Improving Neurocognitive Deficits and Function in Schizophrenia With Transcranial Magnetic Stimulation

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Background and Significance

General Background. Schizophrenia confers significant disability and morbidity to the affected individual and substantial financial burden to society [1]. While schizophrenia has a significant impact on the overall Veteran population, its impact is particularly acute for Veterans of recent conflicts. Among Veterans of wars in the Middle East treated within VA health care facilities within a recent 4-year period, the prevalence of schizophrenia has been estimated to be 2% [2], a rate considerably higher than that found in non-Veteran populations in the U.S. and worldwide [3]. The significant impact of schizophrenia on Veterans' welfare is perhaps best illustrated by a recent study that identified schizophrenia, along with major depression, as conferring significant risk for homelessness [4]. It is now recognized that cognitive deficits are a major source of disability in schizophrenia [5]. Cognitive deficits are enduring, essentially treatment refractory, and largely responsible for the difficulty that the vast majority of individuals with this condition experience in maintaining meaningful employment or living independently. Psychosis, in contrast, although impairing in its own right, often responds to treatment and has been shown to have less impact on long-term functionality [6]. These features of cognitive deficits suggest that developing new and effective treatments for cognitive deficits will have significant impact on the health and well being of Veterans.

Repetitive transcranial magnetic stimulation (rTMS) May be Beneficial for Cognitive Deficits. rTMS is a non-invasive procedure, in which the administration of a transient magnetic field induces electrical currents in specific, targeted brain regions. rTMS is FDA approved for the treatment of depression and is being investigated in the treatment of a wide variety of neuropsychiatric conditions, including PTSD, OCD, bipolar disorder and Alzheimer's Disease. For schizophrenia, rTMS represents one of the most promising treatments for cognitive deficits. Not only is there evidence that rTMS can improve cognition among non-patient samples, as demonstrated by a recent meta-analysis [7]; several studies have also reported improvements in cognition in schizophrenia following rTMS to the prefrontal cortex [8]. This includes a recent randomized control study showing fairly strong improvement in working memory (WM) performance following bilateral dorsolateral prefrontal cortex (DLPFC) rTMS (Cohen's d = .92 when comparing rTMS treated vs. sham groups) [9].

Proposed Research will Address Gaps in the Literature. The application of rTMS for cognitive deficits in schizophrenia is in its infancy and we currently do not have any information on the effectiveness of rTMS for U.S. Veterans with schizophrenia. This population possesses unique characteristics and challenges for the application of new treatments such as rTMS. Therefore, the primary objective of this study is to obtain pilot data supporting the efficacy of rTMS to remediate cognitive deficits in schizophrenia among Veterans. This data will be necessary to implement future effectiveness trials with larger samples sizes that will be needed to establish rTMS as a viable treatment modality for Veterans.

Impairments in Gamma Oscillations Hypothesized to Underlie Cognitive Deficits in Schizophrenia. A secondary goal of this study is to advance our understanding of the neural mechanism of cognitive deficits. Toward this goal, we will test the gamma oscillation hypothesis of cognitive deficits in schizophrenia. Gamma oscillations are high frequency (30-80 Hz) oscillations resulting from the synchronization of activity among neuronal populations during cognition and information processing [14, 15]. While the precise mechanisms for cognitive deficits in schizophrenia are likely complex, involving multiple systems and processes [10], several lines of evidence converge on the centrality of impaired gamma oscillations in this condition [11-13]. This evidence includes findings pointing to a reduction in GABAergic signaling in schizophrenia. GABA is the major inhibitory neurotransmitter in the brain and GABA signaling is thought to be critical for the synchronization of firing among populations of pyramidal neurons. One of the most important physiological consequences of deficits in GABA signaling and synchronization of neuronal activity in schizophrenia is the inability to generate oscillations in the gamma range during cognition [11]. Our group and others have reported consistent evidence that gamma oscillations are disturbed in schizophrenia [16-20] during a range of PFC-dependent higher-order cognitive processes, including WM. We will test our hypothesis by determining whether rTMS induces changes in the level

of cognition-evoked gamma oscillations measured by electroencephalography (EEG), and whether these changes are associated with improvements in cognitive performance.

