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Predicting cognitive decline using neuropsychiatric symptoms in prodromal Lewy body dementia: A longitudinal study

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ABSTRACT

Introduction: Neuropsychiatric symptoms (NPS) in Lewy body dementias (LBD) occur frequently and early in disease progression. Such symptoms are associated with worse quality of life, caregiver burden and functional limitations. Limited evidence exists, however, outlining the longitudinal relationship between NPS and cognitive decline in prodromal LBD.

Methods: 123 participants were derived from three cohort studies. Patients with mild cognitive impairment (MCI) relating to probable dementia with Lewy bodies (MCI-LB, n = 67) and Parkinson's disease (PD-MCI, n = 56) completed comprehensive cognitive and neuropsychiatric assessment and were followed up longitudinally. Linear regression and mixed effects models assessed the relationship between baseline NPS and cognition at baseline and over time.

Results: In MCI-LB, overall NPS burden was associated with declines over time in executive function ($p = 0.026$) and processing speed ($p = 0.028$) and baseline aberrant motor behaviour was associated with declines in attention ($p < 0.025$). Anxiety was significantly associated with poorer visuospatial functioning ($p = 0.016$) at baseline and poorer attention both at baseline ($p = 0.017$) and across time points ($p = 0.024$). In PD-MCI, psychosis was associated with poorer executive functioning at baseline ($p = 0.008$) and across time points ($p = 0.002$) but had no association with changes longitudinally.

Conclusions: Core neuropsychiatric components of LBD are not strongly associated with cognition in prodromal disease. This may suggest that neuropathological mechanisms underlying NPS may not be the same as those underlying cognitive impairment. Non-core NPS, however, may be more directly associated with cognitive change. Future studies utilising neuroimaging techniques are needed to explore the neuropathological basis of NPS in prodromal LBD.

1. Introduction

High prevalences of neuropsychiatric symptoms (NPS) are often described in Lewy body dementias (LBD), including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), both in the dementia stages [1,2] and, more recently, in prodromal disease [3,4]. NPS in neurodegenerative conditions are known to relate to increasing disease severity and cognitive decline [3,5,6] and increasingly, studies have shown further detrimental effects on people living with LBD including a worse quality of life, increased caregiver burden and

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distress, and an increased likelihood of nursing home placement [7–9].

In both PD and DLB, individuals at the dementia and mild cognitive impairment (MCI) stages often experience symptoms such as anxiety, apathy, depression, delusions and hallucinations [5,10,11], and share similar cognitive deficits, such as attention impairments and executive dysfunction [4,12,13]. The relatively high prevalence of NPS within LBD groups compared with other common dementia subtypes, such as Alzheimer's disease (AD) [4,8], suggests that such symptoms, rather than simply reflecting a comorbidity of cognitive decline, or a consequence of living with dementia, may result from specific aetiological mechanisms underlying the LBD dementia syndrome. Despite their prevalence, however, relatively little research exists investigating the longitudinal associations between NPS burden and cognitive decline in prodromal LBD. Elucidating this relationship could provide a better understanding of the mechanisms underlying NPS in LBD, informing improved protocols for clinical management, personalised patient care and clinical trial stratification. The present study, therefore, utilised rich datasets from three longitudinal cohorts including individuals in the prodromal stages of DLB (MCI-LB) and PDD (PD-MCI). Using the Neuropsychiatric Inventory (NPI) along with detailed cognitive assessment, the presence of baseline NPS were investigated in relation to cognitive decline in several domains. It was hypothesised that among PD-MCI and MCI-LB groups, NPS would relate to steeper declines in global cognition, attention, and executive function.

2. Methods

2.1. Participants

Participants were derived from three cohort studies carried out in the North East of England: LewyPro, 123I-MIGB Scintigraphy Utility as a biomarker for Prodromal DEmentia with Lewy Bodies (SUPErB) and Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in PD (ICICLE-PD). Recruitment processes, clinical assessment, and diagnoses for each of these cohorts have been reported in detail elsewhere [4,12,14]. All participants provided written informed consent.

