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CO-INVESTIGATOR(S) AND THEIR HOME DEPARTMENTS: <ul style="list-style-type: none">- Sarah H. Lisanby, MD – Director of the Division of Brain Stimulation and Therapeutic Modulation, Department of Psychiatry Columbia University;- Helen B. Simpson, MD, PhD – Division of Therapeutics, Director of the Anxiety Disorders Clinic and of the OCD Research Program, Department of Psychiatry Columbia University;- Lawrence S. Kegeles, MD, PhD – Division of Translational Imaging, Department of Psychiatry Columbia University;- Benjamin D. Greenberg, MD, PhD - Department of Psychiatry and Human Behavior, Warren Alpert Medical School Brown University;- James F. Leckman, MD – Child Study Center Yale University Medical School.

PROJECT TITLE: MODULATION OF PREMOTOR AND MOTOR CIRCUITS IN OBSESSIVE-COMPULSIVE DISORDER (OCD): A TRANSCRANIAL MAGNETIC STIMULATION (TMS) AND MAGNETIC RESONANCE SPECTROSCOPY (MRS) STUDY.

SYNOPSIS OF PROPOSAL: (use only space provided below; minimum 11 point font)

The aim of this translational research project is to develop a novel treatment for patients with medication-resistant OCD, informed by the neurocircuitry, neurochemistry, and neurophysiology of the disorder. There is evidence that premotor and motor circuits are dysfunctional in OCD. Here we will examine the neurophysiological (Aim 1) and neurochemical (Aim 2) correlates of that dysfunction, and attempt to normalize activity in premotor and motor circuits through individually MRI-targeted neuronavigated transcranial magnetic stimulation (TMS) (Aim 3). TMS, a non-invasive procedure that allows stimulation of the brain using magnetic fields, will be used to measure intracortical excitability in OCD patients (Aim 1). We will use MRS to measure brain metabolites that may underlie the hypothesized cortical hyperexcitability (Aim 2). We will then use TMS as a treatment to test whether correcting that hyperexcitability will exert clinical benefits (Aim 3). In particular, the pre-Supplementary Motor Area (SMA)/BA6 and the ventral Anterior Cingulate Cortex (ACC), which have extensive connections and together play a central role in the higher cortical control of motor subroutines and the organization of motor actions in sequential order, will be our targets. Our open label and sham controlled studies were the first showing a significant effect of pre-SMA TMS in refractory OCD. By using TMS as neurophysiological probe we will measure the mechanisms of intracortical excitability in OCD which combined with MRS results will improve the understanding of its pathophysiology and circuitry. By using TMS as treatment tool the clinical results will show whether MRI-guided TMS applied over pre-SMA could improve OCD symptoms. If we find that normalizing hyperexcitability in the premotor/motor circuit improves OCD symptoms, this result would support the model that the hyperexcitability represents a part of the pathophysiology of OCD rather than a compensatory response to the illness. We will also test whether TMS measures of cortical excitability and MRS measures of brain metabolites track with clinical response, shedding light on the mechanisms of action of a novel therapeutic intervention and representing novel biomarkers that may be useful in developing new treatments and tracking clinical progress. These results will support our planned R01.

CURRENT SOURCES OF RESEARCH FUNDING (include begin/end dates and total direct costs)

This MRS study is presently not funded.

PENDING APPLICATIONS FOR RESEARCH FUNDING (include proposed begin/end dates and total direct costs)
N/A

12 MONTH BUDGET (July 1, 2009 to June 30, 2010)	
SALARIES with FRINGE: (%) effort, PI salary with fringe.	
SUB-TOTAL	\$
EQUIPMENT: Laboratory analysis, Earplugs, EMG electrodes, skin preparation supplies, computer media for quantitative analysis of EMG measures.	
SUB-TOTAL	\$
PATIENT CARE COSTS: Patients travel reimbursement.	
SUB-TOTAL	\$
ALL OTHER EXPENSES: MRI scans and computer media for quantitative analysis of MRI measures. \$ per scan (for acquisition + MRS analysis), 2 scans per subject, 10 subjects	
SUB-TOTAL	\$
TOTAL PROPOSED BUDGET	\$50,000

DETAILED BUDGET JUSTIFICATION: (use only space provided; minimum 11 point)

