Full Title: Testing TMS Enhancement of Visual Plasticity in Schizophrenia

Excerpt from IRB Protocol 7/31/2017, modification 10/17/2017

Lay Summary

Learning and memory impairments are commonly observed in schizophrenia spectrum disorders. Alterations in "long-term potentiation" (LTP), a basic mechanism underlying learning and memory, may explain this impairment. This project will assess fMRI visual plasticity, thought to reflect LTP, in participants with and without schizophrenia spectrum disorders. Previous studies have shown that visual plasticity is impaired in schizophrenia. The major goal is to determine if Transcranial magnetic stimulation (TMS) enhances visual plasticity in schizophrenia. Transcranial magnetic stimulation (TMS) provides a non-invasive means for altering brain electrical neural activity. TMS has been approved by FDA for treatment of depression. Other applications have not been approved but it has been used in a wide range of clinical research especially in neurology and psychiatry. TMS sessions will be conducted before two MRI scans (sham/placebo and real TMS) with two weeks in-between to assess whether TMS stimulation to the visual cortex will enhance visual plasticity in patients with schizophrenia-spectrum disorders. This project may provide a better understanding of the underlying neurobiological mechanisms responsible for learning and memory deficits in schizophrenia.

Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

To test the hypothesis that TMS simulations to the occipital cortex will modulate capacity for visual plasticity in patients with schizophrenia spectrum disorders. The TMS location of the occipital cortex site will be individually localized.

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.: We will implement a between-subject study design such that order of sham and active rTMS will be allocated to subjects randomly.

Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

There are no studies that have directly investigated plasticity mechanisms with TMS in conjunction with multimodal neuroimaging to determine if LTP-like plasticity is impaired in schizophrenia, or if plasticity can be modulated with TMS. This project serves to extend a project carried out by our group in which multimodal neuroimaging methods such as functional MRI (fMRI), arterial spin labeling (ASL), and proton magnetic resonance spectroscopy (1H-MRS), learning and memory tasks, and a novel visual plasticity paradigm drawn from basic science known to induce LTP-like changes were utilized to conduct exploratory research. Findings indicated that this novel visual plasticity paradigm was able to induce LTP changes in control volunteers and that glutamatergic metabolites predict visual plasticity in humans (Wijtenburg et al., under review). Previous human studies that used this visual plasticity paradigm successfully demonstrated robust visual plasticity in healthy subjects as reflected by an increase in fMRI BOLD activation, and impaired visual plasticity in schizophrenia as indicated by reduction in visual evoked potentials, but this would be the first study to incorporate a TMS component in an effort to enhance visual plasticity in schizophrenia.

Supporting Literature

Learning deficits are linked to poorer functional outcomes and quality of life in schizophrenia. These deficits may reflect alterations in the basic cellular mechanism underlying learning, long-term potentiation (LTP). Our previous work indirectly supports this hypothesis. First, we found robust impairments on translational hippocampal dependent 8 radial arm task (Spieker et al., 2013) and hippocampal-relational learning task (Spieker et al.,2014; Rowland et al., 2010) in schizophrenia. We also showed altered fMRI BOLD response in the hippocampus, the brain region important for successful declarative learning and memory formation in schizophrenia (Rowland et al., 2010). Last, our pilot data in schizophrenia suggests altered glutamate (Glu), the neurotransmitter fundamental to LTP.

LTP is typically studied in rodents. Briefly, LTP is induced through high-frequency electrical stimulation. LTP in the hippocampus is the most studied region, but LTP-like changes occur in other regions such as the visual cortex. Using a modified visual plasticity paradigm known to induce LTP-changes in rodents, several human studies successfully demonstrated robust visual plasticity in healthy subjects as reflected by an increase in fMRI BOLD activation or visual evoked potentials (Clapp et al., 2005; Clapp et al., 2012). Relevant this project, one study demonstrated impaired visual plasticity in schizophrenia as indicated by reduction in visual evoked potentials (Cavus et al., 2012). However, there are no multimodal imaging studies with a TMS component to assess visual plasticity in schizophrenia. This study will extend the previous EEG study and multimodal neuroimaging work conducted in our lab. It will determine whether TMS will enhance visual plasticity in schizophrenia-spectrum disorders.

