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Evidence for Cortical Inhibitory and Excitatory Dysfunction in Obsessive Compulsive Disorder

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Several lines of evidence suggest that obsessive-compulsive disorder (OCD) is associated with an inability to inhibit unwanted intrusive thoughts. The neurophysiological mechanisms mediating such inhibitory deficits include abnormalities in cortical γ-aminobutyric acid (GABA) inhibitory as well as *N*-methyl-D-aspartate (NMDA) receptor-mediated mechanisms. Molecular evidence suggests that both these neurotransmitter systems are involved in OCD. Transcranial magnetic stimulation (TMS) represents a noninvasive technique to ascertain neurophysiological indices of inhibitory GABA and facilitatory NMDA receptor-mediated mechanisms. In this study, both mechanisms were indexed in 34 patients with OCD (23 unmedicated and 11 medicated) and compared with 34 healthy subjects. Cortical inhibitory and facilitatory neurotransmission was measured using TMS paradigms known as short-interval cortical inhibition (SICI), cortical silent period (CSP), and intracortical facilitation (ICF). Patients with OCD demonstrated significantly shortened CSP ($p < 0.001$, Cohen's $d = 0.91$) and increased ICF ($p < 0.009$, Cohen's $d = 0.71$) compared with healthy subjects. By contrast, there were no significant deficits in SICI. After excluding patients with OCD and comorbid major depressive disorder (MDD) from the analysis, these differences remained significant. Our findings suggest that OCD is associated with dysregulation in cortical inhibitory and facilitatory neurotransmission. Specifically, these findings suggest impairments in $GABA_B$ receptor-mediated and NMDA receptor-mediated neurotransmission. These findings are consistent with previously published genetic studies implicating $GABA_B$, and NMDA transporter and receptor genes in OCD. It is posited that dysregulation of such mechanisms may lead to the generation and persistence of intrusive thoughts that form the basis for this disorder.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2–3% (Karno *et al*, 1988; Ruscio *et al*, 2010; Weissman *et al*, 1994) and is associated with high psychosocial morbidity (Koran *et al*, 1996; Richter *et al*, 2003). Neuroimaging studies have implicated dysfunction in frontostriatal circuitry in the pathophysiology of OCD (Graybiel and Rauch 2000; Saxena *et al*, 1998; Whiteside *et al*, 2004), demonstrating abnormal metabolic activity in the orbitofrontal cortex, anterior cingulate cortex (ACC), medial prefrontal cortex, and caudate nucleus. Functional magnetic resonance imaging (fMRI) studies have provided further evidence for inhibitory dysregulation in OCD by demonstrating increased activation in the bilateral–ventrolateral prefrontal cortex, ACC, parahippocampal cortices, left temporal cortex, and in the dorsal brainstem (van den Heuvel *et al*, 2005). Neurophysiological studies also demonstrate enhanced precentral somatosensory evoked potentials, and a tonic high level of cortical excitability of motor and related areas (Rossi *et al*, 2005). Investigations of neurocognitive function in tandem with fMRI have suggested that this may relate to deficits in cognitive inhibitory function and response control (Chamberlain *et al*, 2005; Page *et al*, 2009; Woolley *et al*, 2008). For example, OCD patients tend to make inappropriate motor responses to non-target stimuli when performing Go/No-Go tasks, in which subjects have to make a simple motor response (such as pressing a button) as quickly as possible

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when target/non-target stimuli are presented (Maltby *et al*, 2005; Page *et al*, 2009). Such alterations may lead to a reduced ability of patients to inhibit intrusive thoughts, impulses, images, and repetitive motor responses (Yucel *et al*, 2007), creating the clinical phenomena of OCD.

Additional evidence supports the involvement of γ-aminobutyric acid (GABA) and glutamatergic neurotransmission in OCD, including magnetic resonance spectroscopy studies, which suggest alterations in glutamate concentrations in the caudate in pediatric OCD (Rosenberg *et al*, 2000), and genetic studies implicating the glutamate transporter gene *SLC1A1* (Arnold *et al*, 2006; Dickel *et al*, 2006), the glutamate N-Methyl-D-aspartate (NMDA) subunit receptor gene *GRIN2B* (Arnold *et al*, 2004; Dickel *et al*, 2006), as well as the $GABA_B$ receptor 1 (*GABBR1*) gene as susceptibility genes in OCD (Zai *et al*, 2005). Collectively the above represents compelling evidence that OCD is associated with deficient inhibition and excessive facilitation in the cortex.