In brief, the ICICLE-PD study recruited newly diagnosed PD patients from the community and hospital outpatient clinics in Newcastle-upon-Tyne and Gateshead, UK and 99 healthy controls between June 2009 and December 2011. Participants were re-assessed at 18-month intervals for up to 72 months. Parkinson's was diagnosed by a movement disorder specialist according to the UK Brain Bank criteria [15]. Full exclusion criteria have been published elsewhere [12]. Briefly, participants were excluded if they had significant cognitive impairment at presentation (Mini Mental State Examination (MMSE) < 24) or a pre-existing diagnosis of dementia, an atypical parkinsonian syndrome, or insufficient English to complete assessments. At baseline, participants completed a comprehensive schedule of neuropsychological tests. Participants were included in this analysis if they were classified as PD-MCI at baseline using modified level II Movement Disorder Society (MDS) Task Force PD-MCI criteria [12,16]. Participants were classified as PD-MCI if they reported subjective cognitive decline and performed 1.5 standard deviations (SD) or more below the mean of appropriate norms (controls) on at least two neuropsychological tests across five cognitive domains.

Participants were recruited to LewyPro (February 2013 to February 2016) and SUPErB (March 2016 to September 2019) from older adult medicine clinics, memory clinics and neurology clinics in the North East and Cumbria. Both studies recruited older adults $\geq$60 years old who met National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for MCI [17]. MCI-LB was diagnosed by an expert panel according to research criteria for probable MCI-LB [11]. As such, probable MCI-LB was diagnosed only in cases in which participants had either at two or more of the four core symptoms of DLB (i.e., cognitive fluctuations, complex visual hallucinations, clinical rapid eye movement behavioural sleep disturbance or parkinsonism) or one core symptom with one positive imaging biomarker (123I-FP-CIT (Ioflupane) single photon emission computed tomography or cardiac 123I-MIBG). The "one year rule" was applied such that no participants were included who had evidence of motor parkinsonism more than one year prior to the onset of cognitive decline. Participants were followed up at 12-month intervals.

2.2. Cognitive assessment

All participants undertook a comprehensive battery of cognitive tests. Details of test batteries for each study have been described previously [4,12]. Global cognitive function was assessed using the Mini Mental State Examination (MMSE). Further tests assessing the domains of executive functioning (letter and category fluency), visuospatial skills (clock drawing), memory (delayed word recall), attention (reaction time tests), and processing speed (difference between simple and choice reaction times) were selected from each study. Where test protocols differed between studies details have been outlined in Supplementary Table 1. Patients taking dopaminergic medication were assessed in an "ON" motor state.

2.3. Clinical assessment

Motor symptom severity was measured using the MDS Unified Parkinson's Disease Rating Scale – Motor Examination (MDS-UPDRS-III) and NPS were assessed using the Neuropsychiatric Inventory (NPI), administered to informants. In the present study regression analyses focussed only on ten NPI items assessed on the original version [18] (NPI-10), excluding appetite changes and sleep disturbance. Only one participant presented with euphoria, therefore this symptom was also removed from further analyses.

2.4. Data analysis

2.4.1. Baseline

Continuous data from patient groups were examined for normality using histograms and Shapiro-Wilks tests. Between group differences were assessed using Independent T and Mann-Whitney U tests as appropriate with Bonferroni corrections to account for multiple comparisons. Categorical data were compared using Chi-squared or Fisher's exact tests.

A principal component analysis using varimax rotation was used to determine a reduced number of Lewy body related neuropsychiatric factors to include in regression analyses. Explaining 80.26% of the total variance, five factors were identified corresponding to psychosis (delusions and hallucinations), affective disorder (apathy and depression), and agitation (aggression, irritability, and disinhibition), including anxiety and aberrant motor behaviour (AMB) as independent symptoms that did not load onto any other factors. These five factors were chosen for their high level of explained variance, limited cross loadings, and meaningful face validity. Composite NPS scores were created by multiplying NPI symptom sub-scores (severity x frequency) by their factor loading and summing sub-scores within each factor.

Associations between NPS and cognitive function were assessed using linear regression models computed using IBM SPSS Statistics (Version 27.0). Logistic regression was used to evaluate the relationship between baseline NPS and performance on both clock drawing and pentagon copying. Due to limited variability in these data, participant scores were binarized according to a median split. Each model included the three NPS composite scores, as well as anxiety and aberrant motor behaviour scores, along with age, sex, years of education and MDS-UPDRS III scores as confounding factors. Separate models including two predetermined NPI measures were used to assess the relationship between cognition and overall NPS burden. These included the NPI-10 total score, calculated by summing the sub-scores of ten NPI items, excluding appetite changes and sleep disturbance, and the NPI-4 score, which sums the scores of hallucinations, delusions, depression, and

apathy, found in previous studies to be particularly sensitive to LBD [19]. In cases in which residual plots revealed non-normality, sensitivity analyses were conducted using robust regression with the *rlm* function in the R software (Version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria) and only results that were found to retain significance in these analyses are reported.

