number of peaks in GMFA to further examine the shape of the cortical response. Peaks were identified semi-automatically in MATLAB.

Time-frequency representation and spectral power of TMS-evoked potentials. The time-frequency representation of cortical activity for each subject and electrode was calculated by means of hanning Fast Fourier Transform (FFT) tapering using the 'newtimef' function in EEGLAB (Fig. 1E). We calculated the absolute time-frequency power without baseline correction and by setting 'baseline' in 'newtimef' to NaN. We applied a sliding window size of 200 ms in width to the average clean data over a 2-second time interval (-1000 ms to 1000 ms post TMS) to optimally separate out both the low and high frequency components. We then used post-hoc frequency binning to quantify the absolute spectral power (i.e., $\mu\text{V}^2/\text{Hz}$) for individual frequency bands of delta (1–3.5 Hz), theta (4–7 Hz), alpha (8–11 Hz), beta (12–28 Hz), and gamma (30–50 Hz) oscillations for a time window starting from 50 ms post TMS to 500 ms post TMS presentation. A time window width of 450 ms was chosen as it is long enough to include the mean power of at least one half cycle of the lowest frequency analyzed but not too long relative to the mean SP_{dur}. However, it should be noted that the sliding window size of 200 ms used here does not include a full cycle

of frequencies less than 5 Hz, and therefore delta frequency may not be accurately detected.

Statistics

For each variable, descriptive values are reported as mean ± standard deviation. using Spearman's rank correlation coefficient, the cortical-peripheral (i.e., EEG–EMG) correlation maps were obtained to investigate the relationship between: 1) SP_{dur} and the 'amplitude' of cortical activity by examining the correlations between SP_{dur} and GMFA_{amp} and TEP_{amp} for each electrode (Figs. 1A and C); 2) SP_{dur} and TEP 'components' by examining the correlations between SP_{dur} and TEP_{components} of P60, N100, P190 and N280 (Fig. 5), and between SP_{dur} and the number of peaks of the GMFA (Fig. 3); 3) SP_{dur} and 'duration' of cortical activity by examining the correlations between SP_{dur} and GMFA_{dur} and TEP_{dur} for each electrode (Figs. 1A and D); 4) SP_{dur} and the 'spectral power' of TEP by examining the correlations between SP_{dur} and the overall spectral power (1–50 Hz) and the spectral power for each frequency band for each electrode (Figs. 1A and E); 5) Finally, the correlation between the possible confounding contribution of MEP response was examined by obtaining the correlation between the maximum peak of the rectified MEP amplitude and TEP_{amp}, TEP_{components}, TEP_{dur}, the spectral power for each frequency band, as well as GMFA_{amp} GMFA_{dur} and the number of peaks of the GMFA. For analyses 1 through 4, partial correlation was employed controlling for the MEP amplitude.

For cortical-peripheral correlation maps, correlation coefficients were presented as head plots and by setting non-significant ($p > 0.05$) Spearman's r values to zero, depicted as green color in topographic plots (Figs. 4B, D, 6B, D, and 7B, C). The Spearman's r values were Fisher z transformed (i.e., $z = 0.5 \ln[(1 + r)/(1 - r)]$) to visually depict the localization of maximal EEG–EMG correlation across cortical regions. Furthermore, to control for multiple comparisons (i.e., 6 GMFA–EMG comparisons + 62 electrodes × 16 TEP–EMG comparison + 8 TEP_{components}–EMG comparisons = 1006 comparisons) we used the Benjamini and Hochberg (1995) procedure for controlling for false discovery rate (FDR). This method is suggested to be best suited for exploratory studies of focally and broadly distributed effects (Groppe et al., 2011a, 2011b). The names of the electrodes that survived this correction (adjusted $p = 0.0015$) are highlighted and listed for each EEG metrics in Table 1. For the purpose of the topographic EEG–EMG correlation maps, however, we chose to represent all correlations with $p < 0.05$ to illustrate also the areas that were moderately correlated with SP_{dur}. As such, we refer to correlations with p value between 0.0015 and 0.05 as moderately significant correlations. Furthermore, to examine the effect of cortical regions on TEP_{dur}, a one-way repeated

measure analysis of variance (ANOVA) was employed. Post-hoc pairwise comparisons were performed using Bonferroni correction to account for multiple comparisons, and Mauchly's test of sphericity was used to determine if the assumption of sphericity was met. Finally, to test the difference between two correlations, we used the method proposed by Meng et al. This method is based on the Fisher z transformation and provides a test and confidence interval for comparing two correlated correlations (Meng et al., 1992). Statistical analyses were performed using MATLAB statistical toolbox (The MathWorks, Inc. Natick, MA, USA) and SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

EMG response to TMS

The mean onset, duration and offset of SP averaged across subjects were 19.2 ± 2.6 ms, 132.3 ± 38.2 ms and 153.4 ± 37.8 ms, respectively. The onset of the absolute SP (i.e., the onset of EMG silence after MEP) was 67.1 ± 2.7 ms. The mean peak-to-peak MEP amplitude and the mean maximum amplitude of the rectified MEP were 26.6 ± 7.6 mV and 14.2 ± 3.4 mV, respectively, averaged across subjects. Please note that our EMG amplitudes seem to be higher than the average EMG amplitudes reported in other studies. This is likely due to our EMG amplifier setting such as the gain. However, this setting does not affect our results as we used the same amplifier setting in all subjects.

EEG response to TMS

Global EEG response to TMS

Amplitude of Global Mean Field Amplitude. The average maximum amplitude of the global cortical activity (i.e., GMFA_{amp}) during SP was 8.8 ± 3.2 μ V across subjects. The SP_{dur} correlated moderately ($r = 0.63$, $p = 0.0067$) with the GMFA_{amp} (Fig. 2C). We did not find a correlation between the MEP amplitudes and the GMFA_{amp} ($p = 0.42$). The mean latency of GMFA_{amp} was 94.6 ± 21.3 ms across subjects.

Duration of Global Mean Field Amplitude. The mean GMFA_{dur} across subjects was 253.7 ± 118.2 ms. There was a moderately significant correlation between SP_{dur} and GMFA_{dur} ($r = 0.66$, $p = 0.0036$; Fig. 2D). We did not find a correlation between the MEP amplitudes and the GMFA_{dur} ($p = 0.12$). The SP_{dur} and the corresponding GMFA_{dur} in subjects with short (less than one SD below the mean SP_{dur}) and long SP_{dur} (more than one SD above the mean SP_{dur}) are illustrated in Fig. 3.

Local EEG response to TMS

Amplitude of TMS-evoked potentials. The correlations between SP_{dur} and TEP_{amp} were significant ($p < 0.0015$) at multiple electrodes overlying the bilateral motor, contralateral fronto-temporal, and contralateral parieto-occipital cortices (Fig. 4B; Table 1). Fig. 4C illustrates the strong correlation ($r = 0.83$, $p = 0.00004$) between SP_{dur} and the TEP_{amp} at FC3 electrode. The mean amplitude and latency of the TEP_{amp} averaged across significant electrodes were 9.3 ± 2.2 μ V and 93.2 ± 6.8 ms, respectively, across subjects.

The correlation between MEP amplitudes and TEP_{amp} was moderately significant at two electrodes (F1: $r = 0.50$, $p = 0.04$; CB1: $r = 0.49$ $p = 0.04$ Fig. 4D).

The average TEP_{amp} latency is illustrated on a topographic map (Fig. 4E). The topographic illustration of TEP_{amp} latency demonstrates that the TEP_{amp} latency was shorter in the ipsilateral hemisphere, in electrodes closer to the site of stimulation, and longer for the contralateral cortex. Therefore, in an exploratory analysis, we compared the TEP_{amp} latency between ipsilateral and contralateral hemisphere.

Table 1
Summary of EEG–EMG correlation maps corrected for multiple comparisons.

| | $P < 0.0015$ | |
|----------------------|---|-----|
| | SP | MEP |
| TEP _{amp} | (FC3), (C3, CP1, CP3), (FT8), (TP8), (C6), (PO8) ($r = 0.83$), ($r = 0.78$, $r = 0.71$, $r = 0.74$), ($r = 0.80$), ($r = 0.73$), ($r = 0.77$), ($r = 0.74$) | – |
| TEP _{dur} | C1 ($r = 0.72$) | – |
| TEP _{power} | | |
| All | (FC3), (C3), (FT8), (C6) ($r = 0.85$), ($r = 0.84$), ($r = 0.78$), ($r = 0.75$) | – |
| Delta | (FC3), (C3, CP1), (FT8), (C6) ($r = 0.76$), ($r = 0.84$, $r = 0.75$), ($r = 0.76$), ($r = 0.74$) | – |
| Theta | (FC3), (C3, CP1), (FT8), (C6) ($r = 0.81$), ($r = 0.83$, $r = 0.74$), ($r = 0.77$), ($r = 0.76$) | – |
| Alpha | (FC3), (C3), (FT8), (C6, CP4) ($r = 0.90$), ($r = 0.83$), ($r = 0.76$), ($r = 0.72$, $r = 0.71$) | – |
| Beta | FC3 ($r = 0.76$) | – |
| Gamma | – | – |

