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Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study

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Parkinson's disease has a long prodromal stage with various subclinical motor and non-motor manifestations; however, their evolution in the years before Parkinson's disease is diagnosed is unclear. We traced the evolution of early motor and non-motor manifestations of synucleinopathy from the stage of idiopathic rapid eye movement (REM) sleep behaviour disorder until defined neurodegenerative disease. During 2004–16, we recruited and then annually followed 154 polysomnography-proven patients with idiopathic REM sleep behaviour disorder, of whom 55 phenoconverted to defined parkinsonism or dementia. Longitudinal data on multiple prodromal features, including the Unified Parkinson's Disease Rating Scale parts I–III, quantitative motor tests, olfaction, colour vision, cognition, and autonomic functions were gathered annually (average = five follow-up visits, range: 2–12 years). The same measures were also assessed in 102 age- and sex-matched healthy control subjects. By looking backward from the time of dementia or parkinsonism diagnosis, we examined trajectories of each prodromal feature using mixed effect models. Based on analysis, olfactory loss was first to develop, with predicted onset >20 years before phenoconversion. This was followed by impaired colour vision, constipation, and erectile dysfunction, starting 10–16 years prior to phenoconversion. At 7–9 years before phenoconversion, slight urinary dysfunction and subtle cognitive decline could be detected. Among motor symptoms altered handwriting, turning in bed, walking, salivation, speech, and facial expression began to be disrupted starting 7–11 years prior to parkinsonism diagnosis, but remained mild until soon before phenoconversion. Motor examination abnormalities began 5–7 years before phenoconversion, with the alternate tap test having the longest interval (8 years before phenoconversion). Among cardinal motor phenotypes, bradykinesia appeared first, ~5–6 years prior to phenoconversion, followed by rigidity (Year –3) and tremor (Year –2). With direct prospective evaluation of an idiopathic REM sleep behaviour disorder cohort during phenoconversion, we documented an evolution of prodromal manifestations similar to that predicted by pathological staging models, with predicted prodromal intervals as long as 20 years.

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Abbreviations: DLB = dementia with Lewy bodies; iRBD = idiopathic REM sleep behaviour disorder; MoCA = Montreal Cognitive Assessment; MSA = multiple system atrophy; REM = rapid eye movement; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Parkinson's disease is a common neurodegenerative disorder with a broad range of motor and non-motor features. Although formally defined by motor parkinsonism, a prodromal stage precedes the clinical diagnosis for decades before (Berg *et al.*, 2015). The prodromal phase of Parkinson's disease has not only mild motor disturbances, but also non-motor aspects such as olfactory dysfunction, constipation, dysautonomia, and sleep disorders (Berg *et al.*, 2015). This is consistent with staging models in which Parkinson's disease pathology gradually progresses from olfactory tracts, peripheral autonomic neurons and lower brainstem before affecting the substantia nigra (Braak *et al.*, 2003; Adler and Beach, 2016). Of note, the long prodromal stage of Parkinson's disease provides a unique opportunity to provide disease modifying treatment earlier.

Despite considerable advances, the natural history of how the various manifestations evolve throughout the prodromal stages remains unclear. There have been a few attempts to trace evolution of prodromal Parkinson's disease, most notably in case-control studies nested in large population-based ageing cohorts (Darweesh *et al.*, 2017*a*, *b*). However, any population-based study's large sample size produces limits on the depth of variables that can be assessed. Having a cohort at very high risk of neurodegeneration would allow deeper phenotyping over longer time periods.

Since 2004, we have prospectively followed a cohort of patients with idiopathic rapid eye movement (REM) sleep behaviour disorder (iRBD), which is the strongest prodromal marker for neurodegenerative synucleinopathy (Berg *et al.*, 2015). In this study we assessed a broad panel of non-motor and motor features and tests, measured repeatedly each year. This allowed us to directly observe the trajectories of prodromal neurodegeneration. Previously, we had reported early findings focusing on evolution of motor manifestations, olfaction, colour vision, cognition, and autonomic manifestations gathered over 5–7 years in a smaller sample (Postuma *et al.*, 2011*b*, 2012, 2013; Genier Marchand *et al.*, 2018). Here we investigated the combined trajectories of a broad range of prodromal motor and non-motor manifestations of synucleinopathies, tracing backwards from the time of phenoconversion, using statistical modelling to illustrate a holistic picture of the evolutionary timeline of motor and non-motor features of Parkinson's disease. Specifically, we assessed: (i) how different markers evolved over time, and when each marker began to deviate from normal control values; (ii) how progression trends of prodromal markers might differ between those who developed a primary parkinsonism (Parkinson's disease) versus a dementia-first [dementia with Lewy bodies (DLB)] phenoconversion; and (iii) at what time point, and with what sensitivity or specificity could individual prodromal features identify a given individual with prodromal synucleinopathy.

Materials and methods

Participants

In this longitudinal study, 154 participants with idiopathic REM sleep behaviour disorder were recruited from the Centre for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, Canada from 2004 to 2016 (of these, eight have died before phenoconversion and eight others were lost to follow-up). The project was approved by the local institutional review board and all participants signed informed consent forms to participate. Details of inclusion and exclusion criteria, as well as study evaluations have been described previously (Postuma *et al.*, 2009*b*, 2015*b*). Briefly, individuals were eligible for inclusion if diagnosis of iRBD was confirmed by polysomnography according to the International Classification of Sleep Disorders-II criteria at recruitment (American Academy of Sleep Medicine TFC, 2007; Montplaisir *et al.*, 2010), with history of harmful or potentially harmful motor manifestations or complex motor behaviours during REM sleep on polysomnographic-synchronized videotape recording (Hauri, 2007). Following the comprehensive neurological examination, any patient with parkinsonism and/or dementia at enrolment were excluded. All patients with iRBD were followed annually and full clinical assessments were performed until the time of conversion to parkinsonism. In each follow-up visit, the same movement disorders specialist (R.B.P.) evaluated each participant for parkinsonism or dementia, using diagnostic criteria for either DLB according to McKeith criteria (McKeith *et al.*, 2005), Parkinson's disease according to UK Brain Bank criteria (Hughes *et al.*, 1992) or multiple system atrophy (MSA) based on the consensus diagnostic criteria (Gilman *et al.*, 2008).

From this group, 55 have eventually phenoconverted to parkinsonism or dementia; these were the primary cohort studied. For comparison, we also assessed a group of 102 control subjects free of any neurological or sleep disorders (examined with the same measures, evaluated at a single time point), and a group of 69 Parkinson's disease patients with associated RBD (average disease duration = 10.1 years), described previously elsewhere (Romenets *et al.*, 2012; Anang *et al.*, 2014).

Clinical assessments and tests

At baseline and each follow-up visit, a comprehensive list of motor and non-motor features was repeatedly assessed until the time of phenoconversion (range: 2–12 years). The measurements included:

(i) Motor manifestations: (a) motor symptoms, assessed by the Unified Parkinson's Disease Rating Scale (UPDRS)-Part II; (b) motor signs, assessed by the UPDRS-Part III for motor signs (Martinez-Martin *et al.*, 1994); and (c) motor phenotype: We performed calculations for each individual component of the scale, as well as summations for total scores of tremor, bradykinesia, rigidity (Muller *et al.*, 1997) and postural instability–gait difficulty (PIGD) as described previously (Stebbins *et al.*, 2013).

(ii) Quantitative motor tests: (a) Alternating Tapping Test: hand motor speed (Taylor Tavares *et al.*, 2005); (b) Purdue Pegboard: hand dexterity/speed, finger-eye coordination (Postuma *et al.*, 2006); and (c) 3-meter Timed Up and Go Task: gait speed (Podsiadlo and Richardson, 1991).

(iii) Non-motor manifestations: (a) apathy, as scored by the UPDRS Part I; (b) hallucinations, as scored by the UPDRS-Part I; (c) depression, as scored by the UPDRS-Part I; (d) olfaction, assessment of odour discrimination using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty *et al.*, 1984) (cross-culturally validated 12-item version) (Postuma *et al.*, 2009*a*); (e) colour vision, assessed by the Farnsworth-Munsell 100 Hue colour test (FM100) (Birch *et al.*, 1998); (f) autonomic symptoms, assessment of urinary symptoms, erectile dysfunction and constipation using the Unified Multiple System Atrophy Rating Scale (UMSARS) (Wenning *et al.*, 2004); (g) orthostatic hypotension, by manual measurement of blood pressure in supine and standing positions (after 1 min); and (h) cognition: education-adjusted Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005), and the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975).

Statistical analysis

All univariate and multivariate analyses, and statistical modelling were implemented using IBM SPSS Statistics software (version 23.0), Microsoft Excel 365 and *R* version 3.2.2.

Timeline definitions

The primary measure of interest was the evolution of each variable over time in the prodromal period. Therefore, for each patient who phenoconverted to defined disease, the year of phenoconversion was set at Year 0. All measures in each of the previous years were then plotted backwards in time before phenoconversion (Year –1, Year –2, etc. to Year –10). Because many patients phenoconvert within the first few years after diagnosis, each measure has fewer estimates as the prodromal interval increases; a minimum number of four participants with actual observation at that time point was required for entering into analysis.

