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BRIEF COMMUNICATION

Improvement in borderline personality disorder symptomatology after repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex: preliminary results

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Objective: Current treatment for borderline personality disorder (BPD) involves psychological and pharmacological interventions. However, neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) may positively affect BPD symptomatology. The objective of this study was to evaluate the clinical and neuropsychological effects of rTMS on the dorsomedial prefrontal cortex (DMPFC) in BPD patients.
Methods: Fourteen patients with BPD were randomized into two groups (active vs. sham) for 15 sessions of rTMS on the DMPFC. Clinical effects were measured using the Borderline Symptoms List (BSL), Clinical Global Impression Scale for BPD (CGI-BPD), Borderline Evaluation of Severity over Time (BEST), Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), and Barratt's Impulsiveness Scale (BIS). Neuropsychological effects were determined by a Stop-Signal Task (SST), the Wisconsin Card-Sorting Test (WCST), and the Iowa Gambling Test (IGT).
Results: Within-group comparison showed significant differences ($p < 0.05$) in CGI-BPD (total score and six of nine psychopathologic domains), BEST, HDRS, HARS, and IGT scores for active modality.
Conclusion: The 5 Hz-DMPFC rTMS technique was well tolerated and lessened the severity of BPD symptomatology, especially abandonment, affective issues, interpersonal relationships, suicidal behavior, anger, and paranoid ideation. Cognitive improvement was seen in decision-making. Additional studies are needed to fully evaluate the effects of rTMS on BPD symptomatology.
Clinical Trial Registration: NCT03832777.

Keywords: Borderline personality disorder; repetitive transcranial magnetic stimulation; dorsomedial prefrontal cortex

Introduction

Due to its high prevalence (up to 5.9% of the population),[1] borderline personality disorder (BPD) is one of the personality disorders most often reported to health services.[2] The core of its symptomatology includes high impulsivity, emotional disturbance, and unstable interpersonal relationships[3]; anger management problems, self-injury, and suicidal behaviors may be associated.[3] Comorbid depression, anxiety, substance abuse, and posttraumatic stress disorder are frequent.[2] Studies have identified neurobiological disruptions associated with BPD that involve genetic (hypermethylation of the *HTR2A*, *MAOA*, and *MAOB* genes),[4] molecular (alterations of the serotoninergic or dopaminergic systems),[1] and/or structural and functional changes in the fronto-limbic network (FLN).[5] Their findings demonstrate hyperactivity of the amygdala and poor functioning of prefrontal structures like the dorsolateral (DLPFC) and dorsomedial prefrontal cortices (DMPFC),[1] the latter linked to emotional regulation.[1]

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Treatment may seek to achieve maintenance (psychotherapy, dialectical behavior therapy, or mentalization-based therapies) or control acute symptoms (pharmacology with antidepressants, neuroleptics, and mood stabilizers).[2] Both are required to stabilize symptomatology.[2] Many studies show that these different treatments attain only low-to-moderate effect sizes, and that pharmacological therapy may produce adverse effects that reduce patient compliance.[6]

Considering the pathophysiology of BPD, the neural changes reported to occur in calcium dynamics, neurotransmitter release, and neurotrophic factors upon application of neuromodulatory techniques such as repetitive transcranial magnetic stimulation (rTMS)[7] could improve BPD symptomatology.[1] rTMS stimulates the cerebral cortex in a relatively focalized, painless, safe, and noninvasive manner,[8] fostering neural changes that could exert effects on inhibitory (< 1 Hz) and excitatory (> 5 Hz) stimulation.[7] It is approved by international organizations including the American Psychiatric Association (APA) for treating major depressive disorder (MDD).[9] Case reports and randomized trials of rTMS conducted on the right and left DLPFC[1] at low and high frequencies (1 Hz, 5-10 Hz) have reported some improvement in BPD symptomatology and decision-making. Due to its high connectivity with the prefrontal cortex (PFC), the cerebellum has also been explored as a target for high-frequency rTMS, with improvement in affective neuropsychological tasks.[1] The DMPFC is known to have a significant impact as a target for high-frequency rTMS protocols (20 Hz and iTB, intermittent theta-burst stimulation)[1] that have shown improvement in patients with MDD and comorbid BPD. Reyes et al. reported clinical effects of rTMS at 1-5 Hz when targeting the DLPFC.[1] This frequency has a high safety rate and tolerability, because it lessens the risk of seizures.[9] Although no studies of have evaluated the effect of DMPFC stimulation at frequencies < 10 Hz on BPD symptoms, background information on the DLPFC[1] suggests that rTMS could exert clinical benefits on BPD symptomatology. Hence, the objective of the present study was to evaluate the clinical and neuropsychological effects of rTMS on the DMPFC at a frequency of 5 Hz in patients with BPD.

