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Cognitive and neuropsychiatric profiles distinguish atypical parkinsonian syndromes

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Atypical parkinsonian syndromes are distinguished from Parkinson's disease (PD) by additional neurological signs and characteristic underlying neuropathology. However, they can be diagnostically challenging, rapidly progressive and are often diagnosed late in disease course. Their different demographic features and prognoses are well studied, but the accompanying cognitive and psychiatric features may also facilitate diagnosis. Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) may cause cognitive and behavioural manifestations that overlap with frontotemporal dementia, including non-fluent aphasia, apathy and impulsivity. Clinical diagnostic criteria have limited sensitivity, with pathologically confirmed PSP often having presented an initial clinical syndrome other than PSP-Richardson's syndrome.

Here, we integrate cross-sectional multicentre baseline data from the PROSPECT-M-UK and Oxford Discovery cohorts. This allowed us to compare cognitive and psychiatric features across a total of 1138 people with PSP, CBS, multiple-system atrophy (MSA) and idiopathic PD. Data from the different cohorts were harmonized and compared using multiple linear regression.

There were five key results: (i) different syndromes showed distinctive cognitive profiles, using readily applicable 'bedside' screening tools. Frontal executive dysfunction was most evident in PSP, visuospatial deficits in CBS, with milder deficits in memory and executive function in MSA, as compared with PD; (ii) the most prevalent neuropsychiatric features were depression and anxiety in CBS, apathy in PSP, with sleep disturbances common in PD. As expected, apathy correlated positively with impulsivity across all disorders. Neuropsychiatric features were generally better at discriminating between atypical parkinsonian syndromes than were the cognitive domains; (iii) both cognitive function and motor severity declined with disease duration, and motor function predicted cognition in PSP, CBS and PD but not in MSA, suggesting that in MSA cognitive and motor dysfunction are decoupled; (iv) plasma neurofilament light chain (NFL) levels, measured in a subset of patients, correlated with cognitive deficits in PSP, but not motor deficits; (v) cognitive deficits contributed to the impairment in activities of daily living after controlling for motor severity, with every two points on the Montreal Cognitive Assessment worsening the Schwab and England score by one point.

In anticipation of future neuroprotective therapies, we present a classifier to improve diagnostic accuracy for atypical parkinsonian syndromes *in vivo*. Longitudinal cohort studies with resources for neuropathological gold standard diagnosis remain important to validate better diagnostic tools for people with PSP, CBD, MSA and atypical parkinsonism.

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Introduction

While cognitive decline and neuropsychiatric symptoms are recognized as major non-motor features of idiopathic Parkinson's disease (PD),[1,2] they are a prominent feature of atypical parkinsonian syndromes (APS), progressive supranuclear palsy (PSP), corticobasal degeneration syndrome (CBS) and multiple system atrophy (MSA).[3,4] These disorders are typically contrasted across a range of motor, ocular, autonomic and cerebellar clinical features. Although relatively distinct in their classical presentations and underlying neuropathology, APS are clinically, genetically and pathologically heterogeneous[5,6] and are frequently misdiagnosed. They are less common than PD, with a reported age-adjusted prevalence (5 per 100 000 for PSP and MSA)[7,8] that is approximately 40 times less common than prevalence rates reported for PD (108–257 per 100 000).[9] PSP, CBS and MSA progress more quickly than PD, leading to significantly reduced life expectancy.[5,6,10] Here, we assess the cognitive and neuropsychiatric deficits in APS[1] and compare to deficits in PD.[11] As for PD,[12-14] these domains affect burden and survival in PSP and CBS cohorts.[10,15]

Cognition is rich and multidimensional in nature, making it challenging and time-consuming to clinically assess, particularly with people whose illness also causes severe communication deficits or cognitive slowing.[4] However, neurobehavioural profiling can index the function of various brain regions to associated neurotransmitters. A range of psychiatric manifestations may also be associated with these conditions including depression, anxiety, impulsivity, apathy, hallucinations, delusions, anger and emotional lability. We ask whether these differ across the various clinical syndromes and how cognition differs between people with PD, PSP, CBS and MSA, presenting to movement disorders and memory clinics. Establishing cognitive and neuropsychiatric discriminators may help facilitate earlier and more accurate diagnosis, improve understanding of related pathophysiology and permit tailored treatments.

In this study we test whether PSP, CBS and MSA have distinctive patterns of cognitive deficits compared with each other and with PD. We also test whether cognitive deficits correlate with neuropsychiatric symptoms, or with motor severity, and assess the impact of cognitive and neuropsychiatric deficits on patients and families. We studied cognitive and neuropsychiatric profiles across 1138 individuals with four diagnoses: PSP ($n = 100$), CBS ($n = 50$) and MSA ($n = 53$) and PD ($n = 935$). We sought to establish cognitive profiles for the different conditions, correcting for age and disease duration. By comparing profiles across the range of movement disorders, using tools that are readily used in a healthcare setting, we aim to provide clinical pointers to improve diagnostic accuracy and management of these challenging conditions.

Materials and methods

Study design

The PROSPECT-M-UK natural history cohort comprises seven UK study sites (London, Oxford, Cambridge, Newcastle, Brighton,

Newport and Manchester).[5] We obtained study-wide ethical approval from the Queen Square research ethics committee (14/LO/1575). We recruited patients for baseline assessment between September 2015 through to February 2020. We excluded patients with other known neuropsychiatric conditions.

Oxford Discovery recruited PD patients diagnosed within 3.5 years between September 2010 and October 2015, from a Thames Valley UK population base.[16]

Participants: diagnostic criteria, sampling and reclassification

All analyses were cross-sectional. Data were brought together from two large cohorts of patients: the Oxford Parkinson's Disease Centre (OPDC) Discovery[16] and PROSPECT-M-UK cohorts.[5] We used the latest diagnostic criteria for all groups, based on clinical assessment at the time of diagnosis. Note that at the time the study was set up, we defined PROSPECT patients entering the study as having: PSP, following the 1996 National Institute of Neurological Disorders and Stroke and the Society for PSP Inc. (NINDS-SPSP) criteria[17]; CBS, following the Armstrong criteria[18]; or MSA, following the revised Gilman criteria.[19] The PROSPECT cohort also included patients with indeterminate progressive movement or cognitive disorders, thought likely to have an atypical parkinsonian syndrome (based on having atypical clinical features for PD) but not meeting any of the above diagnostic criteria, as indeterminate cases. We reclassified PROSPECT study cases with a diagnosis of PSP, CBS or indeterminate phenotype according to current Movement Disorder Society (MDS)-PSP criteria at the end of baseline recruitment.[20] Our rationale for PSP reclassification was that, at the start of the PROSPECT study, we were aware that the PSP criteria were insensitive. So, we included patients with syndromes that were atypical, intermediate or cognate with PSP. With the introduction of the 2017 revised MDS criteria, most of these additional cases fell within the new clinical definition of PSP while retaining high correlation with pathological PSP.[21] All reclassified PSP cases fulfilled at least 'possible' diagnostic criteria. The PSP cases included Richardson's syndrome, subcortical (PSP-parkinsonism, PSP-progressive gait freezing) and cortical (PSP-speech/language, PSP-frontal, PSP-CBS) subtypes (Supplementary Fig. 3). The PROSPECT cohort also included patients who were truly indeterminate, who were not included in the present analysis. Patients were also assessed 12 months later, when the clinician diagnosis was re-assessed. These labels were the same as the initial diagnoses in most cases (Supplementary Fig. 1).

