

# Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease

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Idiopathic rapid eye movement sleep behaviour disorder is an important risk factor in the development of Parkinson's disease. Numerous potential predictive markers of Parkinson's disease may present before motor symptoms emerge, but testing of these markers in rapid eye movement sleep behaviour disorder has been performed only in small studies. There has been no comparison of markers between patients with idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease, and between men and women. We evaluated an array of potential Parkinson's disease predictive markers in 159 patients; including 68 with idiopathic rapid eye movement sleep behaviour disorder, 36 controls, 34 Parkinson's patients with rapid eye movement sleep behaviour disorder and 21 Parkinson's patients without rapid eye movement sleep behaviour disorder. Compared with controls, patients with idiopathic rapid eye movement sleep behaviour disorder demonstrated substantial olfactory loss ( $P < 0.001$ ). Olfaction was more impaired in Parkinson's disease than idiopathic rapid eye movement sleep behaviour disorder and did not differ between Parkinson's patients with, or without, rapid eye movement sleep behaviour disorder. Numerous measures of motor function including the Unified Parkinson Disease Rating Scale alternate tap, Purdue Peg Board and Timed 'Up and Go' were impaired in idiopathic rapid eye movement sleep behaviour disorder compared with controls ( $P < 0.01$ ). All of these motor measures were worse with Parkinson's disease than with idiopathic rapid eye movement sleep behaviour disorder, regardless of rapid eye movement sleep behaviour disorder status. Autonomic symptoms and systolic blood pressure drop were impaired in patients with idiopathic rapid eye movement sleep behaviour disorder compared with controls ( $P = 0.003$ ). Orthostatic abnormalities in Parkinson's disease were found in the group with rapid eye movement sleep behaviour disorder ( $P < 0.001$ ). However, Parkinson's patients without rapid eye movement sleep behaviour disorder were not different than controls and had less impairment than those with idiopathic rapid eye movement sleep behaviour disorder ( $P = 0.004$ ) and Parkinson's patients with rapid eye movement sleep behaviour disorder ( $P < 0.001$ ). Colour vision was impaired in idiopathic rapid eye movement sleep behaviour disorder compared with controls ( $P < 0.001$ ). However, only Parkinson's patients with rapid eye movement sleep behaviour disorder had abnormalities significantly different than controls ( $P < 0.001$ ), and there were significant differences between Parkinson's patients with or without rapid eye movement sleep behaviour disorder ( $P < 0.04$ ). Idiopathic rapid eye movement sleep behaviour disorder patients had slightly increased harm avoidance scores on personality

testing ( $P=0.04$ ). Other than slightly better performances among women in the Purdue Peg Board, there was no difference in any measure between men and women, suggesting similar pathogenic processes underlying rapid eye movement sleep behaviour disorder. Patients with idiopathic rapid eye movement sleep behaviour disorder demonstrate abnormalities in numerous potential markers of neurodegenerative disease—these markers are heterogeneous, generally correlate with each other and occur equally in men and women. Although these abnormalities are usually intermediate between control values and Parkinson's patients, autonomic dysfunction and colour vision appear to be more linked to rapid eye movement sleep behaviour disorder status than Parkinson's disease, suggesting a unique pathophysiology of these abnormalities.

**Keywords:** REM sleep behaviour disorder; Parkinson's disease; prediction

**Abbreviations:** FM-100 = Farnsworth–Munsell 100 Hue test; MMSE = Mini-Mental State Examination; RBD = rapid eye movement sleep behaviour disorder; UPDRS = Unified Parkinson Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test

## Introduction

Idiopathic rapid eye movement sleep behaviour disorder (RBD) is characterized by loss of the normal atonia that accompanies rapid eye movement sleep. Consequently, patients may talk, gesture, punch or kick in association with dream content (Schenck *et al.*, 1987). Approximately 80%–90% of patients are male and the reasons for this striking sex difference are unclear. Recent studies have documented that patients with RBD are at substantial risk of developing neurodegenerative disease, in particular Parkinson's disease and Lewy body dementia, with risk estimates ranging from 20% to 45% at 5 years (Schenck *et al.*, 1996; Iranzo *et al.*, 2006; Postuma *et al.*, 2009), and 40% to 65% at 10 years (Schenck and Mahowald, 2003; Iranzo *et al.*, 2008; Postuma *et al.*, 2009).

Patients with Parkinson's disease have numerous abnormalities other than those in the motor system. These include depression, anxiety, personality changes, olfactory loss, visual changes, cognitive decline and autonomic abnormalities (Chaudhuri *et al.*, 2006). Many of these abnormalities are found early in the disease course, and patients often report that symptoms were present before the onset of motor manifestations. However, because of difficulties in identifying pre-motor stages of Parkinson's disease, direct testing of these potential predictive markers has been limited (Hawkes, 2008).

