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Neuropsychiatric, neuropsychological, and neuroimaging features in isolated REM sleep behavior disorder: The importance of MCI

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ABSTRACT

Background: Mild cognitive impairment (MCI) is frequently diagnosed in patients with isolated rapid eye movement (REM) sleep behavior disorder (iRBD), although the extent of MCI-associated neuropathology has not yet been quantified. The present study compared the differences in neuropsychiatric, neuropsychological, and neuroimaging markers of neurodegeneration in MCI-iRBD and iRBD patients with normal cognition.

Methods: Sixty-one patients with iRBD were included in the study: 30 patients were included in the MCI subgroup (RBD-MCI) and 31 in the normal cognition subgroup (RBD-NC). Both groups underwent neuropsychiatric and neuropsychological assessments to evaluate psychopathological symptoms and neuropsychological functions. Brain [18F]FDG PET and 123I-FP-CIT-SPECT were performed to evaluate brain glucose metabolism and nigrostriatal dopaminergic function in convenient subgroups of patients, respectively.

Results: Neuropsychological measures generally confirmed overall cognitive decline in patients with iRBD-MCI. Immediate long-term verbal memory and visuospatial functions, as well as attentional-executive impairment were evident in the MCI group compared to the NC group. Neuroimaging results indicated reduced brain glucose uptake in the bilateral posterior cingulate cortex and more evident nigrostriatal deafferentation in the RBD-MCI group. There were no differences in psychopathological symptoms between the two groups.

Conclusions: This study confirmed that iRBD patients with MCI had a more impaired cognitive status that those with NC. Moreover, the MCI subgroup presented reduced cerebral glucose consumption in brain areas critical for cognition, and a more severe deafferentation of the nigro-striatal regions, highlighting the importance of identifying iRBD patients with MCI for urgent neuroprotective trials.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a multifaceted parasomnia characterized by involuntary and random motor activity during dreaming caused by the absence of REM sleep-associated atonia [1]. It is recognized that idiopathic or isolated RBD (iRBD) represents a premotor condition with an increased risk of developing neurodegenerative disorder due to alpha-synucleinopathies at follow-up [2]. Accordingly, follow-up studies have demonstrated that iRBD patients are at a high risk of developing neurodegenerative diseases, particularly Parkinson's disease (PD), Lewy body dementia (LBD), and multiple system atrophy, with development of one of these diseases in more than 50% of cases 12 years after the initial diagnosis [2]. Therefore, early detection of iRBD patients who are at an increased risk of

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phenoconversion is essential for clinicians, and it is important to plan neuroprotective trials for these patients [3].

Mild cognitive impairment (MCI) is a frequent diagnosis in patients with iRBD, and it has been suspected that the occurrence of MCI can increase the risk of phenoconversion to alpha-synucleinopathies, or may even be an early manifestation [4]. Notably, patients with iRBD had a 2.2-fold increased risk of developing MCI over 4 years [5]. Moreover, the occurrence of MCI can drive conversion to LBD more than PD [6]. Therefore, the co-occurrence of iRBD and MCI deserves increased attention when considering the optimization of follow-up strategies. MCI can manifest as a deficit in different cognitive domains, and the cognitive deterioration typically reported by iRBD patients is associated with alexithymia [7] and psychopathological symptoms, such as depression, anxiety [8,9], and apathy [10].

Previous studies found MCI to be regarded as a frequent feature of iRBD affecting 50% of patients [11]. The pathophysiological mechanism underlining the association between RBD and MCI is still questionable, although some studies claimed perturbations of cerebral metabolic patterns to be a potential explanation. Considering neuropsychological and psychological characteristics, previous studies highlighted a notable lower performance on the Digit Span, and on semantic and letter verbal fluency in RBD patients with MCI as compared to RBD patients with normal cognition [12]. Some authors investigated psychopathological symptoms (i.e., depression, anxiety) in RBD patient with and without MCI, but no differences were evident [13].

Based on these premises, considering the importance of testing the cognitive performance of patients with iRBD since the presence of MCI can modify the treatment strategy and follow-up protocol of those patients, this study aimed to evaluate the importance of MCI in patients with iRBD and the effect of this diagnosis on different neuropsychiatric, neuropsychological, and neuroimaging markers. At this aim, patients with MCI-iRBD were compared to iRBD patients with normal cognition, to test the effect of MCI on cognitive functioning and markers of neurodegeneration in a multimodal approach. To increase the novelty and importance of this study we defined MCI in iRBD patients according to standard criteria and following a comprehensive neuropsychological evaluation.

