Evidence for inhibitory deficits in the prefrontal cortex in schizophrenia

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Abnormal gamma-aminobutyric acid inhibitory neurotransmission is a key pathophysiological mechanism underlying schizophrenia. Transcranial magnetic stimulation can be combined with electroencephalography to index long-interval cortical inhibition, a measure of GABAergic receptor-mediated inhibitory neurotransmission from the frontal and motor cortex. In previous studies we have reported that schizophrenia is associated with inhibitory deficits in the dorsolateral prefrontal cortex compared to healthy subjects and patients with bipolar disorder. The main objective of the current study was to replicate and extend these initial findings by evaluating long-interval cortical inhibition from the dorsolateral prefrontal cortex in patients with schizophrenia compared to patients with obsessive-compulsive disorder. A total of 111 participants were assessed: 38 patients with schizophrenia (average age: 35.71 years, 25 males, 13 females), 27 patients with obsessive-compulsive disorder (average age: 36.15 years, 11 males, 16 females) and 46 healthy subjects (average age: 33.63 years, 23 females, 23 males). Long-interval cortical inhibition was measured from the dorsolateral prefrontal cortex and motor cortex through combined transcranial magnetic stimulation and electroencephalography. In the dorsolateral prefrontal cortex, long-interval cortical inhibition was significantly reduced in patients with schizophrenia compared to healthy subjects ($P = 0.004$) and not significantly different between patients with obsessive-compulsive disorder and healthy subjects ($P = 0.5445$). Long-interval cortical inhibition deficits in the dorsolateral prefrontal cortex were also significantly greater in patients with schizophrenia compared to patients with obsessive-compulsive disorder ($P = 0.0465$). There were no significant differences in long-interval cortical inhibition across all three groups in the motor cortex. These results demonstrate that long-interval cortical inhibition deficits in the dorsolateral prefrontal cortex are specific to patients with schizophrenia and are not a generalized deficit that is shared by disorders of severe psychopathology.

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Abbreviations: EEG = electroencephalography; LICI = long-interval cortical inhibition; OCD = obsessive-compulsive disorder; PFC = prefrontal cortex; TMS = transcranial magnetic stimulation
Introduction

Schizophrenia and obsessive-compulsive disorder (OCD) are psychiatric disorders associated with significant psychopathology and personal suffering. Schizophrenia is characterized by hallucinations, delusions, cognitive deficits and negative symptoms (American Psychiatric Association, 2000). OCD is an anxiety disorder associated with the occurrence of unwanted and disturbing intrusive thoughts, images or impulses (obsessions), followed by repetitive ritualistic behaviours (compulsions) completed in stereotyped succession (American Psychiatric Association, 2000). There are substantial areas of overlap between schizophrenia and OCD (Lee et al., 2009). Both are lifelong chronic conditions sharing a similar distribution for age at onset and affect both males and females equally (Lee et al., 2009). Studies show that the rate of co-morbidity between schizophrenia and OCD is ~7–26% (Eisen et al., 1997; Fabisch et al., 1997; Porto et al., 1997; Poyurovsky et al., 1999; Tibbo et al., 2000). Abnormalities of the prefrontal cortex, anterior cingulate, caudate nucleus, the basal ganglia, the thalamus, and the cerebellum have been implicated in both schizophrenia and OCD (Tibbo and Warneke, 1999; Gross-Isseroff et al., 1997; Porto et al., 1997; Poyurovsky et al., 1999; Tibbo et al., 2000). Abnormalities of the prefrontal cortex, anterior cingulate, caudate nucleus, the basal ganglia, the thalamus, and the cerebellum have been implicated in both schizophrenia and OCD (Tibbo and Warneke, 1999; Gross-Isseroff et al., 2003; Venkatasubramanian et al., 2009). Both disorders have been shown to have poor global functional performance (Cavedini et al., 2002; Light and Braff, 2005a, b; van den Heuvel et al., 2005). Finally, both disorders also respond to dopaminergic antagonists and serotonin reuptake inhibitors, suggesting pathophysiological overlap (Poyurovsky and Koran, 2005).

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, critical in modulating cortical excitability and neuroplasticity (DeFelipe et al., 1986; Schieber and Hibbard, 1993). Cortical inhibition represents a neurophysiological index of GABAergic inhibitory neurotransmission in the human cortex (Krnjevic, 1997; Daskalakis et al., 2007). Several lines of evidence suggest that cortical inhibition is impaired in severe psychiatric disorders. For example, previous transcranial magnetic stimulation (TMS) studies have demonstrated deficits in cortical inhibition in patients with schizophrenia (Daskalakis et al., 2002, 2008a; Fitzgerald et al., 2002a, b, 2003; Wobrock et al., 2008, 2009, 2010; Liu et al., 2009), OCD (Greenberg et al., 1998, 2000; Richter et al., 2012), major depressive disorder (Fitzgerald et al., 2004; Bajbouj et al., 2006b; Lefaucheur et al., 2008; Levinson et al., 2010), and bipolar disorder (Levinson et al., 2007). These findings suggest that many severe psychiatric disorders are associated with deficits in GABAergic receptor-mediated inhibitory neurotransmission. However, these findings were demonstrated in the motor cortex, a cortical region of limited interest in the pathophysiology of psychiatric disorders.