Transcranial magnetic stimulation (TMS) represents a noninvasive method through which to assess brain inhibitory neurotransmission. Two of the main inhibitory paradigms used are short-interval cortical inhibition (SICI) and cortical silent period (CSP) (Cantello *et al*, 1992; Kujirai *et al*, 1993). SICI consists of a subthreshold conditioning pulse followed by a suprathreshold test pulse. If the interstimulus interval (ISI) ranges from 1 to 5 ms, the motor-evoked potential (MEP) response is inhibited by 50–90% (Kujirai *et al*, 1993). In CSP, motor cortical stimulation is superimposed on background electromyographic activity. A cessation of electromyographic activity occurs, producing a silent period (Fuhr *et al*, 1991). SICI and CSP appear to reflect cortical GABAergic inhibitory neurotransmission. SICI appears to index $GABA_A$ receptor-mediated inhibition (Ziemann *et al*, 1996a), whereas CSP is more closely related to $GABA_B$ receptor-mediated inhibition (Siebner *et al*, 1998; Werhahn *et al*, 1999). For example, it has been shown that lorazepam, a drug that facilitates $GABA_A$ neurotransmission, increases SICI (Ziemann *et al*, 1996b). Moreover, the duration of SICI is comparable to the duration of $GABA_A$-mediated inhibitory postsynaptic potentials (IPSPs) (Davies *et al*, 1990). Also, the CSP demonstrates a similar time course as the $GABA_B$ receptor-induced IPSP (Roick *et al*, 1993) and baclofen, a $GABA_B$ agonist, leads to CSP lengthening (Siebner *et al*, 1998). TMS can also be used to examine cortical facilitation using the paired pulse paradigm known as intracortical facilitation (ICF), in which a subthreshold conditioning pulse precedes a suprathreshold test pulse by 10–20 ms and results in MEP potentiation compared with the suprathreshold test pulse alone. ICF reflects the activity of excitatory postsynaptic potentials transmitted by NMDA glutamate receptors (Ziemann *et al*, 1998).

Three studies have examined SICI, CSP, and ICF in OCD. Greenberg *et al,* 1998 compared 12 OCD patients (7 on fluoxetine and 5 unmedicated) with 12 healthy volunteers. They reported that OCD patients had decreased SICI (Greenberg *et al*, 1998). The same author conducted a second study in which 16 OCD patients were enrolled (9 medicated and 7 unmedicated). OCD patients had decreased SICI compared with 11 healthy controls. No differences in CSP were found (Greenberg *et al*, 2000). Finally, a study comparing 20 subjects with Tourette's Disorder (TD) and comorbid OCD, and attention deficit hyperactivity disorder with 21 healthy controls showed that OCD patients had shortened CSP and decreased SICI (Ziemann *et al*, 1997a).

In this study, we aimed to investigate SICI, CSP, and ICF in a larger and primarily unmedicated sample of OCD patients. Based on the molecular findings described above, we hypothesized that OCD patients would demonstrate neurophysiological deficits that were consistent with dysregulation of $GABA_B$ and NMDA neurotransmission.

PATIENTS AND METHODS

Subjects

This study included 34 right-handed patients (mean age = 40.94 ± 12.38 years, 15 men and 19 women) with a DSM-IV diagnosis of OCD confirmed by the Structured Clinical Interview for DSM-IV (SCID), and 34 matched healthy right-handed volunteers (mean age = 40.41 ± 10.26 years, 16 men and 18 women). In healthy subjects, psychopathology was ruled out using the personality assessment inventory (PAI; Psychological Assessment Resources). The PAI is a self-administered, objective inventory of adult personality and psychopathology (eg, personality, depression, somatic disorders, anxiety, anxiety-related disorders, and schizophrenia). It is composed of nonoverlapping clinical, treatment, interpersonal, and validity scales. Specifically, the PAI measures manifestation of clinical syndromes, providing information to assist diagnosis, treatment, and screening for all psychopathology corresponding to DSM-IV categories (Morey, 1991, 1996). For healthy controls, exclusion criteria included a self-reported comorbid medical illness or a history of drug or alcohol abuse. Patients with OCD had a history of at least 1 year of duration of symptoms and were between 18 and 65 years of age. Exclusion criteria included comorbid schizophrenia, psychotic or bipolar affective disorder, neurological disease, as identified by history and/or laboratory screening, active drug or alcohol abuse, any comorbid medical condition that might require urgent intervention, and current pregnancy.