In TMS literature, high-frequency rTMS (900 stimulations; 15 mins in total) has been shown to facilitate an effect in the occipital cortex for at least 15 minutes (returned to baseline about 15 minutes later) (Fierro et al., 2005). An alternative approach is theta-burst stimulation (TBS), in which a three-pulse 50-Hz burst is applied at 5 Hz. TBS over motor cortex can induce similar or even longer lasting effects than conventional rTMS with less number of stimulations, less intensity and better tolerability (Huang et al., 2005). TBS over frontal cortex for depression treatment has been established as equally efficacious and safe compared to high frequency rTMS (Li et al., 2014). However, the effects of TBS over occipital are not well-demonstrated yet. We will apply conventional high-frequency TMS or TBS over occipital cortex. For both TMS protocols, no more than 3000 pulses will be delivered in each session.

Study Procedures

Informed Consent Process: A member of the research staff will describe in full the protocol and risks/benefits of the study to the potential participant. The potential participant will be informed that, if enrolled in the study, s/he will have the right to withdraw from the study at any time for any reason. The consent form will be reviewed in detail, and the subject will have an opportunity to read it and ask any questions he/she might have concerning the study procedures. All subjects will receive a copy of the signed consent form for their records. The consent process will be conducted in a private office with the door closed in order to protect the subject's privacy.

In addition, we use the Evaluation to Sign Consent form with prospective participants with schizophrenia to ensure their understanding of the study. A member of the research staff

will meet as many times as needed with potential participants to discuss the research study with them. Further, participants are required to give adequate responses on the Evaluation to Sign Consent form prior to study entry to ensure that they understand the risks of the study and how to respond if they experience any distress or wish to withdrawal from the study at any time.

After each eligible volunteer is consented, the volunteer will participate in clinical and cognitive assessments, MRI training (if needed), and two TMS/MRI sessions conducted 2 weeks apart. This study will take from 9 to 11 hours to complete over the course of three visits to MPRC.

Visit 1: Consent procedures and clinical / cognitive assessments.
All participants will complete informed consent procedures and will be screened for MRI safety compatibility. All participants will be interviewed using the Levels of Functioning Scale (LOFS) and will complete the SCID-5-RV interview if one from the past year is not already on file from engagement in another study with our program. Patients will be evaluated for psychopathology with the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), and the Brief Negative Symptom Scale (BNSS). All subjects will complete: (1) learning/memory and processing speed tasks drawn from the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; (2) computerized tests of learning and memory ; (3) the Levels of Functioning Scale (LOFS) to assess overall functioning. This visit will vary in length based on diagnostic group and individual variance on factors such as openness during interviews, speed of processing during assessments, whether the SCID interview will be needed, etc. Visit length is estimated to be between 3-5 hours in total.

Visit 2: TMS and MRI.
TMS. Two separate TMS sessions will be conducted (one sham and one active, randomly assigned) that will take up to 1.5 hours each. These sessions will precede MRI scans, which will take place on the same visit. TMS pulses are applied to the brain guided by the Brainsight (Rogue Research, Montreal, Canada) brain navigation system. The TMS coil will be operated by a trained operator during the whole session to allow for optimal fixation and correction whenever slippage threatened to occur. Sham rTMS will use a sham coil or will use a real coil tilted away from the scalp at an angle of 90° for sham treatment. Sham mimics the sound of the TMS without actually stimulating the brain with TMS.

MRI Training. Participants may be asked to do training on the fMRI tasks in a mock scan session. This training session will give participants a chance to become familiar with the MRI process if they have never had an MRI for research purposes. Participants will follow the same procedures as with the "real" MRI, in a mock scan environment. If requested, this session would take 5-30 minutes depending on comfort level of the individual participant.

MRI. The MRI will measure structure, function, and chemistry of the brain. The MRI session will take about 1.5 hours. Prior to the MRI, participants will be asked to complete a standard questionnaire. The purpose of this questionnaire is to ensure that it is safe for them to enter

the MRI. For the MRI, participants will be asked to lie still on a bed in the MRI, which is a big donut-shaped magnet. During the structural MRI, MRS, and ASL, participants simply lie still. During the functional magnetic resonance imaging (fMRI), participants will be asked to look at a fixation cross on a projection screen. Participants will stare at a flashing checkerboard pattern, and a camera will be mounted such that eye movement/closure can be monitored. Participants will be trained prior to the MRI. The MRI will take place at the UM Center for Brain Imaging Research (CBIR) at the Maryland Psychiatric Research Center (MPRC).

*As noted in visit 1 breakdown, we may use some assessments done in other studies if repeating them is not necessary. Similarly, data collected here may be combined with data from other studies when appropriate. Data collected from this study may be combined with other related studies during data analysis. Modifications in task parameters and equipment settings, such as fMRI scanning sequences, sound level, number of presentations, target speed and so on, are unavoidable. Some subjects maybe asked to return to repeat a task due to such changes. They may also be asked to repeat various tasks if data from a previous session was incomplete or became corrupted in some way.

