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A systematic literature review of fMRI and EEG resting-state functional connectivity in Dementia with Lewy Bodies: underlying mechanisms, clinical manifestation, and methodological considerations

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Highlights

- Functional connectivity differs between patients with DLB and healthy individuals
- Connectivity in large-scale networks, alpha, and beta is consistently decreased
- Attentional, visual, executive, and DMN networks show interconnectivity patterns
- Some cognitive problems are linked with greater connectivity disturbances
- Methodological approaches used may impact the directionality of connectivity

Keywords

Dementia with Lewy Body, functional connectivity, resting-state networks, imaging methodology, MRI, EEG

Abstract

Previous studies suggest that there may be important links between functional connectivity, disease mechanisms underpinning the Dementia with Lewy Body (DLB) and the key clinical symptoms, but the exact relationship remains unclear. We performed a systematic literature review to address this gap by summarising the research findings while critically considering the impact of methodological differences

on findings. The main methodological choices of fMRI articles included data-driven, seed-based or regions of interest approaches, or their combinations. Most studies focused on examining large-scale resting-state networks, which revealed a consistent decrease in connectivity and some associations with non-cognitive symptoms. Although the inter-network connectivity showed mixed results, the main finding is consistent with theories positing disconnection between visual and attentional areas of the brain implicated in the aetiology of psychotic symptoms in the DLB. The primary methodological choice of EEG studies was implementing the phase lag index and using graph theory. The EEG studies revealed a consistent decrease in connectivity on alpha and beta frequency bands. While the overall trend of findings showed decreased connectivity, more subtle changes in the directionality of connectivity were observed when using a hypothesis-driven approach. Problems with cognition were also linked with greater functional connectivity disturbances. In summary, connectivity measures can capture brain disturbances in the DLB and remain crucial in uncovering the causal relationship between the networks' disorganisation and underlying mechanisms resulting in psychotic, motor, and cognitive symptoms of the DLB.

1. Introduction

Dementia with Lewy Bodies (DLB) is the second most prevalent form of neurodegenerative dementia accounting for approximately 15 to 25% of all cases (I. G. McKeith et al., 1996; Ian G. McKeith et al., 2017). DLB, similar to Parkinson's Disease Dementia (PDD), results from an abnormal build-up of Lewy bodies (i.e., primarily composed of aggregated alpha-synuclein protein) in the limbic and neocortical areas and brain stem. Clinical symptoms can be divided into cognitive (e.g., cognitive and memory disturbances), psychotic (e.g., visual hallucinations), and motor manifestations (e.g., Parkinsonism). Visual hallucinations are an important clinical distinguishing criterion (Ian G. McKeith et al., 2017; Thomas et al., 2018) as approximately 80% of DLB patients report experiencing them. The current clinical distinction between DLB and PDD is based on the timing of the onset of cognitive decline relative to motor symptoms (Gomperts, 2016) while neuroimaging biomarkers are used as a supplementary aid for diagnosis (McKeith et al., 2017). Possible mechanisms of psychiatric symptoms in DLB include impaired visual perception and attention (Collerton et al., 2005), neurotransmitter system dysfunction (Russo et al.,

2019), impairments in brain connectivity and networks dysregulation (van den Heuvel & Sporns, 2011), or their combination (Tsukada et al., 2015).

More studies exploring brain connectivity and its relationship to the pathophysiology of symptoms in DLB have been emerging. There is some evidence from the research on Parkinson's Disease (PD) that demonstrates the dysfunctional engagement of large-scale brain networks in the pathophysiology of hallucinations in PD (Shine et al., 2015). A disruption in the top-down (i.e., memory intrusion and inhibition problems) and bottom-up processes (i.e., dysfunctional sensory processing) may contribute to the occurrence of hallucinations in neurodegenerative conditions (Spinosa et al., 2022). Furthermore, further evidence suggests a potential relationship between connectivity dysfunction and other cognitive and motor symptoms in DLB and other alpha-synucleinopathies such as cognitive fluctuations (Matar et al., 2022; Peraza et al., 2014), memory-related problems (Aoki et al., 2019), and motor problems (Tang et al., 2022).

Therefore, examination of functional connectivity in conditions like DLB is critical in our understanding of how the brain functions as a complex network of functionally related regions, how observed dysregulations relate to the underlying pathology and the instrumental role of this relationship in intricate cognitive processes. Connectivity is considered a potential disease biomarker in neurodegenerative conditions where the evidence base is greater, such as in Alzheimer's Disease; however, its significance remains inconclusive in DLB (Hohenfeld et al., 2018). Hohenfeld and colleagues further suggested that methodological variety in relatively limited literature poses the main impediment to finding a valid and reliable resting-state fMRI biomarker across neurodegenerative conditions. Therefore, a lack of data and a wide range of methodological approaches can both influence the outcomes.

This review aims to provide a detailed summary of the key findings in the literature while highlighting differences and linking them with the potential influence of the methodological differences of different studies. This extends recently published reviews of resting-state functional connectivity in patients with neurodegenerative disorders that experience visual hallucinations (Spinosa et al., 2022), structural and functional connectivity findings in DLB (Habich et al., 2023), and a meta-analysis of large-scale network dysfunction in alpha-synucleinopathy (Tang et al., 2022). While

some articles here overlap with recently published reviews; the present systematic literature review fills the gap in our understanding of how different methodological choices might impact the directionality and veracity of findings in resting-state functional connectivity in the DLB and a potential association with underlying mechanisms and their clinical manifestation.

2. Methods

We performed a systematic literature review of studies on resting-state functional connectivity in DLB. Articles for this literature review were obtained through a systematic search of PubMed, Ovid (Medline and Embase), Web of Science, Scholar, and references from pertinent articles from January 2000 to November 2022. The study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; (Moher et al., 2009)).

The search strategy was performed in October 2022 and included keywords “Dementia with Lewy Bodies”, “DLB”, and “alpha synucleinopathy” and their synonyms and acronyms. The further search consisted of functional neuroimaging keywords such as “functional magnetic resonance”, “electroencephalography”, and “magnetoencephalography” and their synonyms and acronyms. We additionally searched for common keywords related to network and connectivity analysis and methodologies such as “Independent Component Analysis”, “seed-based”, “network”, their synonyms and acronyms, and specific resting-state networks. All studies investigating functional connectivity in DLB were included as well as the studies with the mixed groups of DLB and PD/PDD. Studies on structural, dynamic, and metabolic connectivity were excluded from the search. Further exclusion criteria consisted of studies published in other languages than English, animal model studies, post-mortem studies, reviews and meta-analyses, case studies, and task-based studies. All abstracts were screened independently by two reviewers.

3. Results

The literature search resulted in a total of 194 articles. After removing the duplicates, this left 144 articles of which 30 were found relevant after the abstract screening process. After accessing full-text versions, an additional 10 articles were excluded due to either not having a direct between-group comparison between patients with DLB and healthy controls or focusing on dynamic connectivity. Other excluded articles used

measures that can be used for assessing connectivity (e.g., coherence) but without directly concluding what their findings meant within the scope of connectivity. A total of 20 articles were therefore included in the qualitative synthesis. The summary of these steps is in the PRISMA chart (Figure 1).

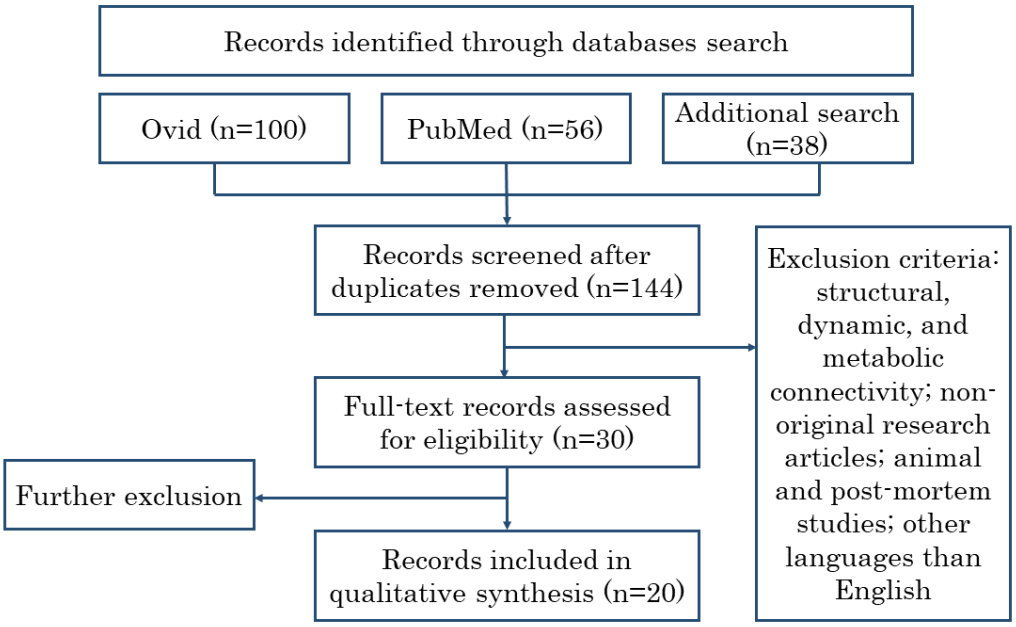

Figure 1. PRISMA chart highlighting all the steps in the literature search and screening process with resulting numbers of articles at each step.

