Resting-state EEG Microstates Change in rTMS stimulation in Parkinson's Disease Patients

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Aim: The aim of this study was to evaluate the effects of the left pre-supplementary area (preSMA) high-frequency repetitive Transcranial Magnetic Stimulation (rTMS) on motor symptoms and resting-states electroencephalographic (EEG) microstates change in Parkinson's Disease (PD) patients.

Methods: The study included right-handed 8 patients (1 female, 7 males). The motor symptoms were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS). Ten sessions of rTMS with 5 Hz frequency were applied to the left pre-SMA region over two weeks. The resting-state EEG was recorded on eyes closed condition with BrainAmp 32 channel DC system. The resting-state EEG recordings and clinical assessments were performed once before the TMS sessions and repeated one week after the last session. The microstates analyses were performed using Microstates analysis tool into MATLAB for EEGLAB (http://www.thomaskoenig.ch/Download/EEGLAB_Microstates). For statistical analysis, JAMOVI was used. For all tests, the significance value was accepted as $p<0.05$.

Result: The Transition Probability from D to C was statistically significant higher than the transition probability from D to C after rTMS ($p=0.045$, $p=0.008$). There was a significant improvement in the UPDRS-Total and the UPDRS-motor scores after the rTMS ($p <0.05$). Conclusion: These data demonstrate that it is possible to change in EEG microstates spectrum after rTMS may be related to improving motor symptoms. In addition, the results showed that rTMS produced the transition probability alterations in the EEG microstates.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. The disease manifests a chronic and progressive course by affecting the central nervous system. PD is characterized by movement disorders [1]. Although many patients benefit from medications at an early stage, this effect decreases as the disease progresses [2].

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive and reliable method that can modulate corticospinal excitability over the selected brain region. Many studies show that it can be an effective treatment tool in neurodegenerative diseases [3]. The pathophysiology of neurodegenerative disorders is linked to neurophysiological changes. For this reason, neurophysiological evaluation is important in terms of both diagnosis and follow-up of the treatment course [4].

Microstate analysis is a method in which the electrical potentials on the multi-channel electrode array are defined topographically in EEG and provides information with a temporal resolution at the level of milliseconds. These different topographies, called "microstates", are topographies of electric potentials recorded across the scalp in a multichannel array and remain constant for 80-120 ms before changing. Microstate analysis takes into account the signal from all electrodes simultaneously to create a global representation of the functional state in the brain, which allows us to use the EEG signal as a potential neurophysiological parameter. Many studies have shown that the characteristics of EEG microstate time series vary according to behavioral states, personality types, and neuropsychiatric disorders. Studies suggest that microstate time series can provide insight into the neural activity of the resting brain. EEG microstate analysis has been proposed as a powerful, inexpensive, and potentially clinically feasible neurophysiological method to examine and evaluate the global functional states of the brain in health and disease [5,6].

This analysis enables the EEG recording to be transformed into a series of topographic maps. Although there are many possible maps in the multichannel recording, the majority of the signal (usually> 70% of the total topographic variance) can be represented with just a few topographies. Most studies examining the resting-state EEG reported the same 'four microstates' explaining most of the global topographic variance. These four maps have right-anterior left-posterior, left-anterior right-posterior, midline frontal to occipital, and midline mostly frontal topographies, and they are labeled A, B, C, and D. When examining the microstate time series, the parameters looked at are; the mean duration or lifetime of each microstate, the average time that a particular microstate remains constant when it appears; the frequency of occurrence of each microstate, the frequency per second of a microstate during the recording period; the coverage of a microstate, the ratio of total recording time dominated by the microstate to the total time. The possibilities for the transition from one microstate to another are also not random, and the transition order between microstates is also potentially important [5,6].

The transitions between microstates can be interpreted to represent sequential activation of different neural networks, and the time series of the microstates in the resting-state EEG seems to reflect the activities of the neural structures of the brain at rest. Many studies have suggested that there is a link between resting-state networks (RSNs) and EEG microstates identified by functional magnetic resonance imaging (fMRI), suggesting that the RSNs of fMRI may be the same as those that cause microstates. Especially Britz et al. reported in 2010 that microstates A, B, C, and D correspond to RSNs defined as phonological processing, visual network, saliency network, and attention network, respectively [7].

The aim of this study is to characterize the microstate changes in PD and to show the effect of rTMS administration on motor performance by microstate analysis.