Missing data

Missing data were handled with multiple imputation methods. If a single visit was missed, we imputed missing data for the in-between years with fit-regression lines for each measure. No imputation was made if data were missing in the first or the last year of observation. One iRBD individual had experienced drug-induced parkinsonism during the follow-up, which resolved when the agent was stopped (Fereshtehnejad *et al.*, 2018). The subject's motor data for that specific period were omitted and imputed as methods described above. To take into account effects of healthy ageing, the control normal reference scores were age-adjusted using linear regression.

Univariate statistical comparisons

Univariate comparisons between iRBD and healthy individuals, as well as parkinsonism first-converters and dementia first-converters were performed using independent samples *t*-test, for each time point. Because of the small sample size, we applied non-parametric Mann-Whitney U-test to compare numeric measures between MSA-converters and other synucleinopathies.

Evaluation of prodromal intervals

To estimate the time of divergence from normal control values, we performed regression modelling, following a prespecified selection order strategy to select the best fitted model. The initial step was basic linear regression in which time (i.e. Year 0, Year –1, Year –2, etc.) was considered as the independent variable and the manifestation's score value as the outcome. In the next step, we fitted a weighted least squares (WLS) linear regression to take into account the number of drop-outs in each time point and accordingly weight the average scores for each year. Lastly, we fitted a non-linear third-degree polynomial regression to assess the trend of progression over time. To reduce overfitting, we used linear regression as the default model; increasing complex models were selected only if there was clear improvement in the estimate, which we defined as a $\geqslant 10\%$ increase in R^2 compared to the linear model.

Comparison of slopes

To compare the rate of progression between different groups (iRBD versus controls, or parkinsonism first-converters versus dementia first-converters), linear mixed effect models were applied. In each model, the effect of time and individual trends were considered as fixed effects, while adjusting for the effect of baseline age and group differences at enrolment. The intercept and slope were considered as random effects as per standard protocols. The estimates and their 95% confidence intervals (CI) for the interaction between time and group therefore describe the extra annual change in the prodromal outcome that occurred in the group of interest versus the reference group.

Combining features

To combine trajectories of all motor and non-motor manifestations, each of which are measured by different scales, we normalized all the scores from 0 to 100. The 0 value was set as the normal age-matched control value. For the maximum 100 score, we estimated the scores of Parkinson's disease–RBD patients with moderately-advanced Parkinson's disease by taking the value of the mean + 1 standard deviation (SD) of the Parkinson's disease values in our cohort (i.e. the worse 15th percentile of established Parkinson's disease). So, the 'maximum' 100 score does not reflect the maximum possible score on each scale (which would vary depending on characteristics of each scale) but rather the scores of patients severely affected by Parkinson's disease. From these values, a severity score was calculated for each prodromal manifestation using the following formula:

$$\text{Severity score} = \frac{\begin{array}{c}(\text{year average value in RBD} \\ -\text{year average value in reference})\end{array}}{\begin{array}{c}[(\text{PD}-\text{RBD average value} + 1\,\text{SD}) \\ -\text{last year average value in reference}]\end{array}} \times 100\% \quad (1)$$

This method also adjusted for the effect of ageing by deducting the corresponding values measured in healthy controls from both nominator and denominator, for each manifestation. Note that this standardization was used only for cross-variable comparison; for calculating other variables (prodromal intervals, sensitivity/specificity, etc.), the raw data were used.

Diagnostic utility of prodromal markers

We assessed how accurately each prodromal measure could discriminate iRBD phenoconverters from healthy controls at the time of conversion (Year 0), as well as 2, 4 and 6 years prior to phenoconversion. For overall accuracy, we assessed receiver operating characteristic (ROC) curves, calculating area under the curve (AUC) for each measure. The best cut-off score was selected based on the value that maximized sensitivity while retaining a specificity (>75%) to distinguish phenoconverters at Year 0. We used the same cut-off score to calculate the number of true positives, true negatives, false positives and false negatives in Years 0, –2, –4 and –6. Finally, sensitivity, specificity, positive and negative likelihood ratios were calculated for every prodromal measure to summarize their predictive performance to detect phenoconverted iRBD individuals from healthy controls in each year.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Results

Study participants

Of 55 individuals with iRBD who eventually converted to defined parkinsonism or dementia at the time of analysis, 38 (69.1%) were male, baseline age was 64.6 ± 9.5 years, and duration of RBD dated from history of dream enactment onset was 8.2 ± 9.0 years (duration from polysomnogram diagnosis to baseline examination was <1 year). Phenoconversion occurred an average of 4.6 ± 2.5 years from baseline. In terms of primary manifestations, 29/55 (52.8%) developed parkinsonism first of whom 25/55 (45.4%) patients were diagnosed with Parkinson's disease and 4/55 (7.3%) with MSA. Twenty-six (47.2%) participants either phenoconverted to dementia first or developed dementia in the first year [within the first year of dementia diagnosis, 24/26 had at least one cardinal sign of parkinsonism at diagnosis, and 15 already met full MDS criteria for parkinsonism (Postuma *et al.*, 2015*a*)]. Baseline clinical characteristics of the patients with iRBD who phenoconverted and healthy controls are summarized in Supplementary Table 1. Many prodromal features were already present in the iRBD participants from the baseline visit (see previous publications for description of predictive value from baseline; Postuma *et al.*, 2009*b*, 2015*b*).

Evolution of manifestations during prodromal stages

The values of each prodromal manifestation at each time point are illustrated in Figs 1–4. Estimated prodromal intervals and % severity at time of diagnosis are provided in Table 1. Using relative severity scores on a scale ranging between 0 to 100%, we also overlaid trajectory trends of various motor and non-motor manifestations into one timeline, which is provided in Fig. 5. What follows is a summary of the primary findings from this analysis.

Motor markers

Motor examination

For motor examination signs, there was generally slow progression in the early prodromal stages, with a faster acceleration in the last 1–2 years before phenoconversion. Accordingly, for motor features and tests, cubic polynomial regressions fitted best to the actual dataset (all $R^2 > 0.93$). Motor signs on UPDRS-Part III first deviated from normal values an estimated 6.5 years prior to phenoconversion (with the first statistically significant difference from controls at Year –5, Fig. 1). The overall annual progression was 2.05 points per year (95%CI: 1.67–2.44), significantly different than normal ageing ($P < 0.001$, Table 2). At phenoconversion, UPDRS-Part III values approximated 35% of scores for moderately-advanced Parkinson's disease (note, however, that the patients with Parkinson's disease were treated with dopaminergic therapy).

We also examined the trajectories of individual cardinal motor features (Fig. 2) and single UPDRS-Part III motor signs (Fig. 3A). Changes in speech and voice were first to appear, crossing normal values at 6–7 years prior to phenoconversion, with statistically significant difference since Year –4. This was followed by hypomimia, limb bradykinesia, and decreased arm swing at Year –5. Rigidity appeared later than bradykinesia, at 3–4 years prior to phenoconversion. All these markers approximated 30–45% of that of advanced treated Parkinson's disease at phenoconversion. Resting tremor appeared relatively late, crossing threshold 1–2 years before diagnosis, and was generally very mild at diagnosis; note, however, that only 16.3% (9/55) patients had any rest tremor at diagnosis, and so tremor values are highly uncertain.

Quantitative motor testing

Between the motor tests, the Alternating Tapping Test deviated the earliest from normal values, with an estimated interval of 12.9 years prior to phenoconversion, and the