3.1. Demographics and patients' characteristics

The summary of study demographics can be found in Table 1. All included studies compared their findings between the DLB group and healthy controls. On top of that, multiple studies compared their results with those of patients with PDD (Babiloni et al., 2018; Mehraram et al., 2020; Peraza et al., 2018; Peraza, Colloby, et al., 2015), patients with PD (Seibert et al., 2012) and patients with Alzheimer's Disease (Babiloni et al., 2018; Chabran et al., 2018, 2020; Dauwan et al., 2016; Franciotti et al., 2013; Galvin et al., 2011; Kenny et al., 2012, 2013; Lowther et al., 2014; Ma et al., 2022; Peraza, Taylor, et al., 2015; Peraza et al., 2018; van Dellen et al., 2015). The demographic information provided by Chabran et al. (Chabran et al., 2020) did not match the final number of included participants, likely due to exclusions.

The sample size of patients with DLB ranged from 15 to 79 in the fMRI studies and 25 to 66 in the EEG studies, with the median values of 18 and 38 respectively. The sample

size of healthy controls ranged from 15 to 40 in the fMRI and 17 to 80 in the EEG studies, with the median values of 21 and 53 respectively. Two fMRI studies had a mixed sample of patients with Lewy Body Dementia (LBD; (Schumacher et al., 2021)) and PD-related dementia (Seibert et al., 2012). Some cohorts seemed to overlap (Peraza, Colloby, et al., 2015; Peraza, Taylor, et al., 2015); (Kenny et al., 2012, 2013; Lowther et al., 2014); (Dauwan et al., 2016; van Dellen et al., 2015); (Mehraram et al., 2020; Peraza et al., 2018).

The age of the participants and the gender balance were reported in all studies. All ages were rounded to one decimal place. Where information was only provided in %, the male-to-female ratio was additionally calculated for consistency of reporting. The mean age of patients with DLB ranged from 65.5±9 to 80.6±6 in fMRI studies and from 70±9 to 78.2±7 in the EEG studies. On average, 39.2% of the patients' sample were female in the fMRI and 31.1% in the EEG studies, while 47.7% of the healthy controls were female in the fMRI studies and 31.0% in the EEG studies. 57.9% of all the studies consisted of less than 10 female patients, with as few as two (Seibert et al., 2012) or three female patient participants (Peraza et al., 2014). Other characteristics such as the level of educational attainment, the ethnic background of the participants and the nature of the disorder (i.e., probable vs possible) were not consistently reported in the studies.

Patients' performance on various cognitive scales and scales assessing the symptoms of DLB was also reported across studies. All studies reported patients' performance on the Mini-Mental State Examination (MMSE). Cambridge Cognitive Battery Test (CAMCOG) and Clinical Dementia Rating (CDR) were also used frequently while other cognitive tests varied from one study to another. To examine patients' neuropsychiatric symptoms, the hallucinations subscale of the Neuropsychiatric Inventory (NPI) and Clinical Assessment of Fluctuations (CAF) were frequently used. Four studies (Aoki et al., 2019; Chabran et al., 2018, 2020; Seibert et al., 2012) did not specify whether patients with DLB were taking any form of medication for their symptoms. The rest of the studies specified that patients were taking cholinergic, acetylcholinergic, or dopaminergic medication, or their combination.

3.2. Neuroimaging pre-processing characteristics

All studies utilised a resting-state paradigm, thus not being confounded by task-dependent differences in brain function. However, Chabran and colleagues (Chabran et al., 2018) used an inter-task resting-state sequence of a visuoperceptual task. Four fMRI studies (Franciotti et al., 2013; Kenny et al., 2012, 2013; Ma et al., 2022) and six EEG studies (Aoki et al., 2019; Babiloni et al., 2018; Dauwan et al., 2016; Mehraram et al., 2020; Peraza et al., 2018; van Dellen et al., 2015) reported that participants were instructed to keep their eyes closed during the scanning period. In other fMRI studies, participants were instructed to keep their eyes open (Peraza, Colloby, et al., 2015; Peraza, Taylor, et al., 2015; Seibert et al., 2012).

The image acquisition and pre-processing steps varied among the fMRI studies considerably. All studies used a 3T scanner with an exception of two (Franciotti et al., 2013; Seibert et al., 2012) that used a 1.5T scanner. While Peraza and colleagues (Peraza, Taylor, et al., 2015) did not mention the scanner type in the article, the authors confirmed they used a 3T scanner. All studies performed a motion correction step, yet by using various techniques. The majority of studies used spatial smoothing of a 6-8mm kernel, while one study did not provide the information (Galvin et al., 2011). Space normalisation was done in the two most common spaces, either in the MNI space (Chabran et al., 2018, 2020; Lowther et al., 2014; Ma et al., 2022; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Peraza, Taylor, et al., 2015; Schumacher et al., 2018, 2021; Seibert et al., 2012) or in the Talairach space (Franciotti et al., 2013), or their combination (Kenny et al., 2012, 2013). Galvin and colleagues (Galvin et al., 2011) did not specify the atlas space used. The inclusion of other steps such as frequency filtering or slice-timing correction differed largely among the studies.

As for the EEG studies, the electrodes were either positioned in a 10-20 setup with a sampling frequency of 500 Hz (Aoki et al., 2019; Dauwan et al., 2016; van Dellen et al., 2015) or a 10-5 setup with a sampling frequency of 1024 Hz (Mehraram et al., 2020; Peraza et al., 2018). Babiloni and colleagues (Babiloni et al., 2019) positioned the electrodes in a 10-20 setup with a sampling frequency of 128 Hz. All studies filtered out the frequencies (i.e., >30Hz; (Babiloni et al., 2019; Dauwan et al., 2016; Peraza et al., 2018; van Dellen et al., 2015)) and/or the components (Aoki et al., 2019; Mehraram et al., 2020) that were particularly affected by muscle artefacts, eye movements and microsaccades. Two studies (Aoki et al., 2019; Dauwan et al., 2016) did not report using the Fourier transform on the data. Data were filtered with a consistent range of

8-13Hz and 13-30Hz (Aoki et al., 2019; Dauwan et al., 2016; Peraza et al., 2018; van Dellen et al., 2015), or 8-13.5Hz and 14-20.5Hz (Mehraram et al., 2020) on the alpha and beta bands respectively. On the theta band, data were filtered with a frequency range of 4-8Hz (Aoki et al., 2019; Dauwan et al., 2016; van Dellen et al., 2015), or 4-7.5Hz (Mehraram et al., 2020), or 4-5.5Hz (Peraza et al., 2018). Babiloni and colleagues (Babiloni et al., 2019) used a more complex experimental setup by additionally exploring transition frequencies and individual alpha frequency peaks. Delta and gamma bands were not reported consistently or filtered out in the pre-processing steps.

3.3. Analytical approaches and methodological choices

3.3.1. Connectivity methodological choices

A thorough summary of resting-state functional connectivity and methodological approaches used to investigate between-group differences in dementia-related research can be found in our previously published review (Kucikova et al., 2021). Briefly, the two most common approaches include a so-called hypothesis-driven approach and a data-driven approach. Both, the hypothesis-driven and data-driven approaches should contain a scientific hypothesis; however, that of hypothesis-driven studies often focuses on specific brain regions while not considering others. When implementing a hypothesis-driven approach, a series of Regions of Interest (ROI; i.e., different brain areas) is chosen *a priori* to the analysis, followed by the assessment of the connectivity between them, typically on a voxel-by-voxel basis. Alternatively, the connectivity between specific seeds in the brain and the rest of the brain might be assessed. Seeds might represent any collection of brain voxels. In a data-driven approach, the activity in the brain is parcellated into the networks of synchronous brain activity (i.e., resting-state networks). The connectivity within or between those networks is then assessed by using methods such as Independent Component Analysis (ICA). Further approaches can be implemented to obtain a more detailed overview of the connectivity properties (e.g., graph theory). While data-drive approaches are typically explorative, hypothesis-drive approaches are typically confirmatory in nature. Nevertheless, both approaches are complementary. The summary of the methodological choices and related findings is provided in Table 2 and Table 3.