Antonio Mantovani, MD, PhD (PI): The PI will be responsible for IRB protocol development and adherence, patient recruitment/screening, patient treatments, and overall management of the study. The delivery of TMS in a clinical trial is workforce intensive, requiring 1 hr of clinician time for each of 20 treatments in the acute course per patient, or a total of 200 hours of direct patient contact for the trial. **Sarah H. Lisanby, MD (Co-I):** Director of the Division of Brain Stimulation and Therapeutic Modulation at the NYSPI-Columbia University. Over the proposed 1 year, Dr. Lisanby will donate time for weekly meeting with the PI in order to follow the progression of the study. Dr. Lisanby donated the TMS device and is covering the other costs involved in conducting this trial, including the clinical infrastructure. Salary support is not requested. **Helen B. Simpson, MD, PhD (Co-I):** Director of the Anxiety Disorders Clinic, and of the OCD Research Program at the NYSPI-Columbia University. Over the proposed 1 year, Dr. Simpson will donate her time as needed for this project. She will be the independent evaluator, in charge of administering biweekly the psychometric scales (Y-BOCS, HDRS, HARS, CGI). Salary support is not requested. **Lawrence S. Kegeles, MD, PhD (Co-I):** Associate Professor of Clinical Psychiatry and Radiology at NYSPI-Columbia University, over the proposed 1 year, Dr. Kegeles will dedicate (%) of his time for this project. He will be the person in charge for the acquisition of the MRI scans. Salary support is not requested. **Benjamin D. Greenberg, MD, PhD,** Associate Professor of Psychiatry and Human Behavior at Brown University, and **James F. Leckman, MD,** Director of the Child Study Center at Yale University Medical School will serve as **Consultants:** over the proposed 1 year, Dr. Greenberg and Dr. Leckman will donate time as needed for weekly conference calls in order to follow the progression of the study. Salary support is not requested. Along with Drs Lisanby, Simpson, and Kegeles, Dr. Greenberg and Dr. Leckman reviewed the draft of the proposed research study.

EQUIPMENT

Laboratory analysis for screening patients, Earplugs, EMG electrodes, skin preparation supplies, computer media for quantitative analysis of EMG measures.

PATIENT CARE COSTS

Patients travel reimbursement (Monthly MTA Metro Card or NYSPI Parking Fees).

ALL OTHER EXPENSES

MRI scans (2 per subject, pre and post TMS) and computer media for quantitative analysis of MRI measures.

SIGNATURES OF APPROVAL

- A. I certify that the information presented in this proposal is, to the best of my knowledge, complete, accurate, and developed according to practices commonly accepted within the scientific community.

Signature of Principal Investigator

Date

- B. I have reviewed this application and take responsibility for ensuring that the necessary space, personnel, and facilities which are mentioned in the application which pertain to my Department will be available for this project should it be funded. I recommend that this application be submitted.

Signature of Department Chairman

Date

REMINDERS

DO NOT INCLUDE LETTERS OF SUPPORT.

REVIEW APPLICATION WITH SENIOR FACULTY.

IRVING INSTITUTE/CLINICAL TRIALS OFFICE 2009 PILOT STUDY AWARD PROPOSAL

TITLE: MODULATION OF PREMOTOR AND MOTOR CIRCUITS IN OBSESSIVE-COMPULSIVE DISORDER (OCD): A TRANSCRANIAL MAGNETIC STIMULATION (TMS) AND MAGNETIC RESONANCE SPECTROSCOPY (MRS) STUDY.

GOALS: The aim of this translational research project is to develop a novel treatment for patients with medication-resistant Obsessive Compulsive Disorder (OCD), informed by the neurocircuitry, neurophysiology, and neurochemistry underlying the disorder. Studies provide evidence that, in addition to the commonly cited orbitofrontal-limbic-basal ganglia circuits implicated in OCD, premotor and motor circuits are likely involved as well. Indeed, our pilot data show that neuromodulation of the pre-SMA (supplementary motor area) via TMS was effective in reducing OCD symptoms in medication resistant patients. Here we will examine the neurophysiological and neurochemical correlates of motor circuit dysfunction in OCD, and examine the impact of TMS neuromodulation to normalize activity in these circuits. The specific aims are:

- 1) Neurophysiology: to measure primary motor cortex (M1) excitability using TMS, assessing measures related to GABA-ergic tone (intracortical inhibition - ICI), testing the hypothesis that OCD patients will show reduced intracortical inhibition relative to normative values.
- 2) Neurochemistry: to quantify concentrations of Glutamate/Glutamine (Glx) and Gamma Amino Butyric Acid (GABA) metabolites in the anterior cingulate cortex (ACC) of OCD patients using MRS, testing the hypothesis that GABA will correlate with neurophysiological measures from Aim 1.
- 3) Neuromodulation: to test a TMS paradigm of pre-Supplementary Motor Area (pre-SMA) stimulation that would normalize transsynaptically the hypothesized M1 hyperexcitability, would affect concentrations of Glx and GABA, and treat OCD symptoms. In this open-label pilot, we test the hypothesis that ICI and MRS measures will show a within-subject increase following low frequency TMS applied to the pre-SMA, and that these changes will correlate with clinical improvement.