2. Methods

2.1. Participants

We included patients with iRBD admitted to the Sleep Medicine Center of the Neurological Clinic at the University of Rome "Tor Vergata". All patients were diagnosed with iRBD according to the guidelines presented in the International Classification of Sleep Disorders, 3rd Edition, and diagnosis was confirmed based on anamnestic data and video-polysomnographic recording [14].

The exclusion criteria were as follows: systemic and/or neurologic infectious, inflammatory, or autoimmune diseases; diabetes; concomitant major psychiatric or other neurological disorders; and a previous history of stroke or cerebral infarctions documented on magnetic resonance imaging (MRI). In particular, we included patients exclusively affected by iRBD and not showing a possible iatrogenic cause of the sleep disorder or concomitant neurological or psychiatric disorders. The presence of MCI was evaluated according to the Movement Disorder Society (MDS) Task Force diagnostic criteria [15], using two levels of assessments: (1) at the screening level, with the Mini-Mental State Examination (MMSE) score of <24; (2) using psychometric tests through a cognitive test-based classification, requiring impairment (>1.5, standard deviations below the mean score, in the range recommended for the MCI diagnosis) on any two cognitive test scores and cognitive complaint [16]. Based on the diagnosis of MCI, all patients underwent a neurocognitive battery to diagnose MCI, and were stratified into two groups based on the results: i) iRBD patients affected by MCI (iRBD-MCI), and ii) iRBD with normal cognition (iRBD-NC).

All patients in the two groups underwent psychological and neuropsychological assessments to evaluate their psychopathological symptoms and neuropsychological functioning. Patients who underwent 2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography ([18F]FDG PET) (n = 32) and 123I-Ioflupane (FP-CIT) single-photon emission computed tomography (SPECT) (123I-FP-CIT-SPECT) (n = 37) were included in subgroup analysis. The flowchart in Fig. 1 summarizes the recruitment and selection processes. The study protocol was considered observational by the Internal Review Board of the Local Ethical Committee, and was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (protocol code: RS 76/14). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

2.2. Instruments

2.2.1. Neuropsychiatric evaluation

Depressive symptoms. The Beck Depression Inventory-II (BDI-II) [17] and Hamilton Depression Rating Scale (HAMD) [18] were used to assess depressive symptoms. The HAMD evaluates the somatic and behavioral outcomes of depression, whereas the BDI-II accentuates subjective depressive experiences [19]. The BDI-II consists of 21-items with four possible responses, with higher total scores indicating greater severity of symptoms. Scores ranging from 0 to 13 indicate minimal or no symptoms, 14–19 indicate mild depressive symptoms, 20–28 indicate moderate depressive symptoms, and 29–63 indicate severe depressive symptoms. The HAMD contains 17 items with responses scored on a 3-to 5-point scale that assesses somatic and psychological outcomes of depression, as well as overall symptomatology.

Anger. The State-Trait Anger Inventory (STAXI) [20], a 44-item self-report questionnaire, was used to measure three distinct facets of anger: state anger, trait anger, and anger outbursts. Higher scores indicated higher levels of anger.

Anxiety. The Hamilton Anxiety Scale (HAMA) [21] was used to evaluate the severity and relief of anxiety and consisted of 14 items to be answered on an interval scale from 0 to 4. The HAMA assesses somatic anxiety and mental anxiety symptoms experienced in the past week.

Alexithymia. The Toronto Alexithymia Scale (TAS) [22] is a 20-

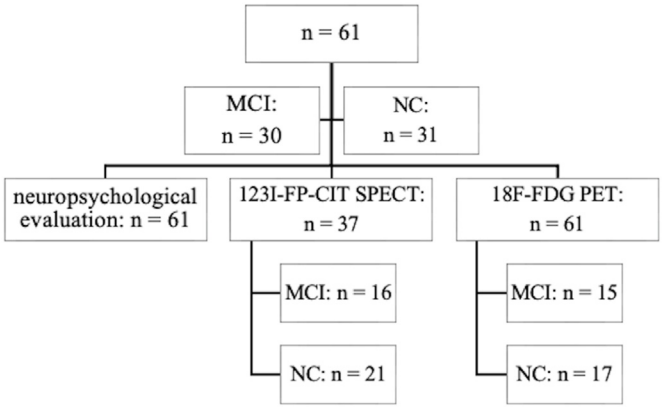

Fig. 1. Recruitment and selection process of the sample
NC: normal cognition; MCI: mild cognitive impairment.

items questionnaire assessing difficulties in perceiving, differentiating, and expressing emotions. It comprises three scales: difficulty in identifying feelings, difficulty in describing feelings, and externally oriented thinking.

