RESEARCH ARTICLE

Vulnerability of multiple large-scale brain networks in dementia with Lewy bodies

Arianna Sala^{1,2} | Silvia Paola Caminiti^{1,2} | Leonardo Iaccarino^{1,2} | Luca Beretta² | Sandro Iannaccone³ | Giuseppe Magnani⁴ | Alessandro Padovani⁵ | Luigi Ferini-Strambi^{1,6} | Daniela Perani^{1,2,7}

¹Vita-Salute San Raffaele University, Milan, Italy

²In Vivo Human Molecular and Structural Neuroimaging Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy

³Clinical Neuroscience Department, San Raffaele Turro Hospital, Milan, Italy

⁴Department of Neurology, IRCCS San Raffaele Hospital, Milan, Italy

⁵Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

⁶Department of Clinical Neurosciences, San Raffaele Scientific Institute, Neurology, Sleep Disorders Center, Milan, Italy

⁷Nuclear Medicine Unit, IRCCS San Raffaele Hospital, Milan, Italy

Correspondence

Daniela Perani, Vita-Salute San Raffaele University, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Nuclear Medicine Unit, IRCCS San Raffaele Hospital, Via Olgettina 60, Milan, Italy.
Email: perani.daniela@hsr.it

Funding information

EU FP7 INMIND Project (FP7-HEALTH-2013), Grant/Award Number: 278850; IVASCOMAR project "Identificazione, validazione e sviluppo commerciale di nuovi biomarcatori diagnostici prognostici per malattie complesse", Grant/Award Number: CTN01_00177_165430

Abstract

Aberrations of large-scale brain networks are found in the majority of neurodegenerative disorders. The brain connectivity alterations underlying dementia with Lewy bodies (DLB) remain, however, still elusive, with contrasting results possibly due to the pathological and clinical heterogeneity characterizing this disorder. Here, we provide a molecular assessment of brain network alterations, based on cerebral metabolic measurements as proxies of synaptic activity and density, in a large cohort of DLB patients ($N = 72$). We applied a seed-based interregional correlation analysis approach ($p < .01$, false discovery rate corrected) to evaluate large-scale resting-state networks' integrity and their interactions. We found both local and long-distance metabolic connectivity alterations, affecting the posterior cortical networks, that is, primary visual and the posterior default mode network, as well as the limbic and attention networks, suggesting a widespread derangement of the brain connectome. Notably, patients with the lowest visual and attention cognitive scores showed the most severe connectivity derangement in regions of the primary visual network. In addition, network-level alterations were differentially associated with the core clinical manifestations, namely, hallucinations with more severe metabolic dysfunction of the attention and visual networks, and rapid eye movement sleep behavior disorder with alterations of connectivity of attention and subcortical networks. These multiple network-level vulnerabilities may modulate the core clinical and cognitive features of DLB and suggest that DLB should be considered as a complex multinetwork disorder.

KEYWORDS

connectivity, default mode network, FDG, PET, resting-state network, synuclein

1 | INTRODUCTION

A decade of evidence suggests that the molecular and pathological alterations underlying neurodegenerative diseases invariably pass through

the derangement of large-scale brain networks (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). This class-wide phenomenon suggests that neurodegenerative diseases should be considered as "networkopathies" (Warren, Rohrer, & Hardy, 2012). Crucially, large-scale networks are diversely affected by different neurodegenerative diseases, and even by their variants, with different syndromes featuring distinct patterns of network vulnerability (Lehmann et al., 2013; Seeley et al., 2009). For

Arianna Sala, Silvia Paola Caminiti, and Leonardo Iaccarino should be considered joint first author.

instance, previous studies have consistently shown that the default mode network (DMN) is specifically vulnerable in Alzheimer's disease (AD) whereas the anterior salience network is specifically vulnerable in behavioral variant of frontotemporal dementia (see Pievani, Filippini, van den Heuvel, Cappa, & Frisoni, 2014). Together with these results, a large body of structural and functional connectivity studies has prompted the idea that disease-specific brain connectivity signatures exist (Pievani et al., 2014).

In the case of dementia with Lewy bodies (DLB), previous studies applying either seed-based or independent component analysis to resting-state functional MRI (rs-fMRI), have provided conflicting evidence on whether and how large-scale networks are affected (Franciotti et al., 2013; Galvin, Price, Yan, Morris, & Sheline, 2011; Kenny, Blamire, Firbank, & O'Brien, 2012; Kenny, O'Brien, Firbank, & Blamire, 2013; Kobeleva et al., 2017; Lowther, O'Brien, Firbank, & Blamire, 2014; Peraza et al., 2014; Sourty et al., 2016). Considering the DMN, some of these studies reported reduced (Galvin et al., 2011; Lowther et al., 2014), preserved (Franciotti et al., 2013; Peraza et al., 2014; Schumacher et al., 2018; Sourty et al., 2016), or increased (Galvin et al., 2011; Kenny et al., 2012) functional connectivity. Reports on other large-scale networks are also heterogeneous, describing connectivity alterations in either attention (Kobeleva et al., 2017; Sourty et al., 2016), salience, executive, (Lowther et al., 2014), basal ganglia (Lowther et al., 2014; Schumacher et al., 2018), frontoparietal (Peraza et al., 2014; Sourty et al., 2016), temporal, or sensory-motor networks (Peraza et al., 2014; Schumacher et al., 2018). Of note, only one study reported connectivity alterations within the visual networks (Sourty et al., 2016), which is remarkable considering the consistent occipital cortex vulnerability reported in DLB (Caminiti et al., 2019).

From a methodological standpoint, the heterogeneity of these results might be related to differences in modeling of functional connectivity (Lowther et al., 2014) and use of relatively small case series, possibly hampering statistical power and reproducibility of these results (Adhikari et al., 2018; Button et al., 2013).

Still, it is reasonable to consider that the long-recognized *pathological* and *clinical* heterogeneity intrinsic to DLB condition, for example, variable cortical-subcortical distribution of α -synuclein pathology and/or concomitant amyloid- β pathology, might also have a role in the heterogeneity of the reported large-scale networks alterations. Of note, in a previous study in early DLB, we showed that metabolic connectivity changes map onto the underlying major pathology. We reported indeed severe connectivity alterations in the regions early affected by α -synuclein spreading, as well as in the degenerated dopaminergic and cholinergic pathways. This study represented the first in vivo assessment of the brain metabolic connectivity alterations arising from DLB hallmark pathological changes (Caminiti, Tettamanti, et al., 2017).

Crucially, in the present study, we aimed at assessing instead the association between core clinical features and neuropsychological aspects in DLB and large-scale networks, considering, as unique features of this study, both local network topography and internetwork communication. Resting-state networks (RSNs) connectivity has been linked to core processes of human cognition, and it is of special

interest in the relationship with cognitive deficits in neurologic and psychiatric disorders (van den Heuvel & Hulshoff Pol, 2010). Notably, the relationship between large-scale RSN alterations and clinical and neuropsychological deficits, and how brain networks alterations can drive phenotypical differences, remains to be determined in DLB. Here, we aim at identifying the brain connectivity signatures in a large DLB patient series with respect to clinical and neuropsychological presenting features. Considering the complexity of its underlying pathology and the heterogeneity of its clinical presentation, we hypothesize that connectivity alterations in DLB cannot be restricted to a single brain network, but should involve clusters of diverse brain networks, especially involving posterior brain sectors.

2 | METHODS

2.1 | Patients

From a large clinical cohort referred to the Neurology Department and the Nuclear Medicine Unit of San Raffaele Hospital (Milan, Italy) between 2010 and 2016, we retrospectively selected 72 patients with a diagnosis of probable DLB. Expert neurologists made the diagnosis of probable DLB in accordance with the International DLB Consortium criteria (McKeith et al., 2005). Diagnosis was confirmed after serial neurological and cognitive examinations, and by means of detailed clinical interviews with patients and caregivers. Patients were defined as probable DLB when they presented with at least two core symptoms (i.e., cognitive fluctuations, visual hallucination [VH], or parkinsonism), or one core symptom plus at least one suggestive feature, namely rapid eye movement sleep behavior disorder (RBD), severe neuroleptic sensitivity, or low dopamine transporter uptake at single-photon emission computed tomography (SPECT) or positron emission tomography (PET), according to the consensus guidelines (McKeith et al., 2005). The RBD diagnosis was made according to the international diagnostic criteria (American Academy of Sleep Medicine, 2014). The prevalence of DLB core clinical features across the whole cohort is available in Table 1. As supportive information for the diagnosis, neurologists also considered the presence of the typical DLB-like hypometabolism pattern, namely hypometabolism involving the medial and/or lateral occipital cortex, and the temporoparietal and frontal cortex (Caminiti, Alongi, et al., 2017; Caminiti et al., 2019; McKeith, Boeve, Dickson, Halliday, et al., 2017). Other imaging and cerebrospinal fluid (CSF) biomarkers were available in some of our cases, as follows: dopamine transporter (DAT) imaging (available in $N = 14$; abnormal in $N = 13$); MRI ($N = 52$; $N = 49$ with preserved medial temporal lobe structures); CSF ($N = 37$; $N = 25$ with abnormal CSF Ab42; $N = 15$ with abnormal CSF p-tau; $N = 5$ with abnormal CSF t tau; $N = 4$ with abnormal CSF on all measures; $N = 6$ with abnormal CSF Ab42 and p-tau).