RATIONALE: Controlled trials have demonstrated that two types of treatment are efficacious for patients with OCD: serotonin reuptake inhibitors (SRIs), and cognitive-behavioral therapy (CBT). Unfortunately up to 40-60% of patients do not have a satisfactory outcome and face substantial distress and functional impairment (Simpson et al. 2006). The rationale of this research project is to study the neurobiological dysfunctions of treatment resistant OCD patients and consequently develop a novel treatment for them.

Neurobiological models of OCD have linked obsessive and compulsive symptoms to deficits in the inhibition of irrelevant information and in response control (van den Heuvel et al. 2005). Such deficits may reflect a reduced capacity of patients with OCD to inhibit intrusive or ritualistic cognitions and motor response tendencies and have been linked to excessive activity of some brain regions, including the medial frontal cortex, ventral frontal cortex, and basal ganglia (Saxena & Rauch 2000).

Recent neurophysiologic and neuroimaging studies suggest that the premotor and motor areas are hyperactivated in OCD patients possibly to compensate for biochemical abnormalities or because primarily involved in the pathogenesis of this potentially disabling condition (Greenberg et al. 1998, 2000; Yücel et al. 2007). Whether the hyperactivation in premotor regions is primary or compensatory is difficult to resolve by neurophysiological or functional neuroimaging studies alone. Focally altering cortical excitability via TMS represents a means of testing the functional role of these findings.

TMS, a non-invasive procedure that allows stimulation of the brain using magnetic fields, will be used to measure intracortical excitability in OCD patients (Aim 1). We will use MRS to measure brain metabolites in OCD that may underlie this hyperexcitability (Aim 2). We will then use TMS to modulate regional brain activity and affect the functioning of a distributed network to determine whether correcting motor hyperexcitability will exert therapeutic benefit in OCD (Aim 3). In particular, the pre-SMA/BA6 and the ventral ACC, which have extensive connections and together play a central role in the higher cortical control of motor subroutines and the

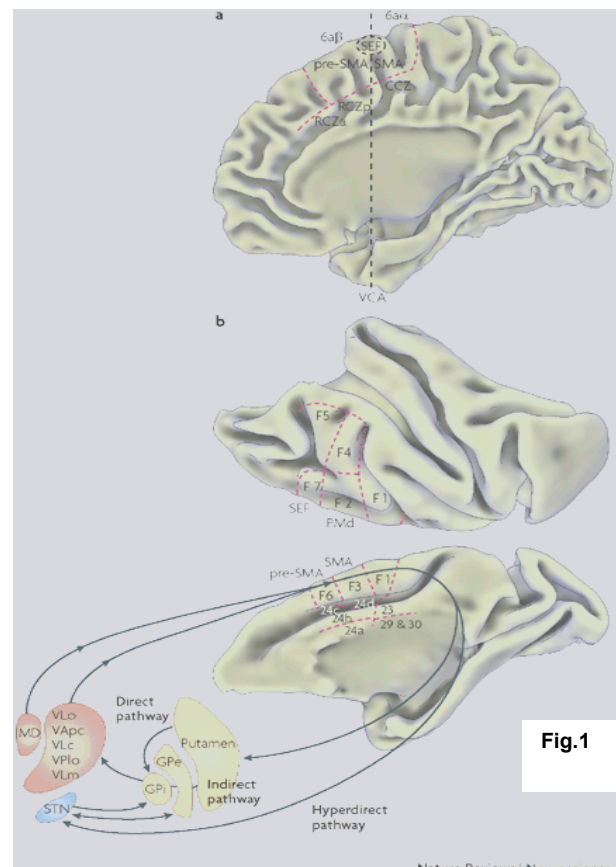


Fig.1

organization of motor actions in sequential order (Fig. 1), may be useful TMS targets to understand the significance of the pre-SMA/ACC hyperactivation found in OCD, and eventually test whether by inhibiting this system through the pre-SMA OCD patients will show a clinical improvement.