Gamma Oscillation as a Potential Marker of rTMS Effects on the DLPFC. A better understanding of neural mechanisms holds the potential to yield clinically useful biomarkers predictive of rTMS treatment response. The availability of predictors would be useful because psychiatric treatments typically are ineffective for a substantial proportion of subjects and predictors would promote the judicious use of treatments so that only those individuals most likely to benefit are exposed to the risks and costs of treatment.. The emerging literature on rTMS suggests that this treatment modality also suffer from this limitation. In the study by Barr et al., a substantial proportion of subjects did not benefit from TMS. In fact, a close examination of their data indicates that ~31.5% of subjects experienced lower performance post treatment compared to pre treatment. Although rTMS is generally considered safe, it, nonetheless, is a procedure that alters function of the targeted brain tissue. Thus, an additional goal of this proposal is to obtain preliminary support for pretreatment (baseline) gamma activity as a predictor of rTMS remediation of cognitive deficits in schizophrenia. We will evaluate the potential utility of gamma oscillations as a response predictor by testing whether baseline levels of gamma is associated post-treatment improvements in cognitive performance.

Innovation. The proposal represents an innovative approach to new treatment development for cognitive deficits associated with schizophrenia. We are not aware of any studies that have applied rTMS to Veterans for this purpose. The use of EEG frequency analysis to gauge the neurophysiologic effects of rTMS represents a novel combination of sophisticated methods. This combination also represents a mechanism-based approach to treatment development. Moreover, this approach promises to yield early indications for clinically relevant predictive information. We are not aware any studies that have examined potential predictors of rTMS efficacy to remediate cognitive deficits in schizophrenia. With the successful completion of this project, there is the potential translate our findings towards personalized treatment for Veterans suffering from cognitive deficits in schizophrenia.

Preliminary Studies

Evidence of the ability to study Veterans with schizophrenia. The PI of the grant has applied his extensive experience in conducting schizophrenia studies to establish the necessary clinical research infrastructure to enroll research subjects with this condition at the VA Palo Alto Health Care System. Within a recent six-month period, his research group has enrolled 15 subjects with schizophrenia for a pilot cognitive neuroscience at the VAPAHCS, which translates into a recruitment rate of 30 subjects/year.

Experience conducting studies with rTMS enhancing cognitive performance. The PI and a Co-Investigator (MM) have recently completed a study investigating the effects of rTMS on cognition. Although the primary goals of this study differ from this proposal, it nonetheless demonstrates the investigators' experience in administering rTMS to improve cognition, and to safely and effectively complete rTMS studies. A total of 27 subjects completed this prior experiment, which experienced no adverse outcomes and no subjects dropping out. Figure 1 displays the results of one arm of this study and shows rTMS was associated with speeding of responses with preserved accuracy, during a cognitive control task. A manuscript summarizing these results is currently undergoing peer-review. The growing experience of the PI with rTMS will be further supported by Dr. Yesavage and Dr. George, who each have extensive track records in using rTMS with diverse neuropsychiatric populations.

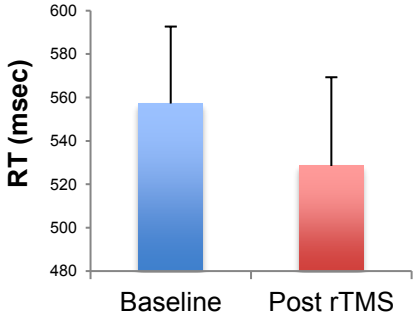

Figure 1. Group mean performance on a working memory task (RT – reaction time) in 14 healthy subjects in response to rTMS to right DLPFC, vs no-stim; effect of rTMS on RT $p < 0.05$ (paired t test).

Measuring cognition associated gamma oscillations. The investigators of this study have extensive experience conducting the sophisticated analytic methods necessary to quantify cognition associated gamma oscillations. To illustrate this point, we present the following two sets of preliminary data. First, the PI and one of the Co-Is of this grant, MM, were among the first investigators to report cognition-associated deficits in gamma oscillations in schizophrenia, Fig. 2 [16].