Methods

This single-blind crossover study randomly assigned an equal number of rTMS sessions to both modalities. We describe preliminary results for the first modality by comparing the two study groups (active vs. sham). Patients were blindfolded during each procedure.

Participants

Forty patients (31 women, 9 men) were recruited at the Nervous System Clinic (Clínica del Sistema Nervioso), Universidad Autónoma de Querétaro, and the Queretaro Mental Health Centre (Centro Estatal de Salud Mental [CESAM]) in Mexico. Mean age was 26.03 ± 7.08 years. The inclusion criteria were: BPD diagnosis by DSM-IV-R[3] and the Diagnostic Interview for Borderline Personality Disorder-Revised (Spanish version, DIB-R) (score > 7),[10] stable pharmacological treatment, and psychotherapy within the previous month. Subjects contraindicated for rTMS were excluded[9] (Figure 1A). All participants gave their informed consent under the terms of the World Medical Association Declaration of Helsinki.

Clinical and neuropsychological evaluations

Patients were evaluated at baseline with validated Spanish versions of the Borderline Symptoms List, short version (BSL), Clinical Global Impression for BPD (CGI-BPD), and Borderline Evaluation of Severity over Time (BEST) scales to assess initial BPD symptoms.[11] Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HDRS); anxiety by the Hamilton Anxiety Rating Scale (HARS); and impulsivity by Barratt's Impulsivity Scale (BIS).[12-14]

Neuropsychological tests were performed to assess specific domains: inhibitory response (Stop-Signal Task, SST), decision-making (Iowa Gambling Test, IGT), and cognitive flexibility (Wisconsin Card-Sorting Test, WCST). Clinical evaluations (BSL, CGI-BPD, HDRS, HARS, BIS) were performed weekly, but neuropsychological performance was evaluated at the end of each modality, with application of the BEST instrument.

rTMS protocol

Magventure MagPro R30 equipment was used. A Cool D-B80 coil was placed on the DMPFC following the 10/20 positioning system (40% distant from vertex-nasion, locating Fpz).[15] A sleep mask and earphones isolated patients from external stimuli. The motor threshold (MT) was obtained daily by placing the coil on the motor cortex to evoke a visual response on the abductor muscle of the thumb.[15] All subjects underwent 15 sessions of 5-Hz rTMS, once a day, five days a week, at 100% of MT. In total, 30 trains were applied, each consisting of 50 pulses, with a 10-s inter-train interval. Half of the participants received the active modality; the other half received the placebo mode. In the active modality, the coil was placed on the DMPFC and connected to the stimulator; whereas in the placebo modality, the Cool D-B80 coil was placed on the subject's head with the Cool B-65 A/P coil connected to the equipment. It was held in the hands with the TENS equipment placed on the forehead and connected to the coil.

Statistical analyses

IBM SPSS Statistics version 17 and GraphPad Prism version 7 for Windows were used for all statistical analyses. Comparison between age groups was performed by the nonparametric Mann-Whitney *U* (MWU) test. Gender distribution was determined by Fisher's exact test. Differences within (Wilcoxon test) and between groups (MWU) were analyzed, data were normalized to decrease the risk of type I (false-positive) findings and control the false discovery rate (FDR) for multiple-hypothesis testing; the Kolmogorov-Smirnov test was applied, and p-values were adjusted by the Benjamini-Hochberg method.

