ORIGINAL ARTICLE

Detecting the Cognitive Prodrome of Dementia with Lewy Bodies: A Prospective Study of REM Sleep Behavior Disorder

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Study Objectives: Long-term studies in REM sleep behavior disorder (RBD) have shown a high rate of conversion into synucleinopathies. We aimed to prospectively follow-up a large cohort of RBD patients to identify cognitive markers for early detection of prodromal dementia.

Methods: Seventy-six idiopathic RBD patients underwent polysomnography and a complete neuropsychological and neurological assessment and were then followed for a mean of 3.6 years. Cognitive characteristics at baseline were compared between patients who remained disease-free and those who developed a synucleinopathy, and between those who developed dementia first and those who developed parkinsonism first. Receiver operating characteristic curves were calculated to assess the diagnostic value of cognitive tests for detecting prodromal dementia.

Results: At follow-up, 34 patients developed a neurodegenerative disease: 19 parkinsonism-first and 15 dementia-first. RBD patients who first developed dementia were impaired at baseline in all cognitive domains (attention/executive functions, learning/memory, and visuospatial) compared to patients who developed parkinsonism. Moreover, 93% of patients who first developed dementia had mild cognitive impairment at baseline compared to 42% of patients who developed parkinsonism. RBD patients who developed parkinsonism first were similar at baseline to disease-free RBD patients on cognition. In dementia-first patients, two cognitive tests assessing attention and executive functions (Stroop Color Word Test and Trail Making Test) reliably predicted dementia (area under the curve ≥0.85) compared to parkinsonism-first patients or controls.

Conclusions: This study shows that cognitive tests assessing attention and executive functions strongly predict conversion to dementia in RBD patients, and may be useful endpoints to determine the effectiveness of interventions to prevent cognitive deterioration in RBD patients.

Keywords: REM sleep behavior disorder, Parkinson's disease, dementia with Lewy bodies, cognition, neuropsychological assessment.

Statement of Significance

This study shows specific cognitive markers of neurodegeneration in REM sleep behavior disorder (RBD) patients who will develop dementia. Attention and executive functions testing had high sensitivity to predict dementia in this population. Therefore, cognitive testing could be used with other markers of neurodegeneration in future clinical trials in RBD.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia in which individuals act out their dreams during REM sleep.[1] It is frequently associated with synucleinopathies, such as dementia with Lewy bodies (DLB), Parkinson's disease (PD), and multiple system atrophy (MSA).[2,3] Long-term studies in RBD patients have estimated a 25–30% risk of neurodegenerative synucleinopathy at 3 years, 33–47% at 5 years, 66% at 7.5 years, 76% at 10 years, and 81–91% at 14 years.[4–6] Thus, as a specific and sensitive prodromal syndrome, RBD provides a promising opportunity to investigate potential preclinical markers of synucleinopathies.[7] Although DLB and PD are overlapping processes,[8] there may be important differences in neurodegenerative mechanisms between individuals who develop dementia as their first neurodegenerative syndrome versus those who develop a primary parkinsonism. If so, it would be important to identify specific markers for these different clinical syndromes in RBD.

Various predictors of conversion into defined neurodegenerative diseases have been identified in longitudinal studies of RBD.[5,9–15] In general, these prodromal markers were highly similar between dementia-first and parkinsonism-first convertors.[11–13] Cross-sectional studies on cognition in RBD patients have reported impaired attention and executive functions, episodic memory, and visuospatial abilities.[16] Moreover, approximately 50% of RBD patients have mild cognitive impairment (MCI), a risk factor for the development of dementia in PD and for DLB.[16] To date, only three longitudinal studies on cognition have been conducted in RBD.[17–19] These studies found deterioration in cognitive function, consistent with evolving neurodegeneration. However, it is still unclear if there is a specific baseline cognitive profile in RBD patients associated with primary conversion into dementia. Also, the optimal neurocognitive tests for early detection of prodromal DLB in RBD remain undefined.

The purpose of this study was to prospectively follow a large cohort of RBD patients in order to identify cognitive markers of prodromal DLB and determine whether these cognitive markers could differentiate conversion subtypes (dementia-first vs. parkinsonism-first patients).

METHODS

Participants and Procedures

All procedures were performed at the Centre for Advanced Research in Sleep Medicine at the Hôpital du Sacré-Coeur de Montréal (Quebec, Canada). The hospital's ethics committee approved the study, and all subjects signed a written consent before participating. A total of 92 idiopathic RBD patients were recruited from April 2004 to September 2014. For inclusion, patients had to be aged 40–85; had completed at least 5 years of education; had undergone at baseline polysomnographic (PSG) recording and clinical, neurological, and neuropsychological assessments; and had undergone at least one

annual follow-up examination. Exclusion criteria were dementia or other neurodegenerative disease at baseline, RBD associated with narcolepsy, untreated major depression, encephalitis, EEG abnormalities suggesting epilepsy, untreated or incompletely treated sleep apnea (hypopnea–apnea index >15), drug-induced RBD (ie, excluding those taking antidepressants when subjective RBD symptoms started), chronic obstructive pulmonary disease, head injury, or brain tumor. For further analysis, each RBD patient who developed a primary dementia (n = 15) was then pair-matched for age (at baseline), sex, and education with two healthy controls (n = 30) who were participating in our ongoing project on sleep and cognition in aging. Controls were included to determine optimal cutoff scores on cognitive tests, particularly for scores that differed significantly in our group analysis between dementia-first patients and parkinsonism-first patients. Controls were examined once at baseline with the same assessment as patients, were free of neurodegenerative disease and MCI, and had a normal PSG exam.