Second, we conducted a pilot study to demonstrate our ability to measure gamma oscillations during the execution of the proposed WM task. Individuals with schizophrenia (n=5) and demographically matched healthy control cohort (n=5) completed the WM task (Fig. 4) while undergoing EEG recording. Figure 3 shows the EEG time-frequency spectrograms within the gamma range (30-80 Hz) using the proposed processing and analytic procedures. Although we will not be studying control subjects in this proposal, the results from control subjects from the pilot study are shown to illustrate the elicitation of gamma oscillations by the proposed WM task, particularly during the delay period. In contrast, there is relatively little gamma activity found in the schizophrenia sample. This deficit is further illustrated by the contrast between groups. Patients responsive to rTMS are predicted to show increased gamma activity, resembling the control subjects' results.

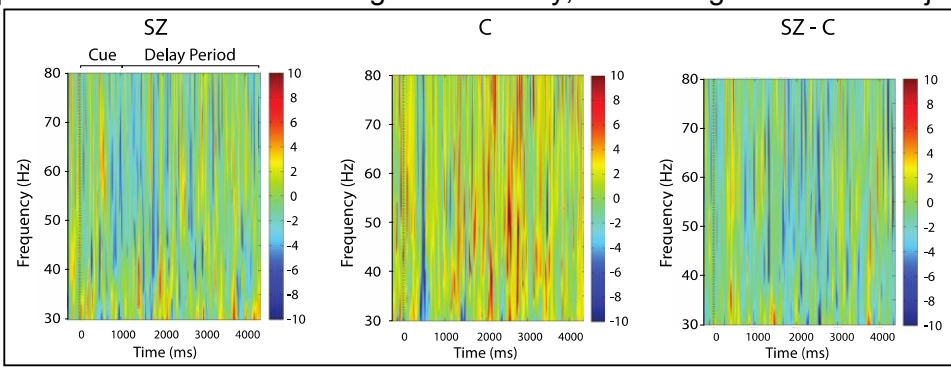

Figure 3. Spectrograms of gamma power deficits in schizophrenia during cue and delay periods of the proposed WM task. The magnitude of gamma power (expressed as T-values of the between group difference) is plotted across time for the cue delay interval for the WM task (see Methods section for details). Plots are of the average of frontal electrodes. Left panel: schizophrenia group (n=5); middle panel: healthy control group (n=5); right panel: schizophrenia group minus control group. Time zero represents the cue onset.

Research Design and Methods

Overview of General Design

We will utilize a randomized, double-blind, parallel-groups design. After clinical assessment to confirm diagnosis of schizophrenia (SZ) or schizoaffective disorder (SAD), subjects will be randomized (by computer algorithm) to either the active or sham arms. During the pre-treatment phase, subjects will be tested on the WM task while undergoing EEG to determine baseline cognitive performance and gamma levels. They will then receive rTMS or sham in the 4-week treatment phase, at the end of which subjects will be tested again on the WM task with EEG.

Subjects

Table 1. Experimental Design

	Phase			
Clinical Assessment	Baseline	Randomization	Treatment	Post-treatment
	Week 1	End of Week 1	Wk 2 → Wk 6	Wk 7
Telephone Screen	WM Task		rTMS	WM Task

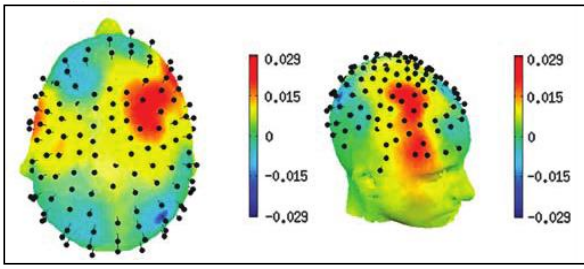

Figure 2. Scalp topography of control-related gamma oscillation power deficits in schizophrenia group compared to a healthy comparison group during the delay period of cognitive control task. Right frontal EEG leads show the most prominent deficits in schizophrenia. Left and right panels show superior and right lateral views respectively. From Minzenberg et al. [17].

Office Evaluations (SCID)	EEG Functional Status	[rTMS, Sham]	Sham	EEG Functional Status

A total of 24 subjects (12 rTMS and 12 sham) with SZ or SAD between the ages of 18 and 55 will be studied. Veterans will be recruited from a variety of sources including VAPHCS mental health clinics. We will consult with our system's Office of Data Analytics to identify potential subjects. We have already identified 366 veterans within the VAPAHCS population meeting the inclusion/exclusion criteria. We will work with this office to identify these veterans' VA clinicians who will assist in recruitment efforts. The study will be open to both men and women, regardless of race and ethnic origin. Details of demographics of the local VA population can be found in pg. 1 of the Human Subjects section.

