Published in final edited form as:

Psychosomatics. 2018 November ; 59(6): 601–606. doi:10.1016/j.psych.2018.03.001.

Right Temporoparietal Junction Transcranial Magnetic Stimulation in the Treatment of Psychogenic Non-epileptic Seizures: A Case Series

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Abstract

BACKGROUND—Psychogenic non-epileptic seizures (PNES) may involve hypoactivity in the right temporoparietal junction (TPJ), suggesting a promising target for therapeutic neuromodulation. In this proof-of-concept case series, we aimed to investigate the tolerability and potential efficacy of high frequency repetitive Transcranial Magnetic Stimulation (rTMS) over the right TPJ to decrease non-epileptic seizure rates.

METHODS—Seven subjects with video-EEG documented PNES without comorbid epileptic seizures were recruited. The rTMS protocol involved thirty stimulation sessions administered twice per day over three weeks. Each session consisted of three thousand pulses of high frequency (10 Hz) rTMS applied over the right TPJ. Tolerability was monitored throughout treatment. Weekly PNES counts were recorded at baseline, during treatment, and at post treatment intervals as the primary outcome measure. Additional psychometric scales assessing dissociation and functional neurological symptoms were collected at baseline and within 1-week post treatment as secondary outcome measures.

RESULTS—Treatment with rTMS was well tolerated by all participants. Participants reported a decrease in weekly seizure rates post vs. pre-treatment, which was sustained at 3-month follow-up. Improvement was also reported on the Dissociative Experiences Scale and the Conversion Disorder Subscale of the Screening for Somatoform Symptoms-7 Scale.

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Conflict of interest:
None

CONCLUSION—High-frequency rTMS over the right TPJ represents a promising treatment for PNES that warrants additional research.

Keywords

psychogenic nonepileptic seizures; repetitive transcranial magnetic stimulation; dissociative seizures; neuromodulation; conversion disorder

Introduction

Patients with psychogenic non-epileptic seizures (PNES)/dissociative seizures represent a highly prevalent and disabling subtype of Functional Neurological Disorders (FND, a.k.a. Conversion Disorder).¹ Individuals with PNES display paroxysmal alterations in consciousness and motor function that are phenotypically distinct from epileptic seizures and show an absence of epileptiform abnormalities on ictal EEG.² PNES are also difficult to treat, costly to healthcare systems, and associated with markedly impaired health-related quality of life.^{3–6}

Many patients with PNES indicate a lack of an appreciable sense of control over their seizures; instead, individuals describe their seizures as involuntary or lacking in self-agency.^{7,8} Impairments in self-agency perception in FND have been theorized to relate to deficits in feed-forward processing (a.k.a. corollary discharge), which arise from impaired delivery of afferent sensory-motor inputs to the inferior parietal lobe/temporoparietal junction.⁹ In addition, there may be an overlap between impaired self-agency perception and dissociation, particularly since the inferior parietal lobe/temporoparietal junction has also been connected to the neurobiology of dissociation.¹⁰ Recent neuroimaging studies have demonstrated aberrant regional activity and functional connectivity alterations in the right TPJ in PNES^{11,12} and other motor FND populations.¹³ Despite the increased understanding of the neurobiology of PNES and related motor FNDs,^{11,13} there are few effective treatments, and many patients remain symptomatic despite treatment adherence.^{14,15}

The neuroimaging literature has identified broadly distributed neural circuit alterations in FND, including involvement of right-lateralized temporo-parietal regions.¹² Several studies have connected the right TPJ to the pathophysiology of FND, including, for example, an fMRI study which showed right TPJ hypoactivation and diminished right TPJ - sensorimotor functional connectivity in 8 patients with functional tremor.⁸ Similar right TPJ - sensorimotor functional connectivity alterations have been described in a larger cohort of 35 patients with FND compared to controls.¹⁶

Several groups have also investigated the use of TMS as a treatment of FND.^{17–19} One study observed a decrease in non-epileptic seizure frequency in a sample of 42 PNES patients using low frequency (1 Hz) large-field rTMS applied to the midline fronto-central area.²⁰ Another small placebo-controlled study demonstrated no subjective improvements in a functional weakness cohort despite measuring improved muscle strength.²¹ No studies have previously investigated rTMS applied to the right TPJ in PNES.

Given right TPJ functional abnormalities across FND populations, and theorized contributions of this region to self-agency perception and dissociation, this area may be an important node in the pathophysiology of PNES. Increasing right TPJ cortical excitability using high frequency (10 Hz) rTMS may be a potential treatment for PNES. In this pilot proof-of-concept case series, we aimed to investigate the tolerability and feasibility of a 30-session high frequency (10 Hz) rTMS protocol over the right TPJ in patients with PNES.

