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Brain network connectivity underlying neuropsychiatric symptoms in prodromal Lewy body dementia

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ABSTRACT

Neuropsychiatric symptoms (NPS) are prevalent, emerge early, and are associated with poorer outcomes in Lewy body dementia (LBD). Research suggests NPS may reflect LBD-related dysfunction in distributed neuronal networks. This study investigated NPS neural correlates in prodromal LBD using resting-state functional MRI. Fifty-seven participants were included with mild cognitive impairment (MCI) with Lewy bodies (MCI-LB, n = 28) or Parkinson's disease (PD-MCI, n = 29). Functional MRI assessed connectivity within five resting-state networks: primary visual, dorsal attention, salience, limbic, and default mode networks. NPS were measured using the Neuropsychiatric Inventory. Principal component analyses identified three neuropsychiatric factors: affective disorder (apathy, depression), psychosis (delusions, hallucinations) and anxiety. Seed-to-voxel connectivity maps were analysed to determine associations between NPS and network connectivity. In PD-MCI, affective symptoms and anxiety were associated with greater connectivity between limbic orbitofrontal cortex and default mode areas, including medial prefrontal cortex, subgenual cingulate and precuneus, and weaker connectivity between limbic orbitofrontal cortex and the brainstem and between the salience network and medial prefrontal cortex (all $pFWE<0.001$). Psychosis severity in PD-MCI correlated with connectivity across multiple networks (all $pFWE<0.001$). In MCI-LB, no significant correlations were found between NPS severity and network connectivity. However, participants with anxiety demonstrated a trend towards greater connectivity within medial prefrontal areas than those without ($pFWE=0.046$). Altered connectivity within and between networks associated with mood disorders may explain affective and anxiety symptoms in PD-MCI. Neural correlates of NPS in MCI-LB, however, remain unclear, highlighting the need for research in larger, more diverse LBD populations to identify symptomatic treatment targets.

1. Introduction

Neuropsychiatric symptoms (NPS) such as depression, apathy, anxiety, and psychosis are a common and particularly distressing aspect of dementia, contributing significantly to a reduced quality of life (Global Parkinson's Disease Survey Steering Committee, 2002), accelerated functional decline (Borda et al., 2020) and increased caregiver burden (Schrag et al., 2006). The cost to both individuals and healthcare systems is substantial, with NPS being a significant risk factor for earlier institutionalisation and cognitive decline (Aarsland et al., 2000; Breitve et al., 2018).

In Lewy body dementias (LBDs), including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), NPS are highly prevalent, even in prodromal groups, tending to be more severe and

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common than in Alzheimer's disease (Bjoerke-Bertheussen et al., 2012; Donaghy et al., 2018; Leroi et al., 2012). Despite a growing body of research, the pathophysiological basis of NPS in LBD remains poorly understood, particularly in the prodromal phases of mild cognitive impairment (MCI). Understanding the mechanisms of NPS in early LBD is essential for the development of appropriate therapeutic targets for symptomatic treatment; an un-met need which is amplified by their association with disease severity and cognitive decline (Leroi et al., 2012; Rosenberg et al., 2013).

In Parkinson's disease (PD), multiple neuropathological factors, both structural and functional, are postulated to contribute to apathy, depression, anxiety, and visual hallucinations (Alzahrani and Venneri, 2015; Carey et al., 2021; Dan et al., 2017; Wen et al., 2016). Degeneration within multiple neurotransmitter systems has been implicated as a potential mechanistic factor in NPS development (Bohnen et al., 2007; Fischer et al., 2021; Maillet et al., 2016; Remy et al., 2005). However, despite some overlapping evidence suggesting an involvement of prefrontal, limbic and cortico-striatal circuits, (Alzahrani and Venneri, 2015; Carey et al., 2021, 2020; Dan et al., 2017) and a role of visual pathways in visual hallucinations, (Firbank et al., 2018) the neural correlates of NPS in PD remain unclear, with most research excluding those with cognitive impairment or dementia (Alzahrani and Venneri, 2015; Wen et al., 2016). Similarly, studies into the neural mechanisms of NPS in DLB are relatively scarce, (Pezzoli et al., 2017) particularly for symptoms other than visual hallucinations. While neuroimaging studies in hallucinating PD and DLB patients have established disruptions to functional connectivity (FC) and structural integrity of both bottom-up visual pathways and top-down visual attention streams, (Pezzoli et al., 2017; Shine et al., 2015) neurochemical and neuropathological analyses have, as in PD, suggested a role of impaired neurotransmission pathways in depression, delusions and apathy in DLB (Ballard et al., 2000; Patterson et al., 2019; Roselli et al., 2009; Sharp et al., 2008). A paucity of neuroimaging studies investigating these non-core NPS, (McKeith et al., 2017) however, has so far resulted in limited evidence of these NPS-related neurotransmission changes at a macro functional or structural level (Pezzoli et al., 2017).

Although both PDD and DLB share similar clinical presentations and pathophysiology, their differentiation, as either separate entities or two ends of a LBD clinical spectrum, has been the subject of significant debate (Jellinger and Korczyn, 2018). Despite recent proposals that Lewy body disease is a single disease entity, of which the LBDs represent an advanced and more homogenous stage, (Borghammer et al., 2024) subtle differences between the two conditions in cognitive presentation and neuroimaging characteristics (Jellinger and Korczyn, 2018) further extend to manifestations of NPS. PDD and DLB may not only demonstrate differences in severity and prevalence of NPS, (Chiu et al., 2016) but have further shown inconsistencies regarding the efficacy of pharmacological interventions (Emre et al., 2010). Relatedly, there is little clinical consensus regarding appropriate management of NPS in LBDs, with national guidelines offering only brief recommendations for pharmacological management of non-Alzheimer's dementia and no specific recommendations for managing LBD related NPS (National Institute for Health and Clinical Excellence, 2018). Additionally, despite diagnostic criteria existing for LBD related MCI, (Litvan et al., 2012; McKeith et al., 2020) imaging studies of 'non-demented' PD groups have rarely stratified cognitively normal individuals from those with prodromal dementia, and to date only very few studies have investigated NPS in prodromal DLB (Donaghy et al., 2020, 2018). Identifying therapeutic targets in early disease groups, which may be sub-type specific, represents an important first step in the development of clinical guidelines for the management of NPS throughout the course of LBD.

Resting-state functional MRI (rs-fMRI) allows for the evaluation of activity within intrinsic brain networks and their relationship with cognition and psychiatric symptoms. In PD, general NPS burden has been found to correlate negatively with FC in limbic corticostriatal pathways and positively with FC between cerebellar and occipito-temporal areas (Tinaz et al., 2021). Individually, however, specific symptoms have been found to have quite different neural signatures (Dan et al., 2017). Depression in PD has been associated with both hypo- and hyperconnectivity within and between the default mode network and limbic networks (Dan et al., 2017; Hu et al., 2015). Anxiety has been associated with increased FC within the brain's 'fear circuit' (i.e., amygdala and associated regions) and between the amygdala and the salience network, (Carey et al., 2020) whereas apathy has been associated with decreased connectivity within the limbic network and subcortical regions (Dan et al., 2017). As a core diagnostic criterion of DLB, (McKeith et al., 2017) visual hallucinations are widely studied in LBD. Previous fMRI studies have demonstrated altered connectivity within the default mode network, visual network and attention networks in PD and DLB groups with visual hallucinations, (Pezzoli et al., 2017; Shine et al., 2015) but such findings have so far not been replicated in MCI-LB.