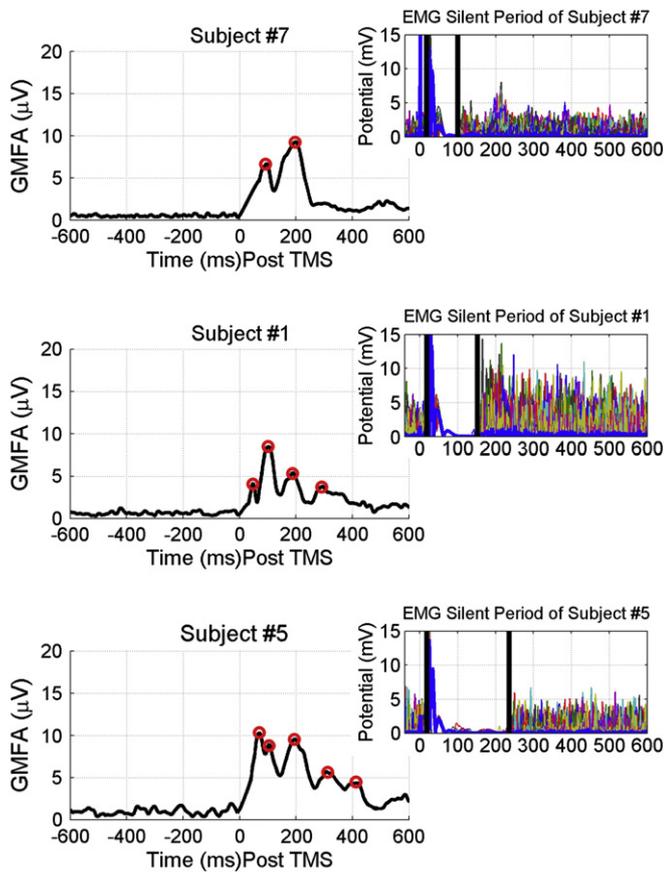


Fig. 3. Single subject data demonstrating the global brain response to TMS in the silent period paradigm. In all figures, the x-axes represent time in milliseconds relative to TMS pulse. In the left column, waveforms represent the Global Mean Field Amplitude (GMFA), the y-axes represent EEG potential in μV , and the red circles represent the GMFA peaks. The right column demonstrates the peripheral EMG silent period (SP), the y-axis represents EMG potential in mV, and waveforms represent the rectified EMG recording from the abductor pollicis brevis muscle for all trials (colored waveforms) and averaged across trials (the blue bold waveform). The first solid vertical black line represents the onset of MEP which is often marked as the onset of silent period. The second vertical black line marks the emergence of background EMG activity and the end of silent period. The three rows illustrate the GMFA and the corresponding EMG silent period of representative subjects with short SP duration (subject #7: $SP_{\text{dur}} = 90$ ms which is \leq one standard deviation from the mean SP duration across subjects), average SP duration (subject #1; $SP_{\text{dur}} = 133$ ms which is approximately the same as mean SP duration) and long SP duration (subject #5: $SP_{\text{dur}} = 218$ ms which is \geq one standard deviation from the mean SP duration).

We performed a two-tailed paired-t test comparison between the TEP_{amp} latency in the ipsilateral motor area (mean latencies at electrodes FC5, FC3, FC1, C5, C3, C1, CP5, CP3, and CP1) and the contralateral motor area (electrodes FC6, FC4, FC2, C6, C4, C2, CP6, CP4, and CP2). We found that the TEP_{amp} latency was slightly ($t = -1.8$, $df = 17$, $p = 0.08$) longer in the contralateral (103.3 ± 26.9 ms) compared to the ipsilateral motor area (93.3 ± 18.04 ms). Furthermore, there was a strong significant correlation between the TEP_{amp} latency of the contralateral motor area and SP_{dur} ($r = 0.84$, $p = 0.00001$) which was slightly ($p = 0.089$, one-tailed (Meng et al., 1992)) stronger than the correlation between the TEP_{amp} latency in the ipsilateral motor area and SP_{dur} ($r = 0.69$, $p = 0.002$).

Finally, we found a strong correlation between SP_{dur} and the number of peaks of GMFA ($r = 0.82$, $p = 0.00005$, Fig. 2E). The number of peaks of GMFA did not correlate with MEP amplitudes ($p = 0.34$).

Components of the TMS-evoked potentials. Following the TMS pulse several negative (i.e., N100, N280) and positive (i.e., P60, P190) deflections were seen at the vertex (Figs. 5A–B). We did not consider the earlier TEP components (e.g., N15, P30, and N45) since the TMS-related

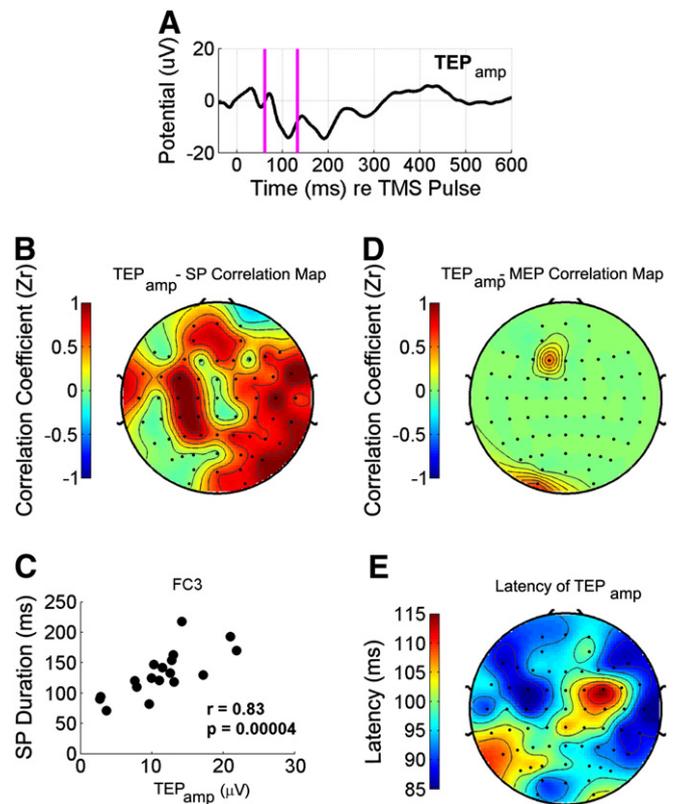


Fig. 4. The amplitude of TMS-evoked potentials during TMS-induced silent period. A) The x-axis represents time in milliseconds with respect to TMS pulse, and y-axis represents EEG potential in μV . The waveform is TMS-evoked potential (TEP) in one electrode (i.e., C3) in a subject. This figure illustrates that for each electrode the maximum amplitude of the TMS-evoked potential (TEP_{amp}) was measured within the time interval that corresponded to the peripheral EMG silent period (SP) as illustrated in Figs. 1C and B) The topographic representation of the EEG–EMG correlation map between the TEP_{amp} and the SP duration. The colors encode the adjusted Z transformed Spearman's rank correlation coefficient (Z_r) values obtained by setting to zero the r values of non-significant correlations ($p > 0.05$), depicted as green in the color map. C) Each point represents data from an individual subject. The x-axis represents the average TEP_{amp} in FC3 electrode that significantly ($p = 0.00004$) correlated with the peripheral SP duration. Please note that this correlation is not an estimation of the true effect size. D) A topographic representation of the EEG–EMG correlation map between the TEP_{amp} and the amplitude of the TMS-induced motor evoked potential (MEP). Similar to panel C, colors encode the adjusted Z transformed Spearman's rank correlation coefficients (Z_r). E) The colors encode the mean latency (ms) of TEP_{amp} relative to TMS delivery for each electrode averaged across subjects. This map represents the temporal evolution of the TEP_{amp} that seems to have shorter latencies near the stimulation site (i.e., blue colors over the left motor cortex) compared to distal interconnected cortical regions such as the homologous contralateral hemisphere (i.e., red colors).

artifacts contaminated this time window in several subjects. The P60 component was observed posterior to the stimulation site (Fig. 5C) in electrodes corresponding to the ipsilateral motor cortex (i.e., CP1, CP3 and C1) in more than two thirds of the subjects. The mean amplitude and latency of P60 component across subjects and electrodes were 5.0 ± 2.1 μV and 58.8 ± 2.5 ms, respectively, and the largest mean amplitude of the P60 component was at electrode T7 (Fig. 5C). We found no significant correlation between the average amplitude of the P60 component and SP_{dur} ($r = 0.36$, $p = 0.16$) or MEP amplitude ($p = 0.10$) (Fig. 5C).

The N100 component was detected in electrodes corresponding to the fronto-central, and ipsi- and contralateral motor cortices (i.e. F1, FZ, FC1, FCZ, FC2, FC4, C1, CZ, and C2) in more than two thirds of the subjects. The mean amplitude and latency of N100 component across subjects and electrodes were 8.6 ± 2.5 μV and 94.3 ± 9.5 ms, respectively, and the largest average amplitude was at FCZ electrode. We found a significant correlation between the average absolute

