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Research Article

Does rTMS Help in Improving the Global Neuropsychological Functioning of Parkinson's Disease Patients: A Pilot Study

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease that on average causes 3.2 million DALY's (Disability-adjusted life years) and over 2,00,000 deaths globally [1]. The disease presents with debilitating cognitive and behavioural symptoms leading to a compromised quality of life. Repetitive Transcranial Magnetic Stimulation (rTMS) is a contemporary neuromodulation technique that applies focal stimulation and brings about changes in cortical excitability in a specific brain region. There is a lacuna in the existing literature on the relationship between rTMS and neuropsychology of PD patients, and hence a pilot study was planned to understand the effect of rTMS on the global neuropsychological functioning of PD patients. A 20Hz rTMS intervention was conducted over the left dorsolateral prefrontal cortex (dlpfc). 23 patients diagnosed with PD that passed the eligibility criteria received 5 sessions/week x 2 weeks = 10 sessions of rTMS. Patients were assessed on memory, executive functioning, quality of life, behavioural symptoms, and clinical impairment at baseline, 1 month and 3 months post last day of intervention. Wilcoxon Sign Rank test (p = 0.05) was used to compare differences in overall neuropsychological functioning before and after rTMS. It was found that rTMS at 20Hz over left dlpfc improved delayed general and auditory memory after 10 sessions. This suggests that rTMS when accompanied by usual pharmacological therapy could be beneficial for PD patients with memory concerns.

Keywords: *Neuropsychology; Neuroscience; Parkinson's Disease; Repetitive Transcranial Magnetic Stimulation; Cognition; Memory*

Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder, second largest after Alzheimer's Disease [2]. Along with slowness, resting tremors, bradykinesia, rigidity and gait difficulty, PD also presents many Non-Motor Symptoms (NMS) such as depression and cognitive decline in memory, executive functioning, visuospatial functioning, and attention [3]. Cognitive dysfunction impacts the Quality of Life of patients and also increases the chances of disability, burden of caregivers [4,5] and depression [6]. Longitudinal studies demonstrate that nearly 50% of those diagnosed with PD develop dementia within 10 years [7]. Increased mortality due to development of dementia makes timely clinical management of cognitive decline an important part of treatment [8].

Within India, the neuropsychological status of patients is largely under diagnosed and may go untreated because of the lack of uniform assessments, trained professionals and scarce awareness of mental health in the country [9]. These neuropsychological deficits are often

experienced as more debilitating than motor symptoms [10] by the PD patients and negatively affect their quality of life [11]. Although there is a lack of curative measures for the disease, technological advances like rTMS are now being considered as potential management techniques [12]. There is a need to study these potential treatment options for rehabilitation of neuropsychological deficits experienced by PD patients.

Repetitive Transcranial Magnetic Stimulation (rTMS) works on the principle of electromagnetic induction and is a fairly painless technique for modulation of cortical excitability and functions of specific brain regions [13-15]. Single pulse TMS produces one magnetic pulse at a time whereas Repetitive TMS or rTMS has the ability to deliver repeated single magnetic pulses of the same intensity to a brain region [16]. The non-invasive procedure has shown to be most promising for treatment-resistant depression worldwide [17,18]. The FDA (Food and Drug Administration) permitted marketing of TMS as a treatment for major depression in 2008 and OCD in 2018 [19].

When it comes to Parkinson's disease, rTMS has shown positive effects on cognitive impairment in PD patients [20,21]. Dinkelbach (2017) suggested Dorsolateral Prefrontal Cortex (DLPFC) to be the brain site for both depression and cognitive dysfunction treatment [22], whereas Randver (2018) stipulated DLPFC to be more concerned with PD related depression [23]. Jasaui (2019) also supported the site of DLPFC in treating depression as its' concerned with emotion regulation network, cognition and executive functioning [24,25]. While there have been positive results of rTMS in treating PD, many studies also show controversial and unclear outcomes. A systematic review of 7 studies and 96 subjects saw that rTMS improved cognitive function but didn't achieve significant results [26].

Aim of the Study

The current study aims to explore the long-term effect of rTMS over left dorsolateral prefrontal cortex region on overall neuropsychological functioning of PD patients in India.

