BRIEF REPORT

The Motor Dysfunction Seen in Isolated REM Sleep Behavior Disorder

Cristina Simonet, MD, PhD,[1]
Laura Pérez-Carbonell, MD,[2]
Miquel A. Galmés-Ordinas, PhD,[3]
Brook F.R. Huxford, BSc,[1] Harneek Chohan, MSc,[1]
Aneet Gill, BSc,[1] Guy Leschziner, MD, PhD,[2]
Andrew J. Lees, FRCP, PhD,[4]
Anette Schrag, FRCP, PhD,[5] and
Alastair J. Noyce, FRCP, PhD[1*]

[1]*Centre for Preventive Neurology, Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom* [2]*Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom* [3]*Division of Cancer Therapeutics, The Institute of Cancer Research, London, United Kingdom* [4]*Reta Lila Weston Institute, Institute of Neurology, UCL and National Hospital, London, United Kingdom* [5]*Department of Clinical and Movement Neuroscience, UCL Institute of Neurology, London, United Kingdom*

ABSTRACT: Background: Isolated Rapid Eye Movement (REM) sleep Behavior Disorder (iRBD) requires quantitative tools to detect incipient Parkinson's disease (PD).

Methods: A motor battery was designed and compared with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) in people with iRBD and controls. This included two keyboard-based tests (BRadykinesia Akinesia INcoordination tap test and Distal Finger Tapping) and two dual tasking tests (walking and finger tapping).

Results: We included 33 iRBD patients and 29 controls. The iRBD group performed both keyboard-based tapping tests more slowly ($P < 0.001$, $P = 0.020$) and less rhythmically ($P < 0.001$, $P = 0.006$) than controls. Unlike controls, the iRBD group increased their walking duration ($P < 0.001$) and had a smaller amplitude ($P = 0.001$) and slower ($P = 0.007$) finger tapping with dual task. The combination of the most salient motor markers showed 90.3% sensitivity for 89.3% specificity (area under the ROC curve [AUC], 0.94), which was higher than the MDS-UPDRS-III (minus action tremor) (69.7% sensitivity, 72.4% specificity; AUC, 0.81) for detecting motor dysfunction.

Conclusion: Speed, rhythm, and dual task motor deterioration might be accurate indicators of incipient PD in iRBD. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: REM sleep behavior disorder; Parkinson's disease; bradykinesia quantitative tools

***Correspondence to:** Prof. A. J. Noyce, Centre for Preventive Neurology, Wolfson Institute of Population Health, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK; E-mail: a.noyce@qmul.ac.uk

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Isolated Rapid Eye Movement (REM) sleep Behavior Disorder (iRBD) is characterized by loss of REM atonia by video-polysomnography (v-PSG).[1] Several prospective longitudinal studies have shown that more than 80% of patients with iRBD develop an α-synucleinopathy after 10 years.[2-4] Although Parkinson's disease (PD) has been described to be the commonest final diagnosis in patients with iRBD, 43.5% patients with iRBD eventually developed dementia with Lewy bodies and 4.5% multiple system atrophy.[4]

Motor dysfunction seems to be the strongest predictive marker of PD conversion in patients with iRBD.[4] A multicenter study followed over 1000 iRBDs during 3 years.[5] Motor markers were estimated to require the lowest sample sizes to prove 50% of drug efficacy in neuroprotective clinical trials.

Clinical rating scales are widely used to follow-up "at risk" cohorts and as an outcome measure in clinical trials. However, they are not designed for use in the early stages of PD and may not be sensitive enough for subtle motor anomalies.[6] Therefore, having a precise tool for early motor dysfunction in at-risk people will have important implications when neuroprotective treatments become available.

Methods

Patients with iRBD were identified from the Sleep Clinic at Guy's Hospital.[7] All had a v-PSG confirmed iRBD. Controls were recruited from the PREDICT-PD study.[7]

Exclusion criteria included having a formal diagnosis of dementia, PD, essential tremor, motor neuron

disease, multiple sclerosis, or polyneuropathy. We included 33 patients with iRBD and 29 controls. Groups were comparable with respect to age, sex, medical comorbidities, and years of education (Supplementary Table S1).