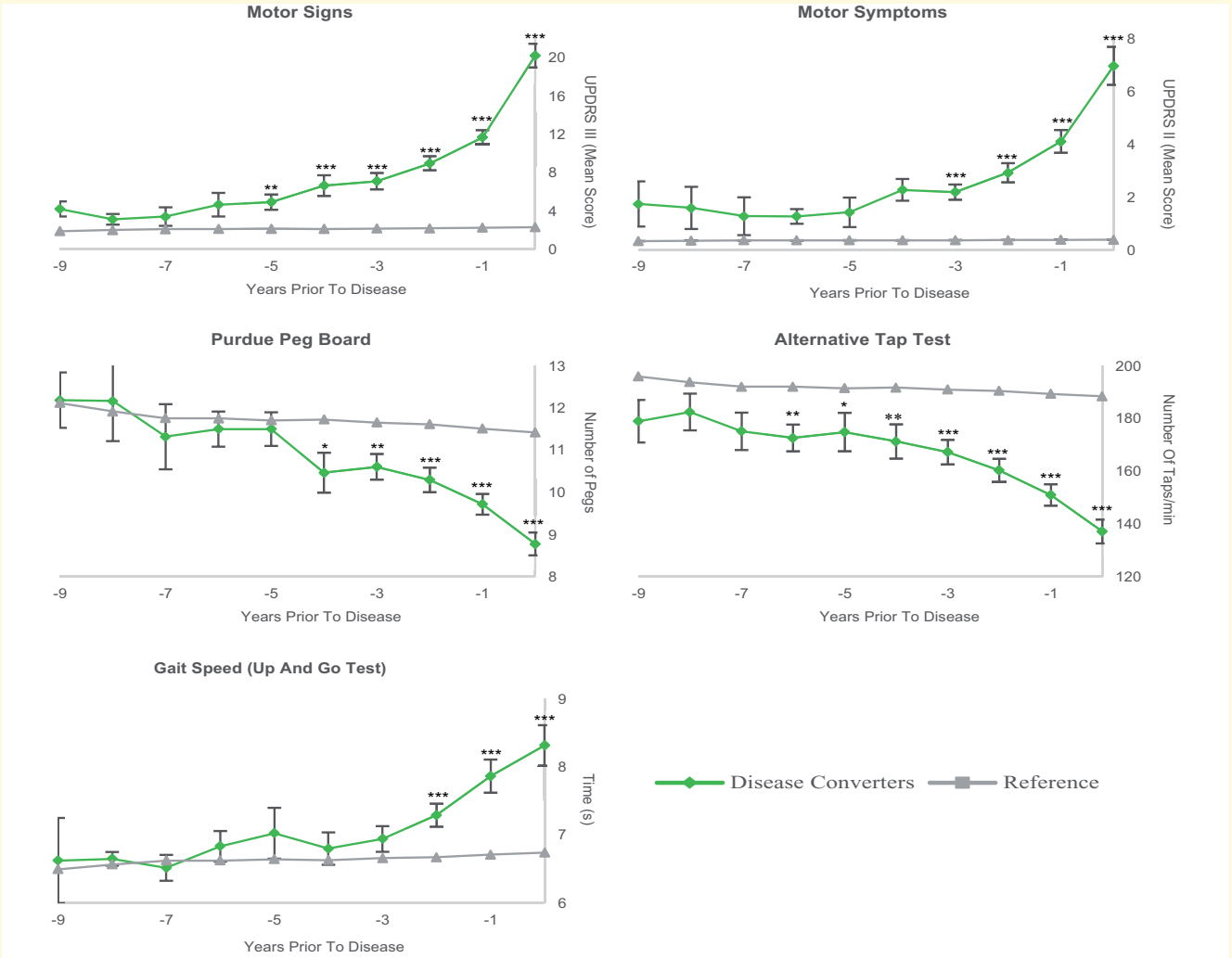

Figure 1 Progression of motor manifestations and quantitative motor testing from prodromal stages to phenoconversion. The error bars represent 95%CI using standard error of mean (SEM). Statistical significant differences (RBD versus control values) in each year are shown as: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

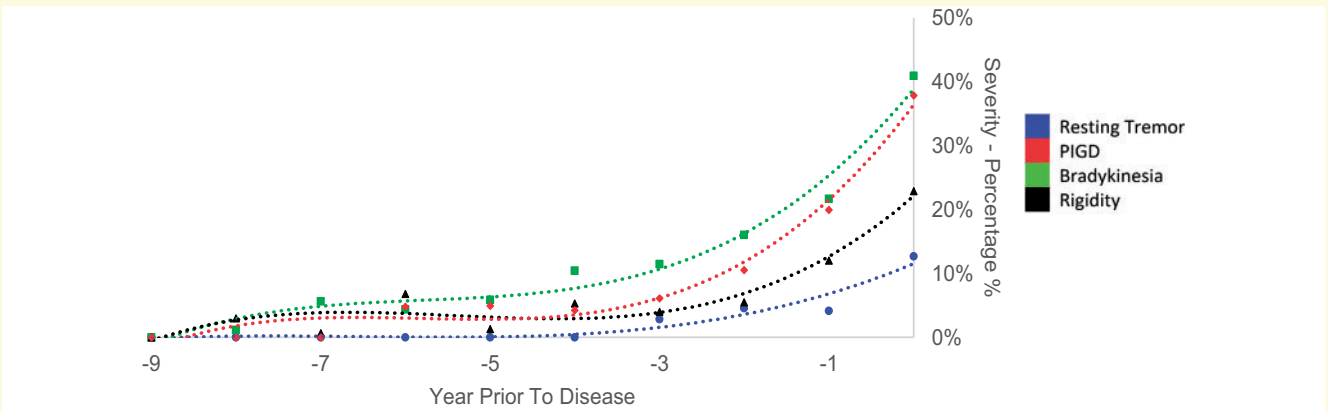

Figure 2 Progression of the cardinal parkinsonism features from prodromal stages to phenoconversion.

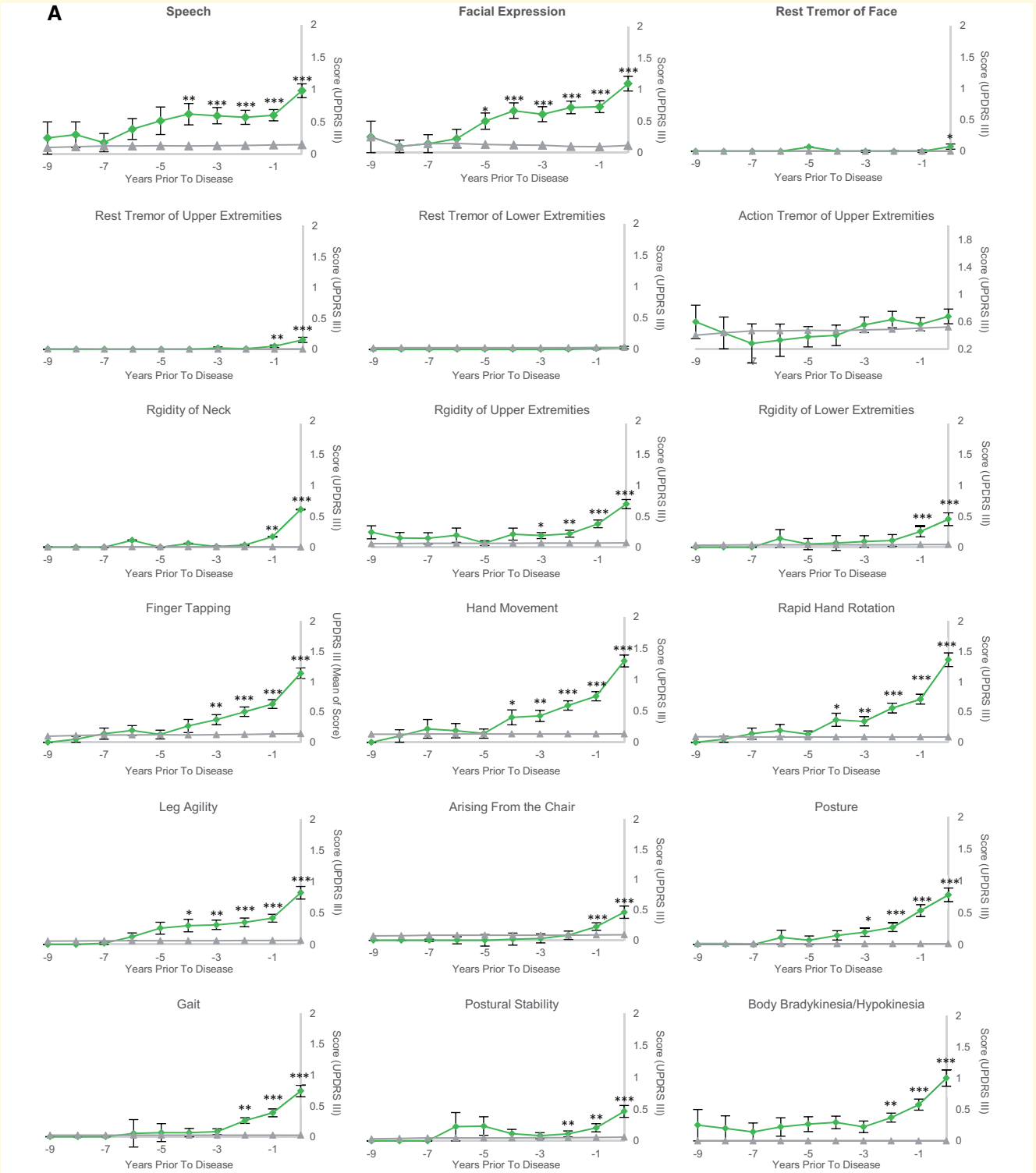

Figure 3 Progression of individual motor signs (UPDRS Part III items) (A) and motor symptoms (UPDRS-Part II items) (B) from prodromal stages to phenoconversion. The error bars represent 95%CI using SEM. Statistical significant differences in each year are shown as: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

