

# Characterization of Glutamatergic and GABA<sub>A</sub>-Mediated Neurotransmission in Motor and Dorsolateral Prefrontal Cortex Using Paired-Pulse TMS–EEG

Robin FH Cash<sup>1,2,3,6</sup>, Yoshihiro Noda<sup>1,4,6</sup>, Reza Zomorodi<sup>1</sup>, Natasha Radhu<sup>1,2</sup>, Faranak Farzan<sup>1</sup>, Tarek K Rajji<sup>1,4,5</sup>, Paul B Fitzgerald<sup>3</sup>, Robert Chen<sup>2</sup>, Zafiris J Daskalakis<sup>1,4,5</sup> and Daniel M Blumberger<sup>\*,1,4,5</sup>

<sup>1</sup>Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, ON, Canada; <sup>2</sup>Division of Neurology, Department of Medicine, University of Toronto, Division of Brain, Imaging and Behaviour—Systems Neuroscience, Toronto Western Research Institute, University Health Network, Toronto, ON, Canada; <sup>3</sup>Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred, Melbourne, VIC, Australia; <sup>4</sup>Department of Psychiatry, University of Toronto, Toronto, ON, Canada; <sup>5</sup>Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are noninvasive transcranial magnetic stimulation (TMS) measures of GABA<sub>A</sub> receptor-mediated inhibition and glutamatergic excitatory transmission, respectively. Conventionally these measures have been restricted to the motor cortex. We investigated whether SICI and ICF could be recorded from the dorsolateral prefrontal cortex (DLPFC) using combined TMS and electroencephalography (TMS–EEG). We first characterized the neural signature of SICI and ICF in M1 in terms of TMS-evoked potentials (TEPs) and spectral power modulation. Subsequently, these paradigms were applied in the DLPFC to determine whether similar neural signatures were evident. With TMS at M1, SICI and ICF led to bidirectional modulation (inhibition and facilitation, respectively) of P30 and P60 TEP amplitude, which correlated with MEP amplitude changes. With DLPFC stimulation, P60 was bidirectionally modulated by SICI and ICF in the same manner as for M1 stimulation, whereas P30 was absent. The sole modulation of early TEP components is in contradistinction to other measures such as long-interval intracortical inhibition and may reflect modulation of short latency excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs). Overall, the data suggest that SICI and ICF can be recorded using TMS–EEG in DLPFC providing noninvasive measures of glutamatergic and GABA<sub>A</sub> receptor-mediated neurotransmission. This may facilitate future research attempting to ascertain the role of these neurotransmitters in the pathophysiology and treatment of neurological and psychiatric disorders.

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## INTRODUCTION

Transcranial magnetic stimulation (TMS) provides a non-invasive method to study human cortical neurophysiology. The integrity of various cortical circuits can be measured using different conditioning-test stimulus (TS) protocols. Short-interval intracortical inhibition (SICI) describes the suppression of a TS given at short intervals of 1–6 ms following a subthreshold conditioning stimulus (CS), first identified by Kujirai *et al* (1993). This is followed by a period of motor-evoked potential (MEP) facilitation at longer CS-TS

ISIs of ~7–25 ms, known as intracortical facilitation (ICF) (Claus *et al*, 1992; Kujirai *et al*, 1993). SICI is mediated by fast ionotropic GABA<sub>A</sub> receptors, specifically those subtypes bearing the  $\alpha 2$  or  $\alpha 3$  subunit (Di Lazzaro *et al*, 2006a; Ilic *et al*, 2002; Ziemann *et al*, 1996). SICI is thus thought to arise because the CS activates a low threshold inhibitory system, which generates a hyperpolarizing inhibitory postsynaptic potentials (IPSPs) inhibiting the cortical output evoked by a subsequent TS (Ilic *et al*, 2002; Kujirai *et al*, 1993). ICF is mediated by glutamate (Liepert *et al*, 1997; Schwenkreis *et al*, 2000) and may be evoked by the summation of excitatory postsynaptic potentials (EPSPs) from CS and TS. ICF is thought to reflect excitatory transmission largely through the NMDA receptor (Mori *et al*, 2011; Schwenkreis *et al*, 1999; Ziemann *et al*, 1998). SICI and ICF are common noninvasive measures of cortical excitability and are abnormal in a number of movement and cognitive disorders (Chen and Curra, 2004).

Previous TMS neurophysiological studies have been largely restricted to the primary motor cortex (M1), owing to the

\*Correspondence: Dr DM Blumberger, Temerty Centre for Therapeutic Brain Intervention, Head, Late-Life Mood Disorders Clinic, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, 1001 Queen St. W. Unit 4-115, Toronto, ON M6J 1H4, Canada, Tel: +1 416 535 8501, Fax: +1 416 583 4613, E-mail: daniel.blumberger@camh.ca

<sup>6</sup>These authors contributed equally to this work.

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ease of recording electromyographic (EMG) motor output in target muscles. However, the ability to noninvasively investigate SICI and ICF in other areas would be highly desirable, for example, in prefrontal areas, which are more directly involved in cognitive disorders (Julkunen *et al*, 2011). Recent technical advances have enabled the concurrent recording of electroencephalographic (EEG) responses to TMS (Ilmoniemi and Kicic, 2010), thus providing a potentially more direct measure of induced changes in neuronal activity and extending the use of TMS to non-motor areas (Daskalakis *et al*, 2008; Fitzgerald *et al*, 2008). Such studies have demonstrated EEG neurophysiological correlates of cortical inhibitory circuits such as GABA<sub>B</sub>-mediated long-interval intracortical inhibition (LICI) in motor and dorsolateral prefrontal cortex (DLPFC) (Daskalakis *et al*, 2008; Fitzgerald *et al*, 2008). Changes in this paradigm have been associated with schizophrenia (Farzan *et al*, 2010; Radhu *et al*, 2015) and predict treatment response to magnetic seizure therapy in depression (Sun *et al*, 2016). Changes are typically characterized by modulation in the amplitude of components of the TMS-evoked potential (TEP) and modulation of oscillatory power at different frequencies. TEP components are thought to reflect changes in cortical excitability potentially related to longer lasting underlying IPSPs and EPSPs rather than neural firing (Premoli *et al*, 2014a).

