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Original Article

Brain cholinergic alterations in idiopathic REM sleep behaviour disorder: a PET imaging study with ^{18}F-FEOBV

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ABSTRACT

Background: REM sleep behaviour disorder (RBD) occurs frequently in patients with synucleinopathies such as Parkinson's disease, dementia with Lewy body, or multiple system atrophy, but may also occur as a prodromal stage of those diseases; and is termed idiopathic RBD (iRBD) when not accompanied by other symptoms. Cholinergic degeneration of the mesopontine nuclei have been described in synucleinopathies with or without RBD, but this has not yet been explored in iRBD. We sought to assess cholinergic neuronal integrity in iRBD using PET neuroimaging with the ^{18}F-fluoroethoxybenzovesamicol (FEOBV).

Methods: The sample included 10 participants evenly divided between healthy subjects and patients with iRBD. Polysomnography and PET imaging with FEOBV were performed in all participants. Standardized uptake value ratios (SUVRs) were compared between the two groups using voxel wise t-tests. Non-parametric correlations were also computed in patients with iRBD between FEOBV uptake and muscle tonic and phasic activity during REM sleep.

Results: Compared with healthy participants, significantly higher FEOBV uptakes were observed in patients with iRBD. The largest differences were observed in specific brainstem areas corresponding to the bulbar reticular formation, pontine coeruleus/subcoeruleus complex, tegmental periacqueductal grey, and mesopontine cholinergic nuclei. FEOBV uptake in iRBD was also higher than in controls in the ventromedial area of the thalamus, deep cerebellar nuclei, and some cortical territories (including the paracentral lobule, anterior cingulate, and orbitofrontal cortex). Significant correlation was found between muscle activity during REM sleep, and SUVR increases in both the mesopontine area and paracentral cortex.

Conclusion: We showed here for the first time the brain cholinergic alterations in patients with iRBD. As opposed to the cholinergic depletion described previously in RBD associated with clinical Parkinson's disease, increased cholinergic innervation was found in multiple areas in iRBD. The most significant changes were observed in brainstem areas containing structures involved in the promotion of REM sleep and muscle atonia. This suggests that iRBD might be a clinical condition in which compensatory cholinergic upregulation in those areas occurs in association with the initial phases of a neurodegenerative process leading to a clinically observable synucleinopathy.

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1. Introduction

REM sleep behaviour disorder (RBD) is a parasomnia characterized by a loss of normal skeletal muscle atonia and the occurrence of vigorous movements during REM sleep [1,2]. RBD is frequently reported in patients with synucleinopathies such as Parkinson's Disease (PD), dementia with Lewy body (DLB), and multiple system atrophy (MSA) [3,4], but may also occur alone and be diagnosed as idiopathic RBD (iRBD).

Several prospective cohort studies have shown that a large percentage of patients with iRBD eventually develop a synucleinopathy [2,5–9]. The conversion rate was found to vary between 33% and 50% after four to six years [7], and 81%–91% after a follow-up of 14–16 years [10,11]. Yet, evidences of underlying neurodegenerations was found to occur in almost all individuals presenting with iRBD [12,13].

The pathophysiology of RBD is thought to involve the neurochemical systems of the brainstem that modulate muscle atonia during REM sleep [14]. These neurochemical systems are known to be affected in PD, DLB, and MSA, although severity and specificity of these lesions differ considerably among these diseases. Cholinergic degeneration of the mesopontine tegmentum (MPT) is a common hallmark of all these synucleopathies however, and some authors [9,15] have suggested a direct involvement in RBD pathophysiology. This is supported by a PET imaging study [16] conducted in PD patients with the acetylcholinesterase ligand ^{11}C-PMP, showing lower uptakes in patients with RBD as compared to those without RBD.

In iRBD, the structural integrity of the central cholinergic systems has not been explored yet. We sought therefore to investigate this question using PET imaging with ^{18}F-fluoroethoxybenzovesamicol (FEOBV). This radiotracer exhibits a very high binding affinity and specificity for the vesicular acetylcholine transporter (VAChT) [17], and may be considered as the best *in vivo* surrogate marker of the density of cholinergic nerve terminals [18–20].