This study aimed to investigate resting-state network alterations as a possible mechanism of NPS in MCI-LB and PD-MCI, using a retrospective analysis of data collected in two large cohort studies. Five resting-state networks were investigated: the default mode network, limbic network, salience network, visual network and dorsal attention network. It was hypothesised that affective symptoms such as apathy and depression would likely correlate with FC in networks typically implicated in affective disorders, such as the default mode network and limbic network (Dan et al., 2017; Hu et al., 2015). Anxiety was hypothesised to correlate with FC within and between the limbic network and salience network (Carey et al., 2020). Contrastingly, psychosis was hypothesized to relate to FC of attention networks, default mode network and the visual network (Pezzoli et al., 2017; Shine et al., 2015).

2. Methods

2.1. Participants

Individuals diagnosed with either MCI-LB or PD-MCI were identified from two cohort studies conducted in the North East of England; Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in PD (ICICLE-PD) (Yarnall et al., 2014) and 123I-MIGB Scintigraphy Utility as a biomarker for Prodromal Dementia with Lewy Bodies (SUPErB) (Hamilton et al., 2021). Full exclusion criteria, recruitment processes and clinical assessment protocols for both studies have been reported in further detail elsewhere (Donaghy et al., 2018; Thomas et al., 2018; Yarnall et al., 2014).

Between June 2009 and December 2011, ICICLE-PD recruited newly diagnosed PD patients from outpatient clinics in Newcastle upon Tyne and Gateshead, UK. PD was diagnosed by a movement disorder specialist according to the Brain Bank Criteria (Hughes et al., 1992). Participants were excluded if they presented with pre-existing dementia or severe cognitive decline (Mini Mental State Examination$<$24), atypical parkinsonism, or insufficient English to complete cognitive assessments. A diagnosis of PD-MCI was made according to modified level II Movement Disorder Society task force criteria (Litvan et al., 2012; Yarnall et al., 2014) if participants performed 1.5 standard deviation or more below the means of matched healthy controls on at least two cognitive tests across five domains. Participants had a mean disease duration of 7 months since a formal PD diagnosis and were followed up at 18-month intervals for a mean of 3.9 years (standard deviation [SD]$=$1.9). Diagnoses were confirmed at the latest follow-up.

Between March 2016 and September 2019, SUPErB recruited older adults ($\geq$60 years) from memory, older adult medicine, and neurology clinics in the North-East and Cumbria. MCI-LB patients all met the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for MCI at baseline (Albert et al., 2011). In line with the McKeith et al., (2020) criteria, a diagnosis of probable MCI-LB was made by an expert consensus clinical panel (AJT, PCD, JPT) if participants presented with

≥ 2 core clinical 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) (McKeith et al., 2020). No participants were included in SUPErB who had evidence of parkinsonian motor symptoms over a year prior to the onset of cognitive decline. Participants were followed up for a mean of 2 years (SD=1.7) and diagnoses were based on information from the latest follow-up clinical evaluations.

Written informed consent from all participants was obtained according to the Declaration of Helsinki. Both 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).

2.2. Neuropsychiatric assessment

In both cohort studies, NPS were assessed using the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). The NPI is a questionnaire administered to caregivers or informants to ascertain the presence of a range of NPS in a patient during the past month. A total of 12 symptoms are scored according to their frequency and severity to give a symptom total score (frequency x severity).

Overall neuropsychiatric burden was determined using the NPI-10 and NPI-4 scores. The NPI-10 reflects the total NPI score, excluding the domains of appetite and sleep disturbance. The NPI-4 is the sum of the total NPI scores in the domains of delusions, hallucinations, depression and apathy, found to be a sensitive marker of LBD (Del Ser et al., 2000).

2.3. MRI

2.3.1. Data acquisition

All MRI data were acquired using a 3 T Philips Intera Achieva scanner with an eight-channel head coil receiver. For ICICLE-PD, T1-weighted (T1w) images were acquired using a magnetization prepared rapid gradient echo (MP-RAGE) sequence with repetition time (TR) = 9.6ms, echo time (TE) = 4.6ms, inversion time = 1250ms, flip angle 8°, field of view (FOV)= 240x240 matrix, slice thickness = 1.2, pixel size = 1.15x1.15. rs-fMRI images were obtained using a gradient-echo planar imaging sequence with TR = 3000ms, TE = 40ms, FOV = 260x260, matrix = 80x78, 25 contiguous axial slices with thickness = 6 mm, reconstructed pixel size = 2x2mm, and 128 fMRI volumes (06:24 min). In SUPErB, whole brain T1w volumetric images were acquired using a MP-RAGE sequence: TE = 4.6ms; TR = 8.3ms; inversion time = 1250ms, flip angle 8°, sensitivity encoding factor = 2; in-plane FOV = 216x240mm, acquisition matrix 216x208; slice thickness = 1.0 mm; reconstructed voxel size = 1.0×1.0mm. rs-fMRI scans were obtained with participants being instructed to lie in the scanner with their eyes closed and using a gradient-echo planar imaging sequence with TR = 2072 ms, TE = 30 ms, FOV = 192x192, matrix = 64x62, 33 slices with thickness = 3mm and slice gap = 1mm, pixel size = 3x3mm, and 290 volumes (10:00 min).

2.3.2. Image processing and seed extraction

Results included in this manuscript come from preprocessing performed using fMRIPrep 20.0.6 (Esteban et al., 2019). T1w images were corrected for intensity non-uniformity and skull stripped with ANTs (version 2.2.0). Brain tissue segmentation of cerebrospinal fluid (CSF), white matter and grey matter was performed on the brain-extracted T1w using FSL FAST (FSL 5.0.9) (Zhang et al., 2001). Volume-based spatial normalization to standard MNI space (MNI152NLin6Asym) was performed through nonlinear registration with ANTs.

A reference volume for each participant and its skull stripped version were generated using custom methodology of fMRIPrep. The BOLD reference was then co-registered to the T1w reference using FSL's FLIRT (Jenkinson et al., 2002) with the boundary-based registration cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using MCFLIRT (Jenkinson et al., 2002). The BOLD time-series were resampled onto their original, native space by applying the transforms to correct for head-motion and spatially normalised into MNI space (MNI152NLin6Asym). Automatic removal of motion artifacts using independent component analysis (ICA-AROMA) (Pruim et al., 2015) was performed on the normalised resting-state time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6 mm full-width half-maximum. Framewise displacement (FD) was calculated to determine the severity of motion present in each participant. Participants with a mean FD above 0.5 mm were excluded from further analysis. Mean signals from the CSF and white matter were additionally extracted and regressed out of the data along with a set of physiological regressors extracted to allow for component-based noise correction. Principal components were estimated after high-pass filtering of the preprocessed data (using a discrete cosine filter with 128 s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor).