Sample size and data analysis:

The power analysis is based previous published research using this visual plasticity paradigm in healthy participants and one published EEG study using this paradigm in schizophrenia since there are no multimodal imaging studies of visual plasticity in SZ. Estimating a magnitude of effect, Cohen's f2= 0.8 (based on between group differences), a sample size of 35-40 per group provides power greater than 90%. Even if we conservatively estimate approximately 10% of data loss due to subject attrition (5%) and poor quality data due to movement (5%), we can expect complete data on approximately 35 subjects per group for the main aim. This sample size should provide sufficient power to detect an effect.

Statistical analysis will be performed using the SPSS software package. The main dependent variable is fMRI visual cortex BOLD signal, before and following the high frequency stimulation. This is the measure of visual plasticity. Between group differences will be investigated with 2 (group) X 2(time) ANOVA with repeated measure on time. The relationship between the fMRI visual cortex and MRS glutamate will be examined for each group separately with correlation analysis.

Participant Eligibility

Inclusion criteria:

1 Male or Female between the ages of 18-65

2 Ability to give informed consent (18 and above)

3 For patient participants, Evaluation to Sign Consent (ESC) score of 10 or above

Exclusion criteria

1 Any history of seizures or seizure disorder

2 Any family history of epilepsy in first-degree relatives

3 Significant alcohol or other drug use (substance dependence within 6 mos. or substance abuse within past 1 month) other than nicotine or marijuana dependence

4 Any major medical illness that may affect normal brain functioning; examples include, but are not limited to, stroke, CNS infection or tumor, or other significant neurological conditions
5 Taking > 400 mg clozapine per day
View 6 Failing TMS screening questionnaire
7 Cardiac pacemakers, implanted medical pumps, intracardiac lines, or any acute, unstable cardiac disease with intracranial implants (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal objects within or near the head, excluding the mouth, that cannot be removed safely
8 History of head injury with loss of consciousness for over 10 minutes or history of brain surgery
9 Cannot refrain from using alcohol and/or marijuana for 24 hours prior to experiments, or cigarette smoking 30 minutes prior to experiments
10 Women who are or may be pregnant (child-bearing potential but not on contraceptive and missing menstrual period, self-report, or by positive pregnancy test)

Recruitment

Healthy control subjects will be recruited from the Maryland Psychiatric Research Center (MPRC) subject pools. We provide the list of inclusion and exclusion criteria for the volunteers (see inclusion/exclusion criteria). All persons who qualify for this study are referred to the research team (PI and/or PI staff) and then contacted and asked if they would like to participate in this study.

Potential subjects with schizophrenia will be recruited through the Maryland Psychiatric Research Center clinics. Clinic staff members will be provided with the inclusion/exclusion criteria for the current study. They will identify subjects who are likely to be interested in participation and referred to the research team (PI and/or PI staff). Study coordinators may also recruit from local clinics and day programs that the Neuroimaging Research Program has recruited from in the past for other studies.

Contact information would be obtained from all qualified, interested persons for scheduling purposes.

Our participants with schizophrenia are not decisionally impaired. We use the Evaluation to Sign Consent (ESC) form to ensure their understanding of the study. A member of the research team on this protocol will meet as many times as needed with potential participants to discuss the research study with them. Further, participants are required to give adequate responses on the ESC form prior to study entry to ensure that they understand the risks of the study and how to respond if they experience any distress or wish to withdraw from the study at any time. If the patient expresses a further desire to participate, the research team member will proceed with the consent process.

Our participants with schizophrenia are not decisionally impaired. Participants are required to give adequate responses on the ESC form prior to study entry to ensure that they understand the risks of the study, and how to respond if they experience any distress or wish to withdrawal from the study at any time.

Participation in this study is voluntary. All participants are free to withdraw consent at any time. A participant's refusal to participate will not affect current or future medical

care in any way at the University of Maryland Baltimore, University of Maryland Medical System. Participants will be told of any significant new findings that develop during the study that may affect their decision to participate in the study. Subjects will be paid $15.00 per hour for the clinical and cognitive testing, interviews, and mock scan training session (if needed). They will be paid $100.00 for each MRI. These amounts are standard for this type of testing and not considered coercive.

Research Related Risks

Confidentiality:

There is a possible risk of loss of confidentiality. However, we take precautions to prevent such an event from happening. All research data are stored, in both electronic and hard copy form, with ID numbers rather than names or other personal identifiers. Research data is not recorded on any form that requires identifiers. All data with identifiers are maintained separately from research data. Hardcopies of all research forms are stored under double-locked conditions. Computer files are handled via a local area network (LAN) maintained behind a Juniper SSG-550 firewall with multiple layers of protection against unauthorized intrusion. Databases are maintained on the center's server and are additionally protected by a 5-tiered system involving restricted access at the desktop, directory, database, reporting and table levels. Permissions for data access are set by the PI.