2. Methods

2.1. Subjects

The study sample consisted of 10 participants, with five patients diagnosed with iRBD, and five healthy volunteers, all recruited at the Centre for Advanced Research in Sleep Medicine (CARSM) of the « Hôpital du Sacré-Cœur », Montreal, Canada. All participants underwent a semi-structured interview centred on sleep disorders and conducted by a physician (JM) specialised in sleep medicine. Patients with iRBD fulfilled the clinical and polysomnography (PSG) diagnostic criteria of RBD according to the International Classification of Sleep Disorders (third edition) [1]. Exclusion Criteria were any evidence of sleep disorders sharing RBD features, such as sleepwalking, night terrors or untreated sleep apnoea syndrome. Participants with neurological conditions such as degenerative disease, stroke, epilepsy, or head trauma were excluded on the basis of both a structural T1 MRI scanning, and a complete neurological examination, including the UPDRS motor scale, performed by a neurologist (RP) specialised in movement disorders. None of the patients or controls were taking any medication known to affect cholinergic transmission. Healthy participants had no history of abnormal behaviours during sleep.

MRI and PET scanning procedures were conducted at the PERFORM research centre of the Concordia University, Montreal, Canada. A one-night polysomnographic (PSG) recording was also performed at the CARSM, in all participants. Research Ethics Boards of both PERFORM and CARSM have approved the study protocol. Informed consent was obtained from all subjects prior to participation in the study.

2.2. Polysomnographic (PSG) recording

PSG recording included the EEG EOG, and EMG from sub-mental and bilateral anterior tibialis, and extensor digitorum superficialis muscles (EDSMs) in the upper limb. Oral/nasal airflow, as well as thoracic/abdominal movements and oximetry were recorded to exclude sleep hypopnoea syndrome. Sleep stages scoring and quantification of tonic and phasic activity of the mentalis muscle were based on a method developed for RBD patients and described in detail elsewhere [21], using 30s epochs. The PSG diagnosis of RBD was confirmed by using the SINBAR group method based on quantification of any 3-sec miniepochs of REM sleep containing EMG activity (tonic or phasic) of the mentalis muscle or phasic EMG activity in the right or left EDSMs, with a cutoff value of 32% [22].

2.3. Image acquisition

All participants first underwent a structural T1 MRI (3T GE Discovery MR750), followed by a ^{18}F-FEOBV PET scan (GE Discovery PET/CT 690) performed on the same day. Both MRI and PET scans were conducted at the PERFORM centre of Concordia University (Montreal, Canada). ^{18}F-FEOBV was synthesized on the same day at the Cyclotron Facility of the McConnel Brain Imaging Centre of the Montreal Neurological Institute (Canada). The FEOBV precursor was purchased from commercial vendor (ABX Advanced Biochemical Compounds GmbH, Germany).

FEOBV was administered by slow IV bolus injection with radioactive doses varying between 160 and 340 MBq. A short, low kV CT scan for attenuation correction, was first performed. PET data acquisition was in 3D list mode and started 3 h after injection, for a 30 min duration, divided in six frames of 5 min each. A head holder was used to minimize head motion during the scan.

2.4. Image processing

PET images were reconstructed using an OP-OSEM (Ordinary Poisson-Ordered Subset Expectation Maximization) algorithm correcting for scatter, random coincidences, attenuation, decay and dead time; frame based motion corrections was also performed if needed. The MINC software toolbox was used to perform all image analyses (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC) with the following steps: (1) MR images of all participants were first co-registered to the MNI-152 standard reference template by the CIVET image-processing pipeline, using a 6-parameter affine transformation and non-linear spatial normalization; (2) Time-averaged PET images were normalized as a function of the injected dose of tracer and the subject's weight to obtain standard uptake values (SUVs); (3) The PET SUVs image was then co-registered to the subject's own MRI, and from there to the MNI-152 template using the linear and non-linear transformations obtained in the first step; (4) Standardized uptake value ratio (SUVR) maps were generated by using supratentorial white matter as the reference region; (5) smoothing of the PET SUVR images was performed using a Gaussian kernel of 4 mm. No correction for partial volume effect was applied to the PET imaging data.

2.5. Data management and analyses

The distribution of demographic and clinical variables was verified with the Shapiro–Wilk test for small groups, and non-parametric comparisons were performed with Mann–Whitney *U* tests. Chi-square tests were used to compare the two groups on

gender and psychotropic medications. Descriptive statistics were computed separately in each group, for all the sleep macrostructural PSG variables.

