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Project Title: **Transcranial Magnetic Stimulation in the treatment of non-epileptic seizures: A Case Series**

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Summary (250 words max single spaced):

BACKGROUND: Psychogenic non-epileptic seizures (PNES) is a poorly understood psychiatric condition for which there are currently few effective treatments. Recent neuroimaging studies have implicated right temporoparietal junction (TPJ) hypoactivity as an important contributor to the pathophysiology of PNES. Impaired function in this area may decrease awareness of motor intention and self-agency, causing individuals to perceive their movements as involuntary. In this case series we aimed to investigate the tolerability of high frequency repetitive Transcranial Magnetic Stimulation (rTMS) over the right TPJ in patients with PNES, and its ability to decrease the frequency of non-epileptic seizures.

METHODS: Eight patients with PNES completed this study. Thirty sessions of high frequency (10 Hz) rTMS were applied over the right TPJ, with a total of 3000 pulses each session. Tolerability was recorded throughout treatment. Weekly PNES counts were recorded at baseline, throughout treatment, and at post treatment intervals. Psychometric self-rating scales were used as secondary outcome measures conducted at baseline and within 1-week post treatment.

RESULTS: Treatment with rTMS was well tolerated within our sample. A significant decrease in weekly seizure frequency was observed over treatment time course and three month follow up ($F= 3.15$, $p = 0.008$). Significant improvement was also appreciated on the Dissociative Experience Scale ($p= 0.028$) and Conversion Disorder Subscale ($p= 0.023$) post-treatment.

CONCLUSION: High-frequency rTMS over the right TPJ represents a novel, feasible, and potentially efficacious treatment for PNES, possibly correcting for right TPJ hypoactivity. Further randomized controlled trials incorporating fMRI biomarkers are needed to confirm our results.

Student Signature

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Primary Supervisor Signature

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Transcranial Magnetic Stimulation in the treatment of non-epileptic seizures: A Case Series

Introduction

Psychogenic non-epileptic seizures (PNES) is a distressing neurobehavioral condition at the interface of neurology and psychiatry.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), this disorder is classified as a subtype of Functional Neurological Symptom Disorder (FNSD/FND), also known as Conversion Disorder (CD).[2] PNES are seizure-like activity, including abrupt recurrent changes in behavior, or consciousness with no epileptiform abnormalities on EEG.[3] It is estimated that 5% - 20% of patients admitted to epilepsy units are diagnoses with PNES, and a further 20 - 30% of patients whose seizure activity is initially considered to be intractable epilepsy are also eventually diagnosed with PNES.[3] These numbers make PNES as common as Parkinson's disease,[1] as physically restricting, and causing even greater impact on mental health and quality of life.[4] Prevalence rates of psychiatric comorbidities among PNES patients have been noted throughout the literature to be high.[5] Patients with PNES often present with multiple psychiatric conditions including mood and anxiety disorders. Problems involving emotion dysregulation, dissociation, psychological trauma, and reports of previous abuse are common.[5]

The study of PNES and other somatic symptoms were first described in 19th century medical literature as "hysteria" by Charcot.[6] Freud later coined the term "conversion" to describe the expression of repressed emotions through somatic symptoms.[7] Current conceptualizations of PNES integrate both psychological, and neurophysiological mechanisms which elucidate aberrant regional and functional connectivity patterns in the neurobiology of patients with PNES.[1] The exact pathophysiology of the disorder however, still remains poorly understood.

The DSM-5 describes this group of Functional Neurological Disorders (FNDs) as symptoms of altered voluntary movement, however patients presenting with PNES indicate no sense of voluntary control. FND movements utilize voluntary motor pathways, yet patients with PNES repeatedly describe experiencing their symptoms as involuntary, or lacking in self agency.[8] Self agency is the experience that one intends to cause the action that one performs.[9] In a sense, self agency is the epitome of free will, allowing oneself to experience the self as the author of one's own movements. Self agency is believed to arise from the comparison of feed forward signals (the predicted outcome of a movement), and actual sensory feedback from the movement itself.[8] Numerous studies have identified the right Temporoparietal Junction (right TPJ; Brodmann area 39) as being a seed region in the multisensory integration of this process.[8–15] In essence, the right TPJ is what allows for motor intention; discrimination of involuntary from voluntary movement.[16]

Recent literature has demonstrated aberrant regional and functional connectivity involving right TPJ hypoactivity in patients with PNES[3,19,20] as well as in other FND.[8,16] 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.[17,18] 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 eleven patients with PNES was found in a global networks involving emotion (the insula), movement (precentral sulcus), and executive control (the inferior frontal gyrus and parietal cortex).[17] The authors were further able to correlate these connectivity differences to elevated dissociation scores within their patient sample.[17]

Despite growing awareness of the neurobiological networks involved in PNES, there are currently few effective treatments for the disorder.[1,23] Given the findings of right 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.[3] A decrease in motor intentional awareness, and therefore self-agency may result in an inability to take authorship over one's movements, thus perceiving them as involuntary. In light of 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 (10 Hz) repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive method of brain stimulation, is known to increase focal cortical activity. Applied over the right TPJ, it may then serve to correct TPJ hypoactivity observed in patients with PNES.

A number of studies report previous success with the use of rTMS in the treatment of FND as well as PNES. A recent systematic review of transcranial magnetic stimulation in the treatment of FND by Pollak et al.[24] has highlighted the results of a study conducted in 2011 by Dafotakis M et al.[25] This pilot study demonstrated symptom improvement in 7 out of 11 patients with psychogenic tremor using inhibitory rTMS (0.2–0.25 Hz) over the motor cortex. Parain et al.[26] also showed a decrease in non-epileptic seizure frequency in a sample of 42 PNES patients. In this study however, low frequency (1 Hz) large-field rTMS was used over the midline fronto-central area, covering a surface area 30 times larger than a figure eight coil. As a result of the large cortical area effected by this protocol, the mechanism of seizure improvement could not be localized.

In this case series we aimed to investigate the tolerability and feasibility of a 30-session high frequency (10 Hz) rTMS protocol over the right TPJ and to explore its effect on the frequency of non-epileptic seizures in PNES. We hypothesized that treatment with high frequency rTMS over the right TPJ would decrease the frequency of non-epileptic seizures in patients with PNES.

Methods

A. Participants

A total of 9 patients with convulsive type PNES were recruited for the study. One patient was subsequently excluded from the study as their seizure activity was determined to be non-convulsive type PNES (M.M.). PNES subjects were recruited from the pool of referrals to the Neuromodulation and Neuropsychiatry Unit, St Boniface Hospital, Winnipeg. PNES diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnostic criteria,[2] and confirmed through video recording and monitoring with EEG. In addition, structured neuropsychiatric interview was performed to assess patient's psychiatric comorbidities. Eligible candidates were identified by the participating neuropsychiatrist (M.M.). Inclusion criteria involved adults between the ages of 18 - 65 with confirmed convulsive type PNES. PNES subjects with evidence of previous or comorbid epileptic seizures, or any other major comorbid neurological disease were excluded from the study. Other exclusion criteria included patients currently taking medication that is known to reduce seizure-threshold (e.g. Bupropion), patients currently pregnant, with severe medical conditions, or comorbid psychotic disorder, bipolar disorder, or active substance use disorder.