2.4.2. Longitudinal

The relationship between baseline NPS and cognitive decline over 36 months was assessed using R software and *lme 4* to perform linear and logistic mixed effects analyses, chosen for the robustness of these models against missing data, loss to follow-up and variations in time intervals. Models included random intercept and random slope with cognitive test performance as outcomes and baseline NPS composite scores as fixed effects, along with the interaction terms between each NPS composite and time (i.e., Psychosis × Time, Agitation x Time, Affective Disorder × Time, Anxiety × Time, AMB × Time). Covariates again included age at baseline, sex, years of education and a longitudinal assessment of MDS-UPDRS III scores. As in baseline analyses, separate models determined the relationship between total NPI-10 and NPI-4 scores and cognitive decline over time. A Benjamini-Hochberg procedure was applied to all regression analyses, including cross-sectional and longitudinal models, controlling for the false discovery rate ($p \leq 0.028$).

To assess the impact of dopaminergic medication on the interaction between NPS and cognition, models were further run replacing MDS-UPDRS III scores with baseline Levodopa Equivalent Daily Dose (LEDD).

3. Results

3.1. Baseline demographics and cognitive function

Details of participant inclusion and exclusion are outlined in Fig. 1. Of the 136 participants identified, 123 completed the NPI at baseline, comprising n = 67 MCI-LB participants and n = 56 PD-MCI participants. At the time of data locking, participants had been followed up for a mean of 2.5 years (Standard deviation = 1.9, Min = 0, Max = 6).

Demographic, clinical and baseline cognitive data are presented in Table 1. Data of those missing the NPI are presented in Supplementary Table 2. Both groups were mostly male. PD-MCI participants were significantly younger than MCI-LB ($p = 0.002$) and MCI-LB had lower MMSE scores than PD-MCI ($p < 0.001$).

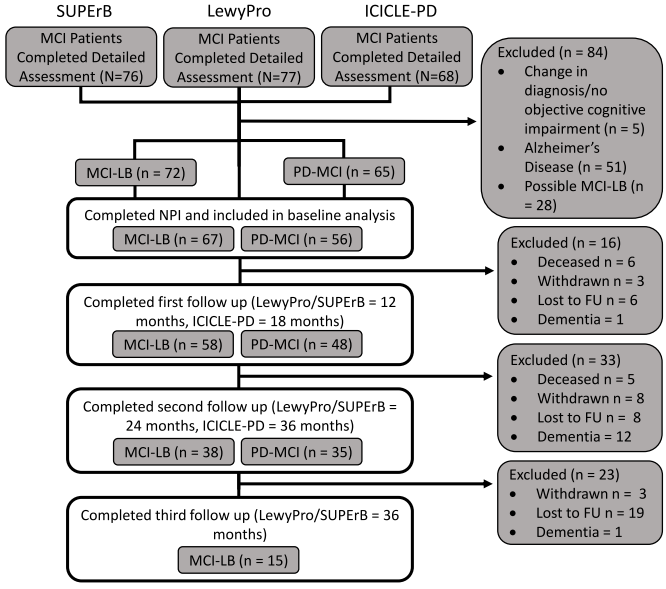

Fig. 1. Inclusion and exclusion of participants at each stage of study. For the purposes of this study MCI-LB were included only if they adhered to diagnostic criteria for probable MCI-LB with possible MCI-LB patients being excluded. Follow up for SUPErB was still ongoing at the time of analysis and as such 'Lost to FU' includes those who had yet to complete follow up for each time point. FU, Follow up.

Table 1
Baseline demographic, cognitive and neuropsychiatric data.