This past decade has seen significant developments in the concurrent use of TMS with electroencephalography (EEG) to directly assess the neurophysiology of the motor and dorsolateral prefrontal cortex (PFC) (Daskalakis et al., 2008b; Fitzgerald et al., 2008; Taylor et al., 2008; Farzan et al., 2010b; Miniussi and Thut, 2010). TMS-EEG allows for the measurement of a paired-pulse paradigm known as long-interval cortical inhibition (LICI), whereby a supra-threshold conditioning stimulus is followed by a supra-threshold test stimulus at long interstimulus intervals (e.g., 50–200 ms), associated with the suppression of neuronal activity (Claus et al., 1992; Valls-Sole et al., 1992). A relationship between EMG and EEG measures of LICI has been found in the motor cortex (Daskalakis et al., 2008b; Farzan et al., 2010b). Additionally, LICI has demonstrated high test-retest reliability in the motor cortex and dorsolateral PFC (Farzan et al., 2010b). Evidence suggests that LICI is mediated by slow inhibitory postsynaptic potentials via activation of GABA<sub>B</sub> receptors. For example, LICI is potentiated by baclofen (GABA<sub>B</sub> receptor agonist) (McDonnell et al., 2006). Furthermore, LICI is optimal at 100–150 ms (Sanger et al., 2001) comparable to the time course of the GABA<sub>B</sub> inhibitory postsynaptic potential, peaking at 150–200 ms post-stimulus (McCormick, 1989). Lastly, LICI is evoked by a suprathreshold conditioning stimulus (Valls-Sole et al., 1992) as GABA<sub>B</sub> receptor-mediated responses have higher activation thresholds and their inhibitory influence is longer (Deisz, 1999a; Sanger et al., 2001).

GABA plays a pivotal role in the generation and inhibition of gamma oscillations in the cortex (Whittington et al., 1995, 2000; Traub et al., 1996; Wang and Buzsaki, 1996; Bartos et al., 2007; Brown et al., 2007; Leung and Shen, 2007). Research has shown that GABA<sub>B</sub> receptor-mediated inhibitory postsynaptic potentials contribute to the generation of gamma oscillations (Whittington et al., 1995; Wang and Buzsaki, 1996; Bartos et al., 2007) and GABA<sub>B</sub> receptor-mediated inhibitory postsynaptic potentials are associated with the inhibition of gamma oscillations (Whittington et al., 1995; Brown et al., 2007; Leung and Shen, 2007). Many studies involving neuropsychiatric disorders have focused on abnormalities in gamma oscillations because of its association with higher order cognitive processes including sensory processing, attention, working memory, and executive functioning, all domains in which patients with schizophrenia are impaired (Uhlhaas et al., 2008). For example, patients with schizophrenia have impairments in gamma oscillatory activity in response to 40 Hz auditory stimulation (Light et al., 2006), during perception of gestalt objects (Spencer et al., 2003) and during working memory performance (Cho et al., 2006; Barr et al., 2010). Disrupted gamma oscillatory activity has also been demonstrated in schizophrenia using TMS and EEG (Ferrarelli et al., 2008; Farzan et al., 2010a; Frantseva et al., 2014). One of the aims of this study was to replicate findings by Farzan et al. (2010a) in which TMS-EEG was used to assess LICI in the motor cortex and dorsolateral PFC in patients with schizophrenia compared with bipolar patients and healthy subjects. Bipolar patients were included as they are often treated with dopamine antagonists and can have...
comparable levels of psychopathology. It was demonstrated by Farzan et al. (2010a) that only patients with schizophrenia had significant deficits in the inhibition of gamma oscillations that were specific to the dorsolateral PFC. These results suggest that impairments in the inhibition of gamma oscillations in schizophrenia may be closely associated with the pathophysiology of the disorder.

Thus, this study had two main objectives. The first was to assess LICI in patients with schizophrenia and OCD in both the dorsolateral PFC and motor cortex using TMS-EEG. The second aim was to evaluate the diagnostic specificity of LICI in schizophrenia and OCD, because of the comparable levels of psychopathology severity and the similar pharmacology that are used to treat these two disorders. The core study hypotheses were that both patients with schizophrenia and OCD would show LICI deficits in the dorsolateral PFC relative to healthy subjects and deficits would be significantly greater in patients with schizophrenia.

Materials and methods

A total of 111 participants were included [38 patients with schizophrenia (average age: 35.71 years, 25 males, 13 females), 27 patients with OCD (average age: 36.15 years, 11 males, 16 females) and 46 healthy subjects (average age: 33.63 years, 23 females, 23 males)] at the Centre for Addiction and Mental Health in Toronto, Canada. The handedness of the participants were: schizophrenia patients (33 right-handed, three left-handed, two ambidextrous), OCD patients (25 right-handed, two left-handed), healthy subjects (39 right-handed, four left-handed, three ambidextrous). All subjects gave their written informed consent and the protocol was approved by the Centre for Addiction and Mental Health in accordance with the Declaration of Helsinki. The Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) confirmed the diagnosis of schizophrenia or OCD. In healthy subjects, psychopathology was ruled out by the Structured Clinical Interview for DSM-IV and subjects were only included in the study if they had no first-degree relative diagnosed with a psychiatric disorder. Exclusion criteria for both patients and healthy subjects included: (i) individuals meeting DSM-IV criteria for substance abuse or dependence in the last 6 months, with the exception of nicotine; (ii) concomitant major and unstable medical or neurological illness; (ii) experiencing suicidal ideation; (iv) pregnant; (v) positive urine toxicology screen for drugs of abuse; (vi) any magnetic material or any other conditions that would preclude the MRI scan or TMS-EEG measures; and (vii) clinically significant claustrophobia. The exclusion criteria established by international safety standards for TMS were followed (Rossi et al., 2009). The TMS Adult Safety Screen (Keel et al., 2001) was administered to all subjects.

