The Role of Fast or Slow Repetitive Transcranial Magnetic Stimulation as Adjunct Therapy in Civilian Post-Traumatic Stress Disorder

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Background

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition in response to one or more traumatic events including interpersonal violence, accidents, disasters or military action. PTSD can occur at any age and is characterized by clusters of symptoms of consisting of (a) event re-experience, (b) avoidance, and (c) hyper-vigilance (1). In the US, the lifetime prevalence of PTSD in the general population is estimated at 7.5% while in Canada it is estimated at 9.2% (2;3). PTSD in civilian (ie: non-combat veterans) populations has been associated with higher health care costs in comparison to those with Major Depression, and associated with higher costs even when adjusted to depression and other comorbidities (4;5).

Pharmacological and psychological modalities for PTSD are intended to ameliorate symptoms and improve function. A wide range of treatments have been examined and used clinically to treat PTSD. These include antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (6-11), and therapies such as Eye Movement Desensitization and Reprocessing, and Trauma Focused Cognitive Behavioral Therapy (12-16). A systematic review conducted by the National Institute for Clinical Excellence found there was some evidence for psychological treatments in comparison to wait-listed controls, and limited evidence for the use of pharmacological treatments compared to placebo in patients with PTSD (17).

Repetitive transcranial magnetic stimulation (rTMS) is a well-tolerated and non-invasive treatment that utilizes a high powered magnetic field to create electromagnetic energy to depolarize cortical neurons up to 3 cm below the surface of the scalp. The treatment is delivered by a magnetic coil placed at the surface of the scalp below the target brain area while the patient is fully awake, and no anesthesia is required. Depending on the frequency of the stimulation, it can enduringly increase or decrease brain activity in specific brain regions resulting in changes in monoamine levels (18;19) and brain metabolism (20). Very few adverse events are experienced by patients. The occurrence of a seizure during rTMS is extremely rare and only 16 cases have been reported in the literature through decades of research and clinical practice worldwide with tens of thousands of patients. The frequency of seizure with rTMS is not entirely clear. Nevertheless, it is a rare risk that is always discussed during the consent process, and those at elevated risk for seizures (eg: prior history of seizures, on medications or substances known to trigger seizures) are screened out. No seizures have ever occurred at our VGH rTMS clinic.

Repetitive transcranial magnetic stimulation has been shown to be safe and effective in the treatment of major depressive disorder (MDD) (21-41) is now an approved treatment for MDD by Health Canada (since 2002) and the U.S. Food and Drug Administration. The parameters of rTMS treatment include location (usually targeting the dorsolateral prefrontal cortex [DLPFC]), hemisphere (right or left), and intensity. Studies have shown high frequency (>3Hz) rTMS can lead to long-term potentiation, and low frequency (1 Hz) rTMS can can lead to long-term inhibition of neurons, both of which can be effective in treating MDD through direct and indirect changes (42;43). For depression, both high frequency (10-20 Hz) rTMS over the *left* DLPFC and low frequency (1 Hz) rTMS over the *right* DLPFC have shown efficacy (44).

There is now emerging evidence of efficacy of rTMS in the treatment of other psychiatric disorders such as panic disorder and anxiety (45-53). However, the utility of rTMS in the treatment of PTSD has not been extensively studied and only a limited number of studies exist with small sample sizes, and differing methodologies. PTSD can lead to abnormal changes in brain metabolism in certain cortical and subcortical areas. Two of the most frequent positron emission tomography (PET) and functional

magnetic resonance imaging (fMRI) findings suggest decreased activity in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex, while increased amygdala activation is commonly seen (54;55). These brain regions have reciprocal connections to DLPFC so by altering brain function in one accessible (to rTMS) region such as the DLPFC, it can indirectly lead to changes in other regions (56). Moreover, studies of those with PTSD have shown greater abnormality in the right hemisphere compared to left hemisphere, making the right side a more specific target for brain stimulation (57). These changes could theoretically lead to improvement in PTSD symptoms.

Preliminary uncontrolled studies suggest that rTMS has an effect on PTSD symptoms. Grisaru and colleagues treated 10 patients with *bilateral* rTMS using 0.3 Hz for 30 stimuli in a single session (58) while McCann et al. treated two patients for 10 sessions of 20 Hz rTMS over the *left* DLPFC (59). Both studies showed improvement in core PTSD symptoms, but the effects were transient. Rosenberg examined the effects of rTMS with *left* DLPFC at 1 Hz or 5 Hz in 12 patients with comorbid PTSD and MDD (60), and found large effects on depressive symptoms and smaller, but statistically significant, improvement in PTSD symptoms.