Studies have explored the electrophysiological TMS–EEG correlates of SICI and ICF in M1 (Ferreri *et al*, 2011; Manganotti *et al*, 2012; Paus *et al*, 2001). One of these studies explored SICI and ICF at sufficiently high temporal resolution and with adequate power to identify changes in TEP components (Ferreri *et al*, 2011). SICI attenuated and ICF enhanced the amplitude of positive deflections at a latency of 30 ms (P30) and 60 ms (P60), whereas the amplitude of the negative trough at 45 ms (N45) was partially affected. The influence of SICI and ICF on cortical TEPs in prefrontal cortex and on oscillatory power remains unknown.

In the present study we first characterized the TMS–EEG neural signature of SICI and ICF in M1 in terms of TEP component amplitude and spectral power modulation. Subsequently these paradigms were applied in DLPFC to determine whether similar neural signatures were evident, with the aim of enabling the future use of these paradigms as novel measures of GABA<sub>A</sub> and glutamate receptor-mediated neurotransmission in prefrontal cortex.

## MATERIALS AND METHODS

### Participants

Twelve right-handed adults (six female, aged 22–57 years; mean age  $39 \pm 12$  years) participated in the main component of the present study to investigate SICI from the M1 (M1–SICI) and DLPFC (DLPFC–SICI) as well as ICF from the DLPFC (DLPFC–ICF). The influence of ICF with M1 stimulation (M1–ICF) was tested in 21 right-handed adults (14 female, aged 23–56 years; mean age  $32 \pm 10$  years) in a separate session owing to time constraints. Exclusion criteria included a self-reported comorbid medical illness, smoking, use of prescription medication, or a history of drug or alcohol abuse. Psychopathology was ruled out using the

Structured Clinical Interview for DSM–IV Axis I Disorders. Participants abstained from caffeine intake prior to commencing the study, although it is thought that caffeine does not influence SICI and ICF (Orth *et al*, 2005). Written informed consent was obtained from each participant. The experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Centre for Addiction and Mental Health.

### Experimental Design and Procedures

**EMG recordings.** EMG was recorded from the relaxed first dorsal interosseous of the dominant (right) hand according to previously published methods (Daskalakis *et al*, 2002).

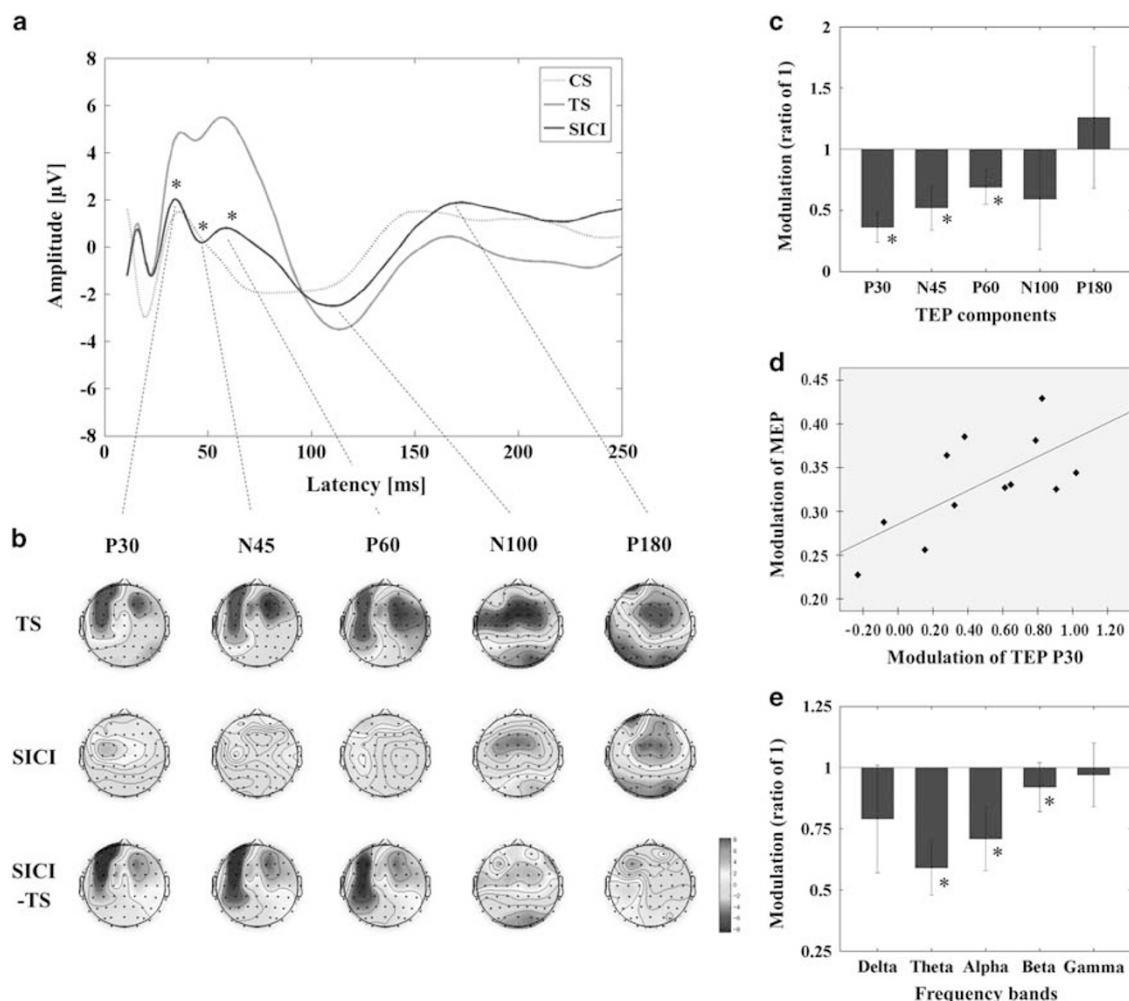
**TMS.** Monophasic TMS pulses were administered to the left M1 hotspot using a 70 mm figure-of-eight coil, and two Magstim 200 stimulators (Magstim Company Ltd., UK) connected via a Bistim module. MEP data were collected using Signal (Cambridge Electronics, UK). DLPFC stimulation was performed with the coil centered between F3 and F5 electrodes, which provides the most accurate estimation of left DLPFC (border of BA9 and BA46) and low inter-subject variability in the absence of MRI-guided neuronavigational equipment (Fitzgerald *et al*, 2009; Rusjan *et al*, 2010).

