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Electroencephalogram slowing predicts neurodegeneration in rapid eye movement sleep behavior disorder

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ABSTRACT

A large proportion of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) develop a synucleinopathy, mostly Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Therefore, identifying markers of neurodegeneration in iRBD could have major implications. We aimed to assess the usefulness of electroencephalography (EEG) spectral analysis performed during wakefulness for predicting the development of a neurodegenerative disease in iRBD. Fifty-four iRBD patients, 28 of whom developed Parkinson's disease, multiple system atrophy, or dementia with Lewy bodies (mean follow-up: 3.5 years), and 30 healthy controls underwent at baseline a resting-state waking EEG recording, neurological exam, and neuropsychological assessment. Absolute and relative spectral powers were analyzed for 5 frequency bands in frontal, central, parietal, temporal, and occipital regions. The slow-to-fast $[(\delta + \theta)/(\beta 1 + \beta 2)]$ power ratio for each of the 5 cortical regions and the dominant occipital frequency were calculated as an index of cortical slowing. Patients who developed disease showed higher absolute delta and theta power in all 5 cortical regions compared to disease-free patients and controls. The slow-to-fast power ratio was higher in all regions in patients who developed disease than in the 2 other groups. Moreover, patients who developed disease had a slower dominant occipital frequency compared to controls. The only significant difference observed between disease-free iRBD patients and controls was higher absolute delta power in frontal and occipital regions in iRBD patients. Specific EEG abnormalities were identified during wakefulness in iRBD patients who later developed a synucleinopathy. EEG slowing is a promising marker of neurodegeneration in iRBD patients.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal muscle atonia during REM sleep associated with dream-enacting motor activity (American Academy of Sleep Medicine, 2005). There is increasing evidence that many idiopathic RBD (iRBD) patients eventually develop a synucleinopathy: Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA) (Iranzo et al., 2006; Postuma et al., 2009, 2015; Schenck et al., 2013). A recent study of 170 iRBD patients estimated that the risk of developing a synucleinopathy after iRBD diagnosis was 90.9% at 14 years (Iranzo et al., 2014). Given the lengthy interval between iRBD onset and the development of a neurodegenerative disease, it is vital to find sensitive markers of neurodegeneration to identify iRBD individuals at higher risk of developing disease. This could lead to a major breakthrough in iRBD pathophysiology, with important clinical implications such as the development of neuroprotective agents.

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Several longitudinal studies have identified markers of neurodegeneration in iRBD patients. REM sleep atonia loss (Postuma et al., 2010), impaired olfaction and color discrimination (Postuma et al., 2011), decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity (Iranzo et al., 2010b), quantitative motor dysfunction (Postuma et al., 2012b), and abnormal metabolic network activity (Holtbernd et al., 2014) have been associated with increased risk of PD or DLB (Postuma et al., 2015). Furthermore, gray and white matter anomalies and cognitive deficits have been identified as potential markers of PD or DLB in iRBD patients (Gagnon et al., 2012; Manni et al., 2013; Rahayel et al., 2015; Scherfler et al., 2011). However, for the latter results, it remains unclear whether they are predictive of subsequent conversion. Identifying new markers of neurodegeneration in iRBD could help more accurately predict disease outcome in individuals, in addition to improving the understanding of how the disease progresses with time.

Resting-state electroencephalography (EEG) is a noninvasive and inexpensive technique that has been shown to accurately predict progression from mild cognitive impairment (MCI) to DLB and to predict dementia incidence in PD (Bonanni et al., 2015; Klassen et al., 2011). Therefore, quantitative EEG (qEEG) could serve as a marker of neurodegeneration in iRBD. So far, cross-sectional studies have revealed EEG slowing in iRBD patients (Fantini et al., 2003), and recent studies have associated EEG slowing with the presence of MCI in iRBD (Iranzo et al., 2010a; Rodrigues Brazete et al., 2013; Sasai et al., 2013). Thus, EEG abnormalities could reflect dysfunctional neuronal networks, probably underlied by early neuropathological changes.

The aim of this prospective longitudinal study was to assess the usefulness of qEEG abnormalities as markers of neurodegeneration by examining baseline resting-state EEG in RBD patients who developed PD, DLB, or MSA (iRBD C+) compared with RBD patients who remained disease free (iRBD C−) and healthy controls. We also aimed to examine whether qEEG changes can differentiate patients who will develop PD or MSA instead of DLB.

