ORIGINAL ARTICLE

Abnormal Intracortical Functions in Parkinson's Disease with Rapid Eye Movement Sleep Behaviour Disorder

*Amitabh Bhattacharya**, *Nitish Kamble**, *Ravi Yadav*, *Albert Stezin*, *Pramod Kumar Pal*

ABSTRACT: ***Background:*** Rapid eye movement sleep behaviour disorder (RBD) is considered to be one of the most frequent and important prodromal symptoms of Parkinson's disease (PD). We aimed to study the neurophysiological abnormalities in patients of PD-RBD and PD without RBD (PD-nRBD) using transcranial magnetic stimulation (TMS). ***Methods:*** Twenty patients each of PD-RBD and PD-nRBD were included in the study in addition to 20 age and gender-matched healthy controls. RBD was identified using the RBD screening questionnaire (RBDSQ). All the subjects were evaluated with single and paired-pulse TMS and parameters such as resting motor threshold (RMT), central motor conduction time (CMCT), silent period (SP), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were recorded. ***Results:*** The mean age of the controls and PD patients with and without RBD was comparable. There were no significant differences in RMT, CMCT and silent period between the two patient groups. SICI was present in all the three groups with significant inhibition noted in PD-RBD group ($p < 0.001$). ICF was absent in patients of PD-RBD (0.19 ± 0.11) and PD-nRBD (0.7 ± 0.5) when compared to controls (1.88 ± 1.02) with profound impairment in patients with PD-RBD ($p < 0.001$). The mean MoCA score was found to be significantly different in all the three groups with a worse score in patients with RBD (23.10 ± 2.55; $p < 0.001$). ***Conclusions:*** PD-RBD patients have significantly greater inhibition and reduced intracortical facilitation suggesting enhanced GABAergic and reduced glutaminergic transmission. These abnormalities may underlie the different pathophysiological process observed in these patients.

RÉSUMÉ : Fonctions intra-corticales anormales chez des patients atteints de la maladie de Parkinson et de trouble du comportement en sommeil à mouvements oculaires rapides. ***Contexte*** **:** Le trouble du comportement en sommeil (TCM) à mouvements oculaires rapides est considéré comme l'un des symptômes prodromiques les plus fréquents et les plus importants de la maladie de Parkinson (MP). Nous avons voulu étudier les anomalies neurophysiologiques chez des patients parkinsoniens atteints de ce trouble et chez des patients parkinsoniens n'en étant pas atteints, et ce, au moyen de la stimulation magnétique transcrânienne (SMT). ***Méthodes*** **:** En plus de 20 témoins en santé appariés selon l'âge et le sexe, 20 patients du premier groupe (atteints du TCM) et 20 autres du deuxième groupe (non atteints du TCM) ont été inclus dans cette étude. Les signes de TCM à mouvements oculaires rapides ont été identifiés au moyen d'un questionnaire de dépistage (*RBD screening questionnaire*). Tous les patients ont été ensuite évalués à l'aide de la SMT à impulsion simple et appariée. Notons par ailleurs que des paramètres portant sur le seuil moteur au repos (SMR), le temps de conduction motrice centrale (TCMC), la période de silence (PS), l'inhibition intra-corticale à intervalle court (IICIC) et la facilitation intra-corticale (FIC) ont été définis. ***Résultats*** **:** L'âge moyen des témoins et des patients des deux groupes s'est révélé comparable. Aucune différence notable n'a émergé entre ces groupes de patients en ce qui regarde le SMR, le TCMC et la PS. Des signes d'IICIC étaient présents au sein de tous les sujets à l'étude. Ils se sont avérés particulièrement notables au sein du groupe de patients atteints de TCM ($p < 0{,}001$). On a dénoté une absence de FIC chez les patients atteints de TCM ($0{,}19 \pm 0{,}11$) et ceux qui n'en étaient pas atteints ($0{,}7 \pm 0{,}5$) en comparaison avec les témoins en santé ($1{,}88 \pm 1{,}02$), une altération profonde étant par ailleurs observée chez les premiers ($p < 0{,}001$). Enfin, les scores à l'échelle MoCA sont apparus nettement différents selon les trois groupes, les plus faibles ayant été obtenus par les patients atteints de TCM ($23{,}10 \pm 2{,}55$; $p < 0{,}001$). ***Conclusions*** **:** Les patients atteints de TCM à mouvements oculaires rapides ont donné à voir des signes d'inhibition nettement plus importants ainsi qu'une réduction de la FIC, ce qui suggère une augmentation de la transmission GABAergique et une réduction de la transmission glutamatergique. Il est donc possible que ces anomalies sous-tendent le processus physiopathologique différent observé chez ces patients.