**Measurement of SICI and ICF.** SICI was studied according to established methods (Kujirai *et al*, 1993). An ISI of 2 ms was used to avoid contamination by excitatory interneurons (Peurala *et al*, 2008), and as this ISI optimally suppresses late I-waves and MEP amplitude (Di Lazzaro *et al*, 1998). CS intensity was 80% RMT. TS intensity was set to evoke a MEP of 1 mV peak-to-peak amplitude when delivered alone, which is considered optimal for evoking SICI, whereas lower TS intensities do not reliably evoke SICI (Daskalakis *et al*, 2002; Sanger *et al*, 2001; Wagle-Shukla *et al*, 2009). In fact, SICI delivered with a lower TS at  $\sim$ RMT would have the potential to elicit facilitation rather than inhibition (c.f. Figure 1b, Ilic *et al*, 2002). At last, the use of near threshold TS intensities would not allow investigation of the relationship between TMS–EEG and TMS–EMG measures of SICI and ICF. ICF was measured using the same CS and TS intensities and an ISI of 10 ms (Kujirai *et al*, 1993). Hundred trials were delivered per condition.

**EEG recording and signal preprocessing.** EEG was recorded as previously described (Daskalakis *et al*, 2008), and preprocessing was performed in line with published methodology (Radhu *et al*, 2015; Rogasch *et al*, 2014) as outlined in supplementary information.

### Data Analysis

**Analysis of SICI and ICF.** Averages are expressed as mean  $\pm$  (SEM). MEPs evoked by single and paired pulse (conditioned–test) stimulation for each subject were averaged in each condition. For EMG and EEG, SICI and ICF were calculated from MEP or TEP amplitudes as ((CS.TS)/TS) and expressed as a percentage or ratio. For TMS–EEG, first, the area under the TEP curve (time window 20–200 ms) was computed with the Hilbert transform method for each



**Figure 1** Inhibitory influence of SICI on TEPs with TMS over MI. (a) Group averaged TEPs following TS (red; delivered at a time equal to 0 ms), SICI (CS, TS) (blue) and CS alone (dotted line; delivered at  $-2$  ms, that is, 2 ms prior to TS). P30, N45, and P60 were significantly reduced in amplitude by SICI. (b) Topographical display of the suppression of TEP components by SICI. (c) Amplitude suppression of TEP components by SICI (mean  $\pm$  SEM) is displayed as a ratio of 1 (1 is equivalent to no change relative to the TEP amplitude of TS alone;  $*P < 0.05$ ). Note that TEP latency varied according to individual, TEP and condition leading to phase cancellation in the average trace and voiding direct comparison between (a) and (c) in all figures. (d) The suppression of MEP amplitude by SICI and of P30 TEP was significantly positively correlated (Pearson's correlation,  $r = 0.678$ ,  $p = 0.015$ ,  $N = 12$ ). (e) Modulation of cortical oscillatory power. MI-SICI was associated with a significant decrease in power in the theta, alpha, and beta bands ( $*P < 0.05$ ). A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

ROI (Supplementary Figure 1). The Hilbert transform is a measure of the amplitude envelope and power changes in cortical oscillatory activity and thus identifies the cortical region in which these changes in neural activity evoked by SICI and ICF are greatest. Subsequently, the influence of SICI and ICF on the amplitude of individual TEP components (P30, N45, P60, N100, and P180) was computed for each ROI. Although some (Premoli *et al*, 2014b), but not all (Daskalakis *et al*, 2008; Ferreri *et al*, 2011, 2012; Paus *et al*, 2001) studies have subtracted the influence of CS alone, the present data for SICI and conversely ICF clearly indicate bidirectional changes in the amplitude of TEP components that are clearly unrelated to the influence of CS alone. Thus, for simplicity and greater transparency in this case, CS amplitude was not subtracted from the CS.TS waveform.

Modulation of the specific frequencies with SICI/ICF paradigms were investigated from the delta to gamma band range (ie, delta: 0.3–3 Hz, theta: 4–7 Hz, alpha: 8–14 Hz, beta:

14–30 Hz, gamma: 30–50 Hz) in a time window of 2000 ms following TS.

**Statistical analyses.** Statistical analysis on main effects (and sub-effects) was performed using repeated (and multivariate) measure analysis of variance (ANOVA; MANOVA) and two-tailed paired t-tests with SPSS (version 19.0). Additional details are provided in supplementary information.

## RESULTS

### MEP Amplitude Modulation

MEP amplitude was significantly attenuated by SICI ( $32.3 \pm 3.7\%$  of TS alone, mean  $\pm$  SEM;  $t_{11} = -8.506$ ,  $P < 0.0001$ ). For SICI, TS alone gave an MEP amplitude of  $1.13 \pm 0.32$  mV, which was attenuated to  $0.36 \pm 0.11$  ( $n = 12$ ). For ICF,

MEP amplitude was significantly facilitated ( $168.4 \pm 8.0\%$  of TS alone;  $t_{15} = -5.532$ ,  $P = 0.01$ ). TS alone evoked an MEP amplitude of  $1.03 \pm 0.03$  mV, which was facilitated to  $1.73 \pm 0.09$  mV ( $n = 21$ ).