Six articles used EEG to investigate functional connectivity, while 14 articles used fMRI. The main methodological choices of the fMRI studies included implementing ICA (Lowther et al., 2014; Peraza et al., 2014; Schumacher et al., 2018), using a seed-based or ROI approach (Chabran et al., 2020; Galvin et al., 2011; Kenny et al., 2012, 2013; Peraza, Colloby, et al., 2015; Schumacher et al., 2021; Seibert et al., 2012), graph theory (Peraza, Colloby, et al., 2015; Peraza, Taylor, et al., 2015), or their combination (Chabran et al., 2018; Franciotti et al., 2013). The main methodological choice of the EEG studies was graph theory and implementation of the phase lag index (PLI; i.e., a synchronisation estimate between time series) (Babiloni et al., 2019; Dauwan et al., 2016; Mehraram et al., 2020; Peraza et al., 2018; van Dellen et al., 2015).

3.3.2. Statistical analytical approaches

For between-group statistical analysis, fMRI studies used dual regression (Lowther et al., 2014; Peraza et al., 2014), analysis of variance (ANOVA) (Franciotti et al., 2013; Peraza, Taylor, et al., 2015), non-parametric permutations (Peraza, Colloby, et al., 2015; Schumacher et al., 2018, 2021), two-sample t-test (Seibert et al., 2012), general linear model (Chabran et al., 2020), random effects analysis (Galvin et al., 2011), partial correlation analysis (Ma et al., 2022), and voxel-by-voxel analysis followed by cluster analysis (Chabran et al., 2018; Kenny et al., 2012, 2013).

The statistical choices of the EEG studies mainly included ANOVA, while two studies used its non-parametric form (i.e., the Kruskal-Wallis test) (Dauwan et al., 2016; Mehraram et al., 2020). Peraza and colleagues (Peraza et al., 2018) used parametric ANOVA and log-transformed all EEG scores of variability and standard deviation to approximate their distribution to a Gaussian. Alternative methods included a multivariate general linear model (GLM) (Babiloni et al., 2019; Dauwan et al., 2016; Mehraram et al., 2020; Peraza et al., 2018; van Dellen et al., 2015) and the Student's t-test (Aoki et al., 2019).

The majority of EEG studies performed a post-hoc analysis to control the Family-Wise Error Rate (FWER; i.e., the probability of obtaining at least one false positive in a group of tests) using methods such as Bonferroni correction (Aoki et al., 2019; Babiloni et al., 2018; Peraza et al., 2018; van Dellen et al., 2015) and Holm-Bonferroni correction

(Mehraram et al., 2020); however, one study used the False Discovery Rate approach (FDR; the proportion of false positive among all rejected tests) (Dauwan et al., 2016). In fMRI studies, several articles controlled FWER using Bonferroni correction (Franciotti et al., 2013; Ma et al., 2022; Peraza, Taylor, et al., 2015). Alternatively, some used a permutation approach with the threshold-free cluster enhancement method (TFCE) (Lowther et al., 2014; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Schumacher et al., 2018, 2021) and two studies used an FDR approach (Chabran et al., 2020; Seibert et al., 2012).

To investigate the association between connectivity and cognition and/or clinical measures, the majority of EEG studies used a non-parametric test, Spearman's rank correlation coefficient (Aoki et al., 2019; Babiloni et al., 2018; Dauwan et al., 2016; Mehraram et al., 2020; van Dellen et al., 2015), while only one study used the parametric Pearson's correlation (Peraza et al., 2018). In the fMRI studies, four studies used Spearman's rank correlation (Chabran et al., 2018; Peraza et al., 2014; Schumacher et al., 2018, 2021), four studies used the Pearson's correlation (Chabran et al., 2020; Franciotti et al., 2013; Peraza, Taylor, et al., 2015; Seibert et al., 2012) and one study used partial correlation analysis (Ma et al., 2022). Unlike Pearson's correlation, Spearman's method makes no assumptions about the distribution from which the sample observations are drawn. However, Spearman's correlation is based on the assumption that variables have a monotonic relationship. Of the four studies that used Spearman's correlation in fMRI, three reported that they did not find any significant relationship (Chabran et al., 2018; Schumacher et al., 2018, 2021) and one reported an uncorrected significant relationship (Peraza et al., 2014).

Table 1. The summary of demographic characteristics across the studies.

Note: DLB = Dementia with Lewy Body, PD = Parkinson's Disease, PDD = Parkinson's Disease Dementia, PDR = Parkinson's-related Dementia, LBD = Lewy Body Dementia, HC = healthy control, AD = Alzheimer's Disease

		Patients (DLB)			Healthy controls			
Reference	**Patients' group**	**Sample size**	**Age (±SD)**	**Gender (M/F)**	**Sample size**	**Age (±SD)**	**Gender (M/F)**	**Modality**
Aoki et al. (2019)	DLB vs HC	41	78.2±6.7	22/19	80	44.2±20	57/23	EEG
Babiloni et al. (2018)	DLB vs HC vs AD vs PDD	34	75.1±1.1	11/23	40	72.9±1.1	16/24	EEG
Chabran et al. (2018)	DLB vs HC vs AD	26	65.5±9	12/14	22	65±9	10/12	fMRI
Chabran et al. (2020)	DLB vs HC vs AD	92	70.1±9.4	39/40	22	66.5±7.8	11/11	fMRI
Dauwan et al. (2016)	DLB vs HC vs AD	66	70±9	52/14	66	70±7	52/14	EEG
Franciotti et al. (2013)	DLB vs HC vs AD	18	75±1	9/9	15	74±2	5/10	fMRI

Galvin et al. (2011)	DLB vs HC vs AD	15	71.7±9.1	11/4	38	73.9±6.6	12/26	fMRI
Kenny et al. (2012)	DLB vs HC vs AD	15	80.6±6	9/6	16	76.3±8.3	9/7	fMRI
Kenny et al. (2013)	DLB vs HC vs AD	15	80.6±6	9/6	16	76.3±8.3	9/7	fMRI
Lowther et al. (2014)	DLB vs HC vs AD	15	80.6±6	9/6	40	77.8±4.5	20/20	fMRI
Ma et al. (2022)	DLB vs HC vs AD	30	67.4 ±5.3	17/13	33	64.9 ±9.3	15/18	fMRI
Mehraram et al. (2019)	DLB vs HC vs AD vs PDD	25	76.2±6.2	20/5	18	76.3±5.5	11/7	EEG
Peraza et al. (2014)	DLB vs HC	16	76.2±5.7	13/3	17	77.3±4.7	14/3	fMRI
Peraza et al. (2015)a	DLB vs HC vs PDD	18	77.2±6.1	13/5	17	76.9±5.8	14/3	fMRI
Peraza et al. (2015)b	DLB vs HC vs AD	18	77.2±6.1	13/5	17	76.9±5.8	14/3	fMRI
Peraza et al. (2018)	DLB vs HC vs AD vs PDD	25	75.8±6.5	20/5	17	76.2±5.6	10/7	EEG

Schumacher et al. (2017)	DLB vs HC	31	78.1±6.7	19/12	31	76.4±7.2	22/9	fMRI
Schumacher et al. (2021)	LBD vs HC	46*	75.9±6.9	34/12	31 HC	76.4±7.2	22/9	fMRI
Seibert et al. (2012)	PD vs PRD vs HC	18*	72±7	16/2	19	76±9	8/11	fMRI
van Dellen et al. (2015)	DLB vs HC vs AD	66	70±9	52/14	66	70±7	52/14	EEG

Table 2. The summary of the methodological choices and related findings in fMRI studies.