Methods

Sample

23 patients (15 male and 8 female) diagnosed with Parkinson's disease by Neurologists (according to UK Bank criteria) were recruited from the Out-patient Department (OPD) of Neurology Clinic at All India Institute of Medical Sciences (AIIMS), New Delhi, India. An informed consent was taken from the participants who fulfilled the eligibility criteria for recruitment and all information regarding the rTMS procedure was explained.

Male	15 or 65.21%
Female	8 or 34.78%
Age (years)	50 - 80 years
Educational Qualification	Illiterate (n = 1) Primary (n = 4) Middle (n = 4) Matric (n = 2) Inter/Diploma (n = 4) Graduate (n = 6) Master/Professional (n = 1) Not Known (n = 1)
Marital Status	Married (n = 22) Widow (n = 1)
Family type	Joint (n = 11) Nuclear (n = 9) Extended (n = 2) Not known (n = 1)
NEST	0-5
DART	0-3
HYS	1-4

Table 1: *Demographic characteristics at baseline.*

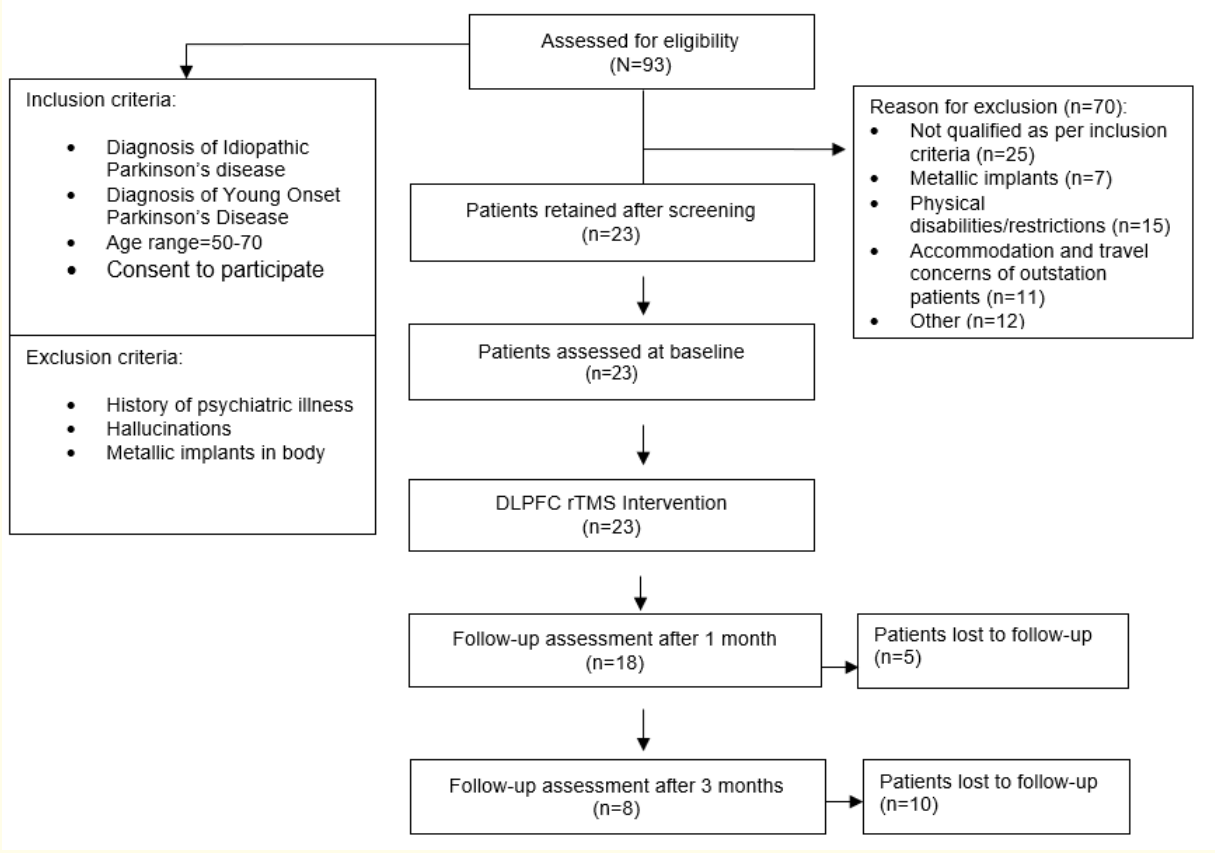

Figure 1: *Study design showing recruitment of patients.*

Study procedure

The pilot study took place at All India Institute of Medical Sciences (AIIMS), New Delhi, India after receiving an Institutional ethical clearance (Ref No.: IEC/NP-39/06.02.2015). This was done to assess the feasibility to carry out an RCT (CTRI Reg. No.: CTRI/2019/11/021847). A baseline assessment was done on memory (auditory, delayed, immediate, working, and short-term memory) (3), executive functioning (phonemic fluency), quality of life, behavioral symptoms, and clinical impairment. The recruited patients that fulfilled the eligibility criteria were provided the rTMS intervention for five days per week for two weeks followed by assessment on the same baseline domains after 1 month and 3 months. Dementia Assessment by Rapid Test (DART) [27] and Neuropsychological Evaluation Screening Tool [28] were used to obtain clinical profile of the patients at baseline. The Hoehn and Yahr stage [29] was used to obtain the severity of the disease.

TMS

The repetitive magnetic stimulation was administered over the left Dorsolateral Prefrontal Cortex (DLPFC) using Magstim Rapid 2 Plus (Magstim Co, Ltd, Wales, UK) stimulator with a 70 mm figure of 8 coil for 5 sessions/week x 2 weeks = 10 sessions. Each session was fifteen minutes in duration and consisted of twenty five trains of rTMS (2s of 20Hz/train, 40 pulses/train). In total, the brain was

stimulated with 1000 pulses over a period of 15 minutes. Wait period between the trains was 31 seconds. DLPFC was measured as being 5cm anterior in the parasagittal plane from the primary motor area [30]. Before administration, Motor Evoked Potential (MEP) was calculated for each patient manually to determine the power of the rTMS session. It was ensured that the patients were in ON-state when the session took place i.e. the effect of medication was present.