Since patients with RBD are at risk of developing Parkinson's disease, we hypothesized that many of these potential early Parkinson's disease markers would be present in patients with idiopathic RBD. In 2006, we reported the results of a small case–control study that documented substantial abnormalities of olfaction, colour vision, autonomic function and motor function in patients with idiopathic RBD. Since 2006, we have nearly tripled the size of this cohort and can now examine these markers in more detail and with increased statistical power. In addition, the cohort size now allows assessment for differences in these markers between men and women. Finally, completion of a similar protocol in patients with established Parkinson's disease (Postuma *et al.*, 2008a, b) allows direct comparison of these features between patients with idiopathic RBD and those with Parkinson's disease either with or without RBD.

## Materials and methods

### Subjects

Patients with RBD were recruited from the sleep disorders laboratory at the Hôpital du Sacré Coeur, Montreal, Quebec. Ethics approval was obtained from the research ethics board of the hospital and all patients gave informed consent to participate according to the Declaration of Helsinki. The presence of RBD was defined according to standard International Classification of Sleep Disorders-II criteria; as an increase of tonic or phasic chin EMG activity during rapid eye movement sleep (Lapierre and Montplaisir, 1992), and either history of elaborate motor activity during sleep associated with dream content, or the presence of behavioural manifestations occurring during rapid eye movement sleep during polysomnographic recording. Controls were selected from the general population and were frequency-matched for age and gender. All controls had polysomnography documenting the absence of RBD. Duration of RBD symptoms was calculated from patient self-report, and duration of objective RBD was defined based upon the date of polysomnogram. To compare idiopathic RBD with RBD in the presence of Parkinson's disease, 55 subjects with idiopathic Parkinson's disease were selected—all Parkinson's patients met UK brain bank criteria for the diagnosis of Parkinson's disease (Hughes *et al.*, 1992). They completed an evaluation protocol similar to the protocol for idiopathic RBD. Thirty-six of these Parkinson's patients were part of a recently published report (Postuma *et al.*, 2008a, b). Patients with dementia [defined as significant impairment on at least two cognitive domains (executive functions and attention, verbal learning and memory, or visuo-spatial abilities) on neuropsychological testing in association with functional impairment due to cognitive impairment] were excluded.

### Procedures

All test procedures were performed identically in patients and controls, as previously described (Postuma *et al.*, 2006). All evaluations were performed by a movement disorders specialist (RP); and for Parkinson's patients, this was blinded to results of polysomnography (the examiner was not blinded to RBD status for controls and idiopathic RBD patients). Variables that could be tested simply and in a clinical office setting were selected, as these would be of most potential practical use in future large-scale diagnostic evaluations. For Parkinson's patients, all evaluations were determined in the medication 'on' condition. All participants underwent a systematic medical history

and a complete neurological examination that included the Unified Parkinson Disease Rating Scale (UPDRS) Parts II and III (Fahn *et al.*, 1987). Three additional quantitative motor indices were used. The first was the alternate tap test, chosen as a test of motor speed in the hands with a moderate requirement of co-ordination and accuracy (Nutt *et al.*, 2000). Subjects were given 1 min to quickly tap two alternating, 2.5 cm diameter metal discs attached to a manual counter, mounted 20 cm apart. The total number of taps in both counters at the end of 1 min was the outcome measure. The second index was the Purdue Peg Board, a test of hand dexterity, motor speed and finger-eye coordination (Desrosiers *et al.*, 1995). Subjects were given 30 s to transfer a series of pins from a dish, one at a time into corresponding holes. This was performed separately in each hand, and the average number of pins placed was used as the outcome measure. The third index was a Timed 'Up and Go' test, which is a measure of gait and transfer speed (Podsiadlo and Richardson, 1991). Subjects were instructed to rise quickly from a chair, walk 3 m, turn and return to sit on the same chair. Two trials were performed and the average of these two trials was the outcome measure.

Odour discrimination was assessed in idiopathic RBD patients and controls with the brief University of Pennsylvania Smell Identification Test (UPSIT) (Doty *et al.*, 1984). This test consists of 12 'scratch and sniff' pads which release an odour when scratched with a pencil and patients choose the correct odour from four options. The Parkinson's disease cohort underwent the full 40 item UPSIT; therefore, to allow comparison between groups, each individual's UPSIT values were transformed into percent expected value for age and sex based upon normative data (Doty, 1995; Doty *et al.*, 1996). Colour vision testing was performed using the Farnsworth–Munsell 100 Hue test (FM-100; Farnsworth, 1943). This test consists of 85 coloured discs, which span the colour spectrum. The discs are scrambled and subjects are instructed to place the discs in the correct order. The total error score was calculated based upon the degree of deviation from the correct placement. No time limit was imposed, to prevent confounding due to subtle motor or cognitive impairment. Patients with corrected visual acuity <20/100, congenital colour blindness, or untreated cataracts affecting vision were excluded from analysis of colour vision—under these criteria, one RBD patient with congenital colour blindness was eliminated from colour vision analysis.