Clinical severity

The 24-construct Brief Psychiatric Rating Scale (BPRS) was used for evaluating psychopathology in patients with schizophrenia (Overall and Gorham, 1962).

Inhibitory deficits in schizophrenia

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Data recording

Transcranial magnetic stimulation

Monophasic TMS pulses were administered using a 7-cm figure-of-8 coil, and two Magstim 200 stimulators (Magstim Company Ltd) connected via a Bistim module. TMS was administered over the left motor cortex and dorsolateral PFC. Inhibition was measured through LICI and indexed through electromyography and EEG at the optimal 100 ms interstimulus interval (Sanger et al., 2001). One hundred TMS stimuli were delivered per condition (paired and single-pulse) every 5 s. The intensity of TMS pulses was determined at the beginning of each experiment and it was set such that it elicited an average motor evoked potential of 1 mV peak-to-peak upon delivery of 20 pulses over the motor cortex. Both the conditioning stimulus and test stimulus were delivered at the same suprathreshold intensity. No significant between-group differences were found for the 1 mV peak-to-peak TMS intensity F[2,108] = 0.794, P = 0.455] (healthy controls = 69.46% ± 13.23%, schizophrenia = 73.03% ± 13.49%, OCD = 69.85% ± 14.53%).

Localization of the motor cortex

The TMS coil was placed at the optimal position for eliciting motor-evoked potentials from the right abductor pollicis brevis muscle, which corresponded to a region between the electrodes FC3 and C3.

Localization of dorsolateral PFC

Localization of dorsolateral PFC was achieved through neuro-navigation techniques using the MINIBIRD system (Ascension Technologies) and MRIcro/registration software using a T1-weighted MRI scan obtained for each subject with seven fiducial markers in place (Daskalakis et al., 2008b; Farzan et al., 2010b). Stimulation was directed at the junction of the middle and anterior one-third of the middle frontal gyrus [Talairach coordinates (x, y, z) = −50, 30, 36] corresponding with posterior regions of Brodmann area 9, which overlap with the superior section of Brodmann area 46.

Electromyography recording

Electromyography was captured by placing two disposable disc electrodes over the right abductor pollicis brevis muscle in a tendon-belly arrangement and motor evoked potentials were filtered (band-pass 2 Hz to 5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design).

EEG recording and preprocessing

To evaluate TMS-induced cortical evoked potentials, EEG was recorded concurrently with electromyography. EEG was acquired through a 64-channel Synamps 2 EEG system. A 64-channel EEG cap was used to record the cortical signals, and four electrodes were placed on the outer side of each eye, and above and below the left eye to closely monitor eye movement artefacts. All electrodes were referenced to an electrode positioned posterior to Oz electrode. EEG signals were recorded DC and with a low pass filter of 100 Hz at a 20 kHz sampling rate, shown to avoid saturation of the amplifiers and
minimize the TMS-related artefact (Daskalakis et al., 2008b, 2012).

EEG recordings were downsampled to 1000 Hz and epoched from −1000 ms to 2000 ms after the test TMS pulse. In both, the single and paired-pulse conditions, the segment from −100 ms to 10 ms was removed (where 0 correspond to the test TMS pulse). This step removes not only the test-pulse TMS in the single-pulse and paired-pulse conditions but also the conditioning TMS pulse in the paired-pulse condition. Traces were visually inspected for artefacts in order to eliminate trials and channels highly contaminated by noise (muscle activity, 60 Hz noise, movement-related activity as well as electrode artefacts). Two rounds of independent component analysis were subsequently applied. The first found was to minimize and remove the typical TMS-related decay artefact that appears in some subjects at specific locations. In each subject, the number of components that needed to be removed to eliminate this kind of artefact varied from 0 to 6. Following this, a bandpass FIR filter was applied from 1 to 55 Hz and a second round of independent component analysis was computed to remove eye-related artefacts (blinks and movements) and remaining muscle components. During this analysis, the subject identity and group was hidden to the researcher using randomly generated files. No actual association of each recording was made to a particular group (healthy, schizophrenia or OCD) when completing the processing steps.

The time frequency decomposition was obtained using the Event-Related Spectral Perturbation (ERSP) analysis in EEGLab. Specifically the analysis was wavelet-based, using a cycle of the complex Morlet wavelet across all frequencies. The ERSP was computed independently for the single-pulse and paired-pulse conditions. The analysis is expressed in decibels of spectral power (μV^2/Hz) after subtracting the log baseline to the whole trial. For comparison, a similar analysis was carried on, in a reduced sample of healthy subjects but using the Discrete Fourier Transform instead of the wavelet (Garcia Dominguez et al., 2014).

The resulting time-frequency decompositions, for single-pulse and paired-pulse conditions, were then subtracted (single-pulse minus paired-pulse), to obtain an index of inhibition. Thus, a value of inhibition was obtained for each subject (46 healthy subjects, 38 schizophrenia patients and 26 OCD patients, 111 in total), site of stimulation (dorsolateral PFC, motor), electrode (1...60), time (400 values, −442 to 1442 ms) and frequency (50 values, 1...50 Hz); that is 266 400 000 data points.

Based on Garcia Dominguez et al. (2014), LICI was assessed with all electrodes and all frequencies from 1–50 Hz. We proceed with a cluster-based analysis that is a development of the one proposed in Maris and Oostenveld (2007), which provides corrections for multiple comparisons due to the large amount of multidimensional data. In this paper, the clusters are defined in the time-frequency space and also include the two extra spatial dimensions of the electrode grid. Using this approach, we effectively reduced the number of total comparisons to only group comparisons by site of stimulation. As, in the original proposal of the cluster test, the relative volume of the cluster depends on the threshold used to define the cluster; we carried out, a fairly intuitive correction which consists of calculating the volumes for a set of many discrete thresholds exhausting all the volumes to produce a single statistic: the average volume t-score across all thresholds.