Neuropsychological assessment

Neuropsychological assessment was done at baseline, one month post treatment, and three months post treatment. The investigator was blinded to the treatment to ensure unbiased scoring. The assessment included Wechsler's Memory Scale (WMS III) [31] which measured auditory memory, delayed memory, immediate memory, and working memory; Digit Span Forward/ backward [32] which measured verbal short-term memory and auditory recall; Stroop test [33,34] which measured response inhibition under executive functioning; Controlled Oral Word Association (COWA) [35,36] which measured phonemic fluency under the domain of executive functioning; Parkinson's Disease Quality of Life scale (PDQL) [37] and Activities of daily living scale (ADL) [38] which measured quality of life, Agitated behavior scale (ABS) [39] which measured behavioral symptoms, and Unified Parkinson's Disease Rating Scale (UPDRS) [40] which measured the stage of clinical impairment of Parkinson's disease.

Statistical analysis

Data was analyzed using the statistical software Stata 16.0. Categorical data was expressed as frequency and percentage whereas quantitative data was presented as median, minimum and maximum scores. Wilcoxon Sign Rank test was used to compare changes in neuropsychological parameters after rTMS intervention. The level of significance was set at 0.05.

Results

	n: 18			n: 8		
	Pre rTMS	**1 Month Post rTMS**	**p**	**Pre rTMS**	**3 Months Post rTMS**	**p**
Memory						
TA	3 (1-5)	3 (1-6)	0.533	3.5 (2-5)	3.5 (2-5)	0.013
TB	5 (8-2)	5 (3-8)	0.787	3.5 (2-5)	7 (4-11)	0.055
TC	6 (0-9)	7 (3-11)	0.039	6.5 (4-9)	8 (3-10)	0.154
TD	7.5 (0-11)	8 (4-12)	0.086	7 (4-8)	8.5 (7-11)	0.029
LISTB	3 (0-6)	3.5 (0-7)	0.176	3 (0-6)	4.5 (1-7)	0.287
SDR	4 (0-9)	4.5 (0-9)	0.476	3.5 (1-9)	5.5 (4-10)	0.013
WL	3 (0-10)	5 (0-8)	0.044	3 (1-10)	6 (4-11)	0.013
LA	0 (0-3)	1 (0-2)	0.489	1.5 (0-2)	2 (0-7)	0.127
LB	2 (0-4)	2.5 (0-5)	0.911	2.5 (0-4)	4 (2-6)	0.117
LC	2 (0-5)	3 (0-6)	0.103	2 (0-4)	4.5 (3-6)	0.013
LD	2.5 (0-5)	3.5 (0-7)	0.062	2 (0-5)	4 (3-8)	0.013
vpa2recall	2 (0-4)	4 (0-6)	0.007	2 (0-4)	4 (3-7)	0.018
vpa2recog	23.5 (20-24)	24 (20-24)	0.035	23.5 (20-24)	24 (22-24)	0.189
wl2recog	20 (12-23)	22.5 (18-16)	0.001	22 (16-23)	23 (20-24)	0.040
Ss	11.5 (5-18)	11.5 (7-23)	0.053	11 (7-16)	11 (7-19)	0.429
DSFB	10.5 (5-15)	10 (6-16)	0.643	10 (6-15)	10 (7-15)	0.430