Cognitive functions were evaluated by a team of neuropsychologists, by means of a thorough neuropsychological battery, as reported in Table 2 (note that all cutoffs applied in our patients' neuropsychological evaluations to define impaired performance, and the relative ranges, refer to Italian tests standardizations).

Patients with either neoplastic or significant vascular lesions, clinically relevant psychiatric disorders or other neurological disorders, or history of drug or alcohol abuse/dependence, were excluded.

All patients, or their informed caregiver, provided written informed consent approved by the San Raffaele Hospital Ethical Committee. The protocols conformed to the Ethical standards of the declaration of Helsinki for protection of human subjects.

2.2 | [18F]FDG-PET procedures

The [18F]FDG-PET scans were acquired using a Discovery STE PET scanner (3.27 mm thickness; 5.55 mm in-plane full width at half

maximum - FWHM), manufactured by GE Healthcare (GE Healthcare Biosciences, Pittsburgh, PA). The [18F]FDG-PET acquisition procedures conformed to the European Association of Nuclear Medicine guidelines (Varrone et al., 2009). Static emission images were acquired 45 min after injecting 185–250 MBq of [18F]FDG via a venous cannula, with 15-min scan duration. All images were reconstructed using an ordered subset-expectation maximization algorithm. Attenuation correction was based on CT scans. Each reconstructed image was visually inspected in order to check for major artifacts.

Image preprocessing was performed using the SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>), running in MATLAB (MathWorks Inc., Sherborn, MA). First, each [18F]FDG-PET image was spatially normalized to a specific [18F]FDG-PET template in the MNI space (Della Rosa et al., 2014). Images were spatially smoothed with an isotropic three-dimensional Gaussian kernel (FWHM: 8–8–8 mm). Global mean scaling was applied to each image in order to account for between-subject uptake variability (Gallivanone, Della Rosa, Perani, Gilardi, & Castiglioni, 2017).

2.3 | [18F]FDG-PET networks analysis

We performed a brain metabolic connectivity analysis in order to investigate changes in RSNs associated with DLB. For comparison, we selected 93 age- and sex-matched healthy controls (HC) ($T = 1.61$, $p = .11$, $\chi^2 = 0.99$, $p = .32$) from the control [18F]FDG-PET database extensively described and included elsewhere (Della Rosa et al., 2014; Perani et al., 2014). Demographics for the HC group are reported in Table 1. Building on the core principle that brain regions whose metabolism is correlated at rest are functionally interconnected (Horwitz, Duara, & Rapoport, 1984), we applied a voxelwise seed-based interregional correlation analysis (Lee et al., 2008). This method was previously validated for [18F]FDG-PET data (Horwitz et al., 1984; Lee et al., 2008) and allows to derive resting-state metabolic networks starting from proper seed regions (Ballarini et al., 2016;

TABLE 1 Demographics and clinical features of the study groups

	DLB (N = 72)	HC (N = 93)
Age at PET scan, mean $\pm$ SD (years)	72.39 $\pm$ 7.62	69.68 $\pm$ 6.05
Gender, mean $\pm$ SD (M/F)	42/30	47/46
Disease duration at PET scan, mean $\pm$ SD (years)	2.50 $\pm$ 1.88	–
MMSE score at PET scan, mean $\pm$ SD	18.66 $\pm$ 4.50	
Time of follow-up, mean $\pm$ SD (years)	2.81 $\pm$ 1.06	
Prevalence of core clinical symptoms		
Hallucinations (N, %)	40 (55.56%)	–
Cognitive fluctuations (N, %)	24 (33.33%)	–
Parkinsonism (N, %)	63 (87.50%)	–
RBD (N, %)	31 (43.06%)	–

Note. Core symptoms defined according to (McKeith et al., 2017).

Abbreviations: DLB, dementia with Lewy bodies; F, Female; HC, healthy controls; M, Male; MMSE, Mini Mental State Examination; RBD: REM behavior sleep disorder; SD, standard deviation.

TABLE 2 Neuropsychological features of the DLB group

Domains	Tests	Mean $\pm$ SD	Test cutoff ^a (and ranges)
Verbal short-term memory	Digit span forward	4.62 $\pm$ 1.34	<4.26 (0–9)
Nonverbal short-term memory	Corsi span forward	2.14 $\pm$ 1.74	<3.46 (0–9)
Verbal long-term memory	Short story—Delayed recall	4.98 $\pm$ 4.51	<8 (0–28)
	Rey verbal learning test—Delayed recall	2.16 $\pm$ 2.84	<4.69 (0–15)
Nonverbal long-term memory	Rey figure—Delayed recall	4.49 $\pm$ 4.07	<9.47 (0–36)
Visuoconstructive abilities	Rey figure—Copy	10.77 $\pm$ 10.22	<28.88 (0–36)
	Clock drawing test	1.30 $\pm$ 2.39	<X ^b (0–10)
Visual selective attention/visual search	Attentive matrices	22.94 $\pm$ 13.65	<31 (0–60)
Visuospatial/logical reasoning	Raven's colored progressive matrices	16.53 $\pm$ 8.61	<18 (0–36)
Word fluency	Semantic fluency	21.13 $\pm$ 9.43	<25 (0– ∞)
	Phonemic fluency	14.44 $\pm$ 11.28	<17 (0– ∞)

Abbreviations: DLB, dementia with Lewy bodies; SD, standard deviation.

^aAll cutoffs and ranges refer to Italian tests standardizations.

^bThere is no single cutoff for the Clock Drawing Test, but it varies according to age and years of schooling.

Iaccarino et al., 2018; Perani et al., 2017; Sala et al., 2017; Tomasi et al., 2017; see also Sala & Perani, 2019 for a recent review).

In the present study, we chose seed regions of individual large-scale networks previously identified by extensive and relevant literature (Jones et al., 2011; Karahanoğlu & Van De Ville, 2015; Seeley et al., 2007; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; Tomasi & Volkow, 2011), as follows: the anterior cingulate cortex/ventromedial prefrontal cortex and posterior cingulate cortex (PCC)/precuneus, respectively for the anterior and posterior DMNs (aDMN and pDMN; Jones et al., 2011; Karahanoğlu & Van De Ville, 2015); calcarine and lateral occipital cortex, respectively for the primary and higher visual networks (Shirer et al., 2012); the anterior insula and inferior parietal lobule, respectively, for the salience and dorsal attention networks (Seeley et al., 2007; Tomasi & Volkow, 2011); the dorsolateral prefrontal cortex (DLPFC) for the executive network (Seeley et al., 2007); the amygdala for the limbic network; the whole basal ganglia for the basal ganglia network (Shirer et al., 2012; Tomasi & Volkow, 2011). Seed regions of interest (ROIs) were defined from a functional RSNS atlas (Shirer et al., 2012) (findlab.stanford.edu/functional_ROIs.html). Since not all seed ROIs were available in this atlas, we added a set of ROIs derived from other dedicated atlases: the inferior parietal lobule was derived from the Jülich histological atlas (Eickhoff et al., 2005); the DLPFC, derived from Sallet's Dorsal Frontal Parcellation Atlas (Sallet et al., 2013); the amygdala, derived from anatomical automatic labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Further details on the selected ROIs are provided in Table S1.

For each network, the average seed uptake was set as variable of interest in a multiple regression model in SPM5, entering age and gender as nuisance covariates, and testing for whole-brain voxelwise correlations. Statistical significance at $p < .01$, false discovery rate (FDR) corrected for multiple comparisons and minimum cluster extent set at $k:100$ voxels, was considered as a reasonable trade-off between statistical robustness and sensitivity (Bennett, Wolford, & Miller, 2009).