Among the 34 patients with OCD, 23 were unmedicated and 11 were medicated. Details regarding medication status are listed in Table 1. Individuals were deemed unmedicated if treatment with serotonin reuptake inhibitors had been discontinued at least 2 weeks before measures were collected (5 weeks washout minimum for fluoxetine) and were not taking any other CNS active medications (eg, benzodiazepines, antipsychotics, NMDA antagonists, mood stabilizers, and antiepileptic drugs). The severity of OCD was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which includes 10 items for rating severity, and a symptom checklist itemizing 45 obsessions and 29 compulsions (Goodman *et al*, 1989a, b). The checklist items were used to derive weighted symptom factor scores for four factors calculated by totaling number of items loading on each factor endorsed by the patient and dividing by total number of possible items based on factor analysis of the Y-BOCS (Summerfeldt *et al*, 1999). The four factors comprised: Factor 1, aggressive obsessions, sexual

Table 1 Demographic and Clinical Characteristics of the Sample

	OCD group ($n = 34$)	Control group ($n = 34$)
Age[a]	40.9 ± 12.38	40.41 ± 10.26
Gender	15 Male	16 Male
	19 Female	18 Female
Mean illness duration	16.65 ± 8.48	NA
Y-BOCS scores current[a]	24.34 ± 6.32	NA
Y-BOCS lifetime[a]	24.43 ± 8.25	NA
BDI scores current[a]	22.75 ± 13.85	NA
Medications (# of subjects, mean dose in mg)	Sertraline (1, 100) Citalopram (2, 140) Quetiapine (3, 217) Venlafaxine (5, 390) Trazodone (1, 100) Gabapentine (2, 2100) Topiramate (1, 50) Methylphenidate (1, 80) Paroxetine (4, 70) Lorazepam (2, 1) Fluvoxamine (1, 160) Fluoxetine (1, 20) Tryptophan (1, 4000) Pimozide (1, 3)	NA

Abbreviations: BDI, beck depression inventory; OCD, obsessive compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a]Data reported as mean ± SD.

obsessions, religious obsessions, somatic obsessions, and checking compulsions; Factor 2, obsessions with need for symmetry or exactness, repeating rituals, counting compulsions, and ordering/arranging compulsions; Factor 3, contamination obsessions and cleaning/washing compulsions; Factor 4, hoarding/saving obsessions and hoarding/collecting compulsions. Depressive symptoms were rated with the Beck Depression Inventory (BDI). Utilizing a BDI cutoff score of 21 (Beck and Beamesderfer 1974), 26.7% of patients with OCD had comorbid depressive symptoms of moderate severity or greater. Based on SCID interview, none of the patients met criteria for Tourette's syndrome. With regard to other comorbid disorders, one (3%) patient with OCD had comorbid agoraphobia, three (9%) had panic disorder, one (3%) had trichotillomania, two (6%) had social phobia, two (6%) had generalized anxiety disorder, one (3%) had skin picking, and three (9%) had specific phobia. Demographic and clinical data for the two groups (ie, patients with OCD and healthy subjects) are listed in Table 1. All subjects reported no drug or alcohol use in the month before testing on SCID interview. This study was approved by the Centre for Addiction and Mental Health Ethics committee, and written informed consent was obtained for each participant.