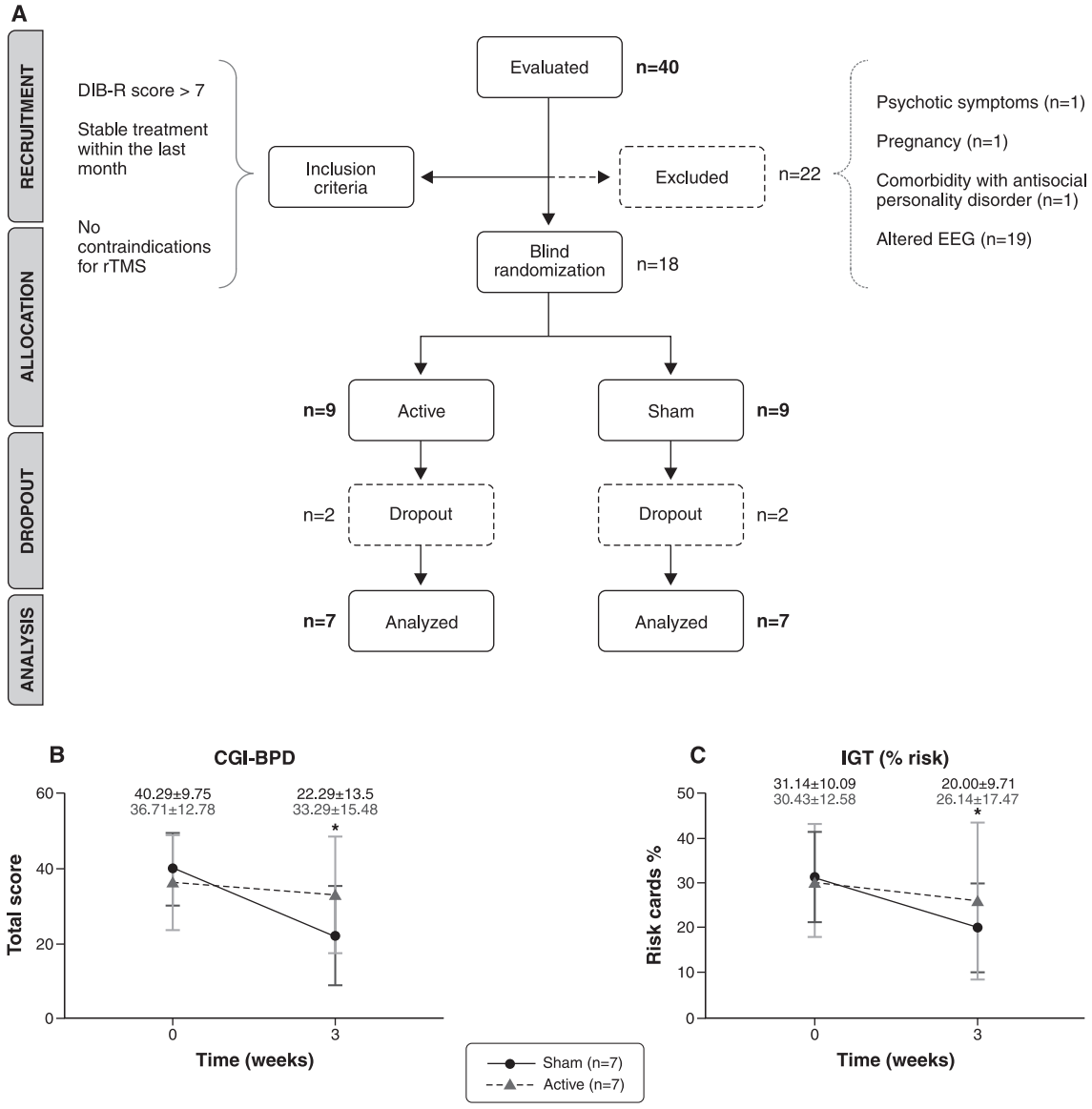

Figure 1 A) Flow diagram of patient recruitment, randomization, and allocation to the two protocol groups (active and sham). One case of dropout was linked to a personal decision (active group, n=1); the others were random, but those potential subjects did not begin the experimental protocol (active group, n=1; sham group, n=2). B, C) Changes in clinical and neuropsychological variables. The X-axis shows the evaluation time (in weeks): 0 (baseline) and 3 (post-treatment); the Y-axis shows the clinical or neuropsychological performance on each test. Data are shown as mean ± standard deviation. B) Clinical Global Impression for Borderline Personality Disorder (CGI-BPD, total score). C) Iowa Gambling Test (IGT, % risk). * $p < 0.05$. DIB-R = Diagnostic Interview for Borderline Personality Disorder-revised (Spanish version); EEG = electroencephalography; rTMS = repetitive transcranial magnetic stimulation.