Changes in large-scale networks connectivity between the two groups were assessed with the Jaccard similarity coefficient (JSC), a well-established metric, also previously adopted for large-scale networks comparison (e.g., Jovicich et al., 2016; Karahanoğlu & Van De Ville, 2015). JSC measures the similarity between large-scale networks by computing the normalized amount of their overlap. Given a large-scale network i and being V the amount of voxels belonging to that large-scale network, JSC is computed as follows:

$$JSC_i = \frac{Vi(DLB) \cap Vi(HC)}{Vi(DLB) \cup Vi(HC)}$$

JSC ranges from 0, indicating no spatial overlap in the large-scale network i across the two groups, to 1, indicating complete overlap.

In addition, we performed a between-network interaction analysis using inter-subject metabolic correlations between large-scale networks' seeds (Di et al., 2012). This approach lies on the assumption that the chosen networks' seeds represent the most important regions in the networks, according to extensive literature (see above) and, thus, any change affecting the networks' seeds will affect the whole networks as

well (van den Heuvel & Sporns, 2013). It follows that the networks' seeds can be deemed as proxies of the whole large-scale networks: variations in seed metabolism explain most of the variance in metabolism of the related network, and the estimation of the interaction between network's seeds allows to capture most of the relevant changes in the interaction between networks, as well. Pearson's product-moment coefficients (r) were computed for each pair of network's seeds and transformed into Fisher's Z-score to test for between-group differences in the magnitude of r coefficients. The null hypothesis was rejected at $p < .05$, uncorrected for multiple comparisons.

2.4 | Large-scale networks associations with core clinical and neuropsychological data

In order to assess whether the presence, or lack thereof, of core clinical symptoms was associated with changes in large-scale networks connectivity, group comparisons were run based on individual symptom status. In order to do so, the total DLB cohort was split into subgroups according to the presence/absence of each clinical symptom of interest, that is, the presence of VH, RBD, parkinsonism, and cognitive fluctuations. Due to the unbalanced distribution of resulting subgroups, confirmed by a one-sample Chi-square test, group comparisons on cognitive fluctuations, and parkinsonism symptoms were not performed. Using seed-based interregional correlation analysis in SPM5 (Lee et al., 2008), large-scale networks were thus estimated for subgroups of DLB patients, respectively, with or without VH, as well as with or without RBD. Age, gender, disease duration (defined as the time-course between the appearance of the earliest clinical symptom as reported by the patient and/or caregivers and the [18F]FDG-PET scan), and Mini-Mental State Examination (MMSE) were entered as nuisance covariates. Again, a statistical threshold of $p < .01$, FDR corrected for multiple comparisons ($k_e > 100$), was adopted. Between-network interaction was also assessed across subgroups as described above.

We also tested whether large-scale networks connectivity was associated with severity of the neuropsychological deficits. To do so, we implemented multiple general linear models in SPM5, testing whether the interaction between mean seed uptakes (S) and neuropsychological test scores (ψ) predicted metabolism in each voxel (Y) of the corresponding large-scale network (i), according to the following equation:

$$Y_i = \alpha + \beta_1 * S + \beta_2 * \psi + \beta_3 * (S * \psi) + \varepsilon$$

This model allows to test whether metabolic connectivity between the seed and each voxel in the rest of the network is modulated by the severity of specific neuropsychological deficits, while factoring out the effects of deficit severity on brain metabolism *per se*, addressing only the modulatory effects on connectivity. Age, gender, disease duration, and MMSE were entered as nuisance covariates. Results were considered significant at $p < .01$, FDR-corrected for multiple comparisons at the voxel level ($k_e > 100$). Given the relatively limited number of voxels being here tested due to masking, we set an

additional threshold of $p < .05$ family wise error (FWE) corrected at the cluster level.

3 | RESULTS

3.1 | [18F]FDG-PET network analysis

Severity of connectivity changes associated with DLB are represented for each large-scale network in Figures 1a and S1. Major differences in connectivity were found in the primary visual network (JSC = 0.331), in the pDMN (0.344) and in the dorsal attention network (0.394), as well as in the limbic network (0.338). Anterior cortical large-scale networks were the least affected, with the executive and the aDMN networks showing the most spared patterns of connectivity (JSC = 0.484; 0.513).

Differences in between-network interaction are shown in Figure 1b and Table S2a. Significant changes in between-network interaction

maximally converged on the visual and attention networks, with the primary visual and the dorsal attention networks being involved in all significantly altered interactions. DLB-related changes in between-network interactions were not limited to reductions or increases in the magnitude of the correlation, but in a reversal of the direction of the correlation towards anticorrelated networks, suggesting a more segregated brain functioning, with engagement of one network associated with suppression of metabolic activity in the other.

3.2 | Large-scale networks connectivity associations with core clinical, neuropsychological data

3.2.1 | Visual hallucinations

VH-related changes in large-scale networks' connectivity are represented in (Figures 2a and S2. Major differences in connectivity maximally

FIGURE 1 Large-scale network analysis. (a) Severity of changes in large-scale network connectivity in DLB patients is shown. Large-scale networks are displayed ordered according to the extent of connectivity changes, as measured by JSC. Lower values of JSC (in red) indicate greater severity of the connectivity change. Posterior cortical and limbic networks are the most affected. Maps displayed here represent prototypical large-scale networks, as derived from the HC group. (b) Connectograms show interactions between networks in DLB and HC, respectively. Only between-network connections significantly different in the two groups are displayed. Blue ribbons indicate presence of anticorrelations; red ribbons indicate presence of positive correlations between networks. Ribbons' width is proportional to the magnitude of the correlation between networks. DLB-related differences in between-network interaction converge on the primary visual and attention networks, with significant changes affecting both the strength and the direction of the interaction. BGN, basal ganglia network; DAN, dorsal attention network; EN, executive network; HVN, higher visual network; JSC, Jaccard similarity coefficient; LN, limbic network; PVN, primary visual network; SN, salience network [Color figure can be viewed at wileyonlinelibrary.com]

involved the attention networks, that is, the salience ($JSC = .067$) and the dorsal attention (0.209) networks. The visual networks, that is, the higher visual (0.326) and the primary visual networks (0.352), also showed consistent changes in connectivity associated with VH. pDMN was at the core of VH-related changes in between-network interactions (Figure 2b; Table S2b). In particular, the presence of VH was associated with a shift in the direction of the correlation and net increase in pDMN interaction with the primary visual and the limbic networks.

3.2.2 | REM-sleep behavior disorder

RBD-related changes in large-scale networks' connectivity are represented in Figures 3a and S3. Major differences in connectivity involved the attention networks, that is, the dorsal attention ($JSC = 0$) and the salience (0.134) networks, as well as the limbic network (0.179). As for the dorsal

attention network, this result ($JSC=0$) is indicative of a severe connectivity weakening associated to the presence of RBD in this network (Figure S3). As for the limbic network, patients with RBD had abnormally, and detrimentally, increased metabolic connectivity between amygdala and the main brainstem nuclei (Figure S3). RBD-related changes in between-network interactions specifically affected the attention, that is, dorsal attention and salience, and subcortical, that is, limbic and basal ganglia, networks (Figure 3b; Table S2c). The presence of RBD was invariably associated with increased *strength* in the correlation between these networks.

Of note, neither DLB-VH+ and DLB-VH−, nor DLB-RBD+ and DLB-RBD− patients significantly differed in the prevalence of the other clinical symptoms or the severity of neuropsychological deficits (Tables S3 and S4). The groups were partially overlapping, with 13 out of 72 patients (i.e., 18.05%) presenting with both VH and RBD.