Symptoms of autonomic dysfunction were assessed with a structured clinical interview, in which orthostatic symptoms, urinary dysfunction, constipation, and erectile dysfunction were graded on a four-point scale, based upon the Multiple System Atrophy rating scale (Wenning *et al.*, 2004). The scale is graded so that a score of 0 indicates no dysfunction, whereas a score of 4 indicates very severe impairment. Blood pressure was measured in the supine position and after standing for one minute, and the orthostatic systolic blood pressure drop was calculated.

Personality measures were assessed with the tridimensional personality questionnaire (Cloninger, 1987). This questionnaire consists of 240 questions, which are divided into four major components: novelty seeking, harm avoidance, reward dependence and persistence. It has been designed as a test of personality variables that are considered to be at least partly biologically determined. Reduction in novelty seeking has been reported in patients with Parkinson's disease (Menza *et al.*, 1993). For global cognitive functioning, the Folstein Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) was performed.

## Analysis

Comparison of idiopathic RBD to controls, and Parkinson's patients with or without RBD, was performed with one-way analysis of variance. Post-

hoc significance was assessed with the Fisher least-squares difference. Correlations between variables were assessed using simple univariate linear regression to correlate estimates of motor function (alternate tap test and UPDRS Part III), vision (FM-100), olfaction (UPSIT-12), systolic blood pressure drop, and cognition (MMSE). For comparison of men to women categorical variables were compared using Fisher's exact test and continuous variables were compared with unpaired student *t*-test. Analysis was computed using Statistical Package for the Social Sciences version 17 statistical software (SPSS, Chicago, IL, USA).

## Results

A total of 68 idiopathic RBD patients (mean symptom duration =  $9.3 \pm 1.1$  years), 36 controls who were age and sex-matched to the idiopathic RBD group, 34 Parkinson's patients with RBD, and 21 Parkinson's patients without RBD were evaluated. Demographic information is presented in Table 1.

### Potential neurodegenerative markers in patients with idiopathic RBD versus controls

Results of testing for all predictive markers is shown for idiopathic RBD patients and controls in Table 1 and Figs 1 and 2. Compared with controls, idiopathic RBD patients demonstrated substantial and significant impairment of olfaction (mean UPSIT =  $7.0 \pm 0.33$  versus  $10.0 \pm 0.31$ ,  $P < 0.001$ ). Colour vision was also substantially impaired (mean FM-100 =  $174.6 \pm 12.5$  versus  $94.5 \pm 11.6$ ,  $P < 0.001$ ). Findings on special senses were heterogeneous; many RBD patients had severe abnormalities whereas some scored in the normal range. Tests of motor symptoms and signs also demonstrated significant differences between patients and controls in all measures; in general these differences were less striking than for special sensory measures. Systolic blood pressure drop was significantly different between RBD patients and controls (mean =  $15.2 \pm 2.1$  versus  $3.7 \pm 2.4$ ,  $P = 0.003$ ); however, most patients with systolic drop did not endorse orthostatic symptoms, and orthostatic symptom scores were not different than controls. All other autonomic symptom scores (constipation, erectile function and urinary function) were worse in RBD patients than controls. RBD patients demonstrated a slight increase in the 'harm avoidance' subscore of the tridimensional personality questionnaire (mean =  $95.6 \pm 2.8$  versus  $85.2 \pm 4.1$ ,  $P = 0.043$ ). Novelty seeking (the subscore previously described as decreased in Parkinson's patients) did not differ between patients and controls, and neither did the 'reward dependence' and 'persistence' subscales. MMSE was worse in RBD patients than in controls ( $P = 0.009$ ) full cognitive assessment results have been published elsewhere (Massicotte-Marquez *et al.*, 2008). RBD patients <50 years generally tested normally on all measures.

### Idiopathic RBD compared with Parkinson's disease with or without RBD

In comparing idiopathic RBD to Parkinson's patients with or without RBD, there were no differences in age or sex distribution

