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QUALITATIVE CHANGES IN PARAMETERS OF PSYCHOGENIC NON-EPILEPTIC SEIZURES IN CHILDREN AND ADOLESCENTS WITH ADJUVANT LOW FREQUENCY RTMS AS COMPARED TO SHAM STIMULATION

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ABSTRACT

Objective: This study investigated the efficacy of adjunctive low-frequency repetitive transcranial magnetic stimulation (rTMS) compared to sham stimulation for treating psychogenic non-epileptic seizures (PNES) in children and adolescents.

Methods: Twenty patients diagnosed with PNES were randomized to receive either active rTMS or sham stimulation over the supplementary motor area (SMA) for ten sessions over two weeks. Clinical severity, seizure frequency and duration, dissociative experiences, anxiety, and depression were assessed before, after treatment, and at two weeks follow-up.

Results: Both groups showed improvements in clinical parameters. However, the active rTMS group demonstrated a significantly greater reduction in overall clinical severity compared to sham at the four-week follow-up. This improvement was not sustained after treatment ended. Additionally, patients with more severe PNES (higher seizure frequency and duration) showed greater improvement with rTMS. There were no significant differences between groups in anxiety or depression scores.

Conclusion: Low-frequency rTMS may offer some benefits for PNES, particularly for patients with severe symptoms. However, the short-lived effects and potential for placebo response necessitate further research with larger sample sizes, longer follow-up periods, and optimized stimulation parameters.

INDEX TERMS: Adjunctive therapy, Children and adolescents, Placebo response, Psychogenic non-epileptic seizures (PNES), Repetitive transcranial magnetic stimulation (rTMS), Sham stimulation, Supplementary motor area (SMA).

I. INTRODUCTION

Psychogenic non-epileptic seizures (PNES) are a debilitating condition that can significantly impact a patient's quality of life. These episodes mimic epileptic seizures but lack the characteristic electroencephalographic (EEG) abnormalities associated with epilepsy [1].

While some patients experience relief through traditional pharmacological and psychological interventions [1], a significant portion remains only partially responsive to these treatments [1]. This unmet clinical need necessitates the exploration of novel therapeutic approaches for PNES.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has emerged as a promising candidate for treating various neuropsychiatric disorders [2]. rTMS works by delivering focused magnetic pulses to specific brain regions, modulating their activity [2]. Depending on the stimulation parameters, rTMS can either excite or inhibit targeted brain areas [2].

There is growing evidence to suggest that rTMS may be beneficial in treating certain conversion symptoms, which are neurological presentations driven by psychological factors [3, 4]. For instance, studies have shown that rTMS can improve motor function in patients with conversion paralysis, a condition where patients experience weakness or paralysis without a neurological cause [3, 4]. These findings provide a rationale for investigating the potential therapeutic effects of rTMS in PNES, another conversion disorder characterized by seizure-like activity.

The supplementary motor area (SMA) is a key brain region involved in motor planning and execution [5]. Functional imaging studies suggest that abnormal connectivity between the SMA and other brain regions, including the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), may play a role in PNES pathophysiology [6, 7, 8]. The OFC is involved in regulating emotions and impulses, while the ACC is implicated in motor control and awareness [6, 7]. Disruption in the communication between these areas could contribute to the generation of PNES episodes [6, 7, 8].

Since directly targeting the OFC with rTMS can be technically challenging due to its location, the SMA presents itself as an alternative target for neuromodulation in PNES [9]. Prior research suggests that stimulating the SMA with rTMS can indirectly influence motor cortex activity, potentially leading to improvements in motor function [10].

This research study aims to investigate the efficacy of low-frequency rTMS over the SMA as an adjunctive treatment for PNES in children and adolescents. We hypothesize that low-frequency rTMS will lead to a reduction in the frequency and severity of PNES episodes compared to a sham stimulation control group. Our findings will contribute to the growing body of knowledge on the therapeutic potential of rTMS for PNES and may pave the way for the development of novel treatment strategies for this challenging condition.

II. METHODS

Participants

- Twenty-one patients diagnosed with Dissociative Convulsions (PNES) fulfilling the inclusion and exclusion criteria were recruited for this study from the K. S. Mani Centre of Cognitive Neurosciences and Erna Hoch Center of Child and Adolescent Psychiatry, Central Institute of Psychiatry (C.I.P), Ranchi, India.
- A purposive sampling technique was employed for participant selection.
- Written informed consent was obtained from the parents or legal guardians after a detailed explanation of the study procedures.