Procedures

TMS was applied to the hand area of the left motor cortex with a figure-of-eight magnetic coil and two Magstim 200 magnetic stimulators (Magstim, Whitland, Dyfed, UK). The coil diameter was 70 mm for each loop. The coil was held tangentially on the head with the handle pointing backward and 45° laterally from the midline. Surface electromyography (EMG) was recorded from the right abductor pollicis brevis (APB) muscle. Subjects were comfortably seated in a chair and maintained a relaxed state throughout the experiment. The RMT was defined as the minimal intensity that produced a MEP of $>50\,\mu V$ in 5 of 10 trials in relaxed APB (Kujirai *et al*, 1993). Measurement of the CSP duration was obtained in moderately tonically active APB (ie, 20% of maximum contraction) by stimulating the motor cortex with intensities of 140% of RMT. This intensity was chosen based on the evidence that suggests that CSP duration at lower stimulus intensities (110 and 120% of MT) mainly reflects activation of $GABA_A$ receptors, whereas CSP duration at the higher stimulus intensities (140% of MT) mainly reflects the activation of $GABA_B$ receptors (Paulus *et al*, 2008). A total of 10 trials were performed. The CSP duration was the time from the MEP onset to the return of any voluntary EMG activity. This is referred to as the absolute CSP and ends with a deflection in the EMG waveform (Tergau *et al*, 1999). The CSP was determined with our previously published automated method (Daskalakis *et al*, 2003). In SICI, a subthreshold conditioning stimulus, which was set at 80% of RMT, preceded a suprathreshold test stimulus (TS), which was adjusted to produce an average MEP of 0.5–1.5-mV peak-to-peak amplitude in the contralateral APB muscle (Kujirai *et al*, 1993). Conditioning stimuli were applied to the motor cortex before the TS at one of five random ISIs: 2 and 4 ms for SICI and 10, 15, and 20 ms for ICF. A total of 72 trials were performed, 12 for each condition. For SICI/ICF, changes in the TS MEP amplitude at each ISI were expressed as a percentage of the mean unconditioned MEP amplitude (Daskalakis *et al*, 2002b). The order of administration of the two paradigms was counterbalanced between subjects to prevent order effects.

Statistical Analysis

Demographic characteristics and severity of clinical symptoms were compared among OCD patients by χ^2 test (for categorical variables). Both the OCD patients and healthy controls groups were checked for outliers. Independent samples *t*-tests were used to test for differences in RMT, CSP, and SICI/ICF between healthy controls and OCD patients, and also for differences in RMT and CI measures between medicated and unmedicated patients. Pearson's correlation coefficient was used for exploring associations between TMS indices (ie, SICI/ICF and CSP) and Y-BOCS total scores, weighted scores for factors 1–4, obsessions and compulsions severity subscales of the Y-BOCS, and BDI scores. In the CSP experiment, the CSP duration served as the dependant variable. For SICI/ICF, the conditioned MEP size, expressed as a ratio of the MEP amplitude of each conditioned response to the unconditioned response at each ISI, served as the dependant variable. All statistical procedures were two-tailed, and significance was set at a α level of 0.05. All analyses were computed with SPSS 15.0 (Statistical Product and Service Solutions, Chicago, IL).

RESULTS

All subjects tolerated the study without difficulty. There was no significant difference between groups in the percentage of male subjects ($\chi^2 = 0.362$, $p = 0.547$) or in age (OCD patients, mean ± SD, 40.9 ± 12.38; healthy controls, 40.41 ± 10.26, $p = 0.848$). There were no significant differences in Y-BOCS scores between medicated and unmedicated patients with OCD ($t(27) = -0.789$, $p = 0.437$). Also, there was no significant difference between medicated and unmedicated patients with OCD in the number of years since the diagnosis of OCD ($p = 0.348$).

Cortical Silent Period

Patients with OCD had significant shorter CSP (mean ± SD = 122 ± 36.3 ms) compared with healthy controls (153.5 ± 32 ms) ($t(66) = -3.8$, $p < 0.0001$, Cohen's $d = 0.91$) (Figure 1). There was no significant difference in CSP durations between medicated and unmedicated OCD patients ($t(32) = -0.261$, $p = 0.796$) (Figure 2). After excluding OCD patients with comorbid MDD (OCD/MDD) from the analysis, the difference in CSP between OCD patients and healthy controls remained significant ($p = 0.032$). Also, there was a difference in CSP between OCD/MDD patients and healthy controls ($p = 0.028$). There were no significant correlations between CSP and Y-BOCS scores ($r = -0.026$, $p = 0.894$) or BDI scores ($r = -0.071$, $p = 0.810$) in OCD patients. Analyzing medicated and unmedicated OCD patients as two separate groups, no correlations were found between Y-BOCS scores and CSP in medicated patients ($r = 0.153$, $p = 0.743$) or in unmedicated OCD patients ($r = -0.11$, $p = 0.63$). Also, no correlations were found between CSP and Factor 1 ($r = -0.068$, $p = 0.71$), Factor 2 ($r = -0.11$, $p = 0.54$), Factor 3 ($r = -0.10$, $p = 0.59$), and Factor 4 ($r = -0.88$, $p = 0.637$) of the Y-BOCS. Finally, no correlations were found between CSP, and obsessions and compulsions severity subscales of the Y-BOCS (all p values > 0.210).