Table 2. Inclusion and Exclusion Criteria

Exclusion Criteria	Inclusion Criteria
1) Pregnant or lactating female	1) Age 18-55 years
2) History of prior adverse reaction to TMS	2) SCID confirmed diagnosis of SZ or SAD
3) On medications known to significantly lower seizure threshold, e.g. clozapine, chlorpromazine, buproprion, clomipramine [21]	3) Stable medication regimen (no change in dose or agents within the 4 weeks prior to study entry and throughout the duration of the study)
4) History of seizures or conditions known to substantially increase risk for seizures	4) Stable social environment and housing to enable regular attendance at clinic visits
7) Implants or medical devices incompatible with TMS	5) Ability to undergo cognitive testing, EEG scans and rTMS
8) Acute or unstable chronic illness that would affect participation or compliance with study procedures, e.g. unstable angina	6) IQ > 80 (WASI full scale score)
9) Substance abuse/dependence (not including caffeine or nicotine) with in one-month period prior to study entry or during study participation	7) In general good medical health
10) Unstable psychiatric symptoms that precludes consistent participation in the study, e.g. active current suicidal intent or plan; severe psychosis	

Initial Telephone Interview. Respondents will be given a brief description of study procedures and research goals. If interested, subjects will be interviewed by telephone regarding their current symptoms, psychiatric and medical histories to determine if we should proceed to an in-person clinical assessment.

In-person assessment. Inclusion and exclusion criteria, outlined in Table 2, will be reviewed in person. For those meeting these criteria, a doctoral level clinician trained to administer the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) will conduct interviews to confirm diagnosis of schizophrenia or schizoaffective disorder. Subjects with history of other Axis I conditions will not be excluded. However, other Axis I conditions have to be either in remission or symptomatic control within at least a 3 month period preceding study entry. Symptoms will be quantified with the Brief Psychiatric Rating Scale (BPRS) [22], Scales for the Assessment of Negative Symptoms (SANS) [23] and Scales for the Assessment of Positive Symptoms (SAPS) [24]. Sub-scores from the BPRS, SANS, and SAPS will be used to derive an index of disorganization [25]. These symptoms will allow for exploratory analyses to determine whether rTMS improves symptoms other than cognitive deficits.

Discussion of Inclusion/Exclusion Issues. Most antipsychotics and antidepressants are thought to lower seizure threshold [21] and this may prompt questions on the safety of administering rTMS to individuals taking these medications. The best available evidence suggests that these agents likely do not significantly increase the risk of rTMS induced seizures. A review of the effects of various psychoactive agents, including antidepressants and antipsychotics [26], revealed that these agents in general do not affect motor threshold, which can be taken as a proxy measure for an agent's effect on cortical excitability, and hence a mediator of seizure potential. A recent review of TMS administered to individuals with schizophrenia in the context of on going antipsychotic treatment concluded that TMS is safe to administer in this population [27]. However, due to the particularly higher seizure risks associated with a few psychotropic agents [21], we will exclude subjects taking these agents. A recent review of TMS for the treatment of PTSD concluded that this treatment is well tolerated [28], suggesting that

PTSD or history of psychological trauma does not likely represent increased risk for adverse events. Therefore, history of trauma will not be an exclusionary factor.