All subjects were consecutively evaluated and treated with a 30-session high-frequency (10 Hz) rTMS protocol. All subjects provided informed consent for this research protocol and all procedures contributing to this work were approved by the University of Manitoba Biomedical Research Ethics Board, and the St. Boniface Hospital Research Review Committee.

B. rTMS Protocol

Motor threshold was determined for each subject prior to the first session of stimulation with rTMS. Motor threshold was 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 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 each session. Each session took approximately 45 minutes. Two sessions were performed 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 had travelled from out of town for treatment and had requested shorter treatment duration. The entire length of treatment for this subject was two weeks (10 weekdays, with three sessions/day). A 15-minute break was given in between sessions for this subject as well. For all participants, each session was comprised of consecutive trains of five-second 10 Hz pulses followed by 30 seconds of no stimulation. Stimulation was applied to the right TPJ using a 70 mm 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 a Brainsight Neuronavigator system. The coil was placed perpendicular to the right TPJ using a stereotactic registration technique. Landmarks calibrated for subjects were recorded to position and scaled to the MNI brain atlas in Brainsight Neuronavigator system (Rogue Research, QC) using a weighted average MRI.

C. Baseline Assessments

Within a week prior to the first session of rTMS, a psychiatric profile including patient's mood, anxiety, dissociative states, psychological trauma, impulsivity, and functional disability was taken on all 8 patients using FND questionnaires designed on Research Electronic Data Capture (REDCap).[27] The Educational Background Assessment (EBA), Montreal Cognitive Assessment (MoCA),[28] Wide Range Achievement Test–3 (WRAT–3),[29] and the Life Events Checklist for DSM-5 (LEC-5)[30] were included as adjunct to scales on FND Questionnaires.

Psychometric instruments used for baseline assessment assessed the following domains: **Mood/Anxiety:** Beck Depression Inventory-II (BDI-II),[31] Spielberger State-Trait Anxiety Inventory (SSTAI),[32] **Dissociation:** Dissociative Experience Scale (DES),[33] **PTSD/Trauma:** Childhood Trauma Questionnaire (CTQ),[34] Connor-Davidson Resilience Scale (CDRS),[35] Life Events Checklist for DSM-5 (LEC-5),[30] **Pain Catastrophizing:** Pain Catastrophizing Scale (PCS)**,**[36] **Somatization and Related Topics:** Conversion Disorder Subscale from the Screening for Somatoform Symptoms-7 scale (SOMS-CD),[37] Toronto Alexithymia Scale 20 (TAS),[38] **Impulsivity:** Barratt Impulsivity Scale (Version 11) (BIS),[39] **Health:** RAND SF-36v1 Health Survey (SF-HS),[40] **Education and Cognition:** Educational Background Assessment (EBA), Montreal Cognitive Assessment (MoCA),[28] and the Wide Range Achievement Test–3 (WRAT-3),[29] and **Handedness:** Edinburgh Handedness Inventory (EHI).[41] Scores on the SSTAI were further broken down into their component sections; the Spielberger State Anxiety Inventory (SSAI) and Spielberger Trait Anxiety Inventory (STAI).[32]

The DES is a 28-item measure of dissociation experiences that occur in daily life; scores on each item range from 0 - 100%, 0% being 'never' to 100% 'always'. The total score for the entire scale is an average of all items. The CTQ is a 25-item measure of abuse and neglect in childhood/adolescent; cumulative results as well as subsections of emotional abuse (EA), emotional neglect (EN), physical abuse (PA), physical neglect (PN) and sexual abuse (SA) were calculated separately. The CDRS is a 25-item measure of resilience. Each item is rated on a 5-

point scale (0 – 4) from 'not true at all' to 'true nearly all the time'. Higher scores on this scale reflect greater resilience. The LEC-5 is a measure of lifetime adverse events in 17 categories. The PCS is a 13-item measure of pain catastrophizing. Each item is rated on a 0 to 4 point scale from 'not at all' to 'all the time'. Higher scores on this scale represent greater pain catastrophizing. The SOMS-CD is a 21-item measure of functional neurological motor and sensory symptoms. Each item begins with 'in the past 7-days' and is scored on a 5-point scale ranging from 'not at all' to 'very severe'. The TAS is a 20-item measure of alexithymia; difficulty identifying and describing emotion. Each item is on a 5-point scale from 'strongly disagree' to strongly agree'. Sores from 52 to 60 equal possible alexithymia, and a score of greater than or equal to 61 equal alexithymia. The BIS is a 30-item measure of impulsiveness. Each item is on a 4-point scale, from 'rarely/never' to 'almost always/always'. A higher score on the BIS indicates greater impulsivity. The SF-HS is a 36-item measure of health. A higher scaled score, out of 100, reflects greater health and decreased functional disability.

D. Measures

PNES Count

Weekly PNES count was the primary outcome measure in this study. Participants recorded non-epileptic seizure activity daily for one-week intervals. Weekly PNES counts were taken at 8 points in time; 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 treatment over a 2-week period. In order 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). For this subject weekly PNES counts were taken at baseline (starting 1 week prior to rTMS treatment), week 1, and week 2 of treatment, as well as 1 week post-treatment (week 3 of treatment for remaining participants), 2 weeks post-treatment (1 week post-treatment for remaining participants), 1 month, 2 months, and 3 months post treatment. Collecting weekly PNES counts at these times for this subject allowed us to maintain consistent data points at all times for all subjects.

Psychometric Testing

Psychometric self-rating scales were used as secondary outcome measures. Specific psychometric tests conducted at baseline were repeated within 1 week post treatment. These tests included: **Mood/Anxiety:** BDI-II, SSAI, STAI, **Dissociation:** DES, **Somatization and Related Topics:** SOMS-CD**,** TAS**,** and **Health:** SF-HS.

E. Data Analysis

PNES Count

Statistical analyses were conducted using SYSTAT version 13.0 (Systat Software Inc., SH, California). A repeated measures ANOVA was used to determine the effect of the treatment condition (rTMS) on the frequency of weekly PNES episodes. We looked at the change in weekly PNES counts across 8 points in time; baseline, week 1, week 2 and week 3 of treatment, as well as week 1,1 month, 2 months, and 3 months post-treatment. Seizure count was used as the within-group factor, and linear regression analysis was performed with the level of significance set to 0.05.

Psychometric Testing

Separate two-tailed paired t-tests were used to compare baseline scores to post-treatment scores on the BDI-II, SSAI, STAI, DES, SOMS-CD, SF-HS, and TAS scales in order to determine variables of significance for stepwise regression in future studies. Welch's t-test (two-sample t tests, assuming unequal variances) was performed to compare baseline and post-treatment sample data on the DES scale (mean and standard deviation) to normative values from a Winnipeg cohort in a study by Ross et al.[42] All t-test statistical analyses were conducted on Microsoft Excel for Mac 2011 version 14.0.0 (RSA Data Security, Inc.) The level of significance for all tests was set to 0.05, two-tailed.