The diagnosis we have chosen to use for the primary analysis was the clinician's response to the question: 'Does the patient have a current clinical diagnosis of PSP, MSA, CBS or atypical parkinsonism syndrome, or is a control?', answered at the baseline visit. Although patients were asked to consider future brain donation, only eight patients had neuropathology available at the time of analysis, so neuropathological labels were not included. In the PROSPECT cohort, a change in clinical diagnosis between baseline and 1 year occurred in 6.2% of cases (15/243), as previously reported.[6] Cases with PD recruited from the OPDC Discovery cohort study were diagnosed using Queen Square Brain Bank clinical diagnostic criteria.[22] In the OPDC Discovery cohort, 5% of patients were excluded on the basis of a diagnosis other than PD being made over a 4.5 year period.

The PROSPECT-M-UK cohort included $n = 905$ people, of whom we selected those who had a Montreal Cognitive Assessment (MoCA)[23] and had a current clinical diagnosis of PSP, MSA or CBS ($n = 203$). Most ($n = 177$) also had data for the Addenbrookes Cognitive Examination III (ACE).[24]

The OPDC Discovery cohort included patients with idiopathic PD, who also had an MoCA assessment. Many patients in this cohort had longitudinal data, but in this study we examined only cross-sectional measurements. Our analysis aimed to examine how neuropsychological and neuropsychiatric features associate with clinical diagnoses. At the time of enrolment into the OPDC Discovery cohort, the time since first symptom was significantly shorter (median 2.9 years) than the other groups (4.4 years), and therefore we subsampled later visits from this cohort to produce a distribution that matched the other groups. This subsampling yielded $n = 935$ people with PD, matched to PROSPECT by the time since first symptom (median 4.3 years).

Clinical assessments

Disease severity measures

All scales were tested while patients were on their normal dopaminergic medications. At each PROSPECT cohort study visit, a neurological history and examination were performed and the PSP rating scale (PSPRS)[25] for PSP and CBS patients, or Unified Multiple System Atrophy rating scale (UMSARS)[26] for MSA patients, was administered by a clinician. In addition, all cases were assessed using the MDS Unified Parkinson's Disease Rating Scale part II and III (MDS-UPDRS-II and III)[27] and Schwab and England activities of daily living scale (SEADL).[28] PD cases from the OPDC Discovery cohort underwent baseline MDS-UPDRS-II and III and SEADL.

Motor symptoms/signs

We used MDS-UPDRS part III[27] in patients with PSP and CBS, and in MSA we used UMSARS part II, which both reflect clinician-reported motor severity.[26] Since UMSARS has slightly different scales (e.g. no score for freezing or spontaneity), values were Z-scored separately for each group, so that scores reflected a patient's relative motor severity within that group. All Discovery PD patients were assessed with MDS-UPDRS part III.

Cognitive features

Demographics and cognitive testing available across PSP, CBS, MSA and PD groups are summarized in Table 1. All patients in both cohorts had a MoCA,[23,24] adjusted for prior educational years. As mentioned above, most patients in the PROSPECT cohort (atypical PD) had the ACE-III. Additional cognitive tests were conducted in some patients but were not included in this analysis. The Edinburgh Cognitive Assessment was completed in a proportion of PROSPECT patients but fewer than the ACE-III. Hayling sentence completion, Spot-the-word, Frontotemporal Dementia-Psycholinguistic Assessments of Language Processing in Aphasia (FTD-PALPA), emotional recognition, Frontal assessment battery, word repetition and fragmented letters were each completed in about 30% of participants. In the Discovery PD cohort, patients were also assessed with phonemic and semantic fluency.[16] Since these datasets were only partial, they were not included in the present analysis.

Neuropsychiatric features

Patients with PSP and CBS had neuropsychiatric features extracted from MDS-UPDRS part I [sleep (1.7), psychosis (1.2), depression (1.3), anxiety (1.4), apathy (1.5)]. Those with PD had neuropsychiatric

Table 1 Demographics of progressive supranuclear palsy, corticobasal syndrome, multiple system atrophy and Parkinson's disease patients

	PSP	CBS	MSA	PD	Statistic	P
n	100	50	53	935		
Age, years, mean (SD)	71.0 (7.4)	68.3 (7.8)	63.2 (9.6)	69.1 (9.4)	$F(3,1134) = 4.71$	0.003
Male, %	61.5	36.0	71.2	63.9	$\chi^2 = 7.83$	ns
Time since symptom onset, years	4.7 (3.7)	4.8 (3.0)	6.8 (3.8)	4.7 (2.3)	$F(3,1134) = 4.81$	0.002
Mean MoCA	22.9 (4.6)	21.2 (7.3)	25.2 (3.6)	24.5 (3.8)	$F(3,1134) = 20.93$	<0.001
Mean ACE (*n*)	77.3 ± 13.7 (89)	71.3 ± 22.3 (39)	83.8 ± 8.2 (49)	(N/A)	$F(2,174) = 7.72$	<0.001

ACE = Addenbrooke's cognitive examination; CBS = corticobasal syndrome; MoCA = Montreal cognitive assessment; MSA = multiple system atrophy; N/A = not applicable; ns = not significant; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

Table 2 Sources of neuropsychiatric data in the four patient groups

Neuropsychiatric data type	PSP	CBS	MSA	PD (Discovery)
Apathy				
MDS-UPDRS 1 (1 Q 0–4)	98/100	49/50	2/53	935/935
CBI (5 Qs: enthusiasm, interest, social, worry, affection, each 0–4)	89	37	41	0
Impulsivity				
MDS-UPDRS 1 'Dopamine dysregulation / ICDs' 0–4	98	48	2	935
CBI ('acts impulsively' 0–4)	87	36	41	0
Psychosis				
MDS-UPDRS 1 (Q2 0–4)	98	49	2	935
CBI (3 Qs: auditory hallucination, visual hallucination, untrue beliefs, each 0–4)	89	37	41	0
Depression				
MDS-UPDRS 1 (1 Q depressed mood, 0–4)	98	49	2	935
CBI (2 Qs, cries, sad)	89	37	41	0
Anxiety				
MDS-UPDRS 1 (1 Q anxious mood, 0–4)	98	49	2	935
Sleep				
MDS-UPDRS 1 (1 Q sleep problems, 0–4)	98	49	2	935
CBI (2 Qs: disturbed at night, more in day, 0–4)	89	37	41	0

CBI = Cambridge Behavioural Inventory; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MSA = multiple system atrophy; ICD = impulse control disorder; PD = Parkinson's disease; PSP = progressive supranuclear palsy; Q = question.

features extracted from the MDS-UPDRS only, which included all factors except impulsivity (Table 2). Those with MSA had UMSARS, which included motor but not neuropsychiatric features. Most patients with PSP, CBS and MSA (PROSPECT-M cohort) had the Cambridge Behavioural Inventory Revised (CBI-R) assessment,[29,30] which provided more detailed observations of neuropsychiatric features including apathy and impulsivity. Patients in the Discovery PD cohort did not have a CBI-R. They were additionally assessed with the Hospital Anxiety and Depression Scale and Beck Depression Inventory,[16] but these were not included in the present analysis.