	MCI-LB	n	PD-MCI	n	Test Statistic	P
Age (M, SD)	74.9 (6.9)	67	70.6 (8.6)	56	3.1	**0.002**
Education	11.0 (2.0)	67	10.0 (2.5)	56	1556.0	0.095
MMSE	27.0 (3.0)	67	28.0 (2.0)	56	997.0	**<0.001**
Sex (% Male)	82		70		2.6	0.11
LEDD	0 (0)	67	150.0 (200.0)	56	493.5	**<0.001**
MDS-UPDRS III Total	21.0 (26.0)	67	29.5 (17.8)	56	1431.0	0.024
SRT (Mean Correct)	379.7 (139.9)	64	371.6 (123.2)	55	1708.0	0.782
CRT (Mean Correct)	660.0 (264.1)	64	575.9 (117.6)	55	1204.0	**0.003**
Difference CRT-SRT	279.2 (164.8)	64	207.1 (72.5)	55	1066.0	**<0.001**
Letter Fluency (P) (M, SD)	9.9 (5.0)	63	–			
Letter Fluency (FAS Total)	28.0 (19.0)	67	25.5 (14.5)	56	1608.0	0.173
Category Fluency (Animals)	11.7 (5.0)	67	18.0 (6.0)	56		
Clock Drawing	5 (1)	67	3 (1)	56		
Pentagon Copy (% Impaired)	36	67	25	56	1.7	0.196
MoCA Delayed Word Recall	–		2.0 (3.5)	52		
ACE Delayed Address Recall	2.0 (4.0)	67	–			
Affective Disorder Factor Score	2.36 (4.96)	67	0 (1.70)	56	1175.5	**<0.001**
Agitation Factor Score	0.77 (3.34)	67	0 (0)	56	1178.5	**<0.001**
Psychosis Factor Score	0 (0.80)	67	0 (0)	56	1389.0	**0.002**
Anxiety Sub-score	0 (2)	67	0 (1)	56	1802.0	0.675
AMB Sub-score	0 (0)	67	0 (0)	56	1661.5	**0.048**
NPI-4 Total	4 (7)	67	0 (2)	56	1030.5	**<0.001**
NPI-10 Total	7 (10)	67	1 (6)	56	988.0	**<0.001**

Data presented are median and interquartile range unless otherwise stated. Significant differences highlighted in bold.
Age: Independent Samples T Test.
Sex, Pentagon Copying: Chi Square Test.
LEDD, Letter Fluency (FAS Total), Education, MMSE, MDS-UPDRS III, SRT, CRT, Difference between CRT and SRT: Mann-Whitney U Tests.
M, Mean; SD, standard deviation; MMSE, Mini Mental State Examination; LEDD, Levodopa Equivalent Daily Dose; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III; SRT, Simple Reaction Time; CRT, Choice Reaction Time; MoCA, Montreal Cognitive Assessment; ACE, Addenbrookes Cognitive Evaluation; NPI, Neuropsychiatric Inventory, AMB, Aberrant Motor Behaviour.

3.2. Baseline neuropsychiatric symptoms

Chi-Square tests found that the MCI-LB group had a significantly greater proportion of individuals with at least one NPS present than the PD-MCI group (97% vs 71%, X^2 (1, n = 123) = 15.99, $p < 0.001$). Fig. 2 shows the percentage of each group with each NPS at baseline. MCI-LB had the highest proportion of individuals with every NPS. Significant between-group differences surviving Bonferroni correction are outlined in Fig. 2.

Mann-Whitney U tests found that MCI-LB had significantly higher total NPI-10 (U = 988.00, $p < 0.001$) and total NPI-4 scores (U =

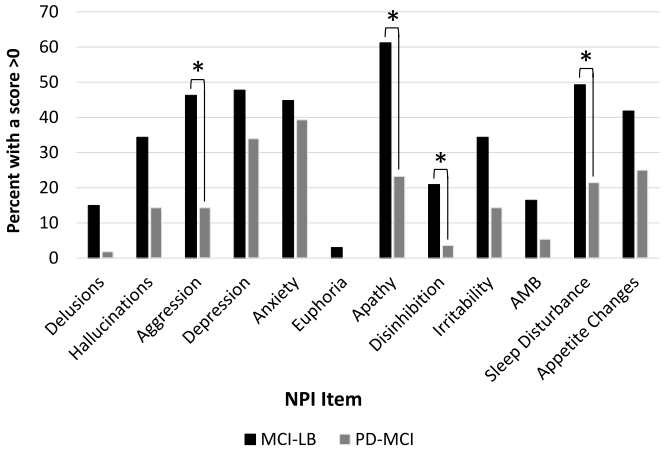

Fig. 2. Bar chart showing the percentage of participants with positive sub-scores on the NPI. Group differences in NPS prevalence were calculated using Chi-Square tests. *Significant difference with Bonferroni corrected $p < 0.05$.

1030.50, $p < 0.001$) than PD-MCI.