Methods

A. Participants

7 adults with PNES-convulsive type were recruited from the Epilepsy Clinic and Neuromodulation and Neuropsychiatry Unit at St. Boniface Hospital, Winnipeg through physician referral. All met criteria for documented PNES using video-EEG.² Psychiatric comorbidities were assessed using the Mini International Neuropsychiatric Interview (MINI).²² Participants with epileptic seizures, other major neurological/medical disorders, history of psychosis, mania or active alcohol or drug use disorder, use of medications that lower the seizure-threshold (e.g. bupropion) and/or pregnant women were excluded. No individuals participated in psychotherapy during this study.

All subjects provided informed consent and this research protocol was approved by the University of Manitoba Biomedical Research Ethics Board and the St. Boniface Hospital Research Review Committee.

B. rTMS Protocol

Motor thresholds were determined prior to the first stimulation session. The motor threshold was defined as the minimum stimulator output that elicited a contraction of the abductor pollicis brevis muscle on 5 out of 10 consecutive pulses. For treatment, rTMS was applied to the target location at 110% motor threshold. Each subject received 30 sessions of high frequency (10 Hz) rTMS over the right TPJ with a total of 3000 pulses per session. Each session took approximately 35 minutes to complete (mean=36.6±3.5 minutes), and participants received two sessions per day with a 15-minute break in-between sessions. The entire length of treatment was three weeks (15 weekdays, with two sessions/day). One exception to this protocol was made for subject 2 who travelled from out of town and requested a shorter treatment duration. The length of treatment for this subject was two weeks (10 weekdays, with three sessions/day).

For all participants, each session was comprised of consecutive trains of five-second 10 Hz pulses followed by 30 seconds of no stimulation. In some cases, due to a higher motor threshold, a slightly longer inter-train interval was required (mean=32.2±3.6 seconds) to accommodate coil cooling. Stimulation was applied to the right TPJ using a 70mm figure-eight coil attached to a MagStim Rapid-2 rTMS machine (MagStim Ltd., UK). The target location (right TPJ – Brodmann area 39) was identified using aBrainsight Neuronavigator system (Rogue Research Inc., QC) with Brodmann areas mapped to a Montreal Neurological Institute average head model brain. Land-marking and scaling procedures were used to scale the average head model brain according to the skull size and shape of each

patient. For treatment, the coil was placed perpendicular to the right TPJ using a stereotactic registration technique. Accuracy of coil placement was monitored and corrected for patient movement or coil drift throughout treatment. Of note, the rTMS protocol was based on accepted treatment protocols for major depression,²³ and observations that twice-daily stimulation appears to be as effective as once-daily administration while potentially aiding treatment adherence.²⁴

C. Measurements of Interest

PNES Count—Weekly seizure count using a seizure calendar was the primary outcome measure. Participants recorded seizure frequency daily for one-week intervals. Weekly seizure counts were taken at 8 time points: baseline (starting 1 week prior to rTMS treatment), week 1, week 2, and week 3 of treatment, as well as 1 week, 1 month, 2 months, and 3 months post-treatment. An exception was made for subject 2 who received an accelerated 2-week treatment. To keep results as consistent as possible, an additional weekly PNES count was taken for this subject: 4 weeks from baseline (corresponding to 1 week post-treatment for remaining participants).

Additional Psychometric Measurements—Within a week prior to the first rTMS session, participants completed a self-report psychometric battery to assess the spectrum of functional neurological symptoms and predisposing factors. Psychometric instruments assessed the following domains: **Sensory-Motor FND Symptoms:** Conversion Disorder Subscale of the Screening for Somatoform Symptoms-7 Scale (SOMS-CD);²⁵ **Health Status:** Short Form-36v1 Health Survey (SF-36);²⁶ **Mood/Anxiety:** Beck Depression Inventory-II (BDI-II),²⁷ Spielberger State-Trait Anxiety Inventory (STAI);²⁸ **Dissociation:** Dissociative Experience Scale (DES);²⁹ **Trauma:** Childhood Trauma Questionnaire (CTQ)³⁰ and the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5).³¹

The above scales were used as secondary outcome measures. The DBI-II, STAI, DES, SOMS-CD and SF-36 (conducted at baseline) were repeated within 1-week post treatment. Participants receiving psychopharmacologic therapies were permitted to continue their medications throughout treatment. Changes to psychotropic medications during treatment and 3-month follow-up were kept to a minimum (Supplemental Table 1).

Tolerability—Daily treatment logs were kept by the technicians responsible for rTMS administration. Patients were queried at each treatment session as to the occurrence of any adverse events or potential side effects, which were then recorded in the logs. Patients were also encouraged to report adverse or novel symptoms in their personal seizure calendars (described above), and they were queried about side effects by the study clinician post-treatment.