2.2.2. Neuropsychological evaluation

Mild cognitive impairment. The MMSE [23] is one of the most commonly used tools to screen for cognitive impairment in older adults. It is composed of 11 major items, and five domains of cognition: (1) orientation, (2) memory, (3) attention, (4) language, and (5) design copying. Scores of two points below the maximum in each independent domain (except design copying) indicate cognitive impairment.

Nonverbal memory. The Rey Osterrieth Complex Figure (ROCF) [24] was used to evaluate visuo-constructional learning and coping skills. The test required participants to randomly recall a complex geometric figure that they had been asked to copy 3 min earlier.

Verbal memory. The Rey 15-word test [25] investigates immediate and long-term verbal memory for nonstructured materials (both Immediate Recall and Delayed Recall).

Executive dysfunction. Participants completed the standard version of the Stroop Task [26] as a measure of executive dysfunction. The test requires identifying the color of a word representing the color itself and consists of a "congruent" condition (e.g., "RED" printed in red ink) and "incongruent" trial (e.g., the word "RED" printed in yellow ink). The competition occurring between two processes is defined as the "Interference effect," in which being activated by contradictory information will result in longer response times (RTs).

2.2.3. 123I-FP-CIT SPECT

DAT-SPECT imaging was performed on 37 patients (MCI, n = 21; NC, n = 16). Each patient was intravenously injected with 185 MBq of [I-123] N-ω-fluoropropyl- 2β-carbomethoxy- 3β-(4-iodophenyl) nortropane (123I-FP-CIT; Amersham Health, UK) that was administered at the same time of the day under the same experimental conditions. Perchlorate (1000 mg) was administered at least 30 min before the radiopharmaceutical injection to block the thyroid uptake of free radioactive iodide15. Imaging was performed according to the standard guidelines [27]. In particular, images were acquired 4 h after 123I-FP-CIT using a dual-head gamma camera (Millennium VG; General Electric Medical Systems, Milwaukee, WI), USA) equipped with low-energy high-resolution collimators. SPECT studies were performed using the following parameters: 128 × 128 matrix, 120 projections (rotation of 360°), and 40 s per projection. The slice thickness was 4.42 mm. Reconstruction was performed using the ordered subset expectation maximization (OSEM) algorithm with two iterations and 12 subsets with a Butterworth filter (cut-off frequency 0.5, order 10) to produce transaxial slices that were attenuation corrected. Attenuation correction was performed according to Chang's method [28] using the coefficient $\mu = 0.11\ cm^{-1}$, after manually drawing an ellipse around the head contour. We used DaTQUANT software to analyze the ^{123}I-FP-CIT striatal uptake [29]. The redirection of the images back to the optimal orientation of the anatomy within the images was performed automatically, and was checked by an experienced nuclear medicine physician (A.C.). To compute the uptake of the radiolabelled compound in both the putamen and caudate nucleus, a predefined voxel of interest (VOI) template was used [29].

2.2.4. [18F]FDG PET

PET scanning was performed in 32 patients (MCI, n = 17; NC, n = 15). The PET/CT system Discovery VCT (GE Medical Systems, Tennessee, USA) was used to assess the brain distribution of [^{18}F] FDG in subjects using a 3D-mode standard technique with the same imaging modalities reported previously by our group, in agreement with standard guidelines [30]. In particular, all subjects fasted for at least 5 h before intravenous injection of [18F]FDG (dose range 185–250 MegaBequerels); the serum glucose level was less than 102 mg/ml in all subjects. PET/CT acquisition was initiated 30 min after [^{18}F]FDG injection in a 256 × 256 matrix. Reconstruction Algorithm OSEM (4 iterations and 12 subsets) [31] with a full width at half maximum (FWHM):5 mm was applied.

We used CortexID™ Brain Imaging (Cortex ID, GE Healthcare) for data analysis. This software allows quantification through the fully automated post-processing of 18F-FDG PET scans. In particular, the software performed age-matched comparisons with a dataset of normal controls. The standardized uptake value ratio (SUVr) was automatically calculated using the pons as the reference region [32].