Cognitive Task: We will administer a visual delayed response WM paradigm as a measure of cognitive function (see Fig. 4). We and others have previously published studies using similar WM paradigms [29] that have revealed robust performance deficits in schizophrenia compared to healthy control subjects with p values ranging between .001-.002 and effect sizes ~ 1.1. This task will be administered at baseline and post treatment to quantify changes in cognition resulting from rTMS. Subjects will be presented with cue stimuli, and after a delay, a probe stimulus will be presented. At this point the subject is to determine if the probe matches one of the cue images. Match probability will be 50%. Trial duration will be 6 sec, with a variable inter-trial interval (1000–2000 ms). Grey scale fractal images were selected for the task because these stimuli are affectively neutral and less prone to verbal encoding compared to most other types of visual stimuli. This feature will discourage variable or shifting encoding strategies across individuals, groups and testing sessions, which, if present, could significantly diminish our ability to detect true treatment effects. There will be a control condition in addition to the WM condition. The trial structure and stimuli of the control trials will be identical to those of the WM trials but subjects will be instructed to passively view the stimuli and register a response with a button press when the probe image appears. Control trials will facilitate more accurate assessment of WM associated gamma oscillations by allowing the investigators to subtract out non-WM associated EEG signals. This will also minimize inter-subject differences that may confound the detection of true experimental effects. There will be 40 trials in each condition and trials will be blocked by condition, with 10 trials/block and a brief rest period between blocks. The condition for the upcoming block will be indicated by text and the condition block order will be pseudorandomized.

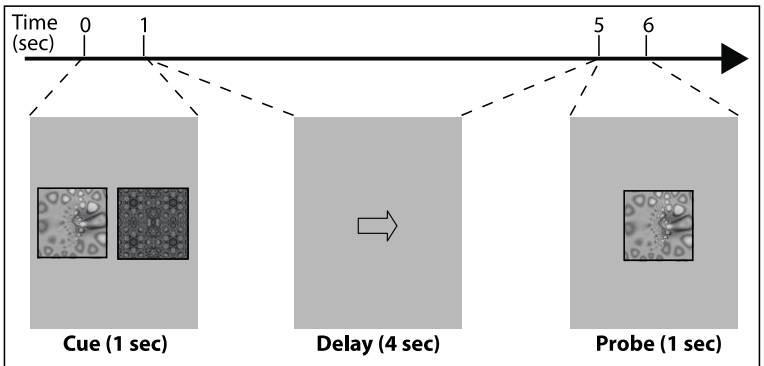

Figure 4. Working Memory Paradigm.

Assessment of Functional Status: To assess the effect of rTMS on real world functioning, we will utilize the Global Functioning: Role Scale (GF). This scale is a well-validated measure of occupational/role functioning in individuals with schizophrenia and related conditions [30, 31]. It is a brief easy to apply 6-item scale that avoids confounding functioning with psychiatric symptoms, a problem found in other commonly used scales such as the Global Assessment of Function. We recently assessed the reliability of this scale in our group. Two raters independently applied this scale on 10 subjects with schizophrenia and these ratings yielded an intraclass correlation = 0.88.

Electroencephalography during Cognitive Task Performance: All EEG gamma procedures have been employed in our published papers [16, 32, 33]. EEG data will be acquired in a shielded room using a Neuroscan 64-electrode Quik-Cap and Neuroscan SynAmps2 hardware, with 1000 Hz sampling rate and 100 Hz low-pass hardware filter, using 32-bit encoding software, eliminating the need for high-pass recording filters, and electrode impedances < 5 kΩ. All channels will be referenced on-line to Cz. Malfunctioning electrodes are excluded and data imported into EEGLab, re-referenced against the average reference, downsampled to 250 Hz, and high-pass filtered at 0.5 Hz. Epochs are extracted from continuous EEG data on each task, from -500 to +3000 ms relative to stimulus onset, and baseline-corrected with pre-stimulus interval (-500 to 0 ms). Trials with incorrect responses are removed. Individual electrodes are excluded if voltage within that trial is > 5 standard deviations from the mean of all electrodes. Independent Components Analysis (ICA) follows ([34] using the “logistic infomax” ICA algorithm [35] with “extended” option of [36]); 75 principal components accounting for the most variance in the signal are derived. Components among the top 15 are identified for rejection via visual inspection of equipotential scalp topography maps, component waveforms, and component time-frequency distributions, and comparison with the data in [37] and [38]. Time-frequency transformation of the data is performed [39] by convolving the epoched EEG with a complex Morlet wavelet function on individual trial segments to identify time-frequency components between 30-80 Hz. Each 1 Hz sub-band is defined by a logarithmically-increasing central frequency and range subject to a Gaussian kernel with constant c = 6. Average gamma power during the baseline is subtracted from task-related gamma power during the trial. Time-frequency

spectrograms are established by pooling oscillatory power across electrodes grouped by topography. Statistical thresholds are empirically-derived via a permutation method [40], to preserve frequency and time-specificity of task and treatment effects and to support statistical inferences made directly upon visual inspection of spectrograms [33, 41].