**Table 1** Features in idiopathic RBD, Parkinson's disease with RBD, Parkinson's disease without RBD and controls

	Controls (n=36), A	Idiopathic RBD (n=68), B	PD-RBD (n=34), C	PD-NRBD (n=21), D	P	Post-hoc significance (LSD)
Age	65.8 (46–87)	68.0 (44–93)	68.8 (49–94)	69.8 (49–83)	0.511	N/A
Sex	28/8 (77.8%)	53/15 (78%)	28/6 (82%)	13/8 (62%)	0.365	N/A
Special senses						
Olfaction (% normal)	99.3 ± 2.8	69.7 ± 3.1	48.1 ± 3.3	51.1 ± 3.5	<0.001	A>B***, A>C***, A>D***, B>C***, B>D*
Colour vision (FM-100)	94.5 ± 11.6	174.6 ± 12.5	193.1 ± 4.9	124.9 ± 4.6	<0.001	A<B***, A<C***, C>D*
Motor function						
UPDRS II	0.35 ± 0.13	2.1 ± 0.28	10.1 ± 1.4	11.3 ± 0.98	<0.001	A<B*, A<C***, A<D***, B<C***, B<D***,
UPDRS III	2.70 ± 0.50	5.8 ± 0.64	23.7 ± 2.1	20.5 ± 2.5	<0.001	A<C***, A<D***, B<C***, B<D***,
Timed 'Up and Go'	6.1 ± 0.19	7.1 ± 0.24	8.6 ± 0.61	7.8 ± 0.46	<0.001	A<B*, A<C***, A<D*, B<C**,
Alternate tap test	195.0 ± 5.3	172.4 ± 4.4	141.4 ± 5.3	155.2 ± 6.4	<0.001	A>B***, A>C***, A>D***, B>C***, B>D**,
Purdue Peg Board	12.1 ± 0.42	10.6 ± 0.27	8.1 ± 0.41	9.4 ± 0.60	<0.001	A>B***, A>C***, A>D***, B>C*, B>D***
Autonomic function						
Systolic blood pressure drop	3.7 ± 2.4	15.2 ± 2.1	23.7 ± 2.1	4.4 ± 3.0	<0.001	A<B**, A<C***, B<C**, B>D**, C>D***
Orthostatic symptoms	0.17 ± 0.098	0.26 ± 0.058	0.88 ± 0.13	0.52 ± 0.20	0.005	A<C***, B<C***, C>D*,
Urinary symptoms	0.04 ± 0.042	0.36 ± 0.073	0.71 ± 0.18	0.40 ± 0.14	0.001	A<C***, B<C*, C>D*,
Erectile symptoms	0.40 ± 0.19	1.60 ± 0.20	2.1 ± 0.25	2.2 ± 0.45	<0.001	A<B**, A<C***, A<D***