Note: DLB = Dementia with Lewy Body, PD = Parkinson's Disease, PDD = Parkinson's Disease Dementia, PDR = Parkinson's-related Dementia, LBD = Lewy Body Dementia, HC = healthy control, AD = Alzheimer's Disease, ICA = Independent Component Analysis, NBM = Nucleus Basalis of Meynert, PCC = Posterior Cingulate Cortex, PVC = primary visual cortex

Reference	Patients' groups	Analytical approach	Brain areas of interest	Connectivity in DLB vs HC
Chabran et al. (2018)	DLB vs HC vs AD	ICA + seed-based	networks	decreased
Chabran et al. (2020)	DLB vs HC vs AD	seed-based	networks	decreased

Franciotti et al. (2013)	DLB vs HC vs AD	ICA + graph theory	networks	decreased
Galvin et al. (2011)	DLB vs HC vs AD	seed-based	networks	mixed
Kenny et al. (2012)	DLB vs HC vs AD	seed-based	hippocampus, PCC, precuneus, PVC	increased
Kenny et al. (2013)	DLB vs HC vs AD	seed-based	caudate, putamen, thalamus	increased
Lowther et al. (2014)	DLB vs HC vs AD	ICA	networks	mixed
Ma et al. (2022)	DLB vs HC vs AD	graph theory	networks	mixed
Peraza et al. (2014)	DLB vs HC	ICA	networks	decreased
Peraza et al. (2015)a	DLB vs HC vs PDD	seed-based	networks	decreased
Peraza et al. (2015)b	DLB vs HC vs AD	graph theory	networks	mixed
Schumacher et al. (2017)	DLB vs HC	ICA	networks	decreased
Schumacher et al. (2021)	LBD vs HC	seed-based	NBM	increased
Seibert et al. (2012)	PD vs PRD vs HC	seed-based	caudate, isthmus cingulate	decreased

Table 3. The summary of the methodological choices and related findings in EEG studies.

Note: DLB = Dementia with Lewy Body, PD = Parkinson's Disease, PDD = Parkinson's Disease Dementia, HC = healthy control, AD = Alzheimer's Disease, ICA = Independent Component Analysis, ROI = Region of Interest, PLI = Phase Lag Index

Reference	Groups	Analytical approach	Connectivity measure	Brain areas of interest	Specific brain areas with significant differences	Connectivity in DLB vs HC
Aoki et al. (2019)	DLB vs HC	ICA	network activity	networks	N/A	decreased
Babiloni et al. (2018)	DLB vs HC vs AD vs PDD	ROI	PLI	whole-brain - frequency bands	central, frontal, parietal, occipital, temporal regions	decreased
Dauwan et al. (2016)	DLB vs HC vs AD	graph theory	PLI	whole brain - frequency bands	posterior regions	decreased
Mehraram et al. (2019)	DLB vs HC vs AD vs PDD	graph theory	PLI	networks	N/A	decreased
Peraza et al. (2018)	DLB vs HC vs AD vs PDD	graph theory	PLI	networks - frequency bands	N/A	decreased
van Dellen et al. (2015)	DLB vs HC vs AD	graph theory	PLI	networks - frequency bands	N/A	decreased

3.4. Main connectivity results

Ten fMRI studies (Chabran et al., 2018, 2020; Franciotti et al., 2013; Galvin et al., 2011; Lowther et al., 2014; Ma et al., 2022; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Peraza, Taylor, et al., 2015; Schumacher et al., 2018) and two EEG studies (Aoki et al., 2019; Mehraram et al., 2020) investigated large-scale resting-state networks. Four other EEG studies investigated the connectivity on the frequency band levels (Babiloni et al., 2018; Dauwan et al., 2016; Peraza et al., 2018; van Dellen et al., 2015). The Default Mode Network (DMN) was the most examined network (Chabran et al., 2018, 2020; Franciotti et al., 2013; Galvin et al., 2011; Lowther et al., 2014; Ma et al., 2022; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Schumacher et al., 2018). Other networks of interest included the executive, executive control, or frontoparietal networks (Chabran et al., 2018, 2020; Lowther et al., 2014; Ma et al., 2022; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Schumacher et al., 2018), the attentional network (Chabran et al., 2018, 2020; Galvin et al., 2011; Ma et al., 2022; Schumacher et al., 2018), the salience network (Chabran et al., 2020; Lowther et al., 2014; Ma et al., 2022), the visual or visual processing networks (Chabran et al., 2018; Galvin et al., 2011; Ma et al., 2022; Schumacher et al., 2018), the sensorimotor or motor networks (Aoki et al., 2019; Ma et al., 2022; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Schumacher et al., 2018), the temporal network (Peraza et al., 2014; Schumacher et al., 2018), and the basal ganglia networks (Lowther et al., 2014; Schumacher et al., 2018).

Most studies reported an overall decrease in functional connectivity in the DLB group. Yet, there were several studies with mixed results (Galvin et al., 2011; Lowther et al., 2014; Peraza, Taylor, et al., 2015) or an overall increase in functional connectivity (Kenny et al., 2012, 2013; Schumacher et al., 2021). Importantly, studies that found the overall increase in functional connectivity examined specific brain areas rather than networks. The directionality of the main conclusions is visually summarised in Figure 2.

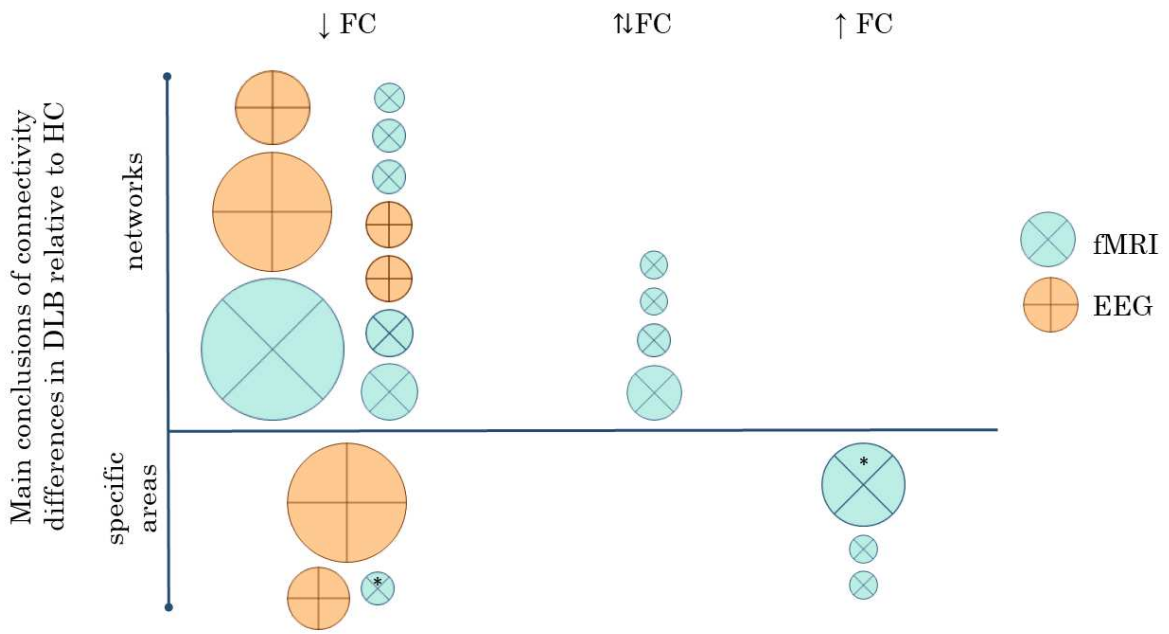

Figure 2. Main conclusions of the directionality of connectivity differences across the studies either in resting-state networks or between specific brain areas. The results are presented in the DLB group relative to healthy controls. The size of each point corresponds with the sample size of patients with the DLB in each study. Studies which used mixed samples of patients with DLB and patients with other forms of dementia are marked by an asterisk. The extended version of this figure annotated with the corresponding studies is provided in the Supplementary Materials.

3.4.1. Networks

Five studies showed decreased connectivity in the patients' group relative to healthy controls within the DMN (Chabran et al., 2018; Franciotti et al., 2013; Galvin et al., 2011; Lowther et al., 2014; Peraza, Colloby, et al., 2015), while two studies showed no between-group differences (Peraza et al., 2014; Schumacher et al., 2018). Several other studies reported no significant between-group differences in multiple other resting-state networks. The visual summary of within-network connectivity findings can be found in Figure 3.

Functional connectivity in patients with DLB exhibited a consistent decrease within multiple other resting-state networks. This included the salience network (Chabran et al., 2020; Lowther et al., 2014), the temporal network (Peraza et al., 2014; Schumacher et al., 2018), the sensorimotor or motor networks (Aoki et al., 2019; Ma

et al., 2022; Peraza, Colloby, et al., 2015; Schumacher et al., 2018), and visual networks (Aoki et al., 2019; Chabran et al., 2018).

