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A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders

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HIGHLIGHTS

- Motor cortex inhibitory and excitatory transcranial magnetic stimulation paradigms were quantitatively assessed in severe psychiatric illnesses.
- Inhibitory deficits are a ubiquitous finding across obsessive–compulsive disorder, major depressive disorder and schizophrenia, by contrast, enhancement of intracortical facilitation is specific to obsessive–compulsive disorder.
- Limitations of transcranial magnetic stimulation studies are reviewed and potential future applications are discussed.

ABSTRACT

Objective: To evaluate transcranial magnetic stimulation (TMS) measures of inhibition and excitation in obsessive–compulsive disorder (OCD), major depressive disorder (MDD) and schizophrenia (SCZ).
Methods: Paradigms included: short-interval cortical inhibition (SICI), cortical silent period (CSP), resting motor threshold, intracortical facilitation, and motor evoked potential amplitude. A literature search was performed using PubMed, Ovid Medline, Embase Psychiatry and PsycINFO 1990 through April 2012.
Results: A significant Hedge's g was found for decreased SICI ($g = 0.572$, 95% confidence interval [0.179, 0.966], $p = 0.004$), enhanced intracortical facilitation ($g = 0.446$, 95% confidence interval [0.042, 0.849], $p = 0.030$) and decreased CSP ($g = -0.466$, 95% confidence interval [−0.881, −0.052], $p = 0.027$) within the OCD population. For MDD, significant effect sizes were demonstrated for decreased SICI (g = 0.641, 95% confidence interval [0.384, 0.898], $p = 0.000$) and shortened CSP ($g = -1.232$, 95% confidence interval [−1.530, −0.933], $p = 0.000$). In SCZ, a significant Hedge's g was shown for decreased SICI ($g = 0.476$, 95% confidence interval [0.331, 0.620], $p = 0.000$).
Conclusion: Inhibitory deficits are a ubiquitous finding across OCD, MDD, SCZ and enhancement of intracortical facilitation is specific to OCD.
Significance: Provides a clear platform from which diagnostic procedures can be developed.

1. Introduction

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, critical for the modulation of cortical excitability and neuroplasticity (DeFelipe et al., 1986; Schieber and Hibbard, 1993). GABAergic neurons constitute 25–30% of the neuronal population in the motor cortex and their horizontal connections can extend up to 6 mm or more (Gilbert and Wiesel, 1992; Jones, 1993). Pyramidal cell activity is synchronized through a balance of inhibitory postsynaptic potentials and excitatory postsynaptic potentials (Krnjevic, 1997). Inhibitory postsynaptic potentials are generated by GABAergic interneurons terminating on the pyramidal cell (Krnjevic, 1997). Cortical inhibition is a neurophysiological mechanism whereby GABA inhibitory interneurons attenuate the activity of other neurons (e.g. pyramidal neurons) in the cortex (Daskalakis et al., 2007).

Transcranial magnetic stimulation (TMS) is a non-invasive method used to assess inhibitory and excitatory mechanisms. TMS was first introduced in 1985 by Barker et al. for investigating the state of motor pathways in patients with neurological

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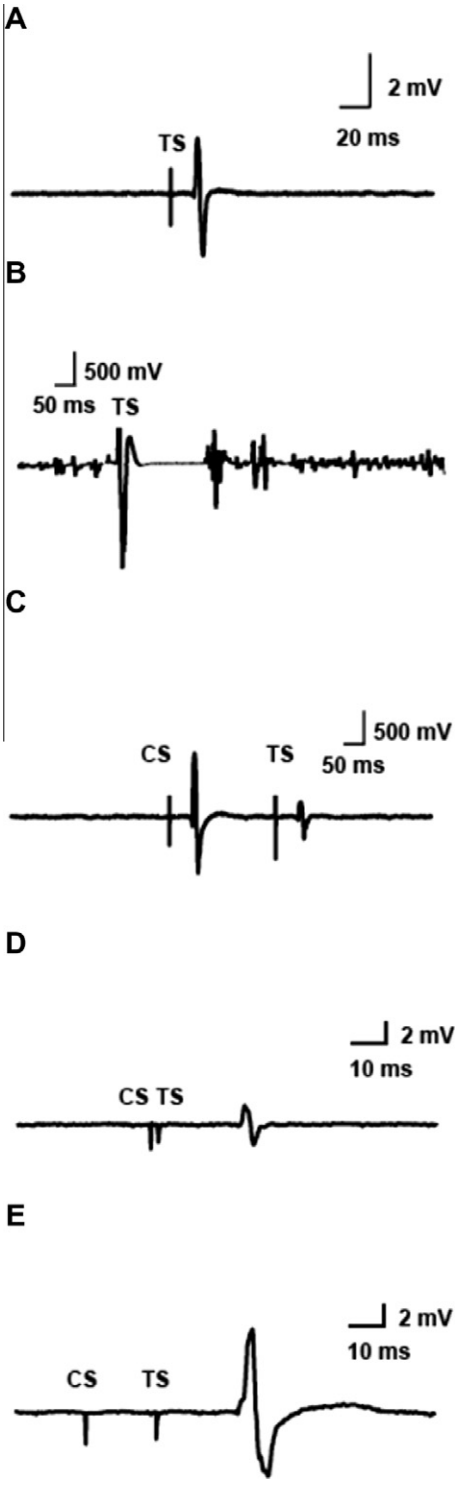

Fig. 1. Electromyography recordings produced by transcranial magnetic stimulation. (A) A single test stimulus applied to the motor cortex producing a motor evoked potential. (B) The cortical silent period (CSP): starts at the onset of the motor evoked potential and ends with the return of motor activity. This is achieved by a 40% suprathreshold pulse applied to the motor cortex while the contralateral hand muscle is tonically activated. (C) Long-interval cortical inhibition (LICI): A suprathreshold conditioning stimulus precedes a suprathreshold test stimulus by 100 ms, inhibiting the motor evoked potential produced by the test stimulus. (D) Short-interval cortical inhibition (SICI): a subthreshold conditioning stimulus precedes a suprathreshold test stimulus by 2 ms, inhibiting the motor evoked potential produced by the test stimulus. (E) Intracortical facilitation: A subthreshold conditioning stimulus precedes a suprathreshold test stimulus by 20 ms, facilitating the motor evoked potential produced by the test stimulus.

disorders and in healthy participants (Barker et al., 1985). They showed that a single TMS pulse applied to the motor cortex could activate cortical tissues associated with the hand or leg muscles and elicit motor evoked potentials (Fig. 1A).