Differences in brain FEOBV distribution in control subjects and patients with iRBD were first explored by SUVR comparisons using voxel-wise statistical t-tests. No correction was applied for multiplicity, but only clusters with more than 100 voxels where included in the analyses to avoid scattered or isolated random voxel differences. Voxel-based statistical t-maps of the brain were then generated, based on a significance threshold of 2.3 ($p < 0.05$) for two-tailed t-tests adjusted for age. This voxel-wise approach was found to be robust, sensitive, and reliable in previous studies [18,20] conducted in small sample of subjects.

Voxel clusters with significant t-values in the relevant brain areas were used to identify areas of interest (AOI). Masks were defined from these AOIs and age corrected Spearman Rank–Order correlations were performed between the mean SUVR values of these AOIs, and both EMG measurements of tonic and phasic activity during REM sleep. Bonferroni corrections were preformed to control for multiple analyses.

3. Results

Demographic and clinical features of the two groups are summarized in Table 1. The male/female ratio was the same in each group. Shapiro–Wilk test for small groups were all significant, hence normal distribution could not be assumed, so that Mann–Whitney *U* tests were used. There was no significant group difference for age, education, or the MoCA cognitive scale. Motor score on the UPDRS-III differed marginally between the two groups, due to a relatively high score (14.5) in one patient with iRBD. All patients with iRBD but none of the control subjects were treated with clonazepam. Usage of other psychotropic medications did not differ between the two groups. Descriptive statistics for all sleep variables are presented in Table 2.

PET images in control subjects revealed the highest FEOBV uptakes in brain regions known to contain cholinergic terminals (Fig. 1), with very high SUVR mean values observed in the striatum (5.88), thalamus (4.61), and cerebellum (4.58). Next highest uptakes were found in the whole brainstem with peak values centred in the mesopontine tegmentum (MPT) (2.58). Substantial uptake was also found in the whole cortex, with greatest values observed in the hippocampus (2.20), and a large medial area encompassing both the cingulate (1.68), and paracentral lobule (1.39). This SUVR brain distribution was similar in patients with iRBD (striatum = 5.64; thalamus = 4.98; cerebellum = 4.22; MPT = 2.90; hippocampus = 2.20; cingulate 1.80; paracentral lobule = 1.84).

Statistical comparisons with voxel wise t-tests found no area of decreased SUVRs in patients with iRBD. Rather, significantly higher values were observed in multiple brain areas of patients with iRBD as compared to control subjects (Fig. 2). The most significant differences were seen in the brainstem, including the upper left medulla ($t = 8.041$, $p = 0.000042$), the upper left dorsal pons ($t = 7.452$, $p = 0.000073$), a large territory of the left MPT encompassing the pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei, and the ventrolateral portion of the periacqueductal grey (vlPAG) ($t = 6.124$, $p = 0.000282$). The rostral extension of this tegmental territory includes the Red nucleus/Substantia Nigra bilaterally (right: $t = 3.825$, $p = 0.005054$; left: $t = 4.418$, $p = 0.002232$). A small but significant SUVR increases was also found in iRBD subjects in the ventromedial part of the right thalamus ($t = 3.262$, $p = 0.011493$). In the cerebellum, SUVR in the right deep nuclei was also higher in patients with iRBD than in controls ($t = 5.841$, $p = 0.000387$). Finally, higher values were observed in iRBD patients in cortical areas including the anterior portion of the right paracentral cortex ($t = 4.478$, $p = 0.002061$), the right anterior cingulate ($t = 3.656$, $p = 0.006438$), and the right prefrontal cortex ($t = 7.301$, $p = 0.000084$). No significant differences were found in other cortical areas, in the hippocampus, or in the striatum. Compared with control subjects, the increased regional FEOBV uptake in patients with iRBD was variable across areas, ranging from +28.1% in the upper medulla, to +8.5% in the thalamus.

Age corrected Spearman rank correlational analyses performed in patients with iRBD revealed relationships between regional increases in FEOBV uptakes and muscle activity during REM sleep (Fig. 3). The anterior paracentral cortex showed a significant correlation with phasic EMG activity, and a nearly significant correlation with tonic EMG activity. Other brainstem AOIs showed also correlations with both tonic and phasic activity, but those were no longer statistically significant after correcting for multiplicity.

Table 2
Sleep macrostructure in the two groups of participants.