2.3. Statistical analysis

Due to the small size of the sample (n < 70) and of the subsamples (<40), as well as the non-normality of the distribution for most of the variables (i.e., Shapiro-Wilk test with p values < .05), non-parametric tests for group comparisons and correlation analyses were computed.

First, descriptive statistics were computed for all the aforementioned variables to characterize the sample in terms of gender, age, level of education, age at iRBD onset, age at diagnosis, iRBD duration, psychiatric comorbidity, and characteristics (e.g., psychotropic drugs, presence of hallucinations, and psychiatric family history). Mean rank comparisons (i.e., Mann-Whitney test) were used to compare iRBD-MCI patients to the iRBD-NC group on demographic, clinical, and neuroimaging features. Kendall correlation analysis was performed to further investigate the association among the variables to examine potential brain functional, neuropsychological, and neuropsychiatric correlates of MCI in iRBD. In conclusion, effect sizes were calculated with equation $Z/\sqrt{n}$ to establish the magnitude of rank differences, whereas the significance of bivariate associations was interpreted using the cut-off of Kendal tau proposed by Botsch [33] (+ or −0.10 to 0.19: weak; + or - 0.20 to 0.29: moderate; + or - 0.30 or above: strong).

Statistical Package for the Social Sciences (SPSS) software (version 25.0) was used for data analysis.

3. Results

3.1. Sociodemographic and clinical characteristics of the study participants

Sixty-one patients with iRBD (78.8% male) were included in this study; the demographic and clinical characteristics are displayed in Table 1 iRBD-MCI patients were older, had lower levels of education, and were older at iRBD diagnosis than the iRBD-NC group (Table 2).

3.2. Neuropsychological assessment

Group comparisons revealed a significant difference in reaction times (RTs) in the Stroop Task, with considerably longer RTs for the color naming list ($p < .05$; $\eta = 0.312$) and for the interference list ($p < .01$; $\eta = 0.437$) in the iRBD-MCI group (Table 2). Visuospatial memory scores showed that the iRBD-MCI group had significantly lower scores on immediate reproduction ($p < .01$; $\eta = 0.508$), delayed reproduction ($p < .01$; $\eta = 0.517$), and immediate recall ($p < .01$; $\eta = 0.520$) than the iRBD-NC group, indicating poor visuospatial function (Table 2).

Table 1
Demographic and clinical characteristics.

	M ±SD/n	Range	NC (N = 31)	MCI (N = 30)
Age	70.07 ± 7.52	47–89	67.52 ± 7.66	72.62 ± 6.59
Gender	N = 48 M	–	n = 24 M	n = 24 M
Education (years)	11.66 ± 4.16	5–22	13.50 ± 2.60	10 ± 4.64
iRBD-related features				
Age at RBD onset (years)	63.12 ± 10.32	20–79	59.55 ± 12.54	66.36 ± 6.52
Age at diagnosis (years)	67.43 ± 7.05	47–80	64.75 ± 7.24	69.86 ± 6.05
RBD duration (years)	5 ± 6.44	0–39	5.6 ± 8.65	4.45 ± 3.55
Psychiatric comorbidity and features				
Depression	n = 13		n = 9	n = 4
Anxiety	n = 9		n = 5	n = 4
Anhedonia	n = 1		n = 1	n = 0
Antidepressants	n = 6		n = 5	n = 1
Benzodiazepines	n = 14		n = 5	n = 9
Antipsychotics	n = 1		n = 1	n = 0
Presence of hallucinations	n = 3		n = 2	n = 1
Psychiatric family history	n = 15		n = 10	n = 5
PD family history	n = 8		n = 4	n = 4

iRBD: idiopathic REM sleep behavior disorder; NC: normal cognition; MCI: mild cognitive impairment; M: men.

Table 2
Differences in RBD-related features, clinical self-report variables and cognitive measures according to the MCI groups.