Material & Method

The study included 8 PD patients and 13 age-matched controls (Table 1). The cognitive symptoms were evaluated with the Neuropsychological Testing Batteries and the motor symptoms were evaluated with the Unified Parkinson's Disease Rating Scale-motor score (UPDRS- III). 5 Hz rTMS was applied on left pre-SMA in PD patients. The rTMS was performed for 10 sessions. Each patient was re-evaluated one week after the end of the sessions. We measured resting EEG microstate parameters in PD (n = 8), and age-matched controls (n= 13) before and after rTMS sessions to investigate neuronal dynamics at the whole-brain level.

rTMS Protocol and Determination of Stimulation Regions: High resolution (1x1x1 mm) T1-weighted MR images were obtained in 3T for TMS neuronavigation. The subject brain is registered to the MNI152 standard brain atlas and pre-SMA identified from the atlas. Then stimulation coordinates back-projected to the native space for TMS neuronavigation. The left pre-SMA in MNI152 coordinates was x = -6, y = 9, z = 60) (See Figure 1) [8, 9].

The resting-state EEG was recorded on eyes closed condition with BrainAmp 32 channel DC system. EEG recordings and clinical assessments were performed once before the TMS sessions and repeated one week after the last session. Two minutes, artifact rejected and 2-20 Hz band-pass filtered resting-state EEG data were analyzed by clustering into four microstate topographies and sequencing. The microstates analyses were performed using the Microstates analysis tool into MATLAB for EEGLAB (http://www.thomaskoenig.ch/Download/EEGLAB_Microstates). For statistical analysis, JAMOVI was used. For all tests, the significance value was accepted as $p<0.05$.

Results

PD's mean age was 70.6 ± 4.63, the mean years of education were 11.4 ± 4.69; The mean age of the healthy controls was 69.2 ± 5.60, and the mean years of education were 9.08 ± 5.25. The mean disease duration of PD was 7.38 ± 2.92. The mean UPDRS motor scores of PD before rTMS were 18.38 ± 5.18, Hoehn and Yahr Scale mean was 2.75 ± 1.16, the MMSE mean was 24.13 ± 1.64. UPDRS-III scores of PD improved significantly after 10 sessions of rTMS administration (Table 1).

In PD, The duration of Class B was longer, but the duration of class D was significantly shorter; Coverage of Class D was significantly less. Transition analysis showed that PD was significantly more likely to switch between class A and B, while healthy controls were significantly more likely to switch between Class C and D. In addition, in our qualitative topographic examination, we found that the Class D topography in PD patients changed (see Figure 2).

After rTMS, the probability of transition from class D to class C increased significantly in PD patients.

	PD			HC
Age (mean ± SD)	70.6 ± 4.63			69.2 ± 5.60
Sex (F/M)	1/7			5/8
Years of Education (mean ± SD)	11.4 ± 4.69			9.08 ± 5.25
MMSE (mean ± SD)	Pre-rTMS	Post-rTMS	P value	27.5 ± 1.33
	24.13 ± 1.64	26 ± 3.07	0.110	
UPDRS-III Motor Subscore (mean ± SD)	Pre-rTMS	Post-rTMS	P value	
	18.38 ± 5.18	13,87 ± 4.73	**0.009**	

Table 1: Demographic, clinical data of the studied groups and sequential assessment. For statistical analysis, paired student's t-test was used. HC: healthy controls

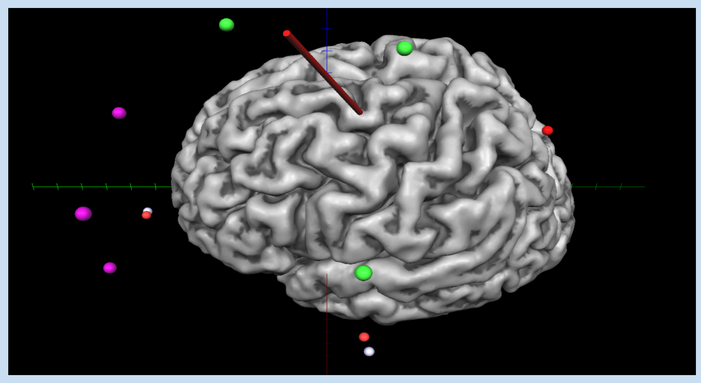

Figure 1: A subject's head MR image rendered by BrainVoyager software and as visualized with markers in CMS20 navigation system.