Results

A. Participants

All 8 PNES patients completed the study. Baseline demographic and clinical information is shown in Table 1. The mean age of participants was 45.3 years (S.D. of 9.10 years). The majority of participants, 75% (n = 6) were female, and 25% (n = 2) were male (one participant having recently transitioned from female to male). As determined using the EHI, 87.5% of participants (n = 7) were right handed, and one participant was ambidextrous. The EBA was used to characterize participants' educational background. A majority of participants (n = 5) were High School Graduates, while only one subject had received a post secondary associate degree (Occupational/Technical/or Vocational). Most subjects were not working (87.5%, n = 7), with 75% of subjects (n = 6) on some form of government assistance for their disability. Comorbid psychiatric diagnosis was made in 75% of participants (n = 6), and 87.5% (n = 7) of participants received some form of psychotropic medication taken on a regular basis.

Specific information on the history of PNES episodes was collected for all 8 participants (Table 2). The mean onset of PNES episodes was 25.5 years of age (S.D. of 17.2), 62.5% (n = 5) reporting an age of onset in adulthood (after 18 years old). The duration of PNES diagnosis was highly variable in this sample with a range of 1 - 41 years, and a mean duration of 17.8 years (S.D. of 15.8). The mean frequency and duration of PNES episodes was 4.54 seizures per week (S.D. of 5.58), and 1.94 minutes (S.D. of 1.55) in duration. The majority of PNES patients in this sample (87.5%, n = 7) reported stress as a trigger for their PNES episodes. Of the participants, 75.0% (n = 6) reported other FND symptoms in addition to PNES. 5 subjects (62.5%) reported both sensory and cognitive symptoms, 4 reported pain symptoms (50.0%), 3 participants reported additional positive motor symptoms other than PNES (37.5%), and 1 subject reported both altered awareness and negative motor symptoms (12.5%). The majority of patients had been hospitalized as a result of their non-epileptic seizures, and had presented multiple times to the emergency room, with a mean of 1.63 (S.D. of 1.19) hospitalizations and 10.7 (S.D. of 13.2) emergency room visits.

B. Tolerability of rTMS

No significant adverse events were observed as a result of rTMS treatment, and no side-effects were distressing enough for participants to stop treatment. Reported possible side-effects included headache or migraine (n = 6, 75.0%), vivid/altered dreams (n = 3, 37.5%), fatigue (n = 3, 37.5%), nausea (n = 1, 12.5%), and one participant reported hallucinations (n = 1, 12.5%).

C. Weekly PNES Count Results

Individual data on weekly seizure counts is seen in Table 3. A notable difference in weekly seizure frequency was seen in the majority of patients by week two of treatment with rTMS (mean 2.25 weekly events, S.D. 2.60) (Table 4). By week one post-treatment, mean weekly PNES counts dropped to 1.75 events per week (S.D. 2.43). Unfortunately, for 3 patients (37.5%) seizure frequency appeared to increase again slightly towards the 3 months follow up, with a mean of 2.13 PNES events weekly (S.D 3.56) at 3 months post-treatment. One subject who was not experiencing seizures at baseline, but who chose to participate in the study due to their long history of non-epileptic seizures, had an increase in seizure activity during treatment (subject 7). The frequency of subject 7's seizures subsequently declined following treatment and this subject was seizure free at 3-month follow up. Despite the slight increase in seizure activity for some subjects following completion of treatment, all subjects, with the exception of subject 7, maintained a reduction in seizure frequency, and 62.5% (n = 5) of participants were seizure free at 3-month follow up. A graph depicting weekly non-epileptic seizure count over time is shown in Figure 1.

A repeated measures ANOVA of seizure counts over treatment time course revealed a significant main effect of weekly PNES count ($F_{7,49} = 3.15$, $p = 0.008$) (Table 4). Post-hoc paired comparisons for repeated measures showed a significant decrease in seizure frequency from baseline to week 2 of treatment, baseline to 1 month follow up, and baseline to 3 months follow up ($p = 0.044$, $p = 0.014$, and $p = 0.024$ for respective pairwise comparisons). A trend-level reduction in seizure activity was appreciated from baseline to week 3 of treatment, baseline to 1 week post-treatment, and baseline to 2 months follow up ($p = 0.083$, $p = 0.073$, and $p = 0.088$ respectively), as well as from week 1 of treatment to week 3 of treatment, week 1 of treatment to 1 week post-treatment, and week 1 of treatment to 1 month post-treatment ($p = 0.078$, $p = 0.093$, and $p = 0.089$ respectively).

D. Baseline Psychometric Assessment Results

Baseline assessment results under the domains of PTSD/Trauma, Pain Catastrophizing, Impulsivity, and Education and Cognition are shown in Table 5. Under the PTSD/Trauma domain mean sample scores on the CTQ were greater than normative values listed by Scher et al.,[43] while our sample mean on the CDRS was lower than that of a study by Connor et al.[35] These differences indicate a greater childhood trauma burden and decreased resilience in our sample. Sample means for subscales on the CTQ including emotional abuse (mean of 14.4, S.D. of 6.99), emotional neglect (mean 12.4 and S.D. of 5.95), physical abuse (mean 14 and S.D. of 7.67), physical neglect (mean of 10.4, S.D. of 5.37), and sexual abuse (mean of 10.5, S.D. of 8.05) were also higher than normative values.[43] No normative data was available to compare to sample scores on part 3 of the LEC-5 'happened to me' 5-point scale.

The sample score for the PCS (mean of 32.6 and S.D. of 37.0) corresponded to greater than the 75th percentile of the distribution of PCS scores in clinical samples of patients suffering with chronic pain, indicating higher levels of pain catastrophizing in our sample.[36] Clinically relevant catastrophizing is indicated on the PCS by a score of 30 or greater. Mean impulsivity as measured by the BIS was calculated for the sample (mean of 71.3 and S.D. of 8.26) and was also greater than a community sample of 700 participants ages 15 to 89 years of age,[44] indicating higher levels of impulsivity within our sample as well.

E. Secondary Outcome Psychometric Results

Secondary outcome measures for Mood/Anxiety, Dissociation, Somatization and Related Topics, and Health are shown in Table 6. Mean baseline scores under the Mood/Anxiety domain, including BDI-II, SSAI, and STAI were greater than normative means listed by Schulte-van et al.[45] and Knight et al.,[46] indicating higher levels of depression, and anxiety in our sample. Although all of the mean scores under the Mood/Anxiety domain decreased post-treatment (indicating improvement) (the sample mean BDI-II score at baseline corresponded to moderate clinical depression on the BDI-II scale, while the mean BDI-II score post-treatment did not meet threshold for clinical depression),[31] there was no significant change between baseline and post-treatment means on any of the psychometric tests in this domain.

Our sample mean for dissociation, as measured by the DES, was significantly greater than that of a study by Ross et al.[42] ($p= 0.020$), who used a Winnipeg cohort to establish normative values for the DES. These results indicate significantly higher dissociation in our sample. Of particular interest in our study was the statistically significant decrease in mean DES scores observed between baseline and post-treatment ($p= 0.028$), showing a decrease in dissociative symptoms following treatment.

A significant decrease was also seen between mean baseline and post-treatment SOMS-CD scores under the domain of Somatization and Related Topics ($p= 0.023$), indicating a decrease in conversion symptoms following treatment. Unfortunately, no normative data was available for comparison to sample means on the SOMS-CD subscale. Baseline and post-treatment means for TAS were higher than TAS normative values cited by Parker et al.,[47] revealing higher levels of alexithymia in our sample. There was no significant difference found between baseline and post-treatment means on the TAS for our sample, and this scale only showed a very slight decrease post-treatment.