No differences were found between groups in either anxiety or AMB. Significant group differences were, however, found in all NPI factor domains ($p \leq 0.002$ for all, see Table 1) such that MCI-LB had significantly higher scores than PD-MCI in all domains.

3.3. Baseline associations between NPS and cognition

No NPS factor was found to relate to MMSE scores at baseline or over time in either participant group. In the MCI-LB group, total NPI-10 scores were significantly associated with steeper declines on letter fluency ($\beta = -0.07$, $p = 0.026$) and CRTs over time ($\beta = 3.80$, $p = 0.028$). Total NPI-10 and NPI-4 scores were not associated with any cognitive domains in the PD-MCI group either at baseline or longitudinally.

In MCI-LB, anxiety was associated with longer SRTs ($\beta = 27.89$, $p = 0.017$) and poorer performance on the pentagon copying task ($\beta = -0.46$, $p = 0.016$) at baseline (Table 2). In PD-MCI, only letter fluency performance showed an association with NPS. Psychosis was significantly related to poorer letter fluency performance at baseline ($\beta = -7.44$, $p = 0.008$) whereas AMB was significantly related to better performance on this task ($\beta = 3.93$, $p = 0.019$).

3.4. Cognitive change over time

After correction for multiple comparisons, significant associations between NPS factors and cognitive change were found in both groups (Table 2). In MCI-LB, higher baseline anxiety scores were significantly associated with slower SRTs across time points ($\beta = 22.39$, $p = 0.024$). Higher sub-scores in AMB were further associated with slowing in both SRTs ($\beta = 20.22$, $p = 0.002$) and CRTs ($\beta = 18.66$, $p = 0.025$) over time.

In PD-MCI, psychosis was again significantly related to poorer letter fluency performance across time points ($\beta = -7.39$, $p = 0.002$) whereas AMB was related to better performance ($\beta = 3.31$, $p = 0.021$). Only anxiety was found to significantly relate to cognitive change over time in PD-MCI, such that higher anxiety scores at baseline were associated with improvements over time on delayed recall ($\beta = 0.34$, $p < 0.001$). Replacing MDS-UPDRS III with LEDD in the models was found to have no impact on the pattern of results either at baseline or longitudinally.

4. Discussion

This study represents one of the first longitudinal investigations assessing the relationship between NPS and progression of cognitive decline in prodromal LBD. Consistent with dementia studies, compared with PD-MCI, MCI-LB demonstrated significantly greater NPS severity and a higher prevalence of all symptoms [2]. However, a higher prevalence of sleep disturbance and visual hallucinations in this group is expected given their inclusion in the diagnostic criteria [11]. Despite showing a higher prevalence and severity of affective symptoms, psychosis, and agitation, these were not associated with cognitive function in MCI-LB either at baseline or longitudinally. This suggests that contrary to our initial hypotheses, many NPS in LBD may be unrelated to cognitive dysfunction in early disease stages, therefore, raising the possibility that NPS may result from differing mechanisms to those underlying cognitive decline. Significant associations were, however, found between total NPI-10 scores and steeper declines in both letter fluency and CRTs over time. This may suggest that despite the limited relationship between cognition and individual NPS, overall neuropsychiatric burden may be an additional marker of disease severity, in line with similar findings in PD and AD [3,5,6]. Furthermore, anxiety sub-scores demonstrated an association with poorer cognitive performance, both at baseline and across time points, in the LBD related domains of attention and visuospatial function [4,13]. Despite evidence suggesting anxiety may be a risk factor of incident cognitive decline in older adults [20], studies in DLB and MCI have often failed to find associations between anxiety and global cognitive decline in the early stages of dementia [21]. In line with this, anxiety in the present study,

Table 2
Linear Regression and Linear Mixed Effects Models: Association between baseline NPS and cognitive scores at baseline and cognitive change over time.