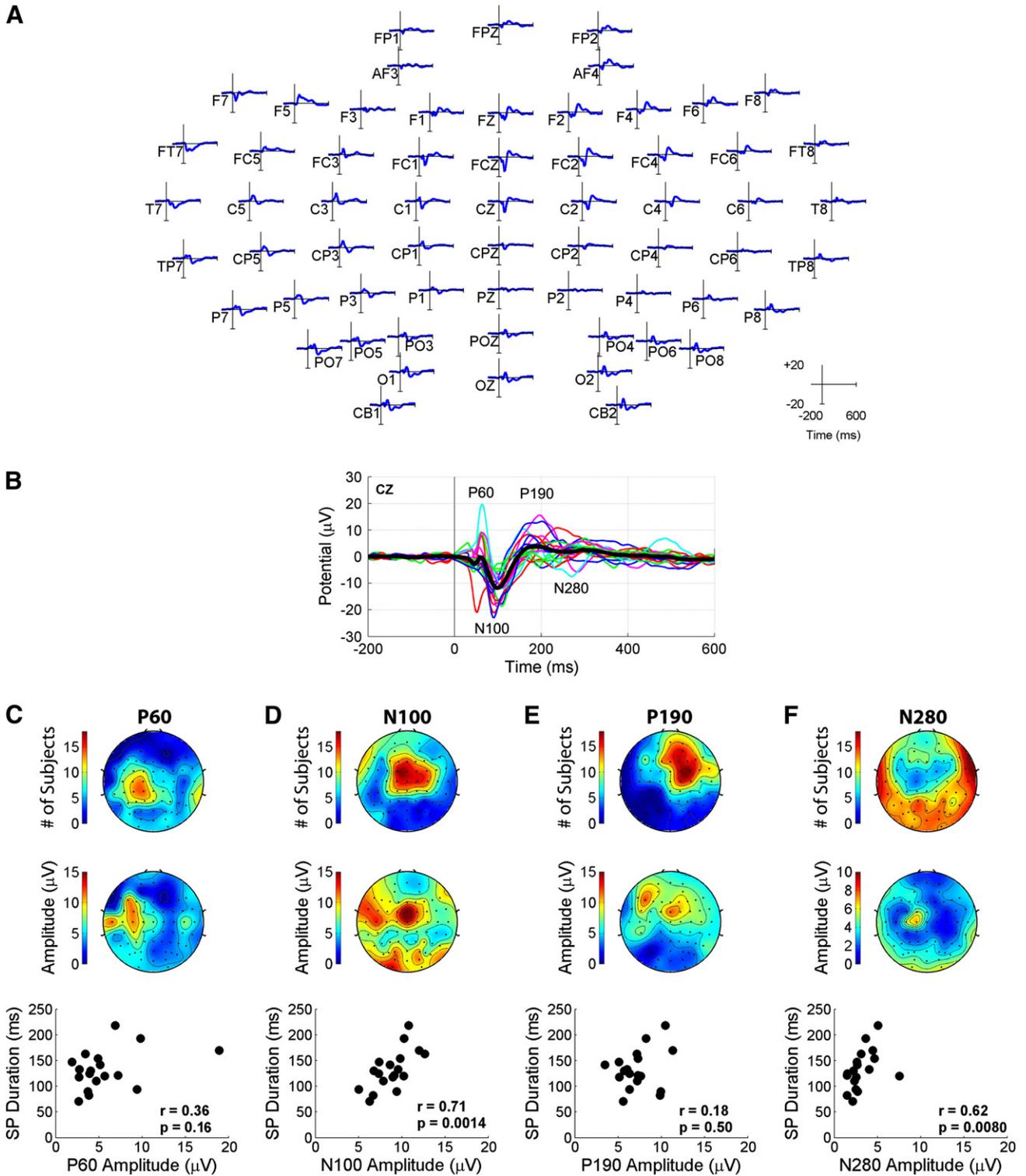


Fig. 5. The association between TEP components and the TMS-induced silent period. A) This panel shows the average TMS-evoked potentials (TEPs) across subjects in all electrodes. B) This figure illustrates TEP components P60, N100, P190, and N280 in CZ electrode for all subjects (represented by waveforms of different colors) and the average across subjects (solid black waveform). In C–E, the top topographic plots show for each electrode the number of subjects in whom the corresponding TEP component could be identified. These plots, therefore, illustrate the average spatial distribution of TEP components across subjects. The bottom topographic plots illustrate the average absolute amplitude of each TEP component across subjects, depicting the location of the maximum amplitude of TEP components. In the scatter plots, each point represents data from an individual subject. These plots illustrate the correlation between the mean absolute amplitude of the TEP components across electrodes and the silent period (SP) duration.

amplitude of the N100 component and the SP_{dur} ($r = 0.71, p = 0.0014$) but not with MEP amplitude ($p = 0.66$) (Fig. 5D).

The P190 component was detected at FC4 electrode in all subjects, and in more than two thirds of the subjects it was detected at

electrodes corresponding to the ipsilateral and contralateral prefrontal cortex and contralateral motor cortex (i.e., FP2, AF4, F1, FZ, F2, F4, F6, FC2, FC4, FC6, C2, and C4). The mean amplitude and latency of P190 component across subjects and electrodes were $6.2 \pm 2.5 \mu V$

and 189.7 ± 18.2 ms, respectively, and the largest mean amplitude was at F5 electrode. We found no significant correlation between the average amplitude of the P190 component and SP_{dur} ($r = 0.18$, $p = 0.50$) or MEP amplitude ($p = 0.79$) (Fig. 5E).

The N280 component was detected bilaterally in temporal, parietal, temporo-parietal, postero-occipital, and occipital electrodes in more than two thirds of the subjects. The mean amplitude and latency of the N280 component across subjects and electrodes were 3.0 ± 1.2 μ V and 292.1 ± 11.7 ms, respectively, and the largest amplitude was detected at C3 electrode (Fig. 5F). We found a moderate correlation between the mean amplitude of N280 component and SP_{dur} ($r = 0.62$, $p = 0.0080$), but not with MEP amplitude ($p = 0.47$).

Duration of TMS-evoked potential. We found a strong correlation between SP_{dur} and TEP_{dur} in the ipsilateral motor cortex (Fig. 6B). Fig. 6C illustrates the significant correlation ($r = 0.72$, $p = 0.0012$) between SP_{dur} and TEP_{dur} at C1 electrode. The mean TEP_{dur} averaged across all electrodes and subjects was 271.5 ± 38.8 ms. The mean

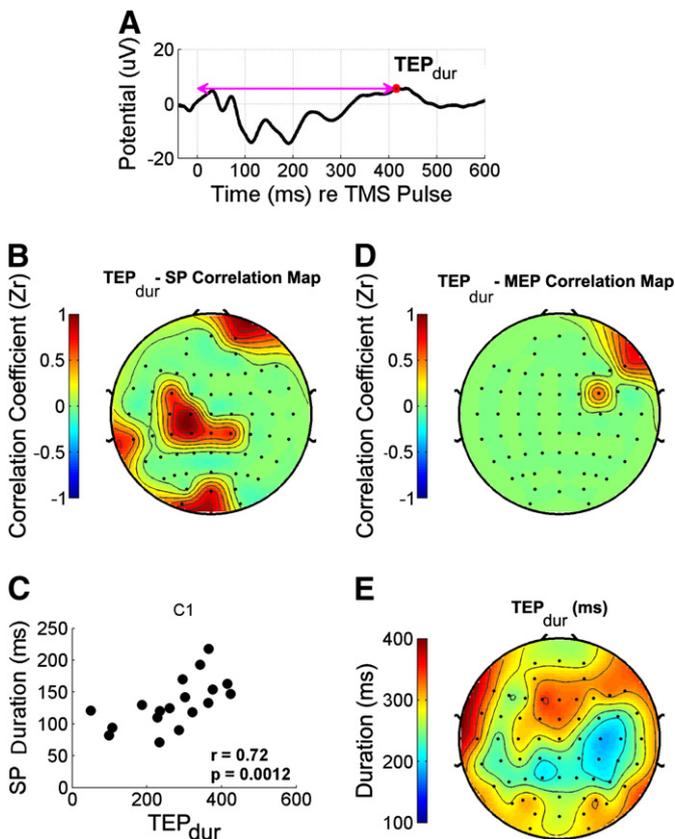


Fig. 6. The association between the duration of TMS-evoked potentials and TMS-induced silent period. A) The x-axis represents time in milliseconds with respect to TMS delivery, and the y-axis represents EEG potential in μ V. The waveform is the EEG potential following TMS in C3 electrode in one subject illustrating that for each electrode, the duration of TMS-evoked potentials (TEP_{dur}) was measured as the latency of the last peak of the TEP that had an amplitude of at least six standard deviation larger than the maximum amplitude of the pre-stimulus interval (-600 ms to -100 ms) in the global mean field amplitude (GMFA) of each subject. B) The topographic representation of the EEG-EMG correlation map between the TEP_{dur} and the silent period (SP) duration. The colors encode the adjusted Z transformed Spearman's correlation coefficient (Zr) values obtained by setting to zero the r values of non-significant correlations ($p > 0.05$), depicted as green in the color map. C) Each point represents data from an individual subject. The x-axis represents the average TEP_{dur} in C1 electrode that significantly ($p = 0.0012$) correlated with SP duration. Please note that this correlation is not an estimation of the true effect size. D) The topographic representation of the EEG-EMG correlation map between the TEP_{dur} and the amplitude of the TMS-induced motor evoked potential (MEP). The colors encode the adjusted Z transformed Spearman's correlation coefficients (Zr). E) This topographic map illustrates the mean TEP_{dur} across electrodes. The colors encode the duration (ms) of TEP for each electrode averaged across subjects.

TEP_{dur} at C1 electrode that significantly correlated with SP_{dur} was 271.9 ± 108.4 ms.

The correlation between MEP amplitudes and TEP_{dur} was moderately significant at two electrodes (F8: $r = 0.51$, $p = 0.03$; FC4: $r = 0.50$, $p = 0.04$; Fig. 6D).

