

Theta Burst Stimulation for Schizophrenia

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# Theta Burst Stimulation in Schizophrenia

## 1. Protocol Title – Theta Burst Stimulation in Schizophrenia

## 2. Purpose of the study

Aim1: Evaluate the effect of theta burst stimulation (TBS) on working memory (WM) in patients with schizophrenia. Hypothesis 1 – There will be significant improvement in WM compared to baseline with one session of TBS.

Aim 2: Evaluate the effect of TBS on gamma and theta oscillations as measured from EEG. Hypothesis 2 – Increase in theta oscillation spectral power and decrease in spectral power of gamma oscillations with one session of TBS.

## 3. Background and Significance

Schizophrenia is an illness known to have cognitive deficits, with a chronic and variable course. There is extensive research on cognitive deficits, with working memory, processing speed and verbal memory being some of the domains affected(1, 2). Some modalities of treatment that have been tried to reverse these cognitive deficits are medications and cognitive behavioral therapy with minimal benefits (3). A few studies have shown modulation of working memory with routine repetitive transcranial magnetic stimulation at frequencies not exceeding 10 to 20 Hz of stimulation (4, 5). Other studies have shown the working memory to be related to gamma oscillations. A few studies have also shown that transcranial magnetic stimulation (TMS) modulates these gamma oscillations as well. There is an extensive body of literature that shows that working memory has contributions from theta and gamma oscillations in the brain. **Theta burst stimulation (TBS) is a form of transcranial magnetic stimulation (TMS)**, that entrains gamma and theta frequencies in the brain. It could be the most appropriate form of brain stimulation for improving cognition in schizophrenia patients because it has been shown to modulate brain oscillations in small samples of patients (6-9). The area for targeting would be the dorsolateral prefrontal cortex which is the site of origin of the gamma oscillations and plays a significant role in working memory (10, 11).

## 4. Design and Procedures

### 4.1 Study protocol overview

The study is designed to be a pilot one evaluating the effect of TBS on WM in patients with schizophrenia. We plan to screen 20 subjects to have 10 participants.

The participant is not responsible for any research-related costs. The participants will be under the purview of their physician who is responsible for the participant's care. The clinical team will first contact potential participants before contact by study team. If subject would like to participate, then the study team will approach subject for the study. The study team will ask for participants' permission to contact their primary care team on the psychiatry inpatient floor so that information can be provided to the primary care team regarding the participant's enrollment during the study.

### 4.2 Screening

We plan to recruit both inpatients and outpatients.

To recruit inpatients, potential participants will be discussed with the primary care team caring for the patient on Williams' Unit which is the inpatient psychiatry floor at Duke Medical Center. Once a potential participant has been identified, the clinical team will first contact potential participant before contact by study team. If

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subject would like to participate, a study team person will approach the patient, discuss the study and desire for participation in person with that individual on the inpatient unit. This will be done day 1. If agreeable the individual will be approached for consent on day 2. For consent, the study would be discussed with the patient by study personnel, and a member of the study team will administer the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) to ascertain validity of the consent given for the study. After providing informed consent participants will undergo a clinical assessment to confirm the inclusion/exclusion criteria.

Outpatients who contact the study team (after seeing the study on [clinicaltrials.gov](https://clinicaltrials.gov)) will be screened over phone based on inclusion and exclusion criteria. If they fulfill criteria, they will be scheduled for the experiment. We do not plan to actively recruit outpatients using study flyers or other materials.

All female subjects in the reproductive age group will be tested for pregnancy using a commercially available test kit specified by Department of Obstetrics and Gynecology. The Pregnancy test must be negative to continue in the study. If sexually active, subjects must agree to use appropriate contraceptive measures for the duration of the study for inclusion. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use and will result in exclusion from the study.

### 4.3 Transcranial Magnetic Stimulation (TMS) administration

On day 2, the patient would be transported from the inpatient unit to the TMS lab in the red zone on the fifth floor following screening and consent process. They would be accompanied by nursing staff. During their visit to the TMS lab a sample TMS session including motor threshold determination will be conducted.

### Treatment Sessions

On day 2, subjects would also be administered left sided theta burst stimulation (TBS) with concomitant EEG monitoring. The subject will be seated in a chair. A 64-channel electrode cap may be applied to the head for EEG recording. EMG electrodes will be applied to the right hand for motor evoked potential (MEP) recording. Subjects will perform BACS before and after the TMS session. EEG and EMG will be recorded throughout the treatment sessions. For theta burst stimulation the active motor threshold would be 80 % as used in most theta burst studies detailed in this review. Subjects would receive theta burst stimulation comprising 50 Hz bursts given at 3 to 5 Hz for close to 10 minutes which comprises 60 trains and 1800 pulses. The subject will be monitored until MEPs return to baseline. A side effects checklist will be completed at the beginning and at the end of the experimental session. All sessions will be performed by one of the protocol investigators, or by a trained and accredited research assistant supervised by the protocol investigators.