The results of randomized controlled trials (RCTs) of rTMS for PTSD have also been promising. In a double-blind, sham-controlled RCT, Cohen et al. examined the efficacy of 14 days of rTMS over the *right* DLPFC, comparing low frequency (1 Hz) to high frequency (10 Hz) in 24 patients with PTSD (61). Results indicated significant improvement in core PTSD symptoms for patients in the 10 Hz treatment group compared to sham, but not the 1 Hz group. Boggio et al. conducted a double-blind, sham-controlled RCT in 30 patients diagnosed with PTSD (62). Patients were randomized to either sham or high frequency (20 Hz) rTMS for two weeks, over *right* or *left* DLPFC. Results showed that both right and left 20 Hz rTMS significantly reduced PTSD symptoms, but the effect was slightly larger on the left side. The reduction in PTSD symptoms was still present at 3-month post-treatment follow-up. Only one study by Osuch et al. examined the effects of rTMS in combination with psychotherapy (63). In a sham-controlled, cross-over study design, 9 patients were randomized to low frequency (1 Hz) or sham rTMS to the *right* DLPFC rTMS in conjunction with imaginal exposure therapy. Results showed no effect for 1 Hz rTMS compared to sham, but the small sample size likely led to a Type II error. Finally, Watts et al. conducted the most recent sham-controlled RCT of 20 patients with PTSD randomized to sham or *right* DLPFC low frequency 1 Hz rTMS over 10 sessions, and found significant improvement in PTSD and depressive symptom scores in the active group over the sham, and this change sustained up to 2 months post-rTMS (64).

The results of these studies suggest that rTMS targeting the right DLPFC can ameliorate symptoms of PTSD, but there are discrepant results about the efficacy of low frequency (1 Hz) vs. high frequency (10-20 Hz). Subjects tolerated the procedure well with no cognitive dysfunction and low dropout rates. Furthermore, the utility of rTMS in conjunction with other therapies such as psychotherapy is unclear, given the one small study to date.

The rTMS program at Vancouver General Hospital (VGH) currently focuses on the treatment of patients with depression. Patients typically receive 20-30 treatment sessions over a 4-6 week period. Sessions are conducted on consecutive days, five days a week, by a rTMS-clinic registered nurse under the supervision of a psychiatrist trained in rTMS. Each session lasts approximately 30 to 40 minutes. The clinic is currently situated right within Centennial Pavilion with ready access to emergency response teams and equipment in the unlikely event of a serious adverse reaction occurring during the treatment. The clinic is slated to move to Willow Pavilion in July 2012, which also has ready access to emergency response.

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The Outpatient Psychiatry Program (OPP) PTSD program at the VGH Health Centre consists of a two-phase, 18 week psycho-educational and behavioural skills program developed from the work of Ogden, Harris, and Najavits aimed at reducing symptoms of PTSD (65-67). Phase One is eight weeks long and includes psychoeducation about psychological trauma. Phase Two is 10 weeks long, and is designed to address longer term or complex traumatic stress disorders. The second phase is based on two models: Trauma, Recovery, and Empowerment (TREM) and Seeking Safety (66;67). Patients are referred from community care providers and are expected to complete the 18 week program if accepted. These patients are not combat veterans since there is already another existing resource for treating those patients elsewhere. Preliminary data from our clinic indicate that those patients completing Phase 1 of our program have very little improvement in their PTSD symptom scores, but Phase 2 can have a greater impact.

The presence of both programs at one site provides a unique opportunity to examine both the short and longer-term effects of rTMS as stand-alone treatment and in combination with psychotherapy. There is a break of 3-4 weeks between Phase 1 ending and Phase 2 beginning, so this period of time allows for rTMS to be conducted for patients willing to undergo this treatment.