Constipation symptoms	0.13 ± 0.092	0.73 ± 0.11	1.1 ± 0.15	1.1 ± 0.22	<0.001	A<B**, A<C***, A<D***, B<C*
Cognition						
MMSE	29.2 ± 0.30	28.0 ± 0.26	28.4 ± 0.24	29.1 ± 0.22	0.014	A>B**, B<D**
Personality						
TPQ novelty	97.3 ± 3.9	92.7 ± 2.0	N/A	N/A	0.25	N/A
TPQ harm avoidance	85.2 ± 4.1	95.2 ± 2.8	N/A	N/A	0.043	N/A
TPQ reward dependence	98.6 ± 3.4	95.3 ± 2.0	N/A	N/A	0.47	N/A
TPQ persistence	117.7 ± 4.9	120.4 ± 2.6	N/A	N/A	0.61	N/A

Results are presented as mean ± standard error. N/A = not applicable; PD-RBD = Parkinson's disease with RBD; PD-NRBD = Parkinson's disease without RBD; TPQ = Tridimensional Personality Questionnaire. Bold values indicate statistically significant values.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

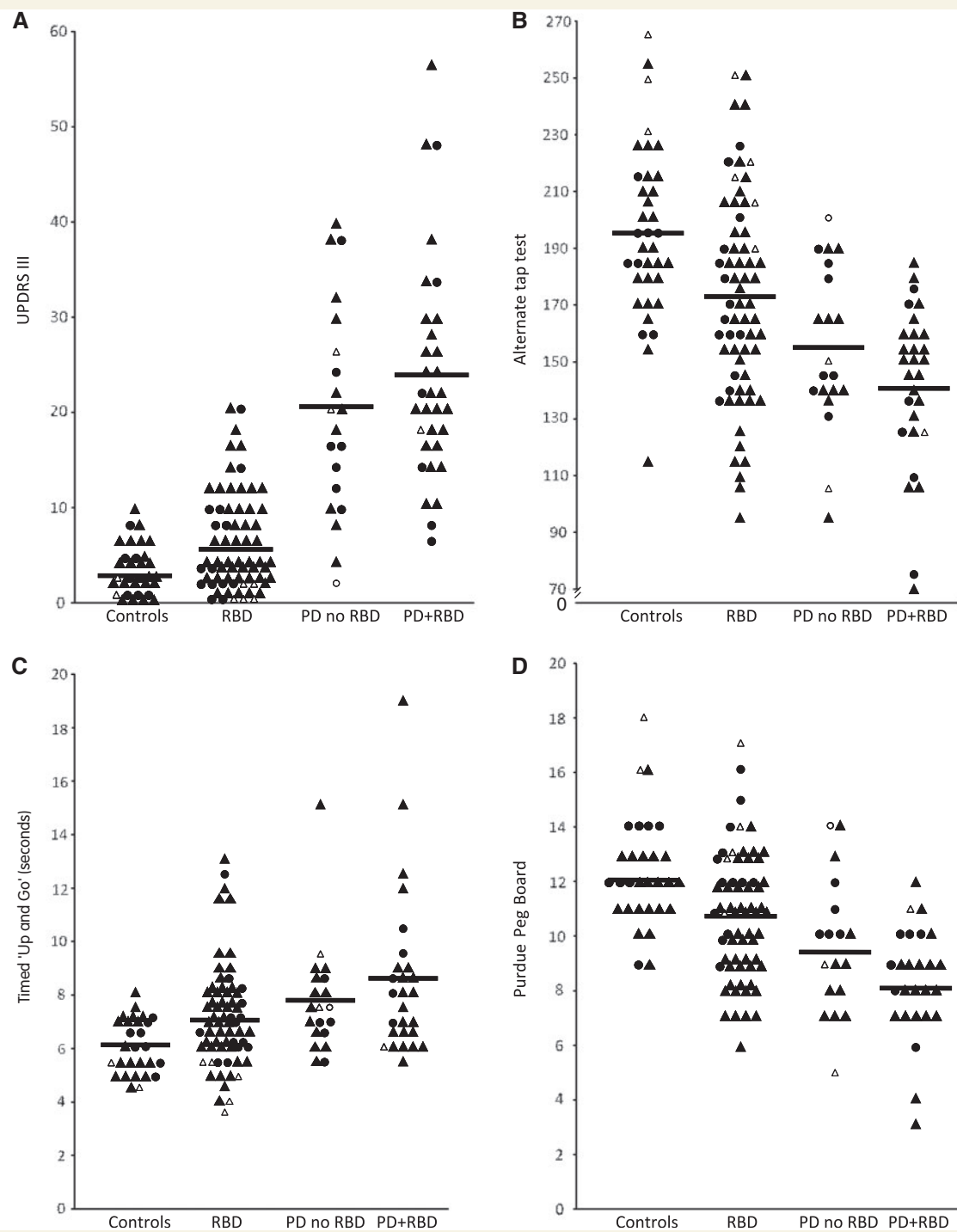
according to group. Most measures demonstrated more abnormalities among patients with Parkinson's disease than in idiopathic RBD. All measures of motor function were worse in Parkinson's disease than in idiopathic RBD, regardless of whether the Parkinson's disease was associated with RBD—there were significant differences in UPDRS parts II and III, the alternate tap test, Purdue Peg Board, and Timed 'Up and Go' between both groups of Parkinson's patients compared with both idiopathic RBD patients and controls. Differences between Parkinson's disease and idiopathic RBD seemed more pronounced in UPDRS III than in other measures. There were no significant differences in motor measures between Parkinson's patients with or without RBD. Similar findings were found for olfaction, erectile dysfunction and constipation.