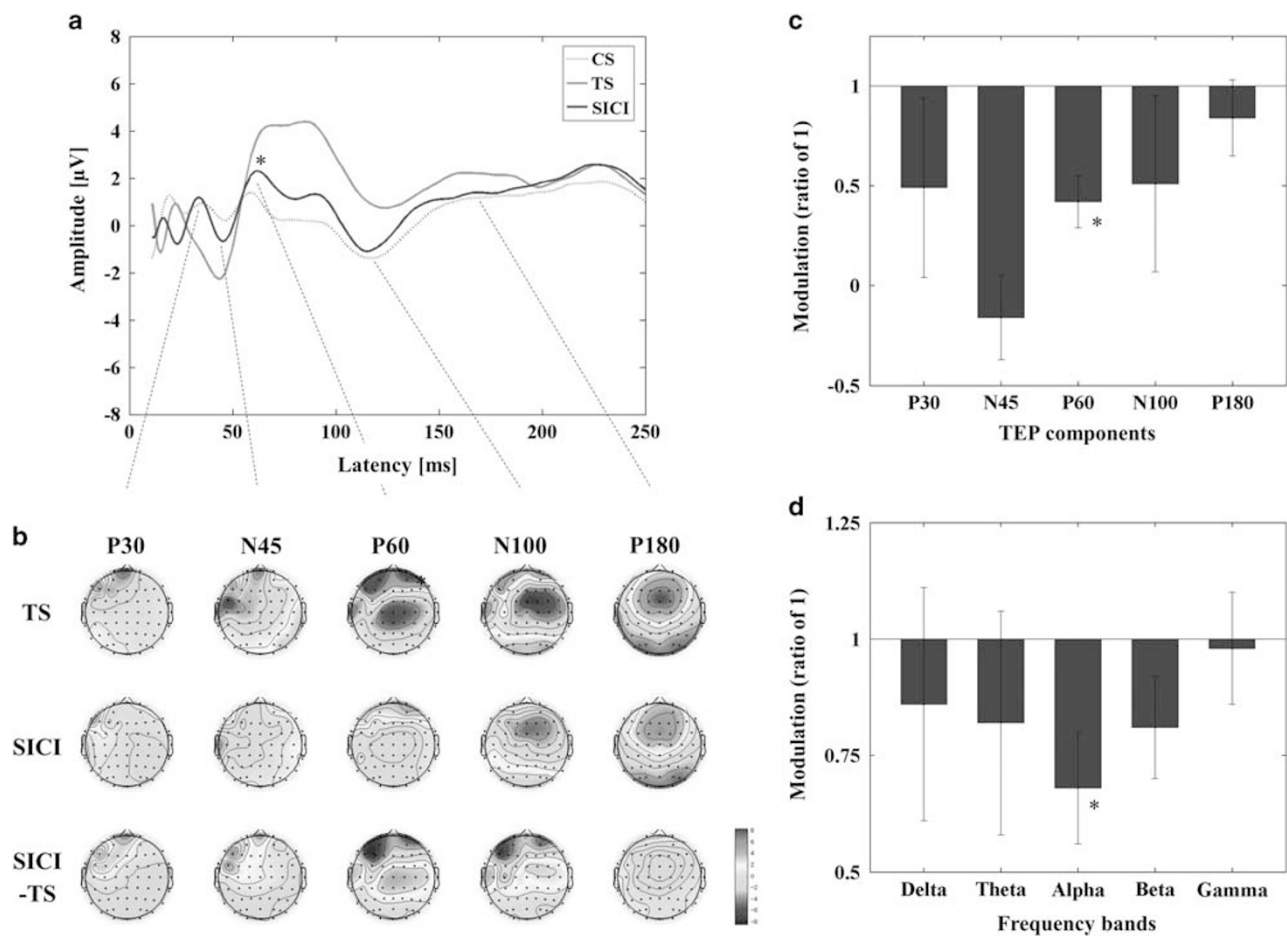
### TEP Power and Amplitude Changes

**M1-SICI.** Results are displayed in Figure 1 and statistics are summarized in Supplementary Table 1. The ANOVA for TEP power showed significant main effects of ROI and condition (TS vs SICI (CS:TS)) as well as a significant ROI-by-condition interaction. MANOVA indicated that for TEP Power the significant interaction of ROI  $\times$  Condition (TS and SICI) was restricted to the left central ROI, with TEP power significantly decreased by SICI (see Supplementary Table 1 and Supplementary Figure 2A). ANOVA of TEP amplitude at this ROI revealed a significant interaction of condition (TS vs SICI) and TEP component. *Post hoc* analyses indicated that M1-SICI suppressed the amplitude of several early TEP components (Figure 1(a-c): (i) TEP P30 (SICI < TS), (ii) TEP N45 (SICI < TS), and (iii) TEP P60 (SICI < TS) (Supplementary Table 1).

**DLPFC-SICI.** Results are displayed in Figure 2 and statistics summarized in Supplementary Table 2. ANOVA and *post hoc* analysis for TEP power showed that the influence of DLPFC-SICI was significant and specific to the left frontal ROI (Supplementary Figure 2B). Further, ANOVA and *post hoc* analyses for TEP values indicated that SICI significantly suppressed P60 amplitude at the left frontal ROI (Figure 2a; Supplementary Table 2) and in its topographical distribution (Figure 2b).

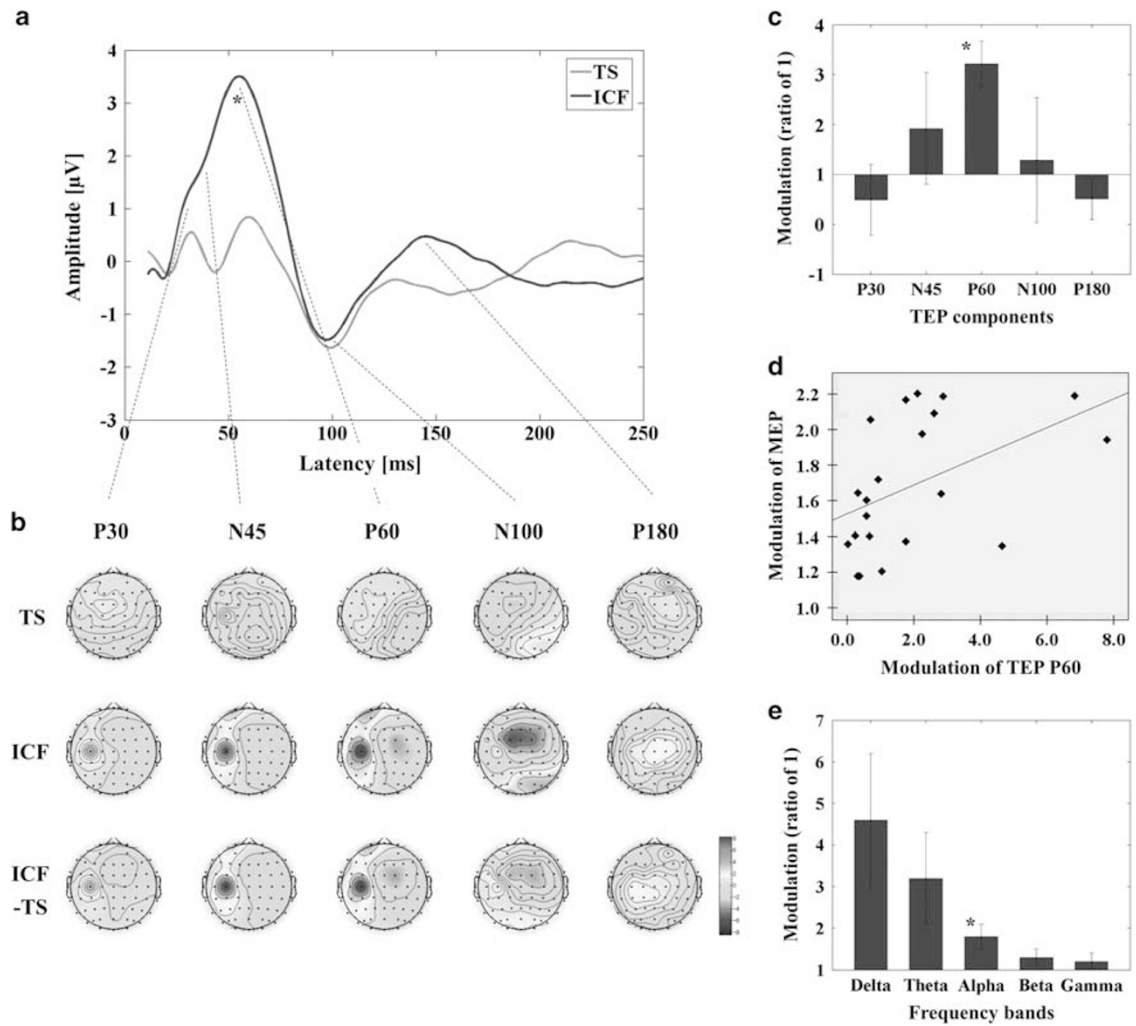
**M1-ICF.** As a complementary analysis, we studied the M1-ICF paradigm to validate the DLPFC-ICF paradigm (Figure 3; Supplementary Table 3). ANOVA and *post hoc* analyses for TEP power revealed that the influence of M1-ICF was most significant at the left central ROI (Supplementary Figure 2(C)). Further, the ANOVA and *post hoc* analyses for TEP values demonstrated that M1-ICF induced significant facilitation of P60 at the left central ROI (TS < ICF) (see Figure 3a-c and Supplementary Table 3).