Risks associated with clinical assessments, interviews, cognitive and neuropsychological testing:

Cognitive tests and psychological ratings are generally considered benign. The subject may become frustrated and tense when he or she encounters difficulty when performing the tests. Careful planning and observation of the subject's response to these sessions will allow the testing to be completed with a minimum of discomfort. Subjects will to take breaks when necessary to help alleviate any discomfort. We ask sensitive clinical information that can be uncomfortable to some patient participants. Some assessments and testing may be boring. Our clinical staff are trained to be sensitive to subjects' emotional response and can provide consultation. Subjects are reminded their participation is voluntary and they can always decline to participant in study activities or withdraw from the study. We provide frequent breaks and also regularly ask subjects whether they need breaks during assessment and testing.

MRI risks:

Magnetic resonance uses strong magnetic fields and weak electromagnetic fields (i.e. radio waves), which have not been associated with adverse effects in patients or laboratory animals. Subjects may experience a feeling of being isolated or confined by the scanner (i.e. claustrophobia). We minimize these discomforts by explaining the procedure in great detail and by maintaining voice contact with the subject at all times. The most likely difficulty will be that a subject is unable to hold still for the MR scan. This would degrade the quality of the image obtained, but it would not be dangerous for the subject. Subjects with a cardiac pacemaker or any piece of metal (e.g. surgical clips or plates, heart valves, cochlear implants, shrapnel fragments) in their body may not participate in this study.

MRI has never been shown to harm a fetus or a pregnant woman (American College of Radiology) but there may be unknown risks Therefore, we will exclude women who are pregnant. Women of child bearing potential will be given a urine pregnancy test to rule out pregnancy.

Risks associated with MR equipment malfunction also exist. MR Safety Officers at the imaging center monitor compliance to safety procedures. Daily quality assurance is conducted each morning to ensure the MR scanner is running properly.

TMS Risks (numbered 1-7):

1) The most serious risk side effect reported for TMS is the accidental causing of seizures, but such episodes have been very rare. We are aware of about 8 cases of TMS related seizures reported in the literature (Rossi et al 2009; Kratz et al 2011). Numerous sham-controlled trials and several meta-analyses support its efficacy in treating depression (reviewed in Loo and Mitchell, 2005; Loo et al., 2007). For example, one of the largest rTMS sham-controlled trials involved 301 pharmacotherapy refractory depressed subjects and showed positive results (O'Reardon et al., 2007). rTMS sessions (120% of motor threshold, 10 Hz, 3000 pulses per session) were conducted for 4 to 6 weeks five times per week. rTMS was well tolerated, with low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain. The incidence of rTMS-induced seizures worldwide is low and roughly comparable to the estimated incidence of spontaneous seizures with antidepressant therapy (0.1– 0.6%) (Pisani et al, 2002), with the safety advantage that seizures occur during or just after the TMS treatment session (rather than after a delay) and are therefore more easily treated. There have been no reports of any subject developing epilepsy or repeated spontaneous seizures after single pulse, double pulse, or repetitive TMS. All TMS-induced seizures to date have been transient and self-limiting, without long-term sequelae (Loo et al, 2008; Rossi et al 2009; Kratz et al 2011). In the current proposed study, the TMS parameters are within published safety guidelines. rTMS is a relatively new technique; the long-term effects of its use are unknown.

Concurrent medication has been implicated as a risk factor in some of the seizures reported with TMS. Early on, some have suggested that certain medications, e.g. tricyclic antidepressants, clozapine and other neuroleptics, should be contraindicated in those receiving TMS (Wassermann, 1998). Since then, hundreds of depressed, schizophrenic and other psychiatric patients, many on concurrent medications, have received TMS in clinical trials with no reports of serious adverse events. In two of the reported seizures cases, psychotropic medication was changed during the TMS course in the days preceding the seizure, i.e., rTMS was continued at the same absolute intensity in the presence of a possibly altered seizure threshold. We will seek to avoid this problem by establishing each subject's resting motor threshold (RMT) at the start of TMS experiments and setting the stimulus intensity relative to that RMT. To further decrease this risk, subjects in the current study are required to stay on prescribed medications and inform research staff before each TMS session of any change in medication regimen. These precautions are based on the premise that medications which alter seizure threshold should also alter the RMT. Studies with drugs such as lorazepam (Ziemann et al., 1996), haloperidol (Ziemann et al., 1997), and anticonvulsants (sulthiame [Siniatchkin et al., 2006]; carbamazepine, gabapentin, topiramate [Inghilleri et al., 2004; Turazzini et al., 2004];