Prior to nuisance regression the whole regressor matrix was denoised using fsl_regfilt with respect to the identified ICA-AROMA noise components and finally grand mean scaling was applied to the denoised data and data were resampled to a 4 mm^3 resolution using ANTs.

Resting-state FC was estimated using a seed-based approach. Given differences in imaging protocols between each cohort study, a seed-based approach was chosen over a data driven approach, such as ICA, to ensure that brain areas representing each resting-state network were identical in each participant group and not influenced by differences in disease subtype or imaging parameters. A total of 21 seed regions were chosen for analysis, representing areas associated with the default mode network, the dorsal attention network, the salience network, the limbic network and the primary visual network as first identified by Yeo et al. (2011). Analysis was restricted to these five networks based on previous literature highlighting specific involvement of each of these networks in PD or DLB in one or more NPS included in the present study (Carey et al., 2020; Dan et al., 2017; Hu et al., 2015; Pezzoli et al., 2017; Shine et al., 2015).

Seed regions were defined as 6mm-spheres identified using peak coordinates taken from regional parcellations included in the Schaefer functional MRI atlas (Schaefer et al., 2018). From this atlas, the default mode network was characterised using six bilateral cortical seeds; two in the medial prefrontal cortex (MNI left hemisphere:-6,46,0, right hemisphere:6,48,0), two in the precuneus (MNI left:-6,-52,34, right: 6,-52, 30) and two in the inferior parietal lobule (MNI left: −48,-64,36, right:54,-50,30). The dorsal attention network was represented by four cortical seeds in the superior parietal lobule (MNI left: −24,-68,50, right:26,-66,52) and frontal eye fields (MNI left: −26,-4,60, right:28,-2, 60). The salience network was represented by five cortical seeds; three covering the bilateral insula cortex (MNI left: −38,12,6 and −42,02,-6, right:26,-66,52) and two in the anterior cingulate cortex (MNI left:-6,20, 34, right: 6,28,30). The limbic network was represented by four seeds, two in the temporal poles (MNI left: −32,2,-38, right:38,0,-38) and two in the orbitofrontal cortex (MNI left:-14,32,-20, right:12,34,-20). Finally, the visual network was characterised by a single seed in the striate cortex (MNI: −6,-92,-2). See Figure 1 for visualisation of seed regions.

2.4. Statistical analysis

2.4.1. Demographic and neuropsychiatric data

Continuous data were examined for normality using Shapiro-Wilks

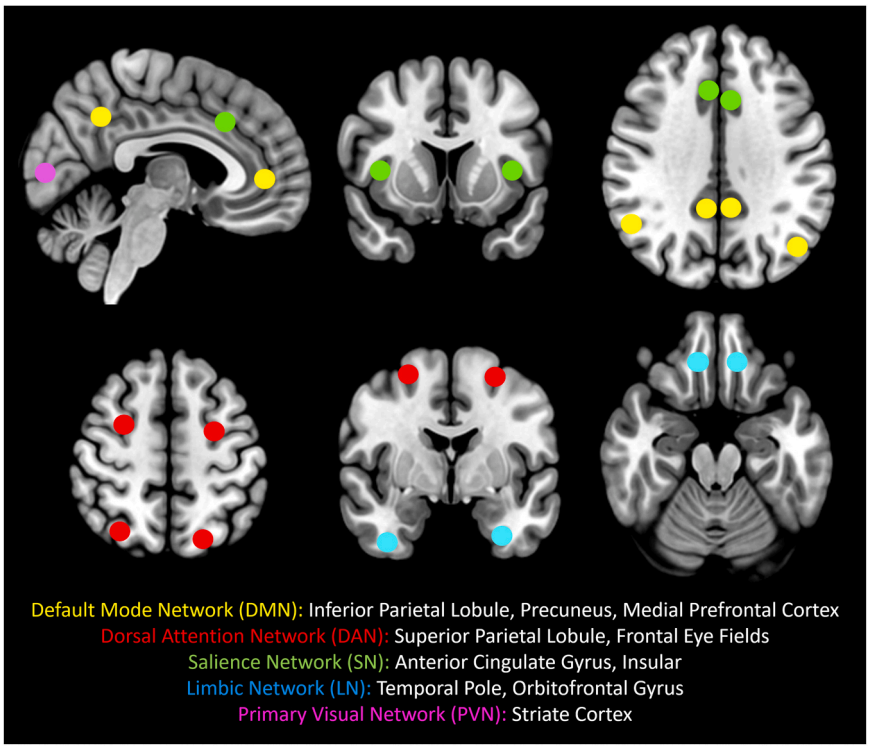

Fig. 1. Visualisation of seed regions selected to represent resting-state brain networks.

tests. Between group comparisons of demographic, cognitive, and neuropsychiatric variables were conducted using Independent samples t-tests or Mann-Whitney U tests as appropriate. Categorical data were compared using Chi-squared tests.

In a previous study, (Wright et al., 2023) 10 of the 12 NPI items assessed (excluding appetite changes and sleep disturbance) were included in a principal component analysis (PCA) using a larger dataset identified from the same cohort studies. In this previous analysis, five neuropsychiatric factors were identified that explained the majority (>80 %) of the total variance in NPI sub-scores. These corresponded to psychosis (delusions and hallucinations), affective disorder (apathy and depression) and agitation (aggression, irritability, and disinhibition) and included anxiety and aberrant motor behaviour as symptoms that did not load significantly onto any factor. Using these neuropsychiatric factors, individual symptom NPI sub-scores (frequency x severity) were multiplied by their factor loadings and summed together within each factor to create composite NPS scores for each participant. In the present study, anxiety, affective disorder, and psychosis were chosen as the symptoms of interest, given their high prevalence in prodromal LBD and association with cognitive decline (Donaghy et al., 2018; Leroi et al., 2012).

2.4.2. *Imaging analysis*

Analyses of FC were performed using CONN release 21.a (Nieto-Castanon and Whitfield-Gabrieli, 2021) and SPM (Penny et al., 2011) release 12.7771. Seed-based connectivity maps were estimated characterizing the patterns of FC between each seed region of interest and the rest of the brain. FC strength was represented by Fisher r-to-Z transformed bivariate correlation coefficients from a weighted general linear model (GLM), (Nieto-Castanon, 2020) defined separately for each pair of seed and target areas, modelling the association between their BOLD signal timeseries.

Group-level analyses were performed using a GLM (Nieto-Castanon, 2020). For each individual voxel, a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables and each NPS as independent variables, controlling for age and sex. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Bilateral seed regions were included in the models simultaneously and an F test determined whether associated FC was significant across either hemisphere. Analyses were masked using the group intersection of subject specific binary brain masks created from the MNI normalised T1w images. Inferences were performed at the level of individual clusters. Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory (Nieto-Castanon, 2020). Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold (as per the recommendation of (Woo et al., 2014), and a familywise corrected p-FWE< 0.005 cluster-size threshold (cluster-size threshold was adjusted for multiple comparisons based on the number of statistical analyses [11 tests of bilateral seed connectivity] performed in each group, $0.05/11 = 0.005$).