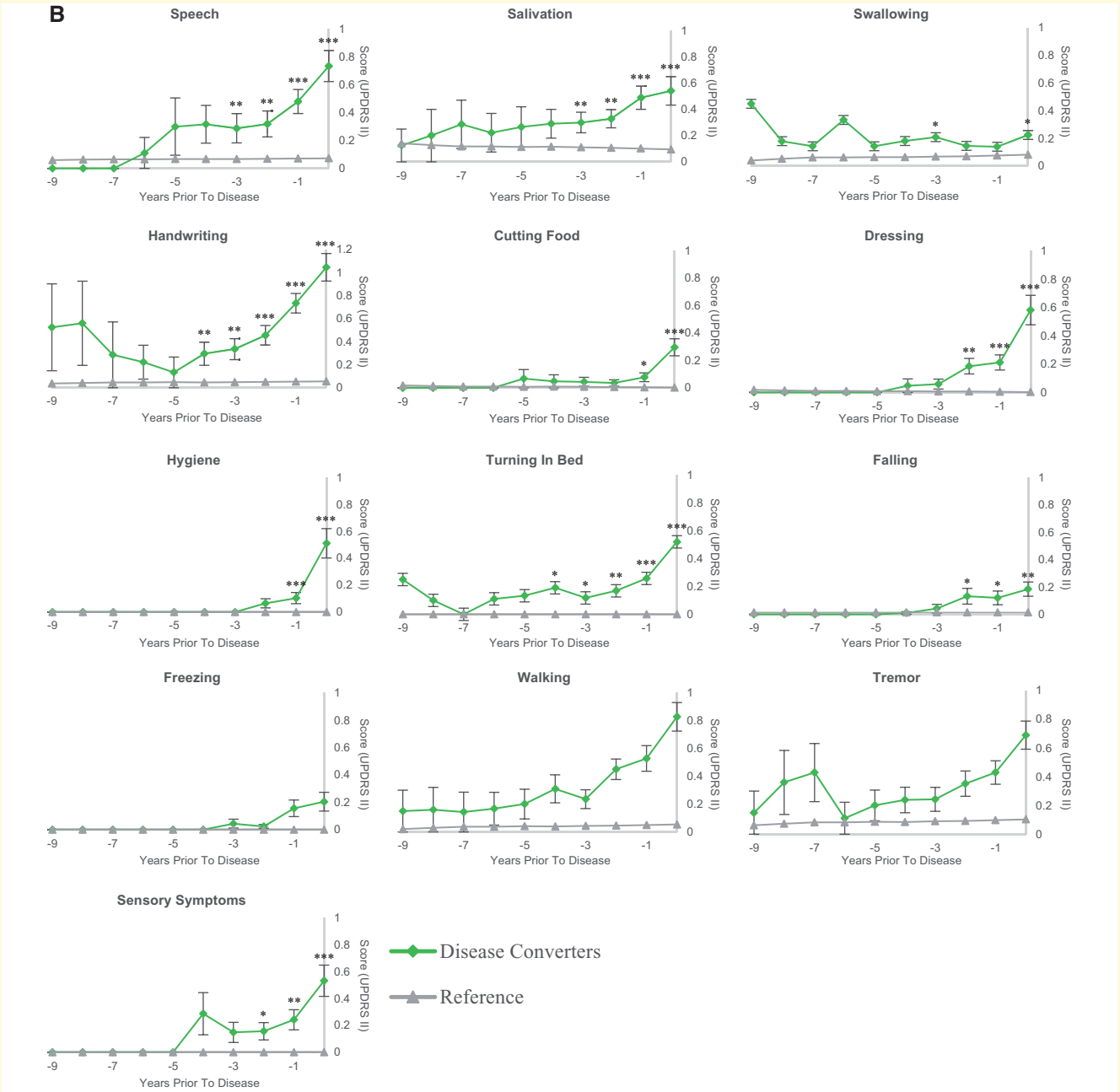

Figure 3 Continued.

first statistically significant difference from controls at Year –6 (Table 1 and Fig. 1). At phenoconversion, Alternating Tapping Test values approximated 50.6% of scores for advanced treated Parkinson's disease patients. The Timed-Up-And-Go and Purdue Pegboard followed a similar trend as was seen for motor signs (UPDRS-Part III). Purdue Pegboard had a shorter observed prodromal interval (7.5 years) and reached 33% of advanced Parkinson's disease values. The Timed Up-and-Go test had the shortest latency at an estimated 6.5 years before phenoconversion, and differences were only significantly different from controls 2 years before phenoconversion (Table 1 and Fig. 1). It was also the least severely-affected at the time of phenoconversion (22.8% of advanced Parkinson's disease values).

Motor symptoms

Motor symptoms on UPDRS-Part II began to deviate from normal values an estimated 9.3 years before phenoconversion (Table 1). However, these were generally mild, with the UPDRS-Part II reaching 25% of advanced Parkinson's disease values at phenoconversion and showing significant difference from controls starting only 3 years before

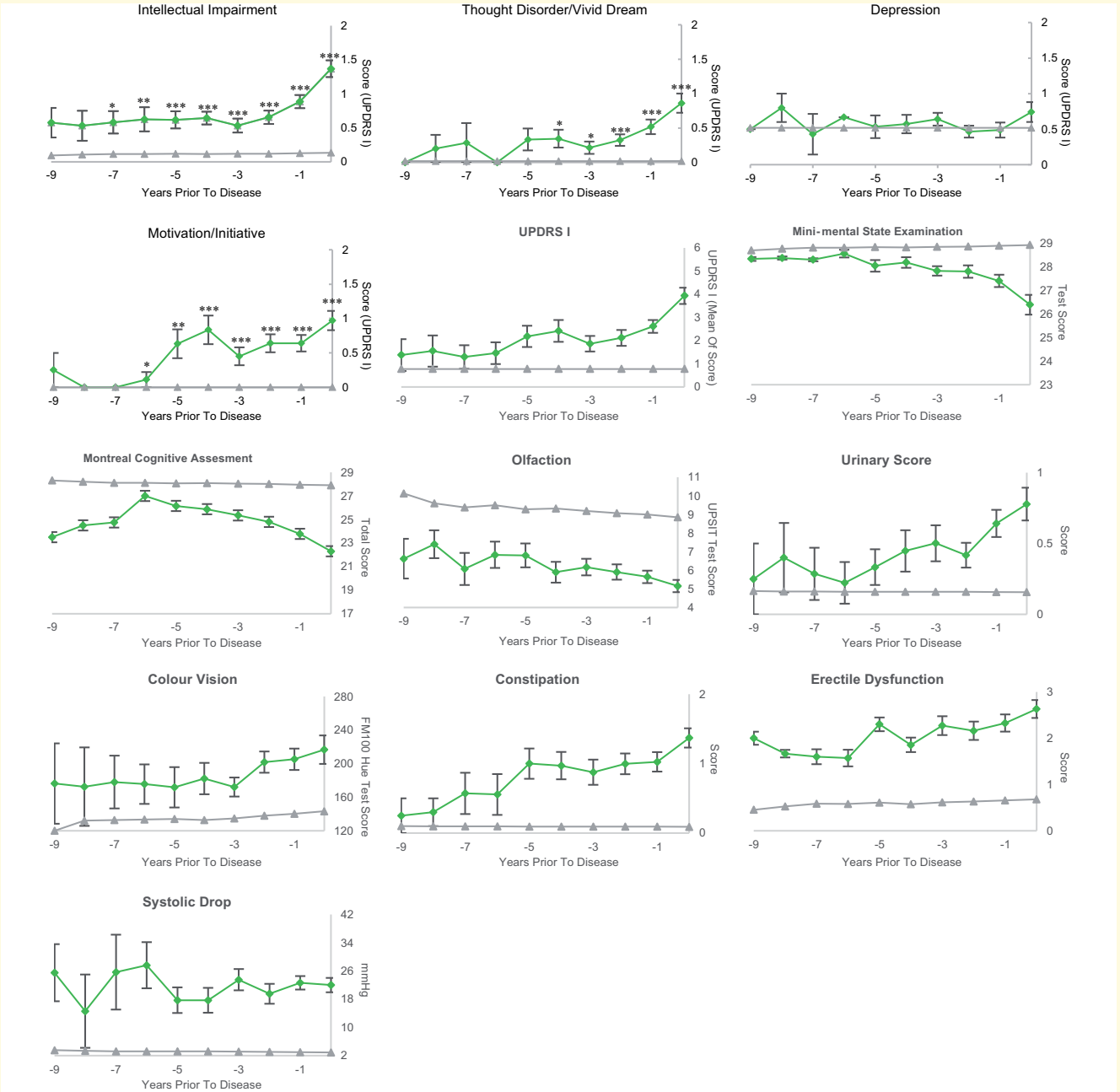

Figure 4 Progression of non-motor manifestations from prodromal stages to phenoconversion. The error bars represent 95%CI using SEM. Statistical significant differences in each year are shown as: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

phenoconversion (Table 1 and Fig. 1). Scores of UPDRS-Part II increased with a pace of 0.70 points per year (95%CI: 0.52–0.89) during the prodromal stage, significantly faster than normal ageing (mixed effects $P < 0.001$, Table 2).

We then investigated the trajectories of single UPDRS-Part II items (Fig. 3B). Alterations in handwriting, axial movements/gait (turning in bed, walking speed) and bulbar symptoms (salivation, and speech) were experienced at the longest prodromal intervals (7–11 years estimated prodromal intervals). By contrast, difficulties with hygiene, cutting food, dressing, swallowing, falls and freezing were minimally evident until 1–3 years before phenoconversion. Tremor was experienced with long latency; however, this was almost always endorsed as action tremor (note that the UPDRS-Part II does not distinguish rest from action tremor).