In Canada, there are no restrictions for the range of mental disorders that rTMS can be used for in treating patients, although MDD is the condition that is the most commonly treated. Based on reports in the literature, we anticipate that right sided rTMS is as safe and tolerable as left-sided rTMS. Therefore, we propose to conduct a study of rTMS in patients with PTSD who are starting the group psychotherapy program at VGH. Since previous research has shown a discrepancy between the efficacy of high versus low frequency rTMS on the symptoms of PTSD, we will examine the use of high (10 Hz) versus low (1 Hz) frequency rTMS delivered over the right DLFPC of patients suffering with PTSD symptoms unrelated to combat. Standardized evaluations will be done to assess for clinical improvements in the PTSD, depressive and anxiety symptom clusters, and for tolerability with monitoring of adverse events and dropout rates.

Primary Hypothesis

The primary hypothesis is that high frequency (10 Hz) rTMS over the right DLPFC will be superior to low frequency (1 Hz) in reducing scores as measured by the PTSD Check List.

Research Method

Subject Recruitment

Subjects will be recruited from the PTSD treatment program conducted at the VGH Outpatient Psychiatry Program (OPP). Mid-way during the Phase 1 of the group psychoeducational program, patients will be approached regarding their willingness to participate in the study. Those subjects expressing interest will receive a description of the study along with an informed consent form that the client can sign if s/he chooses to participate. Should the patient agree to participate, a screening interview will be administered to determine if s/he meets the inclusion / exclusion criteria.

Inclusion criteria: (1) primary diagnosis of PTSD as determined by a structured interview (Mini International Neuropsychiatric Interview, MINI (68)); (2) no change in psychotropic medications within 4 weeks before the start of rTMS; (3) age greater than 19 years and less than 70 years; and (4) competent to give informed consent.

Exclusion criteria: (1) any non-fixed metal object or implant (including cochlear implants) in brain, skull, scalp, or neck within 30 cm of the magnetic rTMS coil; (2) implantable devices, including cardiac pacemakers and defibrillators; (3) other contraindications to rTMS, including history of seizures (except childhood febrile seizures) or recurrent and unexplained syncope, first degree relative with a history of epilepsy, treatment with a medication known to substantially decrease the seizure threshold, and pregnancy; (4) psychiatric diagnoses of psychosis or psychotic disorder (including psychotic depression), bipolar type 1 disorder, organic mental disorders; (5) substance abuse/dependence within the past 3 months; (6) active suicidal risk as judged by the clinician; (7) borderline or antisocial personality disorder; (8) acute medical illness, including cancer; (9) any significant central nervous system disorder such as brain mass, stroke.

Research Design

This will be a prospective, 2-week, double-blind (subject and evaluator) randomized controlled pilot study to assess the effect of repetitive transcranial magnetic stimulation (rTMS) in patients with a confirmed diagnosis of PTSD. The rTMS will target the right DLPFC. Subjects will be randomized into either 1 Hz or 10 Hz treatment arms, or sham arm.. The rTMS will be administered between Phase 1 and 2 of the PTSD OPP, so there will not be concurrent group therapy during the 2-week rTMS sessions. Outcome measures will be assessed at baseline, after 1 week and 2 weeks (completion) of rTMS, and at follow up after Phase 2 of the PTSD OPP group psychotherapy program (approximately 10 weeks after completion of rTMS).

Primary Outcomes

- Changes in PTSD symptoms as measured by – Clinician Administered PTSD Scale (CAPS (69)), patient rated Post Traumatic Stress Disorder Checklist Civilian (PCL-C).

Secondary Outcomes

- Changes in symptoms as assessed by:
  - For Depression – clinician administered Hamilton Depression Rating Scale (17 items) (HAMD), patient rated Quick Inventory of Depressive Symptomatology-Self-report (QIDS-SR (70)).
  - For Anxiety – Beck Anxiety Inventory (BAI), Generalized Anxiety Disorder Assessment (GAD-7).
  - These are all standardized, validated symptom measures that are widely used in clinical and research settings. The QIDS-SR, GAD-7 and PCL-C are also used as routine clinical outcome measures in the PTSD OPP.
- Adverse events, safety, and tolerability
  - Incidence of serious and non-serious adverse events attributable to rTMS (eg: headache, scalp pain, facial pain, dizziness, tinnitus, light-headedness, syncope, seizure).
  - Montreal Cognitive Assessment (MOCA).