Baseline Assessment

Subjects underwent all-night PSG recording in the sleep laboratory. RBD was diagnosed by a sleep specialist (JM) according to the criteria of the International Classification of Sleep Disorders—Second Edition using standard REM sleep atonia cutoff criteria.[1,20] A complete history and neurological exam, including motor[21] and olfaction testing[22] was performed by a neurologist specialized in movement disorders (RBP). Subjects also completed questionnaires to assess depression (Beck Depression Inventory, Second edition (BDI-II)[23] and daytime sleepiness (Epworth Sleepiness Scale).[24]

A complete neuropsychological assessment was performed by a neuropsychologist (JFG). Bedside screening tests for dementia, namely the Mini-Mental State Examination (MMSE)[25] and Montreal Cognitive Assessment (MoCA)[26] were conducted by the evaluating neurologist (RBP). Three cognitive domains were defined, namely attention and executive functions, learning and memory, and visuospatial abilities. The full list of cognitive tests, variables, and normative data used are described in a previous publication.[27] Based on this assessment, the neuropsychologist and neurologist made the cognitive diagnosis, whether normal cognition, MCI, or dementia.

MCI was defined as (1) subjective cognitive complaints by the patient, spouse, or informant in the structured interview or on the Cognitive Failures Questionnaire[28] (total score >24, or responses of 3 (quite often) or 4 (very often) chosen for at least 1 item); (2) objective evidence of cognitive decline, defined as performance ≥1.5 standard deviations below the standardized mean on at least two scores in the same cognitive domain; and (3) no significant decline in functional daily living activities in recent weeks (ie, ability to perform housework, take medication, manage money, and do shopping, on the structured interview) which would be sufficient to meet criteria for dementia.[27] MCI subtypes were defined as MCI single domain (impaired on tasks requiring either attention/executive functions, learning/memory, or visuospatial abilities) or MCI multiple domain (impaired on tasks in at least two of the three cognitive domains listed above).[27,29,30] In this study, MCI was not considered as a neurodegenerative disease per se because the literature shows that a significant proportion of individuals with MCI remain stable or return to normal over time.[31,32]

Follow-up Examination

An annual research follow-up assessment was performed, including a complete neuropsychological assessment and a neurological examination to investigate the presence of neurodegenerative diseases. Follow-up examinations were conducted by a neurologist (RBP) and a neuropsychologist (JFG). If patients were unable to participate in person (usually due to severe dementia or long distance), a telephone conversation with their caregivers supplemented by a clinical chart review was conducted to confirm the neurodegenerative disorder diagnosis, as in our previous studies.[5,11,13] A consensus meeting was held between the neurologist and neuropsychologist to determine the disease diagnosis according to the UK Parkinson's Disease Society Brain Bank criteria for parkinsonism syndrome,[33] guidelines from the consortium on DLB,[34] and a consensus statement on MSA criteria.[35] To avoid circular analyses with the cognitive tests used at baseline, dementia at follow-up was diagnosed using consensus between the neurologist and neuropsychologist based on a modified version of level I criteria for Parkinson's disease dementia proposed by the Movement Disorder Society Task Force including: MMSE <28 or MoCA <25 scores with impairment in at least two cognitive domains and cognitive deficits severe enough to impact daily living (caregiver interview or Pill Questionnaire).[36]

Statistical Analysis

Statistical analyses were performed using SPSS 19.0. Continuous sociodemographic, clinical, and cognitive variables with a normal distribution were compared between groups (disease-free vs. converted; parkinsonism-first vs. dementia-first) using bilateral Student's t tests for independent samples. Nonparametric Mann–Whitney U tests were applied for variables that were not distributed normally. Analyses of covariance were also used when a cognitive variable was correlated with age or subjective RBD duration (>0.30) in dementia-first versus parkinsonism-first analyses and the regression line was homogenous between groups. Chi-square tests (χ^2) were used to compare proportions of sex, antidepressants, anxiolytics, MCI, and subjects with performance ≥1.5 standard deviations below the standardized mean across groups (z-score). Because of the large number of comparisons, Benjamini–Hochberg procedure was used on p-values to adjust for the False discovery rate (FDR) in neuropsychological tests.[37] Both non-corrected and corrected p-thresholds are reported in the tables. Receiver operating characteristic (ROC) curves were generated to assess the sensitivity and specificity of the cognitive tests in order to determine dementia predictability in RBD patients. The optimal cutoff value was defined as the maximum accuracy value, calculated by the Youden Index (y = sensitivity + specificity – 1). Exploratory logistic regression analysis was also performed with three predictors: (1) age, (2) the most valid visuospatial test (Rey–Osterrieth Complex Figure, copy), and (3) the most valid attention and executive functions test (Trail Making Test, part B, time)

obtained from the ROC curve analysis. Statistical significance was set at $p < .05$. When a patient was unable to complete a cognitive task due to severe cognitive impairment, we imputed a score of −3.5 *z*, representing severe impairment.

RESULTS

Of the initial patient cohort, 16 were excluded: three for age outside the inclusion range, six because of neurodegenerative disease at baseline, and seven for PSG that did not confirm RBD or for drug-induced RBD. This left a total of 76 patients (83%) for analysis (see Figure 1). For the final follow-up visit, 64 patients (84%) had diagnosis confirmed on a complete neuropsychological and neurological assessment, 9 patients underwent a neurological assessment and a cognitive screening test (MMSE or MoCA), and 3 (one with dementia, two still idiopathic) were contacted by the neurologist, who conversed with patients or caregivers and reviewed their clinical charts to assess dementia. Thirty-four patients (out of 76; 45%) developed a neurodegenerative disease after a mean follow-up of 3.6 years (range = 1–9 years) (defined as time between their baseline neuropsychological assessment and follow-up examination at year of conversion for dementia/parkinsonism). Nineteen patients developed parkinsonism first (17 PD without dementia at disease conversion, including 9 with normal cognition and 8 with MCI, and 2 MSA), and 15 patient developed dementia first (all met clinical DLB

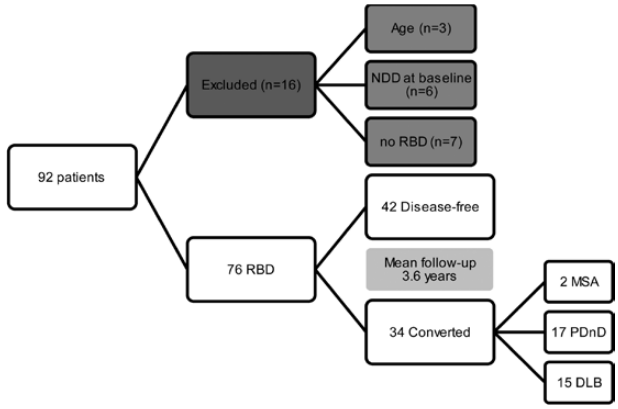

Figure 1—Flow chart of study process representing inclusion criteria. DLB = dementia with Lewy bodies; iRBD = idiopathic rapid eye movement sleep behavior disorder; MSA = multiple system atrophy; NDD = Neurodegenerative disease; PDnD = Parkinson's disease without dementia.