The average TEP_{dur} is illustrated on a topographic map (Fig. 6E). The topographic illustration of the TEP_{dur} demonstrates that the TEP_{dur} was shorter in the motor area and longer in the prefrontal and occipital areas. Therefore, in an exploratory analysis, we investigated the effect of cortical regions on the TEP_{dur} . We performed a one-way repeated measures ANOVA with TEP_{dur} as the dependant variable and cortical area as the factor. We grouped electrodes into seven areas of prefrontal (electrodes: AF3–4, F1–8, and FZ), premotor (FC1–6 and FCZ), motor (C1–6, CZ, CP1–6, and CPZ), temporal (FT7, T7, TP7, FT8, T8, and TP8), parietal (P1–8 and PZ), parieto-occipital (PO3–8 and POZ), and occipital regions (O1–2, OZ, and CB1–2). The ANOVA revealed a significant effect of region ($F = 7.2$, $df = 6$, $p < 0.0001$). Mauchly's test of sphericity indicated that the assumption of sphericity was not violated ($p > 0.05$). Post-hoc analysis using Bonferroni correction (0.05/21 comparisons, adjusted $p = 0.0023$) revealed significant differences between the mean TEP_{dur} of the prefrontal (307.7 ± 78.8 ms) and motor (238.2 ± 64.7 ms) regions ($t = 4.4$, $df = 17$, $p = 0.0004$), prefrontal and parietal (239.1 ± 82.18 ms) regions ($t = 5.0$, $df = 17$, $p = 0.0001$), motor and premotor (279.8 ± 49.6 ms) regions ($t = -3.3$, $df = 17$, $p = 0.004$), motor and temporal (286.8 ± 66.5 ms) regions ($t = -4.8$, $df = 17$, $p = 0.0002$), parietal and temporal ($t = -4.3$, $df = 17$, $p = 0.0005$) regions, and parietal and parieto-occipital (288.8 ± 67.0 ms) region ($t = -3.6$, $df = 17$, $p = 0.002$).

Finally, in an exploratory analysis, we investigated whether the last peak of GMFA (the basis for identification of GMFA_{dur} index), or the N280 component is related to the afferent somatosensory potentials associated with the re-emergence of the background EMG activity following the TMS-induced SP. We identified the mean amplitude of the EMG activity immediately after the SP for a time window of 200 ms in width. We then examined the correlation between the mean EMG activity and the amplitude of the N280 component or the amplitude of the last peak of GMFA. We found no significant correlation between the post SP EMG activity and the N280 component ($r = 0.04$, $p = 0.89$) or the last GMFA peak ($r = 0.07$, $p = 0.78$).

Spectral power. We found a significant positive ($p < 0.0015$) correlation between the absolute power of overall cortical oscillations (1–50 Hz) and SP_{dur} in the contralateral premotor and bilateral primary motor regions (Table 1). The mean spectral power for each individual frequency band is demonstrated topographically in Fig. 7A. Frequency decomposition illustrated that the power of delta, theta, alpha, and beta oscillations correlated significantly ($p < 0.0015$) with SP_{dur} (Fig. 7B; Table 1). The correlation between SP_{dur} and gamma oscillations did not survive the correction for multiple comparisons.

The MEP amplitude only moderately correlated with the gamma oscillations at electrode CZ ($r = 0.52$, $p = 0.034$; Fig. 7C).

Discussion

Through combination of TMS-EMG with concurrent EEG recording, we explored the EEG correlates of the TMS-induced period of EMG silence (i.e., SP), which is suggested to be an index of cortical inhibition in humans. We investigated the cortical origin of SP and the temporal and spectral characteristics of cortical reactivity during SP. Several TMS-EEG indices were defined that may be used in future investigation of cortical inhibitory processes in humans: 1) $TEP_{amplitude/components}$, 2) $TEP_{duration}$, 3) TEP_{power} .

1) $TEP_{amplitude/components}$: The duration of SP (i.e. SP_{dur}) correlated with the maximum amplitude of the global brain response (i.e., GMFA_{amp})

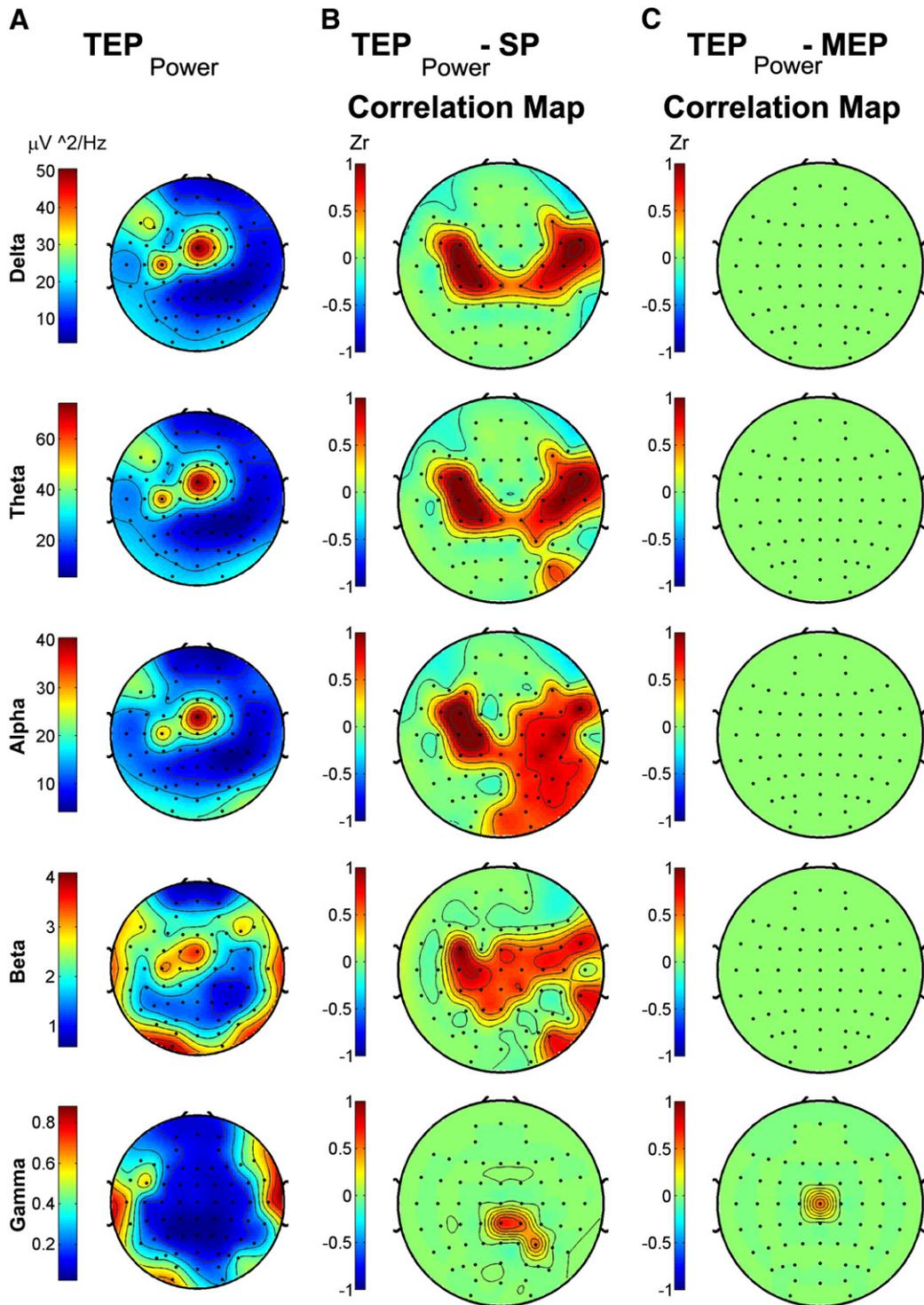


Fig. 7. The association between cortical oscillatory activities and TMS-induced silent period. A) Topographic plots demonstrate the mean power of delta (1–3 Hz), theta (4–7 Hz), alpha (8–11 Hz), beta (12–28 Hz), and gamma (30–50 Hz) cortical oscillatory activities. The power was first calculated by obtaining the time–frequency representation of the average time series (–1000 ms to +1000 ms relative to TMS delivery) for each subject and electrode using hanning FFT tapering with a sliding time window of 200 ms width. The mean power was then calculated by binning and averaging the power of each frequency bands from 50 to 500 ms post TMS. In B and C, colors encode the Z transformed Spearman’s correlation coefficients (r) for the EEG–EMG correlations with $p < 0.05$. B) Topographic plots illustrate the relationship between the power of each cortical oscillatory activity and the silent period (SP) duration. C) Topographic plots illustrate the relationship between the power of each cortical oscillatory activity and the amplitude of the TMS-induced MEP.

to TMS. Further analysis revealed that SP_{dur} significantly correlated with the amplitude of the cortical response (i.e., TEP_{amp}) in the ipsilateral motor (i.e., ipsilateral to the TMS stimulation site) as well as in the contralateral primary motor, temporal and parieto-occipital cortices. Moreover, SP_{dur} correlated with the latency of the TEP_{amp} and this relationship was found to be slightly stronger

in the contralateral compared to the ipsilateral motor area. In this study, similar to previous studies, we could identify the TEP components P60, N100, P190 and N280 at the vertex (i.e., CZ electrode) and several other regions (Ferrerri et al., 2011). We found a strong significant correlation between the N100 component and the SP_{dur} , and a moderate correlation between the N280 component and the SP_{dur}

which was not found for any other peaks or between the TEP components and MEP amplitude.

- 2) TEP_{duration}: SP_{dur} was moderately associated with the duration of the global brain response to TMS (i.e., GMFA_{dur}). It was further found that the SP_{dur} significantly correlated with the duration of the cortical response (i.e., TEP_{dur}) in the ipsilateral motor cortex. The mean TEP_{dur} was found to be longer in the prefrontal, temporal and occipital regions relative to motor and parietal cortices.
- 3) TEP_{power}: Spectral analyses illustrated that SP_{dur} correlated with the absolute power of cortical oscillations (1–50 Hz). Frequency decomposition revealed that SP_{dur} was associated with the power of delta to alpha oscillations in the bilateral motor and contralateral motor, fronto-temporal and parietal areas, and correlated with the power of beta oscillations in the ipsilateral motor area. There were only moderately significant and spatially sparse correlations between the amplitude of the TMS-induced MEP and the temporal and spectral EEG indices of SP.