Non-motor markers

Progression trajectories of non-motor prodromal manifestations are illustrated in Fig. 4. Except for urinary symptoms, linear regression showed the best fit to explain

Table 1 Best fitted regression model to explain progression trajectory of each motor and non-motor manifestations during the prodromal stage up to the time of phenoconversion

Manifestation	R^2	Regression equation	Time of first presentation, year	Relative severity at phenoconversion[a], %
Motor				
Symptoms (UPDRS-II)	0.976[C]	$0.08t^3 + 1.48t^2 + 9.44t + 24.07$	–9.3[e]	25.0
Signs (UPDRS-III)	0.933[C]	$0.13t^3 + 2.43t^2 + 14.68t + 31.25$	–6.5[a]	34.5
Tests				
Up-and-Go (gait speed)	0.963[C]	$0.07t^3 + 1.37t^2 + 9.19t + 23.28$	–6.5[a]	22.8
Alternative Tap	0.975[C]	$0.08t^3 + 1.77t^2 + 13.37t + 50.08$	–12.9[e]	50.6
Purdue Pegboard	0.932[C]	$0.04t^3 + 0.95t^2 + 8.68t + 31.77$	–7.5[a]	33.0
Non-motor				
Olfaction (UPSIT)	0.665[W]	$2.75t + 60.62$	–22.0[e]	63.4
Colour vision (FM100)	0.696[W]	$5.02t + 64.15$	–12.8[e]	67.0
Constipation	0.874[L]	$4.62t + 49.73$	–10.8[e]	53.1
Erectile dysfunction	0.685[L]	$3.55t + 56.69$	–16.0[e]	58.7
Urinary dysfunction	0.856[C]	$0.04t^3 + 0.89t^2 + 7.37t + 27.43$	–6.5[a]	27.8
Orthostatic hypotension	0.025[C]	$0.06t^3 + 0.96t^2 + 4.29t + 58.07$	–15.4[e]	56.7
Cognition (MoCA)	0.837[L]	$4.68t + 35.38$	–6.5[a]	45.5

C = cubic regression; L = linear regression; W = weighted least squares regression; e = estimated; a = actual observation.
Among the linear and weighted least squares regressions, the one with higher R^2 has been selected. We selected cubic non-linear regression only if at least 10% increase in predictability was achieved.
Time of first presentation refers to the time at which the manifestations in RBD patients first deviates from normal, expressed as years before phenoconversion. Relative severity of each manifestation encapsulates to what degree the manifestation has reached a near-maximal value (i.e. that of advanced PD) at the time an RBD patient phenoconverts. See Equation 1 for calculation.

trajectories of non-motor manifestations during the prodromal stage (Table 2).

Hyposmia

Of all markers assessed in this study, hyposmia appeared to be the earliest manifestation. Its estimated prodromal interval was 22.0 years, and results were already clearly different from controls at the earliest measured time points (i.e. Year –9). Moreover, hyposmia progressed slowly in the observed prodromal interval (with no significant difference from that of the normal ageing effects (mixed effects $P = 0.139$, Table 2 and Fig. 4). At phenoconversion, olfactory deficits were already well-advanced, approximating 63.4% of advanced Parkinson's disease values. With elimination of MSA patients, values were 67.0% of advanced Parkinson's disease patients at the time of parkinsonism/DLB diagnosis.

Autonomic dysfunction

Symptoms of constipation, orthostatic hypotension and erectile dysfunction (males only) also occurred relatively early in the prodromal course, with an estimated interval of 10.8 years for constipation, 15.4 years for orthostatic hypotension and 16.0 years for erectile dysfunction (Table 1). Differences were statistically significant 4–6 years prior to phenoconversion. By phenoconversion, these symptoms approximated 53–59% of normal values. Urinary symptoms appeared to be a later complaint with an estimated interval of 6.5 years, demonstrating significant difference from controls starting at Year –3 and values at phenoconversion approximating 27.8% those of advanced Parkinson's disease. Objectively-measured orthostatic hypotension was clearly evident at the earliest time points (and statistically significantly different starting at Year –6, Fig. 4). Unlike the other variables, we saw no evidence of progression at all over the prodromal interval (making calculations of estimated prodromal interval impossible).

Colour vision

The predicted interval of impaired colour vision was 12.8 years (Table 1), and it significantly deviated from normal ageing as early as 4 years prior to phenoconversion (Fig. 4).

Cognition

Cognition began to deviate 5 years before phenoconversion, showing overall subtle changes, with statistically significant decline 3 years before the onset of parkinsonism (Fig. 4). At phenoconversion, cognitive deficits approximated 45.5% of advanced Parkinson's disease values in the entire study population (although it should be noted that phenoconvertors included those with primary dementia). Compared to normal ageing, global cognitive deficit followed a progressive trend with half a unit (95%CI: 0.26–0.76) further decline in MoCA score every year (Table 2).

Other non-motor features

Based on single UPDRS-I items, scores on intellectual impairment and thought disorders were significantly worse than healthy controls as early as 7 and 4 years before phenoconversion, respectively. Apathy started to develop 6 years prior to Parkinson's disease/DLB diagnosis, whereas depression did not show a different trend than normal ageing.

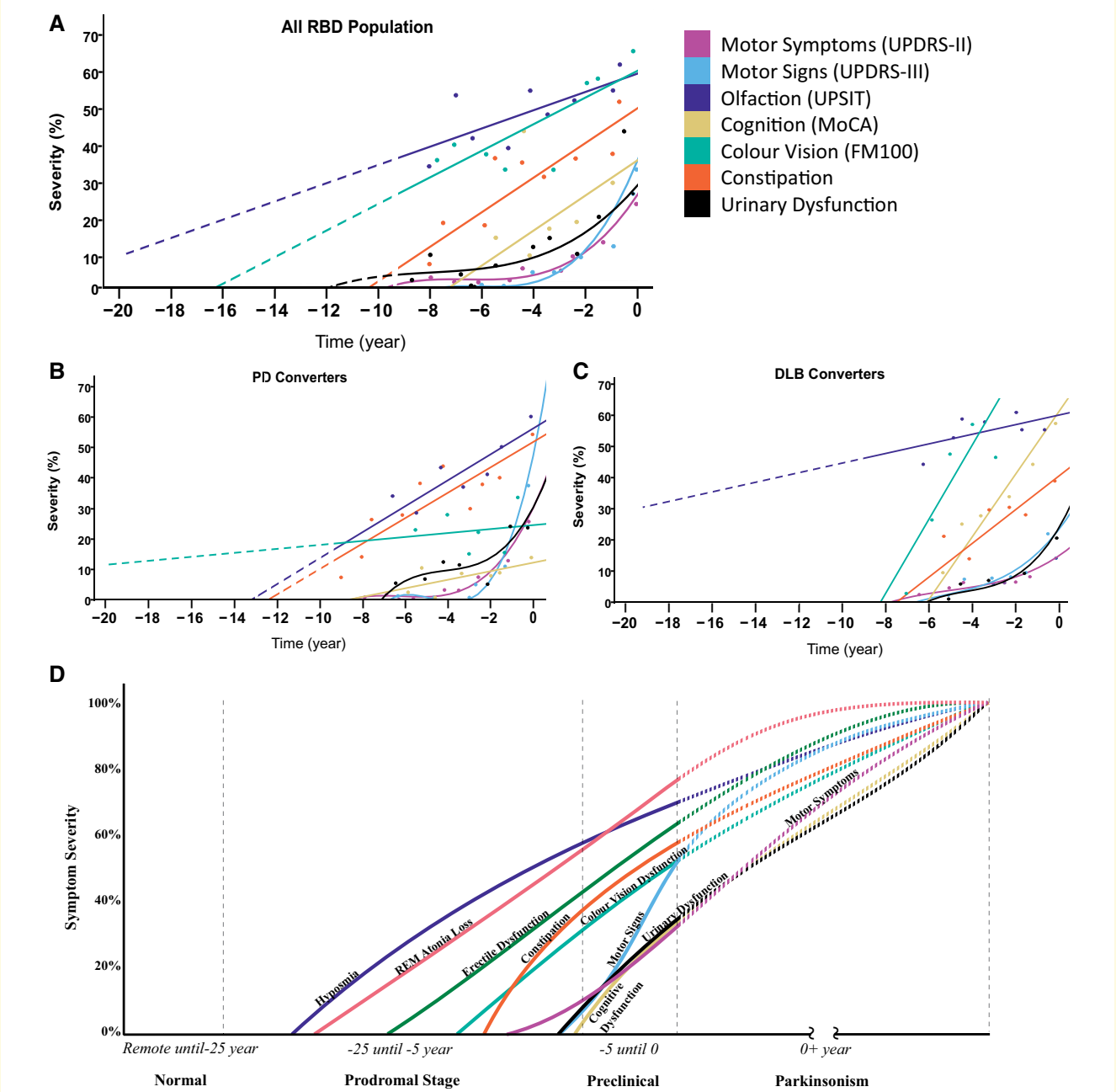

Figure 5 Combined progression trajectory of motor and non-motor manifestations from prodromal stages to phenoconversion based on actual measurements. In the entire study population (**A**), Parkinson's disease-converters (**B**), DLB-converters (**C**) (note that the dashed lines represent expected imputed trends, while the solid lines and the dots demonstrate actual observations). (**D**) Schematic model for progression of motor and non-motor manifestations throughout the prodromal, phenoconversion and advanced stages of patients with idiopathic RBD converting to Parkinson's disease. This schematic illustrates the approximate trajectories of the major motor and non-motor manifestations as patients progress from normal, through idiopathic RBD, to advanced Parkinson's disease. This is based on control data, patients with idiopathic RBD tracked through time, and patients with advanced Parkinson's disease who also have RBD. The predicted progressions after phenoconversion were dotted due to the uncertainty of real symptomatic severity without the influence of dopaminergic treatment. Olfaction is generally the first manifestation to become abnormal and reaches near maximum loss at the time of phenoconversion. We scaled down both cognitive and colour vision dysfunction slopes by half to avoid the bias driven by DLB subjects (the estimated maximum symptoms were based on Parkinson's disease-RBD subjects without dementia at baseline). Autonomic features are similarly present early, and approximate 50–70% maximal values at phenoconversion. REM atonic loss and colour vision loss have patterns similar to autonomic loss. By contrast, motor and cognitive abnormalities start relatively late, and are at only 20–30% maximal values at the time of phenoconversion.