	CTL n = 5	RBD n = 5
Sleep latency (min)	35.2 (33.8)	32.6 (29.5)
% Stage 1	18.1 (9.1)	8.8 (3.3)
% Stage 2	60.7 (9.8)	69.1 (11.0)
TST (min)	354.9 (59.0)	374.6 (29.4)
WASO (min)	116.0 (27.3)	78.9 (33.7)
REM latency (min)	112.6 (89.3)	92.4 (44.9)
% REM	16.7 (7.8)	20.6 (9.9)
Number of REM periods	4.0 (2.3)	3.8 (1.1)
% Phasic EMG in REM	14.1 (7.2)	44.0 (18.8)
% Tonic EMG in REM	1.1 (2.1)	56.8 (36.9)

Descriptive statistics only. TST = total sleep time; WASO = wake time after sleep onset; REM = rapid eye movement sleep; EMG = electromyography.

4. Discussion

We described here for the first time the brain cholinergic systems alteration of iRBD, using molecular imaging with FEOBV, a PET radiotracer that binds selectively to the vesicular acetylcholine transporter [17]. Contrary to the cholinergic depletion described in RBD associated with synucleinopathies [16,23], results obtained

Table 1
Demographic and Clinical Features in the two groups of participants.

	CTL (n = 5)	RBD (n = 5)	Mann Whitney-*U* & Chi-Square §	P
Gender (f:m)	1:4	1:4	1.0 §	–
Age (y)	68.4 (3.4)	60.8 (9.3)	6.0	0.169
MoCA scale (total score)	27.6 (1.9)	28.4 (2.3)	9.0	0.443
UPDRS-III (motor subscale)	1.6 (1.5)	5.9 (5.0)	3.5	0.055
Psychotropics (n of Pts)				
• Clonazepam	0	5	10.0 §	0.002
• Pregabalin	1	2	0.5 §	0.490
• Bupropion	0	1	1.1 §	0.294
• Concerta	0	1	1.1 §	0.294

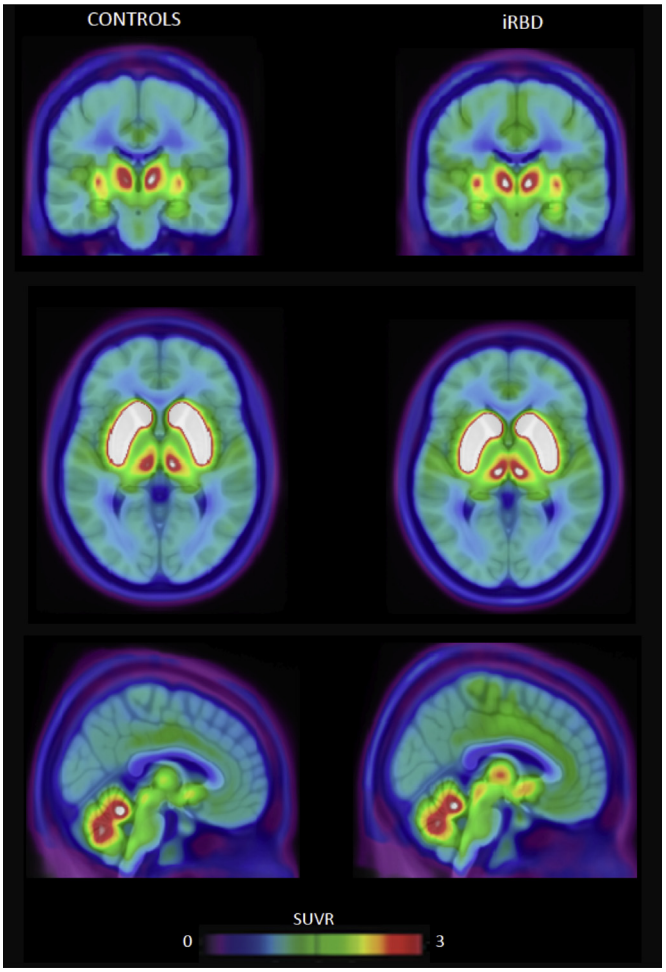


Fig. 1. FEOBV uptakes in healthy participants and patients with iRBD showing cerebral territories rich in cholinergic terminals including striatum, thalamus, cerebellum, brainstem, hippocampus, and cortex. Similar distribution was observed in the two groups.