Keywords: Intracortical facilitation, Parkinson's disease, REM sleep behaviour disorder, Short interval intracortical inhibition, Transcranial magnetic stimulation

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From the Department of Neurology, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, Karnataka, India (AB, NK, RY, AS, PKP)
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Correspondence to: Dr. Pramod Kumar Pal, Department of Neurology, National Institute of Mental Health & Neurosciences (NIMHANS), Hosur Road, Bangalore, Karnataka 560029, India. Email: palpramod@hotmail.com
*Contributed equally to the manuscript. Hence both to be considered as joint first authors.

Introduction

Parkinson disease (PD) is a neurodegenerative disorder characterized by the early death of dopaminergic neurons in the substantia nigra along with a widespread accumulation of intracellular α-synuclein.[1] Bradykinesia, rigidity, tremors and postural instability are the cardinal features. It is also characterized by a wide range of sleep disturbances such as insomnia, daytime somnolence, sleep fragmentation, sleep-disordered breathing (SDB), restless leg syndrome (RLS), nightmares and rapid eye movement (REM) sleep behaviour disorder (RBD).[2] RBD is one of the most important prodromal symptoms and is present in 33–46% of patients with PD.[3] It is characterized by dream enactment behaviour with an increase in muscle tone or phasic muscle twitching during the REM sleep.[4] The mean duration is between 3.7 and 7 years from the onset of RBD to the development of neurodegenerative disease.[5] Patients with PD-RBD have an increased tendency to develop many other non-motor symptoms such as visual hallucinations, psychosis, autonomic disturbances and dementia.[6] It has been shown that RBD is caused by degeneration of the glutamatergic REM-ON and GABA/glycinergic REM-ON neurons in the sublaterodorsal nucleus (SLD).[7] However, the pathophysiologic mechanisms that underlie the development of RBD in PD are still largely unknown.

Transcranial magnetic stimulation (TMS) is a tool to evaluate the neurophysiological changes in the brain by measuring the changes in the excitability of neuronal tissues.[8] Till date, there is only one study done in patients with PD-RBD who found abnormal short-latency afferent inhibition (SAI) but could not find any other significant differences.[9] Hence, we used TMS to specifically explore other neurophysiological abnormalities in patients with PD-RBD and PD-nRBD. We hypothesize that patients with PD-RBD will demonstrate increased neurophysiological abnormalities when compared to patients without RBD. These changes will further help in understanding the abnormalities in the neurotransmitter systems in patients with PD-RBD.

Methods

This prospective study was conducted in the department of Neurology at the National Institute of Mental health and Neuro Sciences (NIMHANS), Bengaluru, India. The institute's ethics committee approved the study and written informed consent was obtained from all the participants (IRB No. NIMHANS/IEC (BS & NS DIV.) 5th MEETING/2017 dated 1st July 2017). The study included 20 patients each of PD-RBD, PD-nRBD in addition to 20 age and gender-matched healthy controls. All patients satisfied the UKPDS brain bank criteria.[10] Patients with age <18 years; history or presence of associated psychiatric illness or other neurological diseases, other sleep disorders; acute or chronic non-compensated medical illness; use of drugs that can affect cognition, mood or drugs that can modulate cortical excitability ; history of alcohol or illicit drug abuse; were not included in the study. Those with the presence of metallic implants, cardiac pacemakers, cochlear implants and other contraindications for TMS were also excluded from the study. Also, patients whose UPDRS-part III "OFF" state upper limb rest tremor score of >2 were also excluded from the study as it can interfere during the TMS experiment.