Inclusion Criteria

- Diagnosis of Dissociative Convulsions (PNES) by Diagnostic

Criteria for Research (DCR) of the International Classification of Diseases - Tenth Edition (ICD-10; WHO, 1993).
- Patients aged 8 to 18 years.
- Right-handed and normotensive.
- Written informed consent obtained from parents, guardians, or caregivers.
- Documented experience of at least one dissociative convulsion (Psychogenic Nonepileptic Seizure) in the past month.

Exclusion Criteria

- Epilepsy or any organic brain disorder.
- Presence of cardiac pacemakers or other implanted metallic objects.
- History of electroconvulsive therapy (ECT) within the past six months.
- History of any major medical illness.
- Uncooperative patients.

Study Design

This was a prospective, hospital-based, randomized, double-blind, sham-controlled transcranial magnetic stimulation (rTMS) study conducted over a period of one year, from December 2012 to October 2013.

Randomization

Following enrolment and confirmation of eligibility, participants were randomly assigned to either the active rTMS group or the sham stimulation group using a computerized randomization process. Allocation concealment was ensured with sequentially numbered, opaque sealed envelopes.

Assessments

- Sociodemographic and Clinical Data Sheet: A semi-structured proforma was used to collect demographic details (age, sex, religion, education, occupation, socioeconomic status, habitat) and clinical data (duration of illness, past medical history, family history of medical or psychiatric illness, pre-morbid temperament). It also included details of a physical examination of all organ systems. Finally, the patient's diagnosis according to ICD-10 DCR was recorded.
- Handedness Preference Schedule (Hindi Version) [Mandal et al, 1992]: This questionnaire assessed participants' hand preference for various daily activities using a 5-point rating scale (1 = never, 5 = always).
- Psychogenic Nonepileptic Seizure Scale (PNES Scale) [Ciancia et al, 2011]: This validated scale assessed the phenomenology and severity of PNES, including anatomic distribution, severity, and duration of motor phenomena, along with associated features. The PNES scale consists of three parts:
    - Part 1: Motor phenomena (tremor, tonic, clinic, hyper motor, atonic, automatisms)
    - Part 2: Associated features (incontinence, tongue biting, drooling, eye closure, hyperventilation, lamenting, crying)
    - Part 3: Total PNES score (sum of phenomenology and associated phenomena scores)
- Adolescent Dissociative Experiences Scale-II (A-DES) [Bernstein and Putnam, 1986]: This 30-item self-report questionnaire assessed dissociative experiences in adolescents. Participants rated the frequency of each experience on a 10-point scale (0 = never, 10 = always).
- Children's Depression Inventory 2 (CDI-2) [Kovacs, 1992]: This 28-item self-report inventory assessed cognitive, affective, and behavioral

signs of depression in children and adolescents aged 7 to 17 years. Participants indicated the statement that best described their feelings and experiences over the past two weeks.

- Hamilton Anxiety Scale (HAM-A) [Hamilton, 1959]: A 14-item clinician-administered rating scale assessed somatic and cognitive anxiety symptoms. Each item was rated on a 0-4 scale, with a total score ranging from 0 to 56.
- Screening Standard Questionnaire for rTMS Candidates [Rossi et al, 2009]: This 15-item questionnaire screened participants for potential contraindications to rTMS.
- rTMS Side-Effects Checklist [Slotema et al, 2010]: This 14-item checklist monitored potential side effects of rTMS after each session.

Treatment Schedule

Participants received rTMS or sham stimulation for five sessions per week over two consecutive weeks, for a total of 10 sessions.

Blinding

Both participants and researchers assessing outcomes were blinded to group allocation (active rTMS or sham stimulation) throughout the study. The sham coil design ensured a similar sensory experience for both groups.

Data Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.0 software.

- **Descriptive statistics:** Sociodemographic and clinical characteristics were summarized using descriptive statistics (frequency, percentage, mean, and standard deviation).
- **Group comparisons:** Independent t-tests and chi-square tests were used to compare baseline characteristics between the active and sham groups.
- **Treatment effects:** Repeated-measures analysis of variance (ANOVA) was used to compare changes in PNES scores, depression scores, anxiety scores, and CGI-S scores between the active and sham groups over time.
- **Correlations:** Pearson's correlation coefficients were calculated to explore potential relationships between various clinical variables and changes in outcome scores following treatment.

Significance level

A two-tailed alpha level of 0.05 was considered statistically significant.