Due to limited variability in the NPS factor scores, additional between-subjects GLM analyses were carried out in which each patient group was further separated into symptomatic and non-symptomatic subgroups according to whether they scored at least 1 or above on each NPS factor. Subgroups of symptomatic (i.e., those with NPS factor scores >0) and non-symptomatic participants (NPS factor scores = 0) in the PD-MCI and MCI-LB groups were first compared in relation to each of the covariates included in the within-subjects GLM to determine their inclusion in the between-subjects models. Again, bilateral regions were included in the models simultaneously and an F test determined whether FC differed significantly between subgroups across either hemisphere.

Inspection of scatter plots suggested an outlier representing a single participant with relatively severe affective symptoms (2.9 standard deviations above group mean) may have affected results in the MCI-LB group. Sensitivity analyses, removing this participant from models in which affective disorder was found to be significantly related to FC, was therefore additionally conducted.

3. Results

3.1. Participants

From each cohort, n=37 participants with PD-MCI and n=34 with MCI-LB were identified with both NPI and fMRI data available at baseline. Of these, six MCI-LB and eight PD-MCI participants were excluded for motion or scan artefacts, leaving 28 MCI-LB and 29 PD-MCI. Mann-Whitney U Tests found no differences between excluded and included participants on any demographic or neuropsychiatric measure (all $p > 0.05$). There were no differences between groups in age ($p > 0.05$) however, the groups did differ in their years of education (p = 0.013, Table 1). All MCI-LB participants were male, whereas six (21 %) PD-MCI participants were female. Independent t and Mann-Whitney U tests found that the MCI-LB group performed worse on measures of global cognition, attention, executive function, and memory than PD-MCI (see Table 1). MCI-LB also demonstrated significantly greater severities in affective symptoms (Mdn: 2.9, IQR: 6.0) than PD-MCI (Mdn: 0.0, IQR: 0.4) *($U = 203.5$, $p < 0.001$)* and overall NPS burden, as measured by both the NPI-4 and NPI-10 compared to those with PD-MCI (see Table 1). The distribution of NPS scores in each group are outlined in Fig. 2. Similarly, the prevalence of NPS was greatest in the MCI-LB group across all symptoms and the proportion of individuals scoring > 0 on affective disorder was significantly greater in MCI-LB than in PD-MCI ($p < 0.001$). According to the NPI, 13 participants experienced visual hallucinations (n = 9 MCI-LB, n = 4 PD-MCI); of these, six also experienced non-visual hallucinations (n = 3MCI-LB, n = 3 PD-MCI). No participants experienced only non-visual hallucinations in the absence of visual hallucinations

Table 1
Demographic, cognitive and neuropsychiatric data.

	MCI-LB (n=28)	PD-MCI (n=29)	Test Statistic	P
Age (M, SD)	74.9 (6.3)	72.1 (7.5)	$t = 1.5$	0.133
Education (Years)	11.0 (2.5)	10.0 (2.0)	$U = 254.5$	**0.013**
Sex n(% Male)	28 (100)	23 (79)	$x^2 = 6.5$	**0.011**
LEDD (M, SD)	-	248.4 (174.6)		
MDS-UPDRS III Total (M, SD)	23.3 (15.2)	27.5 (10.1)	$t = -1.2$	0.232
MMSE	26.5 (3.8)	28.0 (2.0)	$U = 240.5$	**0.008**
Simple Reaction Time (ms)	394.7 (127.3)	349.5 (84.9)	$U = 270.0$	**0.046**
Choice Reaction Time (ms)	607.2 (164.8)	548.2 (79.9)	$U = 256.0$	**0.026**
Difference Choice-Simple Reaction Time (ms)	241.2 (93.2)	219.5 (62.0)	$U = 287.0$	0.087
Letter Fluency (FAS Total) (M, SD)	32.8 (14.3)	25.5 (9.8)	$t = 2.2$	**0.029**
Category Fluency (Animals) (M, SD)	12.3 (5.0)	17.1 (5.6)		
Clock Drawing (ACE, max score = 5)	4.0 (2.0)	-		
Clock Drawing (MMSE, max score = 3)	-	3.0 (1.0)		
Pentagon Copy n(%) Impaired	11 (39)	9 (31)	$x^2 = 0.4$	0.514
MMSE Delayed Word Recall	2.0 (1.75)	3.0 (1.0)	*U= 270.0*	**0.020**
Proportion with Affective Disorder Score > 0 n(%)	22 (79)	7 (24)	$x^2 = 16.9$	**< 0.001**
Proportion with Psychosis Score > 0 n(%)	11 (39)	5 (17)	$x^2 = 3.4$	0.064
Proportion with Anxiety Score > 0 n(%)	13 (46)	9 (31)	$x^2 = 1.4$	0.233
NPI−4 Total	4.0 (8.0)	0.0 (1.5)	$U = 208.0$	**< 0.001**
NPI−10 Total	7.5 (9.8)	0.0 (3.5)	$U = 196.0$	**< 0.001**

Median and interquartile range reported unless otherwise specified.
Group differences in age, MDS-UPDRS III and FAS fluency scores were calculated using independent T tests. Group differences in sex ratios, percentage of participants who were impaired on the pentagon copying task and NPS prevalence were calculated using chi-square tests. Group differences in all other variables were calculated using Mann-Whitney U tests.
Group differences in category fluency scores and clock during scores were not calculated due to differences in testing protocol (category fluency test duration: ICICLE=90 s, SUPErB=60 s, clock drawing test: scored out of 3 in ICICLE, scored out of 5 in SUPErB)
ACE, Addenbrookes Cognitive Examination; LEDD, Levodopa equivalent daily dose; M, Mean; MCI-LB, Mild cognitive impairment with Lewy bodies; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE, Mini Mental State Examination; ms, milliseconds; n, number of participants; NPI, Neuropsychiatric Inventory; PD-MCI, Parkinson's Disease Mild Cognitive Impairment; SD, Standard Deviation

3.2. Functional connectivity

3.2.1. PD-MCI

In PD-MCI, greater affective disorder severity was related to greater connectivity between the precuneus seed of the default mode network and the subgenual cingulate (Fig. 3, Table 2). Similarly, increased