Before proceeding to the group comparisons, we assessed cortical inhibition following the same methodology within each group independently. To achieve this we applied a one-tailed, paired t-test to every voxel or three-tuple (i.e. time, frequency and channel) in the single-pulse versus the paired-pulse protocol. In this case, the null hypothesis was that the single-pulse condition is not larger than the paired-pulse, suggesting no inhibition. The method proceeds as follows:

Step 1: Select all samples whose t-scores are >1.6 and identify all the clusters to which these voxels belong. Clusters are connected sets on the basis of time, frequency and spatial adjacency;

Step 2: In each cluster sum all the t-scores and select the maximum of the obtained values. This value corresponds to the size (or volume) of the major cluster of inhibition and will be denoted by S;

Step 3: Repeat steps 2 and 3 with a new threshold that is 0.2 larger than the previous one, obtaining successively new values for the maximum cluster indexed by the threshold. Until a threshold is reached that does not contain any t-score;

Step 4: Repeat steps 2 to 4 with random reallocation of conditions across all subjects. The number of random reallocations was chosen to be 10 000 for this specific analysis; and

Step 5: Proceed to calculate the proportion of the permuted values that are larger than the original one. This proportion is the P-value.

In Step 3 multiple cluster sizes are calculated, each for a specific threshold. This is represented by a vector. In Step 5 the original vector has to be compared to all the others resulting from the randomization. This calculation proceeds as follows:

Let us denote the values of S as S_{k=1...N}^R, where k refers to the threshold index and the superscript i to the randomization (where 0 is the original un-randomized data). One solution is to compute the following ranks for each i and k:

$$R(a, b) = \sum_{i=1}^{N} H(S_{i}^{a} - S_{i}^{b})$$

H is the step function: H(x > 0) = 1 otherwise H = 0. Also, H counts the number of times a positive difference arises.

That is, for each particular threshold, sum all the randomizations that have a score S higher than randomization a, including the original case a = 0. After obtaining this matrix R, a sum can be performed across the thresholds to obtain a single rank per randomization:

$$R(a) = \sum_{k=1}^{M} R(a,k)$$

The actual P-value can be expressed as the proportion of R-values larger than the original R-values.

The results of these analyses are shown in Figs 1–3 for three different levels of alpha. The comparison between groups proceeds the same way except that (i) in Step 4 the randomization proceeds not by reallocating conditions but subjects between the two populations compared preserving the number of subjects in each; and (ii) the S-values are calculated as the difference between the S-values for each population at the same threshold. The hypothesis is that if sample A is larger than B, then S = S_A - S_B, otherwise the order of the factors does not matter and the P-values are computed from the population of absolute S values is Step 5.
**Figure 1** Dorsolateral PFC stimulation in healthy subjects. Statistical significance of each voxel (single pulse versus paired pulse) in the time-frequency domain corresponding to each specific electrode in healthy subjects when stimulating the dorsolateral PFC. NS = not significant.

**Figure 2** Dorsolateral PFC stimulation in patients with schizophrenia. Statistical significance of each voxel (single pulse versus paired pulse) in the time-frequency domain corresponding to each specific electrode in schizophrenia patients when stimulating the dorsolateral PFC. NS = not significant.
As t-scores are compared across different populations, differences in S-values (i.e. \( S^A - S^B \)) may be confounded by differences in the standard deviation between these two groups. We consider that this effect is not detrimental to the analysis, as it may indicate intrinsic population differences that should be taken into account. However, in order to observe inhibitory differences attributed to the average (and not standard deviation), a secondary analysis was performed in which the t-score results as a pooled standard deviation from the two groups compared. The P-values resulting from this analysis are displayed in Supplementary Table 1.

This method was also applied to subsets of the original 4D space in order to obtain additional information about the contribution of specific frequencies and electrodes to the overall group differences. This time only 2000 random permutations were used. For these purposes the time-frequency space was divided into the five common frequency bands (delta, theta, alpha, beta, and gamma). The local grid of electrodes for the dorsolateral PFC stimulation used the following frontal electrodes: FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6 and FT8, while for the motor stimulation the electrodes were: T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6 and TP8.

In addition to the cluster-based analysis described, a Spearman's rho correlation analysis was performed between the Brief Psychiatric Rating Scale (total score) and the size of the larger cluster of dorsolateral PFC inhibition for each schizophrenia subject. This correlation was also conducted with chlorpromazine equivalents (American Psychiatric Association, 1997; Woods, 2003; Chue et al., 2005; Bezchlibnyk-Butler et al., 2014). The size was determined over the same 4D space previously illustrated by counting significant values of the larger cluster using a single threshold of alpha level: 0.05. The size of the larger cluster of significant values is a way to capture the degree of inhibition at the subject level, since a larger inhibition correlates with the extent of significant voxels of inhibition in the time-frequency-spatial domain.

The methodological approach we follow in this study is a development of the one presented in Garcia Dominguez et al. (2014). We have now added two dimensions to the characterization of the cluster, the electrode grid. In this sense, we are better able to capture and describe all the related responses into a unifying variable. The analysis presented here also overcomes the dependence of the result on the threshold chosen to define the cluster by applying the same analysis over a multiple of different thresholds and expressing the results as a normalized average. This procedure may be considered as virtually threshold-free, as long as a sufficiently small step in the sequence of thresholds is considered.