Executive Function						
SWE	1 (0-7)	1.5 (0-8)	0.489	4 (1-7)	75 (62-364)	0.108
SWT	1.47 (1.19-2.54)	122 (77-293)	0.005	1.32 (1.19-2.15)	2 (0-21)	0.500
SCE	8.5 (1-23)	5 (1-34)	0.887	9 (8-11)	228 (124-281)	0.108
SCT	3.14 (2.15-5.5)	188.5 (124-275)	0.002	3.12 (2.29-5.5)	7 (0-30)	0.312
Seffect	89 (55-213)	59.5 (-102-156)	0.202	112 (70-213)	79 (-109-206)	0.138
Spercentile	91.5 (26-100)	91 (35-100)	0.682	80 (26-97)	86 (29-100)	0.416
COWA	4 (1-13.33)	5.5 (0.66-13)	0.471	4.33 (1-13.33)	5.5 (2-11.33)	0.573
Quality of Life						
PDQL	95.5 (54-142)	82.5 (58-143)	0.472	93.5 (54-118)	92 (52-116)	0.944
ADL	89 (55-213)	59.5 (-102-156)	0.202	112 (70-213)	79 (-109-206)	0.138
Behavioural symptomatology						
ABS	15 (14-22)	15 (14-22)	0.300	15 (14-19)	14 (14-40)	0.448
Clinical impairment						
UPDRS	39 (22-77)	33.5 (19-71)	0.169	40.5 (22-77)	38 (19-67)	0.400

Table 2: *Result scores expressed as median (Minimum-Maximum) at Pre rTMS, 1 month post rTMS, and 3 months post rTMS.*

**Statistical analysis done using Stata 16.0 StataCorp.*

WL: Word List, SDR: Short Delay Recall, WL2 Recognition: Word List 2 Recognition, VPA Recall: Verbal Paired Associates Recall, VPA Recognition: Verbal Paired Associates Recognition, SS: Spatial Span, DSFB: Digit Span Forward Backward, SEFFECT: Stroop Effect, SPERCENTILE: Stroop Percentile, COWA: Controlled Oral Word Association test, PDQL: Parkinson's Disease Quality of Life, SE-ADL: Schwab and England Activities of Daily Living Scale, ABS: Agitated Behavior Scale, UPDRS: Unified Parkinson's Disease Rating Scale.

Memory

The table shows the median scores on the memory domains: learning, auditory memory, working memory, immediate memory and delayed memory. The results show a significant improvement in performance of the PD patients on the auditory immediate memory and recall scores post intervention (7(t2) > 6(t1), p = 0.039; 7(t2) > 3.5 (t1), p = 0.055; 8.5 (t3) > 7 (t1), p = 0.029. The short-delayed recall improved from the baseline to the follow-up assessment 4 months after the intervention with a significant difference (5.5 (t2) > 3.5 (t1, p = 0.013). Performance on delayed general memory and delayed auditory recognition was found to improve post intervention. Scores on recall improved with statistical significance (4 (t2) > 2 (t1), p = 0.007, 4 (t3) > 2(t1), p = 0.018). Scores on recognition also improved with statistical significance from baseline to one month post intervention (24 (t2) > 23.5 (t1), p = 0.035).

Executive functioning

The patients' performance on phonemic fluency showed an improvement but it was not found to be significant (5.5 (t2) > 4 (t1), p > 0.05, 5.5 (t3) > 4(t1), p > 0.05). Assessment of response inhibition was done using Stroop test. Performance of PD patients improved on

the domain of response inhibition after rTMS intervention but the difference was not significant (59.5(t2) > 89(t1), p > 0.05, 79 (t3) > 112 (t1), p > 0.05).