Table 2 Mixed effect models for between-group comparisons of the trajectories of prodromal manifestations

Manifestation/test	Trajectory trend[c] Time × Group interaction	
	Phenoconvertors versus controls[a]	PD-convertors versus DLB-convertors[b]
Motor Signs (UPDRS-III)	**B = +2.05 (+1.67, +2.44) P < 0.001**	B = –0.60 (–1.40, +0.20) P = 0.139
Motor symptoms (UPDRS-II)	**B = +0.70 (+0.52, +0.89) P < 0.001**	B = –0.31 (–0.70, +0.09) P = 0.129
Tremor score	**B = +0.11 (+0.02, +0.19) P < 0.001**	B = –0.09 (–0.27, +0.10) P = 0.347
Rigidity score	**B = +0.32 (+0.22, +0.42) P < 0.001**	B = –0.08 (–0.28, +0.13) P = 0.475
Bradykinesia score	**B = +1.18 (+0.94, +1.41) P < 0.001**	B = –0.46 (–0.96, +0.03) P = 0.068
PIGD score	**B = +0.31 (+0.22, +0.39) P < 0.001**	B = –0.04 (–0.21, +0.14) P = 0.675
Gait Speed (Up and Go Test)	**B = +0.22 (+0.13, +0.31) P < 0.001**	B = –0.01 (–0.18, +0.16) P = 0.888
Alternative Tap Test	**B = –4.91 (–6.59, –3.22) P < 0.001**	B = –2.25 (–5.60, +1.10) P = 0.187
Purdue Pegboard Test	**B = –0.34 (–0.45, –0.22) P < 0.001**	B = –0.19 (–0.40, +0.02) P = 0.079
Constipation	**B = +0.10 (+0.05, +0.16) P < 0.001**	B = +0.05 (–0.06, +0.17) P = 0.371
Erectile dysfunction	**B = +0.11 (+0.01, +0.20) P = 0.032**	B = –0.06 (–0.24, +0.12) P = 0.516
Urinary dysfunction	**B = +0.07 (+0.03, +0.11) P = 0.001**	B = +0.02 (–0.07, +0.10) P = 0.678
Colour vision (FM100)	B = +4.69 (–0.80, +10.19) P = 0.094	**B = +19.08 (+8.53, +29.64) P < 0.001**
Olfaction (UPSIT)	B = –0.11 (–0.26, +0.04) P = 0.139	B = +0.16 (–0.11, +0.43) P = 0.243
Cognition (MoCA)	**B = –0.51 (–0.76, –0.26) P < 0.001**	**B = –1.50 (–2.06, –0.95) P < 0.001**
Orthostatic hypotension	B = +0.17 (–0.75, +1.08) P = 0.718	**B = +2.45 (+0.50, +4.41) P = 0.014**

[a]Control group is the reference condition.
[b]PD-converter is the reference condition.
[c]Mixed effect models adjusted for baseline age;
All statistical significant differences are bolded. B = coefficient.

Combined trajectories

Figure 5A–C illustrates the combined standardized trajectories for all markers. Beginning >20 years before parkinsonism diagnosis, olfactory function starts to decline, yet progresses with a slow trend. This is followed by impaired colour vision and constipation as early as 16 and 10 years prior to phenoconversion, respectively. Within 7 to 9 years before parkinsonism is diagnosed, the first motor manifestations appear, along with slight urinary dysfunction and subtle cognitive decline. Adding time-to conversion to history of dream enactment, RBD itself appears on average 21 years prior to phenoconversion. Most manifestations progress in a linear fashion, except motor signs and symptoms, which exhibit a more rapid progression during the last 2 years prior to phenoconversion. Comparing to patients with relatively advanced Parkinson's disease, hyposmia and impaired colour vision are the most advanced at phenoconversion, reaching >60% their potential severity at the time of parkinsonism diagnosis.

Diagnostic performance of prodromal motor and non-motor features and tests

Estimates of diagnostic accuracy for each prodromal manifestation in differentiating prodromal synucleinopathy from healthy controls are listed in Table 3. At the time of phenoconversion, motor symptoms (UPDRS-Part II), followed by motor signs (UPDRS-Part III) had the highest accuracy to distinguish iRBD phenoconverters from controls. A cut-off score of ⩾4 for UPDRS-Part III, excluding action tremor score, had 92.6% (95%CI: 82.1–97.9%) sensitivity and 95.6% (95%CI: 87.6–99.1%) specificity to discriminate neurodegeneration. Sensitivity decreased at longer prodromal intervals (Table 3), dropping below 50% at Year –4. Among the motor tests, alternative tap not only had the

Table 3 Predictive values and best cut-off scores for the motor and non-motor prodromal features and tests to detect phenoconverted iRBD individuals from healthy controls in different time points

Symptom		Year 0	Year –2	Year –4	Year –6
Motor signs(UPDRS-III)[a]	AUC	0.968 (0.933–1)	0.832 (0.749–0.915)	0.730 (0.600–0.860)	0.599 (0.413–0.784)
	Cut-off	⩾4	–	–	–
	Sensitivity	92.6 (82.1–97.9)	60.5 (44.4–75.0)	43.5 (23.2–65.5)	16.7 (2.1–48.4)
	Specificity	95.6 (87.6–99.1)	95.6 (87.6–99.1)	95.6 (87.6–99.1)	95.6 (87.6–99.1)
Motor symptoms (UPDRS-II)	AUC	0.951 (0.908–0.993)	0.829 (0.744–0.913)	0.846 (0.741–0.952)	0.789 (0.612–0.967)
	Cut-off	⩾2	–	–	–
	Sensitivity	85.7 (72.8–94.1)	63.0 (47.5–76.8)	52.4 (29.8–74.3)	44.4 (13.7–78.8)
	Specificity	92.6 (83.7–97.6)	92.6 (83.7–97.6)	92.6 (83.7–97.6)	92.6 (83.7–97.6)
Gait speed (Up-and-Go Test)	AUC	0.853 (0.776–0.931)	0.765 (0.663–0.868)	0.628 (0.471–0.785)	0.721 (0.524–0.917)
	Cut-off	⩾7 s	–	–	–
	Sensitivity	78.8 (65.3–88.9)	68.9 (53.3–81.8)	47.6 (25.7–70.2)	55.6 (21.2–86.3)
	Specificity	86.5 (71.2–95.5)	86.5 (71.2–95.5)	86.5 (71.2–95.5)	86.5 (71.2–95.5)
Alternative Tap Test	AUC	0.915 (0.865–0.966)	0.809 (0.724–0.894)	0.729 (0.601–0.858)	0.777 (0.645–0.909)
	Cut-off	⩽175	–	–	–
	Sensitivity	84.4 (70.5–93.5)	66.7 (49.8–80.9)	52.4 (29.8–74.3)	55.6 (21.2–86.3)
	Specificity	77.3 (65.3–86.7)	77.3 (65.3–86.7)	77.3 (65.3–86.7)	77.3 (65.3–86.7)
Purdue Peg Test	AUC	0.888 (0.830–0.947)	0.774 (0.685–0.864)	0.733 (0.607–0.859)	0.675 (0.492–0.858)
	Cut-off	⩽22	–	–	–
	Sensitivity	83.0 (70.2–91.9)	62.2 (46.5–76.2)	57.1 (34.0–78.2)	42.9 (9.9–81.6)
	Specificity	81.2 (69.5–89.9)	81.2 (69.5–89.9)	81.2 (69.5–89.9)	81.2 (69.5–89.9)
Constipation	AUC	0.835 (0.756–0.914)	0.780 (0.683–0.876)	0.793 (0.663–0.922)	0.623 (0.404–0.842)
	Cut-off	⩾1	–	–	–
	Sensitivity	74.1 (60.3–85.0)	63.6 (47.8–77.6)	61.9 (38.4–81.9)	33.3 (7.5–70.1)
	Specificity	92.1 (82.4–97.4)	92.1 (82.4–97.4)	92.1 (82.4–97.4)	92.1 (82.4–97.4)
Erectile dysfunction	AUC	0.882 (0.805–0.959)	0.942 (0.889–0.994)	0.947 (0.893–1)	0.929 (0.862–0.995)
	Cut-off	⩾1	–	–	–
	Sensitivity	100 (90.0–100)	100 (90.0–100)	100 (80.5–100)	100 (63.1–100)
	Specificity	79.6 (65.7–89.8)	79.6 (65.7–89.8)	79.6 (65.7–89.8)	79.6 (65.7–89.8)
Urinary dysfunction	AUC	0.711 (0.614–0.808)	0.615 (0.505–0.725)	0.619 (0.471–0.766)	0.536 (0.329–0.744)
	Cut-off	⩾1	–	–	–
	Sensitivity	52.8 (38.6–66.7)	33.3 (20.0–48.9)	33.3 (14.6–57.0)	22.2 (2.8–60.0)
	Specificity	85.7 (74.6–93.2)	85.7 (74.6–93.2)	85.7 (74.6–93.2)	85.7 (74.6–93.2)
Colour vision (FM100)	AUC	0.713 (0.618–0.809)	0.731 (0.633–0.829)	0.668 (0.526–0.810)	0.651 (0.474–0.827)
	Cut-off	⩾153	–	–	–
	Sensitivity	70.4 (56.4–82.0)	77.3 (62.2–88.5)	66.7 (43.0–85.4)	55.6 (21.2–86.3)
	Specificity	61.0 (47.4–73.4)	61.0 (47.4–73.4)	61.0 (47.4–73.4)	61.0 (47.4–73.4)
Olfaction (UPSIT)	AUC	0.889 (0.825–0.954)	0.837 (0.754–0.921)	0.873 (0.765–0.981)	0.872 (0.715–1)
	Cut-off	⩽0.79	–	–	–
	Sensitivity	79.6 (66.5–89.4)	68.2 (52.4–81.4)	66.7 (43.0–85.4)	66.7 (29.9–92.51)
	Specificity	95.4 (87.1–99.0)	95.4 (87.1–99.0)	95.4 (87.1–99.0)	95.4 (87.1–99.0)
Cognition (MOCA)	AUC				
	Cut-off	⩽26	–	–	–
	Sensitivity	73.5 (58.9–85.0)	65.6 (46.8–81.4)	53.8 (25.1–80.8)	50.0 (6.8–93.2)
	Specificity	85.2 (66.3–95.8)	85.2 (66.3–95.8)	85.2 (66.3–95.8)	85.2 (66.3–95.8)