Attentional networks and executive networks exhibited mixed within-network findings. Schumacher and colleagues (Schumacher et al., 2018) and Ma and colleagues (Ma et al., 2022) observed increased within-network connectivity in the attentional network and executive network respectively. On the contrary, others found decreased connectivity within the attentional network (Chabran et al., 2020) and executive networks (Lowther et al., 2014; Peraza et al., 2014; Peraza, Colloby, et al., 2015).

Similarly, between-networks connectivity of the DMN, executive networks, attentional networks, and visual networks exhibited mixed directionality. While the connectivity between the executive networks and the DMN increased in the DLB group (Chabran et al., 2020), the connectivity between the executive networks and the attentional network decreased (Chabran et al., 2018). There was also an increase between the attentional network and the DMN (Galvin et al., 2011) and the executive network and the DMN (Chabran et al., 2020). The connectivity between the visual networks and the DMN decreased (Galvin et al., 2011).

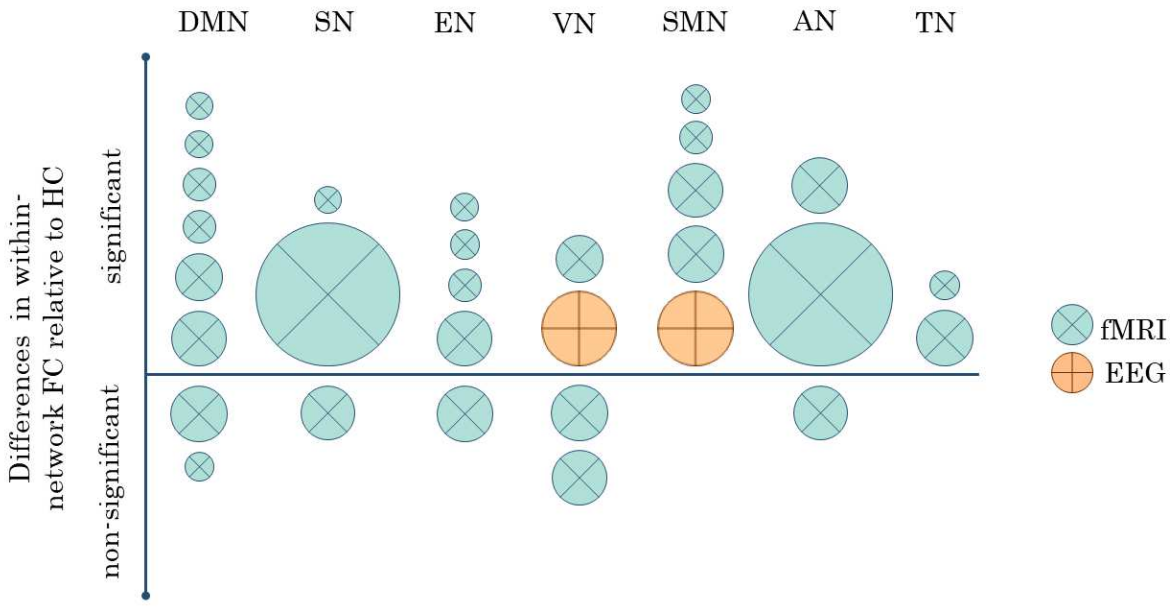

Figure 3. The occurrence of significant and non-significant group differences in large-scale network connectivity across the studies. The size of each point corresponds with the sample size of patients with the DLB in a given study. The extended version of this

figure annotated with the corresponding studies is provided in the Supplementary Materials.

*Note: AN = attentional network, EN: executive network, SMN: sensorimotor network, TN: thalamic network, SN: salience network, DMN: default mode network, VN: visual network, * - includes executive network, executive control network, or frontoparietal network.*

No other networks exhibited significant between-group differences in between-network connectivity. Between- and within- connectivity of the large-scale functional networks is visualised in Figure 4.

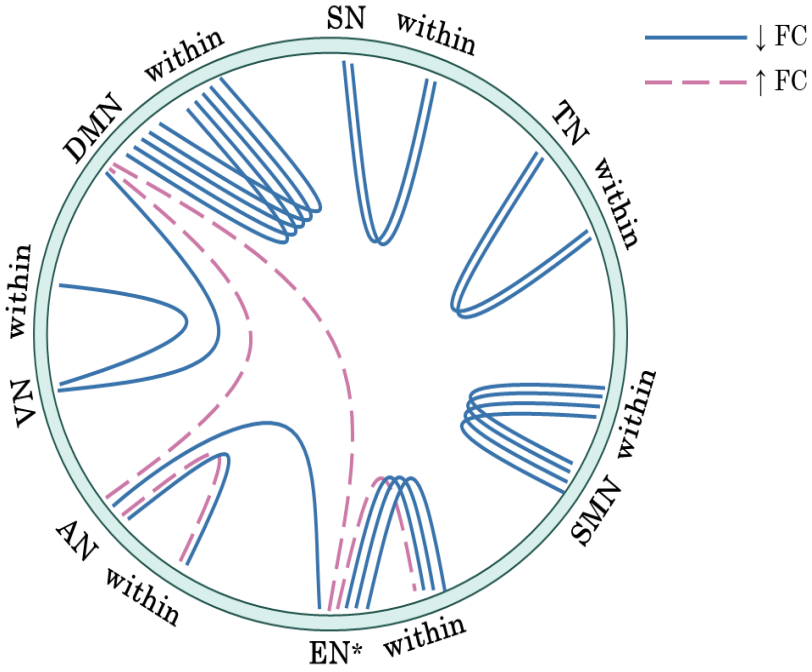

Figure 4. The connectogram of within- and between-networks connectivity of large-scale resting-state networks (EEG and fMRI).

*Note: AN = attentional network, EN: executive network, SMN: sensorimotor network, TN: thalamic network, SN: salience network, DMN: default mode network, VN: visual network, * - includes executive network, executive control network, or frontoparietal network.*

3.4.2. Seed-based and ROI

In total, 28% of fMRI studies used a hypothesis-driven approach (i.e., a seed-based or ROI) with specific brain regions of interest. Both, seed-based and ROI connectivity analyses permit a direct comparison of functional connectivity differences between a brain region and the rest of the brain or between multiple brain regions, respectively.

Three studies observed a general increase in brain connectivity in the DLB group in comparison with healthy controls (Kenny et al., 2012, 2013; Schumacher et al., 2021), while one study observed a decrease (Seibert et al., 2012).

Brain areas used as seeds in the analyses included caudate (Kenny et al., 2013; Seibert et al., 2012), isthmus cingulate (Seibert et al., 2012), nucleus basalis of Meynert (Schumacher et al., 2021), putamen and thalamus (Kenny et al., 2013), and hippocampus, PCC, and PVC (Kenny et al., 2012). There was increased connectivity between the posterior cingulate culmen, anterior cingulate, globus pallidus, and the cerebellar tonsil in the DLB group (Kenny et al., 2012), and between the nucleus basalis of Meynert and occipital cortex in the LBD group (Schumacher et al., 2021). The caudate exhibited increased connectivity with multiple brain areas including the posterior cingulate, precuneus, and culmen (Kenny et al., 2013). On the contrary, decreased connectivity between the caudate and middle frontal regions was observed in the PDR group (Seibert et al., 2012). Notably, two studies (Schumacher et al., 2021; Seibert et al., 2012) had mixed groups of DLB and other types of dementia.

3.4.3. Frequency bands

EEG provides a higher temporal and a lower spatial resolution than fMRI, hence allowing for the exploration of connectivity on different frequencies.

No study concluded an increase in connectivity in any of the frequency bands. Patients with DLB consistently exhibited widespread decreased connectivity in the alpha frequency band (Aoki et al., 2019; Babiloni et al., 2018; Dauwan et al., 2016; Mehraram et al., 2020; Peraza et al., 2018; van Dellen et al., 2015). Aoki and colleagues showed significantly decreased alpha activity in the occipital visual network, which supports the findings from Peraza and colleagues who found a significant decrease in connectivity in the occipital regions. Babiloni and colleagues demonstrated decreased alpha magnitude in the parietal, occipital, and temporal regions.