D. Data Analysis

Statistical analyses were conducted using SYSTAT version 13.0 (Systat Software Inc., CA). The non-parametric Friedman test was used to detect differences in seizure frequency across the 8 different time points with the level of significance set to 0.05. For exploratory secondary analyses, separate non-parametric, Wilcoxon signed-rank tests, were used to

compare baseline scores to post-treatment scores on the BDI-II, STAI, DES, SOMS-CD, and SF-36. The level of significance for all tests was set to 0.05, two-tailed.

Results

A. Participants

All participants with PNES completed the study. Baseline demographic and clinical information is shown in Supplemental Table 1. The mean age of participants was 43.1 ± 8.8 years. The average age of onset of PNES symptoms was 28.3 ± 16.6 years. The mean duration of PNES diagnosis was 14.5 ± 13.8 years, with an average frequency of 5.1 ± 5.7 seizures/week. All subjects also reported other FND symptoms with a mean SOMS-CD score of 16.0 ± 8.9 (Supplemental Table 2).

B. Tolerability of rTMS

No significant adverse events were observed, and no side effects were distressing enough for participants to stop rTMS treatment. Reported side effects included headache or migraine ($n=5$, 71.4%), vivid/altered dreams ($n=3$, 42.9%), fatigue ($n=2$, 28.6%), and one participant reported hallucinations ($n=1$, 14.3%).

C. Weekly PNES Counts

A notable decrease in weekly seizure frequency was seen in all participants between baseline (7.3 ± 5.3 events) and completion of rTMS (1.0 ± 1.3) (See Figure 1). All participants maintained reduced seizure frequencies at 1 month (2.7 ± 2.8), 2 month (2.7 ± 3.9), and 3 month follow-up (2.4 ± 3.7), with 4 of 7 participants remaining seizure free at 3-months post-treatment. The Friedman test revealed a significant difference in PNES count over the 8 time points ($p=0.001$).

D. Secondary Psychometric Outcomes

Post-treatment vs. baseline, participants exhibited statistically significant decreases in DES ($p=0.043$) and SOMS-CD scores ($p=0.028$). There were no other statistically significant changes in the other psychometric measures.

Discussion

This proof-of-concept case series is predicated upon research linking functional alterations in the right TPJ to the pathophysiology of FND.^{8,16,32} Hypoactivations and altered connectivity patterns in the right TPJ have been theorized to relate to impaired self-agency perceptions in FND.⁹ It has been proposed that action-authorship perceptions are, in part, based on a delay between intention and action.³³ However, patients with FND may experience a decrease in this delay potentially leading to the experience of movements without a sense of agency.³⁴ The preliminary findings of this study observing decreased PNES event frequency following right TPJ rTMS lend additional support to a role for the rTPJ in the pathophysiology of FND; larger controlled studies are warranted to rigorously investigate right TPJ neuromodulation as a treatment for PNES.

We speculate that three alternative mechanisms may help explain how neuromodulation of the right TPJ may reduce PNES event frequency. rTMS stimulation over the right TPJ may be viewed as a mechanism to increase right IPL/TPJ activity, thereby, increasing the intention-movement interval and allowing patients sufficient time to gain awareness of motor intention. Alternatively, stimulation with rTMS may simply decrease seizure frequency by correcting for right TPJ hypoactivity and thereby increasing multisensory integration in this area, allowing a greater capacity for self-agency. Lastly, patients with PNES may be particularly prone to suggestibility, so the role of placebo (which itself is a neurobiological process) cannot be excluded.³⁵ Additional research incorporating a sham control group is necessary, and pre and post TMS resting-state functional neuroimaging would help elucidate the mechanism of action.

We note that the treatment effect size and secondary outcome measures should be interpreted with caution given the small sample size and lack of a control group. Furthermore, this case series did not control for potentially confounding effects of psychopharmacologic interventions.

In conclusion, high-frequency rTMS over the right TPJ is a promising strategy for treatment of PNES, which was well tolerated in our cohort. Additional controlled studies are needed to investigate both the potential efficacy and neural mechanisms through which right TPJ rTMS may be an effective treatment for patients with PNES and other motor FNDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to gratefully acknowledge the contributions of our sponsors including the University of Manitoba B.Sc. Med program, St. Boniface Hospital Foundation, the HSC Medical Staff Executive and Rady Faculty of Health Sciences travel fund. DLP was funded by the 1K23MH11983-01A1 and the Sidney R. Baer Jr. Foundation.

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Figure 1. Seizure counts in patients with psychogenic nonepileptic seizures (PNES) receiving rTMS

Weekly seizure count logs kept by patients with PNES receiving rTMS treatment. Note: Subject 2 received two weeks of treatment. For this subject, post-treatment seizure recording begins at 'Tx wk3'. Abbreviations: tx: treatment; wk: week; mth: month; f/u: follow-up.