On the other hand, certain features were more associated with RBD than with the presence of Parkinson's disease. When compared with controls, systolic blood pressure drop was increased in both idiopathic RBD and Parkinson's disease with RBD (mean = 15.2 ± 2.1 and 23.7 ± 2.1 versus 4.4 ± 3.0,  $P < 0.001$ ), but in the absence of RBD, there was no association between Parkinson's disease and blood pressure drop (mean = 3.7 ± 2.4),

and there were significant differences between Parkinson's patients with or without RBD ( $P < 0.001$ ). A similar pattern, although less striking, was present for colour vision testing (Table 1). Colour vision was worse than controls in patients with idiopathic RBD ( $P < 0.001$ ) and Parkinson's disease with RBD ( $P < 0.001$ ), but there was no significant decrease in Parkinson's patients without RBD. Parkinson's patients without RBD had significantly better colour vision than those with ( $P = 0.04$ ).

## Correlations between potential neurodegenerative markers in idiopathic RBD

Since potential predictive markers were variable among idiopathic RBD patients (i.e. some scoring normally whereas others were severely impaired), we examined whether abnormalities on different domains were correlated. We found significant correlations between many, but not all, potential markers of neurodegeneration (Table 2). Olfaction, colour vision, motor function and

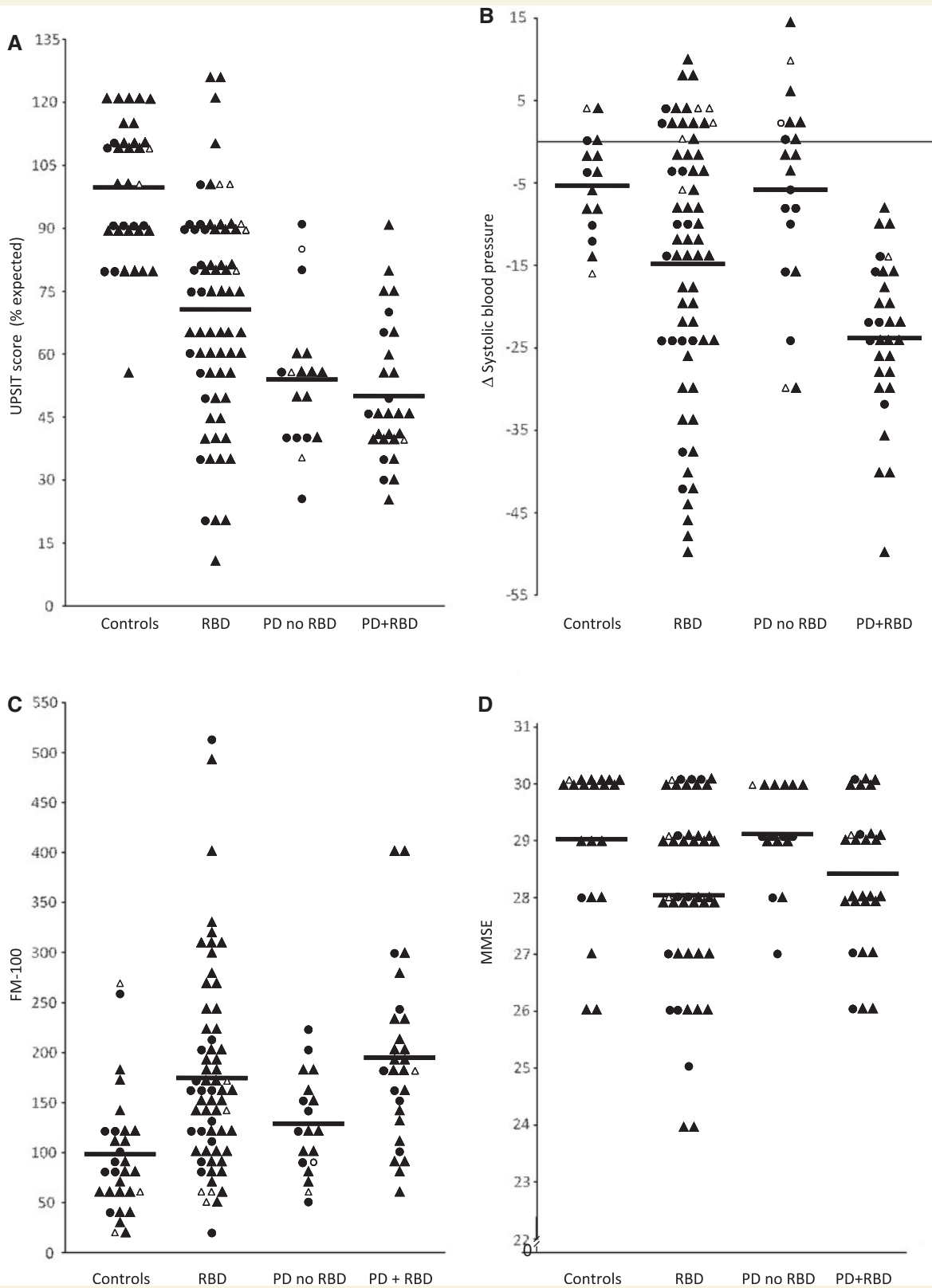


**Figure 1** Quantitative motor measures in normal controls, patients with idiopathic RBD and Parkinson's patients with or without RBD. Horizontal bar indicates the mean value for group. Black triangle = males  $\geq 50$  years; open triangle = males  $< 50$  years; filled circle = females  $\geq 50$  years; open circle = females  $< 50$  years.

cognition were all significantly correlated with each other, such that abnormalities on one domain predicted abnormal results on the other. However, systolic blood pressure drop was correlated only with olfaction and alternate tap test, and there were no significant correlations between blood pressure drop, colour vision, UPDRS and MMSE.

## Sex differences in idiopathic RBD patients

Given the striking difference in RBD occurrence among men and women, we examined whether there were any differences in motor and non-motor characteristics according to sex (Table 3).



**Figure 2** Quantitative non-motor measures in normal controls, patients with idiopathic RBD and Parkinson's patients with or without RBD. Horizontal bar indicates mean value for group. Black triangle = males  $\geq 50$  years; open triangle = males  $< 50$  years; filled circle = females  $\geq 50$  years; open circle = females  $< 50$  years.

**Table 2** Correlations between variables in idiopathic RBD patients

	MMSE	Systolic blood pressure drop	Alternate tap test (motor)	UPDRS III (motor)	FM-100 (vision)
UPSIT (olfaction)	<b>0.33/0.11 (0.01)</b>	<b>-0.38/0.15 (0.002)</b>	<b>0.49/0.24 (&lt;0.001)</b>	<b>-0.50/0.25 (&lt;0.001)</b>	<b>-0.49/0.24 (&lt;0.001)</b>
FM-100 (vision)	<b>-0.53/0.28 (&lt;0.001)</b>	0.17/0.03 (0.17)	<b>-0.50/0.25 (&lt;0.001)</b>	<b>0.45/0.21 (&lt;0.001)</b>	
UPDRS III (motor)	<b>-0.37/0.14 (0.017)</b>	0.14/0.02 (0.27)	<b>-0.62/0.38 (&lt;0.001)</b>		
Alternate tap test (motor)	<b>0.32/0.11 (0.04)</b>	<b>-0.31/0.09 (0.01)</b>			
Systolic blood pressure drop	-0.08/0.00 (0.61)				

Results are presented as ' $R/R^2$  ( $P$  value)'. Note that negativity/positivity of  $R$  depends upon the nature of the variable (higher values for some indicate worse function whereas for others higher values indicate better function). However, for all variables significantly correlated, the direction of the correlation was such that more impairment on one variable was correlated with more impairment on the second. Bold values indicate statistically significant values.