### Methods:

#### Motor Threshold Determination:

Motor threshold (MT) is defined as the TMS pulse amplitude needed to elicit an EMG response of 50  $\mu$ V peak-to-peak average amplitude in a target muscle. MT is the standard in the field for determining the intensity of TMS for everyone to reduce seizure risk. The MEP for the right first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, we will determine the TMS intensity eliciting average MEP amplitude of 50  $\mu$ V peak-to-peak in the first DI muscle

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using an amplitude titration procedure (at least 5/10 trials). Individual MT will be used to determine the intensity of theta burst stimulation for everyone, as recommended by safety guidelines.

### Application of theta burst stimulation (TBS)

A magnetic coil will be placed on the scalp and held in place with frameless stereotaxic equipment, using a sophisticated method of coil placement that will coregister scalp positions directly onto an average brain template. This Frameless Stereotaxic System Brainsight offers real-time three-dimensional display of cortical localization as the TMS coil is moved across the scalp. This will be used for coil positioning. This system uses a programmed robot arm to precisely position the TMS coil, and maintain its position, within 1 mm of the brain target chosen. Earplugs will be worn to protect hearing and low-volume white noise will be played through TMS-compatible headphones to mask the sound of the coil clicks. The intensity of the theta burst stimulation will be 80% AMT as reported in a recent review on parameters of theta burst stimulation and a review on safety of the theta burst stimulation. The participant will be seated comfortably with headphones and earplugs to protect the subject's hearing. The theta burst stimulation parameters (comprising 50 Hz bursts given at 3 to 5 Hz for close to 10 minutes which comprises 60 trains and 1800 pulses) will be kept strictly within consensus safety limits: when kept within these limits, is deemed low risk (12).

### 4.5 Clinical and cognitive assessments/tasks

#### PANSS

The Positive and negative symptoms scale is used to assess the severity of schizophrenia. It has three subscales – positive, negative and general psychopathology. Each of these subscales had 7 items, the maximum scores on each of these subscales in 49, minimum score being 7.

#### BACS – Tasks to be done from the actual BACS battery of tests (13)

*List Learning (Verbal Memory)*. Patients are presented with 15 words and then asked to recall as many as possible. This procedure is repeated 5 times. There are two alternate forms.

*Digit Sequencing Task (verbal working Memory)*. Patients are presented with clusters of numbers of increasing length. They are asked to tell the experimenter the numbers in order, from lowest to highest.

*Token Motor Task (Motor Speed)*. Patients are given 100 plastic tokens and asked to place them into a container as quickly as possible for 60 seconds.

*Verbal Fluency*. Tests of Category Instances (Semantic Fluency) and Controlled Oral Word Association Test (Letter Fluency) are administered. Patients are given 60 seconds to name as many words as possible within a given semantic category, and in two separate trials, patients are given 60 seconds to generate as many words as possible that begin with a given letter. The total number of words from the three trials is the outcome measure.

*Tower of London (Reasoning and Problem Solving)*. Patients look at two pictures simultaneously. Each picture shows 3 different-colored balls arranged on 3 pegs, with the balls in a unique arrangement in each picture. The patients are told about the rules in the task and are asked to provide the least number of times the balls in one picture would have to be moved to make the arrangement of balls identical to that of the other, opposing picture. There are two alternate forms.

*Symbol Coding (Attention and Processing Speed)*. As quickly as possible, patients write numerals 1–9 as matches to symbols on a response sheet for 90 seconds.

Each of the six measures are compared to a healthy control sample to create z-scores, and a composite score is calculated by summing these z-scores and calculating a z-score of that sum. (Keefe et al., 2004b). The composite score has high test-retest reliability in patients with schizophrenia and healthy controls (ICCs > .80).