Table 1—Baseline Sociodemographic and Clinical Characteristics of All RBD Patients.

	All RBD (*n* = 76)	Disease free (A) (*n* = 42)	Converted (B) (*n* = 34)	A vs. B *p* value
Age (years)	67.36 ± 7.13	66.19 ± 6.59	68.79 ± 7.60	ns
Sex, *n* male (%)	56 (74)	33 (79)	23 (68)	ns
Education (years)	12.34 ± 3.81	12.33 ± 3.69	12.35 ± 4.01	ns
RBD duration (subjective)	8.66 ± 9.20	11.07 ± 12.04	6.33 ± 4.22	ns[a]
RBD duration at follow-up (PSG)	6.06 ± 4.60	5.61 ± 4.84	6.62 ± 4.29	ns
Follow-up duration	3.59 ± 2.36	3.48 ± 2.39	3.73 ± 2.33	ns
Antidepressants, *n* (%)	20 (26)	15 (36)	5 (15)	ns
Anxiolytics, *n* (%)	30 (39)	17 (40)	13 (38)	ns
BDI-II	11.48 ± 7.48	12.43 ± 8.07	10.15 ± 6.54	ns
ESS	7.24 ± 4.46	7.33 ± 4.49	7.08 ± 4.59	ns
UPSIT (/12)	7.26 ± 2.64	7.99 ± 2.32	6.35 ± 2.75	.006
UPSIT (% expected)	0.74 ± 0.26	0.81 ± 0.22	0.65 ± 0.28	.009
UPDRS-III	4.63 ± 3.87	3.40 ± 2.63	6.15 ± 4.60	.003
MMSE	28.20 ± 1.68	28.44 ± 1.38	27.94 ± 1.94	ns[a]
MoCA	25.24 ± 2.47	25.08 ± 2.61	25.53 ± 2.26	ns
MCI, *n* (%)	41 (54)	19 (45)	22 (65)	ns
Single domain, *n* (%)	33 (43)	16 (38)	17 (50)	
Multiple domain, *n* (%)	8 (11)	3 (7)	5 (15)	

Data are shown as mean ± SD unless otherwise noted. BDI-II = Beck Depression Inventory Second edition; ESS = Epworth Sleepiness Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; ns = non significant; PSG = polysomnography; UPSIT = University of Pennsylvania Smell Identification Test; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III; RBD = rapid eye movement sleep behavior disorder.

[a]Mann–Whitney.

criteria). Table 1 presents sociodemographic and clinical characteristics of the patient cohort at baseline. As we previously reported, patients who developed a neurodegenerative disease were equivalent on all sociodemographic characteristics to patients who remained disease-free, but showed significantly more impairment on olfaction and motor measures at baseline (Table 1). A trend was also observed (p = .09) for the proportion of MCI at baseline, which was higher in patients who converted. Moreover, RBD patients who developed neurodegenerative disease showed poorer baseline performance on cognitive tests measuring attention and executive functions (Trail Making Test and Verbal semantic fluency) compared to RBD patients who remained disease-free (Table 2). However, when adjusted for the FDR, these differences become statistically insignificant.

Patients Who Developed Dementia First Versus Patients Who Developed Parkinsonism First

No significant differences in sociodemographic variables were found between RBD patients who developed dementia first and RBD patients who developed parkinsonism first, except that dementia-first patients were older (p = .001) and tended to report shorter RBD duration at baseline (p = .09) (Table 3). Therefore, age and subjective RBD duration were

Table 2—Baseline Cognitive Performance on Neuropsychological Tests of all RBD Patients.

	All RBD (n = 76)	Disease free (A) (n = 42)	Converted (B) (n = 34)	A vs. B p value (p' value*)
Attention and executive functions				
Digit span (forward)	5.91 ± 1.31	6.10 ± 1.27	5.68 ± 1.34	ns
Digit span (backward)	4.20 ± 1.06	4.29 ± 1.11	4.09 ± 1.00	ns
Digit span (scaled score)	9.33 ± 2.67	9.67 ± 2.97	8.91 ± 2.21	ns
Stroop III–II, s	66.03 ± 43.99	60.54 ± 26.13	72.53 ± 58.62	ns
Stroop III–II, errors	2.42 ± 3.90	1.42 ± 3.11	3.61 ± 4.45	ns
Stroop IV–III, s	33.69 ± 48.58	24.53 ± 33.79	45.04 ± 61.29	ns
Stroop IV–III, errors	3.33 ± 5.70	2.33 ± 4.56	4.57 ± 6.77	ns
Trail Making Test, Part A, s	49.34 ± 24.81	43.19 ± 16.85	56.94 ± 30.64	.031[a] (.17)
Trail Making Test, Part B, s	132.32 ± 71.74	114.43 ± 55.92	154.41 ± 83.08	.006[a] (.14)
Trail B–Trail A, s	71.95 ± 58.73	58.95 ± 42.07	88.00 ± 71.83	.007[a] (.08)
Verbal fluency (semantic)	30.18 ± 9.72	32.71 ± 8.54	27.23 ± 10.30	.022 (.16)
Verbal fluency (phonetic)	24.59 ± 16.05	23.24 ± 17.60	26.36 ± 13.88	ns
Learning and memory				
RAVLT				
Sum of trials 1–5	40.66 ± 10.55	42.52 ± 9.56	38.35 ± 11.37	ns
List B	4.14 ± 1.84	4.48 ± 1.89	3.71 ± 1.70	ns
Immediate recall	7.55 ± 3.51	7.95 ± 3.28	7.05 ± 3.77	ns
Delayed recall	7.43 ± 3.58	7.83 ± 3.46	6.93 ± 3.72	ns
Recognition	13.26 ± 1.90	13.36 ± 1.68	13.15 ± 2.15	ns[a]
Rey–Osterrieth Complex figure				
Immediate recall	14.45 ± 6.19	15.18 ± 5.82	13.63 ± 6.57	ns
Delayed recall	14.53 ± 5.96	15.55 ± 5.58	13.40 ± 6.24	ns
Visuospatial abilities				
Rey–Osterrieth Complex figure, copy	29.68 ± 4.76	30.21 ± 3.92	29.03 ± 5.63	ns[a]
Block design (scaled score)	9.85 ± 2.76	10.08 ± 3.01	9.52 ± 2.38	ns
Bells test, omissions	2.20 ± 2.44	2.39 ± 2.49	1.92 ± 2.38	ns