**DLPFC-ICF.** Results are displayed in Figure 4 and Supplementary Table 4. ANOVA and *post hoc* analyses for



**Figure 2** Inhibitory influence of SICI on TEPs with TMS over DLPFC. (a) Group averaged TEPs following TS (red; delivered at a time equal to 0 ms), SICI (CS:TS) (blue) and CS alone (dotted line; delivered at -2 ms, ie, 2 ms prior to TS). P60 was significantly reduced in amplitude by SICI, whereas P30 was not apparent in DLPFC. (b) Topographical display of the suppression of TEP components by SICI. (c) Amplitude suppression of TEP components by SICI (mean  $\pm$  SEM) is quantified as a ratio of 1 (1 is equivalent to no change relative to the TEP amplitude of TS alone;  $*P < 0.05$ ). The modulation of TEP components by SICI (mean  $\pm$  SEM) is displayed as a ratio of 1 (1 is equivalent to no change;  $*P < 0.05$ ). (d) Modulation of cortical oscillatory power. DLPFC-SICI was associated with a significant decrease in power specific to the alpha band ( $*P < 0.05$ ). A full color version of this figure is available at the *Neuropsychopharmacology* journal online.





**Figure 3** Facilitatory influence of ICF on TEPs with TMS over MI, recorded in a separate group of 21 individuals. (a) Group averaged TEPs following TS (red; delivered at a time equal to 0 ms) and ICF (CS.TS) (blue). P60 was significantly increased in amplitude by ICF. P30 appeared to be increased in amplitude but was not evident as a distinct peak. (b) Topographical display of the facilitation of TEP components by ICF. (c) The modulation of TEP components by ICF (mean  $\pm$  SEM) is displayed as a ratio of 1 (1 is equivalent to no change relative to the TEP amplitude of TS alone;  $*P < 0.05$ ). (d) The facilitation of the MEP amplitude by ICF and of P60 TEP was significantly positively correlated (Pearson's correlation,  $r = 0.543$ ,  $p = 0.011$ ,  $N = 21$ ). (e) Modulation of cortical oscillatory power. MI-ICF was associated with a significant increase in power in the alpha band ( $*P < 0.05$ ). A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

TEP power revealed that the influence of DLPFC-ICF was most significant at the left frontal ROI (Supplementary Figure 2D). Further, ANOVA and *post hoc* analyses for TEP values demonstrated that DLPFC-ICF induced significant modulation on TEP P60 and N100 at the left frontal ROI (TS < ICF) (Figure 4a-c; Supplementary Table 4).