rTMS Treatment: The rTMS treatment will closely follow that of the Barr et al. study [9], which documented significant improvement in WM performance with rTMS applied to the DLPFC. All rTMS treatments will be administered at the VA Palo Alto Health Care System (VAPAHCS), where several groups are conducting rTMS studies for other neuropsychiatric conditions, including a VA Co-op study on depression led by Dr. Yesavage, one of the collaborators on this study. rTMS will be administered on a MagVenture MagPro R30 unit. Subjects with schizophrenia will receive 20 treatments of rTMS occurring once a day, 5 days a week for 4 weeks, to DLPFC (alternating sessions between left and right hemispheres) at 20 Hz (non-patterned), at 90% resting motor threshold for 25 trains, 30 pulses/train, inter-train interval of 30 sec (750 pulses/hemisphere, a total of 1500 pulses/session/day) in accordance with published safety guidelines [42]. Total duration of daily TMS sessions will be ~50 min. The resting motor threshold will be defined as the lowest intensity that produces a motor evoked potential (measured by EMG of non-dominant abductor pollicis brevis) of at least 50 mV in 50% of the trials. Trained physicians or RNs will administer rTMS blinded to treatment condition, to which subjects will be randomized by software contained in the TMS system. rTMS stimulation coils have a built-in position sensor that ensures that the correct (active or sham) side of the coil faces towards the patient's head. If the coil position is wrong, the operator will get a "Flip Coil" prompt, while maintaining the blind. Blinding will be further facilitated by the delivery of white noise during stimulation to mask the characteristic sounds associated with rTMS, as well as low voltage electrical stimulation of the scalp designed to mimic skin surface stimulation that sometimes occurs with active rTMS administration.

Statistical Analysis

Hypothesis Testing, Aim 1 - Subjects receiving rTMS will show improvements in a) WM performance, and b) occupational/role functioning compared to subjects receiving sham treatment: Change scores (post-TMS vs. pre-TMS) for WM performance accuracy (ΔWM Acc) and Global Functioning (ΔGF) will serve as dependent measures for testing the hypothesis that rTMS improves cognition and functioning, respectively. The hypothesis will be supported if we find greater ΔWM or ΔGF in the active compared to the sham rTMS treated groups. We will use independent samples t-tests and two-sided tests for significance testing, with an alpha level of 0.05. However, given the limited scope of the SPiRE award, our primary goal is not on finding statistically significant differences but rather on determining the directionality of changes and the effect sizes of treatment effects. These data will be critical for determining if there is preliminary evidence that could support proposals for future larger scale studies.

Hypothesis Testing, Aim 2 - Subjects receiving active treatment compared to those receiving sham treatment will show a) increased cognition associated gamma oscillation power, and b) an associated improvement in task performance: Hypothesis 2 will be supported if we find significantly greater Δgamma in the active rTMS compared to the sham treated group. In addition, in the active rTMS treated group, we will conduct Pearson's bivariate correlation between Δgamma and ΔWM. A positive correlation between these variables will support the hypothesis that rTMS improves cognition by increasing gamma oscillations. We will explore the possibility that pre-treatment gamma predicts rTMS responsiveness. We will evaluate this possibility by conducting a median split analysis in which subjects will be binned by their baseline gamma levels. We predict that those in the lower half of the distribution will show higher Δgamma and ΔWM.

Intent-to-treat: We will conduct a modified ITT analysis for hypothesis testing. We will use a modified ITT, which includes only subjects with outcome data, e.g. cognitive performance and EEG at the end of treatment [43], since good proxy measures cannot be imputed. To minimize missing data, we will acquire cognitive performance and EEG within one week of their last TMS session, including those intending to drop out. We will supplement this analysis with a per protocol analysis in which only subjects who completed all TMS treatments will be compared. This is done to determine, in a proof of concept manner, if TMS has the capacity to improve cognition in schizophrenia. We will include a careful examination of whether bias has been introduced due to dropout by determining if there is greater dropout in the treatment group and if significant differences exist in

major demographic and clinical variables of individuals who have dropped out compared to those who have not. We will correct for any significant differences using covariates in our statistical models.