1.1. Inhibitory TMS paradigms

TMS has been used to assess inhibitory processes, these paradigms are referred to as the cortical silent period (CSP) (Cantello et al., 1992), long-interval cortical inhibition (LICI) (Valls-Sole et al., 1992), and short-interval cortical inhibition (SICI) (Kujirai et al., 1993). The CSP duration is measured from the motor evoked potential onset to the return of electromyography activity (Fig. 1B) (Cantello et al., 1992). LICI involves the pairing of a suprathreshold conditioning stimulus followed by a suprathreshold test stimulus at long interstimulus intervals, resulting in inhibition of the motor evoked potential (Valls-Sole et al., 1992) (Fig. 1C). CSP and LICI appear to be assessing $GABA_B$ receptor-mediated inhibitory neurotransmission as evidenced by pharmacological studies (McDonnell et al., 2006; Siebner et al., 1998), the time course of the $GABA_B$ inhibitory postsynaptic potential (McCormick, 1989; Siebner et al., 1998; Werhahn et al., 1999) and the high intensity suprathreshold conditioning stimulus (Sanger et al., 2001). By contrast, SICI is measured by applying a subthreshold conditioning stimulus before the suprathreshold test stimulus at short interstimulus intervals, resulting in inhibition of the motor evoked potential response by 50–90% (Fig. 1D) (Kujirai et al., 1993). SICI has been associated with the $GABA_A$ receptor-mediated inhibitory neurotransmission as demonstrated by the pharmacological effects on this measure (Ziemann et al., 1996a), the time course of the $GABA_A$ inhibitory postsynaptic potential (Wang and Buzsaki, 1996) and the low intensity subthreshold conditioning stimulus (Sanger et al., 2001).

1.2. Excitatory TMS paradigms

TMS has also been used to examine cortical excitability, these paradigms include: the motor evoked potential amplitude, resting motor threshold, and intracortical facilitation. The motor evoked potential amplitude is measured as the average response to a series of pulses applied at a consistent TMS intensity (Zaaroor et al., 2003). The resting motor threshold is defined as the minimal intensity that produces a motor evoked potential >50 μV in 5 of 10 trials in a relaxed muscle (Rossini et al., 1994). Finally, intracortical facilitation is a paired-pulse paradigm whereby a conditioning stimulus is applied to the motor cortex before the test stimulus, resulting in an enhanced motor evoked potential (Kujirai et al., 1993; Nakamura et al., 1997) (Fig. 1E). Intracortical facilitation originates from excitatory postsynaptic potentials transmitted by N-methyl-D-aspartate glutamate receptors (Nakamura et al., 1997). For a review of the pharmacological effects on inhibitory and excitatory TMS paradigms, please see (Paulus et al., 2008).

1.3. Applications within psychiatric disorders

Numerous studies have implicated GABA in the pathophysiology of neuropsychiatric disorders, notably obsessive–compulsive disorder (OCD), major depressive disorder (MDD), schizophrenia (SCZ) and bipolar disorder. Several lines of evidence suggest that cortical inhibition is impaired in these disorders. For example, previous TMS studies have demonstrated deficits in cortical inhibition assessed from the motor cortex in patients with OCD (Greenberg et al., 1998, 2000; Richter et al., 2012), MDD (Bajbouj et al., 2006; Fitzgerald et al., 2004a; Lefaucheur et al., 2008; Levinson et al., 2010), SCZ (Daskalakis et al., 2002, 2008a; Fitzgerald et al., 2002a,b, 2003; Liu et al., 2009; Wobrock et al., 2008, 2009, 2010)

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and bipolar disorder (Levinson et al., 2007). An overall deficit of GABAergic inhibition has been associated with these psychiatric disorders; however, each may have a distinct illness profile and response to treatment. This meta-analysis aims to quantitatively assess TMS evoked measures of inhibitory and excitatory paradigms in OCD, MDD and SCZ.

2. Methods

2.1. Data sources

A literature search was performed using PubMed, Ovid Medline, Embase Psychiatry and PsycINFO 1990 through April 2012.

A description of the exact search terms used:

motor cortex tms and psychiatry, motor cortex tms and mental disorder, motor cortex tms and psychiatric disorder, motor cortex tms and anxiety disorder, motor cortex tms and bipolar disorder, motor cortex tms and mania, motor cortex tms and depression, motor cortex tms and obsessive–compulsive disorder, motor cortex tms and post-traumatic stress disorder, motor cortex tms and schizophrenia, motor cortex tms and major depressive disorder, short-interval cortical inhibition and schizophrenia, short-interval cortical inhibition and depression, short-interval cortical inhibition and ocd, intracortical faciliation and schizophrenia, intracortical facilitation and depression, intracortical facilitation and ocd, cortical silent period and schizophrenia, cortical silent period and depression, cortical silent period and ocd, resting motor threshold and schizophrenia, resting motor threshold and depression, resting motor threshold and ocd, motor evoked potential amplitude and schizophrenia, motor evoked potential amplitude and depression, motor evoked potential amplitude and ocd.

2.2. Study selection

Studies were included if the following criteria were fulfilled:

1. Cortical inhibition or cortical excitability motor cortex measurements were assessed using TMS.
2. Psychiatric disorders were diagnosed in accordance with DSM criteria.
3. The study had no specific "narrow" diagnosis or subgroup, such as depression after stroke or vascular depression.
4. The study included a healthy unaffected comparison group.
5. The data were sufficient to compute Hedge's g (sample size, means, and standard deviations).
6. At least 2 studies per psychiatric disorder/symptom cluster.
7. More than 3 participants per study.
8. Articles written in English.
9. In the case of articles with overlapping samples, the article with the largest sample size was included.

2.3. Data extraction

The following data were acquired: number patients, number of healthy controls, mean and standard deviation of the outcome measure at baseline. When publications contained insufficient or incomplete data, the authors in question were contacted and invited to send additional data so that their study could be included in the meta-analysis.

2.4. Meta-analysis

2.4.1. Hedge's g calculation

We employed standardized meta-analytic techniques used in the literature. A Hedge's g, 95% confidence interval and p-value were calculated (patients versus healthy controls) for each psychiatric disorder for measures of cortical inhibition (SICI, CSP) or excitability (resting motor threshold, intracortical facilitation) and the motor evoked potential amplitude for MDD and SCZ. This was analyzed using Comprehensive Meta Analysis Version 2.0 (Biostat, Englewood, New Jersey) in a fixed effects model. The means and standard deviations of separate studies were weighted according to sample size.

2.4.2. Test of heterogeneity

We evaluated heterogeneity among studies by calculating a Cochran Q, p-value and I^2. Heterogeneity in a meta-analysis refers to the variation in study outcomes between studies (Higgins and Thompson, 2002). The Q statistic is a value that demonstrates how the independent studies varied in terms of their findings. The I^2 statistic is a percentage of variation across studies that is due to heterogeneity rather than chance (Higgins and Thompson, 2002; Higgins et al., 2003). The I^2 ranges from 0% to 100%, a value of 0% means no heterogeneity and 100% means a high level of heterogeneity. A meta-regression was implemented to control for variables such as age and medication status; this allowed for the comparison of multiple sources of heterogeneity. Three or more studies were needed for each variable to complete a meta-regression.

2.4.3. N fail-safe

To examine publication bias, a N fail-safe value was calculated. This value is defined as the number of non-significant unpublished studies needed to make the obtained effect size calculations non-significant. Three or more studies were needed to complete this analysis. We adopted a significance level of $p = 0.05$, 2-tailed for all of the analyses.