Participants were examined according to the motor part of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III),[8] which was used to apply the criteria of Subthreshold Parkinsonism (SP) (>6 points MDS-UPDRS-III minus action tremor).[9]

Motor Battery

Our motor battery included four tests: two keyboard tapping tests (BRadykinesia Akinesia INcoordination test [BRAIN] and Distal Finger Tapping test [DFT]) and two motor tasks in isolation and under a mental task (a 10-m timed walking test and afinger tapping task) (Fig. 1).

The BRAIN[10-12] and DFT[13] tests are validated web-based keyboard tapping tests. They evaluate proximal (BRAIN) and distal (DFT) repetitive upper limb movements (see Supporting Data and Fig.S1 for more detailed information).

Participants were invited to perform the 10-m walking and finger tapping test in isolation and while doing a mental task (listing the months of the year in reverse order and subtracting "3" from "100" continuously, respectively). Finger tapping was assessed using the Slow-Motion Analysis of Repetitive Tapping (SMART) test, which is a video-based tool focused on tracking repetitive finger tapping movements following the same standardized instructions as the MDS-UPDRS-III (finger tapping-subscore) (see Supporting Data and Fig. S2 for more detailed information about the test).[14]

Statistical Analysis

Data normality was assessed using the D'Agostino test. Categorical variables were compared with Fisher's exact test. Quantitative data were compared using the Welch's test for unequal variances.

We used logistic regression and receiver operating characteristic (ROC) curves to define area under the ROC curve (AUC) values for each quantitative motor marker and the MDS-UPDRS-III.[15,16] Spearman's rank correlation was used to determine the independence of motor parameters. A multivariate logistic model was done including the most accurate parameters found to be independent in the correlation analysis. The DeLong test was used to compare ROC curves.

All statistical tests were two-tailed, and adjustments for multiple comparisons were made using the Bonferroni calculation to control for type 1 error. The significance level was set at <0.01. Data analysis used STATA v.13 (StataCorp, College Station, TX).

Ethics approval was granted by the Queen Square Research Ethics Committee (09/H0716/48). Participants consented to take part in the study.

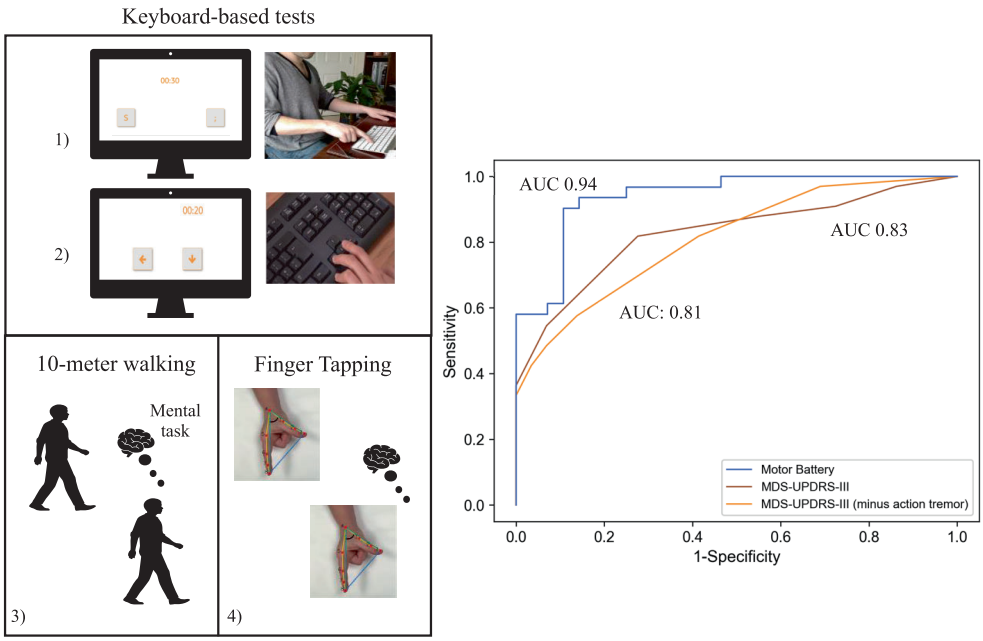

FIG. 1. Motor battery description (left). (**A**) BRadykinesia Akinesia INcoordination (BRAIN) test, (**B**) Distal Finger Tapping (DFT), (**C**) 10-m walking (timed) and under a mental task (timed), (**D**) Slow-Motion Analysis of Repetitive Tapping (SMART) test in isolation and under a mental task. Receiver operating characteristic (ROC) curves to distinguish iRBD patients from controls (right). Motor battery (blue line; AUC, 0.94), the total score of the MDS-UPDRS-III (brown line; AUC, 0.83) and the MDS-UPDRS-III minus action tremor (MDS task force criteria for subthreshold parkinsonism) (orange line; AUC, 0.81) (more details in Supplementary Table S3). AUC, area under the ROC curve; MDS-UPDRS-III; Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III; MDS, Movement Disorder Society. [Color figure can be viewed at wileyonlinelibrary.com]