Variable	MCI (n = 30)	NC (n = 31)		
	(mean rank)	(mean rank)	U	*p*
Age	35.24	23.76	254	*.009*
Education (years)	16.02	27.53	99.50	*.002*
Age at iRBD onset	24.52	18.18	153.50	*.093*
Age at diagnosis	25.14	17.50	140	*.043*
iRBD duration	21.95	21.00	210	*.799*
MMSE	23.46	33.54	251	*.019*
BDI-II				
Total	19.14	24.10	168	*.189*
Somatic	19.02	24.23	165.50	*.166*
Psychological	19.32	23.90	172	*.224*
STAXI				
Trait	20.12	21.93	191.50	*.627*
State	20.95	21.05	209	*.960*
Expression	20.52	21.50	200	*.794*
HAMD				
Total	17.95	25.40	142	*.048*
Somatic	17.45	25.95	131	*.024*
Psychological	19.34	23.88	172.50	*.227*
HAMA	19.27	23.95	171	*.216*
TAS				
Difficulty Identify Feelings	21.55	19.45	179	*.569*
Difficulty Describing Feelings	21.90	19.10	172	*.448*
Externally -Oriented Thinking	23.90	17.10	132	*.065*
Total	23.48	17.53	140.50	*.107*
Stroop Task				
Word reading (s)	14.79	17.92	89	*.183*
Colour naming (s)	30.54	21.28	207	*.026*
Interference list (s)	31.62	18.88	153	*.002*
Rey-Figure (ROCF)				
Immediate reproduction (n)	20.21	36.79	160	*.000*
Delayed reproduction (n)	20.07	36.93	156	*000*
Rey 15-word test				
Immediate recall	19.82	36.48	149	*.000*
Delayed recall	15.86	22.20	102	*.074*

iRBD: idiopathic REM sleep behavior disorder; NC: normal cognition; MCI: mild cognitive impairment; U: Mann Whitney test; all p_s are significant with a value $\leq .05$.

3.3. Neuropsychiatric assessment

The Mann-Whitney comparison (Table 2) showed significant differences in HAMD scores, with the iRBD-MCI group presenting lower scores than iRBD-NC patients on total ($p < .05$; $\eta = 0.304$), as well as on the somatic subscale ($p < .05$; $\eta = 0.348$).

3.4. Differences in cerebral sub-regions: computer-based analysis of 123I-FP-CIT-SPECT

Table 3 shows the differences in nigro-striatal dopaminergic denervation between the two groups. The iRBD-MCI group had a significantly lower tracer binding patients in the right caudate compared with iRBD-NC ($p < .05$; $\eta = 0.400$), and a marginally significant lower tracer binding in the left putamen ($p = .057$; $\eta = 0.312$).

3.5. Differences in cerebral sub-regions: computer-based analysis of [18F]FDG PET

The scores of cerebral subregions are presented in Table 4. The results indicated that patients with MCI showed a significant bilateral SUVr decrease compared to patients with NC in the bilateral posterior cingulate ($p_s < .05$; right lobe: $\eta = 0.400$; left lobe: $\eta = 0.373$) (Table 4).

3.6. Correlation analysis

3.6.1. Demographic, neuropsychiatric, neuropsychological, and iRBD-related features

In the total sample, age and age at iRBD diagnosis were strongly negatively associated with deficits in visuospatial memory, with increased age being accompanied by poorer performance on the Rey delayed reproduction task ($p_s < .05$). The correlation coefficients of Stroop interference suggested higher RTs among women ($p < .05$). Lastly, years of education were strongly and positively associated with MMSE ($p < .05$) and long-term verbal memory, as indicated by Rey Immediate recall scores ($p < .05$). In

Table 3
Nigro-striatal dopaminergic denervation according to the MCI groups.

Variable	MCI (n = 21)	NC (n = 16)	
	(mean rank)	(mean rank)	*p*
Right striatum	16.29	22.56	.080
Left striatum	16.02	21.97	.095
Left caudate	16.24	22.63	.075
Right caudate	15.21	23.97	.015
Left putamen	16.05	22.88	.057
Right putamen	16.10	22.81	.061

NC: normal cognition; MCI: mild cognitive impairment; all p_s are significant with a value ≤ 0.05.

Table 4
PET cerebral metabolic values in the NC and in the MCI group.