3. Results

Table 1 provides the total number of studies that fulfilled the 9 stated criteria for inclusion (described in the methods) and the total number of studies excluded based upon specified reasons. The search was completed by N.R. and the studies were checked for reliability by D.R.J. Studies met the checklist for assessing the methodological quality of studies using TMS (Chipchase et al., 2012).

3.1. Patients with OCD

3.1.1. OCD – resting motor threshold

Fig. 2A illustrates the summary of the Hedge's g analysis as a forest plot based on 2 studies (Greenberg et al., 2000; Richter et al., 2012) that met inclusion criteria. The analysis comprised a total of 50 patients with OCD compared to 45 healthy controls. No significant differences were found in resting motor threshold in OCD. The Hedge's g was $g = -0.251$, 95% confidence interval [−0.658, 0.156], $p = 0.227$. The test of heterogeneity was found to be significant ($Q = 7.822$, $df(q) = 1$, $p = 0.005$, $I^2 = 87.216$). Meta-regression and publication bias analyses were not possible due to the fact that only 2 published studies were available.

3.1.2. OCD–SICI

Fig. 2B displays the summary of the Hedge's g analysis as a forest plot based on 3 studies (Greenberg et al., 1998, 2000; Richter et al., 2012) that met inclusion criteria. This analysis consisted of 62 OCD patients compared to 57 healthy controls. SICI was significantly reduced in OCD. The Hedge's g was found to be $g = 0.572$, 95% confidence interval [0.179, 0.966], $p = 0.004$. The test of heterogeneity was found to be significant ($Q = 36.366$, $df(q) = 2$, $p = 0.000$, $I^2 = 94.5$). The n-failsafe value was found to be 3 unpub-

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Table 1
Number of included and excluded studies.

Psychiatric disorder	Number of studies included in meta-analysis	Reasons for exclusion and number of studies excluded
Obsessive–compulsive disorder	Resting motor threshold (2) Short interval cortical inhibition (3) Intracortical facilitation (2) Cortical silent period (2) Motor evoked potential amplitude (0)	Insufficient data (1) No healthy comparison group (1)
Major depressive disorder	Resting motor threshold (8) Short interval cortical inhibition (3) Intracortical facilitation (3) Cortical silent period (4) Motor evoked potential amplitude (3)	Insufficient data (2) No healthy comparison group (9) Epileptic patients with major depression (1)
Schizophrenia	Resting motor threshold (21) Short interval cortical inhibition (12) Intracortical facilitation (11) Cortical Silent Period (11) Motor evoked potential amplitude (4)	Insufficient data (4) No healthy comparison group (2) Not in english (1)
Bipolar disorder	0	Insufficient data (1) Less than 2 studies for this disorder (1)
Post-traumatic stress disorder	0	Less than 2 studies for this disorder (1)
Social anxiety disorder	0	Less than 2 studies for this disorder (1)

lished studies. A meta-regression was not possible due to 2 studies publishing the values for age.

3.1.3. OCD – intracortical facilitation

Fig. 2C illustrates the summary of the Hedge's g analysis as a forest plot based on 2 studies (Greenberg et al., 2000; Richter et al., 2012) that fit the inclusion criteria. The analysis included 50 patients with OCD compared to 45 healthy controls. Intracortical facilitation was significantly enhanced in OCD. The Hedge's g was found to be $g = 0.446$, 95% confidence interval [0.042, 0.849], $p = 0.030$. The test of heterogeneity was not significant ($Q = 1.162$, $df(q) = 1$, $p = 0.281$, $I^2 = 13.912$). A meta-regression and publication bias analyses were not possible due to only 2 published studies available.

3.1.4. OCD–CSP

Fig. 2D illustrates the summary of the Hedge's g analysis as a forest plot based on 2 studies (Greenberg et al., 2000; Richter et al., 2012) that fit the inclusion criteria. This analysis contained 50 patients with OCD compared to 45 healthy controls. CSP was significantly reduced in OCD. The Hedge's g was found to be $g = -0.466$, 95% confidence interval [−0.881, −0.052], $p = 0.027$. The test of heterogeneity was significant ($Q = 10.435$, $df(q) = 1$, $p = 0.001$, $I^2 = 90.417$). A meta-regression and publication bias analyses were not possible due to only 2 published studies available.

3.2. Patients with MDD

3.2.1. MDD – resting motor threshold

Fig. 3A illustrates the summary of the Hedge's g analysis as a forest plot based on 8 studies (Abarbanel et al., 1996; Bajbouj et al., 2006; Chroni et al., 2002; Grunhaus et al., 2003; Lefaucheur et al., 2008; Levinson et al., 2010; Maeda et al., 2000; Reid et al., 2002) that fit the inclusion criteria. This analysis comprised of 176 patients with MDD compared to 188 healthy controls. No significant differences were found in resting motor threshold in MDD. The Hedge's g was $g = -0.043$, 95% confidence interval [−0.248, 0.161], $p = 0.677$. The test of heterogeneity was not significant ($Q = 16.034$, $df(q) = 9$, $p = 0.066$, $I^2 = 43.87$). The n-failsafe value was found to be 10 unpublished studies. Controlling for age, the meta regression yielded a correlation of $r = 0.04891$ and $p = 0.01399$. Controlling for medications, the meta regression yielded a correlation of $r = 0.40970$, $p = 0.08217$.

3.2.2. MDD–SICI

Fig. 3B illustrates the summary of the Hedge's g analysis as a forest plot based on 3 studies (Bajbouj et al., 2006; Lefaucheur et al., 2008; Levinson et al., 2010) that fit the inclusion criteria. The analysis included 115 patients with MDD compared to 130 healthy controls. SICI was significantly reduced in MDD. The Hedge's g was found to be $g = 0.641$, 95% confidence interval [0.384, 0.898], $p = 0.000$. The test of heterogeneity was significant ($Q = 10.362$, $df(q) = 4$, $p = 0.035$, $I^2 = 61.398$) and the n-failsafe value was found to be 5 unpublished studies. Controlling for age, the meta regression yielded a correlation of $r = 0.03221$ and $p = 0.23094$. Controlling for medications, the meta regression was found to be $r = 0.21356$, $p = 0.44282$.

3.2.3. MDD – intracortical facilitation

Fig. 3C illustrates the summary of the Hedge's g analysis as a forest plot based on 3 studies that fit the inclusion criteria (Bajbouj et al., 2006; Lefaucheur et al., 2008; Levinson et al., 2010). The analysis consisted of 115 patients with MDD compared to 130 healthy controls. No significant differences were found in intracortical facilitation in MDD. The Hedge's g was $g = -0.062$, 95% confidence interval [−0.311, 0.188], $p = 0.628$. The test of heterogeneity was not significant ($Q = 7.465$, $df(q) = 4$, $p = 0.113$, $I^2 = 46.413$). The n-failsafe value was 5 unpublished studies. Controlling for age, the meta regression yielded a correlation of $r = -0.06835$ and $p = 0.00855$. Controlling for medications, the meta regression was found to be $r = -0.16181$, $p = 0.54986$.