Data are shown as mean ± SD unless otherwise noted. ns = non significant; RBD = rapid eye movement sleep behavior disorder; RAVLT = Rey Auditory-Verbal Learning Test; II = Naming; III = Interference; IV = Flexibility.
[a]Mann–Whitney.
*False Discovery Rate adjusted p value.

added as covariates when they correlated with a cognitive test (ie, $p > .30$). Age significantly correlated with the University of Pennsylvania Smell Identification Test (UPSIT), % expected ($R = -0.444$, $p = .008$); the MoCA ($R = -0.552$, $p = .033$); the Stroop Color Word Test III–II, time ($R = 0.503$, $p = .017$), III–II, errors ($R = 0.493$, $p = .020$), IV–III, time ($R = 0.609$, $p = .003$), and IV–III, errors ($R = 0.600$, $p = .004$); the Trail Making Test, part B ($R = 0.419$, $p = .014$) and B–A ($R = 0.438$, $p = .010$), the Verbal semantic fluency ($R = -0.665$, $p = .000$); and the Rey Auditory-Verbal Learning Test (RAVLT), sum of trials 1–5 ($R = -0.381$, $p = .026$), immediate recall ($R = -0.475$, $p = .005$), and delayed recall ($R = -0.421$, $p = .013$). Subjective RBD duration correlated only with the MoCA ($R = 0.587$, $p = .027$). On clinical variables, RBD dementia-first patients performed worse on the MMSE, MoCA, and UPSIT (Table 3). MCI was diagnosed in 93% of dementia-first patients versus 42% of parkinsonism-first patients ($p = .002$). In dementia-first patients with MCI at baseline ($n = 14$), 71% were diagnosed with the single domain subtype (seven with impaired attention/executive functions; three with impaired learning/memory) and 29% were diagnosed with the multiple domain subtype (one with impaired attention/executive functions and visuospatial abilities; one with impaired attention/executive functions and learning/memory; two with all cognitive domains impaired). In parkinsonism-first patients with MCI at baseline ($n = 8$), 88% were diagnosed with the single domain subtype (four with impaired attention/executive functions; two with impaired learning/memory; one with impaired visuospatial abilities) and 12% were diagnosed with the multiple domain subtype with impaired attention/executive functions and learning/memory.

On baseline cognitive tests (Table 4), RBD dementia-first patients performed worse than RBD parkinsonism-first patients (FDR adjusted p value) on the Stroop Color Word Test (III–II, time), RAVLT (sum of trials 1–5) and Rey–Osterrieth Complex Figure (copy, immediate, and delayed recalls). Moreover, a higher proportion of RBD dementia-first patients had significant clinical deficits (performance ≥1.5 standard deviations below the standardized mean) compared to RBD parkinsonism-first patients on the following cognitive tests: the Stroop Color Word Test (III–II, time and errors; IV–III, time), Trail Making Test (parts A and B, B–A), Verbal fluency test (phonetic and semantic), RAVLT (sum of trials 1–5, immediate and delayed recalls), Rey–Osterrieth Complex Figure (copy and delayed recall), and Block design subtest from the Wechsler

Table 3—Baseline Sociodemographic and Clinical Characteristics of Converted RBD Patients.

	Parkinsonism first (A) ($n = 19$)	Dementia first (B) ($n = 15$)	A vs. B p value
Age (years)	65.26 ± 7.28	73.27 ± 5.44	.001
Sex, *n* male (%)	12 (63)	11 (73)	ns
Education (years)	12.47 ± 3.49	12.20 ± 4.71	ns
RBD duration (subjective)	7.33 ± 4.13	4.83 ± 4.06	ns[a]
RBD duration at follow-up (since PSG)	6.71 ± 4.47	6.52 ± 4.20	ns
Follow-up duration	4.05 ± 2.71	3.33 ± 1.75	ns
Antidepressants, *n* (%)	3 (16)	2 (13)	ns
Anxiolytics, *n* (%)	7 (37)	6 (40)	ns
BDI-II	9.54 ± 6.86	11.29 ± 6.24	ns
ESS	7.44 ± 4.69	6.25 ± 4.92	ns
UPSIT (/12)	7.47 ± 2.89	4.93 ± 1.79	.004
UPSIT (% expected)	0.76 ± 0.31	0.50 ± 0.15	.028[b]
UPDRS-III	5.34 ± 3.88	7.17 ± 5.34	ns
MMSE	28.79 ± 1.08	26.79 ± 2.26	.001
MoCA	26.89 ± 1.54	23.50 ± 1.52	008[b]
MCI, *n* (%)	8 (42)	14 (93)	.002
Single domain, *n* (%)	7 (37)	10 (67)	
Multiple domain, *n* (%)	1 (5)	4 (27)	

Data are shown as mean ± SD unless otherwise noted. BDI = Beck Depression Inventory Second edition; ESS = Epworth Sleepiness Scale; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MCI = mild cognitive impairment; ns = non significant; PSG = polysomnography; RBD = rapid eye movement sleep behavior disorder; UPSIT = University of Pennsylvania Smell Identification Test; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III.