[a]The scores for action tremor were not included in the sum of the UPDRS-III.

highest AUC (0.915, 95%CI: 0.865–0.966) to predict phenoconversion at the time of parkinsonism diagnosis, but also remained more sensitive up to 6 years prior to phenoconversion (Table 3). An Alternative Tap Test score ⩽175 was 84.4 (95%CI: 70.5–93.5) sensitive and 77.3% (95%CI: 65.3–86.7%) specific to distinguish phenoconversion. Of note, sensitivity of Alternative Tap Test remained >55% even at Year –6, when UPDRS motor scores were not sensitive and dropped <45%. For Up-and-Go and Purdue pegboard tests, a cut-off score of ⩾7 s and ⩽22, respectively, were found to be the best for predicting phenoconversion. These two motor tests (i.e. Purdue Pegboard and Timed Up-and-Go), however, had lower overall accuracy compared to alternative tapping at all the prodromal years. Among the non-motor manifestations, hyposmia (0.889, 95%CI: 0.825–0.954) had the highest accuracy, followed by erectile dysfunction (0.882, 95%CI: 0.805–0.959), subtle cognitive impairment (0.862, 95%CI:

0.781–0.943) and constipation (0.842, 95%CI: 0.765–0.920) (Table 3). Consistent with its lack of progression over the prodromal period, olfaction was the most stable feature moving backward in time, with good diagnostic utility even 6 years prior to the time of parkinsonism diagnosis. The overall accuracy dropped only modestly between Years 0 and –6 (0.889 to 0.872), and sensitivity remained at 67% even 6 years before diagnosis, with a specificity of 95.4%. Removal of patients with MSA improved this further, where the AUC increased to 0.906. Constipation had also a relatively high specificity (92.1%, 95%CI: 82.4–97.4%) to discriminate phenoconversion from healthy status. All male participants who phenoconverted showed at least some degree of erectile dysfunction even 6 years prior to being diagnosed with parkinsonism. Thus, erectile dysfunction had 100% sensitivity for this discrimination during Years 0 back to –6.

Parkinsonism-first versus dementia-first conversion

We performed subgroup analysis comparing prodromal stages between iRBD individuals who converted to parkinsonism first (i.e. first clinical diagnosis = Parkinson's disease, excluding MSA) versus dementia first (first clinical diagnosis = DLB). For motor features, mixed effects models failed to show any statistically significant between-group difference in trajectories over time (Table 2). However, motor symptoms and signs as measured by UPDRS-Parts II and III, seemed to appear 1–2 years earlier in primary DLB-converters, but progressed faster in primary Parkinson's disease-converters in the last 2 years prior to phenoconversion (Supplementary Fig. 1). As expected by definition, cognition differed significantly between groups. The MMSE started declining in DLB-converters by Year –3 with a rapid pace, with a 1.50-point (95%CI: 0.95–2.06) further annual decline in MoCA score compared to Parkinson's disease-converters (mixed effects $P < 0.001$; Table 2 and Supplementary Fig. 2). In addition, colour vision was more impaired among the DLB-converters, with a 19.1-point (95%CI: 8.53–29.64) faster annual increase in the FM100 test of colour vision (mixed effects $P < 0.001$; Table 2 and Supplementary Fig. 2). DLB-converters also had an extra decline of 2.45 (95%CI: 0.50–4.41) mm Hg per year in systolic blood pressure compared to those who converted to Parkinson's disease (mixed effects $P = 0.014$; Table 2). By contrast, among the Parkinson's disease-converters, constipation and hyposmia followed a slightly more rapid trend of progression compared to DLB convertors.

Multiple system atrophy phenoconverters

Compared to the other synucleinopathies (DLB/Parkinson's disease), the four patients who eventually developed MSA were significantly younger (54.2 ± 7.8 versus 70.4 ± 7.5, $P = 0.001$) and had preserved cognition (MoCA: 26.8 ± 2.5 versus 21.3 ± 5.5, $P = 0.044$) and colour vision (FM100: 87.0 ± 60.1 versus 227.0 ± 122.9, $P = 0.005$) at the time of phenoconversion. MSA-converters may also have had less impaired olfaction (UPSIT %normal = 77.3 ± 44.4 versus 57.6 ± 26.6) and more severe urinary symptoms (1.2 ± 0.4 versus 0.7 ± 0.9) at phenoconversion (with marginal statistical significance levels).

Discussion

The availability of comprehensive longitudinal data from an iRBD cohort provides a unique opportunity to directly trace the trajectories of prodromal Parkinson's disease and DLB. Based on best regression models to fit the actual observed measurements, we estimated that change in olfaction, as the earliest event, begins at least two decades before the estimated onset of clinical symptoms of Parkinson's disease/DLB and continues to worsen with a slow trend until the time of diagnosis (see Fig. 5D for a schematic summary). Orthostatic blood pressure drop is also witnessed very early in the disease course. This is followed by constipation and erectile dysfunction, which start to become abnormal 10–15 years prior to phenoconversion. Colour vision abnormalities appear at a similar time, particularly in those destined to develop dementia first. These non-motor prodromal features all manifest years before observable motor signs. Within 7 to 9 years before parkinsonism is diagnosed, the first observable motor manifestations appear, along with subtle cognitive decline in those destined to develop dementia first. Most manifestations progress in a linear fashion, except motor signs and symptoms, which exhibit a more rapid progression during the last 2 years prior to phenoconversion. Many of these prodromal manifestations can detect prodromal synucleinopathy with high specificity. Sensitivity strongly depends upon the duration before phenoconversion for most measures, except for olfaction, which remains sensitive $\geqslant 6$ years before disease onset.

Because prodromal Parkinson's disease occurs in only 1–2% of the population, few studies have been able to systematically study patients before they develop disease. Focusing mainly on the activities of daily living and motor functioning, a nested case-control study within the prospective Rotterdam cohort recently showed that from 7 years before Parkinson's disease diagnosis, complex daily tasks that require both motor and non-motor skills become impaired (Darweesh *et al.*, 2017*a*). In line with our findings, they also demonstrated that bradykinesia and rigidity commonly occur during the prodromal stage; however, they also found that symptomatic tremor occurred early in the prodromal course (Darweesh *et al.*, 2017*a*). This is likely because action/intention tremor was combined with resting tremor in the Rotterdam study. In our study, symptoms of tremor (including action tremor) had a similarly long latency, while objective evidence of rest tremor, on exam showed a very short latency. For this discrepancy, we should also acknowledge that our study population consisted of RBD cases who represent a more diffuse subtype of Parkinson's disease with a faster disease progression and more severe bradykinesia rather than tremor as their prominent motor phenotype. In the Rotterdam study

cognitive testing also demonstrated abnormalities starting 3–7 years before Parkinson's disease diagnosis (Darweesh *et al.*, 2017*a*, *b*). Although assessment of other non-motor features was limited by the size of the population, there was also evidence that anxiety, depression and laxative use increased gradually during prodromal stages. In our 2012 report focusing on motor manifestations, we also demonstrated the early involvement of voice and face and differing progression pace of the cardinal motor phenotypes (Postuma *et al.*, 2012). We also described the time course of olfaction, colour vision, and autonomic dysfunction in our cohort over a shorter time of follow-up and with a smaller sample size (Postuma *et al.*, 2011*b*, 2013).