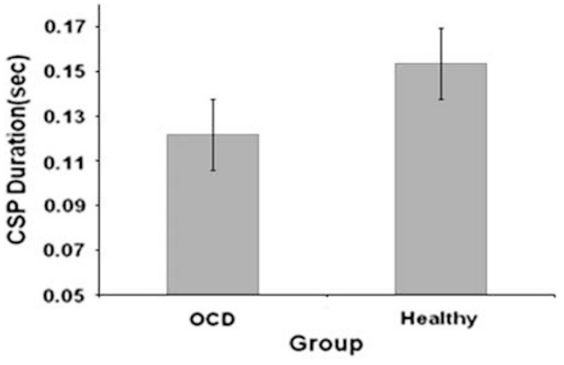

Figure 1 Mean cortical silent period (CSP) duration in 34 patients with obsessive compulsive disorder (OCD) and 34 healthy subjects. Values represent means ± SEMs. There were significant CSP deficits in patients with OCD compared with healthy subjects ($t(66) = -3.8$, $p < 0.0001$, Cohen's $d = 0.91$).

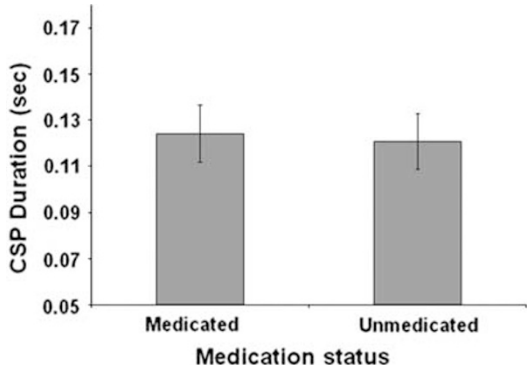

Figure 2 Mean cortical silent period (CSP) duration in medicated and unmedicated patients with OCD. Values represent means ± SEMs. There was no statistically significant difference in CSP duration between medicated and unmedicated patients with OCD ($t(32) = -0.261$, $p = 0.796$). Other abbreviations as in Figure 1.

Short-Interval Cortical Inhibition

There was no difference in unconditioned TS MEP amplitude between controls (mean ± SD = 0.895 ± 0.267 mV) and OCD patients (0.980 ± 0.329 mV) ($p = 0.274$). There were no significant differences in mean SICI between OCD patients (mean ± SD = 0.736 ± 0.55) and controls (mean ± SD = 0.565 ± 0.34) ($t(63) = 1.5$, $p = 0.137$). There was no significant difference in mean SICI between medicated and unmedicated patients with OCD ($t(29) = -0.108$, $p = 0.915$). When we compared OCD/MDD patients to healthy controls, the former had significantly decreased SICI compared with the latter ($p < 0.001$). Also, OCD/MDD patients had decreased SICI compared with OCD patients without MDD ($p < 0.001$). By contrast, there was no difference in SICI between OCD patients without comorbid MDD and healthy controls ($p = 0.99$). There were no significant correlations between SICI and Y-BOCS scores ($r = -1.22$, $p = 0.553$) or BDI scores ($r = 0.446$, $p = 0.169$) in OCD patients. Analyzing medicated and unmedicated OCD patients as two separate groups, no correlations were found between Y-BOCS scores and SICI in medicated patients ($r = -0.442$, $p = 0.38$) or in unmedicated OCD patients ($r = 0.005$, $p = 0.985$). Also, no correlations were found between SICI and Factors 1, 2, 3, and 4 of the Y-BOCS (all p values > 0.146). Finally, no correlations were

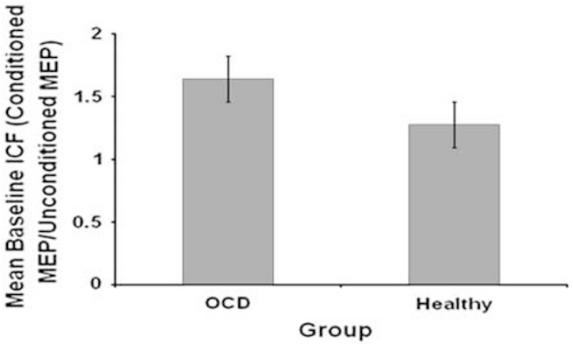

Figure 3 Mean intra-cortical facilitation (ICF) in patients with OCD and healthy subjects. Each measure is expressed as a ratio (mean ± SEM) of the conditioned motor evoked potential (MEP) amplitude to the unconditioned MEP amplitude. ICF was significantly greater in OCD patients than in healthy controls ($t(60) = 2.7$, $p = 0.009$, Cohen's $d = 0.71$). Other abbreviations as in Figures 1 and 2.