Procedures and Methods

After giving written, informed consent, subjects will undergo baseline assessment measures. Eligible subjects will be randomized to one of three treatment arms (high or low frequency rTMS, or sham rTMS). Concealment of allocation will be accomplished using a computerized randomization program that reveals treatment allocation only after the unique subject identifier is entered. The randomization codes will be available on a 24-hour basis in the (unlikely) event that the blind needs to be broken for clinical reasons. The subject will be blind to treatment condition because they will be unaware of the rTMS frequencies or sham condition used in the study. The rTMS nurse will be unblinded, but the

evaluator for clinician-rated assessments will be blind to treatment conditions. The rTMS nurse will not interact with the evaluator, and should any unblinding occur, the evaluator will be replaced.

The secondary outcome measures will be repeated weekly after rTMS session number 5 and 10 (or at termination, for early withdrawals). Adverse events and severity (mild, moderate, severe) will be recorded at each session. Serious adverse events will be defined according to standard Health Canada definitions as those which: a) result in death; b) are life threatening; c) are severely or permanently disabling; d) require inpatient hospitalization; e) result in an incidence of cancer; f) result in a drug overdose or reaction after drug withdrawal. All subjects who withdraw from the study will be asked to state a reason for withdrawal. The outcome measures will also be repeated after completion of the Phase 2 group psychotherapy program (about 10 weeks following completion of the rTMS).

The blind evaluator(s) will receive standardized training to establish inter-rater reliability using videotaped interviews. Reliability of outcome assessment will also be enhanced by using structured inteview guides for the HAMD and CAPS.

Interventions (rTMS Stimulation)
The motor threshold is determined during the first session by applying TMS over the motor cortex in order to get the minimal level of stimulus intensity from the device which will create a contraction in the contralateral abductor pollicis brevis muscle of the thumb. The DLPFC will be targeted by measuring 6 cm anterior to this motor cortex landmark, along the sagittal plane, as the patient will be wearing a swimmer's cap. The intensity of the stimulus is set by going 100-120% of the intensity which determined motor threshold. rTMS therapy over the right DLPFC will be given on 5 consecutive days every week for two weeks for a total of 10 therapy sessions using a Magstim Super Rapid2 (Magstim Company Ltd., Carmarthenshire, Wales, UK) with a Rapid-2 Air Film Coil.

Subjects will receive either active rTMS to the right side at 1 Hz or at 10 Hz, or sham treatment for 37.5 minutes per session. The stimulus parameters that will be chosen for treating subjects will be similar to the parameters currently used at our clinic to stimulate patients with depression. A clinic nurse will always be present to deliver the treatment, and a supervising rTMS psychiatrist will oversee the appropriate placement and intensity of the coil, as well as responding to any adverse event which may arise. Each subject is given appropriate ear protection due to the intensity of the sound from each treatment pulse delivered by the device. Subjects who experience some initial discomfort during the session, such scalp or facial irritation, will prompt trying a different orientation of the coil at the same DLPFC site, which will usually relieve the discomfort. Subjects may leave immediately on their own after the treatment is completed, and may even drive, unless a serious adverse event occurred.

SAMPLE SIZE
Based on the standardized effect size for the primary outcome, the PTSD Check List, as determined by the previous RCT (71;72) (d=1.4), and with alpha set to 0.05 and 80% power, we estimated a sample size of nine subjects/condition. Note that this effect size is regarded as a large effect and is clinically significant.

Data Analysis
All randomized subjects will be included in the analysis based on intent-to-treat. Missing data will be imputed using last observation carried forward (LOCF). The pre-specified primary efficacy endpoint is the adjusted mean change from baseline to endpoint (2 weeks) on the PTSD Check List using LOCF. All comparisons will be analyzed using ANCOVA adjusting for baseline value. The secondary outcomes will also be analyzed using a similar analysis, when appropriate. Post hoc analyses will also

examine observed case data. Categorical data (such as proportions of the sample with adverse events) will be analyzed using chi-square tests or Fisher's test where cell sizes warrant.