A handful of studies have used TMS to treat OCD by modulating activity in prefrontal circuits, with variable results. Greenberg et al. (1997) found that TMS to the right lateral prefrontal cortex decreased compulsive urges significantly for 8 hours. A double-blind study using right prefrontal low-frequency TMS and a less focal coil failed to find significant effects (Alonso et al. 2001). In contrast an open study in a group of refractory OCD patients randomly assigned to right or left dorso-lateral prefrontal cortex (DLPFC) high-frequency TMS found clinically significant and sustained improvement in a third of patients (Sachdev et al. 2001). Recently Prasko et al. (2006) and Sackdev et al. (2007) found that either low or high frequency TMS administered over the left DLPFC did not differ from sham (placebo).

It is possible that the modest results with TMS in OCD might be optimized through selection of more specific brain targets and careful selection of the TMS dosage to achieve desired neurobiological and clinical effects. Studies suggest that motor "intrusive" and repetitive behaviours in OCD may be a consequence of a reduction of cortico-subcortical inhibitory phenomena and a higher than normal level of cortical excitability (Rossi, Mantovani et al. 2005). Greenberg et al. (2000) found that OCD patients, like those with Tourette's Syndrome (TS), had markedly decreased intracortical inhibition (ICI). An altered balance of Glx and GABA in the prefrontal cortex might be hypothesized to be the biochemical basis of such a dysfunction. Elevated Glx levels have been found in prefrontal regions and caudate of treatment-naive OCD patients, and these seem to normalize after treatment (Whiteside et al. 2006).

Given the evidence of deficient motor inhibition and abnormal Glx concentration in OCD, the use of low frequency TMS, reported to be inhibitory on motor cortex excitability, may be a fruitful avenue to explore as a putative treatment. In particular, the pre-SMA, which plays a central role in the higher cortical control of motor subroutines and the organization of motor actions in sequential order, may be a useful TMS target to understand the significance of the premotor and motor hyperactivation found in OCD, and eventually test whether by inhibiting this system OCD patients will show a clinical improvement.

To test the impact of inhibitory low frequency TMS applied to the pre-SMA on cortical excitability and OCD symptoms, TMS was applied daily for 2 weeks at 1Hz, 100% of motor threshold (MT), 1200 stimuli/day, in 10 daily sessions in an open-label pilot study (Mantovani et al. 2006). Ten patients (2 female, mean age: 35.5 ± 13.5) were treated in this open-label study. TMS was added onto ongoing stable doses of pharmacotherapy. Suggestions of clinical improvement were apparent as early as the first week of TMS. At the 2nd week of treatment, improvements were seen, including significant reduction in the Clinical Global Impression (CGI) ($p=0.000$), Yale-Brown Obsessive Compulsive Scale (Y-BOCS) ($p=0.007$), Hamilton Anxiety Rating Scale (HARS) ($p=0.000$), Hamilton Depression Rating Scale (HDRS) ($p=0.001$). Symptom improvements were correlated with a physiological measure (increase in the right hemisphere MT, $p=0.001$). Subsequently we reported clinical benefit in 2 more cases of comorbid OCD and TS (Mantovani et al. 2007).