NC (n = 15) MCI (n = 17)				
Mean rank				
Regions	R	L	R	L
Lateral Prefrontal	18.43	18.20	14.79	15.00
Medial Prefrontal	19.13	18.33	14.18	14.88
Lateral Occipital	17.30	17.67	15.79	15.47
Inferior Parietal	18.40	18.13	14.82	15.06
Superior Parietal	18.30	17.37	14.91	15.74
Anterior Cingulate	19.33	19.80	14.00	13.59
Posterior Cingulate	20.50*	20.23*	12.97*	13.21*
Lateral Temporal	18.20	19.00	15.00	14.29
Medial Temporal	18.33	19.20	14.88	14.12
Precuneus	17.80	18.83	15.35	14.44
Primary Visual	16.20	15.83	16.76	17.09
Sensorimotor	17.47	17.00	15.65	16.06

NC: normal cognition; MCI: mild cognitive impairment; R: right; L: left; *$p \leq .05$.

addition, a negative and strong correlation was observed for Stroop interference, indicating that higher RTs were associated with fewer years of education ($p < .05$) (see Supplementary materials, Table S1). With regard to the NC and MCI groups, increased age was found to be strongly related to high RTs on Stroop word reading ($p < .05$), Stroop color naming ($p < .05$), Stroop interference ($p < .01$), and lower MMSE scores ($p < .05$) in the iRBD-NC group. Moreover, in this sample of patients, performance on the Rey Delayed recall task was incrementally and strongly related to years of education ($p < .05$) (see Supplementary materials, Table S2). In the MCI group, low performance on the Rey Delayed Reproduction Task was strongly associated with the increased age of the participants ($p < .05$), as well as with higher age at iRBD diagnosis ($p < .01$), whereas poor performance on the Rey Delayed Recall Task was strongly related to higher age at iRBD onset ($p < .05$).

3.6.2. 123I-FP-CIT-SPECT, neuropsychiatric, and neuropsychological characteristics

In the group of patients who underwent 123I-FP-CIT-SPECT, strong and positive correlations were observed between striatal dopaminergic denervation in the left caudate and Rey delayed reproduction, Stroop word reading, and Stroop color naming ($p_s < .05$). This latter result was strongly related to denervation in the right striatum and caudate ($p_s < .05$). Finally, significant and strong correlations were found between Stroop interference and denervation in the right striatum, right caudate, and right putamen ($p_s < .05$). With regard to the neuropsychiatric features, a strong correlation was found between right striatum denervation and STAXI score, whereas a negative association was observed between left putamen denervation and HAMA score (see Supplementary materials, Table S3).

In the iRBD-MCI group, performance on Rey immediate recall was negatively and strongly associated with dopaminergic innervations in the right striatum ($p < .05$), right putamen ($p < .05$), and left putamen ($p < .05$). Furthermore, this group also presented significant strong correlations between RTs on Stroop interference and denervation in the bilateral striatum ($p < .01$), bilateral putamen (right: $p < .01$; left: $p < .05$) and right caudate ($p < .01$), which also showed a strong association with higher RTs on Stroop color naming ($p < .05$). The results on neuropsychiatric features revealed a strong association between reduced left caudate-striatal DAT binding and higher STAXI and TAS scores in the iRBD-MCI group. Regarding depressive symptoms, the iRBD-NC group showed a strong negative correlation with striatal DAT binding of the right caudate and BDI-II total score ($p < .05$) (see Supplementary materials, Table S4).

3.6.3. [18F]FDG PET, neuropsychiatric, and neuropsychological characteristics

In the subgroup of patients who underwent [^{18}F]FDG PET, delayed recall was moderately related with greater SUVr in the left medial prefrontal and left lateral temporal ($p_s < .05$), and strongly associated with the left inferior parietal and bilateral posterior cingulate ($p_s < .05$). Moreover, strong associations were found between a high right ($p < .05$) and left ($p_s < .01$) precuneus SUVr and significant difficulties in perceiving, differentiating, and expressing emotions (i.e., TAS total score) (see Supplementary materials, Table S5).

In the iRBD-MCI sample, impairment in Rey delayed recall was strongly related to reduced glucose consumption in the lateral prefrontal cortex bilaterally (ps < .05). With regard to nonverbal memory, impairments in Rey immediate reproduction were strongly associated with lower SUVr in the left anterior cingulate cortices (ps < .05), whereas a strong negative correlation was observed between Rey delayed reproduction and SUVr in the bilateral anterior cingulate cortex in the iRBD-NC group ($p < .05$). Moreover, Rey delayed reproductive impairment was also strongly related to reduced glucose consumption in the right superior parietal cortex In the iRBD-MCI sample ($p < .05$) (see Supplementary materials, Table S6).