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The Role of Fast or Slow Repetitive Transcranial Magnetic Stimulation as Adjunct Therapy in Civilian Post-Traumatic Stress Disorder

Identifiers:	NCT01806168
Unique Protocol ID:	H12-01578
Secondary IDs:	V12-01578
Brief Title:	rTMS in the Treatment of PTSD

Information & Consent Form V4.0
December 10, 2012

SUBJECT INFORMATION AND CONSENT FORM

The Role of Fast or Slow Repetitive Transcranial Magnetic Stimulation as Adjunct Therapy in Civilian Post-Traumatic Stress Disorder

Principal Investigator:

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Co-Investigators:
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Sponsor: Vancouver Coastal Health Research Institute

Emergency contact: 604-875-4111 Ext 67732 or 604-875-4794

You are being invited to take part in a pilot study because you have had a diagnosis of post traumatic stress disorder (PTSD). A pilot study is a small preliminary study conducted before starting a large research study in order to check the feasibility or to improve the design of the research. The purpose of this pilot study is to assess the effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) in subjects with symptoms of PTSD. Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. However, it is important for you to understand what the research involves before you decide to participate in the study. This consent form provides detailed information about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you be penalized or lose the benefit of any medical care to which you are entitled or are presently receiving. Please take time to read the following information carefully and discuss it with your family, friends and doctor before you decide.

WHO IS CONDUCTING THE STUDY?

Drs. Larry Ong and Raymond Lam have received a research grant from Vancouver Coastal Health Research Institute to conduct this study. Drs. Ong and Lam are the principal investigators and the Head of the Department of Psychiatry is fully aware of funds they have received to conduct this study. As a subject in this study you are entitled to know the details of these arrangements and, on request, you will be provided them in writing. Should you have any concerns about these disclosures you may contact the office of the Head of the Department of Psychiatry at 604-822-7310.

BACKGROUND

There are several different methods for treating PTSD including psycho-therapy, counseling, and medication. A treatment that has been used successfully to treat depression is Repetitive Transcranial Magnetic Stimulation (rTMS). rTMS has also been approved by Health Canada for the treatment of symptoms of PTSD but there are only a limited number of studies that have looked at this. rTMS uses a high powered magnetic field to stimulate brain cells below the scalp. The treatment is delivered using a magnetic coil placed at the surface of the scalp below the area of the brain that is to be treated. No anesthesia is required and the subject is completely awake during the treatment. rTMS treatment has been available as a treatment in Canada since 2002. For the treatment of PTSD, research suggests that stimulating the dorsolateral prefrontal cortex (DLPFC) between 1 to 20 Hz. may show improvement in PTSD symptoms.

WHAT IS THE PURPOSE OF THE STUDY

The main purpose of this study is to examine the effects of rTMS on symptoms of PTSD using two different frequencies of stimulation, 1 Hz and 10 Hz versus a sham rTMS.

WHO CAN PARTICIPATE IN THE STUDY?

To be included in this study you must meet the following criteria:

(1) Have a primary diagnosis of PTSD
(2) No change in psychiatric medications within 4 weeks before the start of rTMS
(3) Age greater than 19 years and less than 70 years
(4) Competent to give informed consent.

WHO SHOULD NOT PARTICIPATE IN THE STUDY?

If you have any of the following you should not participate in this study:

(1) Any non-fixed metal object or implant (including cochlear implants) in brain, skull, scalp, or neck within 30 cm of the magnetic rTMS coil
(2) Implantable devices, including cardiac pacemakers and defibrillators
(3) Psychiatric diagnoses of psychosis or psychotic disorder (including psychotic depression), bipolar type 1 disorder, organic mental disorders
(4) Substance abuse/dependence within the past 3 months
(5) Active suicidal risk as judged by the clinician
(6) Borderline or antisocial personality disorder
(7) Acute medical illness, including cancer
(8) Any significant central nervous system disorder such as brain mass, stroke
(9) Other reasons that make rTMS not advisable, including history of seizures (except childhood febrile seizures) or recurrent and unexplained fainting, first degree relative with a history of epilepsy, treatment with a medication known to substantially decrease the seizure threshold, and pregnancy

You **must** be withdrawn from the study if:

(1) You withdraw consent to participate

(2) You are no longer able to comply with the study visit schedule
(3) In the investigators' judgements (for safety or other reasons) it is in the subject's best interest to be withdrawn

WHAT DOES THE STUDY INVOLVE?

The study is being carried out at Vancouver General Hospital. Approximately 27 people like you will take part in the study.