The origin of silent period

The relationship between the peripheral and cortical responses to TMS provides further evidence for the significant contribution of cortical mechanisms, as contrasted with spinal, in the genesis of the TMS-induced SP. We found a weak and non-significant correlation between the MEP amplitude and the EEG metrics presented here, providing evidence that the TEPs measured 50 ms after the TMS pulse are unlikely to be primarily related to the afferent somatosensory potentials associated with the TMS-induced MEPs. This is consistent with the results of a previous TMS–EEG study that also found no correlation between the amplitude of TMS-evoked cortical response approximately 100 ms post TMS and MEP amplitude (Bender et al., 2005). Instead, the amplitude of the TMS-induced MEP has been shown to correlate with the amplitude of the early N15–P30 EEG response (Maki and Ilmoniemi, 2010). We suggest that the previously described TMS-induced N15–P30 complex and the EEG metrics presented here (i.e., N100 component, TEP_{amp}, and TEP_{dur}) may be regarded as the TMS–EEG markers of the fast excitatory and slow inhibitory cortical mechanisms, respectively, consistent with the results of *in vitro* and animal studies as discussed next.

Cortical indices of silent period: temporal characteristics

The temporal characteristics of the cortical response in the CSP paradigm provide further evidence for the involvement of GABAergic neurotransmission in the generation of SP. The mean duration of cortical reactivity (e.g., GMFA_{dur}: 253.7 ± 118.2 ms) is consistent with the duration of GABA_B receptor neurotransmission (Adrian and Moruzzi, 1939; Deisz, 1999; Krnjevic et al., 1964, 1966; McCormick, 1989; Sanger et al., 2001). In the earlier studies of mammalian motor pathways, electrical stimulation applied to an exposed area of cats' motor cortex resulted in an excitatory response followed by a period of complete inactivity of the pyramidal tract (Adrian and Moruzzi, 1939). The excitatory response was reported to last 20 ms followed by a silent period of 150 to 300 ms in duration (Krnjevic et al., 1964). Furthermore, intracellular recordings from slices of the human temporal lobe demonstrated three distinct response phases of fast excitatory, fast inhibitory, and slow inhibitory post synaptic potentials (McCormick, 1989). Pharmacological assessments associated the slow inhibitory response with the activation of GABA_B receptors (McCormick, 1989) which has been documented to have a mean latency-to-peak duration of 135 ms and a mean duration of about 250 ms (Deisz, 1999) consistent with the mean TEP_{dur} observed in this study.

The mean latency of cortical response (e.g., GMFA_{amp} latency: 99.0 ± 31.5 ms) is consistent with the latency of the TMS-evoked N100 component. Furthermore, the observation that the amplitude of the N100 component is strongly and selectively related to SP_{dur}

provides further evidence that the TMS–EEG N100 component may in fact be related to inhibitory mechanism. Previous TMS–EEG studies have shown that a single TMS pulse applied to the motor cortex at rest generates a prominent EEG peak at a latency of about 100 ms (i.e., N100) relative to the TMS onset. Several investigators have proposed that the TMS-evoked N100 component may reflect the activity of GABAergic neurotransmission (Bender et al., 2005; Bonnard et al., 2009; Kicic et al., 2008; Nikulin et al., 2003). In this regard, Nikulin et al. demonstrated that following visually triggered hand movement, the N100 component of EEG response was suppressed while the MEP amplitudes were increased (Nikulin et al., 2003). Similarly, the amplitude of the TMS-evoked N100 appears to be reduced when a motor performance is required at the onset of TMS delivery (Kicic et al., 2008). Furthermore, the N100 component has a larger amplitude and a longer latency in 7–10 year old children (Bender et al., 2005) and has been suggested to go through maturational changes. A recent TMS–EEG study proposed that N100 may be a marker of abnormal brain maturation in children with attention deficit hyperactive disorder (Bruckmann et al., 2012). Therefore, the correlation between SP_{dur} and the N100 component and the TEP_{amp} (which has a latency around 100 ms) may also provide further support that TMS-evoked N100 response may be partly related to the magnitude of intracortical inhibitory mechanisms. We suggest that TEP_{amp} (or N100 component) and TEP_{dur} may reflect the magnitude and the duration of GABA_B receptor activity, respectively, as previously indexed through EMG in LICI and CSP paradigms. Future studies may seek to test this hypothesis by correlating LICI with TEP_{amp} and TEP_{dur}, and examining the effects of pharmacological modulators or specific pathologies.

Cortical indices of silent period: spectral characteristics

The spectral properties of cortical reactivity provide experimental evidence for the differential involvement of cortical oscillatory activities in SP genesis. The SP_{dur} was related to the power of delta to beta cortical oscillations, while gamma oscillations were moderately but not significantly related to SP_{dur}. The prominent contribution of low versus high frequency cortical oscillations to SP_{dur} (e.g., alpha versus gamma oscillations) is in line with the proposed functional roles of cortical oscillations. The cortical alpha oscillations are present throughout the cortex, more dominantly in the occipital cortex but also in the parietal and frontal cortices, and are suggested to reflect a state of lowered excitability and heightened inhibitory processes in the cortex (Brignani et al., 2008; Mathewson et al., 2011). The observed strong correlation between SP_{dur} and the TMS-evoked alpha oscillations in both local and remote cortical areas may further reflect the role of alpha oscillations in mediating inhibitory processes within and in-between brain regions. Cortical activities within beta-range frequency, however, are more dominant in the central region of the cortex, and are associated with movement execution and control. It has been hypothesized that the functional role of beta oscillations may be related to the maintenance of status quo, such as maintenance of sensory-motor state (Engel and Fries, 2010), and prolongation of beta oscillations may result in the deterioration of flexible behavior (Engel and Fries, 2010). Consistently, the correlation between SP_{dur} and TMS-evoked beta oscillations was confined to the motor cortex. Finally, high frequency gamma oscillations, which were not significantly related to SP_{dur}, are more prominently observed during higher order cognitive processing (Fries et al., 2007). Therefore, given the differential association of cortical oscillations to SP_{dur}, deficits in specific cortical oscillatory activities may lead to SP_{dur} impairments. Consequently, SP_{dur} might be a valuable index of the state of the brain oscillatory activity. This can be further investigated in future studies by examining the correlation between pre-stimulus spontaneous or TMS-induced oscillations (versus TMS-evoked oscillations presented here) and SP_{dur}. It should also be noted that while we demonstrate a correlation between selective cortical oscillations (as well

as other EEG indices presented in this manuscript) and SP_{dur} , correlation does not imply causality and there is not enough evidence to confirm that SP_{dur} is a downstream effect of a specific cortical oscillatory activity. Future studies could directly test this notion by assessing the impact of selectively potentiating or suppressing specific cortical oscillatory activities on SP_{dur} .

Cortical indices of silent period: spatial characteristics

The spatial characteristics of the cortical–peripheral correlation maps (e.g., Figs. 4B, 6B, and 7B) and the TEP_{amp} latency and TEP_{dur} (Figs. 4E and 6E) provide experimental evidence for the impact of both local and remote cortical areas on the TMS-induced SP, and are consistent with several previous studies. The cortico–peripheral correlation maps illustrate that the propagation of TEPs seems to result in engagement of inhibitory mechanisms of not only the stimulated region but also the interconnected cortices. Interestingly, there was a slightly stronger correlation between the SP_{dur} and the TEP_{amp} latency in the motor regions contralateral to the TMS stimulation site. It has been previously shown that application of a single TMS pulse to the primary motor cortex at rest results in local neuronal activation that spreads from the ipsilateral motor cortex to premotor, contralateral motor and parietal regions (Ilmoniemi et al., 1997). Similarly, in our study, the spatial characteristics of the TEP_{amp} latency may suggest that TEPs originate from the ipsilateral motor cortex and reach and engage the inhibitory or excitatory mechanisms of the homologous motor areas at a longer latency. Future studies may seek to examine the impact of stimulation intensity on the extent of this propagation. For example, the stimulus–response curve for the EMG measures of the SP in a given individual can be fitted by a sigmoid function demonstrating a linear increase of SP_{dur} with increases in stimulation intensity and then reaching a plateau (Kimiskidis et al., 2005). Future TMS–EEG studies may obtain the stimulus–response curve for the EEG indices of SP_{dur} to further characterize the impact of stimulation intensity on the TEP propagation and the engagement of the inhibitory or excitatory processes of the remote cortical areas.

In addition, the finding that the mean TEP_{dur} differed across cortical areas, with the shortest duration in the motor and the longest in the prefrontal and temporal regions could be explained in several ways. First, these differences may be attributed to the differences in the activation threshold across cortical lobes. Since the stimulation intensity was chosen based on the motor tissue threshold, it is conceivable that the signal that originated in the motor cortex did not produce the same level of cortical reactivity across regions. Similarly, head morphology and the non-homogeneity of the skull to cortex distance may lead to fluctuations in the magnitude of the brain response recorded over the skull surface. Another plausible explanation, however, may be related to the natural properties of different cortical regions. In a TMS–EEG study, Rosanova et al. demonstrated that frontal, parietal and occipital cortices each exhibited their own natural frequency when stimulated with a single pulse of TMS (Rosanova et al., 2009). Similarly, we have demonstrated that LIC1 modulates cortical oscillations differentially in the motor and prefrontal cortices (Farzan et al., 2009) and there was no association between the EEG indices of LIC1 in the dorsolateral prefrontal cortex and motor cortex (Farzan et al., 2010c). Analogous with these studies, it is possible that TEP_{dur} , that herein we suggested to be reflective of the duration of $GABA_B$ receptor activity, may differ across cortical regions due to factors such as the composition of the underlying neuronal population, ion channels or concentration of pre-synaptic GABA available for release in the synaptic cleft. However, it should be noted that unlike the studies conducted by Farzan et al. (2009) and Rosanova et al. (2009), only the motor cortex was stimulated in the current study, and thus the differential responses across regions are not in response to direct cortical stimulation of these regions.