3.2.4. MDD–CSP

Fig. 3D illustrates the summary of the Hedge's g analysis as a forest plot based on 4 studies that fit the inclusion criteria (Bajbouj et al., 2006; Lefaucheur et al., 2008; Levinson et al., 2010; Steele et al., 2000). The analysis comprised of 131 patients with MDD compared to 149 healthy controls. CSP was significantly reduced in MDD. The Hedge's g was found to be $g = -1.232$, 95% confidence interval [−1.530, −0.933], $p = 0.000$. The test of heterogeneity was significant ($Q = 158.857$, $df(q) = 5$, $p = 0.000$, $I^2 = 96.853$). The n-failsafe value was 6 unpublished studies. Controlling for age, the meta regression correlation was $r = 0.01035$ and $p = 0.68408$. Controlling

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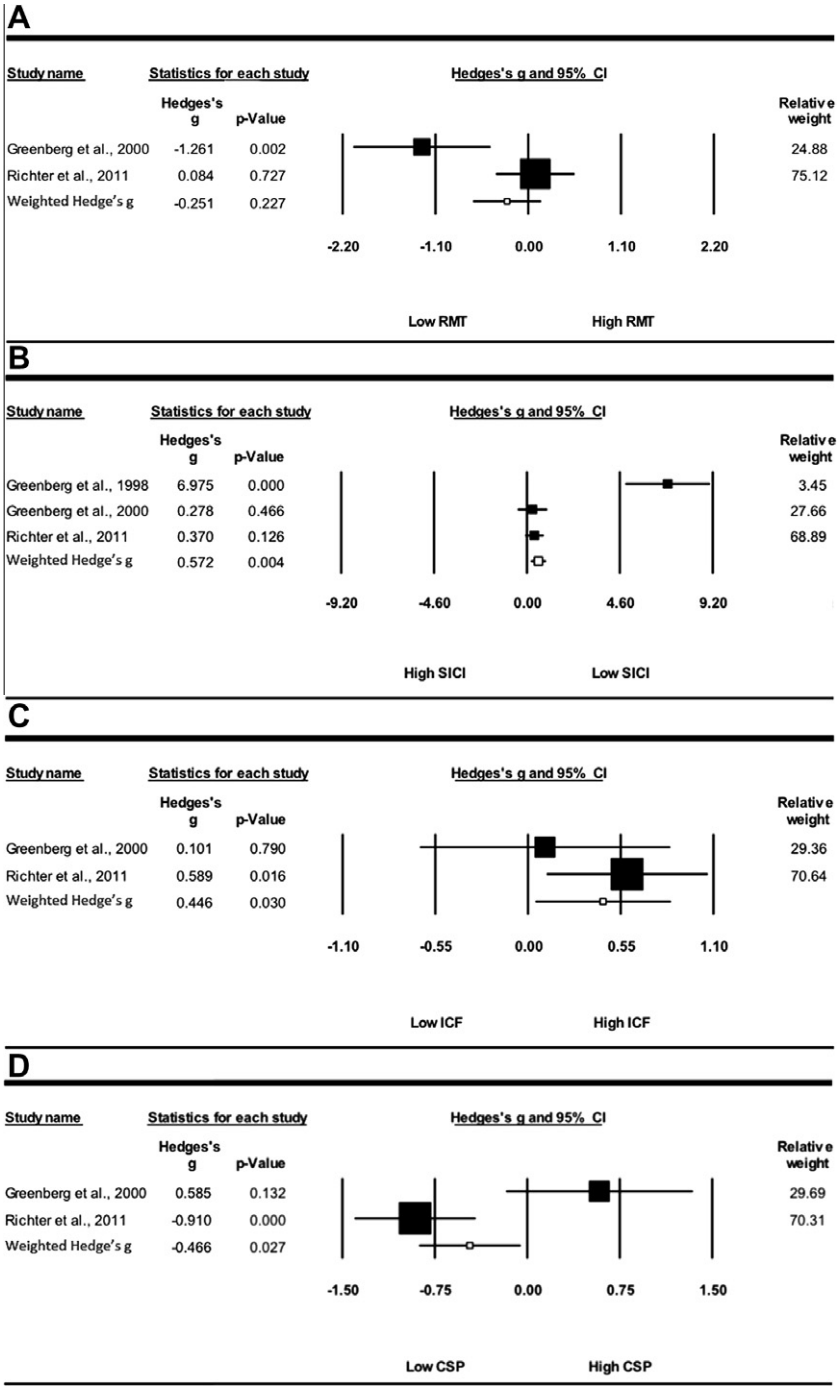

Fig. 2. Forest plot of the Hedge's g analysis for all studies that included patients with obsessive–compulsive disorder compared to healthy controls. (A) Resting motor threshold; (B) short-interval cortical inhibition; (C) intracortical facilitation; (D) cortical silent period.

for medications, the meta regression was found to be $r = 0.69466$, $p = 0.04121$.

3.2.5. MDD – motor evoked potential amplitude

Three studies (Chroni et al., 2002; Reid et al., 2002; Shajahan et al., 1999) that fit the inclusion criteria yielded a Hedge's g of $g = 0.162$, 95% confidence interval [−0.300, 0.623], $p = 0.492$. No significant differences were found in the motor evoked potential amplitude in MDD. The test of heterogeneity was significant ($Q = 6.586$, $df(q) = 2$, $p = 0.037$, $I^2 = 69.633$). This analysis included 34 patients with MDD compared to 37 healthy controls. The *n*-fail-safe value was 3 unpublished studies. Controlling for age, the meta regression yielded a correlation of $r = 0.09093$ and $p = 0.21375$. All studies included medicated patients and a meta-regression for medication was not possible.

3.3. Patients with SCZ

3.3.1. SCZ – resting motor threshold

Fig. 4 displays the Hedge's g as a forest plot based on 21 studies (Abarbanel et al., 1996; Bajbouj et al., 2004; Boroojerdi et al., 1999; Chroni et al., 2002; Daskalakis et al., 2002, 2008a; Eichhammer et al., 2004; Fitzgerald et al., 2002a,b,c, 2003, 2004b; Herbsman et al., 2009; Hoy et al., 2007; Liu et al., 2009; Oxley et al., 2004; Pascual-Leone et al., 2002; Reid et al., 2002; Soubasi et al., 2010; Wobrock et al., 2008, 2009) that met inclusion criteria. No