3.6.4. 123I-FP-CIT-SPECT and [18F]FDG PET

When investigating only patients who underwent both neuroimaging exams (n = 28), strong correlations were observed between striatal dopaminergic denervation in the left putamen, and reduced SUVr in right inferior parietal lobe ($p < .05$) and left lateral temporal cortex ($p < .01$), whereas moderate associations were found for the right superior parietal lobe ($p < .05$), right posterior cingulate lobe ($p < .05$), right precuneus ($p < .05$), and left precuneus ($p < .05$). Moreover, denervation in the right putamen moderately correlated with increased glucose consumption in the right superior and inferior parietal lobes ($p_s < .05$), as well as in the left precuneus ($p < .05$), and in the left lateral temporal cortex ($p < .05$). Reduced striatal DAT binding in the left striatum was positively correlated with reduced glucose consumption in the left precuneus ($p < .05$) and the left lateral temporal cortex ($p < .05$). Finally, reduced striatal DAT binding in the right caudate and left caudate was significantly related to reduced glucose consumption in the left medial temporal lobe ($p < .05$) and left lateral temporal cortex ($p < .05$) (Supplementary materials, Table S7). In conclusion, considering the patients included in the iRBD-MCI subgroup (n = 15), a positive relationship between striatal DAT binding in the left striatum, caudate, and left lateral temporal lobe was observed ($p < .05$) (Supplementary materials, Table S8).

4. Discussion

iRBD patients frequently presents with MCI and 50% of them can be diagnosed with cognitive impairment [11]. The pathophysiological mechanism of MCI in patients with iRBD is still questionable, although some studies have hypothesized that impairment of brain areas can be recognized by measuring cerebral glucose metabolism [34]. In agreement with this hypothesis, neuropsychological and psychological studies have highlighted lower performance in attention and semantic and letter verbal fluency in iRBD patients with MCI than in iRBD patients with normal cognition [12]. Moreover, psychopathological symptoms (i.e., depression and anxiety) have been recognized as precipitating factors for cognitive impairment in iRBD patients co-affected by MCI [13]. Since no undisputed evidence has yet been achieved regarding the association between MCI diagnosis and biomarkers of neurodegeneration in patients with iRBD, the present study comprehensively evaluated different cognitive, psychopathological, and neuroimaging markers in a large group of iRBD patients, distributed based on MCI diagnosis. The main results of the study were the documentation of the altered psychopathological and neuropsychological profiles in iRBD-MCI patients compared to iRBC-NC. Moreover, iRBD-MCI patients showed higher nigro-striatal deafferentation and lower brain glucose consumption in several critical areas for cognitive and behavioral processes than iRBC-NC.

The results of this study concord with previous evidence suggesting that MCI causes increased nigro-striatal deafferentation [35] and pathological changes in gray matter volume [36] in iRBD patients. Moreover, an extensive pattern of cerebral blood flow hypoperfusion in the frontal, cingulate, temporal, and occipital cortices was observed in iRBD patients with MCI compared to iRBD patients without MCI [12,36]. One recent study [37] examined brain metabolism and nigrostriatal dopaminergic functioning related to MCI in iRBD patients using ^{18}F-FDG-PET and ^{123}I-FP-CIT-SPECT, respectively. The authors documented higher glucose hypometabolism in the left cuneus and right precuneus in patients with MCI-RBD than in patients with non-MCI RBD. Moreover, a positive correlation between brain glucose hypometabolism and nigroputaminal dopaminergic activity reduction was observed, suggesting a potentially detrimental cognitive role of the putamen [37].

Consistently, the present study confirmed that the co-occurrence of MCI diagnosis in iRBD patients depicts a clinical picture featuring cognitive deficits, neurobehavioral disturbances, nigrostriatal denervation, and cerebral glucose metabolism impairment in brain areas critical for cognitive functioning. In particular, neuropsychological measures generally showed global cognitive decline in patients with iRBD-MCI, as expected. More specifically, immediate long-term verbal memory, visuospatial immediate and delayed functions, and attentional-executive functions were impaired in iRBD patients with MCI compared to those with NC, as previously documented [38]. Moreover, the iRBD-MCI group reported significantly lower scores on the overall HAMD and HAMD somatic subscales than the iRBD-NC group. This finding is quite novel considering that the previous literature showed increased behavioral symptoms in patients with MCI and RBD, but the lower depressive symptomatology can be related to the lack of insight or imperception of disease in patients with cognitive impairment, thus reducing the recognition of self-reported depressive symptoms [8,39,40]. This speculation may also be extended to other psychopathological measures (HAMA, BDI-II, and STAXI), considering the non-significance of the comparison between MCI and NC iRBD patients. Notably, the non-significant trend of the TAS actually adopted the opposite direction, suggesting that MCI patients may report higher levels of alexithymia (as previously observed [41]), thus demonstrating less recognition of mental distress symptoms than non-MCI patients. These novel results should be validated in future studies with larger sample sizes.