FIGURE 2 Network correlates of VH. (a) Severity of changes in large-scale network connectivity associated with the presence of VH in DLB patients is shown. Large-scale networks are displayed ordered according to the extent of connectivity changes, as measured by JSC. Lower values of JSC (in red) indicate greater severity of the connectivity change. Attention and visual networks are the most affected. Maps displayed here represent prototypical large-scale networks, as derived from the HC group. (b) Connectograms show interactions between networks in DLB-VH+ and DLB-VH− patients, respectively. Only between-network connections significantly different in the two groups are displayed. Blue ribbons indicate the presence of anticorrelations; red ribbons indicate presence of positive correlations between networks. Ribbons' width is proportional to the magnitude of the correlation between networks. VH-related differences in between-network interaction converge on the pDMN. BGN, basal ganglia network; DAN, dorsal attention network; EN, executive network; HVN, higher visual network; JSC, Jaccard similarity coefficient; LN, limbic network; pDMN, posterior default mode network; PVN, primary visual network; SN, salience network [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Network correlates of RBD. (a) Severity of changes in large-scale network connectivity associated with the presence of RBD in DLB patients is shown. Large-scale networks are displayed ordered according to the extent of connectivity changes, as measured by JSC. Lower values of JSC (in red) indicate greater severity of the connectivity changes. Attention and limbic networks are the most affected. Maps displayed here represent prototypical large-scale networks, as derived from the HC group. (b) Connectograms show interactions between networks in DLB-RBD+ and DLB-RBD- patients, respectively. Only between-network connections significantly different in the two groups are displayed. Blue ribbons indicate presence of anticorrelations; red ribbons indicate presence of positive correlations between networks. Ribbons' width is proportional to the magnitude of the correlation between networks. RBD-related differences in between-network interaction converge on the attention, limbic and basal-ganglia networks. BGN, basal ganglia network; DAN, dorsal attention network; DLB, dementia with Lewy bodies; EN, executive network; HVN, higher visual network; JSC, Jaccard similarity coefficient; LN, limbic network; PVN, primary visual network; RBD, REM behavior sleep disorder; SN, salience network [Color figure can be viewed at wileyonlinelibrary.com]

3.2.3 | Neuropsychological deficits

Correlations between neuropsychological deficits and large-scale networks connectivity ($p < .01$ FDR corrected at the voxel level, $p < .05$ FWE corrected at the cluster level) are represented in Figure 4. In detail, connectivity in the primary visual network positively correlated with Attentive Matrices scores, that is, the lower the connectivity in the left calcarine cortex and cuneus, the more severe the deficit in visual selective attention and visual search. Connectivity in the executive network positively correlated with Raven's Colored Progressive Matrices scores, that is, the lower the connectivity in the prefrontal cortex (inferior frontal gyrus, middle frontal gyrus, and superior frontal gyrus), the more severe the deficit in visuospatial/logical reasoning. Of note, no significant effect was found for tests related to the visuo-perceptive domain, that is, Rey Figure Copy and Clock Drawing

Test, likely because of the floor effect due to lack of variability in the tests' scores distribution, with most subjects presenting extremely low scores, indicative of severe visuo-perceptive deficits.

4 | DISCUSSION

So far, the assessment of functional connectivity in DLB was based mostly on rs-fMRI studies, showing heterogeneous results (Franciotti et al., 2013; Galvin et al., 2011; Kenny et al., 2012; Kenny et al., 2013; Kobeleva et al., 2017; Lowther et al., 2014; Peraza et al., 2014; Schumacher et al., 2018; Sourty et al., 2016). We have previously provided thorough evidence for both local and distributed brain metabolic alterations characterizing brain connectomics in DLB, crucially mirroring the underlying pathology and neurodegeneration (Caminiti,

FIGURE 4 Network correlates of neuropsychological deficits. Significant effects of the interaction between neuropsychological deficits and brain metabolic connectivity are shown in the figure. Two significant effects at voxel-level involved the primary visual and executive networks ($p < .01$ FDR corrected, $k = 100$; cluster-level $p < .05$ FWE corrected). (a) As for the primary visual network, connectivity in calcarine cortex and cuneus positively correlated with visual attention deficits, as measured by Attentive Matrices Test, that is, the more severe the deficit the lower the connectivity. (b) As for executive network, connectivity in inferior, medium, and SFg positively correlated with logical reasoning deficits, as measured by Raven's Colored Progressive Matrices, that is, the more severe the deficit the lower the connectivity. FDR, false discovery rate; IFg, inferior frontal gyrus; MFg, middle frontal gyrus; SFg, superior frontal gyrus [Color figure can be viewed at wileyonlinelibrary.com]

Tettamanti, et al., 2017). Here, we adopted another validated [18F] FDG-PET connectivity approach, addressing multiple RSNs and network-level alterations. Notably, this approach allows to reliably estimate topographies of large-scale brain networks using [18F]FDG-PET data, at difference from data-driven approaches, such as independent component analysis, for which problems emerged in the analysis of some RSNs (Di et al., 2012; Savio et al., 2017). For example, it was reported, with [18F]FDG-PET data, a less accurate identification of anteroposterior RSNs in comparison with fMRI data (Di et al., 2012).

Here, we found both local and long-distance metabolic connectivity alterations in the posterior cortical networks, as well as in the limbic and attention networks in DLB, suggesting a widespread derangement of the brain connectome. In addition, network-level alterations were differentially associated with core clinical manifestations, namely VH, with more severe metabolic dysfunction of the attention and visual networks, and RBD, with alterations of connectivity of attention and subcortical networks. In addition, we demonstrated that visual attention and visuospatial neuropsychological deficits are associated with specific alterations in large-scale networks connectivity.

4.1 | RSN signatures in DLB

Metabolic connectivity analysis of the main resting-state large-scale networks revealed a significantly altered brain architecture (Figure 1; Figure S1). Local connectivity derangement alterations mainly targeted posterior cortical networks, that is, primary visual network, dorsal attention and pDMN networks (Figure 1; Figure S1). These networks have been related to visual (Smith et al., 2009) and attentional processing (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) and episodic memory retrieval (Sestieri, Corbetta, Romani, & Shulman, 2011), all consistent with the neuropsychological features of DLB

(McKeith, Boeve, Dickson, Lowe, et al., 2017). These results are partially consistent with those reported in previous fMRI literature, supporting the involvement of visual (Sourty et al., 2016), attention (Kobeleva et al., 2017; Sourty et al., 2016), and pDMN (Galvin et al., 2011; Lowther et al., 2014) networks in DLB.

Our results point at a predominant posterior brain vulnerability that is considered as a distinctive feature of DLB (Caminiti, Alongi, et al., 2017; Garcia-Garcia et al., 2012; Hellwig et al., 2012; Teune et al., 2010). We have previously reported major local and long-range disconnections between occipital cortex and other cortical (i.e., frontal cortex and cerebellum) and subcortical (i.e., brainstem and thalamus) regions (Caminiti, Tettamanti, et al., 2017). The occipital cortex is a core region for the DLB typical hypometabolism pattern, able to accurately discriminate DLB from other Parkinsonian and dementia conditions (Caminiti et al., 2019; Caminiti, Alongi, et al., 2017). Notably, the hypometabolism in occipital lobes is not substantially due to marked structural atrophy, suggesting other underlying mechanisms, such as white matter long-range disconnections (Middelkoop et al., 2001). Cholinergic impairment is thought to underlie the typical hypometabolism in the occipital cortex in DLB (Klein et al., 2010). Cell loss in the nucleus basalis of Meynert (Ch4 intermediate part) affects the cholinergic innervation to occipital-parietal cortical regions in DLB (Liu, Chang, Pearce, & Gentleman, 2015). At group level, occipital hypometabolism was also associated with DLB core clinical symptoms (e.g., (Albin et al., 1996; Caminiti, Alongi, et al., 2017; Chiba et al., 2015; Firbank, Lloyd, & O'Brien, 2016; Graff-Radford et al., 2014; Iaccarino et al., 2018; Ishii et al., 2007; Kantarci et al., 2012; Klein et al., 2010; Minoshima et al., 2001; Perani et al., 2014; Pernecky et al., 2008; Pernecky et al., 2010; Satoh et al., 2010; Teune et al., 2010)). A recent study, clustering DLB patients based on their individual brain hypometabolism maps, found that patients with more severe occipital involvement present a higher prevalence of VH, visuospatial, and visuo-perceptive deficits (Caminiti et al., 2019).

Of note, our results point at pDMN as one of the most vulnerable networks in DLB. As highlighted above, this is consistent with some previous fMRI studies, but in contrast with others (Franciotti et al., 2013; Peraza et al., 2014; Schumacher et al., 2018; Sourty et al., 2016). To this regard, it must be noted that substantial differences exist between our and these studies. Specifically, the most notable differences include: (a) the relatively small sample size in the fMRI studies, ranging from a minimum of 15 to a maximum of 31 patients; (b) the techniques used to assess functional connectivity (independent component analysis vs. seed-based connectivity); (c) the clinical characteristics of the included case series (Peraza, Taylor, & Kaiser, 2015); (d) ongoing dopaminergic treatment and fMRI scan performed in the ON state (e.g., (Peraza et al., 2014; Schumacher et al., 2018))—since, notably, dopaminergic medications have been shown to have a normalizing effect on DMN connectivity (Delaveau et al., 2010).