levetiracetam [Reis et al., 2004]) yield partial support for this premise, with some studies showing no change in RMT, while others found the expected increases in RMT in the presence of anticonvulsant medication. The safe application of TMS in subjects given stimulants such as amphetamine or methylphenidate supports the safety of TMS in subjects using these drugs (Tegenthoff et al., 2003; Gilbert et al., 2006). Clozapine is associated with lowering seizure thresholds. The first study involved patients on clozapine used rTMS at a frequency of 1 Hz and an intensity of 80% of the motor threshold for 20 min for 10 sessions in 7 patients on clozapine (d'Alfonso et al 2002). Subsequent studies on rTMS in treatment-resistant schizophrenia patients (many of them are on clozapine) have generally reported rTMS and other TMS modalities to be safe (d'Alfonso et al 2002; Liu et al 2009; Rosa et al 2007; Daskalakis et al 2008; de Jesus et al 2011). We will involve patients on clozapine or other neuroleptics only if they have been on stable dose of clozapine and other neuroleptics for at least 1 month, and inthe case of clozapine, currently taking no more than 400mg/day. Other factors, such as sleep deprivation, alcohol or excessive caffeine intake, may lower seizure threshold. One subject received rTMS uneventfully until he had two sleepless nights, after which he experienced a seizure (Prikryl and Kucerova, 2005). Subjects in the current study will be issued guidelines for TMS treatment, advising that alcohol and caffeine intake should not be altered (and should be within reasonable limits), medications should be unchanged, and subjects should inform research staff if there is any change in the above, if they have had a sleepless night, or developed any medical illness. Acute alcohol withdrawal is associated with seizures. To minimize this risk subjects with current alcohol dependence are excluded from this study.

Seizure monitoring and management procedures:

All staff administering the TMS are certified in basic adult life support (CPR) and have training in seizure first aid, how to engage the emergency response system, including contacting the covering study physician available in the building. Only staff with the appropriate education and training will actually provide TMS or supervision to subjects.

Subjects will be monitored throughout each TMS session by trained staff who will visually monitor subjects for signs of seizures such as involuntary muscle movements or loss of consciousness. In the event of a seizure, the following procedure will serve to guide staff in order to minimize additional trauma: 1. Protect patient's head and limbs from injury. 2. Ensure an adequate airway. 3. Provide supportive care after the seizure resolves.

a. When jaws are clenched do not attempt to pry open the mouth to insert a mouth gag. At no time should anything be placed in the patient's mouth.

b. When safely able, turn the patient to the side to prevent aspiration and promote drainage of mucus and saliva. Do not force any part of the patient's body during the seizure.

c. Loosen any constrictive clothing.

d. Call for assistance from an in-house physician or by dialing 911 in order to have the patient transferred to the nearest emergency room.

e. Observe patient for initial movements/ sensations, progression of movements, change in respiratory status, skin color, incontinence, level of consciousness, ability to

communicate, level of orientation, duration of seizure activity. If after two minutes, the seizure has not resolved, the treatment option can include administering lorazepam 4 mg IM. May give an additional 4 mg if needed.

If immediate medical assessment or intervention is required, the subject will be referred to the appropriate medical facility. Unexpected or serious adverse events will be promptly reported to the IRB in accordance with IRP policy. Information on all adverse events will be cumulated and reported to the IRB with each continuing review application.

2) Scalp pain, headache, dental pain. The most frequently seen side effects with TMS therapy have been headache, dizziness, scalp pain or discomfort, and muscle twitching. Less frequently reported side effects of TMS therapy include increased auditory threshold. Transient scalp pain may occur with TMS stimulation. The TMS coil may heat up with prolonged use (Pascual-Leone et al., 1991). The coils used in this study will automatically shut off when temperature is over specific limit so this risk is very small. In sham-controlled studies that reported rates of side-effects, about 28% of subjects experienced headache and 39% experienced pain or discomfort during stimulation with active rTMS, compared with rates of 16% and 15%, respectively, after sham rTMS (Loo et al., 2007). There is one report of nausea in two subjects from rTMS over the cerebellum (Satow et al., 2002). A small number of reports described focal pain, discomfort, and other minor symptoms. While headache is common it is not serious and responds well to over the counter analgesics. In a single case report, a 57-year-old women being treated for major depressive disorder reported a pulsating, localized dental twitching in the region of the upper left jaw associated with the rTMS treatment (Ropohl et al., 2004). The pain disappeared during the intertrain interval but emerged again during the next train of stimuli. The pain was dependent on the stimulus intensity and remained despite repositioning of the coil. The cause of the pain is unclear, but may be due to stimulation of the trigeminal nerve by the rTMS magnetic field (Ropohl et al., 2004). The likelihood of this minor transient side effect is minimal, and the participant can stop the intervention if it occurs.

