**Cover Page**

**Study Title:** The efficacy of Transcranial Magnetic Stimulation in the treatment of non-epileptic seizures.

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**Introduction:**

Psychogenic non-epileptic seizures (PNES) is a severely distressing condition that commonly presents in fields of psychiatry and neurology. In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) PNES is classified as a Functional Neurological Symptom Disorder (1). This disorder has been defined as seizure-like activity, including abrupt recurrent changes in behavior, or consciousness with no epileptiform abnormalities on EEG (2). Functional Neurological Symptom Disorder, also known as Conversion Disorder, is listed under Somatic Symptom and Related Disorders. The DSM-5 describes this group of disorders as symptoms of altered voluntary movement (1). However, patients presenting with PNES indicate no sense of voluntary control. It is estimated that about 5%-20% of patients admitted to epilepsy units for monitoring are diagnoses with PNES, and a further 20-30% of patients whose seizure activity is considered to be intractable epilepsy are also eventually diagnosed with PNES (2). Currently there is no effective treatment for PNES. Although functional neuroimaging data increasingly support specific neurobiological dysfunction, the pathophysiology of the disorder remains poorly understood.

Prevalence rates of psychiatric comorbidities among PNES patients have been noted throughout the literature to be high (3). Patients with PNES often present with multiple psychiatric conditions including mood and anxiety disorders. Problems involving emotional dysregulation, dissociation, psychological trauma, and reports of previous abuse are common (3). However, the exact nature of the relationship between PNES and other psychiatric symptoms, whether present or absent altogether, is unclear.

Resting cortical positron emission tomography (PET) studies and functional connectivity analysis on resting state functional magnetic resonance imaging (rsfMRI) have both identified abnormalities in the parietal cortex in patients with PNES. Two recent fMRI studies by van der Kruijs et al. (4 & 5) assessing abnormal connectivity strength in four global networks show support for the role of the temporoparietal junction (TPJ) in the pathophysiology of PNES. Higher functional connectivity in 11 patients with PNES was found in a global network involving emotion (the insula), movement (the precentral sulcus), and executive control (the inferior frontal gyrus and parietal cortex) (5). The authors were further able to correlate these connectivity differences to elevated dissociation scores within their patient sample (4). Whether these finding were a result of dissociative comorbidity, or a direct result of PNES remains unclear.

Additional neuroimaging evidence presented in a study by Arthuis et al. (2) showed abnormal glucose metabolism in sixteen patients with PNES. Arthuis et al. assessed interictal (resting state) cerebral metabolism on sixteen PNES patients originally thought to have intractable epilepsy. Positron Emission tomography (PET) scans using 2-deoxy-2-fluoro-D-glucose (18FDG-PET) showed hypometabolism within the right inferior parietal and central region, and within the anterior cingulate cortex (ACC). The authors of this study further noted the possible significance of these regions contributing to two pathological mechanisms of the disorder; that of emotion dysregulation (ACC hypometabolism) and a compromise of processes responsible for the consciousness of the

self and the environment (right parietal hypometabolism).

Despite growing awareness of the neurobiological networks involved in PNES, there are currently no effective treatments for the disorder. Given the findings of TPJ hypometabolism in patients with PNES, and the contribution of the TPJ to consciousness of self and the environment, this region may very well serve as a major contributor to the pathophysiology of the disorder (2). A decrease in motor intentional awareness, and self-agency may result in an inability to take authorship of ones' movements, thus perceiving them as involuntary. In light of the recent work implicating the TPJ in the pathophysiology of PNES, increasing cortical excitability in this region could provide a novel starting point for the treatment of this disorder. High frequency (20 Hz) repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive method of brain stimulation, is known to increase focal cortical activity. Applied over the TPJ, it may then serve to correct the TPJ hypoactivity observed in patients with PNES.

A recent systematic review of transcranial magnetic stimulation in the treatment of functional neurological symptoms by Pollak et al. (6) has highlighted the results of a study conducted in 2011 by Dafotakis M et al. (7). This pilot study demonstrated symptom improvement in 7 out of 11 patients with psychogenic tremors using inhibitory rTMS. As such, we propose a pilot study of rTMS using a sample size of 15 patients with PNES to demonstrate significant effect.