The spatially distributed effect of TMS is also consistent with the working mechanism of TMS as discussed in the [Introduction](#).

Unlike TES that primarily activates the axon initial of the pyramidal neurons, TMS is suggested to activate pyramidal neurons transynaptically through activation of excitatory and inhibitory interneurons (Day et al., 1989). The horizontal orientation of interneurons may facilitate the activation and propagation of evoked activity across cortical regions recruiting excitatory and inhibitory circuitries along the propagation pathway. This may also, in part, explain the longer duration of TMS (as compared to TES)-induced SP as discussed in the [Introduction](#).

Based on these observations, therefore, one may propose that the cortical component of the TMS-induced SP is a net result of interaction among several cortical areas and their excitatory and inhibitory circuitries. That is, a suprathreshold TMS, capable of activating the slow acting $GABA_B$ receptor mediated neurotransmission, would initially activate the cortical tissue closest to the stimulation site leading to generation of both excitatory and inhibitory post synaptic potentials near the stimulation site. This initial perturbation, if strong enough, may be followed by indirect and secondary activation of the interconnected neighboring and remote cortical tissues, thereby eliciting a cascade of interaction within a distributed network. Consequently, the net outcome of this interaction, rather than the local inhibitory circuitry exclusively, may shape the EMG silent period at the periphery. If true, the integrity of the connectivity between cortical areas should influence SP_{dur} and the modification of cortico-cortical connectivity should result in shortening or prolongation of SP.

Indeed, there are converging lines of evidence in support of this proposal. Consistent with this view, a recent fMRI study demonstrated that the duration of ipsilateral SP was related to the coupling of primary motor cortex and supplementary motor area (Sarfeld et al., 2012). Ipsilateral SP is a period of EMG silence that is obtained when a suprathreshold TMS is applied to the motor cortex ipsilateral to the target muscle and is suggested to be mediated by transcallosal inhibition (Wassermann et al., 1991). Furthermore, the contraction of the lower limb muscles was shown to reduce the TMS-induced SP_{dur} of the upper limb muscle (Tazoe et al., 2007). The modulatory influence of remote muscles on SP_{dur} was suggested to have a cortical origin and was proposed to be related to a decrease in the excitability of the cortical inhibitory pathways (Tazoe et al., 2007). Moreover, SP was prolonged in patients with focal cortical dysgenesis outside the primary motor cortex (Cincotta et al., 2000). Finally, previous studies reported on the prolongation or reduction of SP in the primary motor cortex following perturbation of non-motor regions through repetitive TMS (Furukawa et al., 2010; Munchau et al., 2002; Rollnik et al., 2000). As examples, it was shown that low frequency TMS applied to the midline prefrontal cortex (FZ electrode), but not to the motor cortex, resulted in significant prolongation of SP in the motor cortex (Furukawa et al., 2010). In another study, repetitive TMS over the premotor, but not motor cortex, shortened the SP in the motor cortex (Munchau et al., 2002). The involvement of a distributed network in SP genesis may provide a mechanistic explanation for several clinical observations. This can be explored in future studies by concurrently recording EEG when exploring the impairment of SP in patient populations.

Some limitations should be carefully considered when interpreting the findings of this study. First, correlation does not imply causality and future studies should more directly examine the causal relationships between the EEG metrics presented here and the TMS-induced SP and MEP. Similarly, it should be noted that while we found a selective correlation between specific TEP components and SP duration, and although we did not find an association between the late TEP (GMFA) peaks and the background EMG, we cannot still fully disentangle the contribution of excitatory versus inhibitory mechanisms to the late TEP components. Similarly, although we did not find strong associations between the TMS-induced MEP amplitude and the EEG metrics, we cannot fully rule out the possibility that the earlier EEG responses (e.g., <90 ms) are contaminated by the proprioceptive feedback related to the TMS-induced MEPs. In this regard, due to the relatively large

duration of the TMS-related artifacts (~36 ms post TMS pulse), we were not able to examine the early TEP components that might have been linked to MEP generation and hence more strongly associated with the TMS-induced MEP amplitude. Another limitation of this study is the limited number of TMS stimuli. While in our previous studies we relied on 80–100 pulses, we administered 50 pulses in this study to avoid muscle fatigue. Future TMS–EEG studies should more systematically examine the minimum number of stimuli that are required to obtain reliable results. Finally, we evaluated the EMG–EEG correlation maps at the group level. Future studies should more carefully examine the EMG–EEG correlation map within each subject and at the single-trial level to also comment on the association between the EEG versus EMG variability.

Conclusions

In this study, we explored the local and distributed cortical dynamics that may underlie TMS-induced SP. In particular, we present new EEG measures of TMS-induced SP (e.g., $TEP_{amp/component}$, TEP_{dur} , and TEP_{power}) that provide important insights about the mechanisms that may underlie cortical inhibition, and may offer more sensitive investigative tools for cortical reactivity in neuropsychiatric disorders. While EMG measures provide an index for the peripheral component of cortical stimulation, EEG markers permit examination of the cortical substrates that contribute to SP generation. Future TMS–EEG studies are warranted to explore the EEG measures of SP in patients with both prolonged and reduced SP to further evaluate the validity, reliability and sensitivity of these indices as neurophysiological underpinnings of GABA mediated inhibitory processes. However, we should emphasize that correlation does not imply causality and the results of the current study should be used as a guide to design future hypothesis-driven studies aimed at examining the causal relationships between several of these EEG markers and the TMS-induced SP generation. For example, neuromodulatory interventions such as repetitive TMS or transcranial alternative current stimulation (tACS) may be employed to enhance the power of specific cortical oscillatory activity and examine the effect of this intervention on the duration and amplitude of the TMS-induced SP versus TMS-induced MEP, respectively. Furthermore, neuromodulatory interventions, such as repetitive TMS, may be used to modify the connectivity and the excitability of the local and remote cortical regions to further evaluate the impact of cortico-cortical connectivity on cortical inhibitory processes. Finally, future studies should also investigate the EEG features prior to or at the time of TMS delivery that can predict the duration and the amplitude of the TMS-induced SP versus MEP, respectively. Such endeavors would enhance our understanding of inhibitory mechanisms in health and disease and could aid in the design of disease specific and individually tailored therapies.

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References

Adrian, E.D., Moruzzi, G., 1939. Impulses in the pyramidal tract. *J. Physiol.* 97, 153–199.