**Results**

**Comparing single and paired-pulse conditions**

A within-group cluster-based test was conducted to compare single-pulse and paired-pulse TMS paradigms to assess...
LICI in the dorsolateral PFC and motor cortex for each 3-tuple: electrode, time and frequency. These tests were single-tailed as the null hypothesis (no inhibition) is when the paired-pulse amplitude is larger or equal to the amplitude of the single-pulse. Figures 1 to 3 show the time-frequency map of LICI in the dorsolateral PFC (the corresponding for motor cortex can be found in the Supplementary material). Significant values imply that the single-pulse induced response is higher than the paired-pulse condition. The areas of significant inhibition across the time-frequency plots are designated as three shades of blue corresponding to three different alpha levels: 0.05, 0.01 and 0.001. Figures 1 to 3 show that there was significant inhibition in most channels across many samples of the time-frequency domain in all three groups. Lower frequencies tend to show extended inhibition up to ~400 ms after the test-pulse stimulation, whereas higher frequencies show inhibition over narrower or specific temporal regions. Inhibition is particularly strong over the central, midline channels.

In the dorsolateral PFC, all groups demonstrated significant within-group inhibition, healthy subjects \((P < 0.0001)\), schizophrenia \((P = 0.0018)\), and OCD \((P = 0.0002)\). That is, the single-pulse condition was significantly greater than the paired-pulse condition. For the within-group analysis, the schizophrenia group (Fig. 2) showed a reduced, but not absent, degree of inhibition in relation to healthy subjects (Fig. 1). In fact, in all three groups, the pattern of inhibition in the time-frequency space was similar (Figs 1–3), as well as the topology (Figs 4 and 5).

In the motor cortex (Supplementary Figs 1–3), all groups demonstrated significant within-group inhibition, healthy subjects \((P < 0.0001)\), schizophrenia \((P = 0.0002)\) and OCD \((P = 0.01)\).

**Between-group results**

**Dorsolateral PFC stimulation**

The between-group results were single-tailed to match the core study hypotheses where healthy controls are expected to show more inhibition than schizophrenia and OCD. In addition, the comparison between the two patient groups were two-tailed, as we had no *a priori* hypothesis in this case. Overall inhibition (1–50 Hz), assessed through the cluster mass test, was significantly larger in healthy subjects than in patients with schizophrenia \((P = 0.004, i.e. only 40 random permutations, out of 10000, showed a value for the difference in inhibition larger than the one from the original samples)\). No significant differences were found between patients with OCD and healthy subjects. Significant differences were found between patients with schizophrenia and OCD in overall inhibition \((P = 0.0465)\). Using the same approach, we investigated the contribution of different frequency bands by partitioning the time-frequency space into five frequency bands corresponding to delta, theta, alpha, beta and gamma. LICI was significantly different between

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**Figure 4 Strength of inhibition by electrode.** Each value consists of the sum of all t-scores of inhibition in the major cluster of inhibition in the time-frequency maps for each electrode. These plots show the three groups by frequency bands in the dorsolateral PFC. Values have been normalized within each frequency band. The colour bar is omitted since only the pattern matters, as the actual sum is dependent on the resolution of the time-frequency-spatial domain. HLT = healthy subjects; SCZ = schizophrenia; OCD = obsessive-compulsive disorder.
healthy subjects and schizophrenia in theta ($P = 0.0175$), alpha ($P = 0.0025$), beta ($P = 0.0005$) and gamma frequency bands ($P = 0.0405$). Significant differences were found between schizophrenia and OCD in the theta ($P = 0.0295$), and alpha frequency bands ($P = 0.017$).

**Local grid of electrodes analysis for dorsolateral PFC stimulation**

Overall inhibition (1–50 Hz) was significantly larger in healthy subjects than in patients with schizophrenia ($P = 0.0015$) as well as in the delta ($P = 0.0205$), theta ($P = 0.0065$), alpha ($P = 0.001$), beta ($P < 0.0001$), and gamma frequency bands ($P = 0.008$). No significant differences were found between OCD and healthy subjects. Significant differences were found between schizophrenia and OCD in overall inhibition ($P = 0.0345$), theta ($P = 0.0275$), alpha ($P = 0.018$) and beta frequency bands ($P = 0.032$).

**Effect size for dorsolateral PFC stimulation**

Supplementary Fig. 4 shows the Cohen’s $d$ for each channel in the time-frequency space (dorsolateral PFC). Large effect sizes are displayed between patients with schizophrenia and healthy subjects, as demonstrated in the frontal and midline regions of the time-frequency plot.

**Motor cortex stimulation**

No significant differences were found between patients with schizophrenia and healthy control subjects in LICI across all frequency bands. No significant differences were found between patients with OCD and healthy subjects in LICI across all frequency bands. No significant differences were found between the two patient groups.

**Local grid of electrodes analysis for motor cortex stimulation**

No significant differences were found between patients with schizophrenia and healthy subjects in LICI across all frequency bands. No significant differences were found between OCD patients and healthy subjects in LICI across all frequency bands. No significant differences were found between patients with schizophrenia and OCD.

**Sum of t-score topology**

The sum of $t$-scores over the largest cluster is an index of the strength of inhibition at each channel by band and by region as presented in Figs 4 (dorsolateral PFC) and 5 (motor cortex). In this case, red indicates greater inhibition.
over the specific electrodes in terms of a wider and/or stronger magnitude of effect of inhibition over the time-frequency space.