Moreover, there is some evidence of a decrease in patients' connectivity in the beta frequency band (Aoki et al., 2019; Dauwan et al., 2016; Mehraram et al., 2020) and a less-spread decrease in the theta frequency band which was limited to only several electrodes (Dauwan et al., 2016; Peraza et al., 2018). Decreased beta activity in postcentral regions together with a localised decrease in gamma band activity in the pre-supplementary motor area was observed within the sensory-motor network (Aoki et al., 2019). Importantly, the observed decrease in theta and gamma bands was localised to a small number of electrodes. No between-group differences were observed on the delta band. Figure 5 provides a visual summary of EEG findings across different frequency bands.

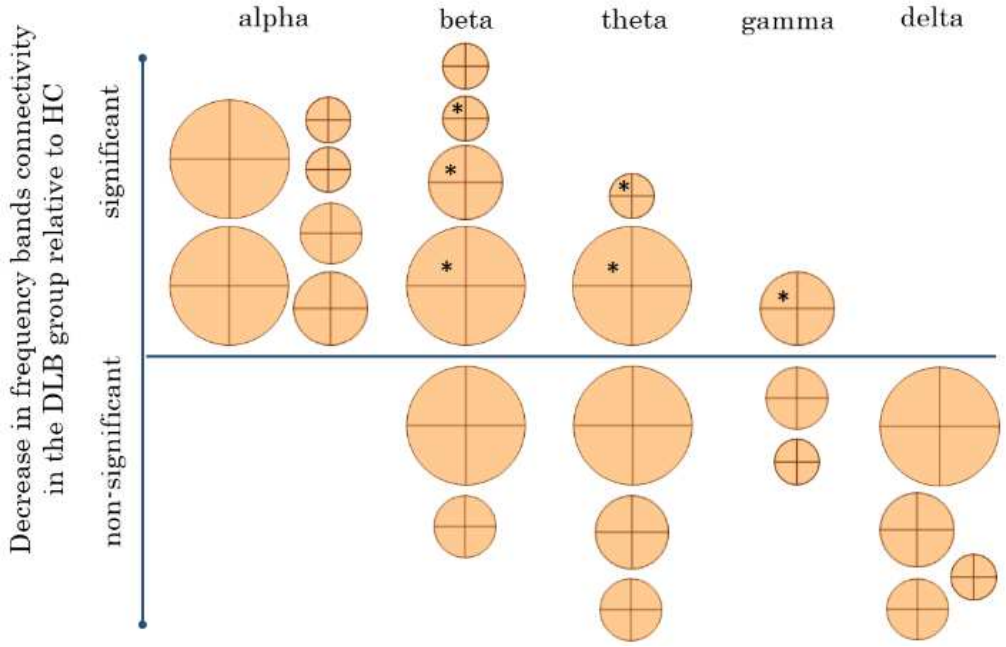

Figure 5. Decrease in connectivity on each frequency band across the EEG studies. The results are presented in the DLB group relative to healthy controls. The size of each point corresponds with the sample size of patients with the DLB in a given study. Studies which used mixed samples of patients with DLB and patients with other forms of dementia are marked by an asterisk. The extended version of this figure annotated with the corresponding studies is provided in the Supplementary Materials.

3.4.4. Graph theory

Graph theory is a mathematical approach that can be applied to functional connectivity analyses to quantify complex measures of connectivity properties. In doing so, it outlines graphs (i.e., networks) that consist of nodes (i.e., brain regions) that are linked via edges (i.e., functional connections). Graph measures can be described on a global (i.e., whole network) or a local scale (i.e., regional). They refer to the information about network integration and segregation, as well as the more detailed information about the organisation of the network, network communication, or information flow. More technical details on graph theory and its application to network analysis can be found in Bullmore and Sporns (Bullmore & Sporns, 2009).

14% of fMRI (Ma et al., 2022; Peraza, Taylor, et al., 2015) and 66.6% of EEG studies (Dauwan et al., 2016; Mehraram et al., 2020; Peraza et al., 2018; van Dellen et al., 2015) applied graph theory to their analyses, while Franciotti and colleagues (Franciotti et al., 2013) applied Granger causality. By using Granger causality, some information comparable to that obtained from graph theory can be computed (e.g., information flow).

Patients with DLB displayed consistent network disorganisation. Specifically, that was shown in networks' rich clubs (Ma et al., 2022), network efficiency (Dauwan et al., 2016), minimum spanning tree (Peraza et al., 2018), clustering coefficient, characteristic path length, network modularity, and node degree (Mehraram et al., 2020), small worldness (Peraza, Taylor, et al., 2015), and information flow (Dauwan et al., 2016; Franciotti et al., 2013).

In other words, the networks of patients with DLB exhibited higher network segregation (Mehraram et al., 2020; van Dellen et al., 2015), particularly in the theta band (Mehraram et al., 2020). Regionally, functional network reorganisation affected the hierarchical structure of the brain from the sensorimotor cortex to the frontoparietal network (Ma et al., 2022). Reduced information flow between the frontoparietal and parietal areas (Franciotti et al., 2013) and between the posterior to anterior areas (Dauwan et al., 2016) was also observed. Further evidence points to the additional disorganisation within the occipital regions (Mehraram et al., 2020; Peraza et al., 2018; Peraza, Taylor, et al., 2015).

3.4.5. Cognition and clinical measures

Multiple studies performed additional analyses to investigate the relationship between functional connectivity and some cognitive functions in DLB. Overall, worse performance on the cognitive, psychological, and clinical tests was linked with greater disturbance in functional connectivity.

57.1% of fMRI (Chabran et al., 2018, 2020; Franciotti et al., 2013; Lowther et al., 2014; Peraza et al., 2014; Peraza, Colloby, et al., 2015; Schumacher et al., 2018, 2021) and 50% of EEG studies (Aoki et al., 2019; Mehraram et al., 2020; Peraza et al., 2018) examined the relationship between functional connectivity and visual hallucinations and/or cognitive fluctuations. Multiple studies found significant negative associations between functional connectivity and visual hallucinations assessed by the NPI scale in both the alpha and beta ranges (Mehraram et al., 2020), and the theta range (Peraza et al., 2018). Additionally, enhanced memory perception network activity correlated with increased hallucinations (Aoki et al., 2019). Patients also showed a relationship between cognitive fluctuations and connectivity dysfunctions in the right hemisphere (Franciotti et al., 2013), left frontoparietal networks (Peraza et al., 2014), and within and between the salience, the DMN, and the frontoparietal networks (Chabran et al., 2020). A positive correlation was observed between the cognitive fluctuations and connectivity between several brain regions within salience and attentional networks (Chabran et al., 2020) and within basal ganglia and limbic networks (Lowther et al., 2014).

Furthermore, patients who performed better on the Trail Making Test (i.e., a measure for attention/cognitive flexibility) showed stronger EEG activity in the beta band in the posterior brain regions (Dauwan et al., 2016). The occipital alpha activity was also positively correlated with attention measures on the revised Wechsler Memory Scale (Aoki et al., 2019). Working memory and attention correlated negatively with functional connectivity strength between non-rich club nodes and positively with functional connectivity strength between rich club nodes and non-rich club nodes (Ma et al., 2022). Rich club organisation is crucial in the global integration of neural information and is considered critical topological property of healthy brains (van den Heuvel & Sporns, 2011).

As for global clinical and cognitive measures, lower MMSE (i.e., a measure of a global cognitive impairment) (Babiloni et al., 2019; Dauwan et al., 2016; Peraza, Taylor, et

al., 2015; van Dellen et al., 2015) and the Visual Association Test scores (i.e., a measure of episodic memory) (van Dellen et al., 2015) correlated with more disturbances in functional connectivity in the DLB group. The activity in the visual perception network correlated negatively with both the scores on the depression and anxiety subscales of the NPI test (Aoki et al., 2019).

Despite analysing the relationship between resting-state connectivity and cognition and/or clinical measures, three studies did not find any significant relationship (Chabran et al., 2018; Schumacher et al., 2018, 2021). Interestingly, Chabran and colleagues reported a significant negative correlation between the posterior DMN synchronisation with the task-paradigm time course and cognitive fluctuations.

3.4.6. Comparisons with other forms of dementia

Multiple studies compared their findings with other neurodegenerative disorders. 64% of fMRI and 83.3% of studies compared DLB with AD, while 14% of fMRI and 66.6% of EEG studies compared DLB with PD/PDD.

In brief, functional connectivity in DLB decreased in comparison with AD in the DMN, salience, and executive networks (Lowther et al., 2014). However, posterior cingulate cortex activity (Franciotti et al., 2013) and putamen activity (Kenny et al., 2013) were increased in patients with DLB in comparison with patients with AD. While some findings were mixed (Babiloni et al., 2019; Galvin et al., 2011), others did not conclude any significant between-group differences between DLB groups and AD groups (Chabran et al., 2018, 2020; Kenny et al., 2012) and DLB groups and PDD groups (Peraza, Taylor, et al., 2015).