- Alagona, G., Bella, R., Ferri, R., Carnemolla, A., Pappalardo, A., Costanzo, E., Pennisi, G., 2001. Transcranial magnetic stimulation in Alzheimer disease: motor cortex excitability and cognitive severity. *Neurosci. Lett.* 314, 57–60.
- Bajbouj, M., Lang, U.E., Niehaus, L., Hellen, F.E., Heuser, I., Neu, P., 2006a. Effects of right unilateral electroconvulsive therapy on motor cortical excitability in depressive patients. *J. Psychiatr. Res.* 40, 322–327.
- Bajbouj, M., Lisanby, S.H., Lang, U.E., Danker-Hopfe, H., Heuser, I., Neu, P., 2006b. Evidence for impaired cortical inhibition in patients with unipolar major depression. *Biol. Psychiatry* 59, 395–400.
- Barker, A.T., Jalinous, R., Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1, 1106–1107.
- Barnow, S., Volker, K.A., Moller, B., Freyberger, H.J., Spitzer, C., Grabe, H.J., Daskalakis, Z.J., 2009. Neurophysiological correlates of borderline personality disorder: a transcranial magnetic stimulation study. *Biol. Psychiatry* 65, 313–318.
- Battaglia, F., Quartarone, A., Ghilardi, M.F., Dattola, R., Bagnato, S., Rizzo, V., Morgante, L., Girlanda, P., 2006. Unilateral cerebellar stroke disrupts movement preparation and motor imagery. *Clin. Neurophysiol.* 117, 1009–1016.
- Bender, S., Basseler, K., Sebastian, I., Resch, F., Kammer, T., Oelkers-Ax, R., Weisbrod, M., 2005. Electroencephalographic response to transcranial magnetic stimulation in children: evidence for giant inhibitory potentials. *Ann. Neurol.* 58, 58–67.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc.* 1, 289–300.
- Benwell, N.M., Mastaglia, F.L., Thickbroom, G.W., 2007. Differential changes in long-interval intracortical inhibition and silent period duration during fatiguing hand exercise. *Exp. Brain Res.* 179, 255–262.
- Bonnard, M., Spieser, L., Meziane, H.B., de Graaf, J.B., Pailhous, J., 2009. Prior intention can locally tune inhibitory processes in the primary motor cortex: direct evidence from combined TMS–EEG. *Eur. J. Neurosci.* 30, 913–923.
- Braune, H.J., Fritz, C., 1995. Transcranial magnetic stimulation-evoked inhibition of voluntary muscle activity (silent period) is impaired in patients with ischemic hemispheric lesion. *Stroke* 26, 550–553.
- Brignani, D., Manganotti, P., Rossini, P.M., Miniussi, C., 2008. Modulation of cortical oscillatory activity during transcranial magnetic stimulation. *Hum. Brain Mapp.* 29, 603–612.
- Bruckmann, S., Hauk, D., Roessner, V., Resch, F., Freitag, C.M., Kammer, T., Ziemann, U., Rothenberger, A., Weisbrod, M., Bender, S., 2012. Cortical inhibition in attention deficit hyperactivity disorder: new insights from the electroencephalographic response to transcranial magnetic stimulation. *Brain* 135 (Pt 7), 2215–2230.
- Chen, R., Lozano, A.M., Ashby, P., 1999. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp. Brain Res.* 128, 539–542.
- Cincotta, M., Borgheresi, A., Guidi, L., Macucci, M., Cosottini, M., Lambruschini, P., Benvenuti, F., Zaccara, G., 2000. Remote effects of cortical dysgenesis on the primary motor cortex: evidence from the silent period following transcranial magnetic stimulation. *Clin. Neurophysiol.* 111, 1340–1345.
- Cincotta, M., Borgheresi, A., Benvenuti, F., Liotta, P., Marin, E., Zaccara, G., 2002. Cortical silent period in two patients with meningioma and preoperative seizures: a pre- and postsurgical follow-up study. *Clin. Neurophysiol.* 113, 597–603.
- Classen, J., Schnitzler, A., Binkofski, F., Werhahn, K.J., Kim, Y.S., Kessler, K.R., Benecke, R., 1997. The motor syndrome associated with exaggerated inhibition within the primary motor cortex of patients with hemiparesis. *Brain* 120 (Pt 4), 605–619.
- Daskalakis, Z.J., Christensen, B.K., Chen, R., Fitzgerald, P.B., Zipursky, R.B., Kapur, S., 2002. Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Arch. Gen. Psychiatry* 59, 347–354.
- Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B., Moller, B., Fountain, S.L., Chen, R., 2008a. Increased cortical inhibition in persons with schizophrenia treated with clozapine. *J. Psychopharmacol.* 22, 203–209.
- Daskalakis, Z.J., Farzan, F., Barr, M.S., Maller, J.J., Chen, R., Fitzgerald, P.B., 2008b. Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS–EEG study. *Neuropsychopharmacology* 33, 2860–2869.
- Day, B.L., Dressler, D., Maertens de Noordhout, A., Marsden, C.D., Nakashima, K., Rothwell, J.C., Thompson, P.D., 1989. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *J. Physiol.* 412, 449–473.
- De Beaumont, L., Lassonde, M., Leclerc, S., Theoret, H., 2007. Long-term and cumulative effects of sports concussion on motor cortex inhibition. *Neurosurgery* 61, 329–336 (discussion 336–7).
- De Beaumont, L., Theoret, H., Mongeon, D., Messier, J., Leclerc, S., Tremblay, S., Ellemberg, D., Lassonde, M., 2009. Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain* 132, 695–708.
- Deisz, R.A., 1999. GABA(B) receptor-mediated effects in human and rat neocortical neurones in vitro. *Neuropharmacology* 38, 1755–1766.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21.
- Di Lazzaro, V., Oliviero, A., Mazzone, P., Pilato, F., Saturno, E., Insoola, A., Visocchi, M., Colosimo, C., Tonali, P.A., Rothwell, J.C., 2002. Direct demonstration of long latency cortico-cortical inhibition in normal subjects and in a patient with vascular parkinsonism. *Clin. Neurophysiol.* 113, 1673–1679.
- Engel, A.K., Fries, P., 2010. Beta-band oscillations—signalling the status quo? *Curr. Opin. Neurobiol.* 20, 156–165.
- Farzan, F., Barr, M.S., Wong, W., Chen, R., Fitzgerald, P.B., Daskalakis, Z.J., 2009. Suppression of gamma-oscillations in the dorsolateral prefrontal cortex following long interval cortical inhibition: a TMS–EEG study. *Neuropsychopharmacology* 34, 1543–1551.
- Farzan, F., Barr, M.S., Levinson, A.J., Chen, R., Wong, W., Fitzgerald, P.B., Daskalakis, Z.J., 2010a. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain* 133, 1505–1514.