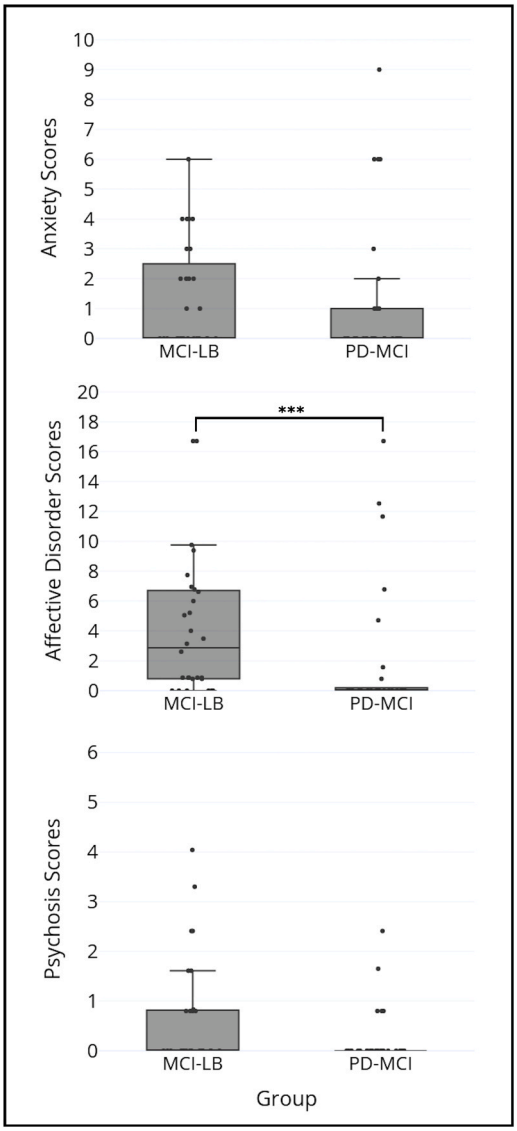

Fig. 2. Boxplots plots showing distribution of NPS scores in each group. Whiskers represent minimum and maximum values. Boxes show the interquartile range with median line. ***p < .001, MCI-LB, mild cognitive impairment with Lewy bodies; PD-MCI, Parkinson's disease mild cognitive impairment.

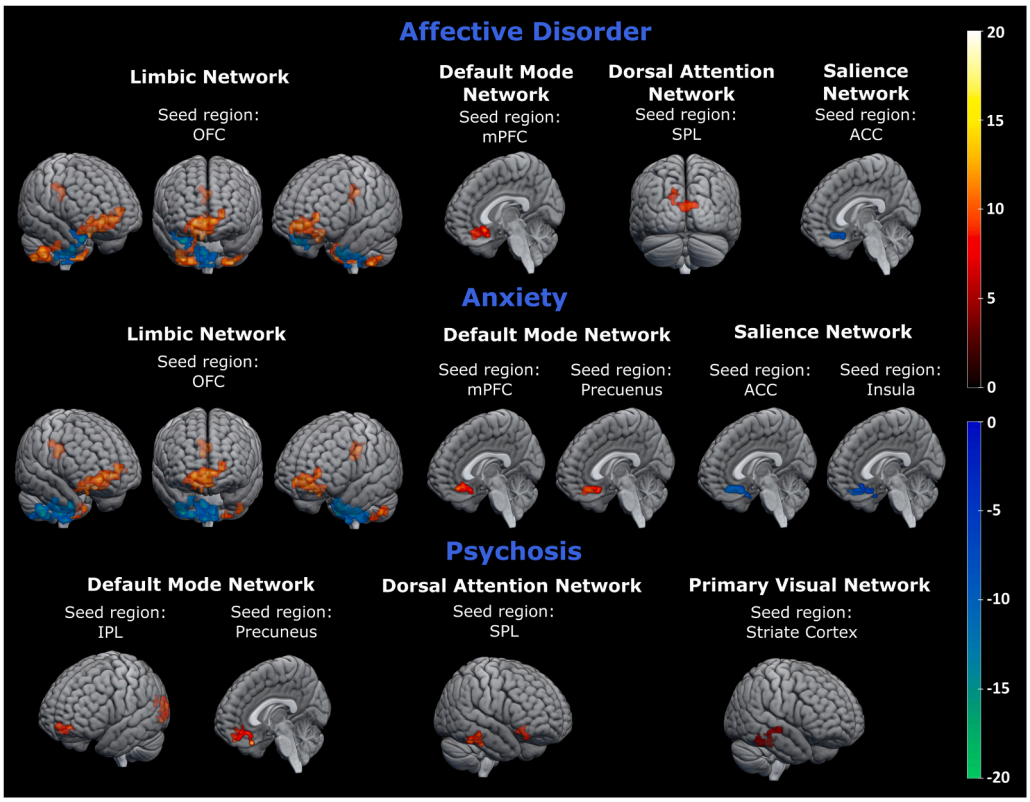

Fig. 3. Brain areas in which seed-based connectivity was significantly related to NPS severity in PD-MCI. All models included age, sex, MMSE scores, MDS-UPDRS II scores and anti-depressant use as covariates. Colour bars represent F statistic. IPL, inferior parietal lobule; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PD-MCI, Parkinson's disease mild cognitive impairment; SPL, superior parietal lobule.

affective severity was associated with greater FC between the orbitofrontal cortex seed of the limbic network and an area surrounding the subgenual cingulate, medial frontal cortex, frontal pole, and orbitofrontal cortex itself, as well as the posterior cerebellar lobes and precuneus. Conversely, a negative association was found between affective disorder severity and FC between the orbitofrontal cortex and the brainstem and between the anterior cingulate of the salience network and the subgenual cingulate.

Anxiety severity in PD-MCI was associated with greater FC between the orbitofrontal cortex seed of the limbic network and areas including the subgenual cingulate, medial prefrontal cortex, cerebellum and precuneus. Negative associations between FC and anxiety were seen between the orbitofrontal cortex and brainstem, as well as right cerebellar regions, and between the insula and anterior cingulate seeds of the salience network and subgenual cingulate and medial frontal cortex (Fig. 3, Table 2).

Psychosis severity in PD-MCI was significantly associated with greater FC between the default mode network and areas of the medial frontal cortex and between the superior parietal lobule in the dorsal attention network and areas of the temporal lobe, orbitofrontal cortex and frontal pole. Greater FC related to psychosis was also seen between the visual network and a right hemisphere cluster spanning the posterior inferior temporal gyrus and middle temporal gyrus. These results are outlined in Fig. 3 and Table 2.

In PD-MCI no differences were found between symptomatic (with affective disorder, anxiety or psychosis) and non-symptomatic subgroups on any covariate, including age, sex ratios, MMSE scores, UPDRS scores or use of anti-depressant medication (all $p > 0.05$). Between-subjects models were therefore run both with and without the inclusion of covariates.

Differences between symptomatic and non-symptomatic participants were found in relation to affective disorder and anxiety. In the basic model, without the inclusion of covariates, PD-MCI participants with symptoms of affective disorder were found to have significantly greater FC between the orbitofrontal cortex seed and surrounding orbitofrontal, medial prefrontal and cingulate regions and the precuneus, than those without (Fig. 4, Table 3). These findings were apparent in both models with and without covariates. In relation to anxiety, no differences were found between symptomatic and non-symptomatic participants in the basic model but participants with symptoms of anxiety were found to have greater within-network connectivity of the default mode network, between the precuneus and medial frontal cortex, than those without, when all covariates were controlled for (Fig. 4, Table 3).

3.2.2. MCI-LB

In MCI-LB, the severity of both anxiety and psychosis were found not to relate to FC of seeds in any network. Affective disorder was related to greater FC between a cluster covering the right posterior inferior temporal gyrus and middle temporal gyrus and seeds across multiple brain networks, including the dorsal attention network ($p < 0.001$), default mode network ($p < 0.001$), limbic network ($p < 0.001$), and salience network ($p < 0.001$). However, these results were not replicated when removing the outlier in sensitivity analyses ($p > 0.05$ for all).