Under the domain of Health, the SF-HS baseline and post-treatment sample means were found to be quite low (indicating poor sample self reported health), both baseline and post-treatment sample means being less than half of the maximum scaled score on the SF-HS. Although no significant difference was observed between pre and post-treatment means, the SF-HS was the only scale to show an increase in mean values from baseline to post-treatment, indicating an increase in sample self reported health and a decrease in functional disability.

Discussion

TPJ Hypometabolism and Mechanistic Considerations

Consistent with our a priori hypothesis, treatment with rTMS over the right TPJ resulted in a significant decrease in the weekly frequency of non-epileptic seizures in patients with PNES. The results of our case series support previous literature findings by Arthuis et al. and Ding et al. implicating right TPJ hypoactivity, and aberrant TPJ functional alterations as contributing factors to the pathophysiology of PNES.[3,19,20]

In 2015, 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 consciousness of the self and environment (right parietal hypometabolism). It is interesting that stroke damage to the inferior parietal cortex (IPC) has also previously been associated with such phenomena as alien hand syndrome,[48] in which movements are experienced by individuals as being outside of volitional control.[16]

Imaging literature on FND has further implicated abnormalities of the right TPJ in the pathophysiology of positive motor FNDs. Results from an fMRI study published by Voon et al.[8] in 2011 showed significant right TPJ hypometabolism and lower functional connectivity between the right TPJ, sensorimotor cortices, cerebella vermis and limbic regions (ventral anterior cingulate and right ventral striatum) in 8 patients with conversion tremor compared to voluntary mimicked tremor.

When the findings of our study are considered in conjunction with Libet's clock paradigm, an even greater understanding of the pathophysiology of PNES is illuminated. In 1983, Libet delineated the difference between motor intention and the movement itself using a scalp recorded potential (EEG), electromyogram (EMG), and revolving clock to record subjects' movement and brain activity.[49] He had healthy subjects recall the 'clock-position' at the time of the initial awareness of their intention to move. In his experiment, Libet showed that the intention to move (W judgment) preceded the actual movement (M judgment) by approximately 200 ms. In fact, Libet et al. showed (as indicated with a scalp-recorded slow negative potential shift), that intentional awareness itself was actually preceded by an unconscious initiation of the will (or volition to move called the *Bereitschaftspotential*, or the readiness potential, RP). A major contributing source of the RP has been now localized to the supplementary motor area (SMA).[22] He hypothesized that the 200 ms delay in intention (W judgment) relative to M judgment allowed for an inhibitory or veto process. The Inferior Parietal Cortex (IPC), as well as the supplementary motor cortex (SMC) have since been identified as primary regions controlling the W judgment, or motor intention (IPC being further upstream in the process than SMC).[16]

A recent fMRI study published by Baek et al. in February of this year, 2017, examined motor intention in 26 patients with FND and 25 healthy controls (HC) using Libet's clock paradigm.[16] FND patients exhibited significant right inferior parietal lobule (IPL; Brodmann area 40) (IPL is encompassed by the TPJ; Brodmann area (BA) 39)[16] hypometabolism and reduced connectivity between the right Inferior Parietal Cortex (IPC) and frontal control regions (dorsolateral prefrontal cortex (dlPFC), and ACC). FND patients also showed a significantly reduced W-M interval compared with HC. The W-M interval was positively correlated with fMRI blood oxygen level dependent (BOLD) activity in the bilateral IPL, primary motor/premotor areas, dlPFC and precuneus, revealing abnormalities in motor intentional awareness underlying functional movements.

Baek et al.[16] further distinguish the role of right IPL (BA 40) from that of the right TPJ (BA 39), both of which are implicated in impairments of intention using Libet's clock.[50]
IPL has been suggested as the focus of intention in voluntary movements, while the whole of TPJ may be more of a comparator system, integrating movement prediction and outcome which gives rise to the feeling of self agency.[16] As a result, two alternative mechanisms, or a combination thereof are conceivable for the correction of right TPJ pathophysiology through stimulation with rTMS. It is possible that in PNES patients, a delay in the W-M interval (preventing sufficient time for an inhibitory process to occur in conjunction with the supplementary motor cortex, (SMC, implicated in motor inhibition)),[51] may primarily reflect right IPL hypoactivity.[16] The decrease in non-epileptic seizure frequency with rTMS stimulation over the right TPJ, may then be viewed as a remedial mechanism which increases right IPL activity, therefore increasing the W-M interval and allowing patients sufficient time for a veto process.

Indeed, the opposite effect has been illustrated in a study by Sirigu et al.[52] who showed a decreased W-M interval in individuals with IPC stroke lesions when compared to cerebella patients and healthy volunteers.[16]

Another possibility involves more completely the increase in capacity for self agency. As previously discussed, self agency is the experience that one intends to cause the action that one performs. This is believed to arise from the comparison of feed forward signals, and actual sensory feedback from the movement itself.[8] Right TPJ; Brodmann area 39, has been identified in numerous studies as being a seed region in the multisensory integration of this process.[8–15] Hypoactivity in this area (including the IPL) may then result in decreased integration of movement prediction and sensory feedback, giving rise to a decreased feeling of self agency. Stimulation with rTMS may simply decrease seizure frequency by correcting for right TPJ hypoactivity and therefore increasing multisensory integration in this area, allowing for discrimination of involuntary from voluntary movement, thus providing a greater ability for self agency. Clearly there is enormous overlap between both mechanisms, and it is impossible to split hairs without further imaging data, and study in the field.

Along with the above studies which show support for the mechanisms that we propose, we acknowledge that these hypotheses do not answer the questions of how and why non-epileptic seizures are initiated, but only serve as an insight into why PNES is experienced as involuntary, and how it is possible that rTMS may decrease the frequency of non-epileptic seizures.[16] Further study using rTMS targeted to the right TPJ, along with functional MRI correlates, and a larger sample size are needed for better characterization of the mechanisms behind the pathophysiology of PNES, and its correction through treatment with rTMS. A study with a control group is further necessary in order to distinguish these effects from placebo, as suggestibility and hypnotizability have also been noted as prominent characteristics within this population.[17,53]

Changes in Dissociation and Conversion Symptoms Pre verses Post-treatment

Of further interest in this study were our sample's significantly elevated dissociation scores, as well as the significant decrease between baseline and post-treatment mean scores on the DES and SOMS-CD. Dissociation has been previously implicated in the pathophysiology of PNES in imaging studies by van der Kruijs et al. assessing abnormal connectivity strength in four global networks.[17,18] Certainly, an increase in rates of trauma, post-traumatic stress disorder (PSTD), and dissociation have been reported in patients with PNES throughout the literature,[1,5,53–58] and it would not be suprising if dissociative networks were in some way responsible for triggering an already lower threshold *Bereitschaftspotential* (RP). Schurger et al. analyzed data from a Libetus interruptus task (a variant of Libet's task) using EEG recordings and a stochastic-decision model to reproduce the shape and time course of RP.[59] They suggested that movements are produced when the accumulation of ongoing spontaneous fluctuations in neural activity cross a certain threshold. Baek et al. further speculate that patients with positive motor FNDs may have a decreased movement threshold and/or increased neuronal subthreshold fluctuations.[16] Indeed, van der Kruijs et al. show evidence in their imaging results of increased activity/functional connectivity in networks involved in dissociation and movement (the precentral sulcus), the precentral sulcus encompassing a major origin of the *Bereitschaftspotential;* the SMA. Taken together, the results of this study support dissociation as a contributing mechanism in the pathophysiology of PNES.