Results

Both groups were comparable in terms of age (mean [standard deviation]; iRBD, 68.88 years [8.07] vs. controls, 69.65 years [7.74]; $P = 0.701$). Male predominance was present in both groups (iRBD, 30/33; control, 25/29; $P = 0.696$). There were no significant differences between groups in terms of vascular risk factors (Supplementary Table S1).

On average, individuals with iRBD scored 5 points more on the MDS-UPDRS-III than controls ($P < 0.001$) (Supplementary Table S1). In contrast with controls, 11 people with iRBD fulfilled criteria for SP. The validated criteria for SP (>6 points MDS-UPDRS-III after excluding action tremor) showed a low sensitivity (42.4%) with high specificity (96.5%) to distinguish between iRBD and controls. Decreasing the cutoff down from 6 to 3 points improved the accuracy with 69.7% sensitivity with 72.4% specificity.

Motor Battery

The overall DFT performance of iRBD was comparable between the dominant and non-dominant hand (Supplementary Table S2). In contrast, iRBDs performed the BRAIN test more slowly with the non-dominant hand. Similarly, controls performed both tests slower with their non-dominant hand (Supplementary Table S2). Considering that the non-dominant hand performance was worse in both groups, we did two separate analyses for each hand. The performance of the DFT and BRAIN test with the dominant hand can be found on the Supporting Data (Supplementary Tables S3 and S4). The overall SMART test performance (in isolation and under a mental task) of iRBD and controls was comparable between the dominant and non-dominant hand (Supplementary Tables S5 and S6). We used the non-dominant hand performance for comparison in both groups to ensure consistency across all tests.

The iRBD group performed the BRAIN and DFT tests more slowly than controls. People with iRBD tapped on average 12 keys (Kinesia Score -KS-) on the BRAIN test ($P < 0.001$) and 7 keys on the DFT ($P = 0.020$) fewer than controls. The iRBD group performed both tests more arrhythmically than controls, based on a much greater variance of traveling time between keystrokes (incoordination score [IS]) in both tests ($P < 0.001$, $P = 0.006$). Although patients with iRBD spent slightly longer dwell time on each key (akinesia score [AT]), the discrepancy between groups was not as evident as with other parameters ($P = 0.018$, $P = 0.017$). All parameters discriminated between iRBD and controls (Supplementary Tables S3 and S4). The number of alternate key taps (KS-BRAIN) and incoordination of single taps (IS-DFT) showed the best discriminatory power (KS-BRAIN: 72.7% sensitivity, 62.1% specificity; IS-DFT: 81.8% sensitivity, 69.0% specificity) (Table 1).

Walking test duration was similar when carried out in isolation ($P = 0.131$), but differed between groups when it was performed under a mental task ($P = 0.001$) (Supplementary Fig. S3). Patients with iRBD took more time to complete the test than controls ($P < 0.001$). The relative change between dual and single task duration was able to differentiate iRBD patients from controls with a 77.4% sensitivity and 72.4% specificity (Table 1).

The SMART test performance was similar in iRBD and controls when performed in isolation. Again, dual tasking unmasked motor anomalies in people with iRBD. Under a mental task, the iRBD group performed the finger tapping with a noticeable smaller amplitude ($P = 0.001$) and slower pace ($P = 0.007$) than controls. People with iRBD decreased 15% their finger tapping amplitude when performing finger tapping under a mental task, whereas controls decreased only 3% ($P = 0.008$). With dual tasking, finger tapping was more erratic (higher coefficient variation (CV) amplitude) in iRBDs who increased 54% their CV compared with 16% increase in controls ($P < 0.001$) (Supplementary Fig. S3). There was no evidence that iRBD patients slowed down their finger tapping velocity to a greater extent than controls (11% vs. 9%; $P = 0.418$). The CV of amplitude under a mental task showed the highest accuracy to distinguish iRBD patients from controls (75.8% sensitivity, 64.3% specificity) (Supplementary Table S7).