In MCI-LB, again no differences were found between symptomatic (with affective disorder, anxiety or psychosis) and non-symptomatic subgroups on any covariate; including age, sex ratios, MMSE scores, UPDRS scores or use of anti-depressant medication (all $p > 0.05$). In MCI-LB, when using the basic between-subjects model, participants with symptoms of anxiety were found to have significantly greater FC between the orbitofrontal cortex and medial prefrontal cortex and surrounding medial frontal and subgenual cingulate regions, than participants with no recorded anxiety (Table 4). However, when all covariates were included in the model, a similar trend was seen in which participants with anxiety (i.e., scoring >0 on sub-score of the NPI)

Table 2
Areas in which seed-based connectivity significantly correlated with NPS in PD-MCI.

Network	Seed Region	Cluster No.	Peak MNI Coordinates			Cluster Size	Cluster Level *pFWE*	Hemisphere	Brain Regions
			x	y	z				
Affective Disorder									
Default Mode Network	Precuneus	1	−4	32	−10	39	< 0.001	Bilateral	SgC, OFC, ACC
Limbic Network	OFC	1	12	44	−6	142	< 0.001	Bilateral	SgC, mFC, ACC, Paracingulate Gyrus, OFC
		2	8	−40	−54	97	< 0.001*	Bilateral	Brainstem, Cerebellum
		3	28	−72	−58	75	< 0.001	Right	Cerebellum
		4	8	12	−26	43	< 0.001	Right	PHG, Amygdala, OFC, SgC
		5	0	−52	34	33	< 0.001	Bilateral	PCC, Precuneus
		6	−32	−48	−58	27	< 0.001	Left	Cerebellum
		7	32	24	−30	23	< 0.001*	Right	Temporal Pole, OFC
Salience Network	ACC	1	12	32	−18	21	0.005*	Bilateral	mFC, SgC. OFC
Dorsal Attention Network	SPL	1	−12	−80	34	53	< 0.001	Bilateral	Cuneus, ICC, SCC
Anxiety									
Default Mode Network	mPFC	1	4	40	−14	34	< 0.001	Bilateral	SgC, mFC, Paracingulate gyrus
	Precuneus	1	8	24	−18	31	< 0.001	Bilateral	SgC, mFC, OFC
Limbic Network	OFC	1	32	−48	−54	202	< 0.001*	Bilateral	Brainstem, Cerebellum
		2	8	28	−18	183	< 0.001	Bilateral	SgC, Paracingulate Gyrus, mFC, OFC, ACC
		3	8	−48	22	53	< 0.001	Bilateral	PCC, Precuneus
		4	−24	−60	−58	30	< 0.001	Left	Cerebellum
Salience Network	Insula	1	−4	28	−18	34	< 0.001*	Bilateral	SgC, OFC, mFC
	ACC	1	−4	28	−18	39	< 0.001*	Bilateral	SgC, OFC, mFC
Psychosis									
Dorsal Attention Network	SPL	1	52	−36	−26	25	0.001	Right	ITG, MTG, FG
		2	24	24	−10	24	0.002	Right	OFC
Default Mode Network	IPL	1	−12	−100	−14	48	< 0.001	Left	Occipital Pole
		2	−4	48	−10	33	< 0.001	Bilateral	mFC, Paracingulate gyrus
	Precuneus	1	−16	44	−22	45	< 0.001	Bilateral	mFC, Paracingulate Gyrus
Primary Visual Network	Striate Cortex	1	60	−36	−22	46	< 0.001	R	ITG, MTG, FG

Within-subjects general linear models determined the association between seed-based connectivity and the severity of each NPS while controlling for age, sex, MMSE scores, UPDRS-III scores and use of anti-depressant medication.
ACC, anterior cingulate cortex; FG, fusiform gyrus; ICC, intracalcarine cortex; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; mFC, medial frontal cortex; MMSE; Mini Mental State Examination; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PCC, posterior cingulate cortex; PD-MCI; Parkinson's disease mild cognitive impairment; SCC, supracalcarine cortex; SgC, subgenual cingulate cortex; SPL, superior parietal lobule; UPDRS, unified Parkinson's disease rating scale
* Negative association between NPS and connectivity.

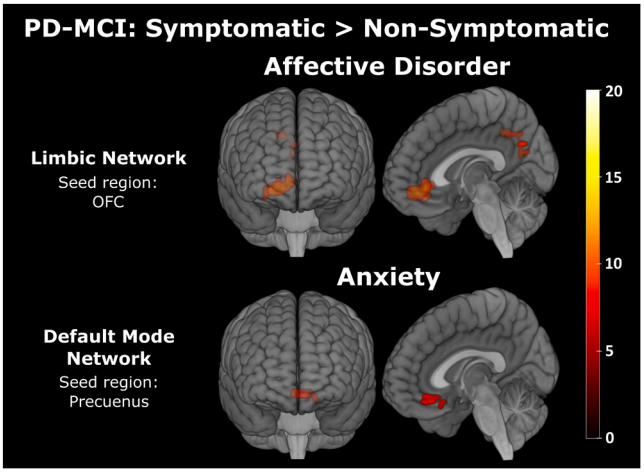

Fig. 4. Brain areas in which seed-based connectivity was significantly greater in symptomatic (NPS score >0) vs non-symptomatic (NPS score = 0) participants in the PD-MCI group. Models included age, sex, MMSE scores, MDS-UPDRS II scores and anti-depressant use as covariates. Colour bar represents F statistic. OFC, orbitofrontal cortex; PD-MCI, Parkinson's disease mild cognitive impairment.

demonstrated significantly greater FC, than those without anxiety (who scored 0), between the orbitofrontal cortex and a small cluster within the subgenual cingulate cortex (pFWE = 0.046) but this did not meet the threshold of significance.

4. Discussion

The aim of the current study was to identify functional neuronal correlates of NPS in PD-MCI and MCI-LB. In PD-MCI, several areas of significant hypo- and hyperconnectivity were identified in relation to the severity of anxiety and affective disorder. Psychosis symptoms were similarly widely associated with connectivity in four out of five resting-state networks. In contrast, despite a greater prevalence and severity of NPS in MCI-LB, none of the resting-state networks were found to relate to symptom severity in this group. However, a trend revealed some differences in seed connectivity between MCI-LB participants with and without symptoms of anxiety (as defined by scoring >0 on the NPI subscore) in medial frontal regions.

The findings related to affective disorders and anxiety in PD-MCI were aligned with our initial hypotheses. Affective disorder severity was associated with hyperconnectivity between the limbic network and default mode network and regions of the subgenual cingulate and medial prefrontal cortex. When comparing subgroups of participants with and without affective disorder symptoms, symptomatic patients were again found to demonstrate significantly greater connectivity within the default mode network and between the limbic orbitofrontal

Table 3
Areas in which seed-based connectivity significantly differed between symptomatic and non-symptomatic individuals in PD-MCI.