Together with a predominant posterior vulnerability, we showed significant connectivity alterations in the subcortical limbic network, seeding from the amygdala. Notably, amygdala is considered an early site of Lewy bodies accumulation (Braak et al., 2003), and amygdala Lewy bodies pathology has been associated with VH (Harding, Broe, & Halliday, 2002). In addition to local-network connectivity changes, we found altered network interaction between primary visual, dorsal attention networks, and other large-scale networks (Figure 1b), consistently with previous fMRI studies in DLB (Peraza et al., 2014; Peraza et al., 2015; Sourty et al., 2016). This finding of a major derangement in between-network connectivity is however in contrast with a recent study (Schumacher et al., 2018), suggesting an overall sparing of long-distance functional connections in DLB. A major determinant explaining this difference might be that, in the latter study, patients were scanned while on dopaminergic medications (Schumacher et al., 2018), known to have normalizing effects on brain connectivity (cf. Tahmasian et al., 2015). Here, we found abnormal internetwork interactions between locally affected networks and also other, relatively spared, networks (e.g., aDMN and salience network) suggesting a long-distance spreading of connectivity alterations through the brain connectome (Warren et al., 2013) (see Figure 1b). The complex DLB connectivity signature fits well with the complexity of its underlying pathology, as well as with the heterogeneity of the clinical phenotype, suggesting that DLB connectivity changes can be best captured by clusters of large-scale networks alterations. At difference, most neurodegenerative conditions are characterized by connectivity changes affecting one main large-scale network (Pievani et al., 2014; Seeley, 2017; Seeley et al., 2009). Crucially, in DLB, a multinetwork derangement is evident since the *early* disease phases, as in our series (disease duration = 2.5 years), suggesting a fast, widespread breakdown of the brain functional architecture. This evidence is in keeping with the “molecular nexopathies” paradigm, which posits that, as the pathological processes evolve, the effects of proteinopathies spread to large-scale networks (Warren et al., 2013). The fact that multiple brain networks are vulnerable in DLB fits well with its multidomain neuropsychological impairment and swift disease progression, even faster than that observed in AD (cf. Mueller, Ballard, Corbett, & Aarsland, 2017).

Of note, we found that the dorsal attention network and aDMN were positively correlated in HC. The finding of a positive correlation between these networks in HC is in contrast with previous fMRI evidence, suggesting that these network might actually be anticorrelated (e.g., Fox et al., 2005). Many factors might explain the discrepancy, specifically: (a) intrinsic differences in the nature of fMRI and FDG-PET data, that measure different biological aspects of neural activity; (b) methodological differences between studies; and (c) sample differences between studies, for example, age of the control group; to this regard, previous rs-fMRI studies have reported that, with aging, the pattern of anticorrelations observed between networks becomes less prominent (e.g., Spreng, Stevens, Viviano, & Schacter, 2016).

4.2 | Large-scale networks alterations and core clinical and neuropsychological profiles

The DLB connectivity alterations in large-scale networks were tightly related to the core clinical symptoms. Notably, this was a major factor driving differences in large-scale networks changes within the sample, with impairment in the primary visual network and pDMN specifically associated with VH, and attention and limbic networks connectivity modulated by both VH and RBD. Thus, the large-scale network alterations associated with VH and RBD go well beyond the alterations of metabolism reported by standard univariate methods (e.g., Iaccarino et al., 2016; Iaccarino et al., 2018). Accordingly, when performing a head-to-head comparison between subgroups presenting with and without VH and RBD in our cohort, we found more severe metabolic alterations in VH+ patients, but limited to the occipital cortex only (Figure S4), and no specific alteration of metabolism associated with RBD (data not shown).

DLB patients with VH had maximally altered metabolic connectivity within the attention and visual networks (Figure 2a; Figure S2). A biological interpretation of these findings points at a cholinergic impairment leading to a breakdown of the functional associations among calcarine cortex, lateral occipital, and parietal cortex (Klein et al., 2010). Taken together, these findings are consistent with models interpreting the emerging of VH as the result of both perceptual and attentional deficits (Collerton, Perry, & McKeith, 2005; Shine, O'Callaghan, Halliday, & Lewis, 2014). Of note, and in keeping with our results (Figure 2b), the presence of VH have been recently posited to result from aberrant interactions *between* large-scale networks (Shine et al., 2014), as also supported by a recent [18F]FDG-PET study (Iaccarino et al., 2018). In particular, it is hypothesized that VH could emerge from an aberrant recruitment of the DMN, leading to inaccurate interpretation of ambiguous percepts (Shine et al., 2014). These findings confirm that the neural correlates of VH go well beyond the visual areas identified with traditional univariate approaches (Figure S4), encompassing multiple large-scale brain networks.

The specific neural mechanisms underlying RBD, recognized as a core clinical feature of DLB (McKeith, Boeve, Dickson, Lowe, et al., 2017), are yet to be fully understood. RBD is thought to be associated with brainstem-related networks involving both afferent and efferent

connections (Schenck, Boeve, & Mahowald, 2013). Autopsies of DLB patients with RBD demonstrated degenerative changes in some of the key brainstem structures involved in REM sleep control, as well as in the neurodegeneration of limbic and neocortical structures (St Louis, Boeve, & Boeve, 2017). Consistently, we here reported that the presence of RBD is associated with increased brainstem connectivity with the limbic network, seeding from amygdala (Figure S3), which is critically implicated in the modulation of arousal (Benarroch, 2015). The amygdala has also been previously reported as more severely hypometabolic in DLB patients with RBD as compared to those without (Iaccarino et al., 2016). In addition, connectivity analysis allowed to reveal novel neural alterations associated with RBD, that is, patients with RBD showed a widespread loss of integrity of attention large-scale networks (Figure 3a), and a modulation in between-networks interactions, with significantly strengthen association between basal ganglia, limbic, and attention networks (Figure 3b). Previous studies also reported functional connectivity alterations in the basal ganglia of subjects with idiopathic RBD (Ellmore et al., 2013; Rolinski et al., 2016). Considering that prevalence of parkinsonism did not differ between DLB-RBD+ and DLB-RBD- groups, we suggest that RBD is intrinsically associated with connectivity changes in the basal ganglia networks, independently of motor impairment. Notably, the presence of RBD was associated with a specific pattern of between-network changes, characterized by consistently strengthened anticorrelations between the dorsal attention, salience, and sub-cortical networks. This is the first study to report such an effect related to RBD. We speculate that this widespread pattern of connectivity changes centered on the dorsal attention network is related to focal alterations of widely projecting brainstem nuclei involved in cortical neuromodulation. Of note, the locus coeruleus, the neurodegeneration of which can be associated with RBD (García-Lorenzo et al., 2013), also includes projections to the attention network (Sara, 2009). There is evidence that reduction of the tonic firing rate in the locus coeruleus affects between-network interactions, possibly increasing segregation between brain networks (cf. Shine, van den Brink, Hernaes, Nieuwenhuis, & Poldrack, 2018), a result that fits well with our findings.

4.2.1 | Neuropsychological deficits

Neural correlates of neuropsychological deficits in DLB remain largely unexplored. Here, we have shown that the neuropsychological deficits found in DLB, that is, visual attention, executive, visuo-perceptive and visuospatial deficits (Cagnin et al., 2013; Hamilton et al., 2008; Johns et al., 2009) are associated with specific alterations in large-scale network connectivity (Figure 4).

In particular, we found that worse performance in visual selective attention and visual search, as measured by the Attentive Matrices test, is related to impaired metabolic connectivity in the primary visual network, supporting the hypothesis that visual cortex desynchronization is a key factor for DLB visual attention deficits (Peraza et al., 2014; Sourty et al., 2016). Previous effective connectivity analyses have consistently shown that the visual cortex represents the main target of the top-

down modulatory processes directed from the attention control network (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Vossel, Weidner, Driver, Friston, & Fink, 2012) and that appropriate modulation of visual cortex activity is crucial for correct visuospatial processing (Vuilleumier et al., 2008). Visuo-perceptual processes are also thought to contribute to visual search deficits (Tröster, 2008). Although it remains to be determined whether impairment in visual attention or visual perception represent the major determinant of visual search deficits, our results suggest a crucial role for a primary visual network derangement.