3. Hearing change: Rapid excitation of the stimulation coil produces clicks that have resulted in transient increase in the auditory threshold of human subjects (Wassermann, 1998; Loo et al., 2001). Permanent threshold shift has been observed in a single individual (Rossi et al 2009). Loo et al. (2001) assessed the auditory threshold before and after 30 sessions of rTMS given over 6 weeks in a depression treatment trial. No significant mean changes were detected. Guidelines require testing of auditory threshold only if subjects receive rTMS at a frequency higher than 1 Hz for four or more weeks. The amount and duration of stimulation a subject will receive from this study is less.

4. Exacerbation or emerging psychiatric symptoms. While TMS is increasingly employed to investigate its therapeutic effects for psychiatric illnesses, it is expected that it can also induce or worsen psychiatric symptoms in some patients. Mania has been induced in a small number of healthy and depressed subjects by high-frequency rTMS to the left dorsolateral prefrontal cortex. Nedjat and Folkerts (1999) reported hypomanic symptoms after a single session of rTMS in three female subjects without a prior history of mood disorder.

Stimulation parameters were comparable to those used in depression treatment studies and studies of mood changes in healthy subjects. Two subjects with unipolar depression have shown manic changes with rTMS treatment. George et al. (1995) reported mild hypomania in a patient with refractory recurrent unipolar depression. This female patient had responded well to previous shorter courses of rTMS, but became hypomanic after nine treatment sessions in the third course. The hypomanic symptoms resolved when rTMS was reduced to treatment every second day. Sakkas et al. (2003) reported on a 55-yr-old depressed male who became hypomanic for the first time after 3 weeks of twice daily rTMS to the left dorsolateral prefrontal cortex and concomitant citalopram. Over the following week, medication was stopped, but rTMS continued. His symptoms deteriorated into mania and rTMS was also stopped. Five months later, a second course of 2 weeks of twice-daily rTMS also resulted in hypomania. rTMS may also have a therapeutic effect in mania, with high-frequency application to the right prefrontal cortex (Erfuth et al., 2000; Grisaru et al., 1998).

There are several reports of mania induced by rTMS in patients with bipolar disorder (Dolberg et al., 2001; Garcia-Toro, 1999; Hausmann et al., 2004; Huang et al., 2004; Sakkas et al., 2003), even while taking mood-stabilizing medications. Cohen et al. (2004) conducted a trial of right prefrontal rTMS for post-traumatic stress disorder, during which two patients developed a manic episode after the third session. One patient was randomized to 1 Hz rTMS and one to 10 Hz. Another subject in this trial developed a 'mild rage attack, probably related to the stimulation' (Cohen et al., 2004). There is a single case report of high-frequency left prefrontal rTMS inducing transient persecutory delusions in a depressed, non-psychotic subject (Zwanzger et al., 2002). Treatment-emergent mania has been reported for low and high frequency rTMS in patients with uni- and bipolar depression (Xia et al., 2008). The overall rate (13 cases) across 53 randomized controlled studies in depression appears to be low (0.84% mania for active rTMS vs. 0.73% for sham rTMS) and even below natural switch rates in patients with bipolar disorders receiving mood stabilizers (2.3–3.45%) (Xia et al., 2008; Rossi et al 2009). Cases of rTMS induced psychotic symptoms, anxiety, agitation, suicidal ideation and insomnia have been reported (Zwanzger et al., 2002; Janicak et al., 2008; Rossi et al 2009); again whether these occur at higher rates compared to the natural course of these symptoms remain unclear (Rossi et al 2009).

In all the above cases, the psychiatric side-effects induced by rTMS were transient, resolving with the cessation of rTMS or rapidly responding to pharmacological treatment. In the current proposed study, subjects will be warned of the possible risk of developing psychiatric complications, in particular, mania or hypomania. While statistically TMS treatments have showed improvement or no effect in psychotic symptoms in schizophrenia, worsening of psychosis has been reported in some patients. For example, d'Alfonso (2002) reported that rTMS has worsened psychotic symptoms in patients on olanzapine but meanwhile all 7 patients on clozapine showed improvement on the voice rating scale. We will use far less total TMS stimulation. If worsening symptoms are identified, we can readily assess and refer patients to proper psychiatric care.