The change in mean SOMS-CD scores from baseline to post-treatment are also of relevance in this study as this scale was introduced as a secondary outcome measure to capture aspects of other FND symptoms as well as PNES. A decrease on this scale post-treatment lends support

for increased right TPJ activity as a mechanism for the correction of this disorder, since right TPJ hypoactivity has been considered pathogenic across a large spectrum of FND.[8,16] Due to the significant decrease in both dissociative and conversion symptoms post-treatment, we suggest these variables be selected for stepwise regression in future studies.

Comorbidities in PNES

Although one cannot fully appreciate the extent of distress and psychopathological comorbidity present in this sample from the demographic information provided in Table 1, the results of this study support previously literature findings of high rates of comorbid psychopathology in patients with PNES. High mean scores on the BDI-II, SSAI, STAI, DES, CTQ, TAS, SOMS-CD, and BIS indicate increased depression, anxiety, dissociation, childhood trauma, alexithymia, multiple conversion symptoms, and increased impulsivity among this sample. While lower scores on the CDRS, and SF-HS suggest decreased resilience, and decreased health with greater functional impairment.

It was not surprising that mean results from the CTQ were higher than normative values since, as mentioned in the previous discussion of dissociation; reports of trauma, PSTD, and dissociation have been consistently noted among this population.[1,5,53–58] Roelofs et al. have noted that childhood maltreatment is a risk factor for FND, and that the magnitiude of adverse life events predicts severity of illness.[55] A recent imaging study by Perez et al. has further demonstrated associations between cingulo-insular structural alterations (previously associated with PTSD) and psychogenic symptoms, childhood abuse burden, and PTSD symptom severity in a sample of 23 patients with FND.[56] An increase in comorbid psychiatric symptoms within our sample suggests that patients with PNES are at greater risk of psychiatric aliments which further impact on their psychological and social wellbeing.

Future Analysis

Findings thus far support the case for a larger study with a control arm and fMRI biomarkers. Furthermore, in consideration of the recent publication by Baek et al.,[16] future directions of investigation into the efficiency of rTMS for PNES should incorporate a pre and post-treatment Libet's clock analysis with fMRI in order to more fully appreciate the effect of high-frequency rTMS to right TPJ on the W-M interval.

Limitations and conclusion

This study is not without limitations. We note that the treatment effect size as well as secondary outcome measures should be interpreted with caution given the small sample size. In right TPJ localization, landmarks calibrated for subjects used a weighted average MRI provided by the Brainsight Neuronavigator system and not the participant's individual MRI, which would have allowed for greater precision in localization of target cortical structures. Although an operator was present at all times to maintain the coil target, patient movement allowed for periodic changes in coil position. Recruitment for our study was greatly limited by the exclusion of patients with confirmed or strongly suspected epileptic seizure. Many participants presented with multiple psychiatric comorbidities, and as such the confounding nature of these conditions cannot be ruled out. We would like to further emphasize that therapeutic interventions in psychiatric conditions are inherently confounded by potential placebo effects.[60] In our case series there may be a strong expectation bias, perhaps bolstered by the apparent intensity of the treatment (nearly daily treatments with sophisticated equipment and operators present). Additionally, there is a potential therapeutic benefit from participants interacting with operators

delivering the rTMS treatment in a positive, participant-focused setting. A sham control arm would be of benefit in future study to control for many of these potential confounding effects.

In conclusion, high-frequency rTMS over the right TPJ represents a novel, feasible, and potentially efficacious treatment for PNES. High frequency rTMS was well tolerated in our patient sample and could be safely used as treatment for PNES. Our case series lends support to previous literature findings implicating right TPJ hypoactivity as a contributing factor to the pathophysiology of PNES.[3,16,19,20] This study further suggests that high-frequency stimulation over the right TPJ may serve as a corrective factor, allowing patients with PNES to regain a sense of authorship (and control) over their movements.

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Conflict of Interest Disclosure:

The authors declare no conflicts of interest.

References:

1. Perez DL, Lafrance Jr WC. Nonepileptic seizures: an updated review. *CNS Spectr*. 2016;21(2016):239-246. doi:10.1017/S109285291600002X.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
3. Arthuis M, Bartolomei F, Mcgonigal A, Guedj E. Resting cortical PET metabolic changes in psychogenic non-epileptic seizures (PNES). *J Neurol Neurosurg Psychiatry*. 2015;86(10):1106-1112. doi:10.1136/jnnp-2014-309390.
4. Hallett M. Physiology of psychogenic movement disorders. *J Clin Neurosci*. 2010;17(8):959-965. doi:10.1016/j.jocn.2009.11.021.
5. Perez DL, Dworetzky B a, Dickerson BC, et al. An integrative neurocircuit perspective on psychogenic nonepileptic seizures and functional movement disorders: neural functional unawareness. *Clin EEG Neurosci*. 2015;46(1):4-15. doi:10.1177/1550059414555905.
6. Veith I. *Hysteria, the History of a Disease*. Chicago, Ill: University of Chicago Press; 1965.
7. Breuer J, Freud S. *Studies in Hysteria*. New York, NY: Birmingham, Ala. Classics of Psychiatry & Behavioral Sciences Library; 1936.
8. Voon V, Gallea C, Hattori N et al. The involuntary nature of conversion disorder. *Neurology*. 2011;74(3):223-228. doi:10.1212/WNL.0b013e3181ca00e9.
9. Decety J, Lamm C. The Role of the Right Temporoparietal Junction in Social Interaction: How Low-Level Computational Processes Contribute to Meta-Cognition. *Neurosci*. 2007;13(6):580-593. doi:10.1177/1073858407304654.
10. Blakemore SJ, Goodbody SJ, Wolpert DM. Predicting the Consequences of Our Own Actions: The Role of Sensorimotor Context Estimation. *J Neurosci Off J Soc Neurosci*. 1998;18(18):7511-7518.
11. Blakemore S, Sirigu A. Action prediction in the cerebellum and in the parietal lobe. *Exp Brain Res*. 2003;153:239-245.
12. Farrer C, Frey SH, Van Horn JD, et al. The Angular Gyrus Computes Action Awareness Representations. *Cereb Cortex*. 2008;18(February):254-261. doi:10.1093/cercor/bhm050.
13. Fink GR, Marshall JC, Halligan PW, et al. The neural consequences of conflict between intention and the senses. *Brain a J Neurol*. 1999;122(3):497-512.
14. Desmurget M, Reilly K, Richard N, Szathmari A, Mottolese C, Sirigu A. Movement intention after parietal cortex stimulation in humans. *Science*. 2009;324(5928):811-813. doi:10.1126/science.1169896.
15. Farrer C, Franck N, Georgieff N, Frith CD, Decety J, Jeannerod M. Modulating the experience of agency: a positron emission tomography study. *Neuroimage*. 2003;18(2):324-333. doi:10.1016/S1053-8119(02)00041-1.
16. Baek K, Doñamayor N, Morris LS, et al. Impaired awareness of motor intention in functional neurological disorder: implications for voluntary and functional movement. *Psychol Med*. 2017;47(9):1624-1636. doi:10.1017/S0033291717000071.
17. van der Kruijs SJM, Bodde NMG, Vaessen MJ, et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry*. 2012;83(3):239-247. doi:10.1136/jnnp-2011-300776.
18. van der Kruijs SJM, Jagannathan SR, Bodde NMG, et al. Resting-state networks and dissociation in psychogenic non-epileptic seizures. *J Psychiatr Res*. 2014;54(1):126-133. doi:10.1016/j.jpsychires.2014.03.010.
19. Ding J, An D, Liao W, et al. Abnormal functional connectivity density in psychogenic non-epileptic seizures. *Epilepsy Res*. 2014;108(7):1184-1194. doi:10.1016/j.eplepsyres.2014.05.006.
20. Ding J-R, An D, Liao W, et al. Altered functional and structural connectivity networks in psychogenic non-epileptic seizures. *PLoS One*. 2013;8(5):e63850.