Notably, the directionality of connectivity results in graph-theoretical studies relates to network organisation and disorganisation rather than the strength of functional connectivity. Therefore, studies reporting their findings only from graph theoretical analyses (Dauwan et al., 2016; Ma et al., 2022; Mehraram et al., 2020; Peraza et al., 2018; Peraza, Colloby, et al., 2015) were excluded from the overall comparisons of directionality to ensure the comparability. In comparison with AD, DLB patients showed more randomised minimum spanning tree in high theta and alpha bands (Peraza et al., 2018) and greater network segregation within the theta band (Mehraram et al., 2020). There were mixed differences between DLB and AD in multiple other graph theoretical properties (Dauwan et al., 2016; Peraza, Colloby, et al., 2015). In

comparison with PDD, DLB patients did not show any significant differences (Mehraram et al., 2020; Peraza, Taylor, et al., 2015). The connectivity strength seems to be the most important discriminatory variable between the disorders (Mehraram et al., 2020; Peraza et al., 2018).

4. Discussion

4.1. Findings

The present systematic literature review demonstrates disruptions in functional connectivity in patients with DLB. In gestalt, this includes 1.) an overall decrease in connectivity in large-scale networks, 2.) disruptions in graph-theoretical properties, 3.) a decrease in connectivity in alpha and beta EEG bands, and 4.) worse cognitive performance linked with more disruptions in connectivity. However, there were several inconclusive differences in connectivity between specific brain areas. Nevertheless, and despite the use of various methodologies, the authors established the key connectivity changes in the areas that overlap with the regions of the DMN, attentional, executive, and visual networks. This implies the widespread damage to the areas that are involved in cognitive, attentional, and emotional processing.

4.2. Demographic and clinical factors

The sample size is an important consideration in neuroimaging research. On one hand, a sufficient sample size is necessary to obtain reliable results; on the other hand, it is challenging to find participants and acquire their brain scans, especially in the later stages of neurodegeneration. On average, the sample size of fMRI studies was smaller than that of EEG studies with as few as 15 (Kenny et al., 2012, 2013; Lowther et al., 2014) and 25 patients with DLB (Mehraram et al., 2020; Peraza et al., 2018), respectively. Studies with a smaller sample size often recognised it as a limitation. Multiple studies also emerged from the limited number of centres. Undoubtedly, the use of functional neuroimaging is informative in psychiatric research, but both lack of power and possible selection bias need to be recognised as the major weaknesses (Marek et al., 2022) and should be cautiously considered in the notion of the present review and resulting generalisability to a wider population of patients with DLB.

While studies reported age, gender, and education consistently and some of them specified using them as covariates in the analyses, no study investigated their direct effect on functional connectivity. Many fMRI studies lacked gender balance with fewer

women in their samples. The ethnic background of participants was rarely reported. Previous research showed that some demographic factors might affect functional connectivity in other disorders (Misiura et al., 2020; Schoonheim et al., 2012) as well as the general predictive accuracy of neuroimaging (Benkarim et al., 2022). For example, the level of education seems to have a protective role on some aspects of cognition (Le Carret et al., 2003) and shows a positive relationship with frontal-temporal-parietal connectivity in healthy elders (Arenaza-Urquijo et al., 2013).

Previous evidence suggests that medication commonly introduced to patients with DLB might alter functional connectivity. For instance, the cholinergic treatment enhances functional network connectivity in mild cognitive impairment (Pa et al., 2013), while some antipsychotic medication can alter connectivity in the DMN (Sambataro et al., 2010) or other resting-state networks (Kraguljac et al., 2016). Matching groups based on their medication treatment or brief medication withdrawal may be challenging due to the wide range of prescribed medication in the DLB. However, controlling for the effect of medication intake in the analysis might eliminate a potential confounding effect. The reviewed studies established a link between psychotic symptoms, problems with attention, and connectivity, but findings from wider cognition are limited.

4.3. Methodological and analytical considerations

4.3.1. Connectivity analytical method and consistency of results

The overall trend of connectivity findings showed a decrease, yet more subtle changes in the directionality of connectivity were observed when using a hypothesis-driven approach. Connectivity within the DMN, executive, and sensorimotor networks was consistently decreased in the DLB relative to healthy controls. This finding was inconsistent with findings from studies investigating functional connectivity between specific brain regions by using seeds of interest or ROI approaches. Speculatively, the increase in connectivity between specific brain areas might reflect a compensatory mechanism for the disruptions in the overall large-scale networks. This could be related to findings from graph theoretical analyses that observed widespread network disorganisation in multiple graph properties. For instance, observed redistribution of the information flow serves as a protective mechanism for some aspects of cognition (Ma et al., 2022). EEG studies showed a consistent decrease in connectivity on alpha

and beta bands and further disorganisation in graph-theoretical properties in regions overlapping with findings from large-scale networks.

The information about functional connectivity can be also inferred from the studies that use regional homogeneity as their methodological choice. For instance, Peraza and colleagues (Peraza et al., 2016) found decreased regional homogeneity in sensory-motor areas, which is in line with several studies (Aoki et al., 2019; Ma et al., 2022; Peraza, Colloby, et al., 2015; Schumacher et al., 2018). The authors linked these findings to motor problems found on the Lewy body disease spectrum. Reduced regional homogeneity in posterior regions in the DLB patients also distinguished them from patients with PDD (Borroni et al., 2015). Interestingly, Dauwan and colleagues (Dauwan et al., 2016) demonstrated disturbances in EEG connectivity flow from posterior to anterior regions by using dynamic connectivity measures. Notably, patients show no reversal in the pattern of directed connectivity, which points out to underlying abnormalities in the posterior areas of the brain.

Taken together, the above findings suggest that changes in functional connectivity are observed regardless of the methodologies implemented. The directionality of those changes, however, might be influenced by the methodology used. Importantly, no standardised imaging pre-processing and analytical pipeline in resting-state research confounds direct comparisons and should be taken into account when interpreting the findings.

4.3.2. Statistical methods and consistency of results

Similar statistical methods used across different studies led to some consistent outcomes; however, some outcomes were consistent irrespective of the statistical approach. For example, for the main connectivity results, the studies that found an overall increase in brain connectivity in the DLB group in comparison with healthy controls (Kenny et al., 2012, 2013; Schumacher et al., 2021), all used a clustering approach in their analysis. Whereas despite implementing different statistical methods, five studies consistently reported a decreased within-network connectivity in the patients' group compared to healthy controls within the DMN (Chabran et al., 2018; Franciotti et al., 2013; Galvin et al., 2011; Lowther et al., 2014; Peraza, Colloby, et al., 2015). However, only two studies that implemented dual regression both found

decreased connectivity within the executive networks (Lowther et al., 2014; Peraza et al., 2014).

From the results of connectivity within frequency bands, all EEG studies reported a decrease in alpha connectivity in the DLB group compared to controls irrespective of statistical methods. However, the two studies that used the Kruskal-Wallis test, both found a decrease in beta connectivity in patients (Dauwan et al., 2016s; Mehraram et al., 2020). Connectivity strength was reported as the most important discriminatory variable between disorders despite using different classifiers – a random forest (Mehraram et al., 2020) and logistic regression (Peraza et al., 2018).

The studies that used the non-parametric Kruskal-Wallis test are likely to have done so on the basis that assumptions for parametric ANOVA have not been met. However, in many cases, a logarithmic transformation of variables would normalise the errors, leading to an over-use of methods such as the Kruskal-Wallis and ultimately loss of power. Given that the studies that used the Kruskal-Wallis test, both found a decrease in beta connectivity (Dauwan et al., 2016; Mehraram et al., 2020), it may be worth examining the impact on beta connectivity with a transformation approach along with ANOVA.

Covariate adjustment is most effective when the covariates are strongly predictive of an outcome. Some studies reported mixed results for the overall connectivity differences between patients and controls (Galvin et al., 2011; Lowther et al., 2014; Peraza, Taylor, et al., 2015); it is notable that they all did not mention any accounting for covariates in their analysis, and speculatively this may have contributed to their inconclusive outcomes. Some other considerations include accounting for multiple comparisons that differed among studies. For instance, the FWER correction may be too conservative given the spatial correlations of neighbouring voxels that typically display similar response patterns within functionally defined brain regions.