Quality of life

Scores on PDQL saw a decline i.e. impairment in patients' quality of life reduced after intervention but this difference was not significant (82.5 (t2) > 95.5 (t1), p > 0.05, 92 (t3) > 93.5 (t1), p > 0.05). The ADL data showed a decline in the level of independence and speed experienced by the patients post intervention but this was also not found to be statistically significant (59.5 (t2) > 89 (t1), p > 0.05, 79 (t3) > 112 (t1), p > 0.05).

Behavioural symptomatology

The scores on the domain of behavioural impairment did not see any significant difference before and after rTMS (14 (t3) > 15 (t1), p > 0.05).

Clinical impairment

There was no significant difference in the clinical impairment of patients after rTMS (33.5 (t2) < 39 (t1), p = 0.169, 38 (t3) < 40.5 (t1), p > 0.05).

Discussion

The aim of the current study was to study the effect of rTMS over left DLPFC on neuropsychological functioning of Parkinson's disease Patients.

Our study showed a significant improvement in memory of the patients post intervention, suggesting that rTMS was favourable for memory of PD patients. Their scores increased on the domains of delayed general memory and delayed auditory memory. Patients performed better on both auditory recall and recognition items post intervention. This result is in accordance with previous RCTs [41] which found temporary improvement in memory after 5Hz rTMS stimulation for elderly PD patients who experienced slight disturbance in memory in the current study, scores on working memory and verbal short-term memory did not show any significant differences after rTMS. The existing literature lacks enough evidence on effect of rTMS on specific memory domains of PD patients. However, a study on healthy older adults [42] did find enhanced immediate recall and delayed recall of verbal memory by high frequency (10Hz) rTMS. More randomized clinical trials on rTMS are needed on specific cognitive domains of Parkinson's Disease patients to understand and collate its findings.

Most of the existing literature in clinical practice has highlighted the effect of rTMS on executive functioning [43-45]. The current pilot study found lesser time taken on Stroop and an increase in produced words on COWA but these scores were not found to be statistically significant. The site of our stimulation was DLPFC which is closely linked to executive functioning [46,47]. Non-significant results could indicate the need for a Neuronavigation arm for a more accurate focal stimulation.

In terms of quality of life, results showed a decline in impairment in the quality of life measured by PDQL but this difference was not statistically significant. Many QoL tools exist in terms of PD, but none of them are developed keeping the Indian population in mind [48]. There is a need for more culture specific PD-QoL tools that take into account the neuropsychological, economic, and socio-cultural concerns of the Indian population. Improved but non-significant results could indicate low sensitivity of the tools used, and also suggest a need for a larger sample size.

A decline in clinical impairment was found using UPDRS but scores were not statistically significant. This could be because of the nature of UPDRS items that include more motor function related items than psychological and cognition that is a function of DLPFC. Hence, UPDRS would not have been as suitable for studying the effect of rTMS at DLPFC area as it would for a motor related site of the brain [49].

The current study included follow-up assessments after one month and three months from the intervention. Previous RCTs have seen a positive effect of repetitive stimulation with PD patients about 5 months [50], 6 months [51] and 12 months [52] from intervention. On the contrary, a study that followed-up 14 days post treatment with rTMS did not find significant results [53]. This could suggest an important role of time and design of the study in obtaining successful rTMS related outcomes. According to Mally (2017), "delayed effect of stimulation" as well as age of the patients contribute to the results, although no significant effect of age has been supported by evidence yet [54,55].

The patients included in the study were also undergoing usual pharmacological therapy. It can be suggested that rTMS when combined with pharmacological therapy helps maintain and improve cognitive functioning in terms of memory of the patients.

Future Directions/Conclusion

The current pilot study helped confirm the feasibility of a similar RCT. Further research needs to be conducted with a larger sample size, culture fair psychometric tools developed for the specific population at hand, and preferably with a neuronavigation arm of the tms device for accurate stimulation. The long-term effects of rTMS particularly with regard to neuropsychological domains and varying frequency [56], stimulation intensity and rTMS coil-type, need to be investigated. Culture fair cognitive assessment tools with high validity, reliability and sensitivity for detection can be employed. Specific cognitive tasks that are a function of the brain site stimulated should be incorporated, such as word naming tasks for measuring executive functioning at dlpfc [57] for better results in the future studies. Follow up after longer time durations can also be done to study the long-term effects of rTMS.

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