Blood samples

Non-fasting serum samples for Neurofilament-light chain (NfL) were taken at the baseline visit and were processed using standardized protocols and stored in 0.5 ml aliquots at −80°C within 60 min of sample collection. Serum NfL was measured using an ultrasensitive single molecule (Simoa) assay.[31]

Data analysis

Harmonization of the MoCA with ACE

The ACE-III scores separately over five cognitive domains and was recorded in all the people with PSP, CBS and MSA, alongside the MoCA. Patients with PD did not have ACE-III, however, and instead had MoCA scores, which were measured in all groups. We therefore used the MoCA scores to impute ACE-III scores. There is considerable overlap between the individual MoCA and ACE tests on some domains, e.g. orientation, clock and cube drawing, fluency. The MoCA has fewer items in some other domains, with lower resolution in episodic memory and language, but has additional executive items including working memory and trails items.

In patients who had both ACE-III and MoCA (i.e. PROSPECT, $n = 177$), we used linear regression to predict the five ACE-III components, using individual question scores of the MoCA. For each ACE-III component (attention, memory, fluency, language and visuospatial), we asked whether it could be predicted using a linear combination of the 12 MoCA questions (trail making, cube drawing, clock drawing, naming, attention, vigilance, serial sevens, language, phonemic fluency, abstractions, delayed recall, orientation). Note that the ACE-III combines phonemic and semantic fluency into one subscale score. To reduce the possibility of overfitting, lasso and ridge regularization was included. This penalizes adding unnecessary terms with large coefficients in the model.

$$\text{ACE-III components} \sim \text{Trails} + \text{Cube} + \text{Clock} + \text{Naming} + \text{Attention} + \text{Vigilance} + \text{Serial} + \text{Language} + \text{Phonemic} + \text{Abstractions} + \text{Delayed} + \text{Orientation}$$

This yielded a 5×12 matrix of weights, that can be used to map the MoCA question scores on to predicted ACE-III domain scores

(Supplementary Fig. 2). The linear regression in-sample predictions had mean absolute errors of 0.9 to 3.1 points for each domain. Then, to compare PD in the Discovery cohort to the other diagnoses, we used these regression weights to create estimated ACE component scores.

The method described included all diagnostic groups in a single regression. However, it is possible that the mapping from MoCA to ACE-III might differ according to disease. In practice, this might mean for example that the ACE Attention score is predicted by MoCA orientation questions in one group, but by MoCA trail making in another group. To test for this possibility, we fitted linear models as above (one for each ACE variable) that also included interaction terms between the MoCA predictors and the diagnoses. In this analysis, none of the Diagnosis × MoCA terms were significant, in predicting any of the five ACE variables. Further, we performed the regression in each group individually (PSP, CBS, MSA) and retrieved similar coefficients.

Harmonization of the CBI with MDS-UPDRS

We sought to compare sleep, psychosis, depression, anxiety, apathy and impulsivity across groups. All patient groups had MDS-UPDRS[27] except MSA patients, who instead had UMSARS,[26] which did not include psychosis, depression, apathy, impulsivity, sleep or anxiety items. All groups except for PD (Discovery) also had CBI, which includes more detailed questions for each of these except sleep and anxiety. We therefore imputed the MDS-UPDRS questions for MSA using CBI. This was done in a similar way to above, taking the CBI features most similar to the MDS-UPDRS question (Supplementary Table 1), and fitting a linear model in the 141 patients who had both, to predict the six UPDRS neuropsychiatric questions in the 41 MSA patients who had CBI. While CBI had several impulsivity questions, the only relevant MDS-UPDRS 1 question is dopamine dysregulation syndrome (DDS), which we used as a surrogate for impulsivity.

Statistics

Comparison of variables across groups

Groups were compared directly using one-way ANOVA for continuous (age, time since symptom onset, cognitive scores, motor scores) and χ^2 for discrete variables (sex), followed up by *post hoc* paired tests, conducted using the statsmodels package in Python (Table 1).

Sliding window means

To visualize the relation between two continuous variables, we used a sliding window, in which quantiles of one variable were used to bin another variable. We took windows of the *x*-variable and computed the mean value of the *y*-variable within that window, along with the standard error of this mean. We used a fixed width Gaussian window over the quantiles of the *x*-data, with width 20% in quantiles. As the sliding window was Gaussian, the weighted mean and standard error were used. We used this to plot cognitive function (MoCA) as a function of disease trajectory (time since symptom onset, motor progression and age). The mean and standard error in each window, width 20 percentiles, were plotted.

Cognition as a function of time and severity

To understand how cognition changed with time since disease onset, MoCA scores were compared using a linear model, predicted by group, time since first symptom (in years) and the interaction of Time × Group. Age was included as a covariate. All patients were entered in a single model, so that the effects of group, time and the interaction Group × Time, could be separately quantified. *Post hoc* pairwise comparisons were performed to compare groups using Mann–Whitney, with Benjamini–Hochberg correction for multiple comparisons. The same model was then tested but using motor severity scores from UPDRS instead of time since first symptom. Group comparisons used PD as the reference category.

To test the differences in trajectories between groups, we used linear models with each variable Z-scored across all groups. Group was a categorical variable and we included its interactions with the continuous variates, allowing the model to capture the different slopes in different groups. In the linear models, groups were coded with PD as the reference. In this analysis, the main effect of disease indicates how different diseases have different overall cognition, and the interaction term indicates how steeply cognition is affected by the variable of interest. Time since disease onset was operationalized using the retrospective date of first symptoms, as estimated by the patients or carers.

Comparing cognitive and neuropsychological profiles across conditions

To directly compare the five cognitive domains across conditions, the scores for each domain was Z-scored across all four groups. A single linear model was used to predict all five domains of the ACE cognitive score, as a function of group. Interactions between domain and group were included to determine whether the conditions affected one domain more than another. We included age, time since first symptom and motor scores as covariates. Comparisons within this model were performed using t-contrasts, using PD as a reference class.