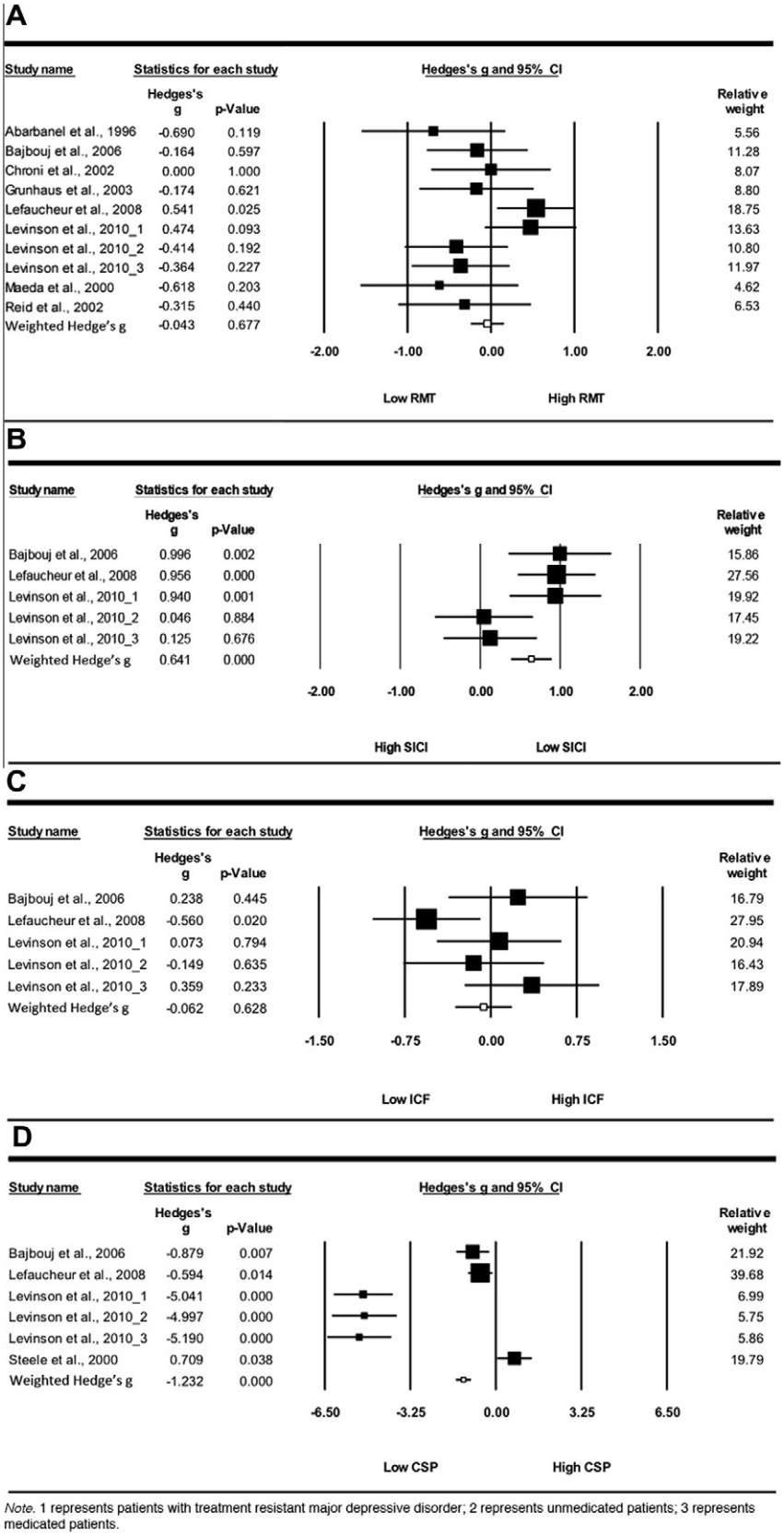

Fig. 3. Forest plot of the Hedge's g analysis for all studies that included patients with major depressive disorder compared to healthy controls. (A) Resting motor threshold; (B) short-interval cortical inhibition; (C) intracortical facilitation; (D) cortical silent period.

significant differences were found in resting motor threshold in SCZ. The Hedges g was $g = 0.067$, 95% confidence interval $[-0.053, 0.186]$, $p = 0.274$. The test of heterogeneity was significant ($Q = 83.977$, $df(q) = 30$, $p = 0.000$, $I^2 = 64.276$). This analysis included 500 SCZ patients and 617 healthy controls. The *n*-failsafe value was 31 unpublished studies. After controlling for age, the

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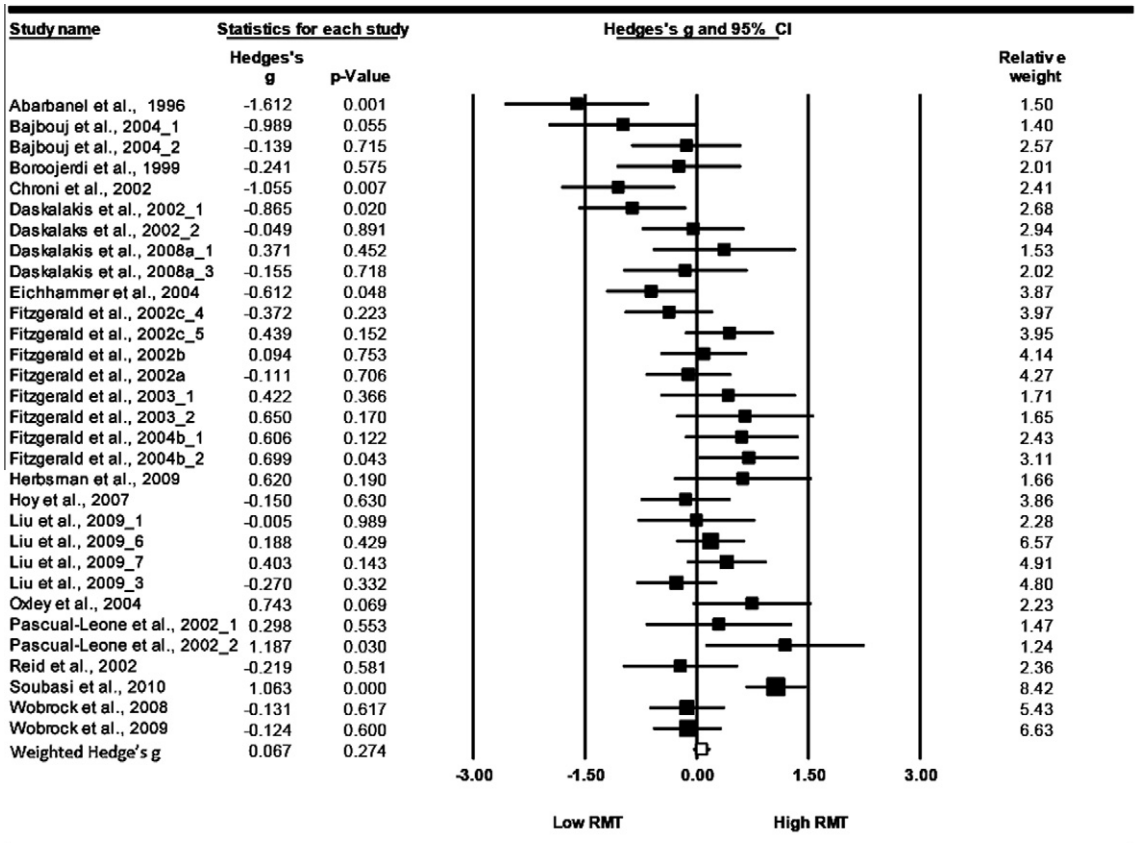

Fig. 4. Forest plot of resting motor threshold Hedge's g analysis for all studies that included patients with schizophrenia compared to healthy controls.