Demographic characteristics, detailed history and neurological examination were recorded. Unified Parkinson's disease rating scale (UPDRS) part III was performed by experienced movement disorder specialists in the "OFF" (12 hours off medication) and "ON" states (defined as the maximum state of functional improvement while on medication, usually assessed 1–2 hours of levodopa challenge). Levodopa equivalent daily dose (LEDD) was calculated. RBD screening questionnaire (RBDSQ) was applied to determine the presence of RBD and a score of >6 was consistent with RBD.[11] Edinburgh's handedness inventory was used to determine handedness.[12]

Cognitive assessment was done using the Montreal Cognitive Assessment (MOCA) in all three groups.

TMS Methods

TMS experiments were performed using Magstim 200 stimulator and figure-of-eight coil. TMS was performed with the subject sitting on a chair. The "hot spot", that is, the optimal scalp position was identified on the left motor cortex and was marked. This contralateral first dorsal interosseus (FDI) muscle was used to record motor responses. The recording was done using two Ag–AgCl electrodes placed over the FDI muscle with the active electrode over the muscle belly and the reference electrode over the tendon (metacarpophalangeal joint of the index finger). Recording was done with the FDI muscle at rest and audio-visual feedback was used to ensure unwanted muscle activity. The coil was held by the examiner such that the handle was pointing backwards (45° to sagittal plane). The stimulus intensity was gradually increased to obtain a satisfactory motor evoked potential (MEP). Consecutive ten responses were recorded and saved for offline analysis. Resting motor threshold (RMT), central motor conduction time (CMCT), silent period (SP), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were the parameters measured.

The minimum stimulus intensity that was able to elicit MEP amplitude of at least 50 μV (peak to peak) with the muscle at rest in five out of ten consecutive stimulations was considered as RMT that was expressed as percentage. To determine CMCT, cortical stimulation was done using 120% of RMT and spinal stimulation was done above the C7 vertebral spinous process. The difference in the latencies between cortical and spinal cord stimulation was reported as CMCT. Suprathreshold stimulus was used to stimulate the left motor cortex while voluntarily contracting the FDI muscle to record SP. While recording contralateral SP (cSP), the amount of contraction of the contralateral FDI was approximately 30%, whereas for the ipsilateral SP (iSP), the ipsilateral FDI was fully contracted. At least five of the total ten consecutive appropriate recordings were used for analysis. The SP was calculated as the duration of the electromyography (EMG) silence. The end of MEP was taken as the onset and the point where the first burst of EMG activity appeared was taken as the end of the silent period. The stimulus intensity used for recording cSP was 120% RMT and for iSP it was 100% stimulator output. Paired pulse stimulation was used to determine SICI and ICF wherein two stimuli (subthreshold conditioning stimulus and suprathreshold test stimulus) were delivered consecutively separated by a short duration (interstimulus interval, ISI). The stimulus intensity used was 80% RMT for conditioning stimulus and 120% RMT for the test stimulus and the ISI was 2 ms for SICI and 10 ms for ICF. All the TMS experiments were done in the OFF state (at least 12 hours after the last dose of

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Table 1: Demographic and clinical characteristics of the study participants

	PD-RBD (n = 20)	PD-nRBD (n = 20)	HC (n = 20)	Significance
Age (years)	59.75 ± 5.77	55.35 ± 9.18	56.40 ± 3.94	0.09
Age at onset (years)	50.30 ± 6.71	49.00 ± 9.01	–	0.93
Duration of PD (years)	8.20 ± 4.84	5.70 ± 3.15	–	0.17
Duration of RBD (years)	4.45 ± 2.84	–	–	–
UPDRS III (OFF)	34.08 ± 12.31	26.98 ± 18.08	–	0.39
UPDRS III (ON)	16.68 ± 10.11	14.90 ± 13.03	–	0.94
More affected side (right/left)	10/10	13/7	–	–
RBDSQ	7.80 ± 1.58	1.90 ± 1.17	–	<0.001
H & Y stage	2.60 ± 0.58	2.23 ± 0.53	–	0.06
LEDD	657 ± 354.74	651.38 ± 250.32	–	0.96
MoCA	23.10 ± 2.55	26.20 ± 2.50	29.35 ± 0.93	<0.001