To demonstrate that these differences in profile could be applied to distinguish the diagnoses, from each other, we built classifiers. A logistic regression classifier was trained to distinguish between pairs of conditions using the five cognitive domains, being tested using leave-one-out cross-validation (LOO-CV). The training data was balanced by random down-sampling of the larger class to the size of the smaller class on each LOO iteration. Further, the five domain scores were zero-centred within each subject so that we factored out the overall severity of cognitive deficits, focusing only on the pattern across cognitive domains. For clarity, these classifiers did not include any covariates in this analysis. The cross-validated accuracy for each pair of diagnoses is reported. The classifiers each yielded out-of-sample predictions for each patient, in logit units. These predicted values were used to calculate receiver operating characteristic curves.

We related cognitive performance to motor symptoms in all groups, and to neuropsychiatric manifestations in PD, PSP and CBS but not MSA, because the MSA apathy and impulsivity questions were only on the CBI and therefore were not matched with the other groups (Table 2).

Testing the effect of cognition on activities of daily living

We tested whether MoCA predicted the impairment in activities of daily living (ADLs), over and above motor disability, using linear regression. First, we established if both MoCA and motor scores predicted Schwab and England ADL score using linear regression. Second, we factored out motor performance using a model where

the Schwab and England ADL score was predicted by motor score and group, and their interaction, and the residuals were taken. These residuals were then predicted in a linear model by MoCA. To determine if this cognitive impact was group specific, we then added group and Group × MoCA interaction terms in the model. To ensure the tests were not influenced by motor dysfunction impacting cognitive scores, we repeated this analysis in two ways. First, the MoCA scores were residualized against motor performance in the same way as the ADLs above. A model was tested where the residuals of the ADL score were predicted by the residuals of the MoCA. Second, we accounted for the possibility that cognitive subtasks were differentially impacted by motor function. The 12 individual MoCA subscales were predicted in a linear model by motor scores, and the residuals were taken, and added together to yield a reconstructed 'motor-normalized' MoCA score. In a further linear model, this reconstructed MoCA was also used to predict the ADL residuals.

Results

Clinical features

Demographics of the patient groups, summarized in Table 1, demonstrated that the PSP group was older than the mean [ANOVA on age, $F(3,1134) = 4.71$, $P < 0.001$; PSP versus PD independent two-tailed $t(1034) = 2.25$, $P = 0.02$; PSP versus MSA $t(151) = 4.31$, $P < 0.001$]. The sex differences between groups was not significant ($\chi^2 = 7.83$, $P > 0.05$). The time of testing after symptom onset ranged from 0 to 10 years, and was later in the disease for MSA patients [$t(1117) = 10.3$, $P < 0.001$]. The breakdown of subtypes of PSP, CBS and MSA are presented in Supplementary Table 2 and Supplementary Fig. 3.

Cognition and cognitive decline most severe in CBS

Cognitive function, as measured by total adjusted MoCA, differed among the groups (non-parametric one-way ANOVA, Kruskal–Wallis $H = 19.0$, $P < 0.001$). As expected, MoCA decreased with age [Fig. 1A; main effect of age, $F(1,1125) = 126.0$, $P < 0.001$]. Global cognitive performance was worse in CBS patients, followed closely by PSP patients [main effect of group, $F(3,1125) = 17.2$, mean CBS MoCA: 20.8 ± 7.1 versus mean PSP MoCA: 22.5 ± 4.4; Fig. 1B and Supplementary Table 3], but scores were similar between MSA and PD (mean 24.9 ± 3.6 versus 24.5 ± 3.8, respectively; coefficients in Supplementary Fig. 4). *Post hoc* pairwise comparisons are presented in Fig. 1B. With longer time from symptom onset, the decrease in MoCA depended on the diagnosis [Group × Time interaction, $F(3,1125) = 11.4$, $P < 0.001$], with a steeper slope in CBS than in PD ($t = 6.0$, $P < 0.001$), PSP ($t = 4.67$, $P < 0.001$) and MSA ($t = 4.23$, $P < 0.001$). After accounting for these differences in slope, time since symptom had only a weak overall effect on cognition [Fig. 1C; main effect of time $F(1,1125) = 4.48$, $P = 0.035$], presumably related to the way patients were recruited. The plots show a quantile-based moving average of the raw data, rather than the linear model fit. Including sex and its interactions in the linear model showed no significant effects and no improvement in fit.

Cognitive deficits did correlate with motor severity [$F(1,1124) = 17.0$, $P < 0.001$], although the slope of this cognitive deficit with respect to motor deficits did not differ significantly between the groups [Motor × Group interaction, $F(3,1124) = 2.57$, $P = 0.053$].

Distinctive cognitive profiles for different syndromes

The cognitive profiles of the groups differed in specific domains [Fig. 2; interaction of Domain × Group, $F(12,5613) = 5.31$, $P < 0.001$].

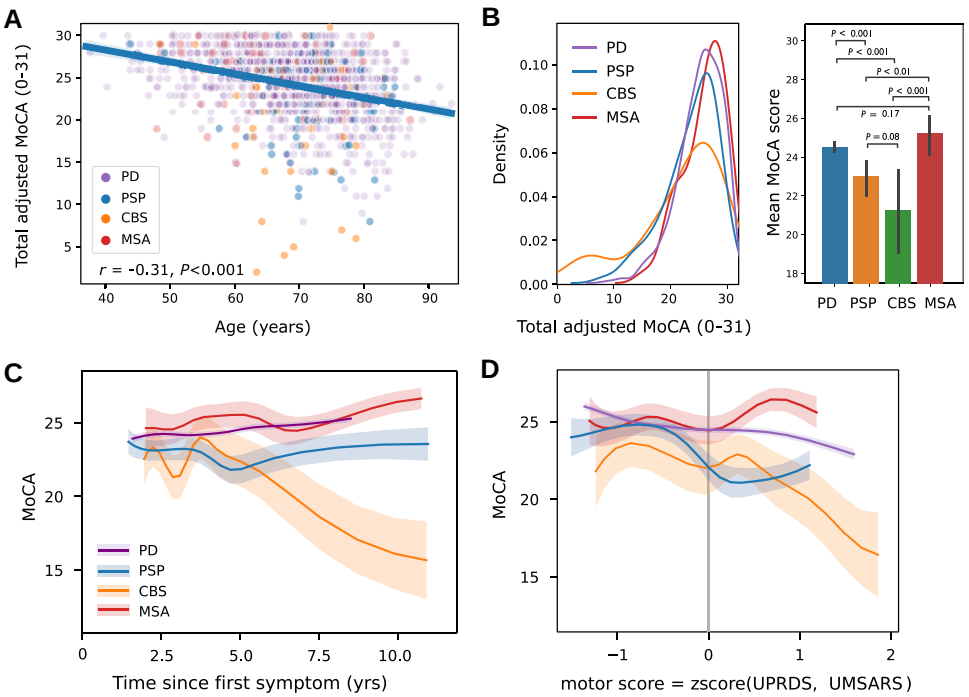

Figure 1 Overall cognition across conditions. (**A**) Cognition declined with age. (**B**) Patients with CBS had the lowest average cognitive scores overall. Curve is a kernel density estimated within each group. *P*-values are from Mann–Whitney tests with Benjamini–Hochberg correction. (**C**) Cognitive scores were not related to time after onset. Line is a moving average of the raw data, calculated as a sliding window mean, i.e. the mean MoCA score of people lying within window bin of 20% of people in the group centred on a given time since first symptom. Error bars indicate standard error of this mean. The curve is illustrative only, noting that the statistic tests used linear models. (**D**) Decline was coupled to motor symptoms, in all groups except for MSA. CBS = corticobasal syndrome; MoCA = Montreal Cognitive Assessment; MSA = multiple system atrophy.