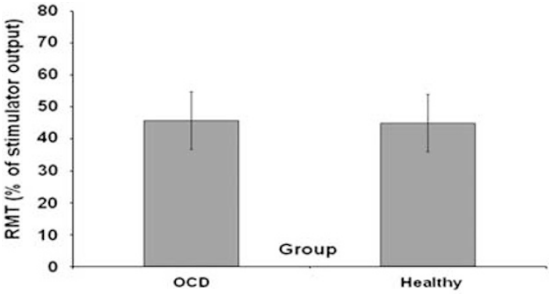

Figure 4 Resting motor threshold (RMT) in OCD patients and healthy subjects. The RMT was defined as the first intensity that produced an MEP of $>50\,\mu V$ in 5 of 10 trials with the abductor pollicis brevis muscle relaxed. Values represent means ± SEMs. The RMT over the left motor cortex was not significantly different in OCD patients compared with healthy subjects ($t(62) = 0.339$, $p = 0.735$). Other abbreviations as in Figures 1, 2 and 3.

found between SICI, and obsessions and compulsions severity subscales of the Y-BOCS (all p values >0.865).

Intracortical Facilitation

The amplitude of the unconditioned TS was the same as for SICI and did not differ between groups ($p = 0.274$). ICF was significantly greater in OCD patients (1.606 ± 0.663) than in healthy controls (1.276 ± 0.418) ($t(60) = 2.7$, $p = 0.009$, Cohen's $d = 0.71$) (Figure 3). There was no significant difference in mean ICF between medicated and unmedicated OCD patients ($t(29) = -0.397$, $p = 0.694$). After excluding OCD/MDD patients from the analysis, the difference in ICF between OCD patients and healthy controls remained significant ($p = 0.045$). There were no significant correlations between ICF and Y-BOCS scores ($r = -0.032$, $p = 0.877$) or BDI scores ($r = 0.082$, $p = 0.810$) in OCD patients. No significant correlations were found between Y-BOCS total scores and ICF in medicated patients ($r = -0.053$, $p = 0.92$) or in unmedicated OCD patients ($r = -0.032$, $p = 0.894$). Also, no correlations were found between ICF and Factors 1, 2, 3, and 4 of the Y-BOCS (all p values >0.146). Finally, no correlations were found between ICF, and obsessions and compulsions severity subscales of the Y-BOCS (all p values >0.424).

Motor Threshold

The RMT over the left motor cortex was not significantly different in OCD patients (mean ± SD = 45.63 ± 9.83) compared with healthy subjects (44.85 ± 8.56) ($t(62) = 0.339$, $p = 0.735$) (Figure 4). There was a significant difference in RMT between medicated (40.2 ± 6.5) and unmedicated OCD patients (48.35 ± 10.2) ($t(29) = 2.29$, $p = 0.03$). The RMT over the left motor cortex was significantly higher in OCD/MDD patients (mean ± SD = 54 ± 14.28) compared with healthy controls (mean ± SD = 44.8 ± 8.5) ($p = 0.014$) and with patients with OCD without MDD (mean ± SD = 43.21 ± 4.8) ($p = 0.010$). In contrast, there was no significant difference in RMT between OCD patients without comorbid MDD and healthy controls ($p = 0.557$). There were no significant correlations between RMT and Y-BOCS scores ($r = -0.064$, $p = 0.762$) or BDI scores ($r = 0.082$, $p = 0.21$) in OCD patients. Analyzing medicated and unmedicated patients with OCD as two separate groups, no correlations were found between Y-BOCS scores and RMT in medicated patients ($r = 0.442$, $p = 0.38$) or in unmedicated OCD patients ($r = -0.07$, $p = 0.776$). Also, no correlations were found between RMT and Factors 1, 2, 3, and 4 of the Y-BOCS (all p values >0.202). Finally, no correlations were found between RMT, and obsessions and compulsions severity subscales of the Y-BOCS (all p values >0.864).