HC: healthy controls; H & Y stage: Hoehn and Yahr staging; MoCA: Montreal cognitive assessment; PD: Parkinson's disease; PD-RBD: Parkinson's disease with REM sleep behaviour disorder; RBD: REM sleep behaviour disorder; RBDSQ: REM sleep behavior disorder screening questionnaire; UPDRS III: Unified Parkinson's disease rating scale.

Table 2: Comparison of TMS parameters of patients with PD-RBD, PD-nRBD and HC

	PD-RBD (N = 20)	PD-nRBD (N = 20)	HC (N = 20)	Significance (PD-RBD vs PD-nRBD vs HC)
RMT	41.05 ± 8.42	39.40 ± 6.30	40.95 ± 6.94	0.80
CMCT	7.86 ± 2.30	7.51 ± 1.50	7.63 ± 1.49	0.95
SP	119.52 ± 28.07	133.09 ± 43.55	116.09 ± 15.15	0.32
iSP	34.88 ± 11.39	33.85 ± 11.46	30.75 ± 10.17	0.58
SICI	0.22 ± 0.17	0.40 ± 0.23	0.56 ± 0.42	<0.001
ICF	0.19 ± 0.11	0.70 ± 0.50	1.88 ± 1.02	<0.001

CMCT: central motor conduction time; cSP: contralateral silent period; HC: healthy controls; ICF: intracortical facilitation; iSP: ipsilateral silent period; PD: Parkinson's disease; PD-RBD: Parkinson's disease with REM sleep behaviour disorder; PD-nRBD: Parkinson's disease without REM sleep behaviour disorder; RBD: REM sleep behaviour disorder; RMT: resting motor threshold; SICI: short-interval intracortical inhibition.

levodopa, 36 hours after the last dose of dopamine agonist and 48 hours after the last dose of clonazepam).

Statistical Analysis

R software (version 3.6.0) was the statistical software used to analyse the data. Shapiro-Wilk test was used to confirm normality of data, which was not significant and therefore, parametric tests were performed. For comparison of means among patients and controls, the one-way ANOVA was used. A Bonferroni corrected value of <0.05 was considered as significant. Finally, the correlations were done using Pearson's correlations to check the relationship between clinical and TMS variables.

Results

Demography

The mean age was 59.75 ± 5.77 years for PD-RBD patients, 55.35 ± 9.18 years for PD-nRBD and 56.40 ± 3.94 years for controls. There were three YOPD patients each in PD-RBD and PD-nRBD group. The age, age at onset, disease duration, LEDD, UPDRS III motor scores or H&Y staging were comparable among the PD-RBD and PD-nRBD groups (Table 1).

Cognitive Assessment

The mean MoCA score in the PD-RBD group was 23.10 ± 2.55 and 26.20 ± 2.50 in the PD-nRBD group as compared to healthy controls (29.35 ± 0.93). The results were statistically significant ($p < 0.001$).

Transcranial Magnetic Stimulation

There was no significant difference observed for RMT, CMCT and SP (both cSP and iSP) between the groups (Table 2). SICI was seen in all the groups, however, significant inhibition was observed in the PD-RBD group (0.22 ± 0.17) when compared to PD-nRBD (0.40 ± 0.23) and healthy controls (0.56 ± 0.42, $p < 0.001$) (Figure 1). ICF was absent in both the PD groups (Figure 2). There was a profound impairment in the ICF in patients with PD-RBD (0.19 ± 0.11) when compared to PD-nRBD group (0.70 ± 0.50, $p < 0.001$).