doi:10.1371/journal.pone.0063850.
21. Schrag AE, Mehta AR, Bhatia KP, et al. The functional neuroimaging correlates of psychogenic versus organic dystonia. *Brain*. 2013;136(3):770-781. doi:10.1093/brain/awt008.
22. 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(13):2396-2403. doi:10.1002/mds.23890.
23. Baslet G, Dworetzky B, Perez DL, Oser M. Treatment of Psychogenic Nonepileptic Seizures: Updated Review and Findings From a Mindfulness-Based Intervention Case Series. *Clin EEG Neurosci*. 2015;46(1):54-64. doi:10.1177/1550059414557025.
24. Pollak TA, Nicholson TR, Edwards MJ, David AS. A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms. *Neuropsychiatry (London)*. 2014:191-197. doi:10.1136/jnnp-2012-304181.
25. Dafotakis M, Ameli M, Vitinius F. Transcranial magnetic stimulation for psychogenic tremor- a pilot study. *Fortschr Neurol Psychiatr*. 2011;79:226-233.
26. Parain D, Chastan N. Large-field repetitive transcranial magnetic stimulation with circular coil in the treatment of functional neurological symptoms. *Neurophysiol Clin / Clin Neurophysiol*. 2014;44(4):425-431. doi:10.1016/j.neucli.2014.04.004.
27. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf*. 2009;42(2):377-381.
28. Nasreddine Z, Phillips N, Bédirian V et al. The Montreal Cognitive Assessment , MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc*. 2005;53(4):695-699.
29. Wilkinson G. *WRAT: Wide Range Achievement Test Administration Manual*. Wilmington, DE: Wide Range, Inc.; 1993.
30. Weathers F, Blake D, Schnurr P. The life events checklist for DSM-5 (LEC-5). 2013. Instrument available from the National Center for PTSD at 2013;wwwptsdvagov. Accessed July 15, 2017.
31. Beck A, Steer R, GK. B. *Beck Depression Inventory-II*. San Antonio, TX; 1996.
32. Spielberger C, Gorsuch R, Lushene R. *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press; 1970.
33. Bernstein E, Pumam R. Development, reliability, and validity of a dissociation scale. *J Nerv Ment Dis*. 1986;174(12):727-735.
34. Bernstein D, Fink L, Handelsman L. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry*. 1994;151:1132-1136.
35. Connor KM, Davidson JRT. Development of a New Resilience Scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety*. 2003;82(April):76-82. doi:10.1002/da.10113.
36. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and Validation. *Psychol Assess*. 1995;7(4):524-532.
37. Rief W, Hiller W. A new approach to the assessment of the treatment effects of somatoform disorders. *Psychosomatics*. 2003;44:492-498.
38. Bagby M, Parker JDA, Taylor GJ. The Twenty-Item Toronto Alexithymia Scale-I. Item Selection and Cross-Validation of the Factor Structure. *J Psychosom Res*. 1994;38(1):23-32.
39. Patton J, Stanford M, Barratt E. Factor Structure of the Barratt Impulsiveness Scale. *J Clin Psychol*. 1995;51(6), pp.(6):768-774.
40. Rand Corperation, Ware Jr. RAND 36-Item Short Form Survey (Version 1.0). https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html. Published 1990. Accessed July 15, 2017.

41. Oldfield RC. The Assessment and Analysis of Handedness: The Edinburgh Inventory. *Neuropsychologia*. 1971;9:97-113.
42. Ross A, Ph D. Dissociative Experiences in the General Population. *Am J Psychiatry*. 1990;147(11):1547-1552.
43. Scher CD, Stein MB, Asmundson GJG, Mccreary DR, Forde DR. The Childhood Trauma Questionnaire in a Community Sample : Psychometric Properties and Normative Data. *J Trauma Stress*. 2001;14(4).
44. Spinella M. Normative Data and a Short Form of the Barratt Impulsivness Scale. *Intern J Neruroscience*. 2007;(December 2005):359-368. doi:10.1080/00207450600588881.
45. Schulte-van M, Yvonne W, Carlier IVE, et al. Reference values for major depression questionnaires: The Leiden Routine Outcome Monitoring Study. *J Affect Disord*. 2013;149(1-3):342-349. doi:10.1016/j.jad.2013.02.009.
46. Knight RC, Waal-manning HJ, Spears CF. Some norms and reliability data for the State Trait Anxiety Inventory and the Zung Self-Rating Depression scale. *Br J Clin Psychol*. 1983;22:245-249.
47. Parker JDA, Taylor GJ, Bagby RM. The 20-Item Toronto Alexithymia Scale III . Reliability and factorial validity in a community population. *J Psychosom Res 55*. 2003;55:269-275. doi:10.1016/S0022-3999(02)00578-0.
48. Scepkowski L, Cronin-Golomb A. The alien hand: cases, categorizations, and anatomical correlates. *Behav Cogn Neurosci*. 2003;Reviews 2:261-277.
49. Libet B, Gleason CA, Wright EW, Pearl DK. Time of Consious Intention to Act in Relation to Onset of Cerebral Activity (Readiness Potential). *Brain*. 1983;106:623-642.
50. Desmurget M, Sirigu A. Conscious motor intention emerges in the inferior parietal lobule. *Curr Opin Neurobiol*. 2012;22:1004-1011.
51. Voon V, Ekanayake V, Wiggs E, Kranick S et al. Response Inhibition in Motor Conversion Disorder. *Mov Disord*. 2013;28(5):612-618. doi:10.1002/mds.25435.
52. Sirigu A, Daprati E, Ciancia S, et al. Altered awareness of voluntary action after damage to the parietal cortex. *Nat Neurosci*. 2004;7(1):80-84. doi:10.1038/nn1160.
53. Dienes Z, Brown, Hutton E. Hypnotic suggestibility, cognitive inhibition, and dissociation. *Conscious Cogn*. 2009;18:837-847.
54. Duncan R, Oto M. Predictors of antecedent factors in psychogenic nonepileptic attacks: multivariate analysis. *Neurology*. 2008;71:1000-1005.
55. Roelofs, K Keijsers, GP Hoogduin K et al. Childhood abuse in patients with conversion disorder. *Am J Psychiatry*. 2002;159:1908-1913.
56. Perez DL, Matin N, Barsky A, et al. Cingulo-insular structural alterations associated with psychogenic symptoms, childhood abuse and PTSD in functional neurological disorders. *J Neurol Neurosurg Psychiatry*. 2017;88:491-497. doi:10.1136/jnnp-2016-314998.
57. Sar, V Akyüz, G Kundakçi T et al. Childhood trauma, dissociation, and psychiatric comorbidity in patients with conversion disorder. *Am J Psychiatry*. 161:2271-2276.
58. Bowman E, Markand O. Psychodynamics and psychiatric diagnoses of pseudoseizure subjects. *Am J Psychiatry*. 1996;153:57-63.
59. Schurger A, Sitt JD, Dehaene S. An accumulator model for spontaneous neural activity prior to self-initiated movement. *Proc Natl Acad Sci U S A*. 2012;109(42):2904-2913. doi:10.1073/pnas.1210467109.
60. Weimer K, Colloca L, Enck P. Placebo effects in psychiatry: mediators and moderators. *Lancet Psychiatry*. 2015;2(March):246-257. doi:10.1016/S2215-0366(14)00092-3.
61. Rossetti HC, Lacritz LH, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology*. 2011;77:1272-1275.