DISCUSSION

Our findings suggest that patients with OCD, irrespective of medications, demonstrate significant CSP deficits and excessive ICF compared with healthy subjects, reflecting a disruption in $GABA_B$ and NMDA receptor-mediated neurotransmission. As described above, such deficits are consistent with proposed mechanisms of OCD pathogenesis (Rosenberg and Keshavan 1998). The observed deficits in $GABA_B$ receptor-mediated inhibition are consistent with a study implicating the $GABA_B$ receptor 1 (*GABBR1*) gene in susceptibility gene to OCD (Zai *et al*, 2005). Additionally, our findings of increased ICF in OCD are in line with a well-replicated finding of association between the neuronal glutamate transporter gene *SLC1A1* and OCD (Arnold *et al*, 2006; Dickel *et al*, 2006; Liang *et al*, 2008; Stewart *et al*, 2007). This gene is highly expressed within the cerebral cortex, striatum, and thalamus regions that are clearly implicated in OCD.

Deficits in $GABA_B$ receptor-mediated inhibition as demonstrated by shortened CSP have been shown in other psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder (MDD) (Daskalakis *et al*, 2002a; Fitzgerald *et al*, 2002; Levinson *et al*, 2007; Liu *et al*, 2009). Therefore, $GABA_B$ deficits may be a more general marker of psychopathology rather than specifically related to OCD. However, previous studies in mood disorders and schizophrenia have not demonstrated a concomitant increase in ICF (Daskalakis *et al*, 2002a; Fitzgerald *et al*, 2002; Levinson *et al*, 2007, 2010). That is, although other psychiatric disorders appear to be associated with CSP and SICI deficits (eg, major depressive disorder and schizophrenia) the pattern of neurophysiological deficits demonstrated in OCD (ie, decreased CSP and increased ICF) may be specific to this disorder. The specificity of these findings is further strengthened by the fact that after excluding patients with OCD and comorbid MDD from the analysis, differences between OCD patients and healthy controls on CSP and ICF measures remained significant. Taken together, such findings represent a potential biomarker for OCD but require replication in future studies, which should also evaluate the heritability of this neurophysiological profile of response.

To our knowledge, our study involves the largest sample of unmedicated patients with OCD ($n = 23$). This is highly relevant as it has been shown that pharmacological treatment with some antipsychotics (eg, clozapine and haloperidol), benzodiazepines (eg, lorazepam, diazepam), antidepressants (eg, citalopram, paroxetine, sertraline, and mirtazapine), and NMDA antagonists (eg, memantine) can

lead to changes in CI in healthy subjects and in patients with schizophrenia and depression (Daskalakis *et al*, 2008a; Minelli *et al*, 2010; Paulus *et al*, 2008). For example, it has been shown that clozapine increases CSP (Daskalakis *et al*, 2008a), haloperidol decreases SICI and increases ICF, diazepam and lorazepam decrease MEP, ICF, and CSP and increase SICI, memantine increases SICI and decreases ICF, citalopram increases MT, CSP, and SICI, and sertraline decreases ICF (Paulus *et al*, 2008; Robol *et al*, 2004; Schwenkreis *et al*, 1999; Ziemann *et al*, 1996a). However, our finding of no significant differences between medicated and unmedicated patients on CSP and ICF indices suggests that these neurophysiological abnormalities are trait related and unaffected by pharmacological treatment. This is further supported by our analyses showing no relationship between symptom severity, based on total Y-BOCS, or obsession/compulsion subscales, suggesting these neurophysiological findings are not state-dependent. Similarly, analysis by symptom subtype was also negative. Although the power of our subtype analysis was limited, the lack of relationship with any one-symptom subgroup is in contradistinction to views that these subtypes may reflect underlying genetic/neurobiological differences.

Dysregulation of cortical activity is presumed to result from aberrantly modulated subcortical input, as shown by studies in disorders that involve basal ganglia pathology, such as Parkinson's disease, TD, focal dystonias, and OCD (Rauch and Savage, 1997). As mentioned, evidence from functional imaging, and the results of stereotactic ablation and deep brain stimulation studies (Greenberg *et al*, 2010) strongly suggest that OCD involves hyperactivity of circuits including the frontal cortex, striatum, globus pallidus, and thalamus. As the motor cortex is the target of a motor corticobasothalamic circuit previously implicated in OCD (Greenberg *et al*, 2000), the deficits of cortical inhibition could be seen as a corollary of the interaction between these hyperactive circuits and the neurons in the motor cortex. A recent metaanalysis (Rotge *et al*, 2009) comparing patients with OCD to healthy subjects reported that OCD patients have a smaller volume in both ACC and OFC, as well as an increase of the thalamic volume, further supporting thalamocortical involvement in the pathophysiology of OCD. It follows that excessively high outputs generated by an enlarged thalamus and transmitted to the cortex via these pathways are not sufficiently inhibited by volume-reduced cortical areas such as the ACC and OFC, resulting in cortical hyperactivity and deficient inhibition.