III. RESULTS

Table 1: Group Comparisons

Variable	Active (N=10)	Sham (N=10)
Sex (Male)	20%	60%
Religion (Hindu)	60%	90%
Education (Primary)	40%	70%
Socioeconomic Status (Low)	80%	70%
Drugs (SSRI)	60%	90%

*Significance at p<.05 (2-tailed)

Table 2: Comparison of Socio-demographic and clinical variables (continuous) between Two Groups

Variables	Active N=10 Mean (SD)	Sham N=10 Mean (SD)	p
Age (In years)	13.8 (2.201)	12.3 (3.056)	0.224
Duration of illness (In months)	6.1 (4.094)	17.9 (20.376)	0.089

No. Of attack (last 1m)	38.8(40.342)	22.8(41.718)	0.412
No. of attack (last 1wk)	13.8(15.002)	5.9(9.694)	0.178
No. of attack (1wk post rTMS)	5.1(10.948)	4.1(8.047)	0.819
No. of attack (2nd. wk. post rTMS)	3.1(8.799)	5.3(11.253)	0.632
No. of attack (3rd. wk. post rTMS)	4.0(8.432)	5.0(9.237)	0.803
No. of attack (4th wk. post rTMS)	3.1(5.152)	4.4(9.766)	0.714
Duration of attack (last 1m)	25.5(28.880)	31.3(36.518)	0.698
Duration of attack (last 1wk)	21.5(28.060)	17.4(18.945)	0.706
Duration of attack (1st wk. post rTMS)	3.8(9.342)	6.2(10.379)	0.593
Duration of attack (2nd wk. post rTMS)	3.0(7.888)	6.2(10.643)	0.455
Duration of attack (3rd wk. post rTMS)	0.7(1.636)	6.4(10.265)	0.100
Duration of attack (4th wk. post rTMS)	2.1(3.034)	5.0(9.933)	0.389

*Significance at p<.05 (2-tailed)

Table 3: Effect of Treatment across Active (rTMS) and Sham (Control) Groups over Time: Scores within Subjects

Variable	Pre-treatment (0 wk)	After 10th session (2 wks)	Post rTMS Treatment (4th wk)	P-value
Total phenomenology score (TPS)	Active (N=10): 58.4±9.912	Active (N=10): 17.2±22.986	Active (N=10): 28.7±26.808	<0.001
	Sham (N=10): 53.7±15.158	Sham (N=10): 23.0±28.425	Sham (N=10): 34.5±30.041	
Total associated phenomena score (TAPS)	Active (N=10): 2.0±0.666	Active (N=10): 0.6±0.843	Active (N=10): 0.7±0.823	<0.001
	Sham (N=10): 1.5±0.707	Sham (N=10): 0.9±1.100	Sham (N=10): 0.9±0.875	
Total psychogenic nonepileptic seizure score (TPNESS)	Active (N=10): 60.3±10.122	Active (N=10): 17.8±23.733	Active (N=10): 29.4±27.411	<0.001
	Sham (N=10): 55.2±15.288	Sham (N=10): 23.9±29.384	Sham (N=10): 35.2±30.705	
Adolescent dissociative experiences scale-II (ADES)	Active (N=10): 44.8±38.694	Active (N=10): 23.1±17.051	Active (N=10): 12.4±11.529	<0.001
	Sham (N=10): 33.2±20.836	Sham (N=10): 23.4±14.531	Sham (N=10): 18.0±14.243	
Hamilton Anxiety Rating Scale (HAMA)	Active (N=10): 10.50±5.254	Active (N=10): 5.5±4.196	Active (N=10): 4.0±4.944	<0.001
	Sham (N=10): 12.6±4.742	Sham (N=10): 9.1±3.784	Sham (N=10): 6.1±3.348	
Childhood Depression Inventory- 2 (CDI)	Active (N=10): 39.6±9.674	Active (N=10): 35.8±9.162	Active (N=10): 33.5±8.276	<0.001
	Sham (N=10): 41.0±9.498	Sham (N=10): 38.7±7.008	Sham (N=10): 34.7±5.677	
Clinical Global Impression Severity Scale (CGI)	Active (N=10): 3.7±1.418	Active (N=10): 1.9±1.100	Active (N=10): 1.5±0.849	<0.001
	Sham (N=10):	Sham (N=10):	Sham (N=10):	

Table 4: Group*Psychopathology (TPS) Interaction with Treatment in Between Group Factor.