In addition, we demonstrated an association between connectivity impairment in prefrontal regions and visuospatial/logical reasoning performance, as measured by Ravens' Colored Progressive Matrices score. The association between visuospatial/logical reasoning and dorsolateral prefrontal cortex has been shown by several fMRI studies in healthy subjects (Krawczyk, Michelle McClelland, & Donovan, 2011; Kroger et al., 2002) and in patients with neurodegenerative dementias (Yoshida et al., 2017). Our results provide further evidence for an association between executive dysfunction and frontal connectivity impairment in DLB, consistent with previous hypotheses (Lee et al., 2010; Sourty et al., 2016).

4.3 | Limitations

The lack of quantitative data available on the severity of clinical symptoms (e.g., Clinician Assessment of Fluctuations or UPDRS scales) at the time of the [18F]FDG-PET scan prevents us from testing the correlation with brain network alterations in our cohort. We thus opted for a direct comparison between subgroups, on the basis of symptom prevalence. In addition, other imaging and CSF biomarkers (i.e., DAT imaging, MRI, CSF A β , p-tau, t-tau) were available in only a subsample of patients, preventing further investigations on other relevant sources of heterogeneity driving large-scale network alterations in DLB. This issue will need to be addressed by future multimodal biomarker studies. We also acknowledge that the reported large-scale networks are estimated at group-level only; available methodological approaches do not currently allow to estimate individual connectivity metrics from a seed-based analysis. We acknowledge that seed-based analysis, while capturing the major connectivity alterations within and between networks, might fail to reveal changes in other network's "peripheral" regions, whose connectivity is not strongly related to the selected seeds. Finally, we acknowledge that reported results for between-network connectivity analysis were not corrected for multiple comparisons.

5 | CONCLUSIONS

The identification of a composite network signature in DLB suggests that combinations of networks are targeted by LB pathology, affecting local network connectivity and between-network interactions. This evidence suggests that DLB represents a multisystem neurodegenerative

disorder, whose pathophysiological processes pass through diverse alterations of the brain connectome.

Crucially, given the tight relationship between brain network impairment and clinical symptoms (i.e., VH and RBD) here reported, we suggest that clinical heterogeneity is supported by distinct patterns of connectivity impairment. The identification of a clinically relevant brain connectivity signature might hold promise to be further validated as biomarker of diagnostic and prognostic relevance in the future, once approaches for estimating seed-based connectivity metrics at the single-subject level become available.

ACKNOWLEDGMENTS

The authors thank Prof Rick Graziani for his valuable assistance. This work was supported by the Italian Ministry of Health (Ricerca Finalizzata Progetto Reti Nazionale AD NET-2011-02346784), the IVASCOMAR project "Identificazione, validazione e sviluppo commerciale di nuovi biomarcatori diagnostici prognostici per malattie complesse" (grant agreement no. CTN01_00177_165430).

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY

Data used in preparation of this study are available from the corresponding author upon reasonable request.

ORCID

Silvia Paola Caminiti <https://orcid.org/0000-0003-4568-1738>

Daniela Perani <https://orcid.org/0000-0002-3421-204X>

REFERENCES

- Adhikari, B. M., Jahanshad, N., Shukla, D., Turner, J., Grotegerd, D., Dannlowski, U., ... Krug, A. (2018). A resting state fMRI analysis pipeline for pooling inference across diverse cohorts: An ENIGMA rs-fMRI protocol. *Brain Imaging and Behavior*, 1–15.
- Albin, R. L., Minoshima, S., D'Amato, C. J., Frey, K. A., Kuhl, D. A., & Sima, A. A. F. (1996). Fluoro-deoxyglucose positron emission tomography in diffuse Lewy body disease. *Neurology*, 47, 462–466.
- American Academy of Sleep Medicine. (2014). *International classification of sleep disorders* (3rd ed.). Darien, IL: American Academy of Sleep Medicine.
- Ballarini, T., Iaccarino, L., Magnani, G., Ayakta, N., Miller, B. L., Jagust, W. J., ... Francisco, S. (2016). Neuropsychiatric subsyndromes and brain metabolic network dysfunctions in early onset Alzheimer's disease. *Human Brain Mapping*, 37, 4234–4247.
- Benarroch, E. E. (2015). The amygdala: Functional organization and involvement in neurologic disorders. *Neurology*, 84, 313–324.
- Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). The principled control of false positives in neuroimaging. *Social Cognitive and Affective Neuroscience*, 4, 417–422.
- Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, 24, 197–211.
- Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *The Journal of Neuroscience*, 28, 10056–10061.
- Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews. Neuroscience*, 14, 365–376.
- Cagnin, A., Gnoato, F., Jelcic, N., Favaretto, S., Zarantonello, G., Ermani, M., & Dam, M. (2013). Clinical and cognitive correlates of visual hallucinations in dementia with Lewy bodies. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84, 505–510.
- Caminiti, S. P., Alongi, P., Majno, L., Volontè, M. A., Cerami, C., Gianolli, L., ... Perani, D. (2017). Evaluation of an optimized [18F]fluoro-deoxy-glucose positron emission tomography voxel-wise method to early support differential diagnosis in atypical Parkinsonian disorders. *European Journal of Neurology*, 24, 687–e26.
- Caminiti, S. P., Sala, A., Iaccarino, L., Beretta, L., Pilotto, A., Gianolli, L., ... Perani, D. (2019). Brain glucose metabolism in Lewy body dementia: Implications for diagnostic criteria. *Alzheimer's Research & Therapy*, 11, 20. <https://alzres.biomedcentral.com/articles/10.1186/s13195-019-0473-4>
- Caminiti, S. P., Tettamanti, M., Sala, A., Presotto, L., Iannaccone, S., Cappa, S. F., ... Perani, D. (2017). Metabolic connectomics targeting brain pathology in dementia with Lewy bodies. *Journal of Cerebral Blood Flow and Metabolism*, 37, 1311–1325.
- Chiba, Y., Fujishiro, H., Ota, K., Kasanuki, K., Arai, H., Hirayasu, Y., ... Iseki, E. (2015). Clinical profiles of dementia with Lewy bodies with and without Alzheimer's disease-like hypometabolism. *International Journal of Geriatric Psychiatry*, 30, 316–323.
- Collerton, D., Perry, E., & McKeith, I. (2005). Why people see things that are not there: A novel perception and attention deficit model for recurrent complex visual hallucinations. *The Behavioral and Brain Sciences*, 28, 737–757 discussion 757–794.
- Delaveau, P., Salgado-Pineda, P., Fossati, P., Witjas, T., Azulay, J. P., & Blin, O. (2010). Dopaminergic modulation of the default mode network in Parkinson's disease. *European Neuropsychopharmacology*, 20, 784–792.
- Della Rosa, P. A., Cerami, C., Gallivanone, F., Prestia, A., Caroli, A., Castiglioni, I., ... Perani, D. (2014). A standardized [(18)F]-FDG-PET template for spatial normalization in statistical parametric mapping of dementia. *Neuroinformatics*, 12, 575–593.
- Di, X., Biswal, B. B., & Alzheimer's Disease Neuroimaging Initiative. (2012). Metabolic brain covariant networks as revealed by FDG-PET with reference to resting-state fMRI networks. *Brain Connectivity*, 2, 275–283.
- Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, 25, 1325–1335.
- Elmore, T. M., Castriotta, R. J., Hendley, K. L., Aalbers, B. M., Furst, E., Hood, A. J., ... Schiess, M. C. (2013). Altered nigrostriatal and nigrocortical functional connectivity in rapid eye movement sleep behavior disorder. *Sleep*, 36, 1885–1892.
- Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *NeuroImage*, 26, 471–479.
- Firbank, M. J., Lloyd, J., & O'Brien, J. T. (2016). The relationship between hallucinations and FDG-PET in dementia with Lewy bodies. *Brain Imaging and Behavior*, 10, 636–639.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the*