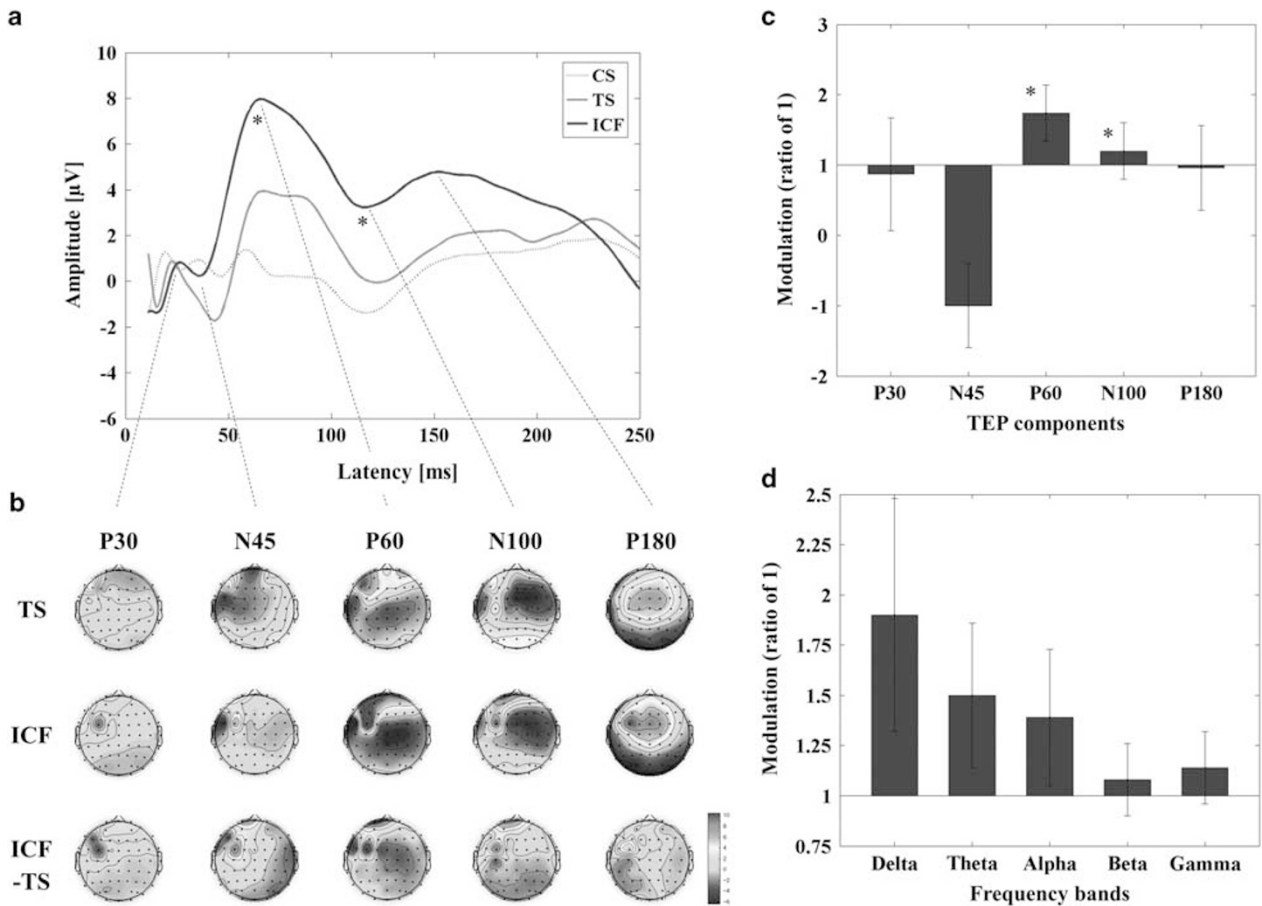
### Topological Distributions of TEPs

For the MI-SICI/ICF paradigms, P30 and P60 showed a slightly lateralized and somewhat frontal topographical distribution extending from the site of stimulation, whereas N100 and P180 showed a bilateral distribution, in broad agreement with previous studies (Ferreri *et al*, 2011; Premoli *et al*, 2014a,2014b). With a TS intensity of  $\sim 1$ mV as used here, TEPs may become somewhat dominated by the P60-N100 complex (Lioumis *et al*, 2009), and this may explain why the first TEP components appear dominated by a broad positive peak (Figure 1b and Figure 3b). This is a limitation

of using a TS of 1mV to reliably elicit SICI and to compare the modulation of TMS-EEG and TMS-EMG amplitude. Nonetheless, P30 and N45 are evident as superimposed on these more dominant TEP components (Figure 1a), and modulation of these components by SICI and ICF is evident topographically (Figures 1,2b), in agreement with the results of Ferreri *et al* (2011, c.f. Table 1). With DLPFC-SICI/ICF paradigms, early TEPs (P30, N45, and P60) showed a more frontal distribution, whereas N100 and P180 had a more central/bilateral distribution (Figure 2b and Figure 4b).

### Modulation of Cortical Oscillatory Power in Different Frequency Bands

ANOVA and *post hoc* analyses for the MI-SICI paradigm indicated SICI significantly decreased power in theta ( $t_{11} = 5.446$ ,  $p < 0.0001$ ;  $SICI_{\theta} < TS_{\theta}$ ), alpha ( $t_{11} = 3.297$ ,  $p = 0.007$ ;  $SICI_{\alpha} < TS_{\alpha}$ ), and beta ( $t_{11} = 4.222$ ,  $p = 0.001$ ;  $SICI_{\beta} < TS_{\beta}$ ) bands. For DLPFC-SICI,



**Figure 4** Facilitatory influence of ICF on TEPs with TMS over DLPFC. (a) Group averaged TEPs following TS (red; delivered at a time equal to 0 ms), ICF (CS;TS) (blue) and CS alone (dotted line; delivered at -10 ms, ie, 10 ms prior to TS). P60 was significantly increased in amplitude similar to M1-ICF, whereas P30 was not evident in DLPFC. In addition, there was a longer lasting increase in EEG-positive potential with a modulation of N100 amplitude. (b) The topographical distribution of TEP components, and their modulation by ICF, is displayed. Note that the topographical distributions of TEPs from TS for DLPFC-ICF and DLPFC-SICI are equivalent, but that the scaling has been adjusted in each case to better visualize the respective changes. (c) The modulation of TEP components by ICF (mean  $\pm$  SEM) is displayed as a ratio of 1 (1 is equivalent to no change relative to the TEP amplitude of TS alone; \* $P < 0.05$ ). Note that DLPFC-ICF increases the positivity of N45 (consistent with M1-ICF), but that this is equivalent to a decrease of the amplitude of N45 in DLPFC-ICF, resulting in a negative ratio. (d) DLPFC-ICF did not modulate power in any frequency band. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

ANOVA and *post hoc* analyses revealed a significant decrease in alpha band power ( $t_{11} = 3.680$ ,  $p = 0.004$ ;  $SICI_{\alpha} < TS_{\alpha}$ ). M1-ICF induced a significant increase in the alpha band ( $t_{20} = -3.300$ ,  $p = 0.004$ ;  $ICF_{\alpha} > TS_{\alpha}$ ), whereas no significant modulation occurred in the DLPFC-ICF paradigm.

### Correlated Modulation of MEP and TEP Amplitude

A significant positive correlation for M1 measures was observed between SICI of MEP and P30 TEP amplitude ( $r = 0.678$ ,  $p = 0.015$ ,  $N = 12$ ) (Figure 1d and for ICF of MEP and TEP P60 amplitude ( $r = 0.543$ ,  $p = 0.011$ ,  $N = 21$ ) (Figure 3d) at the left central ROI.

## DISCUSSION

### Summary

Using simultaneous TMS and EEG, we demonstrated that SICI and ICF are associated with bidirectional modulation of neuronal activity, and that this is consistent for TMS applied

to motor and prefrontal regions. With M1 stimulation, there was a significant association between the level of modulation of TEP and MEP amplitude, suggesting that the TMS-EEG measures were representative of neural excitability changes evoked by SICI and ICF. These findings pave the way for future noninvasive investigation of inhibitory and excitatory physiological activity in prefrontal cortex for patients with neurologic and psychiatric disorders and distinction between aberrant GABA<sub>A</sub> and GABA<sub>B</sub> receptor-mediated neurotransmission.