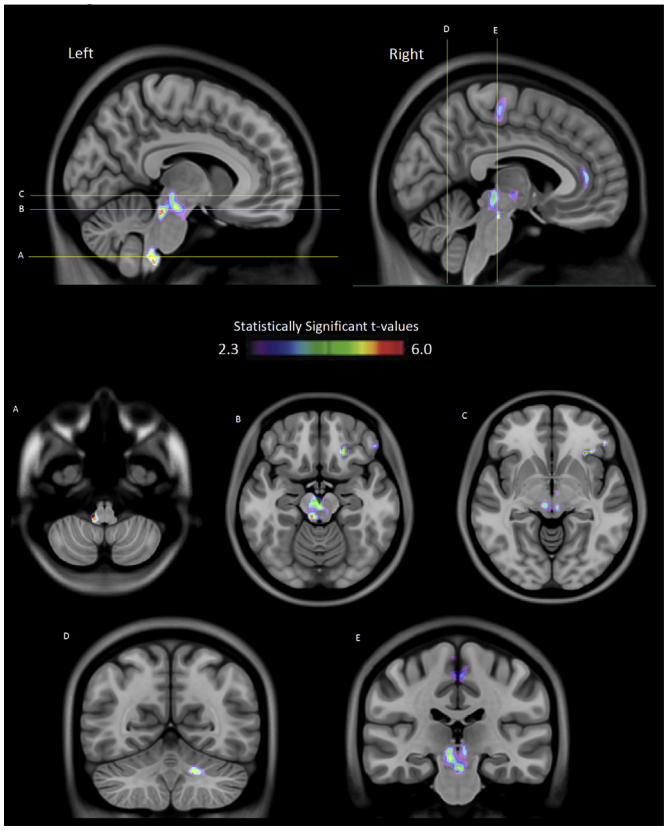
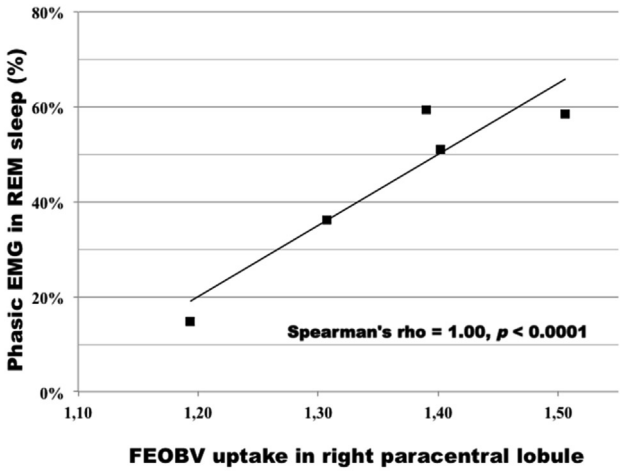


Fig. 2. Voxel based t-tests maps showing significantly higher FEOBV uptakes in patients with iRBD than in control subjects. Differences were seen in the mid and upper medulla, upper dorsal pons, mesopontine tegmentum, cerebellum, ventral thalamus, and cortical areas that include the cingulate, medial pre-central, and prefrontal cortex.

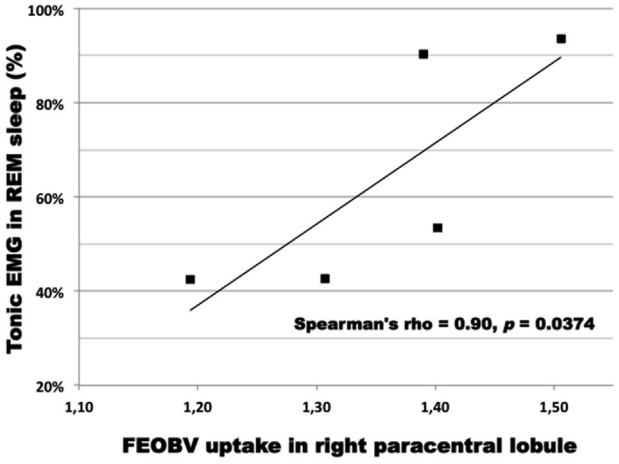
here in iRBD suggest increased cholinergic nerve terminals in multiple brain areas, as FEOBV regional uptake is known to reflect that parameter [19,20]. The largest changes were seen in the bulbar and MPT areas containing structures involved in REM sleep and muscle atonia [14,15]. Those include the bulbar reticular formation, locus coeruleus/subcoeruleus complex, vlPAG, and red nucleus/subtantia nigra areas, all known to receive and to be responsive to projections from the PPT & LDT (Ch5, Ch6) cholinergic cells [24–26]. Increased FEOBV uptakes were also found in deep cerebellar nuclei, medio-ventral thalamus, medial precentral cortex, anterior cingulate, and prefrontal cortex, also known to receive cholinergic inputs from the PPT & LDT [27,28]. Most of the cortical and subcortical structures innervated by the striatal and basal forebrain (Ch1-Ch4) cholinergic systems did not differ between the two groups, suggesting that a specific abnormality of the PPT & LDT cholinergic systems may be present in iRBD.