Group	*n*	Dependant Variable	Significant Predictors	β (SE)	p	Robust Regression	
						β (SE)	p
Linear Regression Analysis							
MCI-LB	67	Simple RT [a]	Anxiety	27.34 (11.33)	0.020	15.92 (6.45)	0.017
		Pentagon Copying[b]	Anxiety	−0.46 (0.20)	0.016		
PD-MCI	56	Letter Fluency (FAS)	Psychosis	−7.44 (2.69)	0.008		
			AMB	3.93 (1.62)	0.019		
Linear Mixed Effects Models							
MCI-LB	64	Simple RT	Anxiety	22.39 (9.68)	0.024		
			AMB x Time	20.22 (6.19)	0.002		
	64	Choice RT	AMB x Time	18.66 (8.08)	0.025		
PD-MCI	56	Letter Fluency (FAS)	Psychosis	−7.39 (2.32)	0.002		
			AMB	3.31 (1.40)	0.021		
	52	Recall	Anxiety x Time	0.34 (0.07)	0.000		

Significant results with Benjamini Hochberg correction.
RT, Reaction Time.
All models included age at baseline, sex, years of education and MDS-UPDRS III scores.
[a] Sensitivity analysis conducted using robust standard errors due to non-normality of residuals.
[b] Binary logistic regression.

despite showing an association with cognition cross sectionally, did not relate to steeper declines in performance over time, suggesting that the negative impacts of anxiety on test performance may be of little consequence in the longitudinal course of pathological decline. A significant association was, however, found between AMB and slowing of RTs over time, both in SRT and CRT, in MCI-LB. Currently, neurobiological and neuropsychological correlates of AMB are under studied and poorly understood. However, studies in dementia patients have found correlations between these symptoms and grey matter volumes within both anterior cingulate and insula cortex [22]. Given the early involvement of the insula in DLB [23], it's possible that manifestations of AMB in MCI, particularly in the presence of concordant attention deficits, are reflective of early pathological change.

Lack of associations between cognition and known DLB related NPS such as psychosis and affective disorders [11], may suggest that the well-established neuropsychiatric component of DLB arises in a manner that is mechanistically independent of neurophysiological changes underlying co-occurring cognitive decline. In contrast, the development of non-core NPS, such as anxiety, may contribute an additional burden on cognitive functioning or reflect more directly a neuropsychiatric consequence of specific neurophysiological degeneration relating to cognitive dysfunction.

The relationship between NPS and cognition in PD-MCI differed considerably to MCI-LB. In the former group, psychosis severity significantly related to poorer letter fluency performance, a widely used test of executive function, both at baseline and across time points. Previous longitudinal studies similarly found significant associations between psychosis and letter fluency performance in PD [24] and executive dysfunction is now well established, along with attention deficits and visuospatial impairment, as representing a core cognitive correlate of psychotic symptoms in these patients [25].

Contrary to findings in MCI-LB, AMB in PD-MCI was found to relate positively to letter fluency performance. Impulse controls disorders are a well-documented phenomenon in PD, thought to relate primarily to excessive medication induced dopaminergic stimulation [26]. Although inclusion of LEDD as a covariate had little impact on these results, it is possible that mild stereotyped motor behaviours in the PD-MCI group reflect individual sensitivities to dopamine modulation. Studies reporting a beneficial effect of dopamine modulation on higher order executive functions [27], support the possibility that heightened responses to medication may contribute to the development of AMB while simultaneously facilitating preservation of cognition. However, the number of PD-MCI with these symptoms was very few, the average LEDD dose was very low, and this association was only significant when controlling for the more prominent negative association between executive function and psychosis. More research is therefore necessary to determine whether such findings might be of clinical relevance.

Only anxiety was found to relate to change in cognition over time among the PD-MCI group. Higher anxiety sub-scores were associated with improvements over time in delayed recall. At baseline however, although not significant, a trend was found in which greater anxiety scores in PD-MCI were associated with poorer memory performance. It is possible that resolution of mild anxiety over time exaggerated learning effects found to be present across individuals, due to the amelioration of negative effects cross-sectionally.

4.1. Strengths and limitations

This study represents the first longitudinal investigation into the impact of a range of NPS on cognitive change in prodromal LBD. The combined cohorts included were drawn from the same geographical area and all benefit from deep phenotyping with well characterised disease groups using robust definitions of MCI. As a retrospective analysis however, some methodological limitations remain. Firstly, the neuropsychological tests included in the present analysis were limited to those that were comparable across cohorts, meaning that interrogation of some cognitive domains was lacking. In particular, lack of a robust measure of executive function may explain why the present findings did not reflect previous studies that have demonstrated significant associations between depression, apathy and anxiety and executive functioning in PD [28]. Despite these limitations, the tests included did span a wide range of assessments in several cognitive domains, providing the best possible basis with which to determine associations between cognition and NPS in this retrospective cohort should they exist. Furthermore, the NPI, although widely used in dementia studies, has some limitations regarding reliance on informant ratings, which have previously shown poor concordance with participant rated NPS [29]. Subsequent research may, therefore, consider including participant rated measures in their analyses. Additionally, symptoms in this prodromal cohort were very mild. It is possible that in a larger sample of individuals with higher, more clinically relevant NPI scores and more severe cognitive impairment, stronger relationships may be seen between NPS and cognition. Shared neuropathological processes underlying both neuropsychiatric and cognitive declines may, therefore, have been underestimated in this analysis. However, understanding the pathogenesis of these symptoms in even very mildly affected individuals is important for the early implementation of treatment and interventions. Future studies should aim to determine the neuropathological basis of these very early manifestations of NPS using multi-modal neuroimaging.