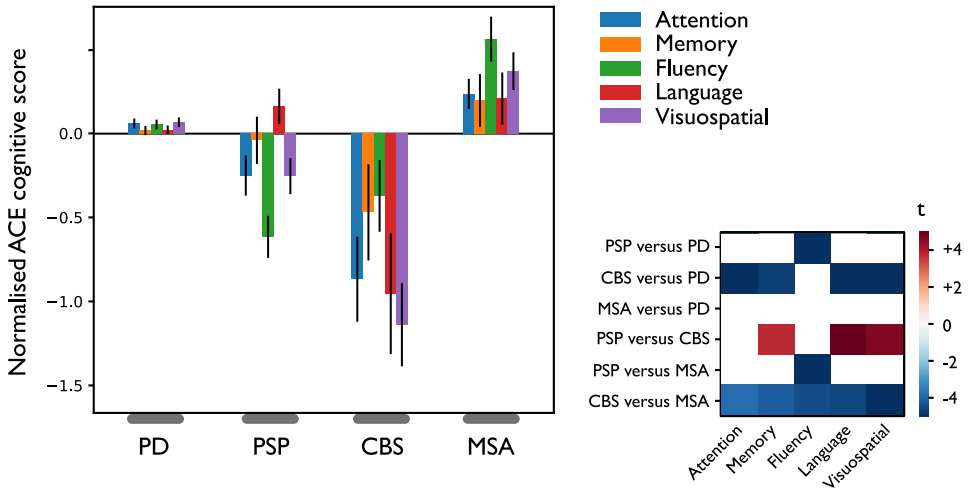

Figure 2 Distinctive patterns of cognitive impairment in different disorders. (**A**) Mean values of each ACE domain, after Z-scoring each domain across the groups. Patients with CBS had significantly worse visuospatial function, whereas PSP had worse executive function. Error bars are standard error of the mean. (**B**) Matrix of contrasts, indicating which cognitive domains differed between groups, in a linear model that included age, time since first symptom and motor score as covariates. The pairwise *t*-statistic (truncated to range −5 to +5) is shown only for contrasts that were significant at $P < 0.05$ after Bonferroni correction for 30 comparisons. ACE = Addenbrooke's Cognitive Examination III; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

Pairwise contrasts using PD as the reference category demonstrated that PSP was characterized by worse verbal fluency [PSP versus PD, $t(5613) = 6.86$, $P < 0.001$, corrected for 30 multiple comparisons], CBS by worse visuospatial [$t(5613) = 7.75$, $P < 0.001$] and fluency performance (model coefficients in Supplementary Table 4). Qualitatively identical results were obtained using a mixed model accounting for a subject-wise intercept. When we excluded participants with longer disease duration (symptoms starting >7.5 years before testing), weaker but qualitatively similar results were obtained (Supplementary Fig. 5).

We next applied classifiers to distinguish between each pair of diagnoses. Note that these classifiers used only the relative pattern of deficits, after subtracting out a patient's overall performance level. The classifiers achieved an area under the curve (AUC) of 71% in distinguishing PD from PSP, 74% distinguishing PSP from CBS, 68% PSP from MSA and 67% CBS versus PD; but was at chance for MSA versus PD, and CBS versus MSA (Supplementary Fig. 6A). The classifiers performed at a very similar level after residualizing the ACE scores for age, suggesting that the results cannot be explained by age-dependent shifts in the pattern of cognitive deficits. The coefficients for the classifiers can be found at http://osf.io/mz98x.

Distinctive neuropsychiatric profiles for different syndromes

Next, we examined neuropsychiatric features of each syndrome. For MSA these data were imputed from the CBI. To put each domain on a comparable scale, as for cognitive scores above, the score for each domain was Z-scored across all four groups. The profiles differed across conditions [Fig. 3A; interaction of six psychiatric Dimensions × Group, $F(15,6696) = 21.4$, $P < 0.001$]. The component t-contrasts showed that patients with PSP and CBS were more likely to suffer from apathy, anxiety and depression than PD (Fig. 3B and for statistics see Supplementary Table 5), whereas anxiety was highest in CBS and sleep disturbance was most common in PD. Since impulsivity on the UPDRS is only indexed by dopamine dysregulation, we aimed to further understand impulsivity and apathy using questions from the CBI (Fig. 3C). CBI was assessed in more patients with MSA and reports impulsivity rather than dopamine dysregulation. PSP was the most strongly associated with both impulsivity and apathy. In keeping with previous work, apathy and impulsivity were positively correlated in this group (Fig. 3D).[32]

On a group level, impulsivity (CBI impulsivity question > 0) was present in 54% of PSP (46/86), compared with 26% of CBS (10/38) and 12% of MSA (5/42). Therefore, impulsivity conferred an odds ratio of 3.34 for PSP relative to CBS and 8.6 for PSP relative to MSA. On the other hand, carers of people with PSP made similarly few endorsements on questionnaire items related to psychotic phenomena and related behavioural change (CBI items on seeing or hearing things that are not really there and bizarre ideas that cannot be true), being present in 16% of PSP (14 of 89) versus 19% of those with CBS (7 of 37).

These observations suggested that the relative pattern of neuropsychiatric features could help with diagnosis. To assess this, a classifier was trained to discriminate diagnoses based on psychosis, apathy, depression and dopamine dysregulation syndrome (DDS from UPDRS—note that true impulsivity measured on CBI was not available in PD or in 30% of CBS). Again, mean symptom scores for each person were subtracted from their feature scores, to emphasize only the pattern, not the overall neuropsychiatric burden, in individuals. The classifier was able to discriminate PSP from PD with an AUC of 73%, and from CBS at 62% (Supplementary Fig. 6B). Moreover, it could discriminate PD from MSA with 83% AUC and from CBS with 65% AUC.