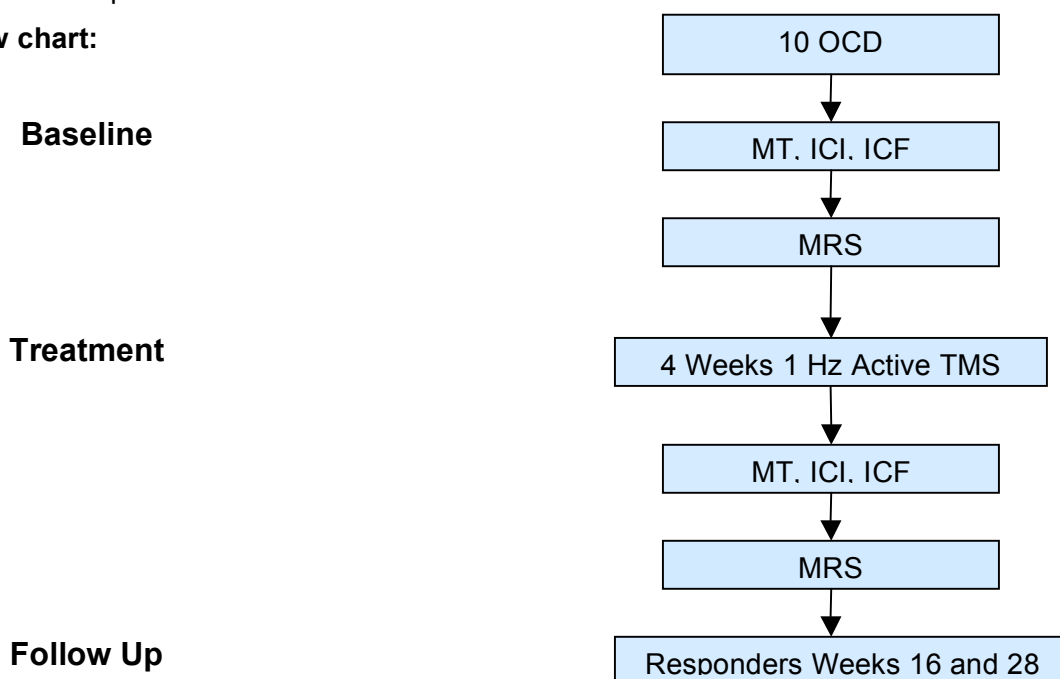
To follow up these pilot data, and test the efficacy of a longer course of TMS applied to the pre-SMA of OCD patients, we conducted and just concluded a randomized sham-controlled trial. TMS was applied daily for 4 to 8 weeks at 1Hz, 100% of motor threshold, 1200 stimuli/day (Mantovani et al. submitted). Twenty-one patients (10 female; mean age= 39.6 years, $SD=9.2$) were randomly assigned to 4 weeks of active or sham TMS. Partial responders received 4 additional weeks of active TMS. 12 patients met criteria for concurrent major depression. 11 patients had been receiving stable SSRI pharmacotherapy for at least 12 weeks before and during the trial. Repeated measures ANOVA revealed significantly better improvement in OCD with active compared with sham TMS ($p=0.031$). Response rate, defined as a $\geq 25\%$ decrease on the Y-BOCS, was 22% with sham and 67% with active TMS. At 4 weeks, patients receiving active TMS showed 25% improvement, compared with 12% with sham ($p=0.001$). After 8 weeks in the open-label cross-over, OCD symptoms improved from 28.2 ± 5.8 to 14.5 ± 3.6 ($p < 0.01$). Improvements were sustained at 3 month follow up ($p=0.023$). The active group showed significant reductions in depression ($p=0.002$) and anxiety ($p=0.001$) as well. In patients randomized to active TMS, MT measures on the right hemisphere increased significantly over time. At the end of 4 weeks of TMS the abnormal hemispheric laterality found in the group randomized to active TMS normalized. Active TMS significantly increased cortical silent period (CSP) on the left hemisphere ($p=0.039$) and significantly decreased intracortical facilitation (ICF) on the right hemisphere ($p=0.049$).

These results are consistent with our previous open trials which reported similar improvement of OCD after TMS to the pre-SMA. In both studies, clinical improvements were associated with normalization in baseline hyperexcitability of motor cortex. The effect of pre-SMA stimulation on motor cortex excitability may be explained by the fact that TMS over pre-SMA not only affects neurons at the point of stimulation, but it also influences excitability in connected areas. Direct stimulation of the primary motor cortex has been demonstrated to affect the striatum. It is therefore possible that the clinical improvements in our sample may have been due to a combined action on cortical and subcortical structures (transsynaptically stimulated).

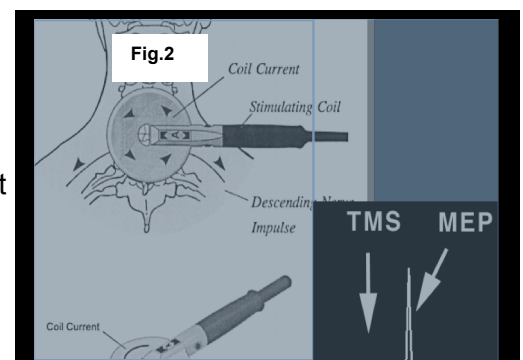
METHODS: The first phase of the study will test the motor system excitability in OCD by using single and paired pulse TMS to study MT, intracortical inhibition (ICI) and ICF in M1 on the right and left hemisphere (Aim 1), and will measure the concentrations of Glx and GABA in the ACC by MRS (Aim 2). The second phase of the study will evaluate the clinical efficacy of TMS in a 4-week open-label trial of TMS on pre-SMA (Aim 3). We propose an open-label trial for this pilot feasibility study, so that we can collect the pilot data need to support a successful R01 to perform the more definitive randomized controlled trial with a sham-control. The third phase of the study will test the motor system excitability and will measure Glx and GABA in the ACC of OCD after the TMS treatment. This study goes beyond replication of prior work in this area by using in the same sample of OCD patients 2 strategies (ICI and MRS) that allow us to test the hypotheses about the involvement of the premotor and motor circuitry underlying OCD symptoms. Furthermore, we will explore the impact of TMS applied as treatment of OCD. To address the limitations of prior work, we will study a uniquely well-characterized circuit (pre-SMA-ACC-M1) in a sample of OCD patients. We will analyze predictors of treatment response including OCD subtypes and symptom dimensions, severity of illness, motor cortex excitability and concentrations of Glx and GABA. We will assess discreet response to TMS of individual OCD symptoms (five symptom dimensions: contamination/cleaning, symmetry/order/repeating/counting, hoarding, aggressive obsessions and checking, and sexual and religious obsessions) whether or not tic-related.