MRI volumetry has been performed in PD patients with and without RBD [29], and abnormalities were found to be more extensive in the former than in the later for brainstem and cortical regions similar to those found to be affected in iRBD in the current study. Moreover, recent FDG-PET studies were conducted in both iRBD and PD with RBD [30–32], and revealed a typical RBD-related network characterized by increased metabolic activities also found in brain regions that includes the brainstem, thalamus, cerebellum, sensorimotor, and mediofrontal cortex. This network expression was elevated in iRBD, and seems to decrease with disease progression toward PD [32]. Taken together, these findings suggest a specific pattern of brain alteration associated with RBD, which involves structures innervated by the PPT and LDT cholinergic systems.

The increased FEOBV binding observed in the current study in patients with iRBD might be in line with the increased number of PPT & LDT cholinergic cells described in one post-autopsy RBD case of combined Lewy body and Alzheimer's disease pathology [9]. However, it is more likely that this increased FEOBV activity corresponds rather to a compensating sprouting of the cholinergic terminals taking place at the time of the iRBD early neurodegenerative process. Such a sprouting has been described already for other neurochemical systems in various neurodegenerative diseases [33]. For example, clinical symptoms in PD usually start when there is about 60% dopaminergic cells death in the substantia nigra compacta (SNc), suggesting a compensating process along the preclinical years during which a sprouting process is known to occur on the dopaminergic cell terminals [34,35]. Given that iRBD is considered a prodromal condition evolving over many years before fulfilling the clinical criteria of a synucleinopathy [7,8,10,11], one may suggest that cholinergic degeneration starts at the time of iRBD, which might in turn induces a compensating sprouting of the cholinergic nerve terminals. Evolution toward a full synucleinopathy syndrome would be associated with more severe neurodegeneration, so that sprouting may not be sufficient to compensate. This may explain why in the current study cholinergic uptake was increased in iRBD, while [16] described reduced



A)



B)

Fig. 3. Correlations between FEOBV uptake mean values in the anterior paracentral cortex and both (A) phasic, and (B) tonic EMG activity during REM sleep. P values not corrected for multiplicity in the graph.

cholinergic terminals in RBD associated with PD. It may also account for the results obtained with spectroscopy showing neuronal losses in RBD associated with synucleiopathy but not in iRBD [36].

In addition to the increased cholinergic terminals in iRBD, results of the current study revealed significant relationships between these structural changes and both tonic and phasic activities during REM sleep. It should be stressed however that the best predictive area was not observed with the brainstem structures involved in REM sleep atonia, but rather with the medial precentral cortex. This result is concordant with electrophysiological data [37,38] showing motor cortex and pyramidal tract neurons activation during REM sleep. Moreover, spontaneous brain activity in the motor cortex was found altered in PD with RBD, but not in PD without RBD [39], suggesting a role of this cortical area in RBD symptomatology. Actually, RBD motor activities occurring during REM sleep are highly coordinated and similar to stereotypical movements seen during wakefulness, suggesting similar involvement in both conditions.

The neurochemical systems involved in iRBD pathophysiology is not well known. The strong link between RBD and PD suggests that the nigrostriatal dopaminergic system might play a role. For example, mild cytotoxic lesions of the SNc were able to trigger RBD symptoms in monkeys [40] despite the absence of parkinsonian symptoms. In addition, imaging studies have documented a dopamine cell loss in iRBD [41–43], which was also correlated with motor activity during REM sleep [42,44] and found to be a good predictor of synucleinopathy conversion within 3–5 years [45]. However, although dopamine degeneration in iRBD appears as a good biomarker of an early evolving synucleinopathy, it is not totally clear how it can directly be involved in iRBD symptomatology per se. Mesencephalic dopaminergic neurons do not appear to alter their discharge rate across the REM & non-REM sleep cycle [46], and are therefore not presumed to play a primary role in REM sleep induction and maintenance, or in muscle atonia during REM sleep [14,47]. Moreover, a previous imaging study [16] revealed no difference of dopamine lesions between PD patients with and PD patients without RBD. Serotonergic systems were not found to differ either between the two groups in this study, while cholinergic systems were more affected in PD patients with RBD than those without RBD, especially in the thalamus, which receive most of its innervation from the PPT & LDT nuclei [27].