**Table 3** Potential neurodegenerative markers in women with idiopathic RBD compared with men

	Men (n = 53)	Women (n = 15)	P-Value
Age	67.3 ± 1.5	70.8 ± 2.1	0.27
Duration of RBD symptoms	9.6 ± 1.3	8.2 ± 1.6	0.61
Duration since polysomnogram	2.8 ± 0.47	2.4 ± 0.77	0.59
Special senses			
Olfaction (UPSIT-12)	6.9 ± 0.38	7.3 ± 0.65	0.71
Colour vision (FM-100)	178.9 ± 13.7	159.4 ± 30.1	0.54
Motor function			
UPDRS II	2.2 ± 0.32	1.8 ± 0.58	0.63
UPDRS III	5.8 ± 0.71	5.9 ± 1.5	0.95
Timed 'Up and Go'	7.1 ± 0.28	7.1 ± 0.48	1.0
Alternate tap test	171.8 ± 5.3	174.4 ± 7.4	0.82
Purdue Peg Board	10.3 ± 0.30	12.0 ± 0.54	<b>0.019</b>
Autonomic function			
Systolic blood pressure drop	15.3 ± 2.4	14.9 ± 3.9	0.94
Orthostatic symptoms	0.28 ± 0.068	0.20 ± 0.107	0.40
Urinary symptoms	0.32 ± 0.080	0.53 ± 0.17	0.24
Erectile symptoms	1.6 ± 0.20	N/A	N/A
Constipation symptoms	0.65 ± 0.13	1.0 ± 0.24	0.22
Cognition			
MMSE	28.1 ± 0.29	27.9 ± 0.59	0.76
Personality/psychiatric			
TPQ novelty seeking	91.7 ± 2.6	95.0 ± 2.8	0.55
TPQ harm avoidance	94.2 ± 3.6	98.9 ± 4.4	0.54
TPQ reward dependence	93.0 ± 2.0	100.6 ± 4.4	0.10
TPQ persistence	121.3 ± 3.2	118.3 ± 4.7	0.67

Results are presented as mean ± standard error. N/A = not applicable. Bold values indicate statistically significant values.

We found no difference in age or duration of RBD between men and women. Neither were there differences in any measure of autonomic function, olfaction, colour vision, cognition or personality. All motor measures were the same with the exception of the Purdue Peg Board, in which women demonstrated slightly better performance (mean = 12.0 ± 0.54 pegs versus 10.3 ± 0.30,  $P = 0.019$ ).

## Discussion

This study describes the largest cohort of RBD patients for whom complete neurologic examination and testing of ancillary measures of neurodegeneration were performed. We describe here four principal findings:

- (1) Expanding upon our initial study of 25 patients (Postuma *et al.*, 2006), we find numerous potential predictive markers of Parkinson's disease in patients with idiopathic RBD. These are heterogeneously distributed and some RBD patients are completely normal on all variables.
- (2) Most predictive markers in idiopathic RBD are correlated with each other, such that abnormalities on one domain are associated with other abnormalities. Autonomic dysfunction, however, is not generally correlated with other markers.
- (3) For most predictive markers, RBD patients show intermediate values between controls and Parkinson's patients. However, systolic blood pressure drop, MMSE, and colour vision are more linked to the presence of RBD than Parkinson's disease, with statistically significant differences in these markers among Parkinson's patients with or without RBD.
- (4) Despite the striking difference in RBD occurrence, there were no differences in potential Parkinson's disease markers in men and women.

## Potential predictive markers in idiopathic RBD

We have found evidence of numerous potential predictive markers of Parkinson's disease in patients with idiopathic RBD. These include substantial, although heterogeneous, abnormalities of olfaction, colour vision and motor function. This finding suggests that these markers may predict the development of a clinically defined neurodegenerative syndrome, although prospective studies (currently underway) will be required to confirm this.

The increased statistical power associated with this larger cohort has now allowed detection of statistically significant increases in 'harm-avoidance' personality characteristics. Evidence for a specific premorbid personality in Parkinson's disease is slowly accumulating (Menza *et al.*, 1993; Evans *et al.*, 2006; Ishihara and

Brayne, 2006). The 'typical Parkinson's personality' is often characterized as introverted, sober, reliable, responsible and inflexible; retrospective analyses suggest that these characteristics are life-long. Following the report of Menza *et al.* (1993) that described specific changes in personality testing on the tridimensional personality questionnaire, we used the same questionnaire, and found a different profile in RBD patients compared with controls. Whereas Parkinson's patients were described as having reduced novelty seeking, we found only a weak trend towards reduced novelty seeking, but we did find increased harm avoidance. Harm avoidance and novelty seeking are related constructs, so it is possible that both groups have similar characteristics. The predictive value of these personality changes is unclear – differences were small between patients and controls, so it is unlikely that assessment of personality will be able to add much information to estimating risk of neurodegeneration in idiopathic RBD. This will be directly assessed as this cohort continues to be followed.