**Objective:**

To conduct an open label pilot study in order to investigate the feasibility of repetitive Transcranial Magnetic Stimulation (rTMS) over the right TPJ, in decreasing the frequency of PNES episodes.

**Hypothesis:**

We hypothesize that 30 sessions of rTMS on 15 patients with PNES will decrease the frequency of non-epileptic seizures.

**Methods:**

This study is an open label pilot study that aims to investigate the feasibility of repetitive Transcranial Magnetic Stimulation (rTMS) in decreasing the frequency of PNES episodes. A psychiatric profile including patient's mood, anxiety, dissociative states, psychological trauma, impulsivity, and functional disability will be taken on all 15 patients using Research Electronic Data Capture (REDCap). Subsequently, patients will receive high frequency brain stimulation (20 Hz) over the right TPJ using TMS. Two sessions of TMS will be administered each weekday for 15 days, with a total 3000 pulses each session. Since there is no current data on the expected effect size of rTMS in this population of individuals, this study is an open label pilot study to assess the feasibility of rTMS as a treatment for PNES. As such, results of the questionnaires including patients' symptom severity and scores on REDCap scales will be analyzed using linear regression

analysis to determine the effect of the treatment condition on PNES episodes and functional impairment. The significance level for this test will be set to 0.05.

As this is a pilot study, we will also be evaluating the effect size and the feasibility of a more definitive project in the future. We will be observing patient response and tolerability to rTMS.

***Eligibility and Screening:*** Eligible participants will be adults who have been officially diagnosed with PNES. Additionally, participants will have to have been previously monitored with video-EEG to confirm that seizures are non-epileptic in origin. The participating study psychiatrist will assess all referrals to the Neuromodulation and Neuropsychiatry Unit for eligibility criteria. This diagnostic assessment will include a full medical history review, a semi-structured neurological examination, and a neuropsychological evaluation. This assessment will be performed as part of the regular standard of care for these patients and is not unique to this study.

***Inclusion criteria:***

i) Adults with confirmed PNES

***Exclusion criteria:***

i) Evidence of previous or comorbid epileptic seizures (as shown by video-EEG monitoring)
ii) Any other major comorbid neurological diseases
iii) Currently taking medications that are known to reduce seizure-threshold
iv) Currently pregnant

***Patient Recruitment:*** Patients will be recruited from the pool of referrals to the Neuromodulation and Neuropsychiatry Unit, St Boniface Hospital. Eligible candidates will be identified by the participating psychiatrist. They will be informed about the voluntary nature of the study and will be asked for permission for a research assistant to approach them regarding potential participation in the study. All consents will be voluntary and the participants will be free to withdraw from the study at any time. Patients will be reassured that their care will not be affected as a result of withdrawal from or deciding not to participate in the study. If a patient wishes to participate in the study, a research assistant will review the study consent form with that individual. The participant will then sign the consent form and be given a copy of the form for their records.

***Sample Size:*** This is a study is an open label pilot study that aims to investigate the feasibility of high-frequency repetitive Transcranial Magnetic Stimulation (rTMS) in decreasing the frequency of PNES episodes. Since there is no current data on the expected effect size of rTMS in this population of individuals with PNES, we have based our pilot sample size on current literature describing a confidence interval approach to pilot study sample size calculations by Cocks et al. (14). In this study, we have estimated a minimum effect size of 0.5 for the use of rTMS in the treatment of PNES. Using an 80% one-sided CI with an effect size of 0.5, Cocks et al. suggest a pilot sample size of at

least 9% of the main planned trial. Assuming a 5% significance level, and 80% power, we anticipate a main trial with a sample size of 128 participants. This allows for a pilot study sample of 12 participants to show effect, as described by Cocks et al. (14). We have included a sample size of 15 patients with PNES for this study. Our goal is to estimate the effect size for future definitive studies.