Ethics statement

The study was approved by the bioethics committee of Universidad Autónoma de Querétaro (CBFMUAQ; clinicaltrials.gov: NCT03832777).

Results

The groups were comparable in terms of age, education, and gender (Table 1). Between-group analyses showed statistical differences after treatment in the Impulsiveness domain of CGI-BPD ($U = 9$; $Z = -2.02$; $p = 0.044$) and anxiety ($U = 5$; $Z = -2.50$; $p = 0.012$), with lower scores in the active group (Table 1). Within-group analyses were also performed. After rTMS, the active group showed statistical differences for BPD symptoms on their total CGI-BPD scores ($p = 0.028$), as well as in abandonment ($p = 0.034$) and paranoid ideation ($p = 0.027$) subscores; total BEST scores ($p = 0.028$), depression ($p = 0.015$), and anxiety ($p = 0.015$). Impulsiveness showed no statistical differences for either group, according to the BIS (active, $p = 0.156$; sham, $p = 0.687$) and CGI-BPD (active, $p = 0.125$; sham, $p = 0.687$).

For the neuropsychological domains, only decision-making showed statistical differences for both items in the

Table 1 Sociodemographic variables, adverse effects reported during treatment, and baseline/post-treatment comparisons of the sham and active groups in relation to clinical and neuropsychological variables

Items	Sham (n=7)	Active (n=7)
Sociodemographic		
Age	28.14±8.31	24±6.29
Schooling	15.29±1.97	15.43±5.28
Gender, male/female (% male)	3/4 (42.85)	2/5 (28.57)
Adverse effects during the rTMS protocol, n (%)		
Local discomfort in application area	0/7 (0.0)	1/7 (14.28)
General headache	2/7 (28.57)	1/7 (14.28)
Dizziness	0/7 (0.0)	1/7 (14.28)
Seizures	0/7 (0.0)	0/7 (0.0)
Others	0/7 (0.0)	0/7 (0.0)

	Baseline		Post-treatment	
	Sham (n=7)	Active (n=7)	Sham (n=7)	Active (n=7)
Clinical characteristics				
BPD symptom evaluation				
BSL	41.86±23.31	52.29±22.91	37.71±35.44	29.14±32.71
CGI-BPD	36.71±12.78	40.29±9.75	33.29±15.48	22.29±13.5*
Abandonment	3.42±1.51	4.71±1.60	3.42±2.37	2.42±2.29
Unstable relationships	4.14±1.34	4.28±1.49	4±1.91	2.14±1.34*
Identity disturbance	3.42±1.51	3.57±1.27	3.28±2.13	3±1.52
Impulsivity	4.57±0.97	4.85±1.46	5.14±1.95	2.71±1.97†
Suicidal behavior	2.57±1.51	4.28±1.70	1.85±2.26	2.42±1.98
Affective instability	4.85±0.89	5.42±0.78	4.42±1.98	3.14±1.67
Emptiness	4.42±1.13	4.85±1.46	4±2.38	3.28±2.21
Anger	4.14±1.77	4.85±1.21	3.57±2.29	2.14±1.67
Paranoid ideation	2.28±1.60	3.42±1.71	2.42±2.14	1.28±0.75*
BEST	37.71±8.95	44.43±13.07	38.57±14.77	29.57±11.72*
Depression				
HDRS	25.86±7.05	27±9.34	24±13.54	15.43±9.50*
Anxiety				
HARS	23.71±4.92	23.71±7.76	23.29±13.11	11±8.428*†
Impulsiveness				
BIS	64.29±13.07	61.43±19	62.57±21.27	46.57±24.86
Neuropsychological				
Inhibitory response				
SSD	522.5±150.2	428.5±182.8	555.7±121.1	450.1±197.2
SSRT	238.8±47.45	264.2±51.6	235.5±51.81	230.5±29.7
Decision-making				
Risk cards %	30.43±12.58	31.14±10.09	26.14±17.47	20±9.71*
Total score	25.71±13.8	23.86±14.94	41.29±25.01*	41.14±13.12*
Cognitive flexibility				
Correct response	53.71±3.14	49.57±8.18	55±2.82	51.86±7.94
Perseverative response	1.57±1.51	2.28±2.05	2±1.63	1.714±2.56
Delayed perseveration	0.57±0.78	0.85±1.21	0.57±1.13	0.285±0.755
Time	212.7±52.26	276.6±92.51	205.4±48.76	253.1±54.02