### Influence of SICI and ICF on TEP and MEP Amplitude with M1 TMS

The modulation of TEP components by SICI and ICF has been investigated previously however the results were inconsistent. Paus *et al* (2001) found no influence of SICI on TEPs however that study may have been underpowered as only five participants survived rejection. Manganotti *et al* (2012) explored the influence of SICI on TMS-EEG potentials on a broader time-scale of seconds rather than

TEP components in the milliseconds immediately following stimulation. The present results in motor cortex are consistent with those of Ferreri *et al* (2011) who used similar methodology. SICI attenuated and ICF enhanced the amplitude of positive deflections at a latency of 30 ms (P30) and 60 ms (P60), whereas the amplitude of the negative trough at 45 ms (N45) was moderately affected by SICI. It appeared as if P30 was potentially increased in amplitude during ICF; however, it was not possible to definitively measure this change as P30 was generally occluded by a marked increase in P60 amplitude during ICF. The masking of P30 by P60 during ICF is consistent with the same phenomenon occurring at higher intensities with single pulse TMS (Lioumis *et al*, 2009). Nonetheless, a shared modulation of the amplitude of these components would be consistent with correlated inhibition of P30 and P60 amplitude in the LICI paradigm (Rogasch *et al*, 2013). The change in P30 and P60 amplitude is consistent with previous studies indicating that these components are particularly sensitive to changes in excitability, gaining in amplitude as stimulus intensity is increased with both M1 and DLPFC stimulation (Kahkonen *et al*, 2005a, b; Komssi *et al*, 2004; Lioumis *et al*, 2009), and being inhibited by LICI (Rogasch *et al*, 2013), the CSP (Farzan *et al*, 2013), and SAI (Ferreri *et al*, 2012). Critically, the degree of modulation of TEP components P30 and P60, respectively, was related to the modulation of MEP amplitude by SICI and ICF in the present study (Figure 1d and Figure 3d) and elsewhere (Rogasch *et al*, 2013), suggesting that these TEP measures reflect similar neural excitability changes to the MEP. Together, these results suggest that P30 and P60 provide sensitive measures of changes in cortical excitability, and provide evidence of a direct relationship between neural activity measured by modulation of P30 and P60 TEP amplitude and more conventional MEP based measures of cortical excitability changes associated with SICI and ICF.

Interestingly N100 TEP amplitude was not influenced by SICI or ICF, in contradistinction to the modulation of N100 by LICI (Rogasch *et al*, 2013) and the CSP (Farzan *et al*, 2013; Kimiskidis *et al*, 2008). N100 is thought to be related to GABA<sub>B</sub>-receptor mediated long lasting IPSP (Premoli *et al*, 2014b), whereas earlier TEP components could be related to a shorter latency EPSP and GABA<sub>A</sub> receptor-mediated IPSP (Premoli *et al*, 2014a). In this sense, the sole modulation of early components may represent a relatively distinct neural signature of SICI or ICF.

### Influence of SICI and ICF on TEP Amplitude in DLPFC

In DLPFC, SICI and ICF were characterized by inhibition and facilitation, respectively, of P60 TEP amplitude, consistent with the results from M1 stimulation, whereas P30 was generally absent in DLPFC with single pulse stimulation. For ICF, it appeared that following P60 there was a longer lasting increase in positive potentials, influencing N100 amplitude. In data sets where N100 has a negative potential, rather than solely representing a trough, this could perhaps be simply explained by the finding that P60 and N100 amplitude may be negatively correlated and P60 may be inversely linked to inhibition (Rogasch *et al*, 2013). The absence of P30 in DLPFC is consistent with previous findings that P30 is expressed to a lesser extent in DLPFC compared

with M1 (c.f. Figure 6A,B and 10A,B Rogasch *et al*, 2014; Van Der Werf and Paus, 2006). Overall early components, in particular P60 TEP amplitude, were most consistently modulated by SICI and ICF across M1 and DLPFC stimulation, and in a bidirectional manner, which was linked to their modulation of MEP amplitude with M1 stimulation. It appears that P60 TEP amplitude may most robustly reflect neural excitability and its modulation by SICI and ICF across M1 and DLPFC. The results provide the first evidence that it might be possible to measure GABA<sub>A</sub> receptor-mediated inhibition or glutamatergic activity with SICI and ICF in non-motor regions using TMS-EEG. In addition, these findings enable direct comparison in future studies of changes in GABA<sub>B</sub> (Daskalakis *et al*, 2008) and GABA<sub>A</sub> receptor-mediated inhibition in prefrontal cortex, which are differentially implicated in psychiatric disorders including major depressive disorder (MDD) and schizophrenia (Deng and Huang, 2006). MDD is associated with region-specific modulation of GABA<sub>A</sub> receptor subunit composition and GABA concentration (Pehrson and Sanchez, 2015), but functional effects on inhibitory strength have been difficult to assess in human using existing techniques. We anticipate that the present noninvasive measures will be of significant benefit for investigation of inhibitory and excitatory strength in neurological disorders, and their modulation by treatment.

As noted above, SICI and ICF showed the same bidirectional modulation of TEP amplitude in M1 and DLPFC. We anticipated that there would be a stronger association between MEPs and M1 TEPs compared with MEPs and DLPFC TEPs. We performed an exploratory correlational analysis between MEP measures and TEP amplitude changes in DLPFC, however no additional correlations were observed. Similarly, other studies have reported an absence of correlations between modulation of specific TEP components in M1 compared to other areas (Farzan *et al*, 2009, 2013; Noda *et al*, 2016), and in the present study this may reflect a difference in the strength of SICI and ICF in M1 compared to DLPFC. This could perhaps be due to differences in GABA<sub>A</sub> or glutamatergic tone. Such differences could suggest that SICI and ICF measured in DLPFC provide unique information compared to SICI and ICF in M1.