5. Other potential adverse effects. Heart rate and blood pressure: No significant changes in blood pressure and heart rate have been detected during rTMS (Foerster et al., 1997; Jahanshahi et al., 1997). A recent paper (Udupa et al., 2007) reported that rTMS treatment

''corrected'' the subclinical cardiac autonomic imbalance which was associated with depression in the trial patients.

Other possible adverse events include syncope, transient local pain, neck pain, toothache, paresthesia, transient cognitive/neuropsychologial changes, burns from scalp electrodes. Staff are trained to keep subject safe in the event of syncope following procedures similar to seizure. Participants are encouraged to report discomfort and take breaks. Visual changes: Two patients with major depression were reported to develop transient visual changes after rTMS of the left DLPFC (Marcolin, 2006). TMS could potentially have aftereffects on EEG/ERP: a safety guideline review of literature showed that most EEG/TMS studies report no after effect although in several studies such effects were noted in the absence of any behavioral effects (Rossi et al 2009).

6. Pregnancy: Safety guidelines suggest that pregnant women be routinely excluded from rTMS trials (Wassermann, 1998). Nahas et al. (1999) reported the uncomplicated inclusion of a depressed and anxious woman in her second trimester of pregnancy in a depression treatment trial. She received 14 daily treatments at 5Hz and 100% motor threshold, with marked clinical improvement. Given the limited knowledge available in this area, pregnant women are excluded from the current study. Women of child bearing potential will be given a urine pregnancy test to rule out pregnancy.

7. Equipment malfunction: As with all instruments, there is a risk of equipment malfunction. The Magstim Rapid2 Plus 1 System (TMS stimulator) is designed to comply with the requirements of the Safety Standard EN60601-1 (90) which is a family of standards whose scope covers the safety, essential performance and electromagnetic compatibility of Medical Electrical Equipment and Systems. Particular designs and requirements are made to minimize the potential risk of TMS unit malfunctions (e.g., grounding issues, coil overheating, abrupt coil disconnection etc).

To ensure grounding safety, all main power connections are made directly to separate, permanent, hospital grade wall outlets. The coil may heat up during the test. If the coil surface temperature reaches its set limit (40oC), the stimulator will automatically stop and go to the inactive mode. The TMS coil is the only parts that contacting or close to participant and it will be removed from participant immediately if there is any sign of TMS malfunction (including coil overheating). If the coil is disconnected from the TMS stimulator during the test, the TMS system will automatically go to the inactive mode and discharge internally so that no stimulation will be given. The TMS stimulator will also automatically go to inactive mode if the stimulator has not been triggered for over 10 minutes.

The TMS System and its accessories are checked for any signs of damage on a weekly basis and double-checked prior to use on a participant. They will not be used if there are any signs of external damage or if any parts are damp or wet. Other electrical devices in the lab and liquids are kept away from the TMS system to prevent potential electrical interference and water damage. The stimulator is covered by a customized cover to repel dust and moisture when not being used.

Potential Benefits and Alternatives

There will be no direct benefit from participation in this study aside from payment. We expect to learn important information about the brain function of persons with schizophrenia from this study. Generally, these study results will contribute to a better understanding of the pathophysiology of schizophrenia. These study results will contribute to a better understanding of abnormal brain activity and chemistry that is associated with learning and memory in schizophrenia. We hope that the results of this study will help facilitate the development of novel treatments (drug and behavioral) for the treatment of cognitive impairments in schizophrenia.

The level of risk associated with this study is outweighed by the potential benefits by contributing to better scientific understanding of key biological and cognitive deficits associated with schizophrenia and for development of better treatment methods. The risk can be effectively managed by carefully designed study and by closely following safety guidelines.

There are no alternatives. Participation is voluntary and the alternative is not to participate.

Withdrawal of Participants

Subjects can be withdrawn if they were found no longer meeting incl/excl criteria or non-compliant to research schedule or appointment, or cannot follow instruction to complete experiments.

The potential participant will be informed that, if enrolled in the study, s/he will have the right to withdraw from the study at any time for any reason.

Further, patients are required to give adequate responses on the Evaluation to Sign Consent form prior to study entry to ensure that they understand the risks of the study and how to respond if they experience any distress or wish to withdrawal from the study at any time.

The Principal Investigator may terminate a subject's participation in the study if there are any circumstances that change the stated risks. In that case, the subject would be compensated for time spent on the study. If a participant voluntarily leaves the study or is terminated by the PI, we will still use any data that has been collected. Once a subject is withdrawn, no further data collection will occur. If a subject withdraws from the study, we plan to use any collected data in our analyses unless the research volunteer explicitly requests that their data not to be used. Subjects will be reimbursed for the portion of the study that they have been participated in.