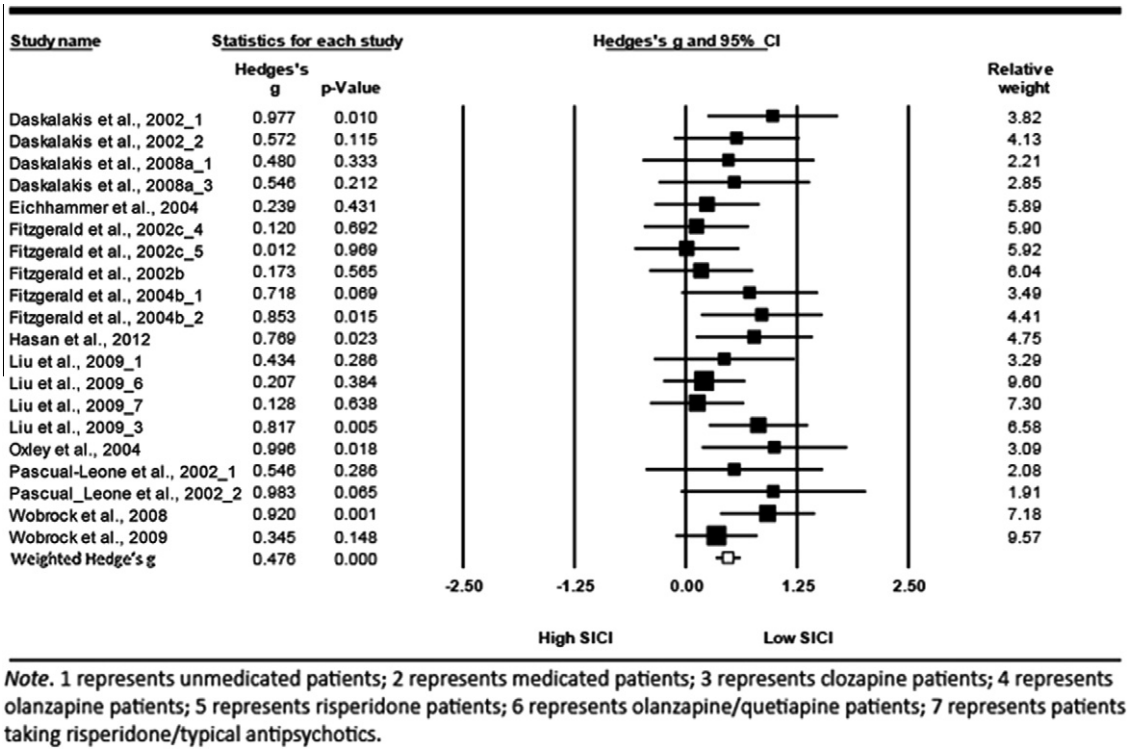

Fig. 5. Forest plot of short-interval cortical inhibition Hedge's g analysis for all studies that included patients with schizophrenia compared to healthy controls.

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meta regression yielded a correlation of $r = 0.02696$, $p = 0.05239$. After controlling for medications, the meta regression demonstrated a correlation of $r = 0.20309$ and $p = 0.19117$.

3.3.2. SCZ–SICI

Fig. 5 displays the Hedge's g as a forest plot based on 12 studies (Daskalakis et al., 2002, 2008a; Eichhammer et al., 2004; Fitzgerald et al., 2002b,c, 2004b; Hasan et al., 2012; Liu et al., 2009; Oxley et al., 2004; Pascual-Leone et al., 2002; Wobrock et al., 2008, 2009) that met inclusion criteria. SICI was significantly reduced in SCZ. The Hedge's g was found to be $g = 0.476$, 95% confidence interval [0.331, 0.620], $p = 0.000$. The test of heterogeneity was not significant ($Q = 19.170$, $df(q) = 19$, $p = 0.446$, $I^2 = 0.887$). The analysis included 335 SCZ compared to 440 healthy controls. The *n*-failsafe was 20 unpublished studies. After controlling for age, the meta regression was found to be $r = 0.01029$, $p = 0.56518$. After controlling for medications, the meta regression demonstrated a correlation of $r = -0.08425$, $p = 0.6429$.

3.3.3. SCZ – intracortical facilitation

Fig. 6 displays the Hedge's g as a forest plot based on 11 studies (Daskalakis et al., 2002, 2008a; Eichhammer et al., 2004; Fitzgerald et al., 2002b,c, 2004b; Hasan et al., 2012; Liu et al., 2009; Pascual-Leone et al., 2002; Wobrock et al., 2008, 2009) that met inclusion criteria. No significant differences were found in intracortical facilitation in SCZ. The Hedge's g was $g = 0.015$, 95% confidence interval [−0.130, 0.160], $p = 0.841$. The test of heterogeneity was not significant ($Q = 17.236$, $df(q) = 18$, $p = 0.507$, $I^2 = 0$). The analysis incorporated 323 patients with SCZ compared to 428 healthy controls. The *n*-failsafe value was 19 unpublished studies. After controlling for age, the meta regression correlation was $r = 0.00200$, $p = 0.91120$. After controlling for medications, the meta regression was found to be $r = -0.11468$, $p = 0.52264$.

3.3.4. SCZ–CSP

Eleven studies yielded a Hedge's g of $g = -0.093$, 95% confidence interval [−0.241, 0.055], $p = 0.218$ (Bajbouj et al., 2004; Daskalakis et al., 2002, 2008a; Fitzgerald et al., 2002b,c, 2004b; Hasan et al., 2012; Herbsman et al., 2009; Liu et al., 2009; Soubasi et al., 2010; Wobrock et al., 2009) (Fig. 7). No significant differences were found in CSP in SCZ. The test of heterogeneity was significant ($Q = 161.499$, $df(q) = 18$, $p = 0.000$, $I^2 = 88.854$). The analysis consisted of 334 SCZ patients compared to 457 healthy controls. The *n*-failsafe was 19 unpublished studies. After controlling for age, the meta regression yielded a correlation of $r = 0.01088$, $p = 0.58550$. After controlling for medications, the meta regression was found to be $r = 0.53667$, $p = 0.00855$.

3.3.5. SCZ – motor evoked potential amplitude

Four studies yielded a Hedge's g of $g = -0.102$, 95% confidence interval [−0.391, 0.187], $p = 0.489$ (Chroni et al., 2002; Enticott et al., 2008; Reid et al., 2002; Soubasi et al., 2010). No significant differences were found in the motor evoked potential amplitude in SCZ. The test of heterogeneity was significant ($Q = 12.134$, $df(q) = 3$, $p = 0.007$, $I^2 = 75.276$). The analysis included 91 SCZ patients compared to 93 healthy controls. The *n*-failsafe was 4 unpublished studies. After controlling for age, the meta regression yielded a correlation of $r = -0.07118$, $p = 0.04532$. It was not possible to conduct an analysis to control for medication status (meta-regression) as all patients were medicated.