### Evidence for a Cortical Origin of ICF

One further aspect of the present findings deserves mention. There is substantial evidence that SICI is mediated at the cortical level, and although ICF is widely assumed to be cortically mediated, to date direct evidence for this has been considerably weaker. Using paired electrical and magnetic stimulation, with the former thought to activate pyramidal cells directly, Kujirai *et al* (1993) demonstrated that SICI involved cortical interneuronal activity and could only be evoked using paired pulse magnetic stimulation. In contrast, ICF could still be evoked with paired electrical and magnetic stimulation. Later, Di Lazzaro *et al* (1998) demonstrated that SICI reduces the amplitude of descending I-waves evoked by the test pulse, providing direct evidence of inhibition at the cortical level, whereas the ICF conditioning pulse had no effect on the amplitude of descending I-wave activity evoked



by the test pulse (Di Lazzaro *et al*, 2006b). Although systemic administration of pharmacological agents has suggested that ICF is mediated by glutamate (for review, see Paulus *et al*, 2008), it was not demonstrated whether this occurred in the spinal or cortical CNS. The present results provide clear evidence that ICF modulates neuronal activity at the cortical level. Additional EPSP summation at the spinal level cannot be excluded (Di Lazzaro *et al*, 2006b; Kujirai *et al*, 1993), however the tight correlation with TEP amplitude suggests that the spinal contribution may be modest.

### Modulation of Spectral Power

The present findings indicate that multiple frequency bands were modulated by SICI in M1, but that modulation was specific to the alpha band with DLPFC–SICI. Similarly, suppression of multiple frequency bands occurs with LICI (Farzan *et al*, 2009) and the cortical silent period (Farzan *et al*, 2013). Differential modulation of spectral properties was also observed previously according to the site of stimulation (Farzan *et al*, 2009), although the present results indicate a greater specificity to lower frequency bands.

As noted above, a consistent finding across DLPFC and M1 was the reduction in alpha power following SICI. Oscillatory activity in the alpha band preceding a task has been associated with functional inhibition (for review, see Jensen and Mazaheri, 2010), and whereas activity of inhibitory interneurons is often associated with the gamma rhythm (Bartos *et al*, 2007), GABAergic feedback from interneurons is strongly implicated in the physiological mechanism generating the alpha rhythm (for review, see Mazaheri and Jensen, 2010). Little is known about the modulation of alpha power following stimulation of GABA<sub>A</sub> mediated inhibition; however, the present results appear consistent with the decrease in cortical alpha power that occurs following administration of benzodiazepines (positive allosteric modulators of the GABA<sub>A</sub> receptor) (Berchou *et al*, 1986; Fingelkurts *et al*, 2004; Link *et al*, 1991; Schreckenberger *et al*, 2004).

Modulation in the beta band was specific to M1–SICI. Beta band activity is more dominant in the rolandic area and associated with movement execution and the motor network. Previous studies found that beta power (ie, amplitude) and phase-synchrony are increased following single pulse TMS (Fuggetta *et al*, 2005; Paus *et al*, 2001; Van Der Werf and Paus, 2006), and this increase is specific to M1 stimulation and not induced by stimulation of dorsal premotor cortex (Van Der Werf and Paus, 2006). Beta activity is suppressed by GABA receptor-mediated inhibitory paradigms LICI (Farzan *et al*, 2009) and SAI (Ferreri *et al*, 2012). Beta band activity and SICI have both been closely linked to stopping and response inhibition (Coxon *et al*, 2006; for review, see Schall and Godlove, 2012). Together these findings provide a possible basis for the specificity of beta band modulation to the motor domain and its link to inhibitory activity.

With regard to the theta band, this frequency is more commonly associated with cognitive tasks and it is surprising that this frequency was more modulated in M1 than DLPFC. Interestingly, however, the theta rhythm appears particularly responsive to, and is suppressed following, low frequency rTMS to M1, which has an inhibitory impact on excitability (Van Der Werf and Paus, 2006).

### Limitations

Accuracy could have potentially been enhanced and variability reduced by using MRI rather than EEG-guided neuronavigation. Nonetheless, the TEPs evoked in the present study are consistent with those previously reported using either method. Indeed, both methods produce highly comparable results (compare Lioumis *et al*, 2009; Rogasch *et al*, 2014). Non-MRI-guided neuronavigation is commonly employed and was used in all but one study in a recent review of TMS–EEG studies by Hone-Blanchet *et al* (2015).

The results may be contaminated by the auditory-evoked potential (AEP) from the TMS click, which has peaks ~90 and 180 ms (Rogasch *et al*, 2014). However, these peaks are too broad to explain the bidirectional differences between SICI and ICF—ie, polarity reversal associated with the AEP would require a shift in ISI of ~90 ms, whereas the shift in ISI was just 8 ms. Thus auditory contamination is unlikely to account for the present findings in both motor and frontal cortex, which relate to relatively early components.

In the present study we used a CS intensity of 80% RMT, as this is commonly applied for SICI and ICF in M1 (Kujirai *et al*, 1993). It is not yet clear whether this intensity would be optimal for activating inhibitory and excitatory circuits in DLPFC and this could be explored in future studies. Menstrual status can influence excitability and should be controlled for in future studies (Smith *et al*, 2002).

At last, somatosensory potentials may be induced TMS; however, previous analysis in a similar context indicated that muscle activation is unlikely to influence TMS-elicited potentials (Paus *et al*, 2001). Certainly, the significant decrease in P30, which directly correlated with SICI MEP amplitude changes, occurs too early to be influenced by sensory feedback (minimum ~45 ms). In addition, it is important to note that DLPFC stimulation does not evoke MEPs, and thus the finding that SICI and ICF produced consistent modulation of P60, regardless of the stimulated domain, indicates that these changes are unrelated to sensory feedback and instead related to SICI and ICF. The bidirectional changes in P60 TEP amplitude with SICI and ICF are further suggestive of bidirectional modulation of neural excitability, and are consistent with prior studies of their association with cortical excitability (Farzan *et al*, 2013; Ferreri *et al*, 2012; Kahkonen *et al*, 2005a; Rogasch *et al*, 2013).

In conclusion, these findings provide the first evidence that excitatory and inhibitory cortical circuits SICI and ICF share a similar neural signature across M1 and DLPFC, and suggest that neural excitability changes associated with GABA<sub>A</sub> receptor-mediated inhibition and glutamatergic transmission can be recorded in prefrontal areas. We anticipate that these results will facilitate several advances in our understanding of the pathophysiology and treatment of a variety of neurological and psychiatric disorders.

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