[a]Mann–Whitney.

[b]ANCOVA.

Table 4—Baseline Cognitive Performance on Neuropsychological Tests of Converted RBD Patients.

	Parkinsonism first (A) (*n* = 19)	Dementia first (B) (*n* = 15)	A vs. B *p* value (*p*' value*)
Attention and executive functions			
Digit span (forward)	6.00 ± 1.41	5.27 ± 1.16	ns
Digit span (backward)	4.37 ± 1.12	3.73 ± 0.70	ns
Digit span (scaled score)	9.44 ± 2.48	8.27 ± 1.71	ns
Stroop III–II, s	41.15 ± 34.57	117.85 ± 57.59	**.012**[a] (**.05**)
Stroop III–II, errors	1.85 ± 3.67	6.15 ± 4.41	ns[a]
Stroop IV–III, s	20.23 ± 26.14	85.37 ± 80.98	ns[a]
Stroop IV–III, errors	1.38 ± 4.13	9.74 ± 7.24	ns[a]
Trail Making Test, Part A, s	44.11 ± 12.39	73.20 ± 38.83	.025[b] (.08)
Trail Making Test, Part B, s	116.05 ± 43.72	203.00 ± 96.37	.022[a] (.08)
Trail B–trail A, s	63.05 ± 43.53	119.60 ± 88.39	ns[a]
Verbal fluency (semantic)	30.67 ± 10.35	22.08 ± 8.11	ns[a]
Verbal fluency (phonetic)	31.27 ± 11.62	19.00 ± 14.26	.027 (0.07)
Learning and memory			
RAVLT			
Sum of trials 1–5	43.79 ± 9.40	31.46 ± 10.01	**.010**[a] (**.05**)
List B	3.84 ± 1.71	3.55 ± 1.74	ns
Immediate recall	8.68 ± 2.73	4.99 ± 3.96	ns[a]
Delayed recall	8.32 ± 3.40	5.17 ± 3.44	ns[a]
Recognition	13.58 ± 1.50	12.60 ± 2.73	ns[b]
Rey–Osterrieth Complex Figure			
Immediate recall	17.21 ± 5.80	9.10 ± 4.36	**.000** (**.002**)
Delayed recall	16.63 ± 4.96	9.30 ± 5.30	**.000** (**.002**)
Visuospatial abilities			
Rey–Osterrieth Complex Figure, copy	31.63 ± 3.08	25.73 ± 6.45	**.000**[b] (**.003**)
Block design (scaled score)	10.25 ± 2.18	8.22 ± 2.28	.038 (.09)
Bells test, omissions	2.00 ± 2.56	1.80 ± 2.20	ns

Data are shown as mean ± SD unless otherwise noted. Bold values reached statistical significance of $p < .05$. ns = non significant; RBD = rapid eye movement sleep behavior disorder; RAVLT = Rey Auditory-Verbal Learning Test; II = Naming; III = Interference; IV = Flexibility.

[a]ANCOVA.

[b]Mann–Whitney.

*False Discovery Rate adjusted *p* value.

Adult Intelligence Scale third edition (see Figure 2). No significant differences were found in cognitive tests or MCI frequency at baseline between RBD parkinsonism-first patients and RBD disease-free patients (subgroups means and standard deviations are shown in Tables 2 and 4).

Sensitivity and Specificity of Cognitive Tests for Detecting Dementia-First Patients

Tables 5 and 6 present the optimal cutoff scores (based on the Youden index), sensitivity, specificity, and area under the curve (AUC) for each cognitive test. Dementia-first patients were pair-matched at baseline in terms of age (73.27 ± 5.44 vs. 72.10 ± 5.40; $p = .499$), sex (73 vs. 57% men; $p = .277$), and education (12.20 ± 4.71 vs. 12.70 ± 3.89; $p = .707$) with 30 healthy subjects without cognitive impairment. Using ROC curve analysis comparing dementia-first convertors and controls, the best predictors (AUC ≥ 0.85) of dementia were the Stroop Color Word Test (III–II, time), Trail Making Test (part B, time), Verbal fluency test (phonetic and semantic), and RAVLT (sum of trials 1–5). When comparing dementia-first

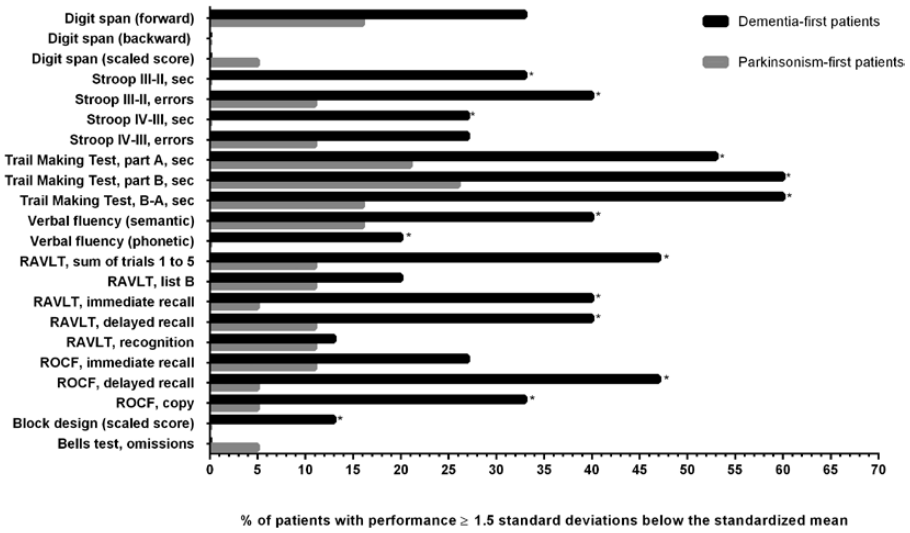

Figure 2—Percentage of patients with impaired performance on neuropsychological tests. *Statistically significant difference between groups (p = .05); RAVLT = Rey Auditory-Verbal Learning Test; ROCF = Rey–Osterrieth Complex Figure; Stroop components: II = Naming, III = Interference, IV = Flexibility.