Experimental Design: In the first phase 10 patients with DSM-IV-TR diagnosed OCD will first undergo measurements of MT, intracortical inhibition (ICI), and ICF in the right and left M1, and after 1 week, an MRS scan of the concentration of Glx and GABA in ACC. In the second treatment phase of the study the same 10 OCD patients will undergo 4 weeks of daily 1Hz TMS to the pre-SMA. They will receive 1 Hz TMS to the pre-SMA. Rating scales, measures of cortical excitability in both M1 and MRS concentrations of Glx and GABA in ACC will be repeated after the end of the 4-week treatment trial and responders will be followed up to 6 months after the last TMS session to evaluate the persistence of benefit.

Flow chart:



TMS Procedures: Single- and paired-pulse TMS will be given with a Magstim TMS device through a figure 8 coil (MagStim Co., U.K.). During TMS, patients and subjects will be seated in a chair, semi-reclined, with head support, wearing earplugs to protect hearing. A mechanical frame holds the coil against the head. MT is the minimum magnetic flux needed to elicit a threshold EMG response (50 μ V in peak to peak amplitude) in a resting target muscle in 5 out of 10 trials using single pulse TMS to the contralateral primary motor cortex (Fig.2). Other measures of cortical excitability collected in this study include paired pulse curves. These measures will be collected at baseline in the all sample, and after the end of the treatment trial. For the paired pulse curve (which is used to generate measures of ICI and ICF), suprathreshold single magnetic pulses (or “test pulse”) applied to the motor cortex are preceded at varying intervals (1-12 ms) by weaker subthreshold single magnetic pulses. The degree to which the motor response to the test pulse is inhibited or facilitated by the preceding pulse yields an index of ICI and ICF, respectively (Fig. 3).



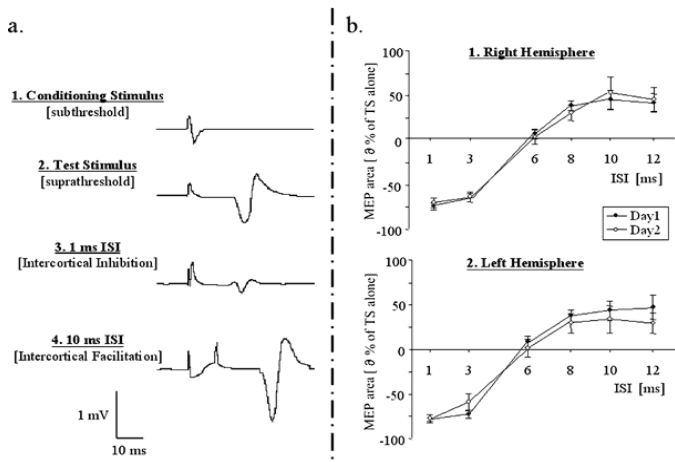


Fig.3

MRS: The *in vivo* human brain GABA- and Glx-edited spectra will be recorded on a 3.0 T GE “EXCITE” MR system at NYSPI, using the J-edited spin echo difference technique with an 8-channel phased-array coil supplied with the instrument. The spectral data will be obtained from a single 2.5 x 2.5 x 3.0 cm voxel that will be localized in the anterior cingulate cortex (Fig. 4). The actual J-editing sequence to be implemented in this study will be a modified

While MT is believed to represent a measure of membrane excitability mainly related to ion channel conductivity, ICI and ICF reflect the function of GABAergic, dopaminergic and glutamatergic mechanisms of intracortical modulation. Repetitive TMS will be given with a Magstim Super Rapid TMS device (MagStim Co., U.K.) through a figure 8 coil. Stimulation parameters will be 1-Hz, 30 minute train (1800 pulses/day) at 110% of resting MT (using the lowest value of right or left hemisphere), once a day, 5 days a week, for 4 weeks. The coil will be positioned over pre-SMA by frameless stereotaxy (Brain Sight) which will allow us to co-register the TMS coil with each patient’s MRI scan. This will enable us to navigate the TMS coil to the pre-SMA with anatomical precision and to monitor on-line the stability of coil placement during each TMS session.