4. Discussion

To our knowledge, this is the first study to provide a quantitative summary of TMS studies evaluating inhibition and excitatory paradigms in severe psychiatric disorders. The literature included ample high-quality studies with effect sizes in the low to moderate and moderate to high range. We found decreased SICI, enhanced intracortical facilitation and reduced CSP within the OCD population. For MDD, decreases in CSP and SICI were demonstrated. Lastly, reductions in SICI were shown in SCZ (summarized in Table 2). These findings suggest that impairments in GABAergic inhibition are a ubiquitous finding in severe psychiatric illnesses.

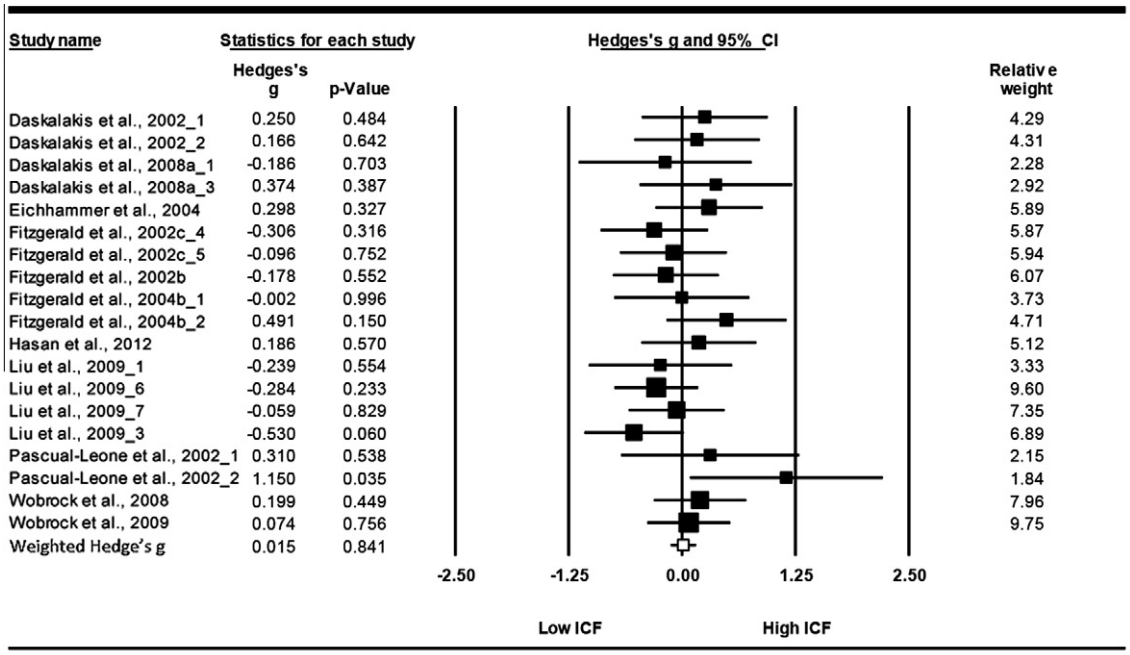

Fig. 6. Forest plot of intracortical facilitation Hedge's g analysis for all studies that included patients with schizophrenia compared to healthy controls.

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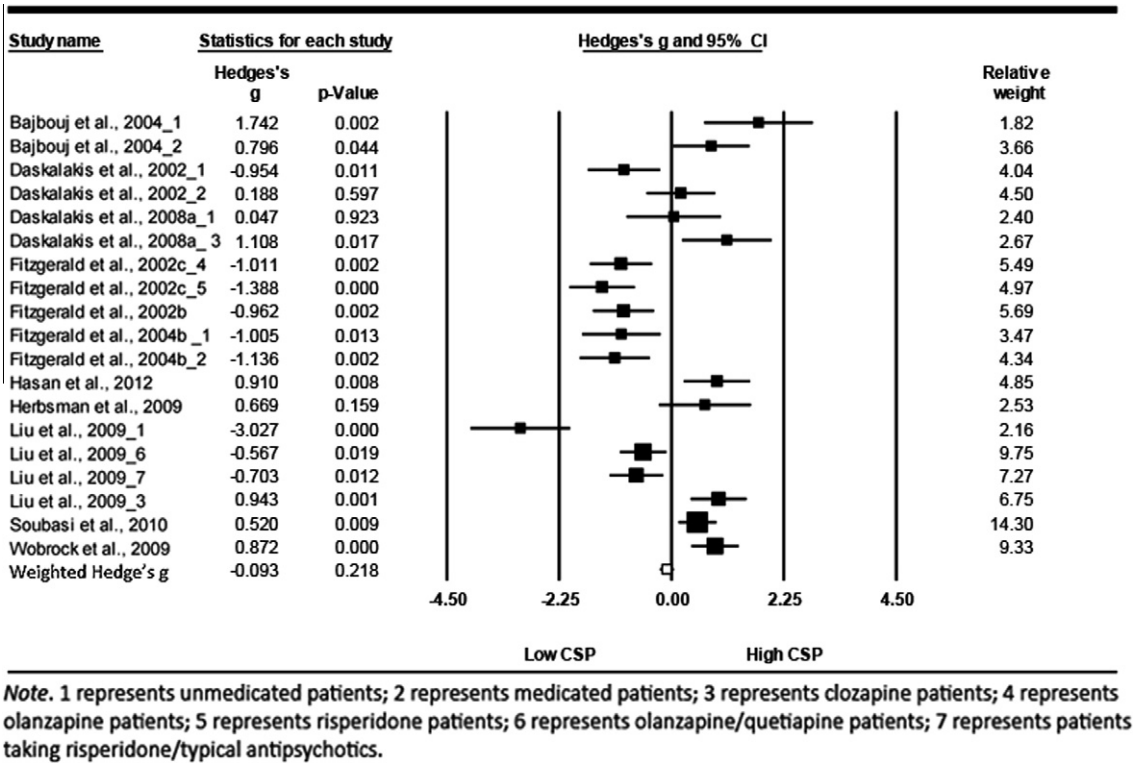

Fig. 7. Forest plot of cortical silent period Hedge's g analysis for all studies that included patients with schizophrenia compared to healthy controls.

Table 2
Summary of significant Hedge's g results in psychiatric populations.