Motor Battery versus MDS-UPDRS-III

The multivariate logistic regression analysis showed that AT-DFT, finger tapping amplitude, and velocity were correlated one to each other; therefore, we did not include them in the combined analysis. The combination of the most salient motor markers (BRAIN [KS, AT, IS], DFT [KS, IS], % change in timed walking, CV amplitude under a mental task) was found to have 90.3% sensitivity and 89.3% specificity (Supplementary Table S8, Fig. 1). The motor battery offered a significantly higher accuracy than MDS-UPDRS-III (minus AT) and MDS-UPDRS-III (total score) ($P = 0.003$ and 0.012, respectively). Both the overall score (81.8% sensitivity, 72.4% specificity) and the MDS-UPDRS-III score without action tremor (69.7% sensitivity, 72.4% specificity) allowed to distinguish between iRBD and control, and between iRBD with and without SP (77.8% sensitivity, 86.4% specificity) (Supplementary Table S8). Combining MDS-UPDRS-III (finger tapping, hand opening/closing, pronation/supination hand movements, and gait) showed a reduced accuracy than taking the total score of the MDS-UPDRS-III with a 60.61% sensitivity for 75.86% specificity (AUC, 0.720; 95% CI, 0.599–0.842).

TABLE 1 *Motor battery: Group comparison and ROC analysis of salient motor markers*

	iRBD (n = 33)	Controls (n = 29)	*P*-value unpaired	*P*-value paired	Sn (%)	Sp (%)	AUC (95% CI); cutoff
BRAIN (ndh)							
KS mean (SD)	49.45 (15.19)	61.03 (9.98)	<0.001[a]	NA	72.7	62.1	0.77 (0.65–0.89); 57
AT mean (SD)	131.43 (50.56)	109.86 (25.89)	0.018[a]		60.6	55.7	0.62 (0.48–0.76); 108.9
IS median (IQR)	5354.66 (2702.75–11478.53)	2375.19 (1640.95–3874.54)	<0.001[b]		63.6	62.1	0.73 (0.60–0.85); 2903
DFT (ndh)							
KS mean (SD)	83.26 (15.76)	90.58 (11.62)	0.020[a]	NA	72.7	51.7	0.66 (0.52–0.80); 92
AT mean (SD)	110.70 (27.56)	102.64 (23.03)	0.017[a]		51.5	62.1	0.58 (0.43–0.72); 105.4
IS median (IQR)	2210.62 (1049.74–3265.58)	800.48 (329.57–1364.56)	0.006[b]		81.8	69	0.76 (0.64–0.89); 950.9
10 m-walking (single task) (s), mean (SD)	8.22 (2.52)	7.49 (0.84)	0.131[a]	NA	NA	NA	NA
10 m-walking (dual task)★ (s), mean (SD)	10.30 (4.09) (24.6% increase)	7.81 (1.42) (4.5% increase)	0.001[a]	<0.001[c] 0.146[d]	77.	72.4%	0.77 (0.65–0.89); 5.2
FT-SMART (single task)	No differences between groups				NA	NA	NA
FT-SMART (dual task)★	see Supplementary Table S7			see Supplementary Table S7			

Abbreviations: ROC, receiver operating characteristic curves; iRBD, isolated rapid eye movement (REM) sleep behavior disorder; Sn, sensitivity; Sp, specificity; AUC, area under the ROC curve; CI, confidence intervals; BRAIN, BRadykinesia Akinesia INcoordination; Ndh, non-dominant hand; KS, kinesia score; SD, standard deviation; NA, not applicable; AT, akinesia score; IS, incoordination score; IQR, interquartile range; FT, finger tapping; SMART, Slow-Motion Analysis of Repetitive Tapping.

[a]Welch's test for unequal variances.

[b]Mann-Whitney test.

[c]Paired *t* test (iRBD single vs. dual task).

[d]Paired *t* test (controls single vs. dual task).

★Sn and Sp refer to the relative change of 10-m walking and FT-SMART under mental task.

Discussion

Our study demonstrated that slow and arrhythmic movements were common findings in people with iRBD, which supports the existing literature showing that people with iRBD have motor dysfunction early in the disease process.[4,5,17-25] Moreover, dual tasking seemed to be able to unmask motor dysfunction not seen when the motor task was carried out in isolation.