Table 1. Demographic and Clinical Data

ID	Age[a]	Sex	EHI/ Handedness	EBA/ Education[b]	Employment	Psychiatric Diagnosis	Medications*
1	56	F	Right	10	Disability	No other psychiatric disorder	Ibesartan (12.5mg); Diltiazem (660 mg); Cymbalta (60mg); Rosuvastatin (10mg); Forxiga (10mg); Jentadueto (2.5mg); Ibuprofen; Acetaminophen
2	40	M	Ambi	12	Disability	Panic Disorder, Major Depressive Disorder	Escitalopram (30mg); **Clonazepam (0.5mg) discontinued during rTMS treatment; Amitriptyline (25mg); Zopiclone (7.5mg)
3	46	F	Right	15	Disability	Hypersomnolence Disorder	Topiramate (125 mg); Valproic Acid (1250mg); Morphine (45mg); Pantoprazole (40mg); Ritalin (10mg); Potassium (600mg); Lorazepam (0.5mg); Levothyroxine (0.025mg); Omega 3 (1200mg); Vitamin D (1000 IU); Vitamin B12 (100mg)
4	43	F --> M	Right	16	Disability	Agoraphobia	Lamotrigine (150mg); Venlafaxine (300mg); Risperidone (2mg); Clobazam (15mg); Ventolin as needed;
5	35	F	Right	13	Unemployed homemaker	Major Depressive Disorder in partial remission	Sertraline (100mg); Lorazepam
6	33	F	Right	13	Disability	Panic Disorder	Botox (q4m); Kenalog (q8-12wk); Imodium (3-4 tabs); Pepto bismol (capsule); Robaxacet (1-2 tabs)
7	53	F	Right	14	Working part time	No other psychiatric disorder	Lamotrigine (150mg); Metformin (500mg); Jardiance (25mg); (2.5mg); Losartan (25mg); Amlodipine (10mg)
8	56	F	Right	10	Disability	Adjustment Disorder with mixed anxiety and depressive features	Lamotrigine (150mg); Ferasulfate; Flexeril (as needed); Clonazepam (as needed); Zopiclone (7.5mg); **Lamotrigine discontinued and Venlafaxine started (37.5mg) after 1mth follow up
Summary	Mean 45.3 (S.D. 9.10)	75% F 25 % M	87.5% RH	12.9	75% on disability	N/A	N/A

*Medications are daily doses unless otherwise stated.
[a] At baseline.
[b]10; 10th Grade, 12; 12th Grade, No Diploma, 13; High School Graduate, 14; GED or Equivalent, 15; Some College, No Degree, 16; Associate Degree: Occupational/Technical/Vocational.
**change in psychopharmacology during treatment or follow up
Abbreviations: EHI, Edinburgh Handedness Inventory; EBA, Educational Background Assessment; ambi, ambidextrous, S.D.; standard deviation, F; female, M; male, RH; right handed.

Table 2. Baseline PNES Description

ID	Age Onset	Duration of PNES Diagnosis	Frequency of PNES Episodes	Duration of PNES episodes	Triggers	Other FND	Hospitalizations for PNES	Emergency Room Visits for PNES
1	55	1 yr	Intermittent, 2/wk	30 sec-several min	Exercise, balance, tapping	Positive motor symptoms, Sensory symptoms, Cognitive symptoms	None	2
2	38	2.5 yrs	Intermittent, daily	2.5 min-3hrs	Stress, headaches, dizziness	Sensory symptoms, Cognitive symptoms	2	None
3	30	15-16 yrs	Intermittent, 2-3/wk	2-10 min	Noise, heat, compact fluorescent lights, stress, crowded environments	Pain	None	None
4	34	1 yr	Intermittent, 1-2/wk	1 min, aura 5-10 min, after effects 1hr	Stress, not eating, tiredness, activity, "my past", fighting (kids and parents), life	None	3	10-15 (9 by ambulance)
5	13	15-20 yrs	1-4/day	5-30 min	Stress, dehydration, exhaustion, too much activity	Positive Motor Symptoms, Negative Motor Symptoms, Sensory Symptoms, Cognitive Symptoms, Pain, Altered awareness	1	More than 40, approx. 15 in last 12 moths
6	23	30 yrs	3/wk	30 sec- 2 min	"Physical sickness with a cold etc," overtired, trouble with stomach pain or back pain, stress	Positive Motor Symptoms, Sensory Symptoms, Cognitive Symptoms, Pain	2	5
7	6	41 yrs	Intermittent, 1 every 3 wks	3-20 min	Strong perfume, pain fumes, stress	None	2	15
8	5	34 yrs	Constant, 2-3/wk	1 min	Stress	Sensory Symptoms, Cognitive Symptoms, Pain	3	11
Mean (S.D.)	25.5 yrs (17.2)	17.8 yrs[a] (15.8)	4.54/wk[a] (5.58)	1.94 min[b] (1.55)	N/A	N/A	1.63 (1.19)	10.7[a] (13.2)

[a]where a range of values was given, the mean of the range of values was used in calculation of the sample mean.
[b] where a range of values was given, the minimum value listed was used in calculation of the sample mean, as subjects reported that seizures of longer duration occurred less frequently.
Abbreviations: yrs, years; wk; week; min; minutes; sec, seconds; approx., approximately, S.D.; standard deviation.

Table 3. Weekly PNES Count

ID	Weekly PNES Count at Baseline	Weekly PNES Count Week 1 of Tx	Weekly PNES Count Week 2 of Tx	Weekly PNES Count Week 3 of Tx	Weekly PNES Count 1st Week Post Tx	Weekly PNES Count 1 month Post Tx	Weekly PNES Count 2 month Post Tx	Weekly PNES Count 3 month Post Tx	Side Effects of Tx
1	10	10	5	3	0	3	0	0	Headache
2	9	1	0	0	2	4	4	4	None reported
3	12	5	7	7	3	7	10	10	"Hallucinations" (note: patient reports that hallucinations are not unusual for her); increased migraine frequency
4	1	1	0	0	0	0	0	0	Fatigue; '"altered dreams"
5	14	15	2	6	2	5	5	3	Bad headache; fatigue; "vivid dreams"
6	1	4	0	0	0	0	0	0	"Very vivid dreams"; headache
7	0	3	3	5	7	1	5	0	Fatigue; headache; nausea
8	4	6	1	3	0	0	0	0	Headache

*Subject 2 received 2 weeks of treatment only, 1st Week Post Tx begins at Week 3 Tx for this subject.
Abbreviations: Tx, treatment.