and parkinsonism-first RBD convertors, the best predictors (AUC ≥ 0.85) were the Stroop Color Word Test (III–II, time; IV–III, errors), Trail Making Test (part B, time), and Rey–Osterrieth Complex Figure (copy). Logistic regression analysis including all RBD patients showed that, in addition to older age (OR 1.212, 95% CI 1.049–1.400, p = .009), poorer performance on the Trail Making Test part B, time (OR 7.776, 95% CI 0.855–70.715, p = .069), and Rey–Osterrieth Complex Figure, copy (4.029, 95% CI 0.861–18.859, p = .077) were independent trending predictors of dementia-first development. The cutoff scores for poor performance on the Trail Making Test part B (≥113 s) and the Rey–Osterrieth Complex Figure (≤30 points) were obtained using the ROC curve analysis for detecting dementia-first convertors compared to healthy controls (Table 5).

DISCUSSION

In this prospective study of 76 REM sleep behavior disorder (RBD) patients over 3.6 years, we found a distinct cognitive profile in patients who developed DLB. RBD patients who developed dementia first had poorer performance at baseline on all cognitive domains: attention and executive functions, learning and memory, and visuospatial abilities, and had a higher proportion of MCI at baseline. In contrast, RBD patients who developed parkinsonism first were similar to patients who remained disease-free on cognitive tests performance or MCI diagnosis frequency. When assessing individual cognitive tests on ROC analysis, we found that those measuring attention/executive functions and learning/memory, especially the Stroop Color Word Test, Trail Making Test, Verbal fluency tests, and RAVLT, best differentiated prodromal DLB from individuals with normal cognition. Moreover, cognitive tests measuring attention/executive functions and visuospatial abilities, especially the Stroop Color Word Test, Trail Making Test, and Rey–Osterrieth Complex Figure, best differentiated prodromal DLB from parkinsonism in RBD patients. Whereas age was a significant predictor of dementia, the Trail Making Test and Rey–Osterrieth Complex Figure were trending predictors in a logistic regression model. This confirms the utility of attention/executive functions and visuospatial testing in RBD to identify patients at risk of dementia. Therefore, our study provides new cognitive markers that predict the conversion of RBD patients to dementia.

Longitudinal studies of disease risk have estimated very high conversion to synucleinopathies in RBD.[4–6] Other studies have found clinical[5,11,13,38] and functional neuroimaging[9,10,12,14,15] markers of conversion in RBD. However, some studies did not consider differences between conversion subtypes (dementia-first vs. parkinsonism-first patients), and others found no differences on their measures. In our study, cognitive anomalies clearly distinguished RBD patients who will develop dementia first from those who will develop parkinsonism first. Therefore, inexpensive, non-invasive, and relatively brief cognitive tests that assess attention, executive functions, episodic verbal learning, and visuospatial abilities can be used to predict conversion subtypes, and could be used in future clinical trials in RBD in order to determine the impact of different interventions on cognitive decline, including physical exercise, cognitive training, and neuroprotective drug trials.

To our knowledge, three longitudinal studies on cognition have been conducted in RBD. The first followed 24 RBD patients and 12 healthy subjects for 2 years (mean interval: 25.8 months). Worse delayed verbal memory (story recall test) and visuospatial abilities (Rey–Osterrieth Complex Figure, copy) were found in patients at baseline and at follow-up. Worse visuospatial attention (Corsi supraspan test) was also observed in patients at follow-up only.[17] The second

Table 5—Psychometric Properties of the Neuropsychological Tests for Detecting RBD Patients Who Developed Dementia First Compared to Matched Healthy Subjects.

	Dementia first	Controls	Sensitivity (95% CI)	Specificity	Cut-off scores[a]	AUC
Digit span (forward)	5.27 ± 1.16	6.28 ± 1.20	0.600 (0.563–0.897)	0.800	≤6	0.73
Digit span (backward)	3.73 ± 0.70	4.74 ± 1.48	0.867 (0.545–0.868)	0.367	≤5	0.71
Digit span (scaled score)	8.27 ± 1.71	9.90 ± 2.26	0.600 (0.542–0.863)	0.667	≤11	0.70
Stroop III–II, s	117.85 ± 57.59	40.67 ± 27.39	0.778 (0.662–1.00)	0.889	**≥64**	**0.85**
Stroop III–II, errors	6.15 ± 4.41	1.44 ± 2.79	0.667 (0.604–1.00)	1.00	≥6	0.82
Stroop IV–III, s	85.37 ± 80.98	36.30 ± 23.75	0.500 (0.309–0.916)	0.900	≥63	0.61
Stroop IV–III, errors	9.74 ± 7.24	2.60 ± 3.44	0.750 (0.573–1.00)	0.600	≥3	0.79
Trail Making Test A, s	73.20 ± 38.83	38.30 ± 12.27	0.667 (0.681–0.954)	0.867	≥48	0.82
Trail Making Test B, s	203.00 ± 96.37	98.00 ± 34.73	0.933 (0.813–1.00)	0.767	**≥113**	**0.91**
Trail Making Test B–A, s	119.60 ± 88.39	59.70 ± 32.67	0.800 (0.657–0.969)	0.800	≥79	0.81
Verbal fluency (semantic)	22.08 ± 8.11	36.32 ± 7.94	0.833 (0.783–0.997)	0.714	**≤30**	**0.89**
Verbal fluency (phonetic)	19.00 ± 14.26	36.48 ± 10.60	0.900 (0.691–1.00)	0.897	**≤26**	**0.87**
RAVLT, sum of trials 1–5	31.46 ± 10.01	45.10 ± 8.96	0.867 (0.734–0.986)	0.767	**≤39**	**0.86**
RAVLT, list B	3.55 ± 1.74	4.53 ± 1.66	0.667 (0.437–0.783)	0.400	≤5	0.61
RAVLT, immediate Recall	4.99 ± 3.96	9.13 ± 2.50	0.800 (0.704–0.985)	0.767	≤6	0.84
RAVLT, delayed recall	5.17 ± 3.44	8.87 ± 3.36	0.733 (0.636–0.924)	0.767	≤6	0.78
RAVLT, recognition	12.60 ± 2.73	13.73 ± 1.14	0.600 (0.443–0.800)	0.633	≤14	0.62
ROCF, immediate recall	9.10 ± 4.36	15.14 ± 5.81	0.800 (0.623–0.953)	0.714	≤12	0.79
ROCF, delayed recall	9.30 ± 5.30	17.26 ± 6.95	0.933(0.661–0.963)	0.588	≤15	0.81
ROCF, copy	25.73 ± 6.45	31.13 ± 3.85	0.733 (0.642–0.919)	0.667	≤30	0.78
Block design (scaled score)	8.22 ± 2.28	10.93 ± 3.19	0.778 (0.557–0.908)	0.481	≤10	0.73
Bells test, omissions	1.80 ± 2.20	1.69 ± 1.76	0.400 (0.241–0.704)	0.586	≥1	0.47