Psychiatric disorder	Summary of significant Hedge's g results of TMS paradigms
Obsessive–compulsive disorder	Deficits in short-interval cortical inhibition (3 studies) (g = 0.572, 95% confidence interval [0.179, 0.966], p = 0.004) Enhanced intracortical facilitation (2 studies) (g = 0.446, 95% confidence interval [0.042, 0.849], p = 0.030) Decreased cortical silent period (2 studies) (g = −0.466, 95% confidence interval [−0.881, −0.052], p = 0.027)
Major depressive disorder	Deficits in short-interval cortical inhibition (3 studies) (g = 0.641, 95% confidence interval [0.384, 0.898], p = 0.000) Shortened cortical silent period (4 studies) (g = −1.232, 95% confidence interval [−1.530, −0.933], p = 0.000)
Schizophrenia	Impairments in short-interval cortical inhibition (12 studies) (g = 0.476, 95% confidence interval [0.331, 0.620], p = 0.000)

The greatest significant effect size was found in patients with OCD for decreased SICI. Furthermore, enhanced intracortical facilitation and shortened CSP were also significant. This finding held strong in spite of the small number of studies. This is in line with the literature which has shown decreased SICI (Greenberg et al., 1998, 2000), shortened CSP (Richter et al., 2012) and enhanced intracortical facilitation (Richter et al., 2012), independent of medication status (Richter et al., 2012). OCD may be associated with a dysregulation of both $GABA_A$ and $GABA_B$ receptor-mediated inhibitory neurotransmission and N-methyl-D-aspartate receptor-mediated excitatory neurotransmission, consistent with genetic findings (Arnold et al., 2006; Dickel et al., 2006; Samuels et al., 2011; Stewart et al., 2007; Voyiaziakis et al., 2011; Zai et al., 2005). Compared to MDD and SCZ, these results provide further evidence to demonstrate that inhibitory deficits in combination with enhanced intracortical facilitation may be specific to OCD.

The greatest significant effect size found in patients with MDD was for shortened CSP. Also, SICI was significantly reduced in patients with MDD. These findings show that a decrease in SICI and shortened CSP may be unique to MDD. For example, Levinson et al. (Levinson et al., 2010) demonstrated that all patients with MDD, regardless of symptom or medication state, demonstrated significant CSP deficits compared with healthy participants. By contrast, only treatment resistant MDD patients demonstrated SICI deficits. Taken together, this data suggests that MDD is associated with deficits in neurophysiological indexes of $GABA_B$ receptor-mediated inhibitory neurotransmission; whereas treatment resistant MDD patients demonstrated deficits in neurophysiological indexes of both $GABA_B$ and $GABA_A$ receptor- mediated inhibition. Previous evidence has suggested that the altered function of the GABAergic system may contribute significantly to the pathophysiology and potential successful treatment of this disorder (Sanacora and Saricicek, 2007).

With regards to patients with SCZ, studies showed significant deficits in SICI, after controlling for age and medications using a meta-regression. This finding shows specificity of decreased SICI as a characteristic of SCZ. Previous research suggests that dysfunctional cortical inhibition may be a mechanism through which symptoms of SCZ are mediated. Altered markers of cortical GABAergic neurotransmission are consistently observed abnormalities in postmortem studies of SCZ (Benes and Berretta, 2001; Lewis et al., 1999; Stan and Lewis, 2012). Similarly, several neurophysiological studies have found a reduction in SICI and CSP duration in both medicated (Daskalakis et al., 2002, 2008a; Liu et al., 2009) and unmedicated patients with SCZ (Daskalakis et al., 2002, 2008a; Liu et al., 2009) suggesting deficits in cortical inhibition of the motor cortex. Taken together, SICI may be a specific attribute when characterizing SCZ.

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5. Clinical implications

This study provides compelling evidence to suggest that impairments in GABAergic inhibition are involved in the pathophysiology of OCD, MDD and SCZ, nevertheless, the overall pattern of these deficits differs. For example, in OCD, research has found inhibitory deficits and enhanced intracortical facilitation, independent of medication status (Greenberg et al., 1998, 2000; Richter et al., 2012). By contrast, Levinson et al. (Levinson et al., 2010) found that all MDD patients showed CSP abnormalities but only treatment-resistant depressed patients demonstrated SICI reductions. Treatment with antidepressants had no apparent effects on either measure though other research has shown that selective serotonin reuptake antidepressants normalize GABAergic deficits in depression through enhanced SICI and decreased intracortical facilitation (Manganotti et al., 2001; Minelli et al., 2010). Finally, unmedicated SCZ patients have demonstrated impairments in SICI and CSP (Daskalakis et al., 2002). Two studies have showed that clozapine-treated SCZ patients demonstrated significantly longer CSP durations, implicating the role of the $GABA_B$ receptor in clozapine (Daskalakis et al., 2008a; Liu et al., 2009). Enhancing inhibition or decreasing facilitation in the cortex through pharmacological or non-pharmacological means (i.e., electroconvulsive therapy, repetitive TMS, magnetic seizure therapy, cognitive behavioral therapy) represent an important approach to targeted treatment. Further investigation is needed to develop these TMS measures as neurophysiological markers of both diagnosis and treatment.

6. Limitations

This study is limited in several ways. First, studies assessing patients with OCD compared to healthy controls had small sample sizes with limited amount of studies published in this field, more work needs to be done in this population. Also, there is an overall lack of diagnostic specificity of these neurophysiological deficits due to the overlap in results. It has been shown that pharmacological treatment can have an effect on cortical inhibition in healthy participants, (Langguth et al., 2008; Robol et al., 2004; Ziemann et al., 1996a,b, 1997, 1998) SCZ (Daskalakis et al., 2008a; Liu et al., 2009) and MDD (Manganotti et al., 2001; Minelli et al., 2010). No such medication effect has been reported in OCD as inhibitory deficits in OCD have been found independent of medication status, suggesting that these neurophysiological abnormalities may be trait related. However, more studies are needed to investigate the impact of medications on cortical inhibition in psychiatric disorders. Furthermore, these measures are traditionally limited to the motor cortex which is a significant limitation since non-motor neurophysiological processes are of primary interest. Other brain areas such as the dorsolateral prefrontal cortex may be more proximal to the pathophysiology of these illnesses and can be measured by combining TMS with electroencephalography (Daskalakis et al., 2008b; Farzan et al., 2010a, b; Fitzgerald et al., 2008). Lastly, there are differences in the TMS methodologies between studies. The following approaches need to be implemented to have consistent measurements, for example, CSP should be measured by stimulating an active contralateral muscle (i.e., 20% of maximum contraction) at 140% of the resting motor threshold (Cantello et al., 1992) (Fig. 1B). LICI should be evaluated by using a suprathreshold conditioning stimulus that precedes a suprathreshold test stimulus at a 100 ms interstimulus interval (Valls-Sole et al., 1992) (Fig. 1C). SICI and intracortical facilitation should be assessed by using a subthreshold conditioning stimulus set at 80% of the resting motor threshold that precedes a suprathreshold test stimulus (Kujirai et al., 1993). SICI is measured at interstimulus intervals of 2 ms and 4 ms and intracortical facilitation is evaluated at interstimulus intervals of 10 ms, 15 ms and 20 ms (Kujirai et al., 1993; Nakamura et al., 1997) (Fig. 1D and E). Following these exact TMS guidelines can ensure rigorous methods across research groups.

7. Conclusion

In conclusion, this meta-analytic review of motor cortex TMS paradigms in OCD, MDD and SCZ have revealed promising findings for objective clinical applications. This study provides a meaningful summary of research in this field demonstrating a clear platform from which further studies and diagnostic procedures can be developed.

Conflict of interest

None.

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