**Effect of antipsychotic treatments**

A between-group cluster-based analysis was conducted for the subset of antipsychotic treated patients with OCD \( n = 8 \) compared to patients with schizophrenia \( n = 8 \) (age and sex-matched) on LICI (dorsolateral PFC). Patients with schizophrenia showed deficits in LICI \( (P = 0.0298) \) with 10 000 randomizations. Additionally, we evaluated the relationship between LICI (dorsolateral PFC) and antipsychotic medications (converted chlorpromazine equivalents) (American Psychiatric Association, 1997; Woods, 2003; Chue et al., 2005; Bezchlibnyk-Butler et al., 2014) in patients with schizophrenia treated with antipsychotic medications \( n = 38 \) (Table 1). This analysis revealed no significant correlation between LICI and chlorpromazine equivalents (Spearman’s \( \rho = -0.0096, P = 0.9542 \)). These results demonstrate that LICI deficits were not related to antipsychotic treatment.

**Clinical severity correlation analysis**

We found a trending correlation between the Brief Psychiatric Rating Scale and the largest cluster of inhibition in 38 patients with schizophrenia (Spearman’s \( \rho = -0.02464, P = 0.0680) \). The greater the Brief Psychiatric Rating Scale score is indicative of increased severity of schizophrenia symptoms. This negative correlation signifies that the higher Brief Psychiatric Rating Scale score is related to a lower degree of inhibition. We ran an outlier detection algorithm using criteria based on Cook’s distance and removed data points whose distance were larger than \( 4/n \) \( (n = \text{number of data points}) \) (Bollen and Jackman, 1990). Two outliers were identified; after their removal the correlation was statistically significant (Spearman’s \( \rho = -0.2855, P = 0.0457 \)).

**Discussion**

To summarize, in the dorsolateral PFC we found significant deficits in LICI in patients with schizophrenia compared to healthy subjects but there were no significant LICI deficits in patients with OCD. LICI deficits in the dorsolateral PFC were also significantly greater in patients with schizophrenia compared to patients with OCD. Finally, there were no significant LICI differences across all three groups in the motor cortex.

**Frontal LICI deficits in schizophrenia**

Two key lines of evidence support our findings of frontal LICI deficits in patients with schizophrenia. First, previous studies have demonstrated reduced GABA inhibitory interneurons in the dorsolateral PFC in schizophrenia (Benes et al., 1991; Akbarian et al., 1995). For example, in schizophrenia, Benes et al. (1991) reported morphological changes in cortical GABA interneurons, by demonstrating a decreased density of non-pyramidal cells in anterior cingulate layers II–VI and in prefrontal cortex layer II. Akbarian et al. (1995) found reduced mRNA in the dorsolateral PFC of patients with schizophrenia (a key enzyme involved in the synthesis of GABA). Impaired GABAergic inhibitory neurotransmission in schizophrenia may be responsible for several of its key phenotypic features. Dysfunctional GABAergic inhibitory neurotransmission may be related to an imbalance between cortical excitation and inhibition (Yizhar et al., 2011). Excessive excitability in the cortex may result in disorganized neuronal activation that may lead to the disorganized behaviour and impulsivity that is commonly found in schizophrenia (Uhlhaas et al., 2006; Uhlhaas and Singer, 2010). Abnormal GABAergic inhibitory neurotransmission may also lead to altered neural plasticity and aberrant neuronal wiring (Gaiarsa et al., 2002). The phenotypic manifestation of such dysfunction includes cognitive dysfunction, behavioural disorganization, delusions and hallucinations (Constantinidis et al., 2002; Kapur, 2003; Lewis et al., 2005).

Additional support for our findings of frontal LICI deficits in patients with schizophrenia relates to the fact that LICI also plays a key role in modulating plasticity and in working memory performance (Deisz, 1999b; Butefisch et al., 2000; Akerman and Cline, 2007; Hoppenbrouwers et al., 2013). For example, our group has previously shown a strong positive correlation between frontal LICI and working memory (Daskalakis et al., 2008c; Hoppenbrouwers et al., 2013). Working memory impairment is considered a core cognitive deficit in schizophrenia (Barrantes-Vidal et al., 2007; de Leeuw et al., 2013). The dorsolateral PFC is a functional brain region critical for higher-order cognitive tasks such as working memory performance (Barbey et al., 2012). In schizophrenia, dysfunctional activation of the dorsolateral PFC may underlie the working memory deficits present in this disorder (Weinberger et al., 1986). This has been demonstrated in both functional MRI (Jansma et al., 2004; Karlsgodt et al., 2007, 2009; Potkin et al., 2009) and neurophysiological studies (Cho et al., 2006; Barr et al., 2010). Lastly, we demonstrated a significant negative correlation between LICI and the clinical severity scores of schizophrenia. Thus, significant impairments in frontal inhibitory neurotransmission may represent an important mechanism underlying some of the key phenotypic features of schizophrenia.
are a larger replication of a previous TMS-EEG study (Farzan et al., 2010a), emphasizing a deficit in the inhibition of frontal gamma oscillations in schizophrenia. In this current study, the findings are extended by showing overall inhibitory deficits in the dorsolateral PFC of OCD patients with schizophrenia. Frontal gamma inhibitory deficits in schizophrenia may be due to the hypofunction of the N-methyl-D-aspartate-receptor (NMDAR). It has been shown that a blockade of the glutamate-mediated excitatory neurotransmission by NMDAR antagonists mimics positive and negative symptoms as well as cognitive deficits in schizophrenia (Krystal et al., 1994). This hypothesis proposes a specific deficit in NMDAR signalling, leading to a decrease in parvalbumin-positive GABAergic interneuron activity and consequent pyramidal cell disinhibition, diminishing GABA synthesis and release (Olney et al., 1999; Gonzalez-Burgos and Lewis, 2012; Moreau and Kullmann, 2013). As reviewed above, there have been several reports suggesting a relationship between GABAergic inhibitory neurotransmission and gamma oscillations in the cortex (Bragin et al., 1995; Whittington et al., 1993; Jefferys et al., 1996; Traub et al., 1996, 1997; Wang and Buzsaki, 1996; Scanziani, 2000; Marrosu et al., 2006; Bartos et al., 2007; Brown et al., 2007). Gamma oscillations appear to be dependent on inhibitory neurotransmission from parvalbumin-containing GABA interneurons. The lack of GABAergic neurotransmission in schizophrenia may translate into excessive gamma oscillations leading to a pathophysiological plasticity (long-term potentiation) and ultimately translate into aberrant learning and inflexible thinking that over time may lead to delusions—a manifestation of erroneous information that is learned and reinforced.