PRESS sequence in which a frequency-selective 180° refocusing rf pulse is interleaved with a non-selective 180° refocusing pulse, such that J-modulation of both the GABA C⁴H resonance at 3.0 ppm and the Glx C²H at 3.7 ppm is inhibited and allowed on alternate scans. Subtracting the two spectra will yield a difference spectrum containing the edited GABA C⁴H resonance at 3.0 ppm and Glx C²H peak at 3.7 ppm. Because this sequence is optimized for GABA detection and not Glx, we will correct the *in vivo* intensity of the Glx resonance by performing MRS signal intensity calibration using a phantom containing a known solution of Glx and GABA. Data processing and quantitation will consist of frequency-domain nonlinear least-squares spectral fitting of the edited spectrum to derive the areas under the GABA and Glx peaks (Fig. 4) using an IDL-based software package developed in the laboratory of Dr. Dikoma Shungu. We will also perform gray matter/white matter/CSF segmentation on a high-resolution T1-weighted MRI to assess potential group differences in these quantities within the study voxels, since neurotransmitter concentration can vary as a function of matter type, to rule out this potential confound.

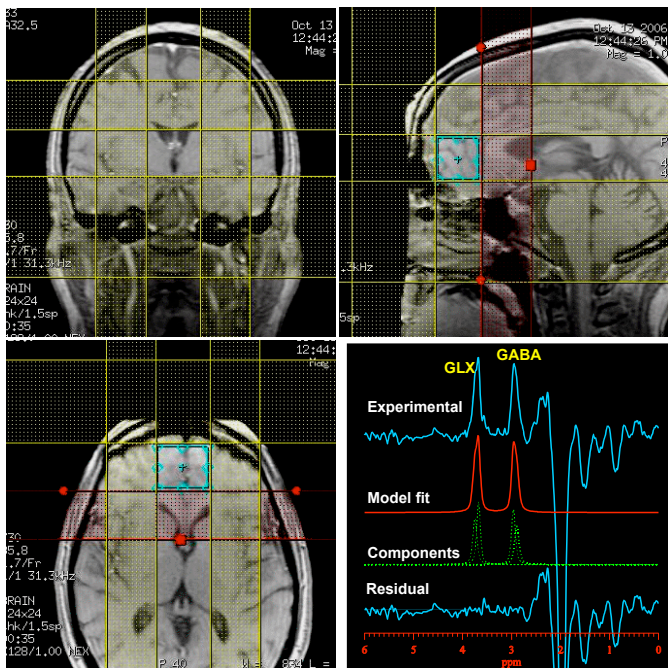


Fig. 4 Midline anterior cingulate voxel (2.5 X 2.5 X 3.0 cm) surrounded by outer volume suppression bands.

Clinical Measures: Standardized clinical measures with established validity and reliability will be used to rate clinical improvement: Y-BOCS/Clinician and Self-rating, HDRS-24, HARS-14, Beck Depression Inventory-II (BDI-II), ZUNG-Self Administered Scale, CGI, Patient Global Impression (PGI). Change in clinical symptoms will be measured by independent raters blinded to treatment group. The primary efficacy measure will be the Y-BOCS. Patients with a 25% Y-BOCS reduction at the end of treatment will be classified as responders.

Sample Size Computation: As this is the first study of the effects of TMS to SMA on MRS measures, formal power analysis is not possible. This pilot study will generate the data needed to adequately power the planned R01. From our previous data of a controlled clinical trial of TMS to the pre-SMA in 21 OCD patients, using a confidence interval of 4 and considering a confidence level of 95%, we found a significant effect of TMS with 10 patients per group. Thus we propose 10 patients in this open-label pilot.

Statistical Analysis: Statistical analyses will be performed using SPSS library, 13.0 version. ITT analysis and a worst case scenario analysis will be computed on the entire sample. Chi-Square and Student t-test will be applied to compare clinical and neurophysiological data before and after TMS. Repeated-measures analysis of variance (ANOVA), with adjustments for non-sphericity, will be applied to evaluate time-dependent effects of TMS on

psychometric scale mean scores. We will use the same statistical approach to test whether TMS affects measures of motor cortex excitability and concentrations of Glx and GABA in ACC. Student t-test will be applied to compare to baseline rating scale mean scores obtained at 3 and 6 month follow-up. Pearson's correlations will be applied to examine the association between changes in scores of depression and anxiety measures, and change in OCD scores and similarly change in clinical global impressions, and change in OCD scores. Baseline HDRS-24 will be used as covariate in the ANOVA (ANCOVA) to examine the effect of depression on OCD symptoms changes. Correlations will be also performed to test whether baseline motor cortex excitability measures and concentrations of Glx and GABA predicted response. All tests will be conducted with two-sided significance levels ($\alpha=0.05$) without corrections for multiple comparisons.