4.4. Potential underlying mechanisms and their clinical manifestations

4.4.1. Neurotransmitters and neuropathology

The observable symptoms in DLB may result from an exceptionally complex faulty interaction on multiple levels including neurotransmitter dysfunction, faulty visual

attention processing, and connectivity disturbances. Multiple studies discussed their findings in relation to defective neurotransmitter systems (Aoki et al., 2019; Babiloni et al., 2018; Chabran et al., 2020; Kenny et al., 2012, 2013; Peraza et al., 2014, 2018; Peraza, Taylor, et al., 2015; Schumacher et al., 2021; van Dellen et al., 2015).

For example, decreased alpha activity in the occipital regions (Aoki et al., 2019; Peraza et al., 2018) may be related to the cholinergic deficit, hypoperfusion, and hypometabolism shown in other studies (Mukaetova-Ladinska et al., 2013). Further differences in connectivity to the early visual areas were observed in the nucleus basalis of Meynert which is the major source of cholinergic innervation to the cortex (Schumacher et al., 2021). The alteration in alpha activity may therefore relate to deficits in visual attention and perception (discussed in section 4.4.2.) due to the flow of information from the occipital cortex to higher cognitive areas contingent on cholinergic function.

While some studies provide more evidence that functional alterations could have the potential to bridge the gap between cholinergic deficits and cognitive impairment in the DLB (Chabran et al., 2020; van Dellen et al., 2015), others highlight the importance of considering coexisting AD neuropathology (Babiloni et al., 2018; Schumacher et al., 2021).

Studies that investigated dynamic connectivity supported the relationship between network dysfunctions and cognitive fluctuations (Matar et al., 2022; Schumacher et al., 2019; Sourty et al., 2016). Such a relationship was further linked to noradrenergic and cholinergic receptors across the cerebral cortex (Matar et al., 2022) and the striatal dopamine transporter availability (Rieckmann et al., 2015). Impairments in multiple neurotransmitter systems, their role in visual hallucinations, and their link to the disinhibition hypotheses are reviewed in more detail elsewhere (Onofrj et al., 2013; Russo et al., 2019).

4.4.2. Attention and perception

Several reviewed studies link their findings with the existing theories about deficits in visual processing and in attention and perception (Aoki et al., 2019; Babiloni et al., 2018; Chabran et al., 2018, 2020; Dauwan et al., 2016; Franciotti et al., 2013; Kenny et al., 2012; Lowther et al., 2014; Ma et al., 2022; Mehraram et al., 2020; Peraza et

al., 2014; Peraza, Colloby, et al., 2015; Peraza, Taylor, et al., 2015; Schumacher et al., 2018, 2021).

The Perception and Attention Deficit Model (Collerton et al., 2005) proposes that visual hallucinations occur as a result of the failure in the integration of sensory information (bottom-up) and prior expectations (top-down). Rather than deficits in the dorsal visual stream (i.e., originating in the early visual cortex and passing through parietal lobes), this theory suggests that the problem occurs later in the information-integration process and could involve the cholinergic dysfunction that affects the ventral visual stream. Other theories extended this relationship by incorporating the network disconnection problem (Tsukada et al., 2013, 2015).

Notably, the mixed inter-network connectivity between the DMN, visual network, attentional network, and executive network is in line with these theories. While the connectivity within those networks was largely decreased in patients with DLB, their between-network connectivity showed an interesting interaction. The connectivity between the DMN and attentional network was increased, as was the connectivity between the DMN and executive network. However, the connectivity between attentional and executive networks was decreased. Furthermore, the DMN and visual network displayed decreased inter-network connectivity. This complex relationship was further supported by network segregation and reduced information flow between the areas that overlap with these large-scale networks observed in graph-theoretical studies.

Further evidence supports a differential role of functional connectivity between hallucinating and non-hallucinating patients (Mehraram et al., 2022). Specifically, connectivity between the DMN and the (ventral) attentional network was decreased, while the occipital lobe was the most disconnected region. This offers additional evidence of an association between cholinergic system dysfunction and functional connectivity abnormalities in patients with visual hallucinations. However, there is a lack of exploration of other potentially key neurotransmitter systems (e.g., 5HT, dopamine) and their influence on functional connectivity in the DLB.

4.5. Limitations and future directions

The current literature primarily offers cross-sectional study designs that do not allow for direct longitudinal comparisons. Similarly, we noticed an imbalance or lack of

information about multiple demographic characteristics such as gender, disease duration, ethnicity, and age. The major limitation of most studies was a sample size. Although challenging to conduct in neurodegenerative disorders, a longitudinal study set-up with a more diverse population could help to reduce these limitations. Some of the related changes might appear in the prodromal stages of the disorder, so focusing the research on identifying early biomarkers may yield important results.

The next steps should include working towards an optimal analytical setup. Present studies are too heterogenous in their set-up to allow for direct comparisons. This is mostly an issue in fMRI studies that lack a standardised pre-processing and analytical pipeline. Implementing a common platform or pipeline for analysis or more efforts towards data sharing might resolve some of these issues in the future. There is still a relative lack of evidence from EEG studies, so the heterogeneity between the pre-processing and analysis is currently not too concerning but may lead to problems in the future. Implementing other approaches of dynamic EEG analysis, such as the analysis of microstates, might capture and characterise the more complex and dynamic organisation of the brain on a temporal level. For instance, Schumacher and colleagues (Schumacher et al., 2019) showed a slowing of microstates in the DLB group in comparison with AD, which suggests the differential diagnostic potential of this type of analysis.

Alternatively, a combination of modalities or implementing less-utilised modalities (e.g., MEG) may improve our understanding of the contribution of resting-state connectivity changes in the DLB to the overall mechanisms of observable clinical symptoms, as well as providing solutions to overcome the issues arising from unstandardised analytical pipelines. Moreover, neuroimaging data can be used as real-life parameters in mechanistic models of neurodegenerative disorders as proposed in our recent work (Kucikova et al., 2022).

In combination with fast-developing machine learning and artificial intelligence models, functional connectivity might inform future research in DLB by enabling identification of distinct neural network patterns that differentiate DLB from other neurodegenerative disorders. For example, implementing deep learning to early detection and automated classification has gained significant attention in AD. The best classification performance was obtained based on the combination of multimodal neuroimaging data

with fluid biomarkers (Jo et al., 2019). The recent systematic review (Warren & Moustafa, 2023) concluded the potential of combining functional neuroimaging including network analysis with deep learning approaches as the state-of-the-art tool for the AD detection, with the emphasis on its use in early identification. Other conclusions that agree with our suggestions include the need for larger sample sizes and more focus on data sharing, data augmentation, and implementing multiple databases.

Distinguishing between disorders by using connectivity measures is promising. For instance, EEG seems to be a powerful tool to highlight widespread visual system and information processing dysfunction across different disorders prone to experiencing hallucinations (daSilva Morgan et al., 2018). The recent systematic literature reviews concluded the high potential of EEG applications in DLB research, mostly for diagnostic purposes (Chatzikonstantinou et al., 2021; Law et al., 2020). Although the differential diagnosis between DLB and other forms of dementia based on functional connectivity was not the primary focus of this review, studies showed potential for using functional connectivity as a differential biomarker. Most studies, however, focused on the comparisons between DLB and AD groups, consistently reporting more disorganised networks and more decreased functional connectivity in DLB in comparison with AD in the DMN network. Other findings were, however, mixed. Consequently, further research focusing on the comparison between PD/PDD and DLB would be highly beneficial, as understanding both similarities and differences between these disorders that largely overlap in their symptomatology is crucial in understanding the underlying mechanistic differences.

5. Conclusions

The overall trend of functional connectivity shows differences between patients with DLB and healthy individuals. These differences mostly point to the decrease in connectivity of large-scale networks and alpha and beta frequency bands. Some differences in the directionality of connectivity were found when using a hypothesis-driven approach. These results might extend other functional and structural neuroimaging findings and offer insight into pathophysiological mechanisms underlying DLB.

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LK designed the study and performed the literature search. The abstracts published until December 2021 were screened independently by LK and HK. KGM and SR screened the abstracts published from January 2022 as part of their placement projects, which was independently checked by LK. The key information from the results and methods sections of all the reviewed articled was extracted by KGM and SR, and subsequently independently checked by LK and HK. LK and HK wrote the manuscript. JTOB, JPT and LS provided the feedback for the manuscript. LS secured the funding, provided the guidance, and oversaw the study.

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