During normal REM sleep, muscle paralysis is intermittently punctuated by muscle twitches. One may therefore consider the RBD symptoms as an exaggeration of these natural motor events, resulting from an over-excitation of the circuit generating twitches. Cellular recordings have shown that muscle twitches during REM sleep are produced by brainstem originating fibres releasing glutamate on the spinal motor neurons [48,49], and that PPT & LDT also discharge in sync with these phasic events [15]. This suggest that the amplified motor activity during REM sleep in RBD could be a consequence of an over-activation of the brainstem network involved in muscle twitches. Results obtained in the current study are concordant with this hypothesis by showing in iRBD the increased cholinergic activity in multiple areas innervated by the PPT & LDT nuclei and known to be involved in REM sleep atonia.

One limitation of the current study is the small sample size, which might prevent from results replication. On the other hand, the highly statistically significant results obtained here in these well-defined iRBD patients may be considered as strength of this study. Most of the previous studies on RBD pathophysiology have been conducted in patients with established neurodegenerative disorders presenting or not with RBD symptoms. This may explain why the cholinergic abnormalities were clearly observed here in spite of the small sample size, while others have not found such evidences on post-mortem tissues [23], or found cholinergic abnormalities in restricted areas of the thalamus and cortex but not the brainstem, using PET imaging with the AChE tracer PMP [16]. Analyses in patients with iRBD may be most enlightening as the degenerative changes may be mild and selective, and thus more revealing.

In the current study, brain areas showing cholinergic alterations in iRBD were concordant with those of Kotagal and coll [16] performed in RBD associated with synucleinopathy, although a decreased PMP activity was observed in the latter study while an increased FEOBV activity was present here. Another difference between the two studies stands on the major brainstem abnormalities observed here with FEOBV, which were not described by Kotagal and coll [16]. This may be explained in part by a greater sensitivity of FEOBV than PMP to detect structural changes of the cholinergic system [50]. While FEOBV is a VAChT radiotracer [17] thought to reliably reflect density of the ACh terminals [19,20], PMP is a tracer of AChE [51], the ACh degrading enzyme, which is anchored on both the pre- and post-synaptic membranes, as well as in the synaptic cleft as a proportion of the ACh turnover. Moreover, AChE as a whole is localized predominatly in cholinergic cell bodies and axons, and some levels of AChE are also present in the non-

cholinergic membranes, contributing therefore to the PMP imprecision. Further PET imaging studies are nevertheless warranted with the FEOBV in order to replicate the present findings with larger samples of patients with iRBD. Longitudinal studies will also be needed to verify the hypothesis of an increased ACh activity in iRBD that evolves toward an ACh hypoactivity in the synucleinopathy associated RBD.

Author contributions

J.M., R.P., J-P.S. and J-F.G. were responsible for the study conception, design, and funding. A.P. was in charge of the whole data acquisition. M.A., C.L.D and M.A.B were responsible for data analyses. M-A.B. and J.M. were responsible for drafting the manuscript, figures, and tables.

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Conflict of interest

Meghmik Aghourian, Jean-François Gagnon, Camille Legault-Denis, Amelie Pelletier, and Jean-Paul Soucy have no potential conflict of interest to declare. Marc-André Bedard reports personal fees from Pfizer Canada, Shire Pharmaceutical, Purdue Pharmaceutical, Merck Canada, and Novartis Canada outside the submitted work. Jacques Montplaisir reports personal fees from Merck, Novartis, and Canopy International, outside the submitted work. Ronald Postuma reports personal fees from Takeda, Roche/Prothena, Teva Neurosciences, Novartis Canada, Biogen, Boehringer Ingelheim, Theranexus, GE HealthCare, Jazz Pharmaceuticals, Abbvie, Jannsen, and Otsuko, outside the submitted work.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.12.020.

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