Autonomic features may be particularly useful for identifying prodromal synucleinopathy. In one 4-year prospective cohort, individuals who presented initially with pure autonomic failure had a 34% risk for phenoconverting to synucleinopathies, particularly if they also had RBD (Kaufmann *et al.*, 2017). Another cohort found that 12/48 patients with delayed orthostatic hypotension converted to Parkinson's disease, DLB, or MSA after 10 years (Gibbons and Freeman, 2015). We have also shown previously that RBD is strongly associated with orthostasis (Postuma *et al.*, 2008). The prolonged prodromal interval for orthostasis observed here suggests that RBD and orthostatic hypotension are very early prodromal features. It is also noteworthy that patients had an 8.2-year RBD symptom interval before diagnosis was made; this reflects important delays in presentation to medical attention and in prompt referral to specialized therapy. If neuroprotective therapy becomes available, it will be especially critical to shorten this diagnostic interval.

With regards to diagnostic potential, among non-motor manifestations, hyposmia was the most specific feature to predict phenoconversion. Moreover, there was a relatively high sensitivity even at prodromal intervals as long 6 years. This suggests that with an appropriate cut-off point (high enough to identify few false positives), hyposmia could be used for screening Parkinson's disease/DLB (noting that the relatively low prevalence of Parkinson's disease and DLB would still imply a relatively low positive predictive value). Among quantitative motor tests, alternative tapping test was the most specific and sensitive. This is an affordable, easily available, and easy-to-use test that could screen for subtle parkinsonism in future cohorts of normal population.

We found some variations in the trajectories of prodromal features between the iRBD subgroup who eventually converted to Parkinson's disease versus those who developed DLB. As per definition, cognitive decline preceded motor dysfunction in DLB-converters, started from 6 years before DLB diagnosis, and quickly worsened with a steady slope. Of interest, MMSE was unable to detect any cognitive deficit in Parkinson's disease-converters during the prodromal stage. MoCA, on the other hand, showed subtle cognitive decline starting almost 5 years prior to diagnosis with a slow progression among Parkinson's disease-converters. This should not be interpreted as evidence that cognitive testing could not detect Parkinson's disease in the general population, because it should be remembered that almost all patients have neurodegenerative synucleinopathy in this cohort. If dementia and parkinsonism are considered to be competing risks, then the fact that a patient develops parkinsonism first may imply that their cognition is relatively preserved (e.g. they are unlikely to have coincidental amyloid pathology) (Genier Marchand *et al.*, 2018). Almost exclusively in DLB-converters, colour vision developed early in the prodromal stages, whereas it remained relatively normal even at diagnosis in Parkinson's disease. This is in line with evidence showing that the performance on the FM100 is related to cognitive impairment (impaired executive functions and visuospatial abilities) and white matter posterior brain alterations in Parkinson's disease (Bertrand *et al.*, 2012). This suggests that the performance on the FM100 in iRBD patients is sensitivity to cognitive impairment, as reported in our studies showing that colour vision could identify patients destined to develop dementia but not parkinsonism-first conversion (Postuma *et al.*, 2011*a*, 2015*b*).

Staging systems of neuropathology in Parkinson's disease/DLB have strongly suggested the existence of a non-motor pathology that precedes neurodegeneration in motor and cognitive areas (Braak *et al.*, 2003; Adler and Beach, 2016). In the original Braak model of Parkinson's disease (Braak *et al.*, 2003), hyposmia and autonomic dysfunctions were predicted to be the first to become abnormal, followed by motor signs. This study is supportive of this model, as hyposmia demonstrated the longest interval, followed by various autonomic manifestations, then motor changes. Aside from the Braak model, there are staging systems in which alternate pathways of spread can affect cortex early before affectation of substantia nigra (Adler and Beach, 2016). The existence of cognitive changes supports this concept; in this cohort, cognitive functions started declining almost at the same time as the manifestation of preclinical motor symptoms, 6–9 years before diagnosis. Recent evidence demonstrated that RBD patients with mild cognitive impairment (MCI) had extensive cortical and subcortical grey matter alterations compared to those without MCI. Thus, it is possible to see cortical changes in a subgroup of RBD patients who are at a greater risk of conversion to DLB versus Parkinson's disease (Rahayel *et al.*, 2018). Note, however, that whereas cognition was only substantially abnormal in prodromal DLB phenoconversion, prodromal motor deficits were clearly present in both Parkinson's disease-first and DLB-first convertors. This might suggest that 'top-down' spread from cortex to substantia nigra is not seen clinically in our cohort. Moreover, it should not be forgotten that different neuronal systems may have different thresholds for clinical presentation (Engelender and Isacson, 2017). Some manifestations may emerge earlier because their corresponding anatomical areas are less able to tolerate synuclein deposition or have less functional reserve (Engelender and Isacson, 2017). In addition to affecting our lead-time estimates,

this may have helped to explain DLB versus Parkinson's disease conversions. For example, up to 30% of cognitively-normal elderly and 70% of patients with MCI show abnormal deposition of amyloid on PET scanning (Chetelat *et al.*, 2013; Petersen *et al.*, 2016). One could hypothesize that those who convert to a dementia-first phenotype might have coincident amyloid deposition, upon which the arrival of even subtle synuclein deposition causes a rapid synergistic neurodegenerative response (Jellinger, 2012).

The minority of iRBD cases who eventually developed MSA were significantly younger at phenoconversion, with more preserved cognition, colour vision, and olfaction, albeit with more severe urinary symptoms compared to Parkinson's disease/DLB phenoconverters. This is in line with a previous prospective study showing that among individuals with pure dysautonomia, MSA-converters were younger with more severe bladder dysfunction, but more preserved olfaction (Kaufmann *et al.*, 2017).

There are some limitations to this study. First, because many patients develop disease in the first few years after baseline, the further we moved from the time of phenoconversion (Year 0), the lower was the sample size. Therefore, estimates become increasingly imprecise at the longer intervals. To mitigate this, we restricted analysis to years with at least four valid measures and applied weighted regression and mixed effects models to consider between-year and between-individual variations in the number of follow-ups. Second, our study relied upon clinical manifestations. Progression scores of these features are inherently dependent on the measure itself, notably its sensitivity to detect subtle abnormalities, and responsiveness to change over time. Moreover, for some of the non-motor manifestations, namely apathy, depression and hallucinations, we relied solely on the UPDRS-Part I items. These single items have demonstrated moderate (i.e. depression and apathy) to strong (i.e. hallucination) correlation with their corresponding comprehensive clinical scales (Gallagher *et al.*, 2012). Third, although many measures were directly observed as they deviated from normal values, the longest-latency variables required back-extrapolation to define a prodromal interval; these long estimates should be considered imprecise. Fourth, although diagnosis of parkinsonism and dementia was made according to standard criteria, some aspects of the diagnosis of phenoconversion (e.g. defining true bradykinesia or delineating substantial functional impact from cognitive loss) remain partially subjective. Therefore, other investigators may have identified phenoconversion slightly earlier or later than we did. Fifth, the overall accuracy and diagnostic parameters are likely to be slightly optimistic compared to how they might perform in real life practice and require replication in an external validation dataset. We also recognize that having annual follow-up visits of an iRBD cohort might have resulted in earlier diagnosis of phenoconversion compared to real life clinical practice (where patients are often diagnosed months to years after symptoms have developed). This implies that results may not fully generalize primary care practices, although it does not influence internal validity of main study question which was to discover trajectories of prodromal neurodegenerative synucleinopathy. Sixth, although our panel was relatively comprehensive in terms of clinical markers, biomarkers such as neuroimaging, heart rhythm measures were measured only at baseline, so cannot be traced over time. Finally, it is critical to emphasize that all participants in our study had iRBD at enrolment. Overall, ~30–50% of Parkinson's disease patients, and 75% of DLB and MSA patients have associated RBD. RBD in the setting of Parkinson's disease generally marks a 'diffuse' subtype, with a strong predominance of non-motor manifestations of autonomic and cognitive dysfunction (Postuma *et al.*, 2011*c*; Fereshtehnejad *et al.*, 2015, 2017; Jozwiak *et al.*, 2017; Kim *et al.*, 2017). Therefore, our findings cannot be directly applied to Parkinson's disease/DLB patients without RBD, who may have less prominent non-motor manifestations (and therefore may have shorter non-motor intervals).

On the other hand, our study had several strengths. Because our cohort was specifically designed to examine prodromal parkinsonism and dementia, we were able to perform relatively deep phenotyping, including a broad list of relevant measures assessed using valid scales. The long follow-up period with repeated measurements enabled us to trace actual (i.e. non-imputed) trajectories for up to 9 years before phenoconversion. Moreover, all measures were applied in the same patients at the same time points, allowing manifestations to be directly compared with each other.

In daily clinical practice, it is not feasible to collect data on all prodromal features. Yet, based on our findings, we highly recommend evaluating individuals at high risk for synucleinopathy (i.e. iRBD) with a basic workup consisting of: (i) motor examination (preferably with UPDRS, optionally adding quantitative motor tests); (ii) office-based cognitive testing (MoCA); (iii) olfactory assessment; and (iv) blood pressure change supine to standing, with screening for constipation and erectile dysfunction.

These tests should require <15 min to perform and target the most informative predictors of phenoconversion in RBD cases.

In summary, the evolution of synucleinopathy from its prodromal stages is becoming increasingly well-defined. There remains an urgent need for disease-modifying therapies to slow down the progression of neurodegeneration from its earliest stages.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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