***Questionnaires:*** Prior to the first session of rTMS, patients will complete a series of questionnaires to assess mood, anxiety, dissociative states, psychological trauma, impulsivity, and functional disability. The majority of these questions will be answered through REDCap software. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Two REDCap questionnaires will be completed by each participant within one week prior to their first session of rTMS:

1) ***FND I Questionnaire***
2) ***FND II Questionnaire***

Additionally, two paper-and-pencil questionnaires will be administered by a research assistant prior to the first session of rTMS:

3) ***Montreal Cognitive Assessment (MoCA)***
4) ***Wide Range Achievement Test–3 (WRAT–3)***

A follow-up REDCap questionnaire will be completed by each participant one week following the last session of rTMS:

5) ***FND Follow-Up Questionnaire***

The FND questionnaires were designed to assess the following symptoms/topics and contain elements of the listed tests:

**Mood/Anxiety:**
- Beck Depression Inventory-II
- Spielberger State-Trait Anxiety Inventory

**Dissociation:**
- Dissociative Experience Scale
- Somatoform Dissociation Questionnaire-20

**PTSD/Trauma:**
- PTSD Checklist-5
- Childhood Trauma Questionnaire
- Connor-Davidson Resilience Scale

**Somatization and Related Topics:**
- Screening for Somatoform Symptoms (SOMS-7) – Conversion Subscale
- Patient Health Questionnaire 15 Somatic Symptom Severity Scale
- Pain Catastrophizing Scale

**Other Measures of Interest:**
- Barratt Impulsivity Scale (Version 11)
- Relationship Scales Questionnaire (Attachment Scale)
- Toronto Alexithymia Scale 20
- Ways of Coping Scale – Revised Version

**Laboratory Designed Participant Questionnaires:**

Educational Background Assessment
Edinburgh Handedness Inventory
SF-36v1 Health Survey

***MRI localizer:*** Prior to rTMS treatment, patients will undergo a structural MRI scan. Images from this scan will be used in the neuronavigation software used in conjunction with the rTMS machine, to allow for the precise localization of target cortical structures in each participant's brain. Scans will be acquired using a T1-weighted fast spin-echo sequence. The image resolution will be about 1x1x1 mm. Each scan typically takes about 15 minutes.

***rTMS:*** Participants will then begin rTMS therapy. Treatment will consist of 30 sessions of rTMS treatment. Each session will take roughly 20 minutes. We will perform two sessions per day with a 15 minute break in between sessions. As such, the entire treatment length will be three weeks (15 weekdays, with two session/days). Stimulation will be applied to the right TPJ using a 70mm figure eight coil attached to a MagStim Rapid-2 rTMS machine (MagStim Ltd., UK). Motor threshold will be defined as the minimum stimulator output that elicits a contraction of the abductor pollicis brevis muscle on 5 out of 10 consecutive pulses. For the active stimulation condition, rTMS will be applied to the target location at 110% motor threshold. Sessions will last 20 mins and will comprise consecutive trains of two-second 20 Hz pulses followed by 28 seconds of no stimulation. The target location will be identified using a Brainsight Neuronavigator system (Rogue Research, QC) loaded with each patient's structural MRI scans.

***Analysis****:* This is a study is an open label pilot design in which all participants will be exposed to active stimulation. Results from questionnaires; including patients' symptom severity and scores on REDCap scales will be analyzed using linear regression analysis to determine the effect of the treatment condition (rTMS) on PNES episodes and functional impairment. The significance level for this test will be set to 0.05.

As this is a pilot study, we will also be evaluating the effect size and the feasibility of a more definitive project in the future, while observing patient response and tolerability to rTMS.

***Anticipated risk:*** The primary major adverse side-effect associated with rTMS is the rare occurrence of induced seizure. For this reason, a history of seizures is normally considered a contraindication for rTMS treatment. However, participants recruited to this study will be diagnosed with PNES confirmed by video-EEG monitoring. This means that our participants will not have a history of epileptic-seizures. For this reason, our study participants should be at no greater risk of experiencing an rTMS-induced electrogenic seizure than the general population. Furthermore, seizure-induced events associated with rTMS are thought to mainly occur when protocols are used that fall outside of generally accepted safety guidelines proposed by Rossi et al. (16). Our protocol falls within these guidelines, and the proposed study procedures and materials have been used without incident with several different psychiatric populations.

Minor side-effects sometimes associated with rTMS treatment include headache and fatigue. These side-effects are transient and are not known to persist following the end of therapy. Headaches can usually be ameliorated through the use of over-the-counter pain relief medications. The neuropsychological questionnaires do not pose any physical risks to participants.