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### 4.7 Timeline of assessments

Assessments	B (Day 1)	MT (Day 1)	TMS (Day 2)	Post (Day 2)
Consent	X			
PANSS	X			X
CGI	X	X		
Edinburg handedness Questionnaire	X			
BACS	X			X

### 5. Subject Selection - Inclusion and exclusion criteria

Inclusion Criteria	Method of ascertaining
Inpatients with schizophrenia age group of 18-50	Self-report and clinical judgement
No other DSM diagnoses	Hospital chart
Right handed males and females	Edinburg handedness questionnaire
May have mild positive symptoms	Positive symptoms subscale(PANSS) $\leq 21$
May have negative symptoms	Negative symptoms subscale (PANSS)
Ability to provide informed consent	Self-report
No restriction on concomitant medications given	Hospital chart
<b>Exclusion criteria</b>	
Intellectual disability	Hospital chart, clinical exam
Any organic brain illness	Hospital chart and clinical exam
Presence of dementia symptoms or traumatic brain injury	Hospital chart and clinical exam
Primary diagnosis of substance use	Hospital chart and clinical exam
Seizure disorder	Hospital chart and clinical exam
Actively symptomatic with PANSS positive symptom sub-scale $>21$ .	PANSS administration
Concurrently receiving ECT	

### 6. Subject recruitment and compensation

We will recruit inpatients from the inpatient unit at Duke Medical Center. Inpatients admitted on Williams' Ward in Duke South (4th floor red zone) will be approached for participation after discussion with their primary care team. Capacity to consent will be assessed by a member of the treatment team who is not an investigator on this study (such as the inpatient attending psychiatrist, nursing staff). Study team members (who are not members of the subject's clinical team) will approach potential subjects after the study is introduced to potential subjects first by the primary care team members. For both subjects, recruitment would proceed as follows: 1) study team member reviews charts of inpatients deemed eligible for the

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study admitted at Duke Medical Center 2) Discuss with primary care team if the subject is appropriate 3) A member of patient's primary care team asks patient if they want to hear about study and 4) With patient agreement, study team member discusses study with them. Study team member discussing informed consent will fully disclose and explain the risks and benefits of the study procedures, and answer the patient's questions about the study and the material presented in the informed consent form. Alternatives to study participation will be discussed, and the voluntary nature of participation in the study will be emphasized. This consent discussion will be documented in a consent note placed in the patient's chart. Outpatients who wish to participate in the study will be screened over phone.

Patients would be compensated for their participation in the study. Subjects would be compensated for time spent in the study. Rate of compensation would be \$10/hour – amounting to a total of \$30.

We do not plan to recruit subjects who are involuntarily committed on the unit. If they do appear as potential subjects while screening hospital charts, we will wait until they are converted to voluntary status before approaching them for recruitment into the study. Conversion of status from involuntary to voluntary occurs once subject's illness symptoms have improved and are closer towards remission.

- 7. Consent Process** – see Section 14 of the e-IRB submission form
- 8. Subject's Capacity to Give Legally Effective Consent** – All patients recruited for this study must have capacity to give legally effective consent. For consent, the study would be discussed with patient by study personnel and a member of their primary treating team will administer the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) to ascertain validity of the consent given for the study.

- 9. Study Interventions** – This has been described in detail in section 4.3

### **10. Risk/benefit assessment**

There are no known long-term health risks to the use of rTMS per se when operated within consensus safety guidelines(14). The Duke Medical Center Institutional Review Board recently classified two similar research applications of rTMS proposed by the PI as a “non-significant risk” (Protocols 20218 and 24349). In 2008, the FDA approved the use of high frequency rTMS in the treatment of depression. Also in 2008, an international consensus conference on safety guidelines for rTMS met, including representatives from our own labs (Drs. Lisanby and Peterchev). Their report (14) systematically reviewed the thousands of healthy subjects and patients who have undergone rTMS in order to allow for a better assessment of relative risks. The relative infrequency of adverse events using rTMS was noted. They concluded that in the case of Class 3 studies (studies involving indirect benefit and low risk in normal subjects and patients that are expected to yield important data on brain physiology or safety, but have no immediate relevance to clinical problems), normal volunteers should be permitted to participate in rTMS research when it is likely to produce data that are of outstanding scientific or clinical value. They also concluded that this research can be performed in a non-medical setting (i.e., psychology labs, robotics labs, research institutions, etc. as opposed to a hospital or appropriately equipped outpatient clinic). The Rossi et al. consensus report went on to suggest safety guidelines based on the now rather extensive international experience with rTMS. These guidelines include the rTMS intensity and timing parameters considered safe, training, and planning for and managing emergencies. We will follow these guidelines, and have incorporated them into our screening and session procedures.