Our model predicts that, as a function of the TMS treatment, OCD patients changes in baseline MT, ICI and ICF, and also in baseline concentrations of Glx and GABA will correlate with symptoms improvement. We will test the therapeutic effect of 20 sessions of 1Hz TMS on the pre-SMA, predicting that OCD patient subgroups will respond differently to our TMS paradigm, and because we will intervene preferentially on premotor and motor circuits we predict a higher response in those patients with tic-related OCD. We will also study the effect of 20 sessions of pre-SMA 1Hz TMS on primary motor cortex excitability and concentrations of Glx and GABA in ACC predicting that the chronic administration of 1Hz TMS on the pre-SMA will produce an effect on MT(\uparrow), ICI(\uparrow), and ICF(\downarrow) and on Glx (\downarrow) and GABA (\uparrow).

Significance: Given the severity of disability from OCD, its significant prevalence (2-3%), and its relative lack of response to currently available treatments in 40-60% of cases, treatment development targeted to OCD patients has the potential of making a significant clinical impact. Previous RCTs using DLPFC TMS have produced negative results on OCD symptoms. Our open label and sham controlled studies were the first showing a significant effect of pre-SMA TMS in refractory OCD. Our study design includes significant improvements over previous studies. We will characterize the neurobiological substrates of the premotor and motor circuit functioning in OCD (Aim 1 and 2), and will intervene on those by using a focal coil placed on the individual pre-SMA by a stereotaxis method called Brain Sight which will allow us to co-register the TMS coil with each patient's MRI scan. This will enable us to navigate the TMS coil to the pre-SMA with anatomical precision and to monitor on-line the stability of coil placement during each TMS session. By stimulating the pre-SMA we aim to affect transsynaptically the contiguous ACC and M1 and test our model-driven hypotheses that the pre-SMA is a suitable target for the treatment of OCD (Aim 3).

Interdisciplinary Research Team: The research team has extensive training in TMS trial design as well as OCD clinical trials. The study will involve experts in OCD and well-known researchers in TMS and MRS. I am a psychiatrist with a PhD in Neurophysiology, and a Postdoctoral research experience in the Division of Brain Stimulation and Therapeutic Modulation at the Department of Psychiatry of Columbia University. I am currently an Associate Research Scientist at the Department of Psychiatry of Columbia University. I have received standardized training in TMS delivery in the context of other controlled trials, and established inter-rater reliability in motor threshold determination. My collaborators are Dr. Sarah H. Lisanby, Director of the Division of Brain Stimulation and Therapeutic Modulation of Columbia University, Dr. Helen B. Simpson, Director of the Anxiety Disorders Clinic and the Obsessive Compulsive Program at Columbia, and Dr. Kegeles, Associate Professor of Clinical Psychiatry and Radiology at Columbia. Dr. Benjamin D. Greenberg, Associate Professor of Psychiatry and Human Behavior at Brown University, and Dr. Leckman will serve as consultants considering their expertise in the pathophysiology and treatment of OCD.

FUTURE PLANS. This is the first TMS study to test the theory that restoring inhibitory control in pre-SMA over motor-limbic circuits will affect the neurophysiology and neurochemistry implicated in the disorder. The results of this study on the impact of TMS on brain excitability measures, biochemical metabolites, and clinical symptoms of OCD patients will contribute to our understanding of the neural circuits underlying OCD, and will form the basis of our planned R01 (deadline June 5th, 2010) to examine the neurophysiology and neurochemical effects of 1 Hz rTMS to the pre-SMA in the treatment of OCD. That planned study will be a randomized controlled trial with physiology and MRS measures pre/post the rTMS therapeutic intervention. A matched control group will also be included in the planned R01, but was beyond the scope of this pilot grant mechanism.

Drs. Lisanby, Simpson and Kegeles at Columbia University together with Drs. Greenberg at Brown University and Leckman at Yale University have already expressed their interest in the involvement of their research groups and facilities in the next multicenter clinical trial of TMS for the treatment of OCD. I am already actively collaborating with Dr. Leckman in a bicenter project with TMS for individuals with severe Tourette's Syndrome (NIH Grant 1R21MH082323-01).

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