Our findings of increased RMT and decreased SICI in the left hemisphere of OCD patients with comorbid MDD but not in OCD patients without comorbid MDD are in line with previous studies that have demonstrated increased RMT and SICI deficits in patients with MDD (Lefaucheur *et al*, 2008; Levinson *et al*, 2010), and suggest a more marked GABAergic deficit in this population. The fact that OCD patients with comorbid MDD also appeared to demonstrate larger CSP deficits and excessive ICF compared with OCD patients without comorbid MDD, albeit not significantly so, further confirms this finding. This is consistent with neuroimaging studies using positron emission tomography that have demonstrated pathophysiological correlates common to unipolar depression, bipolar depression, and OCD patients with comorbid MDD (Baxter *et al*, 1989). A pattern of reduced metabolic activity in the left hippocampal region common to patients with MDD and patients with concurrent OCD and MDD, but not in OCD patients alone, has also been previously reported (Saxena *et al*, 2001). When considered together, these studies suggest that a diagnosis of comorbid MDD adds a separate element of pathophysiology independent of OCD itself.

Our results differ from previous studies in some important ways. First, it was previously reported that the RMT, a marker of ion-channel induced excitability in the cortex (Chen *et al*, 1997; Ziemann *et al*, 1996b) that is unrelated to GABA (Ziemann *et al*, 1996b), glutamate (Liepert *et al*, 1997; Ziemann *et al*, 1998), or dopamine transmission (Ziemann *et al*, 1997b), was decreased in patients with OCD (Greenberg *et al*, 2000).These differences were not found in our study. Such findings could be accounted for by differences in symptoms severity in our sample compared with previous samples owing to the large number of unmedicated patients. That is, our sample of patients with OCD had greater symptom severity (ie, moderate to severe illness, as reflected in a mean Y-BOCS of 24.34) compared with the sample by Greenberg *et al* (2000), which reported subclinical mean severity of 14.6 on the Y-BOCS. We also included a higher percentage of unmedicated patients (67.6%) compared with 43.75% in the aforementioned study. Greenberg *et al* (2000) did not find CSP differences between patients with OCD and healthy controls. This may be simply related to the lower stimulation intensities used to generate the CSP (ie, 110 and 120% of MT) (Greenberg *et al*, 2000). By contrast, our findings are indeed consistent with Ziemann *et al* (1997a), who reported shorter CSP and no differences in RMT between patients with TD and comorbid OCD, and healthy subjects. Given these inconsistencies, however, independent replication is warranted.

Our study has some limitations. First, the measurement of CI was restricted to the motor cortex. As mentioned, several brain areas have been implicated in the pathophysiology of OCD including the OFC, DLPFC, basal ganglia structures, ACC, and SMA. Thus, the motor cortex may not be an ideal brain structure to identify abnormalities in a disorder that is more closely related to thoughts and behavior. Recent studies combining TMS with EEG have been shown to effectively measure CI in non-motor cortical regions (Daskalakis *et al*, 2008b) and should be used to extend our findings to brain regions more closely related to the pathophysiology of this disorder. Second, we evaluated patients with OCD and healthy subjects at a single time point. One of our future directions is to evaluate CI before and after treatment for OCD (eg, serotonin reuptake inhibitors and cognitive behavioral therapy) to determine whether or not potentiation of CI and/or normalization of cortical inhibition or facilitation are related to therapeutic response in these patients.

In summary, our neurophysiological findings suggest that OCD is associated with a dysregulation of both $GABA_B$ receptor-mediated inhibition and of NMDA receptor-mediated facilitation. Future studies are needed to replicate such findings, evaluate their potential as biomarkers by exploring the heritability of such an intermediate phenotype, and also evaluate such abnormalities in different cortical regions that are also postulated to be more closely

associated with the pathophysiology of this disorder (ie, DLPFC and OFC).

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