Considering the neuroimaging markers of neurodegeneration measured in patients with iRBD, the novelty of the present study is the comparison between groups and their correlation with cognition and psychological status. Considering the neuroimaging results, iRBD-MCI patients showed decreased striatal dopaminergic innervation in the right caudate and, to a lesser extent, in the remaining areas of both striata. This finding highlights the importance of diagnosing MCI in iRBD patients, as it is indicative of an increased presynaptic dopaminergic deficit, thus substantiating clinical data showing a higher risk of early conversion to alpha-synucleinopathies in iRBD patients co-affected by MCI [42]. Moreover, the lateralized difference in SPECT data may reflect the previously documented higher presynaptic dopaminergic damage in the right caudate of PD patients with MCI than in those with NC [43]. This dopaminergic deficit in iRBD patients is also correlated with attention deficits, memory impairment, and symptoms of depression and anger, thus combining clinical and psychopathological evidence of nigrostriatal neurodegeneration in iRBD patients. Moreover, [^{18}F]FDG PET data has indicated a significant reduction in glucose consumption in the bilateral posterior cingulate cortex of iRBD-MCI patients compared to iRBD-NC patients, in the context of a global reduction in cerebral glucose metabolism in patients with iRBD and MCI. Considering the significant cerebral glucose hypometabolism in iRBD-MCI patients, the reduced uptake of glucose in the posterior cingulate cortex emerged, since the critical role of this brain area in memory function, information processing, and object recognition [42]. This brain area is indeed currently recognized as a central hub for cognitive processes, and its dysfunction is considered an early sign of neurodegeneration [44]. This finding agrees with previous neuroimaging studies of iRBD patients showing alterations in glucose consumption in the anterior, parietal, and posterior cingulate gyrus [34,45], and hypothesizing a typical cerebral pattern of FDG uptake in those patients, quite similar to that of PD patients [46].

Finally, the correlations between 123I-FP-CIT-SPECT and [18F] FDG PET data also documented the relationship between reduced striatal DAT uptake and altered glucose consumption in the frontal, temporal, parietal, cingulate, and precuneus cortices of patients with iRBD.

The present findings highlight the presence of a diffuse neurodegenerative process affecting the entire brain of iRBD patients, possibly reflecting the higher risk of phenoconversion in iRBD-MCI than in iRBD-NC patients.

Despite the clinical significance of the results documented in this study, several limitations should be noted. First, cross-sectional nature of this study did not allow us to demonstrate an increased risk of phenoconversion in patients with iRBD co-affected by MCI. Second, although the sample of patients was quite large for a single sleep medicine center study, the number was still not sufficient to use parametric analyses, and thus only preliminary observations could be drawn. Moreover, considering the use of non-parametric analyses, it was not possible covariate the results for age and education, although patients with MCI showed a lower degree of education and were older. Future studies should be planned to confirm this preliminary data in higher group of patients. Third, selection bias may have affected the results, as only a subgroup of patients agreed to undergo ^{123}I-FP-CIT SPECT and/or [^{18}F]FDG PET. Moreover, the use of MMSE is not explicitly recommended by the MDS Task Force diagnostic criteria for detecting MCI [15], although MMSE is currently used in common clinical practice to screen and evaluate cognitive domains in patients with suspected cognitive decline. However, future studies should entertain the opportunity to use alternative

and more structured instruments to identify MCI in idiopathic RBD patients [47].

However, this study contributes to enhancing the current knowledge about cognitive, psychological, and nuclear medicine markers in iRBD, and encourages the stratification of iRBD patients according to the presence of MCI from the time of diagnosis in order to establish preventive strategies, individual follow-up, and possibly disease-modifying treatments using both pharmacological and non-pharmacological approaches.

5. Conclusions

In conclusion, MCI has recently been proposed as an early sign of phenoconversion in patients with iRBD [46], although a wide consensus has not been reached on this point. This study aimed to provide a more clear focus on the importance of early recognition of MCI at the time of iRBD diagnosis, since iRBD-MCI patients present more altered markers of neurodegeneration compared to iRBD patients with NC, and thus can be considered more prone to early conversion during follow-up and possibly need a more urgent and individualized approach for setting neuroprotective strategies [42].

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.08.018.

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