Activities of daily living are affected by cognition independently of motor score

First, we demonstrated that cognition impacts on ADL scores. Univariate linear regression demonstrated that MoCA strongly predicted ADL scores (Fig. 4A), with a coefficient of 1.10 [$t(1128) = 8.29$, $P < 0.001$], indicating that 10 points drop in MoCA is associated with 11% reduction in ADL score. However, they were also well predicted by motor severity [Fig. 4B; $t(1128) = 13.5$, $P < 0.001$], which itself correlates with MoCA. To ask whether there is an independent effect of cognition after factoring out motor disability (with which it is

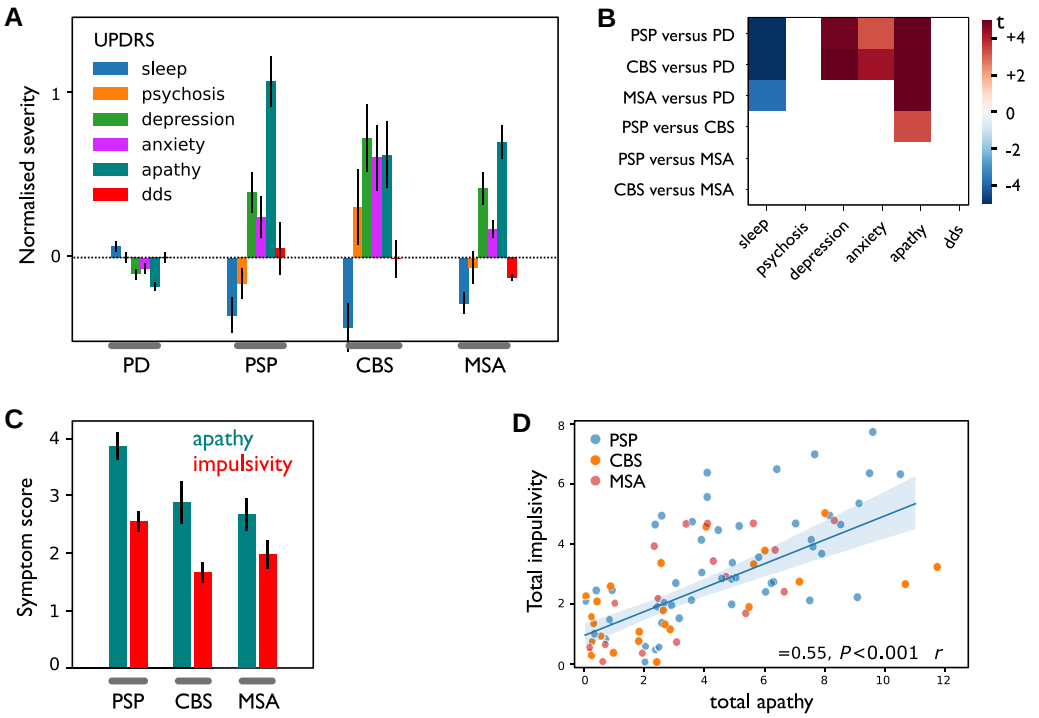

Figure 3 Neuropsychiatric features of atypical syndromes. (**A**) Mean severity of each neuropsychiatric feature, from MDS-UPDRS and UMSARS. (**B**) Pairwise contrasts between the diagnoses, indicating which diagnoses differed in the severity of the features. Colours indicate where $P < 0.05$ Bonferroni corrected. (**C**) More fine-grained impulsivity and apathy data was available from the CBI in a subset of patients. PSP led to greater apathy and impulsivity than other conditions. (**D**) Across conditions, apathy correlated positively with impulsivity. CBI = Cambridge Behavioural Inventory; CBS = corticobasal syndrome; dds = dopamine dysregulation syndrome; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MSA = multiple system atrophy; PD = Parkinson's disease; PSP = progressive supranuclear palsy; UMSARS = Unified Multiple System Atrophy Rating Scale.

strongly correlated), the residuals of SEADL were taken with respect to motor severity using a linear model that included group as a factor (Motor score × Diagnosis), and these residuals were then regressed against MoCA. MoCA strongly predicted SEADL residuals after having factored out motor effects [Fig. 4C; $F(1,1128) = 6$, $P < 0.001$]. In terms of effect size, one standard deviation worsening of motor score impacted SEADL by 6.9%, and one standard deviation worsening of cognitive function impacted SEADL by 5.5%. Splitting this effect by diagnosis revealed that it did not vary by group [interaction of Group × MoCA, $F(3,1122) = 0.45$, $P = 0.71$]. Cognition was an important contributor to ADLs for CBS, PD and PSP (all $P < 0.05$) but less so in MSA (Fig. 4D).

To ensure these findings were not driven by cognitive scores being influenced by motor deficits, we obtained the same result when we used MoCA scores after they had been adjusted for motor scores and diagnosis ($z = 3.99$, $P < 0.001$). To account for the possibility that motor deficits may differentially impact cognitive subtests, we repeated this analysis after correcting the MoCA subscales individually for motor scores; the re-constructed motor-normalized MoCA also predicted ADLs ($t = 3.54$, $P < 0.001$).

Biomarkers of neurodegeneration track cognitive function

A subset of patients with PSP ($n = 69$) and CBS ($n = 30$) had NfL measurement in plasma. Patients who did or who did not have NfL measurements did not differ in basic characteristics (Supplementary Table 6). We assessed the relationship of NfL to cognitive and motor function using linear regression in each group (Fig. 5A). NfL predicted MoCA in PSP [$t(68) = 2.46$, $P = 0.016$] but not MDS-UPDRS motor score [$t(67) = 0.08$, $P = 0.93$; Fig. 5B]. In the smaller CBS group, NfL neither predicted MoCA [$t(29) = 0.15$, $P = 0.89$] nor MDS-UPDRS motor score [$t(29) = 0.43$, $P = 0.67$]. To directly compare whether NfL tracked motor versus cognitive function in PSP, both MoCA and MDS-UPDRS motor score were included as predictors. The relationship between cognition and NfL remained strong [$t(67) = 2.44$, $P = 0.017$] while motor function remained unpredictive of NfL. This effect remained when including age as a covariate [$t(66) = 2.24$, $P = 0.028$] or the number of years since symptom onset [$t(66) = 2.41$, $P = 0.019$]. NfL did not predict proxies of rate of change over time (Supplementary Table 7). Together, these results indicate that cognitive function was specifically related to NfL.