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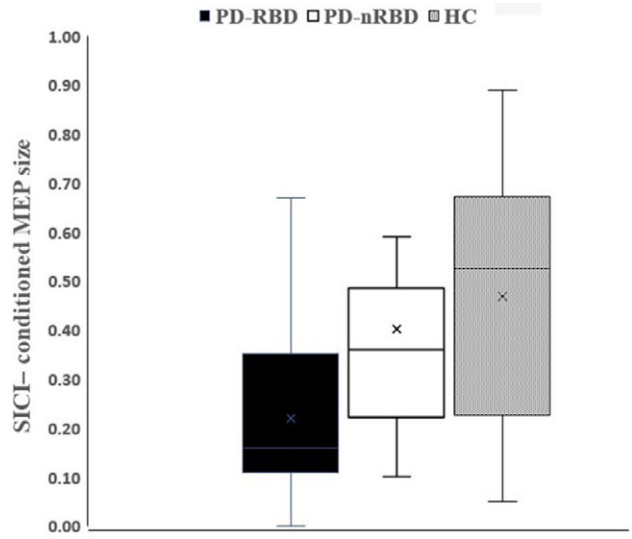

Figure 1: *Short-interval intracortical inhibition in the study participants.*

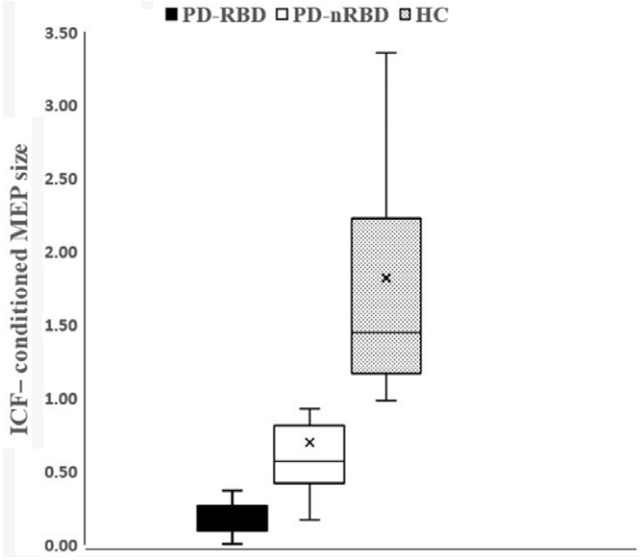

Figure 2: *Intracortical facilitation in the study participants.*

In the PD-RBD group, the mean MoCA score negatively correlated with the UPDRS III-OFF score ($r = -0.54$, $p < 0.05$) whereas there was a positive correlation between MoCA and mean SICI in both the groups (PD-RBD, $r = 0.20$; PD-nRBD, $r = 0.45$, $p < 0.05$). There was no correlation between ICF and MoCA scores.

Discussion

TMS is a neurophysiological tool that is used to evaluate motor cortical excitability.[8] Neurotransmitter integrity of the motor circuitry can be assessed by studying the changes in the inhibition and facilitation properties of the brain using TMS.[13] In our study, we performed TMS in PD-RBD and PD-nRBD patients and found that the ICF was absent in both the groups with a more pronounced abnormality in PD-RBD group. Also, significant inhibition (SICI) was observed in the PD-RBD group. Our results showed comparable changes in the single pulse parameters, that is, RMT, CMCT and SP in our cohort. Many studies have shown that RMT is a basic measurement of the excitability of the motor cortex. The SP measures intracortical inhibitory circuits which are a function of GABA-B transmission whereas the CMCT assesses the corticospinal neuronal integrity.[14] Thus, in our study, the overall excitability of the cortex and the cortico-spinal conductivity remain preserved.