Data presented as mean ± standard deviation, unless otherwise specified.
BEST = Borderline Evaluation of Severity Over Time; BIS = Barratt Impulsivity Scale; BPD = borderline personality disorder; BSL = Borderline Symptom List; CGI-BPD = Clinical Global Impression for Borderline Personality Disorder; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; SSD = Stop Signal Delay; SSRT = Stop Signal Reaction Time.
Mann-Whitney *U* test for between-group comparison; Wilcoxon test for within-group comparison.
* $p < 0.05$ within groups, pre- vs. post-treatment; † $p < 0.05$ between groups.

active group (risk card %, p = 0.031; total score, p = 0.031). The sham group showed significant differences only for total IGT scores (p = 0.031) (Table 1; Figures 1B, 1C).

Discussion

This was the first study to applied 5-Hz rTMS (a low-excitatory frequency) on the DMPFC and evaluate changes in clinical symptomatology and neuropsychological domains (decision-making by IGT) in patients with BPD. To our knowledge, the previous study by Feffer et al.[16] is the only one to have targeted the DMPFC in this patient population, albeit with high frequencies (20-Hz rTMS and iTBS). Their work showed improvement in depressive symptomatology in a three-case series of MDD co-morbid with BPD.

Our preliminary results are similar to those reported previously for clinical areas (anger, affective instability, impulsiveness) with the application of high-frequency rTMS (10 Hz) to the left[17] and right DLPFC.[18,19] Cailhol et al.[18] observed improvement in neuropsychological areas (decision-making). While most BPD studies apply fewer sessions with higher excitatory frequencies, earlier works by Reyes et al.[20] showed that at lower frequencies (which enhance tolerability with a lower risk of adverse effects), applying rTMS to the left and right DLPFC (5 Hz and 1 Hz, respectively) yielded similar improvement in all clinical domains, as reported by the CGI-BPD and other clinical instruments, like the Beck Depression Inventory (BDI), BIS, HARS, and BEST.

BPD symptomatology is related to neurobiological deficits in cortical areas, with altered connectivity and hypofunctionality in frontal structures, and aberrant function in subcortical structures, with hyperactivity in the amygdala and hippocampus.[1] Both cortical and subcortical areas operate as isolated structures and via connections to the frontal lobes through the FLN.[5] In this sense, the effects of the rTMS protocols could be related to the induction of changes in this deficits.

Most research on the clinical application of rTMS in psychiatric pathologies,[9] including BPD,[1] has focused on DLPFC as a treatment target, using figure-of-eight or butterfly-shaped coils. However, both the DLPFC and DMPFC play a key role in emotion regulation, decision-making, and impulsivity modulation. In addition, the DMPFC has a fundamental role in processes of social cognition; for example, Feffer et al.[16] demonstrated the relation between the DMPFC and emotional cognition, noting this area as a main target for emotional regulation. From a technical point of view, stimulation of the DMPFC requires a different methodology, using coils that allow stimulating deeper regions of the cortex ($>$ 5 cm), which is perhaps easiest with double-cone coils[9] with an angle of 120°. In this sense, the importance of our work resides in exploring the effect of rTMS over the DMPFC on clinical and cognitive symptoms in patients with BPD.

Some limitations must be noted, especially the small sample size, which precluded obtaining sufficient results for a representative comparison and impeded an adequate distribution of patients by pharmacological and psychological treatment. Despite these shortcomings, our findings do indicate the need for additional studies to analyze the usefulness of the rTMS approach in cases of BPD, especially to assess the application of rTMS in different anatomical targets or combinations of targets as a function of BPD symptoms.

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Disclosure

The authors report no conflicts of interest.

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