Quantitative motor tools have already been found to be more accurate than standardized clinical scales,[17] probably because they are designed for use in the early stages of PD, which can explain their floor effect and insensitivity in the prodromal phase of PD.[26] Arora and colleagues[21] developed a smartphone-based set of quantitative motor assessments including tremor analysis, finger tapping, voice recording, balance, and reaction time test. Internal validation using machine learning showed that they were highly effective in discriminating between people with iRBD, PD patients, and controls. However, given that sophisticated algorithms are mathematically complex, a high discrimination accuracy of a machine learning algorithm does not necessarily denote high clinical explanatory power. In contrast, our motor battery did not require sophisticated equipment and used simple analysis methods that allow easy clinical interpretation.

Finger tapping seems to be one of the earliest clinical markers of subclinical bradykinesia in people with iRBD, which makes it an appealing biomarker of phenoconversion in PD.[27] Slow alternate tap test was found to be one of the earliest clinical signs of PD (8 years before diagnosis) with a high prediction power of conversion to parkinsonism.[28] Alternate tap test obtained relatively good sensitivity and specificity up to 3 years before diagnosis (80% sensitivity, 75% specificity) and had one of the longest prodromal intervals (8 years) in a separate longitudinal study.[29] In line with previous studies, we found that the number of alternate taps in the BRAIN test alone had a slightly higher sensitivity (73%) than the alternate tap test used by Fereshtehnejad and colleagues[28] 2 years before phenoconversion (66.7%). Similar to our video-capture finger tapping test (SMART), Krupička and collaborators[22] used a contactless system to track the finger tapping task in the MDS-UPDRS-III. They tested 40 iRBD patients and found that they had a more pronounced decrement in the amplitude of finger tapping than controls. Their test was able to distinguish iRBD from controls with 76% sensitivity and 63% specificity, which is comparable to the accuracy seen in the SMART test under a mental task (79% sensitivity and 61% specificity). Higher incoordination scores when using both keyboard-tapping tests appeared to be another common denominator in our cohort, which is in agreement with the findings from another study, suggesting that rhythm disturbances could be a potential early PD marker in iRBD.[30] The advantage of our keyboard-based tests compared to previous methods is that they can be used remotely, enabling a large scale applicability. Based on the promising results of dual tasking in finger tapping, our future research will be focused on creating a similar remote dual-tasking test.

The effect of dual tasking on unmasking motor dysfunction has mainly been studied in gait.[31] Attention may serve as a cognitive compensatory mechanism for motor dysfunction in posture control and gait.[32] During the early stages of PD it has been proposed that patients activate attention circuits to compensate for their motor dysfunction.[33,34] As disease progresses, compensatory mechanisms break down with the emergence of motor symptoms. Dual tasking might be able to disrupt these mechanisms by interrupting attention loops. The effect of dual tasking on gait has also been studied in healthy older people where no change was found.[35] In our study, both groups had similar age, but differed in terms of cognitive function. Patients with higher cognitive burden might be more susceptible to challenging conditions, which could explain the differences seen between the effect of dual tasking on motor performance (walking duration and finger tapping) in iRBD patients compared with controls. A follow-up of our cohort will be relevant to determine if individuals with iRBD more susceptible to dual tasking conditions are at a higher risk of future cognitive impairment.

Our study has some limitations. Observer bias in the MDS-UPDRS-III scoring could not be ruled out because of lack of a blinded assessment. To overcome this limitation, video recordings were independently examined by two movement disorder experts (A.J.L. and A.J.N.) who were blinded to case/control status. Given that rigidity could not be ascertained from the videos, we used rigidity scores from the in-person assessment. A difference between raters of ≥5 points on the MDS-UPDRS occurred for six of 62 subjects (9.6%). These were rescored jointly in a second round with finally reaching an agreement. Another limitation was related to the high proportion of males included (ratio 9:1), although it is recognized that iRBD tends to affect males more than females. Because of the cross-sectional nature of our study, there was a lack of information of motor changes over time. A follow-up of this group will be crucial to know which markers, if any, predict a future diagnosis of PD or other neurodegenerative disorder.

To conclude, the tests used in this study detected early markers of motor dysfunction not captured by standardized clinical scales. Slow speed and loss of rhythm in upper limb tapping, and worsening with dual tasking, might represent early motor dysfunction in iRBD.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique

C.S.: 1A, 1B, 1C, 2A, 2B, 2C. 3A, 3B
L.P.C.: 1B, 2C, 3B
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