Data are shown as mean ± SD unless otherwise noted. Bold values = best predictors; AUC = area under the curve; CI = confidence interval; RBD = rapid eye movement sleep behavior disorder; RAVLT = Rey Auditory-Verbal Learning Test; II = Naming; III = Interference; IV = Flexibility; ROCF = Rey–Osterrieth Complex Figure.

[a]Maximum accuracy value calculated by the Youden Index (*y* = sensitivity + specificity – 1).

study followed 20 RBD patients for 3.6 years (mean interval: 43 months). Worsening of cognitive performance was found in 45% of patients, mainly in visuospatial abilities, and a worsening of scores on non-verbal logic (Raven Coloured Matrices) and attentional (Attentive matrices) measures was shown.[18] The most recent study followed 84 RBD patients (mean interval: 50.8 months), of whom 18 had converted at follow-up including 1 with spinocerebellar ataxia, 10 with parkinsonism first (9 PD, 1 MSA), and 7 with dementia first (4 DLB, 3 Alzheimer's disease). Only worse visual attention (Trail Making Test, part A) at baseline differentiated between patients who developed a neurodegenerative disease from disease-free patients.[19] In summary, these previous results indicate that cognition deteriorates with time in RBD patients, particularly in visual attention and visuospatial abilities. However, the small sample sizes did not allow statistical comparisons between patients who converted and those who remained disease-free,[17,18] or between conversion subtypes (dementia-first vs. parkinsonism-first patients).[19]

In this study, we showed that the cognitive deficits reported in the "idiopathic" stage of RBD were observed mainly in patients at risk of developing dementia. Cognitive tests that assess attention and executive functions are optimal for early detection of DLB in RBD patients. The RAVLT is a verbal-learning task that requires good attention and executive functions, especially for encoding and freely retrieving information that is needed for learning. Thus, good performance on this cognitive test requires good vigilance, attention, concentration, and the development of optimal strategies.[39,40] The pattern of verbal-learning deficits (reduced encoding and free retrieval) reported in our study in RBD patients is similar to that reported in PD and mild DLB patients.[41,42] Moreover, adding a visuospatial task to the neuropsychological assessment increases the predictivity for dementia in RBD patients. This is consistent with the prominent attention/executive functions and visuospatial declines that are seen early in DLB patients and in PD patients at risk of dementia.[43] Furthermore, studies have found that patients who convert to DLB show worse performance at baseline on cognitive tests measuring visuospatial functions

Table 6—Psychometric Properties of the Neuropsychological Tests for Detecting RBD Patients who Developed Dementia First Compared to Parkinsonism-First Patients.

	Dementia first	Parkinsonism first	Sensitivity (95% CI)	Specificity	Cut-off scores	AUC
Digit span (forward)	5.27 ± 1.16	6.00 ± 1.41	0.600 (0.459–0.833)	0.632	≤6	0.65
Digit span (backward)	3.73 ± 0.70	4.37 ± 1.12	0.867 (0.481–0.845)	0.368	≤5	0.66
Digit span (scaled score)	8.27 ± 1.71	9.44 ± 2.48	0.600 (0.451–0.830)	0.556	≤9	0.64
Stroop III–II, s	117.85 ± 57.59	41.15 ± 34.57	0.875 (0.683–1.00)	0.692	**≥52**	**0.86**
Stroop III–II, errors	6.15 ± 4.41	1.85 ± 3.67	0.750 (0.495–0.986)	0.846	≥4	0.74
Stroop IV–III, s	85.37 ± 80.98	20.23 ± 26.14	0.750 (0.443–0.971)	0.615	≥24	0.71
Stroop IV–III, errors	9.74 ± 7.24	1.38 ± 4.13	0.750 (0.743–1.00)	0.769	**≥3**	**0.89**
Trail Making Test A, s	73.20 ± 38.83	44.11 ± 12.39	0.750 (0.497–0.984)	0.692	≥49	0.74
Trail Making Test B, s	203.00 ± 96.37	116.05 ± 43.72	0.875 (0.669–1.00)	0.846	**≥152**	**0.85**
Trail Making Test B–A, s	119.60 ± 88.39	63.05 ± 43.53	0.875 (0.485–0.986)	0.769	≥79	0.74
Verbal fluency (semantic)	22.08 ± 8.11	30.67 ± 10.35	0.778 (0.608–0.970)	0.667	≤30	0.79
Verbal fluency (phonetic)	19.00 ± 14.26	31.27 ± 11.62	0.889 (0.537–0.988)	0.733	≤27	0.76
RAVLT, sum of trials 1–5	31.46 ± 10.01	43.79 ± 9.40	0.778 (0.558–0.997)	0.800	≤37	0.78
RAVLT, list B	3.55 ± 1.74	3.84 ± 1.71	0.400 (0.274–0.673)	0.579	≤4	0.47
RAVLT, immediate recall	4.99 ± 3.96	8.68 ± 2.73	0.889 (0.569–1.00)	0.800	≤9	0.79
RAVLT, delayed recall	5.17 ± 3.44	8.32 ± 3.40	0.778 (0.473–0.927)	0.733	≤7	0.70
RAVLT, recognition	12.60 ± 2.73	13.58 ± 1.50	0.600 (0.413–0.798)	0.579	≤14	0.61
ROCF, immediate recall	9.10 ± 4.36	17.21 ± 5.80	0.778 (0.689–1.00)	0.800	≤13	0.84
ROCF, delayed recall	9.30 ± 5.30	16.63 ± 4.96	0.889 (0.684–0.997)	0.667	≤14	0.84
ROCF, copy	25.73 ± 6.45	31.63 ± 3.08	0.778 (0.692–1.00)	0.733	**≤31**	**0.85**
Block design (scaled score)	8.22 ± 2.28	10.25 ± 2.18	0.667 (0.477–0.930)	0.533	≤10	0.70
Bells test, omissions	1.80 ± 2.20	2.00 ± 2.56	0.600 (0.247–0.719)	0.400	≥1	0.48