Figure 1. Seizure frequency from baseline to 3-month follow up

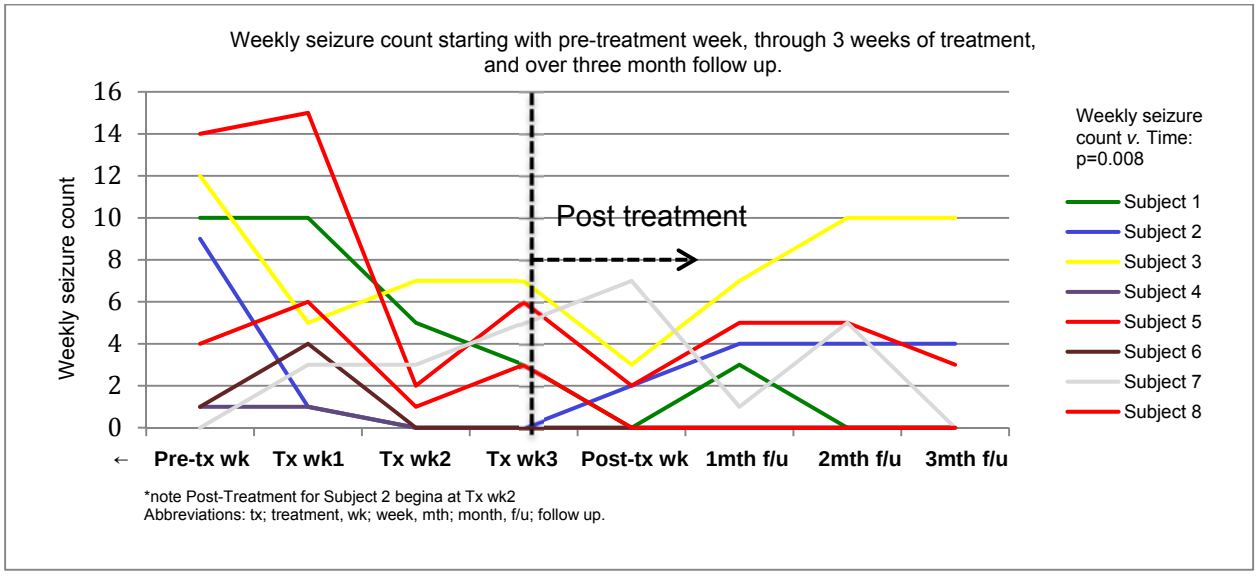

Table 4. Weekly PNES count as a function of time over treatment and follow up

	Weekly PNES Count										
n	Baseline Mean (S.D)	Week 1 Tx Mean (S.D.)	Week 2 Tx Mean (S.D.)	Week 3 Tx Mean (S.D.)	Week 1 Post Tx Mean (S.D.)	1 mth Post Tx Mean (S.D.)	2 mth Post Tx Mean (S.D.)	3 mth Post Tx Mean (S.D.)	*F-Ratio*	*df*	Weekly PNES Count *v.* Time : *p*
8	6.38 (5.53)	5.63 (4.78)	2.25 (2.60)	3.00 (2.43)	1.75 (2.43)	2.50 (2.67)	3.00 (3.66)	2.13 (3.56)	3.15	7	0.008

Abbreviations: Tx, treatment, mth; month

Table 5. Baseline Psychometric Results

	PTSD/Trauma			Pain Catastrophizing	Impulsivity	Education and Cognition	
ID	CTQ	CDRS	LEC-5	PCS	BIS	MoCA	WRAT-3
1	63	53	15	18	72	26	29
2	70	33	78	43	75	24	25
3	42	78	4	117	55	27	35
4	58	21	55	7	80	27	34
5	86	73	55	30	78	26	35
6	34	65	5	9	76	24	34
7	26	87	9	2	64	25	39
8	114	49	80	35	70	26	30
Mean	61.4	57.4	37.6	32.6	71.3	25.6	32.6
(S.D.)	(28.9)	(22.7)	(32.9)	(37.0)	(8.26)	(1.19)	(4.37)
Range	*26-114*	*21-87*	*4-80*	2-117	*55-80*	*24-27*	*25-39*
Population Mean (S.D)	31.7(10.3)[a]	80.4 (12.8)[b]	N/A	20.9(12.5)[c]	64.2(10.7)[d]	23.4(4)[e]	N/A
N	971	577		851	700	2653	

Abbreviations: CTQ, Childhood Trauma Questionnaire; CDRS, Connor-Davidson Resilience Scale; LEC-5, Part 3 of Life Events Checklist for DSM-5, PCS; Pain Catastrophizing Scale; BIS, Barratt Impulsivity Scale (Version 11); MoCA, Montreal Cognitive Assessment; the WRAT–3, Wide Range Achievement Test–3, S.D.; standard deviation.
[a]Scher et al.[43]
[b]Connor et al.[35]
[c]Sullivan et al.[36] (study sample used an injured worker cohort through Workers Compensation Board).
[d]Spinella.[44]
[e]Rossetti et al.[61]

Table 6. Baseline verses Post-Treatment Psychometric Results

	Psychometric Test	Population Mean (S.D.) N	Baseline Mean (S.D.)	Post Tx Mean (S.D.)	Baseline v. Post Tx Psychometric Test Results: p[1]
Mood/Anxiety	BDI-II	3.74(4.74)[a] 1295	26.0 (14.97)	15.1 (9.80)	0.17
	SSAI	35.0 (8.58)[b] 1141	46.0 (15.1)	39.1 (11.31)	0.30
	STAI	31.9 (8.18)[b] 1120	50.3 (11.0)	48.1 (9.56)	0.55
Dissociation	DES	10.8 (10.2)[c] 1055	33.3(21.2)	26.0 (16.22)	0.028*
Somatization and Related Topics	SOMS-CD	N/A	14.0 (10.0)	8.38 (7.01)	0.023*
	TAS	45.57(11.35)[d] 1933	55.0 (14.8)	50.5 (14.1)	0.28
Health	SF-HS	N/A	38.5 (17.2)	43.5 (17.2)	0.28

[1] results from separate two-tailed paired t-tests
*$p<0.05$
Abbreviations: Post Tx; Post Treatment, S.D.; standard deviation, Pop.; population, BDI-II; Beck Depression Inventory-II, SSAI; Spielberger State Anxiety Inventory, STAI; Spielberger Trait Anxiety Inventory, DES; Dissociative Experience Scale, SOMS-CD; Conversion Disorder Subscale from Screening for Somatoform Symptoms (SOMS-7), TAS; Toronto Alexithymia Scale 20, SF-HS; RAND SF-36v1 Health Survey.
[a]Schulte-van Maaren et al.[45]
[b]Knight et al.[46]
[c]Ross.[42]
[d]Parker et al.[47]