Studies of TMS in PD have shown inconsistent results. Most of the studies have shown normal RMT in PD patients.[13,15] CMCT is the time required to excite the motor cortical neurons, conduction through the corticospinal or corticobulbar tract and cause excitation of the motoneuron in the cranial nerve nucleus or spinal cord. This also is usually normal in PD patients; however, some studies have reported shorter CMCT.[16,17]

SICI is believed to be mediated by GABA receptors. Few studies have reported reduced SICI or normal SICI in these patients.[13,18] Interestingly, another study showed normalization of reduced SICI after levodopa therapy.[18] In contrast, Chu et al. did not observe any significant difference in the SICI values in PD in the ON and OFF state.[19] Studies of deep brain stimulation of the subthalamic nucleus have shown that reduced SICI in the medication ON and OFF state tends to normalize. However, there is only little effect of globus pallidum stimulation on SICI.[20] In addition, it has been found that in newly diagnosed PD patients the SICI is reduced on the affected side and normal on the less affected side.[21]

Besides, results have been variable with respect to ICF. Studies have demonstrated, ICF to be mediated through the glutamatergic circuits.[14,19,22–25] While some studies talk of ICF being reduced in PD, others have found ICF to be normal in these patients.[18,26] We found significantly reduced ICF in both PD groups in comparison to healthy controls.

Until date, there are no studies reported in the literature that has evaluated SICI and ICF in patients with PD-RBD. However, there only two studies using TMS in patients with isolated RBD (iRBD). The SICI (0.36 ± 0.17) and ICF (1.18 ± 0.21) was normal in one study whereas in another study the ICF (0.8) was absent which is similar to our study.[27]

In a recently study by Ammann et al., patients with PD had reduced SICI even in the early stage with no difference in the ICF.[28] The results are contradictory to our results wherein we found enhanced SICI and reduced ICF. The TMS technique employed is similar in both the studies. The difference in the results could be due to various causes such as: our PD patients are slightly younger compared to the other study and have a much earlier age at presentation.

Our patients were young and the average age at onset was around 50 years compared to previous studies (about 55 years). There were three YOPD patients each in PD-RBD and PD-nRBD group. In addition, in our study, TMS was done in the medication OFF state. In addition, TMS was only performed on left hemisphere, while there were patients in both the groups who had either right or left side being more affected. All these factors, could possibly bias the results making it different from the previous studies.

The pathophysiological mechanisms of RBD are still debated. Studies indicate that GABA/glycinergic REM-ON neurons in the ventromedial medullary formation and the spinal cord

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causes muscle atonia during REM sleep. Furthermore, these GABA/glycinergic REM-ON neurons are activated by the glutamatergic neurons in sublatero-dorsal tegmental nucleus (SLD) of the pons during the onset of REM sleep.[7,29] Patients with RBD can have all types of movements basically due to loss of tonic inhibition and motor neuron excitation.

Pathological studies which have included RBD as a frequent phenomenon in neurodegenerative disorders have found neuronal cell death in the brainstem region such as locus subcoeruleus, pedunculopontine nucleus, gigantocellular reticular nucleus (Gi), and also amygdala.[23] Based on previous studies, RBD occurs due to the degradation of the SLD glutamatergic REM-ON neurons situated in the RMg, GiA, and GiV. As shown in our study, the loss or reduction of ICF correlates with the loss of glutaminergic neurons required to maintain atonia in REM sleep.

It is also true that the degeneration of the brainstem glutaminergic neurons does not occur simultaneously in other brain areas. Both our PD groups had loss of ICF suggesting degeneration of glutaminergic neurons. However, this degeneration of glutaminergic neurons in the brainstem can have a network effect due to the diffuse projections of these neurons to the cerebral cortex.

In addition, it is possible that the RBD changes are receptor specific as SP was normal and SICI was enhanced in our study.[15] We hypothesize that the enhanced SICI could be due to the network effect.