- National Academy of Sciences of the United States of America, 102, 9673–9678. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1157105&tool=pmcentrez&rendertype=abstract>
- Franciotti, R., Falasca, N. W., Bonanni, L., Anzellotti, F., Maruotti, V., Comani, S., ... Onofri, M. (2013). Default network is not hypoactive in dementia with fluctuating cognition: An Alzheimer disease/dementia with Lewy bodies comparison. *Neurobiology of Aging*, 34, 1148–1158.
- Gallivanone, F., Della Rosa, P., Perani, D., Gilardi, M. C., & Castiglioni, I. (2017). The impact of different 18FDG PET healthy subject scans for comparison with single patient in SPM analysis. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*, 61, 115–132.
- Galvin, J., Price, J., Yan, Z., Morris, J., & Sheline, Y. (2011). Resting bold fMRI differentiates dementia with Lewy bodies vs. Alzheimer's disease. *Alzheimer's Dementia*, 76, 1797–1893.
- García-García, D., Clavero, P., Salas, C. G., Lamet, I., Arbizu, J., Gonzalez-Redondo, R., ... Rodriguez-Oroz, M. C. (2012). Posterior parietooccipital hypometabolism may differentiate mild cognitive impairment from dementia in Parkinson's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, 39, 1767–1777.
- García-Lorenzo, D., Longo-Dos Santos, C., Ewencyk, C., Leu-Semenescu, S., Gallea, C., Quattrocchi, G., ... Lehericy, S. (2013). The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. *Brain*, 136, 2120–2129.
- Graff-Radford, J., Murray, M. E., Lowe, V. J., Boeve, B. F., Ferman, T. J., Przybelski, S. A., ... Kantarci, K. (2014). Dementia with Lewy bodies: Basis of cingulate island sign. *Neurology*, 83, 801–809.
- Hamilton, J. M., Salmon, D. P., Galasko, D., Raman, R., Emond, J., Hansen, L. A., ... Thal, L. J. (2008). Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies. *Neuropsychology*, 22, 729–737.
- Harding, A. J., Broe, G. A., & Halliday, G. M. (2002). Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain*, 125, 391–403.
- Hellwig, S., Amtage, F., Kreft, A., Buchert, R., Winz, O. H., Vach, W., ... Meyer, P. T. (2012). [18F]FDG-PET is superior to [123I]IBZM-SPECT for the differential diagnosis of parkinsonism. *Neurology*, 79, 1314–1322.
- Horwitz, B., Duara, R., & Rapoport, S. I. (1984). Intercorrelations of glucose metabolic rates between brain regions: Application to healthy males in a state of reduced sensory input. *Journal of Cerebral Blood Flow and Metabolism*, 4, 484–499.
- Iaccarino, L., Marelli, S., Iannaccone, S., Magnani, G., Ferini-Strambi, L., & Perani, D. (2016). Severe brain metabolic decreases associated with REM sleep behavior disorder in dementia with Lewy bodies. *Journal of Alzheimer's Disease*, 52, 989–997.
- Iaccarino, L., Sala, A., Caminiti, S. P., Santangelo, R., Iannaccone, S., Magnani, G., & Perani, D. (2018). The brain metabolic signature of visual hallucinations in dementia with Lewy bodies. *Cortex*, 108, 13–24.
- Ishii, K., Soma, T., Kono, A. K., Sofue, K., Miyamoto, N., Yoshikawa, T., ... Murase, K. (2007). Comparison of regional brain volume and glucose metabolism between patients with mild dementia with Lewy bodies and those with mild Alzheimer's disease. *Journal of Nuclear Medicine*, 48, 704–711.
- Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., ... Chertkow, H. (2009). Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology*, 23, 765–777.
- Jones, D. T., MacHulda, M. M., Vemuri, P., McDade, E. M., Zeng, G., Senjem, M. L., ... Jack, C. R. (2011). Age-related changes in the default mode network are more advanced in Alzheimer disease. *Neurology*, 77, 1524–1531.
- Jovicich, J., Minati, L., Marizzoni, M., Marchitelli, R., Sala-Llonch, R., Bartrés-Faz, D., ... Frisoni, G. B. (2016). Longitudinal reproducibility of default-mode network connectivity in healthy elderly participants: A multicentric resting-state fMRI study. *NeuroImage*, 124, 442–454.
- Kantarci, K., Lowe, V. J., Boeve, B. F., Weigand, S. D., Senjem, M. L., Przybelski, S. A., ... Jack, C. R. (2012). Multimodality imaging characteristics of dementia with Lewy bodies. *Neurobiology of Aging*, 33, 2091–2105.
- Karahanoglu, F. I., & Van De Ville, D. (2015). Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks. *Nature Communications*, 6, 7751.
- Kenny, E. R., Blamire, A. M., Firbank, M. J., & O'Brien, J. T. (2012). Functional connectivity in cortical regions in dementia with Lewy bodies and Alzheimer's disease. *Brain*, 135, 569–581.
- Kenny, E. R., O'Brien, J. T., Firbank, M. J., & Blamire, A. M. (2013). Subcortical connectivity in dementia with Lewy bodies and Alzheimer's disease. *The British Journal of Psychiatry*, 203, 209–214.
- Klein, J. C., Eggers, C., Kalbe, E., Weisenbach, S., Hohmann, C., Vollmar, S., ... Hilker, R. (2010). Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology*, 74, 885–892.
- Kobeleva, X., Firbank, M., Peraza, L., Gallagher, P., Thomas, A., Burn, D. J., ... Taylor, J.-P. (2017). Divergent functional connectivity during attentional processing in Lewy body dementia and Alzheimer's disease. *Cortex*, 92, 8–18.
- Krawczyk, D. C., Michelle McClelland, M., & Donovan, C. M. (2011). A hierarchy for relational reasoning in the prefrontal cortex. *Cortex*, 47, 588–597.
- Kroger, J. K., Sabb, F. W., Fales, C. L., Bookheimer, S. Y., Cohen, M. S., & Holyoak, K. J. (2002). Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: A parametric study of relational complexity. *Cerebral Cortex*, 12, 477–485.
- Lee, D. S., Kang, H., Kim, H., Park, H., Oh, J. S., Lee, J. S., & Lee, M. C. (2008). Metabolic connectivity by interregional correlation analysis using statistical parametric mapping (SPM) and FDG brain PET; methodological development and patterns of metabolic connectivity in adults. *European Journal of Nuclear Medicine and Molecular Imaging*, 35, 1681–1691.
- Lee, J. E., Park, H.-J., Park, B., Song, S. K., Sohn, Y. H., Lee, J. D., & Lee, P. H. (2010). A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. *Journal of Neurology, Neurosurgery, and Psychiatry*, 81, 320–326.
- Lehmann, M., Madison, C. M., Ghosh, P. M., Seeley, W. W., Mormino, E., Greicius, M. D., ... Rabinovici, G. D. (2013). Intrinsic connectivity networks in healthy subjects explain clinical variability in Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, 110, 11606–11611.
- Liu, A. K. L., Chang, R. C.-C., Pearce, R. K. B., & Gentleman, S. M. (2015). Nucleus basalis of Meynert revisited: Anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. *Acta Neuropathologica*, 129, 527–540.
- Lowther, E. R., O'Brien, J. T., Firbank, M. J., & Blamire, A. M. (2014). Lewy body compared with Alzheimer dementia is associated with decreased functional connectivity in resting state networks. *Psychiatry Research*, 223, 192–201.
- McKeith, I., Boeve, B., Dickson, D., Lowe, J., Emre, M., & Al, E. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB consortium. *Neurology*, 89, 88–100.
- McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., ... Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies. *Neurology*, 89, 88–100.
- McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'Brien, J. T., Feldman, H., ... Yamada, M. (2005). Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. *Neurology*, 65, 1863–1872.
- Middelkoop, H. A. M., van Der Flier, W. M., Burton, E. J., Lloyd, A. J., Paling, S., Barber, R., ... O'Brien, J. (2001). Dementia with Lewy bodies