Group Comparison	Network	Seed Region	Cluster No.	Peak MNI Coordinates			Cluster Size	Cluster Level *pFWE*	Hemisphere	Brain Regions
				x	y	z				
No covariates included										
Affective Disorder (n = 7) > No Affective Disorder (n = 22)	**Limbic Network**	OFC	1	28	24	−14	42	< 0.001	Right	Frontal pole, ACC, OFC, Paracingulate gyrus
			2	20	−72	34	29	< 0.001	Right	Precuneus, PCC
Covariates included: Age, Sex, MMSE, UPDRS-III, antidepressant use										
Affective Disorder (n = 7) > No Affective Disorder (n = 22)	**Limbic Network**	OFC	1	16	44	−06	61	< 0.001	Right	Frontal pole, ACC, OFC, Paracingulate gyrus
			2	4	−68	22	22	0.001	Right	Precuneus
Anxiety (n = 9) > No Anxiety (n = 20)	**Default Mode Network**	Precuneus	1	4	40	−14	22	0.004	Bilateral	mFC, Paracingulate gyrus

Groups were determined as having some level of symptomatic affective disorder or anxiety by a score > 0 on the NPI derived affective disorder or anxiety NPS factors
Between-subjects general linear models determined differences in seed-based connectivity between participants with and without each NPS while controlling for age, sex, MMSE scores, UPDRS-III scores and use of anti-depressant medication.
ACC, Anterior cingulate cortex; mFC, Medial frontal cortex; MNI, Montreal Neurological Institute; NPS, neuropsychiatric symptoms; OFC, orbitofrontal cortex; SgC, Subgenual cingulate cortex.

Table 4
Areas in which seed-based connectivity significantly differed between symptomatic and non-symptomatic individuals in MCI-LB.

Group Comparison	Network	Seed Region	Cluster No.	Peak MNI Coordinates			Cluster Size	Cluster Level *pFWE*	Hemisphere	Brain Regions
				x	y	z				
No covariates included										
Anxiety (n = 13) > No Anxiety (n = 15)	**Limbic Network**	OFC	1	12	52	−14	71	< 0.001	Bilateral	Medial frontal cortex, Frontal pole, ACC, Paracingulate gyrus
	Default Mode Network	mPFC	1	20	36	−18	39	< 0.001	Right (Medial)	Frontal Pole, SgC, mFC
Covariates included: Age, Sex, MMSE, UPDRS-III, antidepressant use										
Anxiety (n = 13) > No Anxiety (n = 15)	**Limbic Network**	OFC	1	8	28	−14	12	0.046	Bilateral	Medial frontal cortex, SgC

Groups were determined as having some level of symptomatic affective disorder or anxiety by a score > 0 on the NPI derived affective disorder or anxiety NPS factors.
Models did not include any additional covariates
ACC, Anterior cingulate cortex; mFC, medial frontal cortex; mPFC; medial prefrontal cortex; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; SgC, Subgenual cingulate cortex.

cortex and both medial prefrontal and precuneal areas of the default mode network. Hyperconnectivity of the default mode network, in particular within the subgenual medial prefrontal cortex, has not only been described in previous studies of PD groups with depression and apathy, (Dan et al., 2017; Hu et al., 2015) but is further hypothesised to be a key factor in the pathophysiology of major depressive disorder (Drevets et al., 2008). Our findings therefore support the hypothesis that overactive default mode network connectivity, potentially relating to impaired dopaminergic transmission, (Conio et al., 2020) may contribute to the manifestation of mood disorders in PD-MCI.

Similar patterns of hyperconnectivity were also found in relation to anxiety. As seen for affective symptoms, in PD-MCI, anxiety severity correlated predominantly with greater FC between limbic and default mode networks and areas of the medial prefrontal cortex and subgenual cingulate. In between-group comparisons of symptomatic and non-symptomatic individuals, the PD-MCI participants with symptoms of anxiety demonstrated significantly greater within-network connectivity of the default mode network between the precuneus and medial prefrontal cortex than those without anxiety. A similar pattern of hyperconnectivity was seen in MCI-LB patients with anxiety symptoms, who demonstrated significantly greater FC between both the orbitofrontal and medial prefrontal cortex seeds and surrounding medial frontal areas including anterior and subgenual cingulate, when compared with those without symptoms of anxiety. Apathy, anxiety and depression are often difficult to disentangle (Tinaz et al., 2021) and the presence of one or more of these symptoms likely contributes considerably to the reported severity of the others. In the present analysis, however, anxiety was considered independent of apathy and depression due to data-driven PCA findings (Wright et al., 2023). Congruently, increased orbitofrontal cortex activity has been related to anxiety in PD, even in studies controlling for the effects of both depression and apathy (Dan et al., 2017; Wang et al., 2018). Mild presentations of affective disorder and anxiety in LBD, while representing independent symptoms, may, therefore, share some overlapping neural mechanisms. Comorbid presentations of major depressive and anxiety disorders have been associated with significant hyperconnectivity of the limbic network with areas of the default mode network, including the precuneus and posterior cingulate cortex as seen here, despite not being found in individuals presenting with isolated symptoms (Pannekoek et al., 2015). Future research should therefore investigate further whether anxiety, depression and apathy in LBD have distinct vs. overlapping neural signatures, and whether the comorbid expression of these symptoms may point to some specific neuronal dysfunction.

In PD-MCI, affective disorder and anxiety severity were additionally associated with hypoconnectivity between subgenual cingulate and medial prefrontal areas and both the anterior cingulate cortex and insular seeds of the salience network. The salience network is theorised to act as a key moderator in the activation of multiple resting-state networks, including the default mode network and dorsal attention network (Sridharan et al., 2008), which interestingly demonstrated similar hyperconnectivity in relation to affective symptoms in the PD-MCI group. Downregulation of the salience network is considered an important contributory factor in depression, (Conio et al., 2020) and salience network dysfunction has similarly been related to the

manifestation of anxiety in PD, (Maillet et al., 2021) likely owing to its relationship with the brain's 'fear circuit' (Carey et al., 2020). In generalised anxiety disorders, anxiety has been associated both with hyperconnectivity within the default mode network and hypo-connectivity between the default mode and salience networks (Li et al., 2023). The present findings in the PD-MCI group are therefore in line with an integrative model of psychopathology in which NPS are thought to result from dysfunctional within- and between-network connectivity, notably, in the salience and default mode networks (Conio et al., 2020).