Data are shown as mean ± SD unless otherwise noted. Bold values = best predictors; AUC = area under the curve; CI = confidence interval; RBD = rapid eye movement sleep behavior disorder; RAVLT = Rey Auditory-Verbal Learning Test; II = Naming; III = Interference; IV = Flexibility; ROCF = Rey–Osterrieth Complex Figure.

as well as hypometabolism in the parietal and occipital regions, which are known to support visuospatial abilities.[44,45]

Our results also indicate that MCI is a strong risk factor for dementia in RBD. However, mainly due to sample size, we were unable to statistically determine which MCI subtype best predicts dementia in RBD. Although most patients with MCI had impaired attention and executive functions, we found heterogeneous MCI subtypes (single or multiple domain; amnestic or nonamnestic) in our sample. This is similar to other studies in RBD that described heterogeneous MCI subtypes, with attention/executive functions and visuospatial abilities as the main cognitive domains impaired.[18,27,46] In PD with dementia and DLB, MCI is a major risk factor for dementia, but again may present as any MCI subtype, with a profile of impaired attentional, executive, and visuospatial cognitive domains as the most common.[32,47–49] Moreover, although MCI frequency was significantly higher in our patients at risk of developing dementia first, some patients in the disease-free and parkinsonism-first groups had a MCI diagnosis at baseline. MCI progression is highly variable in both the general population and PD patients, with some patients remaining stable or returning to normal cognition.[31,32] Accordingly, we should be careful not to consider all RBD patients with MCI as having a neurodegenerative disease. Further studies are needed to better characterize the evolution of different MCI subtypes in the RBD population and to determine their phenotype and their predictive value for dementia.

The pathophysiology of cognitive impairment in RBD remains to be determined, but may be a combination of subcortical and cortical dysfunctions. Structural neuroimaging studies in idiopathic RBD found cortical thinning, gray matter changes, and white matter anomalies in frontal areas, posterior regions, the substantia nigra, and brainstem structures.[50–54] Moreover, functional neuroimaging studies in RBD found alterations in the basal ganglia network and in striatal dopaminergic transmission similar to those reported in PD.[9,55] However, these studies did not consider patients' cognitive status. Other functional neuroimaging studies have differentiated RBD patients with or without MCI. More severe and widespread EEG slowing and hypoperfusion on resting single-photon emission computerized tomography, mainly in posterior regions, was observed

in RBD patients with concomitant MCI.[56,57] These results and those of this study suggest that the pathophysiological evolution patterns of Lewy body disease differs between idiopathic RBD patients at risk of cognitive deterioration (brainstem to cortex) and those at risk of parkinsonism (brainstem to basal ganglia). This proposal is initially difficult to reconcile with the close similarity between parkinsonism-first and dementia-first patients on essentially all other disease markers,[58] and with the fact that on clinical follow-up of the parkinsonism-first patients in our cohort, the vast majority eventually developed dementia 2–5 years after diagnosis and vice versa (RP, personal communication). Perhaps this indicates that cognitive changes in prodromal dementia have a relatively short latency, unlike other predictors such as olfaction and autonomic changes.[59] Patients would therefore evolve through early prodromal stages in a similar manner, but diverge on short latency markers close to the development of a defined disease, depending on their individual vulnerability to either parkinsonism or dementia.

Some limitations of this study should be noted. First, the relatively small size of the subgroups reduced statistical power of the cognitive tests. Therefore, our ROC curves need to be replicated in a larger, multicentre-study including RBD patients and matched healthy controls. Second, we assessed only patients who sought medical attention for RBD, so the sample may not be completely representative of the heterogeneous RBD population. Third, there was a relatively short-term (3.6 years) latency between baseline and final follow-up assessment so we were generally assessing patients less than 5 years before diagnosis of dementia. As follow-up continues, we will see more patients with longer latencies between baseline assessment and development of dementia, allowing detailed assessment of the evolution of cognitive deficits in a RBD population over a longer period. Moreover, this will identify when and on which cognitive tests the performance of patients at risk of developing dementia first becomes abnormal. Despite these limitations, this study has several key strengths, most notably a standardized assessment of cognitive markers in a well-defined population, a comprehensive cognitive assessment, and a comprehensive longitudinal follow-up. These features are essential for identifying the evolution of cognitive changes in prodromal DLB.

In conclusion, cognitive impairments in idiopathic RBD predict eventual development of DLB. Tests of attention and executive functions best predict dementia, and may serve as outcome measures in future intervention trials of cognitive impairment in the RBD population. Future studies that closely follow RBD patients are needed to assess cognitive decline over years before the diagnosis of dementia, and to further examine the predictive value of neuropsychological measures for neurodegeneration in RBD.

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ETHICS COMMITTEE APPROVAL

All procedures were performed at the Centre for Advanced Research in Sleep Medicine at the Hôpital du Sacré-Coeur de Montréal (Quebec, Canada). The hospital's ethical committee approved the study, and all subjects signed a written consent before participating.

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DISCLOSURE STATEMENT

None declared.