Discussion

This study describes cognitive and neuropsychiatric features from a large longitudinally assessed atypical parkinsonian cohort (diagnosed clinically with PSP, CBS, MSA in PROSPECT-M-UK) and a longitudinal PD cohort (Oxford Discovery). Cognitive and neuropsychiatric profiles were compared across individuals with PSP ($n = 100$), CBS ($n = 50$), MSA ($n = 53$) and PD ($n = 935$), to determine whether the diagnostic groups have distinctive patterns of cognitive deficits, and whether these correlated with motor severity or neuropsychiatric symptoms. Key findings were: (i) people with CBS had the most severe baseline cognitive deficits, and steepest relationship between cognition and symptoms duration, followed by PSP, then MSA and PD who performed similarly; (ii) PSP, CBS and MSA manifested different patterns of cognitive

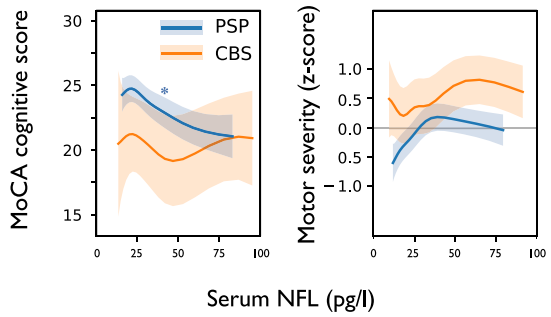

Figure 4 Cognition contributes to activities of daily living. (**A**) Cognitive scores strongly predict activities of daily living. (**B**) Motor severity also predicts activities of daily living. (**C**) After accounting for motor effects, cognitive scores still predict activities of daily living. (**D**) Same split by groups. CBS = corticobasal syndrome; MoCA = Montreal Cognitive Assessment; NFL = Neurofilament light; PSP = progressive supranuclear palsy.

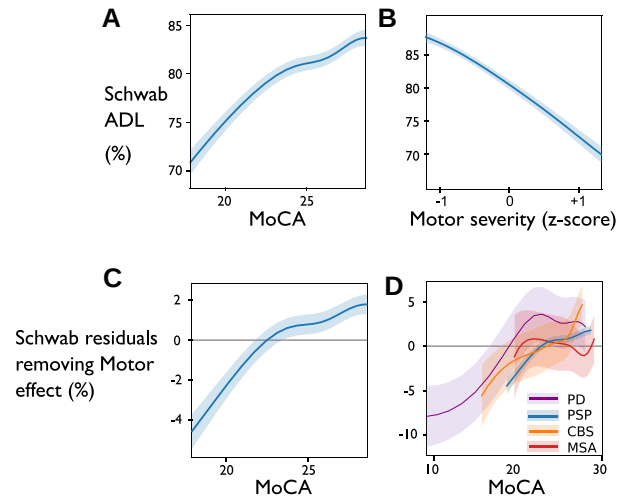

Figure 5 Neurofilament tracks cognition. (**A**) Neurofilament light chain correlated with decline in MoCA, in PSP. Curves are moving averages. (**B**) The correlation with motor severity was not significant. ADL = activities of daily living; CBS = corticobasal syndrome; MoCA = Montreal cognitive assessment; MSA = multiple system atrophy; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

impairment with CBS having worse visuospatial function and PSP having worse fluency (Fig. 2); (iii) there were distinct neuropsychiatric profiles with PSP and CBS more likely to suffer apathy and depression than PD, anxiety was highest in CBS; while sleep disturbance was most common in PD (Fig. 3A); (iv) activities of daily living were affected by cognitive performance independently of motor scores, across the cohort; (v) neurofilament levels predicted cognitive performance, rather than motor scores, in PSP; and (vi) our classifier was able to discriminate PSP from PD with an AUC of 76% and from CBS at 61%. Moreover, it could discriminate PD from MSA with 88% AUC, and from CBS with 66% AUC, which may be clinically useful given the diagnostic challenges PSP, MSA and CBS can pose.

Our results help towards a pragmatic approach for improving the speed and accuracy of diagnostically challenging conditions. Clinicians should combine multiple sources of information when making a diagnosis, from history, examination and tests (whether cognitive, imaging, CSF, skin and/or blood biomarkers). A cognitive differentiator that can be integrated with other diagnostic features will be helpful to many clinicians.

Our strategy of removing the overall severity from the cognitive profiles, before examining classifiers, aimed to remove confounders from the information provided by the classifier. For example, age of presentation, educational level and speed of progression are often considered by clinicians when making clinical diagnoses, and therefore if the outputs of cognitive measures are to be integrated by a clinician, they need to factor out these confounders. In other words, for a classifier to have added-value, it must factor out information that the clinician is already using. For example, imagine that a clinician feels PSP is more likely in view of a person's age, and they now want to incorporate additional evidence from cognitive scores. If the cognitive scores also correlate with age, then simply adding this evidence on would risk 'double counting' the evidence, leading to erroneous conclusions. We believe that these confounds will have less impact if a classifier uses the pattern of relative cognitive strengths and weaknesses, while ignoring the overall severity of cognitive deficits.

Demographics, baseline cognition and cognitive decline

PD and MSA groups were generally younger, and PSP older. With increasing time since symptom onset, CBS had declined most steeply compared with other groups (Fig. 1C). There was a strong negative age effect on total MoCA scores across all four groups. When total MoCA scores were compared using a linear model, time since onset as a predictor only weakly affected cognition, suggesting differential recruitment depending on disease severity. Cognitive deficits were coupled to motor symptoms and signs in all groups except MSA (Fig. 1C and D), as shown in some studies of PSP and CBS,[33,34] but not others.[35] Recently published data from a PROSPECT-M-UK subgroup who underwent brain imaging found the fastest annual decline in MoCA scores occurred in CBS, followed by PSP and then MSA patients, consistent with our results.[6]

Distinct cognitive profiles

Using ACE-III cognitive subdomains, we show that people with CBS are most severely affected across all groups, whereas MSA performed best in all cognitive domains across groups, followed by the PD cohort. These findings are consistent with several previous studies[6,35-38] and a recently published meta-analyses.[37] However, a feature of our classifiers was to control for overall deficits, in order to focus on the cognitive pattern. Patients with CBS had relatively greater dysfunction in visuospatial, attention, memory and language domains. People with PSP had the most severe deficit in verbal fluency, consistent with executive dysfunction, with relatively preserved language and memory.

Distinct neuropsychiatric profiles

People with PSP and CBS were more likely to suffer from apathy and depression than people with PD. Anxiety was highest in CBS, and sleep disturbance most common in PD (Fig. 3A and B). Furthermore, we confirmed that apathy and impulsivity are positively correlated across groups. This positive correlation may be a surprise to some readers, but apathy and impulsivity are characterized not merely by the speed or number of actions, but by impairment in the quality of decisions about whether to act or not act in any given situation. The positive correlation has been reported previously in PSP, CBD, PD as well as in FTD and the normal population

across the lifespan.[34,39] This correlation may reflect diffuse pathology affecting separate reward and control systems in the frontal lobe, affecting their structural or neurochemical integrity,[40] or common deficits in the neurophysiological basis of behavioural decisions.[41] PSP was most strongly associated with both impulsivity and apathy,[34,40] in excess of CBS, MSA and PD, but the relationship between apathy and impulsivity is observed in each group. However, caveats of our analysis are that we had to impute the neuropsychiatric features for MSA from their CBI scores, to align them with the MDS-UPDRS questions, and when comparing impulsivity and apathy (Fig. 3C and D), we excluded PD, since their impulsivity scores were not collected using the same CBI scale. Further, we do not consider sleep problems in themselves to be core neuropsychiatric features, even if sleep disruption may have neuropsychiatric consequences, so we excluded sleep-scale scores from the classifier analysis.