Variable	Active (Baseline)	Sham (Baseline)
Total Phenomenology Score (TPS)	58.4±9.9(0 wk.)	53.7±15.2
	17.2 ±22.986 (after 2 wk.)	23.0 ± 28.425
	28.7 ± 26.808(After 4 wk.)	34.5 ±30.041

V. DISCUSSION

This study investigated the efficacy of adjunctive low-frequency repetitive transcranial magnetic stimulation (rTMS) in treating psychogenic nonepileptic seizures (PNES) in children and adolescents. Here's a breakdown of the key findings and their implications:

Promising Effects, but Need for Further Research:

- Both active and sham groups showed improvements in clinical parameters (TPS, TAPS, TPNES, ADES, HAMA, CDI) over the four-week study period. However, only the active group showed a statistically significant improvement in the Clinical Global Impression Severity Scale (CGI) compared to sham at the four-week follow-up [11]. This suggests that rTMS may have a lasting positive effect on overall clinical improvement, but larger studies are needed to confirm this [12].
- The improvement in the active group was not sustained after the rTMS sessions ended. This suggests that a longer treatment duration might be necessary for a more prolonged effect [13]. Studies by Scho¨nfeldt-Lecuona et al. (2006) observed positive effects in Dissociative Motor Disorder after five weeks of treatment, so a longer duration may be crucial for PNES as well [14].

Targeting and Mechanism of Action:

- The study targeted the Supplementary Motor Area (SMA) for stimulation. While the SMA is involved in motor control, its role in PNES needs further investigation [15]. The lack of significant improvement in anxiety and depression scores (HAMA, CDI) might be due to this targeting, as these disorders are linked to activity in other brain regions like the parietal cortex.

Placebo Response and Future Directions:

- The significant improvement seen in the sham group highlights the high placebo response rate in PNES (up to 75%). This emphasizes the need for larger, well-designed studies with longer follow-up periods to differentiate between true treatment effects and placebo response [16].
- Future studies should explore targeting different brain regions based on the specific symptoms and underlying mechanisms of PNES subtypes.
- Investigating the optimal stimulation parameters, like frequency, intensity, and duration, is also crucial for maximizing treatment efficacy [17].

Correlation of Seizure Characteristics with Treatment Response:

- The study found positive correlations between the number/duration of attacks and the degree of improvement in some clinical scores (TPS, TAPS, TPNES) in the active group at the 4th week. This suggests that patients with more severe seizures might benefit more from rTMS.
- There was also a negative correlation between age and improvement scores (TPS, TPNES) at the 2nd week. This aligns with the idea that younger patients have greater neuroplasticity, making them potentially more responsive to rTMS [18].

Limitations:

- The relatively small sample size (n=20) limits the generalizability of the findings.
- The short follow-up period (four weeks) makes it difficult to assess the long-term effects of rTMS on PNES.

Overall, this study provides preliminary evidence for the potential benefits of rTMS as an adjunctive treatment for PNES. However, further research with larger sample sizes, longer follow-up periods, and optimized stimulation parameters is necessary to confirm these findings and establish rTMS as a viable treatment option for PNES.

V. CONCLUSION

This study investigated the potential of adjunctive low-frequency rTMS as a treatment for PNES in children and adolescents. The findings suggest that rTMS may offer some clinical benefits:

- **Reduced seizure severity:** Patients receiving active rTMS showed a significant decrease in overall clinical severity compared to sham controls.
- **Improved outcomes for severe cases:** Patients experiencing a higher number and longer duration of seizure attacks demonstrated greater improvement with rTMS.

However, limitations restrict the generalizability of these conclusions:

- **Short-lived effects:** The positive effects of rTMS were not sustained after the intervention ended, highlighting the need for potentially longer treatment durations.
- **Placebo response:** Improvements observed in sham group scores indicate a notable placebo effect, emphasizing the importance of larger studies with longer follow-up periods for more definitive results [19].
- **Methodological limitations:** The study design included a relatively small sample size, limited follow-up duration, and potential inaccuracies in sham coil application and targeting.

Future research should address these limitations:

- **Larger, well-designed studies:** Studies with increased sample sizes and diverse participant demographics are necessary to confirm the initial promise of rTMS for PNES.
- **Optimization of stimulation parameters:** Exploring different frequencies, pulse numbers, and session lengths can help establish the most effective and tolerable rTMS protocol for PNES treatment [20].
- **Advanced stimulation techniques:** Utilizing techniques like theta burst stimulation may offer additional benefits.
- **Long-term efficacy evaluation:** Extended follow-up periods are crucial to assess the long-term sustainability of rTMS effects.
- **Integration of neurophysiological measures:** Combining rTMS with quantitative EEG and evoked potential measurements can provide a more comprehensive picture of treatment effectiveness.
- **Precise targeting with neuron avigation:** Utilizing neuron avigation can ensure more accurate targeting of the SMA, potentially enhancing treatment outcomes.
- **Investigation of neural correlates:** Studies combining rTMS with brain imaging techniques like SPECT or PET scans can shed light on the specific brain regions impacted by the intervention in PNES.

In conclusion, while this study provides preliminary evidence for the potential benefits of rTMS in PNES treatment, further research with larger samples, optimized protocols, and longer follow-up periods is necessary to establish rTMS as a viable and long-lasting therapeutic option for this patient population.

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