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## Safety of theta burst stimulation

The Consensus Statement reached at the Sienna Meeting (14) updated previous guidelines includes information about asynchronous trains such as theta burst stimulation (TBS) paradigms including intermittent theta burst stimulation that would be the pattern of stimulation used in this study. A review of the safety of the procedure done by Oberman et al (2011) showed that the incidence of side effects was 0.5 % (Break down comprising headache or other craniofacial pain – 46 %, seizure 2%, muscle contractions 10 %, worsening tinnitus 6%, eye lacrimation 2%, lightheadedness 22%, nausea 2% and non-specific discomfort 10 %) (12). The reviewed population included 67 studies with a combined total subject number of 1040 people, and involving a total number of sessions exceeding 4,500. Of the 1001 subjects 776 were healthy control participants while 225 were clinical patients with both psychiatric and neurological diagnoses. 97 patients in this review received stimulation to the dorsolateral prefrontal cortex.

This review calculated the crude risk *per subject* for a seizure from theta burst stimulation to be 0.1 % while the crude risk per subject of mild adverse events (encompassing the remainder of the reported events) is 5% overall for both patients and healthy controls. As many studies involve multiple sessions of TBS, they calculated the crude risk of seizure *per session* of TBS as approximately 0.02%, and 1.1% for mild adverse events.

This meta-analysis also found that both the reported symptoms and general risk of adverse events during TBS is comparable to or less than other high frequency rTMS protocols (14). Seizure, the most severe reported adverse event, has only occurred once in over 4,500 sessions resulting in a crude risk of 0.02%, while the overall crude risk of any adverse event is estimated as 1.1%. This is comparable with other high frequency rTMS protocols where seizures have occurred in less than 0.1% of patients. The most common reported adverse event during TBS is also the most common in other rTMS protocols, transient headache and neck pain. This adverse event has been reported in up to 40% of patients undergoing high frequency rTMS and was experienced by less than 3% of the subjects receiving TBS. Participation in this study is completely voluntary, and there will be no pressure or time constraints regarding the decision to participate. There are no benefits to the participants except for the compensation, as well as the good will of helping the progress of scientific research. The information learned from this study may aid our understanding of the role of the theta burst stimulation in modulating cognition and brain function in patients with schizophrenia.

## TMS Adverse Events Plan:

Seizure is a theoretical risk with rTMS. In the Rossi et al. report it was stated that “The occurrence of seizures has been extremely rare, with most of the few new cases receiving rTMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold.” As Rossi et al. delineate, “rare” means that 16 cases (out of tens of thousands of rTMS sessions over the last two decades) of seizure related to rTMS have been reported. Eight occurred before safety parameters were established in 1997. Of the other eight reports, six occurred either when the safe rTMS parameters were exceeded or other safety guidelines ignored, and the actual occurrence of a seizure has been questioned in the other two (i.e., convulsive syncope or pseudoseizure may have occurred). In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996 (Duke investigators, Dr. Luber, and Dr. Lisanby were participants), researchers in the field agreed upon a set of rTMS consensus safety guidelines, including recommended stimulation parameters and contra-indications (15), and these consensus guidelines have been recently updated (Rossi et al., 2009). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in rTMS studies (Rossi et al., 2009). The levels of stimulation used in this protocol are well within safety guidelines (Rossi et al., 2009; Wassermann et al. 1998).

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We will screen subjects for known risk factors for seizure with rTMS (medical screening and medical history). Personnel who administer rTMS are trained to recognize a potential seizure event and to act as “first responders” to administer appropriate initial care. All study personnel have undergone Basic Life Saving training, and seizure-specific training. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements, convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the rTMS chair and onto the floor lying down on his or her left side. The subject will be kept lying down on his or her left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. A seizure constitutes a reportable adverse event, and will thus be immediately reported to the IRB via the Safety Events Form mechanism.

The most commonly reported side effect of rTMS is headache. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over the counter pain medications. Neck pain or scalp pain may also occur. Both are usually managed easily with over-the-counter analgesics.

As noted in Rossi et al. (2009), Loo and colleagues reported mild and transient changes in auditory threshold in two depressed patients following a 2-4 week rTMS course of rTMS (16). Cases of tinnitus have been reported after rTMS treatments. In addition, recently in a study investigating the effects of rTMS on symptoms of depression, a patient experienced moderate to severe tinnitus after an rTMS session in which earplugs were not used. Rossi et al. recommended that hearing protection always should be worn during rTMS application, and that individuals with cochlear implants not receive rTMS. In the current study, earplugs will be worn by all subjects during rTMS procedures. Individuals with cochlear implants will be excluded from participation.