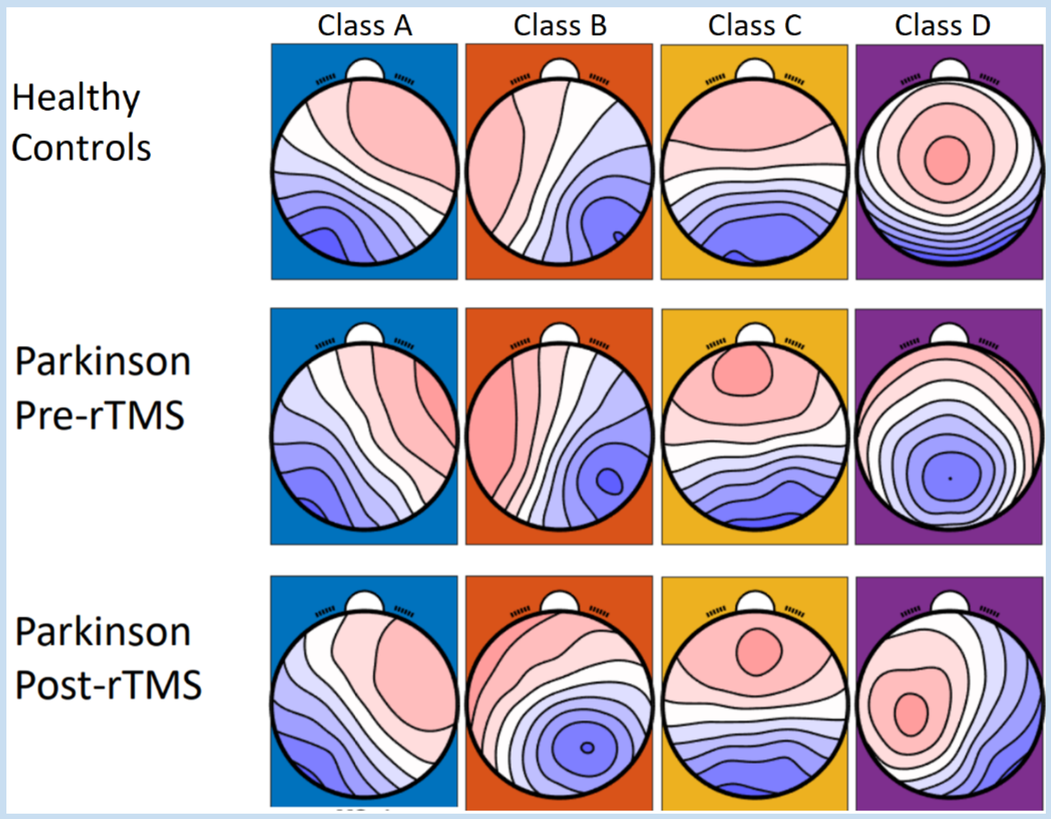

Figure 2: Mean topographic maps of each group are shown. Note that the map sequences are compatible with the literature [6].

Discussion and Conclusion

In an EEG-fMRI study on Dementia with Lewy bodies patients, Schumacher et al. found that functional connectivity in the thalamic/basal ganglia networks was negatively correlated with the mean duration of microstates [10]. The prolonged duration of Microstate B in PD, which we also detected in our study, may be an indicator of decreased connectivity in the thalamic and basal ganglia network.

In RSNs studies, Microstate D has been associated with the frontoparietal network in which areas such as pre-SMA, primary motor cortex, inferior parietal cortex, and superior parietal lobe present functional connectivity [11]. The decrease in Microstate D parameters in PD may be an indication that these areas related to motor skills are affected. In the study reported by Serrano et al., they were pointed out that the topography of Microstate D, which seemed to be affected before levodopa medication in PD, improved after levodopa [4]. Deficiency of Microstate D, previously shown in schizophrenia patients, may be a result of dopamine deficiency in certain brain regions in schizophrenia, and another study in PD, a disease affecting dopamine, concluded that impairment of microstate D could be an indicator of dopamine deficiency [12, 13]. Changes in microstate D, which we also found in our study, may be associated with motor impairment and dopamine deficiency in PD. Increasing the probability of transition from Microstate D to Saliency network associated Microstate C the after rTMS application may be a parameter that reflects the motor recovery in PD.

This study highlights that PD has different microstate parameters that may be specific to movement disorders, rTMS treatment into pre-SMA location has a great potential to interfere with the functional state of the brain. Microstate analysis can be a potential tool for determining neurophysiological disturbances in neurodegenerative diseases and monitoring the effects of novel neuromodulation methods, such as rTMS.

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