- and AD are not associated with occipital lobe atrophy on MRI. *Neurology*, 57, 2117–2120.
- Minoshima, S., Foster, N. L., Sima, A. A. F., Frey, K. A., Albin, R. L., & Kuhl, D. E. (2001). Alzheimer's disease versus dementia with Lewy bodies: Cerebral metabolic distinction with autopsy confirmation. *Annals of Neurology*, 50, 358–365.
- Mueller, C., Ballard, C., Corbett, A., & Aarsland, D. (2017). The prognosis of dementia with Lewy bodies. *Lancet Neurology*, 16, 390–398. [https://doi.org/10.1016/S1474-4422\(17\)30074-1](https://doi.org/10.1016/S1474-4422(17)30074-1)
- Perani, D., Della Rosa, P. A., Cerami, C., Gallivanone, F., Fallanca, F., Vanoli, E. G., ... Gianolli, L. (2014). Validation of an optimized SPM procedure for FDG-PET in dementia diagnosis in a clinical setting. *NeuroImage: Clinical*, 6, 445–454.
- Perani, D., Farsad, M., Ballarini, T., Lubian, F., Malpetti, M., & Fracchetti, A. (2017). The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. *Proceedings of the National Academy of Sciences of the United States of America*, 114, 1690–1695.
- Peraza, L. R., Kaiser, M., Firbank, M., Graziadio, S., Bonanni, L., Onofri, M., ... Taylor, J.-P. (2014). fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. *NeuroImage: Clinical*, 4, 558–565.
- Peraza, L. R., Taylor, J. P., & Kaiser, M. (2015). Divergent brain functional network alterations in dementia with Lewy bodies and Alzheimer's disease. *Neurobiology of Aging*, 36, 2458–2467.
- Perneckzy, R., Drzezga, A., Boecker, H., Ceballos-Baumann, A. O., Valet, M., Feurer, R., ... Häussermann, P. (2010). Metabolic alterations associated with impaired clock drawing in Lewy body dementia. *Psychiatry Research: Neuroimaging*, 181, 85–89.
- Perneckzy, R., Drzezga, A., Boecker, H., Förstl, H., Kurz, A., & Häussermann, P. (2008). Cerebral metabolic dysfunction in patients with dementia with Lewy bodies and visual hallucinations. *Dementia and Geriatric Cognitive Disorder*, 25, 531–538.
- Pievani, M., Filippini, N., van den Heuvel, M. P., Cappa, S. F., & Frisoni, G. B. (2014). Brain connectivity in neurodegenerative diseases-from phenotype to proteinopathy. *Nature Reviews. Neurology*, 10, 620–633.
- Rolinski, M., Griffanti, L., Piccini, P., Roussakis, A. A., Szezyk-krolkowski, K., Menke, R. A., ... Hu, M. T. M. (2016). Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson's disease. *Brain*, 139, 2224–2234.
- Sala, A., & Perani, D. (2019). Brain molecular connectivity in neurodegenerative diseases: recent advances and new perspectives using Positron Emission Tomography. *Frontiers in Neuroscience*, 13, 617. <https://doi.org/10.3389/fnins.2019.00617>
- Sala, A., Caminiti, S. P., Presotto, L., Premi, E., Pilotto, A., Cosseddu, M., ... Borroni, B. (2017). Altered brain metabolic connectivity at multiscale level in early Parkinson's disease. *Scientific Reports*, 7, 4256.
- Sallet, J., Mars, R. B., Noonan, M. P., Neubert, F.-X., Jbabdi, S., O'Reilly, J. X., ... Rushworth, M. F. (2013). The organization of dorsal frontal cortex in humans and macaques. *The Journal of Neuroscience*, 33, 12255–12274.
- Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews. Neuroscience*, 10, 211–223.
- Satoh, M., Ishikawa, H., Meguro, K., Kasuya, M., Ishii, H., & Yamaguchi, S. (2010). Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with Lewy bodies: The Osaka-Tajiri project. *European Neurology*, 64, 337–344.
- Savio, A., Fänger, S., Tahmasian, M., Rachakonda, S., Manoliu, A., Sorg, C., ... Yakushev, I. (2017). Resting state networks as simultaneously measured with fMRI and PET. *Journal of Nuclear Medicine*, 58, 1314–1317. <http://jnm.snmjournals.org/lookup/doi/10.2967/jnumed.116.185835>
- Schenck, C. H., Boeve, B. F., & Mahowald, M. W. (2013). Delayed emergence of a Parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: A 16-year update on a previously reported series. *Sleep Medicine*, 14, 744–748.
- Schumacher, J., Peraza, L. R., Firbank, M., Thomas, A. J., Kaiser, M., Gallagher, P., ... Taylor, J. P. (2018). Functional connectivity in dementia with Lewy bodies: A within- and between-network analysis. *Human Brain Mapping*, 39, 1118–1129.
- Seeley, W. W. (2017). Mapping neurodegenerative disease onset and progression. *Cold Spring Harbor Perspectives in Biology*, 9, a023622.
- Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, 62, 42–52.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience*, 27, 2349–2356.
- Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: Functional and topographic analyses. *The Journal of Neuroscience*, 31, 4407–4420.
- Shine, J. M., O'Callaghan, C., Halliday, G. M., & Lewis, S. J. G. (2014). Tricks of the mind: Visual hallucinations as disorders of attention. *Progress in Neurobiology*, 116, 58–65.
- Shine, J. M., van den Brink, R. L., Hernaus, D., Nieuwenhuis, S., & Poldrack, R. A. (2018). Catecholaminergic manipulation alters dynamic network topology across cognitive states. *Network Neuroscience*, 2, 381–396. https://doi.org/10.1162/NETN_a_00013https://www.mitpressjournals.org/doi/abs/10.1162/netn_a_00038
- Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, 22, 158–165.
- Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., ... Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, 106, 13040–13045.
- Sourty, M., Thoraval, L., Roquet, D., Armspach, J.-P., Foucher, J., & Blanc, F. (2016). Identifying dynamic functional connectivity changes in dementia with Lewy bodies based on product hidden Markov models. *Frontiers in Computational Neuroscience*, 10, 60.
- Spreng, R. N., Stevens, W. D., Viviano, J. D., & Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: Evidence from task and rest. *Neurobiology of Aging*, 45, 149–160. <https://doi.org/10.1016/j.neurobiolaging.2016.05.020>
- St Louis, E. K., Boeve, A. R., & Boeve, B. F. (2017). REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Movement Disorders*, 32, 645–658.
- Tahmasian, M., Bettray, L. M., van Eimeren, T., Drzezga, A., Timmermann, L., Eickhoff, C. R., ... Eggers, C. (2015). A systematic review on the applications of resting-state fMRI in Parkinson's disease: Does dopamine replacement therapy play a role? *Cortex*, 73, 80–105.
- Teune, L. K., Bartels, A. L., de Jong, B. M., Willemsen, A. T. M., Eshuis, S. A., de Vries, J. J., ... Leenders, K. L. (2010). Typical cerebral metabolic patterns in neurodegenerative brain diseases. *Movement Disorders*, 25, 2395–2404.
- Tomasi, D., & Volkow, N. D. (2011). Association between functional connectivity hubs and brain networks. *Cerebral Cortex*, 21, 2003–2013.
- Tomasi, D. G., Shokri-Kojori, E., Wiers, C. E., Kim, S. W., Demiral, Ş. B., Cabrera, E. A., ... Volkow, N. D. (2017). Dynamic brain glucose metabolism identifies anti-correlated cortical-cerebellar networks at rest. *Journal of Cerebral Blood Flow and Metabolism*, 37, 3659–3670.
- Tröster, A. I. (2008). Neuropsychological characteristics of dementia with Lewy bodies and Parkinson's disease with dementia: Differentiation, early detection, and implications for “mild cognitive impairment” and biomarkers. *Neuropsychology Review*, 18, 103–119.

- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15, 273–289.
- van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, 20, 519–534. <http://www.ncbi.nlm.nih.gov/pubmed/20471808>
- van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*, 17, 683–696. <https://doi.org/10.1016/j.tics.2013.09.012>
- Varrone, A., Asenbaum, S., Vander Borgh, T., Booi, J., Nobili, F., Nagren, K., ... Van Laere, K. (2009). EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *European Journal of Nuclear Medicine and Molecular Imaging*, 36, 2103–2110.
- Vossel, S., Weidner, R., Driver, J., Friston, K. J., & Fink, G. R. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *The Journal of Neuroscience*, 32, 10637–10648.
- Vuilleumier, P., Schwartz, S., Verdon, V., Maravita, A., Hutton, C., Husain, M., & Driver, J. (2008). Abnormal attentional modulation of retinotopic cortex in parietal patients with spatial neglect. *Current Biology*, 18, 1525–1529.
- Warren, J. D., Rohrer, J. D., & Hardy, J. (2012). Disintegrating brain networks: From syndromes to molecular nexopathies. *Neuron*, 73, 1060–1062.
- Warren, J. D., Rohrer, J. D., Schott, J. M., Fox, N. C., Hardy, J., & Rossor, M. N. (2013). Molecular nexopathies: A new paradigm of neurodegenerative disease. *Trends in Neurosciences*, 36, 561–569.
- Yoshida, T., Mori, T., Shimizu, H., Yoshino, Y., Sonobe, N., Matsumoto, T., ... Ueno, S. (2017). Neural basis of visual perception and reasoning ability in Alzheimer's disease: Correlation between Raven's colored progressive matrices test and 123 I-IMP SPECT imaging results. *International Journal of Geriatric Psychiatry*, 32, 407–413.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Sala A, Caminiti SP, Iaccarino L, et al. Vulnerability of multiple large-scale brain networks in dementia with Lewy bodies. *Hum Brain Mapp*. 2019;40: 4537–4550. <https://doi.org/10.1002/hbm.24719>