According to previous studies, patients with PD-RBD phenotype tend to have greater cognitive decline as compared to those without the RBD phenomenology.[30] A study done by Chahine et al. found a greater decline in MoCA score every year in PD-RBD involving 423 PD patients that were followed up for 3 years.[31] Our study though does not provide longitudinal reports however, reports increased decline in MoCA scores in the PD-RBD group. There is a greater evidence to support the link between RBD and PDD as well. Marion and colleagues demonstrated that the time to develop dementia after the onset of PD symptoms was significantly less in RBD patients as compared to non-RBD groups.[32]

Our MoCA findings are in line with previous neuropsychological studies demonstrating that cognitive dysfunction in patients with PD is closely related to the presence of RBD.[33] In our study SICI correlated with MoCA but not the ICF. This suggests that SICI is a more reliable parameter in patients with PD-RBD.

Several studies have demonstrated neuropsychological dysfunction even in patients with the idiopathic form of RBD.[34] Deficits in executive function tasks requiring the integrity of the fronto-striatal pathway, episodic memory impairment, as well as visuospatial and visuo-perceptual dysfunctions have often been demonstrated in PD.[35]

Neuropathologic and brain imaging studies performed in PD with cognitive impairment and in patients with RBD have demonstrated common neural alterations in several brainstem nuclei (i.e., substantia nigra, PPN, raphe nucleus, and LC-subcoeruleus complex) and anomalies in their corresponding neurotransmitters (i.e., dopaminergic, cholinergic, noradrenergic, and serotonergic systems).[36]

All of these brainstem structures have diffused projections to the cerebral cortex and perturbations of these neural networks may explain the presence of cognitive deficits in patients with PD-RBD. In particular, the PPN is an important part of a network for maintaining attention, and may control attentional processes through its direct projections to the forebrain.[37,38] Therefore, the core feature of cognitive impairment in PD patients with RBD, as well as in patients with iRBD, seems to be related to a widespread dopaminergic as well as cholinergic dysfunction.

Although the potential role of neurotransmitters such as acetylcholine is quite explored however, the role of dopamine in the patients with PD-RBD remains elusive. However, it is unknown whether dopaminergic dysfunction contributes to the RBD phenomenology in PD.

The results from our study show that there is glutamatergic insufficiency secondary to degeneration of glutaminergic neurons in the SLD. It is likely that in patients who develop RBD, the neurotransmitter deficits are more severe as highlighted by our results. Changes in the brainstem nuclei and neurotransmitters have been demonstrated by the neuropathological and imaging studies in iRBD. Furthermore, these structures have diffused projections to the cerebral cortex which can, therefore, explain, the presence of cortical dysfunction in patients with RBD which was also demonstrated by recent studies of cortical thinning in RBD linked to clinical progression.[27] Hence, TMS could have a role in the premotor stage of PD and can serve as a biomarker in the early stage.

There are a few limitations to our study. The sample size was small. Secondly, the investigators were not blinded to the clinical category of the patients as that can involve a bias in the study. Thirdly, it is known that ICF and SICI are largely mediated by glutamate and GABA, the underlying mechanisms appear to be more complex. The role of other neurotransmitters such as dopamine, noradrenaline, serotonin and acetylcholine particularly for ICF cannot be overlooked, which was not investigated in the present study.[14,26] In our study we tested only the left motor cortex in all the subjects and did not separate them to more affected or less affected sides. This could definitely have affected the results.

Conclusions

Patients of PD-RBD have a significant neurophysiological abnormality in the form of strong inhibition and absent facilitation suggesting an abnormality in the glutaminergic and GABAergic neurons. There could also be involvement of other neurotransmitter systems in these patients. SICI appears to be a reliable parameter of RBD in patients with PD-RBD. Larger studies are required to develop a grading scale for SICI and ICF that can differentiate PD-RBD from PD-nRBD.

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Conflict of Interest

None of the authors have any financial disclosure to make or have any conflict of interest.

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Statement of Authorship

AB: Conception, organization, execution, statistical analysis, writing of first draft
NK: Conception, organization, execution, Manuscript review and critique
RY: Organization, Manuscript review and critique
AS: Conception, Manuscript review and critique
PKP: Conception, supervision, organization, Manuscript review and critique

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