## Correlation between variables in idiopathic RBD

In our previous report, we had noted the presence of substantial correlation between markers of neurodegenerative disease, such that the cohort could be divided into a group that tested normally on most markers, and a group that was abnormal on most markers. In this much larger cohort, we have confirmed these previous findings and were able to expand the range of correlations tested. We have found that measures of motor function, olfaction, colour vision, and cognition are highly correlated with each other, but that measures of autonomic function are not (despite being significantly different than control values). This may suggest that autonomic dysfunction has a pathophysiologic difference from other markers. Of interest, a recent report found abnormalities of cardiac sympathetic innervations in 100% of RBD patients (Miyamoto *et al.*, 2006), which is in striking contrast to the potential neurodegenerative markers in our study, which were heterogeneously distributed. It is possible that autonomic function will be less predictive of eventual neurodegeneration than the other markers; however, this will only be determined in prospective studies.

## Comparison of idiopathic RBD and Parkinson's disease

Due to a similar protocol being performed in patients with Parkinson's disease, we were able to assess the differences in potential predictive Parkinson's disease markers in patients with idiopathic RBD and Parkinson's disease. If abnormalities progress with time, or if the idiopathic RBD group consists of a mixture of those in preclinical stages of Parkinson's disease and those who may have an alternate cause, one would expect mean values in RBD to be intermediate between controls and Parkinson's patients. Accordingly many measures, particularly motor measures and olfaction, were worse in patients with Parkinson's disease than in those with idiopathic RBD. On the other hand, systolic blood pressure drop and colour vision loss were less dependent upon

Parkinson's disease status – rather, they were closely tied to the presence of RBD. Given that these differences are highly statistically significant ( $P$ -value for blood pressure  $<0.001$ ), it is very unlikely that this is a chance finding. There are several potential explanations for this intriguing result. Firstly, these markers could be more severely affected in preclinical Lewy body dementia – this may explain the colour vision result, as we had informally noted that some patients made strategic errors in performing the FM-100, particularly in correcting errors once tiles had been placed. Secondly, abnormalities of these markers (especially autonomic dysfunction) may be an essential substrate for generation of RBD, perhaps by alteration of dream content or arousal systems. A report finding RBD in Guillain–Barre syndrome (Cohen *et al.*, 2005), a peripheral nervous system abnormality with frequent autonomic involvement, may support this notion. Thirdly, there is substantial evidence that Parkinson's disease is heterogeneous (Lewis *et al.*, 2005; Halliday *et al.*, 2008) – perhaps Parkinson's disease is not a single disease, but consists for example, of a mixture between a 'pure' substantia nigra pathologic Parkinson's disease and a relatively 'diffuse' Parkinson's disease, with only the latter having association with RBD and autonomic dysfunction.

## Sex differences in RBD

One of the puzzling features of RBD is its striking male predominance, with 80%–90% patients being male in all cohort studies (Schenck *et al.*, 1987; Stiasny-Kolster *et al.*, 2005; Iranzo *et al.*, 2006; Postuma *et al.*, 2009). This may be partially due to different likelihood of clinical presentation. For example, if women tend to have less violent behaviours in dreams, they may not present for medical advice. Also, because of sex differences in mortality, elderly women are more likely to sleep alone, and so may be unaware of symptoms. On the other hand, there are biological differences in neurodegenerative patterns between men and women—for example, the incidence of Parkinson's disease is clearly increased in men (de Lau and Breteler, 2006). The size of our cohort allowed us to examine, for the first time, differences in neurodegenerative markers in men and women. We found no differences between men and women in autonomic, olfactory, visual, cognitive or psychiatric manifestations of RBD. The only motor difference was a slight increased speed in performance of the Purdue Peg Board. However, this difference may reflect normal baseline differences in function, as normative studies consistently show better Peg Board performance in women [e.g. among young persons applying for factory jobs, the median peg number was 15 for men, and 18.7 for women (Lafayette Instruments, 2009)]. We have also previously found no difference in risk of progression to neurodegeneration in men compared with women (Postuma *et al.*, 2009). Therefore, although RBD is more common in men, the ancillary features (and therefore perhaps the pathogenesis) of the disorder appear to be largely similar in both sexes.

There are some limitations of this study. The breadth of our examination precluded detailed examination of any one feature – formal autonomic testing (e.g. electrocardiogram analysis of QT interval and beat-to-beat variability, tilt table testing), more extensive visual testing (e.g. contrast sensitivity, retinal



tomography), and functional imaging studies (e.g. dopaminergic imaging, whole brain glucose utilization studies) would be of considerable interest in future studies and would help to confirm our results. Although our study is relatively large, power to assess subgroups would be limited—for example, it would be of interest to compare young-onset versus older-onset patients in detail. We assessed numerous outcomes and, as this was an exploratory analysis, there were no adjustments for multiple comparisons (Bender and Lange, 2001), therefore, some of our positive findings could be due to chance. Finally, our evaluation was a single baseline evaluation – definitive proof of the utility of predictive markers of Parkinson's disease in RBD patients awaits prospective studies, which are ongoing.

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