Both affective disorder and anxiety in the PD-MCI group were further significantly associated with greater limbic network connectivity between the orbitofrontal cortex seed and posterior cerebellum, and weaker connectivity between the orbitofrontal cortex and brainstem. The cerebellum is a complex structure known for its role not only in the coordination of motor function but further in the modulation of cognition and emotion through its connections with the limbic system (Blatt et al., 2013). Earlier studies have highlighted the significance of cerebellar function in the manifestation of affective disorders in PD without dementia (Tinaz et al., 2021; Wen et al., 2016). Structurally, it has been reported that PD groups with depression or anxiety exhibit greater atrophy of the cerebellum than those without, with such atrophy being greatest in patients with comorbid NPS (Ma et al., 2018). Such findings suggest that pathological changes of the cerebellum may at least be contributory to the development of affective disorders and anxiety in PD. Furthermore, the pathophysiology of LBD is largely characterised by degradation and deposition of Lewy pathology within brainstem nuclei at the core of multiple neurotransmitter pathways (Seidel et al., 2015). Pathological reductions of dopaminergic, noradrenergic, and serotonergic innervation of cortical and subcortical areas have been implicated in NPS in both PD and DLB (Maillet et al., 2016; Patterson et al., 2019; Remy et al., 2005; Sharp et al., 2008). Reduced connectivity between brainstem and limbic regions related to affective disorder and anxiety in LBD may, therefore, reflect impaired neurotransmission in one or more of these systems. It must be noted however, that significant findings within the brainstem and cerebellum were not replicated in the MCI-LB group or in the PD-MCI group when comparing sub-groups of symptomatic and non-symptomatic participants. Future research replicating such findings in a much larger and more diverse cohort is therefore needed to determine their validity.

In alignment with earlier work, our findings identified hyperconnectivity within the default mode network, (Yao et al., 2014) as well as primary visual cortex and areas of the ventral visual stream, (Dujardin et al., 2020; Yao et al., 2015) associated with psychosis in PD-MCI. However, no significant findings were seen either in the MCI-LB group or the sub-group comparisons between symptomatic and non-symptomatic individuals. Furthermore, the present findings did not replicate evidence for disrupted connectivity in attention networks, often cited as a significant factor in the development of hallucinations in PD and DLB (Shine et al., 2014a; Zorzi et al., 2021a, 2021b). Psychosis was the least prevalent and the least severe symptom across both groups. Analyses were therefore limited by both the range of psychosis severity in this clinic-based cohort and the failure to stratify according to phenomenology (i.e., delusion vs hallucinations, simple vs complex) which may show differing patterns of neural involvement (Shine et al., 2014b). Again, investigation of a much larger LBD cohort is therefore warranted to confirm the validity of the current findings.

4.1. Limitations

The present study has multiple strengths. Participants were in the earliest stages of LBD, well-characterised (followed up at multiple time points) and derived from similar populations within the North-East of England. Using a clinic-based sample, along with the widely used NPI questionnaire, participants' NPS severity scores are likely representative of their manifestation in typical LBD related MCI groups. However, symptoms were very mild. In both cohorts, major depressive disorder was an exclusion criterion and the presence of clinically relevant NPS likely reduces research participation, meaning symptoms may have been less severe than in the wider clinical population. The limited variance in NPS severity and the relatively small sample sizes reduces statistical power and, therefore, may have contributed to the limited findings within the MCI-LB group. The sub-clinical definitions of symptomatic (NPI subscore > 0) vs non-symptomatic patients may similarly explain the limited findings in the sub-group comparisons. Nevertheless, significant findings supporting our *a priori* hypotheses were demonstrated in PD-MCI in correlational models and the between-group analysis revealed similar patterns of hyperconnectivity associated with affective disorder and anxiety in PD-MCI and a similar trend related to anxiety in MCI-LB, suggesting the involvement of the default mode network and medial prefrontal regions in particular may be discernible even in very mild manifestations of LBD mood-related symptoms. Weaker findings in the MCI-LB group may be additionally explained by a number of methodological and non-methodological factors relating to the limitations of caregiver vs self-reported NPS measures (McKinlay et al., 2008), the influence of co-morbid pathologies (Geng et al., 2024) and the potential fluctuating course of NPS in individual participants (Vik-Mo et al., 2020). As previously stated, future research involving a larger and more diverse LBD cohort is therefore needed to validate such findings across the Lewy body spectrum.

A further strength is the inclusion of diagnostic groups in which mechanisms of NPS have rarely, if ever, been addressed using neuroimaging, particularly MCI-LB. Despite the lack of correlational associations seen within the MCI-LB group, sub-group comparisons revealed a similar pattern of default mode hyperconnectivity associated with anxiety as was seen in PD-MCI. This therefore not only supports the conclusion that pathological correlates of anxiety may be shared across LBD sub-types but further represents one of the first indications of the underlying neural mechanisms of this symptom in prodromal DLB. The use of different fMRI protocols in the ICICLE-PD and SUPErB studies, however, is a major limitation that makes comparisons between the two patient groups difficult to determine and may have contributed to the different findings in each. Additionally, differences in the cognitive profile of each group, further demonstrates the often-cited heterogeneity of LBD cohorts, potentially highlighting a difference in underlying neural network dysfunction (Jellinger and Korczyn, 2018). A recommendation for future studies would therefore be the prospective inclusion of both PD and DLB groups using identical imaging protocols to determine the measurable over-lap or distinction of NPS neural correlates in each clinical syndrome.

Finally, in each cohort study, participants were enrolled regardless of their neuropsychiatric profile (exclusion criteria notwithstanding), making controlling for the presence of comorbid NPS in this retrospective analysis somewhat difficult. As such, it cannot be determined to what extent connectivity patterns, particularly relating to anxiety and affective disorder, were truly independent from one another. However, NPS factors were data-driven, based on findings of a PCA, (Wright et al., 2023) suggesting a reasonable level of independence between symptom scores. Although the use of neuropsychiatric factors may limit inferences relating to individual symptoms, understanding the neural bases of such factors, may be of greater relevance to clinical practice. Rather than applying a reductionist approach, aiming to find discrete neural contributions to specific aspects of NPS manifestation, our work helps to determine mechanisms underlying latent factors contributing to commonly co-occurring expressions of NPS, specific to LBD. This may, therefore, have greater benefits for the development of therapeutic approaches aiming to target these overarching mechanisms.

4.2. Conclusions

The present findings highlight the influence of connectivity disturbances across multiple large-scale brain networks in early NPS development in PD-MCI. This has substantial value in informing our

understanding of the neurological mechanisms involved, even in subclinical NPS, within prodromal PD dementia. Dysregulation of the default mode and limbic networks, specifically within medial prefrontal areas and the subgenual cingulate, appear to be a significant contributor to the manifestation of affective disorders and anxiety in PD-MCI. Such a finding is particularly meaningful for the identification of potential treatment targets. The present research is not without its limitations however, and further research into the neuropathological mechanisms of NPS in larger LBD cohorts and in understudied groups, such as MCI-LB, is essential for the development of appropriate treatment protocols for NPS occurring across the spectrum of LBD.

CRediT authorship contribution statement

Matthews Fiona E: Methodology, Funding acquisition. **Yarnall Alison J:** Writing – review & editing, Funding acquisition, Data curation. **Sigurdsson Hilmar P:** Writing – review & editing, Data curation. **Firbank Michael J:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Burn David J:** Writing – review & editing, Resources, Funding acquisition. **Donaghy Paul C:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **O'Brien John T:** Writing – review & editing, Resources, Funding acquisition. **Taylor John-Paul:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Lawson Rachael A:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Thomas Alan J:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Schumacher Julia:** Writing – review & editing, Data curation. **Wright Laura M:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

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Data availability

Data are available upon reasonable request.

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