Privacy and Confidentiality

The consent process will be conducted in a private office with the door closed in order to protect the subject's privacy. All discussions with potential subjects during the consent process will take place in a private room behind closed doors. All individual research assessments will be conducted in a private room behind closed doors.

Data will be stored in locked file cabinets within locked rooms designated for research files. Computerized research data is de-identified will be stored on university computers with 5 levels of password protected security. Scientific reports include only aggregate data; no names or identifying information will be included.

Facilities where research procedures are conducted:

This study will take place at the Maryland Psychiatric Research Center (MPRC) in Baltimore, MD. Office space, computer facilities, and support staff will be provided by MPRC. We are dedicated to providing treatment to patients with schizophrenia and related disorders, educating professionals and consumers about schizophrenia, and conducting basic and translational research into the manifestations, causes, and treatment of schizophrenia. Components of this study will take place in closed office spaces, the TMS Lab, and at the UM Center for Brain Imaging Research (CBIR), located on-site at MPRC.

Laboratory and Research Space:
Neuroimaging Research Program and MRI center. The Neuroimaging Research Program (NRP) and UM Center for Brain Imaging Research (CBIR) are located in a new research facility that houses a research-dedicated human MRI scanner, high performance computational cluster, laboratory space, and office spaces. This center features a state-of-the-art 3-Tesla Siemens MANGETOM Prisma MRI scanner (FDA-approved). It is an interdisciplinary facility dedicated to research and features extensive MRI expertise. It is staffed with two full-time IDEAlicensed pulse-sequence programmers and staff members, including two technologists. An RF laboratory includes a network analyzer, spectrum analyzer, and oscilloscope. The scanner is configured for fMRI experiments including a LCD projector system, fiber optic response boxes, and a PC for stimulus presentation via E-prime. Other home-made software is available that controls the triggers from or to the scanners. Responses from the subjects, if needed, are captured digitally using the same computers. We also have the capability of collecting both the cardiac and respiratory information digitally during any MRI scan. Because a significant portion of the research conducted at both the MR facilities pertains to fMRI, the scanning rooms have been designed with optimum radiofrequency (RF) shielding. All electronic equipment that is brought into the scan room pass through a penetration panel which is conveniently located at the scanner console. Preventive maintenance that involves measurement of temporal stability and noise characteristics are done on a monthly basis over and beyond what is performed by the vendors of the respective machines. A 100 Kilowatt uninterruptible power supply (UPS) provides continuous conditioning of the electrical power for the scanners, shielding the gradient and radiofrequency amplifiers from any fluctuations in building power.

This facility is served by a high-performance computational cluster of 300 processors and five Tesla K20 GPU nodes powered by Rocks Cluster Distribution. The cluster is directly connected to the scanner reconstruction computer via Infiniband network for real-time data reconstruction and analysis. The facility has over 200TB of raid 5 network-based storage with an off-site, real-time back-up and Amazon-cloud based long-term storage backup. A full range of data analysis tools including FSL, AFNI, FreeSurfer, Mango, SOLAR-Eclipse, BrainVisa, LCModel, MIPAV, MRIcro, SPM, and TrackVis are available to be executed in three parallel computational environments: LONI-Pipeline, JIST and SGE. Additional MPRC-developed software including BrainVisa Morphologist (http://www.nitrc.org/projects/brainvisa_ext/) and SOLAR ECLIPSE tools for imaging genetics analyses (http://www.nitrc.org/projects/se_linux/) are available to extramural and intramural researches. Online documentation is available in the form of an Intranet “Wiki” website that provides procedural and other collaborative documentation within

the NRP group and collaborators. A secure FTP and DICOMPACS sites are available for transfer of anonymized imaging data. As part of the NRP, a TMS Lab (15' x 20') houses a Magstim Bistim2 TMS system, a Magstim super rapid2 rTMS system, and a Brainsight brain navigation system (Rogue Institute). A full-time, PhD level TMS specialist is available to support the lab. The TMS systems are integrated with a 64-channel EEG/ERP system to allow recording electrophysiological response of TMS.

Monitoring Plan

Safety monitoring will be conducted by an Independent safety monitor who has been involved in technology intervention, including TMS, and clinical trial studies of schizophrenia. The independent safety officer will review adverse events, enrollment numbers, raw data, procedures reports, and preliminary analyses annually. Safety monitoring results will be reported to the IRB.

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