Cognitive and neuropsychiatric effects on patients and their families

A consistent deficit in PSP is found on domains associated with frontostriatal function, including behavioural change, apathy, executive dysfunction, emotional lability, aggressive outbursts and compulsive behaviour.[34,42,43] This is borne out by impulsivity being more common in PSP compared with CBS (54% versus 26%) and MSA (12%). Therefore, in our data, the presence of impulsivity makes PSP almost five times more likely relative to CBS and MSA, whereas psychotic phenomena and related behavioural change did not discriminate between PSP and CBS (16% versus 19%). Overall, cognitive dysfunction carried a significant burden impacting activities of daily living (Fig. 4C). Cognitive deficits also correlated more strongly with neurodegeneration as indexed by neurofilament levels than motor disability in people with PSP (Fig. 5A). This could indicate that neurofilament levels, in this group, are coupled more strongly to high-volume cortical than low-volume subcortical degeneration. The absence of this correlation in CBS could be due to differences in regions or rate of degeneration, or reduced power in the smaller CBS sample. Our results in PSP align with previous work showing that blood NfL levels correlate with cognition and depression in PD.[44,45] Our study takes this further by demonstrating NfL predicts cognition even after correcting for motor severity.

Clinical implications

We highlight four clinical implications. First, our study highlights variation in phenotype between and within the diagnoses. Second, it will help clinicians recognize the non-motor signs in typical and atypical parkinsonism subtypes. Third, it may benefit the design of clinical trials. Fourth it helps to further mechanistic and pathophysiological studies into the causes of neuropsychiatric features, and thereby how to treat them.

The atypical parkinsonian syndromes can be diagnostically challenging, even though signs and symptoms begin to emerge on average ~8 years before diagnosis.[46] This diagnostic challenge is especially difficult for non-classical presentations of PSP, CBD or MSA. For example, PSP includes the classical presentation described by Richardson and colleagues, represented in the NINDS-SPSP 2016 criteria and later PSP-Richardson Syndrome (PSP-RS) subtype in the MDS-2017 criteria. But, PSP commonly presents with other phenotypes including a parkinsonian disorder mimicking PD (PSP-P), progressive gait freezing (PSP-PGF), and cognitive syndromes including features of a corticobasal syndrome (PSP-CBS), symptoms resembling non-fluent primary progressive aphasia (PSP-SL) and symptoms resembling behavioural variant frontotemporal dementia (PSP-F).[42,47,48]The cognitive manifestations associated with PSP overlap with CBS and frontotemporal dementias. In one autopsy series, 76% of pathologically confirmed PSP had an initial clinical syndrome other than PSP-RS,[49] leading to increased recognition of variant clinical presentations of PSP. Development of the 2016 MDS revised diagnostic criteria sought to address the relatively low sensitivity of previous criteria, applied to non PSP-RS cases. Whereas we categorized patients by their baseline features, some patients' syndromes changed during follow-up. We have reported this diagnostic progression previously.[6]

Our classifier results offer some hope to the specialist or generalist in helping improve diagnostic accuracy for atypical parkinsonian syndromes and PD. However, the classifiers did not distinguish well between MSA and CBS. One explanation for this is simple linear classifiers work optimally for distinguishing homogeneous groups with a high signal-to-noise ratio. We note that the deficits in CBS are heterogeneous, while those in MSA are present but mild. Future work with larger sample sizes could apply non-linear methods to understand this.

Further longitudinal cohort studies with neuropathological gold standard diagnosis are needed. We aim to revisit PROSPECT-M cognitive and neuropsychiatric data once sufficient post-mortem diagnoses emerge over time in both cohorts. People with CBS and PSP tend to have significantly impaired cognition by the time of baseline recruitment, even soon after diagnosis. This implies early cognitive impairment, with reduced MoCA scores in the range commonly associated with dementia (mean CBS: 21.0 ± 7.1 versus mean PSP: 22.7 ± 4.3). MSA and PD are relatively less impaired cognitively, though still most people with PD and MSA were below the normal cut-off of 26. These disorders might therefore be distinguished merely on the presence of cognitive and behavioural features, as has been shown using item-level analysis of the CBI.[50]

However, the pattern, rather than severity, of cognitive deficits is more informative for diagnostic differentiation: patients have different premorbid cognitive ability and will present at different stages with different rates of progression. CBS and PSP patients manifest partially distinct patterns of cognitive deficit (visuospatial versus executive function deficits, respectively) and neuropsychiatric profiles (PSP and CBS more likely to manifest apathy and depression than Parkinson's disease). Lastly, sleep disturbance, including REM sleep behaviour disorder (RBD) is much more common in PD followed by MSA, while RBD is extremely rare in pathologically proven PSP and CBD cases.[51] Despite these differences, our data demonstrates that across all groups cognitive decline is associated with disability, in terms of ADL, over and above the functional deficit that is explained by severity of motor problems.

In order to understand how patients with atypical syndromes compare to PD, we needed to combine information across cohorts that used different scales. Although we leveraged the fact that many patients had both MoCA and ACE, we still required imputation of the ACE in the PD group. This imputation may be imperfect, and a dedicated study with harmonized scales across diagnoses would be useful to validate these results. However, the comparisons between the atypical syndromes (PSP versus CBS versus MSA) are not affected by this issue.

Although our analysis is group based, we hope it will encourage clinicians to use simple clinic-based tests to seek, identify and treat cognitive and psychiatric symptoms. Our results also promote the importance of neuropsychiatric features in future clinical trials; and validate the experience of patients and their families affected

by these symptoms. This was a UK study, and as such, matched the distribution of ethnicities in the UK, against the Census data provided by the UK Office for National Statistics 2021 (https://www.ons.gov.uk/census). The disadvantage of our approach is that we do not have power to look meaningfully for ethnicity differences, but this must be an important consideration for future work.[52] Several studies have highlighted heterogeneity in cognitive decline in PD,[53,54] with some aspects of mild cognitive impairment progressing faster than others. Consequently, a unified prediction of cognitive trajectories is difficult to achieve, and may depend on non-motor subtypes.[55,56] While distinguishing the pattern of cognitive and neuropsychiatric deficits is a powerful way to assist discriminating diagnoses,[50] it may be less useful in late disease stages, where cognitive scores may reach a floor.

In general, our results point to the utility of examining the relative impairment across cognitive and behavioural domains, rather than absolute impairments. In a clinical environment, patients present with varying rates of decline at inhomogeneous stages of disease progression. We argue that clinical diagnostic discrimination can benefit from examining the relative patterns of deficit, normalized to each patient's overall level of function.

Data availability

De-identified data and a data dictionary will be made available following an application to the PROSPECT-M-UK Data Access committee (prospect@ucl.ac.uk), which will be reviewed by the data access committee, including PSP association representatives, independent chair and study principal investigators. The coefficients for the classifiers can be found online at https://osf.io/mz98x.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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