**Expected Results:**

The expected results of this study are that trials of high frequency rTMS over the right TPJ will decrease the frequency of non-epileptic seizures and contribute to a greater understanding of this regions' contribution to the pathophysiology of PNES.

**Expected Conclusion:**

Significant functional impairment in the lives of patients suffering with PNES necessitates the development of effective treatments for this disorder, and further investigation into its pathophysiological mechanisms. An increase in comorbid psychiatric symptoms within this population suggests that patients with PNES are at greater risk of psychiatric aliments, which further impact on their psychological and social wellbeing. The decrease in frequency of non-epileptic seizures, as a result of high frequency rTMS over the right TPJ, shows that rTMS may be a novel and efficient treatment for this disorder. Greater understanding of the biological components of this disorder, in conjunction with their associated psychiatric symptoms, will aid in reducing stigma, and help in the development of effective methods for identification, treatment, and prognosis of this condition.

**References:**

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, Virginia: American Psychiatric Publishing; 2013. Found at: http://dsm.psychiatryonline.org.uml.idm.oclc.org

[2] Arthuis M, Micoulaud-Franchi JA, Bartolomei F, McGonigal A, Guedj E. Resting cortical PET metabolic changes in psychogenic non-epileptic seizures. J Neurol Neurosurg Psychiatry. 2015 Oct 86(10): 1106-12.

[3] Perez DL, Dworetzky BA, Dickerson BC, Leung L, Cohn R, Baslet G, Silbersweig DA. An Integrative Neurocircuit Perspective on Psychogenic Nonepileptic Seizures and Functional Movement Disorders: Neural Functional Unawareness. Clinical EEG and Neuroscience. 2015; 46(1): 4-15.

[4] van der Kruijs SJM, Jagannathan SR, Bodde NMG, Besseling RMH, LAzeron RHC, Vonck KEL, et al. Resting-state networks and dissociation in psychogenic non-epileptic seizures. J Psych Research. 2014 Jul 54:126-133.

[5] van der Kruijs SJM, Bodde NMG, Lazeron RHC, Vonck k, Boon P, Hofman PAM, et

al. Functional connectivity of dissociation in patients with psychogenic nono-epileptic seizures. J Neurol Neurosurg Psychiatry. 2012; 83:239-247.

[6] Pollak TA, Nicholson TR, Edwards MJ, David AS. A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms. J Neurol Neurosurg Psychiatry. 2014; 85:191-197.

[7] Dafotakis M, Ameli M, Vitinius, F et al. Transcranial magnetic stimulation for psychogenic tremor- a pilot study. Fortschr Neurol Psychiatr. 2011; 79:226-233.

[8] Ding j, An D, Liao W, Wu G, Xu Q, Zhou D, Vhen H. Abnormal functional connectivity density in psychogenic non-epileptic seizures. Epilepsy Research. 2014; 108: 1184-1194

[9] Ding j, An d, Liao W, Jinmei L, Wu G, Xu Q, et al. Altered Functional and Structural Connectivity Networks in Psychogenic Non-Epileptic Seizures. PLOS One. 2013; (8)5. Pub Med PMCID: PMC3661726.

[10] Voon V, Gallea C, Hattori N, Bruno M, Ekanayake V, Hallett M. The involuntary nature of conversion disorder. Neurology. 2012 Jan 19;74(3):223-8.

[11] Voon V, Brezing C, Gallea C, Hallett M. Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. Mov Disord 2011; 26:2396-403.

[12] Christopeit M, Simeon D, Urban N, Gowatsky J, Lisanby S, Mantovani A. Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) on Specific Symptom Clusters in Depersonalization Disorder (DPD). Brain Stimulation. 2014; 7(1): 141-150.

[13] Mantovani A, Simeon D, Urban N, Bulow P, Allart A, Lisanby S. Temporo-parietal junction stmulation in the treatment of depersonalization disorder. Psychiatry Research. 2011; 168(1): 138-140.

[14] Cocks K, and Torgerson D. Sample size calculations for pilot randomized trials: a confidence interval approach. J Clinical Epidemiology. 2013; 99: 197-201.

[15] Levkovitz Y, Isserles M, Padberg F, Lisanby S. World Psychiatry. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. 2015; 14(1): 64-73.

[16] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. 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.