2. Methods

2.1. Participants

Patients were recruited at the Center for Advanced Research in Sleep Medicine of the Hôpital du Sacré-Coeur de Montréal. All patients with full EEG montage for resting-state EEG recording at baseline and with at least one follow-up examination after the baseline visit were included in the study. The first valid EEG for each patient enrolled in the study was considered baseline. They also underwent a complete neurological examination by a neurologist specialized in movement disorders (Ronald B. Postuma) and a cognitive assessment by a neuropsychologist (Jean-François Gagnon). Participants also completed the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III), the Farnsworth-Munsell hue test (FM-100), and the University of Pennsylvania Smell Identification test (UPSIT) to assess motor symptoms, color vision discrimination, and olfactory identification. Control subjects for baseline comparisons were recruited mainly through newspaper ads. No controls reported abnormal motor activity during sleep or showed cognitive impairment on neuropsychological testing. The protocol was approved by the hospital's ethics committee, and all participants gave their written informed consent to participate.

All participants underwent video-polysomnography (vPSG), and iRBD was diagnosed by a sleep specialist (Jacques Montplaisir) according to the criteria of the International Classification of Sleep Disorders, second edition (American Academy of Sleep Medicine (2005); Montplaisir et al., 2010). vPSG was performed according to standard methods (Montplaisir et al., 2010). iRBD diagnosis was confirmed by one night of vPSG showing loss of REM sleep muscle atonia and/or excessive phasic activity in addition to motor manifestations during REM sleep or clinical history of parasomnia. Monitoring of oral and nasal airflow and thoracic and abdominal movements as well as oximetry were used to screen for sleep apnea syndrome. All subjects were from 45 to 85 year old, were free of parkinsonism or dementia at baseline, and had an apnea-hypopnea index <15 per hour of sleep. Some patients could not discontinue their medication for clinical reasons at the time of EEG recording and were on antidepressants (iRBD C+, $n = 3$; iRBD C−, $n = 6$) and/or anxiolytics (iRBD C+, $n = 13$; iRBD C−, $n = 8$). Of those taking anxiolytics, 16 were taking clonazepam to treat iRBD (iRBD C+, $n = 11$; iRBD C−, $n = 5$). Controls were free of medication known to influence sleep or EEG activity. Details of other inclusion and/or exclusion criteria and a description of the neuropsychological assessment are published elsewhere (Rodrigues Brazete et al., 2013). Many patients and controls also participated in the previous cross-sectional study on EEG in iRBD (Rodrigues Brazete et al., 2013). MCI was determined according to criteria used in a previous study (Rodrigues Brazete et al., 2013). Patients with MCI and without dementia were considered disease free.

2.2. Follow-up examinations

Patients underwent annual follow-up examinations by a neurologist and a neuropsychologist at the Hôpital du Sacré-Coeur de Montréal. The follow-up protocol was similar to the baseline protocol. If patients refused in-person assessments or were unable to undergo an assessment because of severe disability, either they were assessed by telephone interview or their case was reviewed with their treating physician or caregivers. PD, DLB, and MSA were diagnosed according to standard criteria (Gilman et al., 2008; Hughes et al., 1992; McKeith et al., 2005). Dementia was defined as impairment in 2 cognitive domains on neuropsychological testing with significant functional impairment. For patients without neuropsychological testing at follow-up, dementia was defined as impaired Mini Mental State Examination (<26) (Dubois et al., 2007) or Montreal Cognitive Assessment (<21) scores (Dalrymple-Alford et al., 2010) associated with significant functional impairment (Folstein et al., 1975; Nasreddine et al., 2005). Ultimately, the conversion of iRBD patients during follow-up was established by consensus between the neurologist and neuropsychologist.

2.3. Procedures

2.3.1. EEG spectral analysis and vPSG at baseline

Waking EEG signals (with linked ear reference) were recorded for at least 10 minutes while participants were lying in bed with eyes closed. Recordings were performed within 30 minutes after waking in the morning after vPSG recording to avoid the sleep inertia period. The technicians asked participants to open their eyes periodically to prevent drowsiness, or when they showed signs of sleepiness. A Grass polygraph amplifier system (0.3–100 Hz bandpass) was used with a notch filter (60 Hz) and signals were digitized at a 256-Hz sampling rate using commercial software (Harmonie, Stellate systems). Power spectra were analyzed for all artifact-free sections of wakefulness with eyes closed (for a mean of 90.0 seconds for iRBD patients and 102.5 seconds for controls). The sections were manually selected and were considered artifact free if there were no eye blinks, eye movements, body movements, muscle or electrode artifacts. Fast Fourier transforms (FFT) were computed on nonoverlapping 4-second mini-epochs using a cosine tapering window ($r = 0.4$), producing a 0.25 Hz spectral resolution. Also, mean removal FFT preprocessing was applied to correct for