1. Overview of the Study – Testing Required for Eligibility

To make sure that you are suitable for participation in the study you will have a brief visit with a study physician that will include:

(1) Medical History (your past and present diseases, medical conditions, medicines (prescription and non-prescription)
(2) Interview to assess your PTSD symptoms in addition to completing some questionnaires

2. The Research Intervention

This research study is being done to test two frequencies of rTMS (1 Hz and 10 Hz) and sham rTMS on symptoms of PTSD. Sham rTMS uses a similar magnetic coil like that used in regular rTMS, but the sham magnetic coil has a metal insert that blocks the magnetic field. You will be randomly assigned (i.e. like the flip of a coin) to receive rTMS treatment at 1 Hz or 10 Hz, or the sham rTMS treatment. Whether you are receive the 1 Hz or 10 Hz treatment or sham rTMS treatment will be decided by chance (like tossing a coin). rTMS is currently not used to PTSD symptoms, and has not been systematically evaluated in a large sample of adults.

3. Overall Duration of the Study

The study involves 11 visits over a 2 week period and a final follow up visit at 3 months. Visit 1 will last approximately 90 minutes, the other visits will last about 60 minutes for a total time commitment of roughly 12.5 hours. Each rTMS (1 Hz, 10 Hz, or sham) treatment lasts 37.5 minutes. At each visit a study physician or nurse ask you about all medications you are taking, and your general health. During other visits you will be asked about your PTSD symptoms as well as complete some questionnaires before rTMS treatment. This part of the visit might be a little different from normal therapy.

4. Study Questionnaires

The study includes seven questionnaires. At three of rTMS treatment visits, you will be asked to complete three questionnaires by yourself. The study physician will complete the other four questionnaires that will involve asking some questions about your PTSD as well as other symptoms. You do not have to answer any questions you do not feel comfortable with.

IF YOU DECIDE TO JOIN THIS STUDY: SPECIFIC PROCEDURES

If you agree to take part in this study, the procedures and visits you can expect will include the following:

Visit 1 (Screening)

1. Determine if your meet the inclusion and exclusion criteria for the study.

2. Psychiatric, medical history, reasons to exclude rTMS treatment and other assessments by the study physician.

Visit 2 (Baseline)

1. Start rTMS treatment at 1 Hz, 10 Hz or sham.
2. Check for side effects by the study physician.
3. Complete seven questionnaires (4 by the study physician and 3 by the subject).

Visits 3 to 5

1. Check for side effects by the study physician.
2. Continue rTMS treatment at 1 Hz, 10 Hz or sham.

Visit 6

1. Check for side effects by the study physician.
2. Continue rTMS treatment at 1 Hz,10 Hz or sham.
3. Complete seven questionnaires (4 by the study physician and 3 by the subject).

Visits 7 to 10

1. Check for side effects by the study physician.
2. Continue on rTMS treatment at 1 Hz,10 Hz or sham.

Visit 11 (Completion)

1. Check for side effects by the study physician.
2. Continue rTMS treatment at 1 Hz,10 Hz or sham.
3. Complete seven questionnaires (4 by the study physician and 3 by the subject).

Visit 12 (3 month follow up)

1. Complete seven questionnaires (4 by the study physician and 3 by the subject).

WHAT ARE MY RESPONSIBILITIES?

You must be willing to follow the study psychiatrist's instructions, and go through all the related procedures described above. You will have to see the study physician on the scheduled visits. It is important that you tell the study physician or nurse about any other medication or treatments you are taking before and during the study.

In addition, you will receive sham rTMS treatment or at 1 Hz or 10 Hz. The treatments are identical and both the investigators and you will not know which you are receiving at any stage of the study. You understand that whether you receive sham treatment or treatment at 1 Hz or 10 Hz will be decided by chance (like tossing a coin).

WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECTS OF PARTICIPATING?

According to published studies of rTMS to date, 1 in 20 patients have experienced common side-effects, and 1 in 30,000 have experienced serious side-effects. You may experience none, some or all of the side-effects listed below. However, there have been no reports of lasting consequences.

<u>Common side effects (less than5%):</u>

1) Headache
2) Twitches in the face muscle (during rTMS stimulation)
3) Effects on mood
4) Effects on cognition (Note: rTMS does not affect memory and orientation)

5) Temporary changes in hormones
6) Transient hearing loss

Serious side effects (less than0.00003%)

(1) Seizure during the application of the rTMS stimulation

rTMS treatment should also not be used by women who are pregnant.