Neurophysiology of OCD

We found no significant LICI deficits in patients with OCD relative to healthy subjects in the dorsolateral PFC and motor cortex. Previous research has shown that OCD has been associated with motor cortex impairments in GABA_A receptor-mediated inhibition (Greenberg et al., 1998, 2000), GABA_B receptor-mediated inhibition (Richter et al., 2012) and NMDAR-mediated excitation (Richter et al., 2012). Our findings could be accounted for by the large medicated OCD sample, as the Richter et al. (2012) study which included a majority of unmedicated patients with OCD (68%). Selective serotonin reuptake inhibitors (SSRIs) are the established pharmacologic first-line treatment for OCD (Decloedt and Stein, 2010; Kellner, 2010). In the current study, 63% of the OCD patients (17/27) were medicated with SSRIs. Serotonin is able to modulate excitatory and inhibitory effects, mediated by glutamate and GABA, respectively (Ciranna, 2006). The serotonin receptor (5-HT) induces a decrease of glutamate transmission and a parallel increase in GABA transmission evident in the hippocampus, frontal cortex and the cerebellum (Ciranna, 2006). Previous studies have shown that SSRIs increase GABA by magnetic resonance spectroscopy (Bhagwagar et al., 2004) and TMS (Robol et al., 2004), thus concealing any potential LICI deficits in the present study. The modulatory action of the serotonin receptor (5-HT) may serve as a ‘brake’ on neuronal excitability. Given this inconsistency, replication is warranted to disentangle the effects of medication. Future directions of this work may be to evaluate LICI (TMS-EEG) before and after SSRI treatment for OCD to establish a relationship between inhibition and therapeutic response.

Advancements in analyses

In this paper, we have improved our methodology over previous LICI analyses. Our advanced analyses provide two main benefits: a concise characterization of LICI, including all relevant dimensions in the data (time, frequency, space) that may have been omitted in previous studies; and it addresses the issue of multiple comparisons. Specifically, the analysis allows for the assessment of LICI over the whole brain cortical network by means of an extended time and spatial domain (Garcia Dominguez et al., 2014). The analysis can also be applied to a subset of the original grid to assess the contribution of specific electrodes. Inhibition is characterized as a continuous response over a 4D space and is not linked to a particular fixed preconceived window in this space. Past results have attempted a variety of methodologies because there is not an immediate, easy to recognize, feature that indexes LICI. Previous analyses have revealed evidence for inhibition over a restricted domain, by sacrificing either the temporal, the spatial or the frequency component. Examples are: the fixed window analysis (Daskalakis et al., 2008b; Farzan et al., 2010a, b), the measure of peak amplitude (Rogasch et al., 2013) and the analysis over a 25 ms sliding window (Fitzgerald et al., 2009) at a single 1–40 Hz bandpass. A second major advantage of the analysis is that it tackles the problem of multiple comparisons. We applied a cluster-based permutation analysis, allowing for the use of a single statistic from the whole multidimensional space (Maris and Oostenveld, 2007; Premoli et al., 2014). This global analysis contains the adequate correction for all of the subanalyses between the corresponding groups. In the context of TMS-EEG, limited studies have examined the entire time-frequency and spatial domain since presenting a multidimensional analysis increases the likelihood of committing a type I error due to the problem of multiple comparisons (Maris and Oostenveld, 2007). Taken together, the presented methodology is parameter-free, while at the same time, avoids the multiple comparison issue without the need to discard vital information as done in previous TMS-EEG analyses.

Limitations

This study is limited in several ways. First, patients with schizophrenia were treated with a variety of antipsychotic
Table 1: Description of the psychotropic medications displayed as number of subjects/dose(s)