Risks to the unborn children of pregnant women receiving rTMS are unknown. Pregnant women will be excluded as per IRB policy. If sexually active, the subject must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If the subject has any uncertainty about whether they could be pregnant, another urine pregnancy test will be performed before they can participate in this protocol. The person(s) who will perform the urine pregnancy test will have successfully completed training as directed by the Chair of Obstetrics and Gynecology of the Duke University School of Medicine. The urine pregnancy test kits used for this research study will be those commercially available test kit specified by the Chair of Obstetrics and Gynecology and in routine use at DUHS.

**Costs to the Subject** – Subjects would not incur any costs because of participation in this research study. There would compensation for patients in this study. Subjects would receive standard of care and there are no additional visits as part of the study. **The study sponsor would pay for the TMS procedure.**

## 11. Data Analysis & Statistical Considerations



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The BACS data and EEG data will be analyzed using MATLAB and done by the study coordinator. We will perform multiple t tests to see if one session of theta burst stimulation can modulate working memory performance and EEG in patients with schizophrenia. This is a pilot study and so we limit recruitment to 10 patients.

### 12. Data & Safety Monitoring

Data and safety monitoring will follow standard protocol procedures. Any serious adverse event will be reported within 24 hours to the Duke IRB. Adverse events will be documented and addressed accordingly. The participants will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The participants' well-being will be continuously monitored by the experimenter, and the Principal Investigator will report all serious adverse events in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's standard operating procedures. The study monitor will be Dr. Steven Szabo. Dr. Szabo will ensure the quality of the study and establish that all study staff are complying with the investigational plan and IRB regulations. Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators and a single facility in which the study is being conducted. Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, that accurate, complete, and current records are maintained, that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol, investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. He will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met.

**13. Privacy, Data Storage & Confidentiality** – see Section 12 of the e-IRB submission form and complete the questions in that section

### References

1. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICES conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56(5):301-7.
2. Keefe RS, Fox KH, Harvey PD, Cucchiaro J, Siu C, Loebel A. Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. *Schizophr Res*. 2011;125(2-3):161-8.
3. Young JW, Geyer MA. Developing treatments for cognitive deficits in schizophrenia: the challenge of translation. *J Psychopharmacol*. 2015;29(2):178-96.
4. Barr MS, Farzan F, Arenovich T, Chen R, Fitzgerald PB, Daskalakis ZJ. The effect of repetitive transcranial magnetic stimulation on gamma oscillatory activity in schizophrenia. *PLoS One*. 2011;6(7):e22627.
5. Farzan F, Barr MS, Sun Y, Fitzgerald PB, Daskalakis ZJ. Transcranial magnetic stimulation on the modulation of gamma oscillations in schizophrenia. *Ann N Y Acad Sci*. 2012;1265:25-35.
6. Bor J, Brunelin J, Rivet A, d'Amato T, Poulet E, Saoud M, et al. Effects of theta burst stimulation on glutamate levels in a patient with negative symptoms of schizophrenia. *Schizophr Res*. 2009;111(1-3):196-7.

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7. Hasan A, Brinkmann C, Strube W, Palm U, Malchow B, Rothwell JC, et al. Investigations of motor-cortex cortical plasticity following facilitatory and inhibitory transcranial theta-burst stimulation in schizophrenia: a proof-of-concept study. *J Psychiatr Res.* 2015;61:196-204.
8. Tikka SK, Nizamie SH, Venkatesh Babu GM, Aggarwal N, Das AK, Goyal N. Safety and Efficacy of Adjunctive Theta Burst Repetitive Transcranial Magnetic Stimulation to Right Inferior Parietal Lobule in Schizophrenia Patients With First-Rank Symptoms: A Pilot, Exploratory Study. *J ECT.* 2017;33(1):43-51.
9. Demirtas-Tatlidede A, Freitas C, Cromer JR, Safar L, Ongur D, Stone WS, et al. Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia. *Schizophr Res.* 2010;124(1-3):91-100.
10. Gonzalez-Burgos G, Cho RY, Lewis DA. Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biol Psychiatry.* 2015;77(12):1031-40.
11. Barr MS, Farzan F, Rusjan PM, Chen R, Fitzgerald PB, Daskalakis ZJ. Potentiation of gamma oscillatory activity through repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. *Neuropsychopharmacology.* 2009;34(11):2359-67.
12. Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society.* 2011;28(1):67-74.
13. Keefe RS, Poe M, Walker TM, Harvey PD. The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. *Journal of clinical and experimental neuropsychology.* 2006;28(2):260-9.
14. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009;120(12):2008-39.
15. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol.* 1998;108(1):1-16.
16. Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry.* 2001;49(7):615-23.