During rTMS treatment you will be fitted with a swimmer's cap, and ear protection due to the intensity of the sound from each treatment pulse delivered by the device, You may experience some initial discomfort during the session such as scalp or facial irritation, If so the treating physician will try a different orientation of the coil at the same site which usually eliminates the discomfort.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you agree to participate in this study there may or may not be a direct medical benefit to you. Your PTSD symptoms may be improved during the study but there is no guarantee that this research will help you. The information we get from this study may help us to provide better treatments in the future for patients with PTSD.

You understand that the foreseeable benefits of the study are as follows: The study may decrease or eliminate your PTSD symptoms. You will receive a thorough assessment of your health status during the study. However, you understand that it is possible that you may not receive any benefit from this study and that no guarantees have been made to you. You understand that your PTSD symptoms may not be controlled by the treatments used in this study or may even worsen. You also understand that as a result of being in this study, you have a random chance of receiving sham rTMS treatment or treatment at 1 Hz or 10 Hz.

WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT

If you choose not to participate in this study, you will be provided with the standard treatments that are available for PTSD. You can discuss your options with your psychiatrist before deciding whether or not to participate in this research project.

WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If any new information on the study treatment (rTMS) becomes available which may influence your decision to continue in the study you will be told. If a more effective treatment becomes available it will be offered to you.

WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

Your participation in this research is entirely voluntary. You can stop participating in the study at any time, and you do not have to give any reasons why you are stopping. If you do not want to continue with study treatment or decide to stop for other reasons, you should always speak to the study physician on how and when to stop taking the treatment, as this may affect the symptoms

of your condition. If you decide to stop your participation, you will be asked to come in for a final visit and examination, which will include a brief assessment. If you decide to enter the study you may stop at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled, and your future medical care will not be affected. If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be retained for analysis.

WHAT IF SOMETHING GOES WRONG?

Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities.

By signing this form, you do not give up any of your legal rights and you do not release the study doctor or other participating institutions from their legal and professional duties. There will be no costs to you for participation in this study. You will not be charged for any research procedures. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

CAN I BE ASKED TO LEAVE THE STUDY?

If you are not complying with requirements of the study or for any other reason, the study physician may withdraw you from the study and will arrange for your care to continue. On receiving new information about the treatment, the study physician might consider it to be in your best interests to withdraw you from the study without your consent if they judge that it would be better for your health. Other reasons for stopping your continuation in the study can be that a regulatory agency, such as Health Canada, stops the study.

AFTER THE STUDY IS FINISHED

You may not be able to receive the study treatment after your participation in the study is completed. There are several possible reasons for this, some of which include: The treatment may or may not turn out to be effective or safe. You may not feel it is the best option for you. You may decide it is too expensive and insurance coverage may not be available.

WHAT WILL THE STUDY COST ME?

You will not be paid for taking part in this study. If you need to take time off from work or other activities, this time or loss of wages will not be reimbursed. However, the study treatment, study visits and examinations will be provided at no cost to you during the study. Your expenses in connection with this study, such as travel and parking, will be reimbursed up to $14.00 per visit at each visit with the presentation of receipts.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by Health Canada, University of British Columbia Research Ethics, or Vancouver Coastal Health Research Institute for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

In case of a study-related injury or if you have any questions or desire further information about his study before or during your participation, you can contact Dr. Larry Ong at 604-875-4794 and Dr. Raymond Lam at 604-822-7325. In addition you can contact th Research Subject Information Line: toll free 1-877-822-8598, or email them at RSIL@ors.ubc.ca

WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY?

If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services at 604-822-8598.

SUBJECT CONSENT

- I have read and understood the subject information and consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I have been given the chance to discuss the study and ask questions.
- I consent to take part in the study and I am aware my participation is entirely voluntary.
- I understand that I may withdraw at any time without giving a reason and without this affecting my future care.
- By signing this information and consent form I agree that my personal data, including data relating to my physical or mental health or condition, and race or ethnic origin, may be used as described in this consent form.

I have been told that I will receive a copy of this signed and dated

The Role of Fast or Slow Repetitive Transcranial Magnetic Stimulation as Adjunct Therapy in Civilian Post-Traumatic Stress Disorder study by Dr. Larry Ong

_____
Printed name of subject

_____ _____
Signature of subject Date of signature

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Printed name of witness

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Signature of witness Date of signature

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Printed name of principal investigator or authorized representative

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Signature of principal investigator or authorized representative Date of signature

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Printed name of translator

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Signature of translator Date of signature

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Language translated into