<table>
<thead>
<tr>
<th>Class</th>
<th>Medications</th>
<th>Number of subjects/doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
<td></td>
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<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>n = 11: 200 (2), 250 (2), 300 (5), 350 (1), 475 (1)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>n = 4: 7.5, 12.5, 15, 22.5</td>
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<tr>
<td>Paliperidone</td>
<td>n = 1: 150/4 weeks</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>n = 3: 300 (2), 400</td>
<td></td>
</tr>
<tr>
<td>Quetiapine fumarate</td>
<td>n = 2: 200, 800, 900</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>n = 7: 2 (2), 3 (2), 5, 6, 8</td>
<td></td>
</tr>
<tr>
<td>Risperidone injection</td>
<td>n = 2: 37.5/2 weeks, 75/4 weeks</td>
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<tr>
<td>Ziprasidone</td>
<td>n = 2: 60, 120</td>
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<tr>
<td>Thioxanthenes</td>
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<tr>
<td>Flupenthixol injection</td>
<td>n = 1: 60/3 weeks</td>
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<tr>
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<td>n = 1: 1</td>
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<tr>
<td>Zuclopenthixol injection</td>
<td>n = 2: 100/2 weeks, 280/2 weeks</td>
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<tr>
<td>Phenothiazines</td>
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<td>Fluphenazine decanoate</td>
<td>n = 1: 37.5/2 weeks</td>
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<tr>
<td>Perphenazine</td>
<td>n = 1: 8</td>
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<tr>
<td>Dibenzoazepines</td>
<td></td>
<td></td>
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<tr>
<td>Loxapine</td>
<td>n = 2: 25, 30</td>
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<tr>
<td>Diphenylbutylpiperidines</td>
<td></td>
<td></td>
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<tr>
<td>Pimozide</td>
<td>n = 1: 6</td>
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<tr>
<td>Third generation</td>
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<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
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<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>n = 3: 10, 40 (2)</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>n = 1: 20</td>
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<tr>
<td>Fluoxetine</td>
<td>n = 2: 10, 60</td>
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<tr>
<td>Paroxetine</td>
<td>n = 1: 20</td>
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<tr>
<td>Sertraline</td>
<td>n = 4: 75, 150, 200 (2)</td>
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<tr>
<td>Serotonin–norepinephrine reuptake inhibitors (SNRIs)</td>
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<tr>
<td>Desvenlafaxine</td>
<td>n = 1: 30</td>
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<td>Mood stabilizers</td>
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<tr>
<td>Carbamazepine</td>
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<td>Divalproex sodium</td>
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<td>Lamotrigine</td>
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<tr>
<td>Lithium</td>
<td>n = 4: 900 (2), 1050, 1200</td>
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<td>Topiramate</td>
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<td>Benzodiazepines</td>
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<td>Clonazepam</td>
<td>n = 3: 0.5 (2), 1</td>
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<tr>
<td>Clonazepam prn</td>
<td>n = 1: 0.25</td>
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<td>Lorazepam</td>
<td>n = 1: 2</td>
<td></td>
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<tr>
<td>Lorazepam prn</td>
<td>n = 4: 1 (2), 2 (2)</td>
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<tr>
<td>Others</td>
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<tr>
<td>Benztropine</td>
<td>n = 3: 1 (2), 4</td>
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<tr>
<td>OCD</td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
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<tr>
<td>Citalopram</td>
<td>n = 2: 20, 220</td>
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<tr>
<td>Escitalopram</td>
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<tr>
<td>Paroxetine</td>
<td>n = 3: 10, 25, 60</td>
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</tr>
<tr>
<td>Fluoxetine</td>
<td>n = 2: 80 (2)</td>
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<tr>
<td>Sertraline</td>
<td>n = 2: 100, 250</td>
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<tr>
<td>Serotonin–norepinephrine reuptake inhibitors (SNRIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>n = 1: 120</td>
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<tr>
<td>Venlafaxine</td>
<td>n = 2: 100, 187.5</td>
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<tr>
<td>Tricyclic antidepressants (TCAs)</td>
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<tr>
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<tr>
<td>Bupropion</td>
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<tr>
<td>Antipsychotics</td>
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<tr>
<td>Quetiapine</td>
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<tr>
<td>Mood stabilizers</td>
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</tr>
</tbody>
</table>
medications and other psychotropic medications and were chronically ill, which may have effects on neural oscillations and may explain the lack of motor inhibitory deficits found in this disorder. Future studies should recruit unmedicated patients with schizophrenia and OCD. Second, while pharmacological findings suggest that LICI is mediated by slow inhibitory postsynaptic potentials via activation of GABA_B receptors (McDonnell et al., 2006), the effect of other neurotransmitter systems cannot be completely ruled out (dopamine and serotonin). Third, when interpreting these results, inferences have been made for the role of LICI vis à vis cognition. We did not measure cognition in this study, therefore, there is currently no direct evidence to support these implications. To better link neurophysiological findings to the symptoms of schizophrenia and OCD, future studies should establish better relationships between LICI, cognition and behaviour. Lastly, the TMS evoked potential after 40 ms contains the afferent component in the motor cortex which may affect inhibition, however, any potential artefact is expected to be similar between groups and should not account for group differences.

**Conclusion**

This study shows that impairments in frontal GABA_B receptor-mediated inhibitory neurotransmission are associated with pathophysiology specific to schizophrenia. Conceivably TMS measures of GABAergic and NMDAR functioning could be used as biological markers of novel treatments that are aimed at enhancing inhibition or decreasing excitation in the cortex. Several lines of evidence have suggested that the potentiation in GABA_B receptor-mediated inhibition are associated with clinical improvements as demonstrated by clinical interventions such as meditation (Guglietti et al., 2013), cognitive behavioural therapy (Radhu et al., 2012), repetitive TMS (Daskalakis et al., 2006), electroconvulsive therapy (Bajbouj et al., 2006a) and clozapine treatment for schizophrenia (Daskalakis et al., 2008a; Liu et al., 2009; Wu et al., 2011). These results are promising and suggest the potential of using TMS-EEG in neurophysiological research and in clinical settings.

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### Table I Continued

<table>
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<td>Benzodiazepines</td>
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<td>Lithium</td>
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</table>

prn = pro re nata.
(CIHR), the Brain and Behaviour Research Foundation and the Temerty Family and Grant Family through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

Supplementary material

Supplementary material is available at Brain online.

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