A major limitation for any longitudinal study is missing data. Participants who declined further assessments, were lost to follow-up or died may be participants who had a faster rate of cognitive decline and would have been of particular interest to this study. In addition, although all studies included 36-month longitudinal evaluation, the time interval between assessments varied between studies (12 or 18 months). A key strength of our analysis is the use of linear mixed effects modelling, which has been found to show robustness against missing data [30]. Furthermore, analyses include time as a random effect, taking into account variations in time intervals. Although outside the scope of the current study, the use of longitudinal measurements of NPS may provide a more accurate representation of clinically significant symptoms. Future studies that consider how cognitive function and neuropsychiatric symptoms change in parallel may be beneficial to explore in more detail how cognitive domains and NPS are related in LBD progression.

Finally, neither treatment of NPS nor biomarkers of amyloid or tau were controlled for in this study. It is therefore not possible to speculate how the present findings may have been impacted by concurrent Alzheimer pathology, or possible treatment effects on cognition, particularly in results related to anxiety.

5. Conclusions

In MCI-LB, highly prevalent NPS such as affective and psychotic symptoms, appear to have limited correlation with the manifestation and development of cognitive dysfunction, suggesting that mechanisms of such symptoms in LBD may be unlikely to be revealed by their concurrent neuropsychological deficits. These findings have important implications for clinical disease management, suggesting that purely cognitive interventions and outcome measures may not be sufficient or appropriate to address some of the most distressing symptoms of LBD. Rather, separate, concurrent treatment of NPS, perhaps targeting differing neurophysiological processes, may be necessary for comprehensive disease modifying therapies. NPS review should therefore be considered not only clinically but as additional outcome measures when assessing future interventions.

Ethical approval

Each of the cohort studies received ethical approval from the Newcastle and North Tyneside Research Ethics Committee (ICICLE-PD: REC No. 09/H0906/82, SUPErB: REC No. 15/NE/0420, LewyPro: REC No.

12/NE/0290). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Contributors

LMW contributed to design and execution of statistical analysis and wrote the first manuscript draft. RAL, AJT and PCD contributed to study design and interpreting results. In ICICLE-PD, JOB and DB were involved in project conception and organisation, AJY and RAL were involved in project organisation, project execution and data collection. In SUPErB and LewyPro, AJT was involved in study design and data collection, PCD, JPT and MJF contributed to data collection and FEM contributed statistical advice. All co-authors contributed to critical review of the manuscript.

Data availability statement

Data may be available upon reasonable request to the corresponding author or through the Medical Research Council Dementias Platform UK, study references: 'LewyPro', 'SUPErB' and 'ICICLE-PD'.

Declaration of competing interest

Dr Paul Donaghy has received grant support by the Medical Research Council, the Lewy Body Society and Alzheimer's Research UK. Dr Donaghy has also received payment for lectures by the Neurology Academy and has an unpaid leadership role on the Lewy Body Society Specialist Advisory Committee. Professor John-Paul Taylor is supported by the NIHR Newcastle Biomedical Research Centre. Professor John O'Brien has received grant support from Alliance Medical and Merck, consulting fees from Roche and Biogen and lecture fees from GE Healthcare. Professor O'Brien also participates on advisory boards for TauRx, Novo Nordisk and chairs the research strategy board for UK Alzheimer's Society. Dr Alison Yarnall has received grant support from the Dunhill Medical Trust, EU IMI, NIHR, Parkinson's UK, Michael J Fox Foundation, Weston Brain Institute and Intercept pharmaceuticals. Dr Yarnall has also received funding and/or honoraria from Britannia, UCB, Abbvie, GSK, Teva-Lundbeck, GE Healthcare and Genus for attending educational events. The remaining authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105762.

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