- Farzan, F., Barr, M.S., Levinson, A.J., Chen, R., Wong, W., Fitzgerald, P.B., Daskalakis, Z.J., 2010b. Reliability of long-interval cortical inhibition in healthy human subjects: a TMS-EEG study. *J. Neurophysiol.* 104, 1339–1346.
- Farzan, F., Barr, M.S., Levinson, A.J., Chen, R., Wong, W., Fitzgerald, P.B., Daskalakis, Z.J., 2010c. Reliability of long interval cortical inhibition in healthy human subjects: a TMS-EEG study. *J. Neurophysiol.* 104 (3), 1339–1346.
- Farzan, F., Barr, M.S., Fitzgerald, P.B., Daskalakis, Z.J., 2011. Combination of transcranial magnetic stimulation with electromyography and electroencephalography: application in diagnosis of neuropsychiatric disorders. *EMG Methods for Evaluating Muscle and Nerve Function*, InTech Open Access.
- Fecteau, S., Lassonde, M., Theoret, H., 2006. Intra-hemispheric dysfunction in primary motor cortex without corpus callosum: a transcranial magnetic stimulation study. *BMC Neurol.* 6, 21.
- Ferreri, F., Pasqualetti, P., Maatta, S., Ponzo, D., Ferrarelli, F., Tononi, G., Mervaala, E., Miniussi, C., Rossini, P.M., 2011. Human brain connectivity during single and paired pulse transcranial magnetic stimulation. *NeuroImage* 54, 90–102.
- Fisher, B.E., Wu, A.D., Salem, G.J., Song, J., Lin, C.H., Yip, J., Cen, S., Gordon, J., Jakowec, M., Petzinger, G., 2008. The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Arch. Phys. Med. Rehabil.* 89, 1221–1229.
- Fitzgerald, P.B., Brown, T.L., Daskalakis, Z.J., Kulkarni, J., 2002. A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. *Psychiatry Res.* 114, 11–22.
- Fitzgerald, P.B., Brown, T.L., Marston, N.A., Oxley, T., De Castella, A., Daskalakis, Z.J., Kulkarni, J., 2004. Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. *Schizophr. Res.* 71, 17–26.
- Fries, P., Nikolic, D., Singer, W., 2007. The gamma cycle. *Trends Neurosci.* 30, 309–316.
- Fuhr, P., Agostino, R., Hallett, M., 1991. Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalogr. Clin. Neurophysiol.* 81, 257–262.
- Furukawa, T., Toyokura, M., Masakado, Y., 2010. Suprathreshold 0.2 Hz repetitive transcranial magnetic stimulation (rTMS) over the prefrontal area. *Tokai J. Exp. Clin. Med.* 35, 29–33.
- Gjini, K., Ziemann, U., Napier, T.C., Boutros, N., 2012. Dysbalance of cortical inhibition and excitation in abstinent cocaine-dependent patients. *J. Psychiatr. Res.* 46, 248–255.
- Groppe, D.M., Urbach, T.P., Kutas, M., 2011a. Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review. *Psychophysiology* 48, 1711–1725.
- Groppe, D.M., Urbach, T.P., Kutas, M., 2011b. Mass univariate analysis of event-related brain potentials/fields II: Simulation studies. *Psychophysiology* 48, 1726–1737.
- Ilmoniemi, R.J., Kicic, D., 2009. Methodology for combined TMS and EEG. *Brain Topogr.* 22, 233–248.
- Ilmoniemi, R.J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H.J., Naatanen, R., Katila, T., 1997. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport* 8, 3537–3540.
- Inghilleri, M., Berardelli, A., Cruccu, G., Manfredi, M., 1993. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J. Physiol.* 466, 521–534.
- Inghilleri, M., Berardelli, A., Marchetti, P., Manfredi, M., 1996. Effects of diazepam, baclofen and thiopental on the silent period evoked by transcranial magnetic stimulation in humans. *Exp. Brain Res.* 109, 467–472.
- Ives, J.R., Rotenberg, A., Poma, R., Thut, G., Pascual-Leone, A., 2006. Electroencephalographic recording during transcranial magnetic stimulation in humans and animals. *Clin. Neurophysiol.* 117, 1870–1875.
- Julkunen, P., Paakkonen, A., Hukkanen, T., Kononen, M., Tiihonen, P., Vanhatalo, S., Karhu, J., 2008. Efficient reduction of stimulus artefact in TMS-EEG by epithelial short-circuiting by mini-punctures. *Clin. Neurophysiol.* 119, 475–481.
- Kapogiannis, D., Wassermann, E.M., 2008. Transcranial magnetic stimulation in *Clinical Pharmacology. Cent. Nerv. Syst. Agents Med. Chem.* 8, 234–240.
- Kicic, D., Lioumis, P., Ilmoniemi, R.J., Nikulin, V.V., 2008. Bilateral changes in excitability of sensorimotor cortices during unilateral movement: combined electroencephalographic and transcranial magnetic stimulation study. *Neuroscience* 152, 1119–1129.
- Kimiskidis, V.K., Papagiannopoulos, S., Sotirakoglou, K., Kazis, D.A., Kazis, A., Mills, K.R., 2005. Silent period to transcranial magnetic stimulation: construction and properties of stimulus-response curves in healthy volunteers. *Exp. Brain Res.* 163, 21–31.
- Knikou, M., 2008. The H-reflex as a probe: pathways and pitfalls. *J. Neurosci. Methods* 171, 1–12.
- Komssi, S., Kahkonen, S., 2006. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. *Brain Res. Brain Res. Rev.* 52, 183–192.
- Komssi, S., Kahkonen, S., Ilmoniemi, R.J., 2004. The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. *Hum. Brain Mapp.* 21, 154–164.
- Korhonen, R.J., Hernandez-Pavon, J.C., Metsomaa, J., Maki, H., Ilmoniemi, R.J., Sarvas, J., 2011. Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. *Med. Biol. Eng. Comput.* 49, 397–407.
- Krnjevic, K., Randic, M., Straughan, D.W., 1964. Cortical inhibition. *Nature* 201, 1294–1296.
- Krnjevic, K., Randic, M., Straughan, D.W., 1966. An inhibitory process in the cerebral cortex. *J. Physiol.* 184, 16–48.
- Lefaucheur, J.P., 2005. Motor cortex dysfunction revealed by cortical excitability studies in Parkinson's disease: influence of antiparkinsonian treatment and cortical stimulation. *Clin. Neurophysiol.* 116, 244–253.
- Lefaucheur, J.P., Drouot, X., Menard-Lefaucheur, I., Keravel, Y., Nguyen, J.P., 2006. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology* 67, 1568–1574.
- Lehmann, D., Skrandies, W., 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalogr. Clin. Neurophysiol.* 48, 609–621.
- Levinson, A.J., Young, L.T., Fitzgerald, P.B., Daskalakis, Z.J., 2007. Cortical inhibitory dysfunction in bipolar disorder: a study using transcranial magnetic stimulation. *J. Clin. Psychopharmacol.* 27, 493–497.
- Levinson, A.J., Fitzgerald, P.B., Favalli, G., Blumberger, D.M., Daigle, M., Daskalakis, Z.J., 2010. Evidence of cortical inhibitory deficits in major depressive disorder. *Biol. Psychiatry* 67, 458–464.
- Macdonell, R.A., King, M.A., Newton, M.R., Curatolo, J.M., Reutens, D.C., Berkovic, S.F., 2001. Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy. *Neurology* 57, 706–708.
- Maki, H., Ilmoniemi, R.J., 2010. The relationship between peripheral and early cortical activation induced by transcranial magnetic stimulation. *Neurosci. Lett.* 478 (1), 24–28.
- Maki, H., Ilmoniemi, R.J., 2011. Projecting out muscle artifacts from TMS-evoked EEG. *NeuroImage* 54, 2706–2710.
- Marsden, C.D., Merton, P.A., Morton, H.B., 1983. Direct electrical stimulation of corticospinal pathways through the intact scalp in human subjects. *Adv. Neurol.* 39, 387–391.
- Mathewson, K.E., Lleras, A., Beck, D.M., Fabiani, M., Ro, T., Gratton, G., 2011. Pulsed out of awareness: EEG alpha oscillations represent a pulsed-inhibition of ongoing cortical processing. *Front. Psychol.* 2, 99.
- McCormick, D.A., 1989. GABA as an inhibitory neurotransmitter in human cerebral cortex. *J. Neurophysiol.* 62, 1018–1027.
- McDonnell, M.N., Orekhov, Y., Ziemann, U., 2006. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp. Brain Res.* 173, 86–93.
- Meng, X., Rosenthal, R., Rubin, D.B., 1992. Comparing correlated correlation coefficients. *Psychol. Bull.* 111, 172–175.
- Munchau, A., Bloem, B.R., Irlbacher, K., Trimble, M.R., Rothwell, J.C., 2002. Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. *J. Neurosci.* 22, 554–561.
- Murase, N., Rothwell, J.C., Kaji, R., Urushihara, R., Nakamura, K., Murayama, N., Igasaki, T., Sakata-Igasaki, M., Mima, T., Ikeda, A., Shibasaki, H., 2005. Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. *Brain* 128, 104–115.
- Mutanen, T., Maki, H., Ilmoniemi, R.J., 2012. The effect of stimulus parameters on TMS-EEG muscle artifacts. *Brain Stimul.* 6 (3), 371–376.
- Nakamura, H., Kitagawa, H., Kawaguchi, Y., Tsuji, H., 1997. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *J. Physiol.* 498 (Pt 3), 817–823.
- Nakashima, K., Wang, Y., Shimoda, M., Sakuma, K., Takahashi, K., 1995. Shortened silent period produced by magnetic cortical stimulation in patients with Parkinson's disease. *J. Neurol. Sci.* 130, 209–214.
- Nikulin, V.V., Kicic, D., Kahkonen, S., Ilmoniemi, R.J., 2003. Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. *Eur. J. Neurosci.* 18, 1206–1212.
- Oechsner, M., Zangemeister, W.H., 1999. Prolonged postexcitatory inhibition after transcranial magnetic stimulation of the motor cortex in patients with cerebellar ataxia. *J. Neurol. Sci.* 168, 107–111.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Paus, T., Sipila, P.K., Strafella, A.P., 2001. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. *J. Neurophysiol.* 86, 1983–1990.
- Priori, A., Berardelli, A., Inghilleri, M., Accornero, N., Manfredi, M., 1994a. Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. *Brain* 117 (Pt 2), 317–323.
- Priori, A., Berardelli, A., Inghilleri, M., Polidori, L., Manfredi, M., 1994b. Electromyographic silent period after transcranial brain stimulation in Huntington's disease. *Mov. Disord.* 9, 178–182.
- Radhu, N., Daskalakis, Z.J., Guglietti, C.L., Farzan, F., Barr, M.S., Arpin-Cribbie, C.A., Fitzgerald, P.B., Ritvo, P., 2012. Cognitive behavioral therapy-related increases in cortical inhibition in problematic perfectionists. *Brain Stimul.* 5, 44–54.
- Richter, M.A., de Jesus, D.R., Hoppenbrouwers, S., Daigle, M., Deluce, J., Ravindran, L.N., Fitzgerald, P.B., Daskalakis, Z.J., 2012. Evidence for cortical inhibitory and excitatory dysfunction in obsessive compulsive disorder. *Neuropsychopharmacology* 37, 1144–1151.
- Rollnik, J.D., Schubert, M., Dengler, R., 2000. Subthreshold prefrontal repetitive transcranial magnetic stimulation reduces motor cortex excitability. *Muscle Nerve* 23, 112–114.
- Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., Massimini, M., 2009. Natural frequencies of human corticothalamic circuits. *J. Neurosci.* 29, 7679–7685.
- Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijevic, M.R., Hallett, M., Katayama, Y., Lucking, C.H., et al., 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr. Clin. Neurophysiol.* 91, 79–92.
- Saisanen, L., Pirinen, E., Teitti, S., Kononen, M., Julkunen, P., Maatta, S., Karhu, J., 2008. Factors influencing cortical silent period: optimized stimulus location, intensity and muscle contraction. *J. Neurosci. Methods* 169, 231–238.
- Salerno, A., Thomas, E., Olive, P., Blotman, F., Picot, M.C., Georgesco, M., 2000. Motor cortical dysfunction disclosed by single and double magnetic stimulation in patients with fibromyalgia. *Clin. Neurophysiol.* 111, 994–1001.

- Sanger, T.D., Garg, R.R., Chen, R., 2001. Interactions between two different inhibitory systems in the human motor cortex. *J. Physiol.* 530, 307–317.
- Sarfeld, A.S., Diekhoff, S., Wang, L.E., Liuzzi, G., Uludag, K., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2012. Convergence of human brain mapping tools: neuronavigated TMS parameters and fMRI activity in the hand motor area. *Hum. Brain Mapp.* 33, 1107–1123.
- Sekiguchi, H., Takeuchi, S., Kadota, H., Kohno, Y., Nakajima, Y., 2011. TMS-induced artifacts on EEG can be reduced by rearrangement of the electrode's lead wire before recording. *Clin. Neurophysiol.* 122, 984–990.
- Siebner, H.R., Dressnandt, J., Auer, C., Conrad, B., 1998. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle Nerve* 21, 1209–1212.
- Siebner, H.R., Mentschel, C., Auer, C., Lehner, C., Conrad, B., 2000. 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.* 284, 147–150.
- Stetkarova, I., Kofler, M., 2013. Differential effect of baclofen on cortical and spinal inhibitory circuits. *Clin. Neurophysiol.* 124, 339–345.
- Tamburin, S., Fiaschi, A., Andreoli, A., Marani, S., Manganotti, P., Zanette, G., 2004. Stimulus–response properties of motor system in patients with cerebellar ataxia. *Clin. Neurophysiol.* 115, 348–355.
- Tazoe, T., Endoh, T., Nakajima, T., Sakamoto, M., Komiyama, T., 2007. Disinhibition of upper limb motor area by voluntary contraction of the lower limb muscle. *Exp. Brain Res.* 177, 419–430.
- Teo, J.T., Schneider, S.A., Cheeran, B.J., Fernandez-del-Olmo, M., Giunti, P., Rothwell, J.C., Bhatia, K.P., 2008. Prolonged cortical silent period but normal sensorimotor plasticity in spinocerebellar ataxia 6. *Mov. Disord.* 23, 378–385.
- Tremblay, S., de Beaumont, L., Lassonde, M., Theoret, H., 2011. Evidence for the specificity of intracortical inhibitory dysfunction in asymptomatic concussed athletes. *J. Neurotrauma* 28, 493–502.
- Valls-Sole, J., Pascual-Leone, A., Wassermann, E.M., Hallett, M., 1992. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr. Clin. Neurophysiol.* 85, 355–364.
- Veniero, D., Bortoletto, M., Miniussi, C., 2009. TMS–EEG co-registration: on TMS-induced artifact. *Clin. Neurophysiol.* 120, 1392–1399.
- Wassermann, E.M., Fuhr, P., Cohen, L.G., Hallett, M., 1991. Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology* 41, 1795–1799.
- Werhahn, K.J., Kunesch, E., Noachtar, S., Benecke, R., Classen, J., 1999. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J. Physiol.* 517 (Pt 2), 591–597.
- Ziemann, U., Rothwell, J.C., 2000. I-waves in motor cortex. *J. Clin. Neurophysiol.* 17, 397–405.