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Review Article

Dementia with Lewy Bodies and Functional Magnetic Resonance Imaging Application

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SUMMARY

Dementia with Lewy bodies (DLB) accounting for approximately 10%–20% of dementia cases, and this makes DLB the second most common type of dementia among neurodegenerative diseases. One of the neuropathological hallmarks of DLB is the presence of Lewy bodies, which mainly consist of alpha-synuclein aggregates. However, a mixed pathology with other neurodegenerative dementias is common, which increases the possibility of misdiagnosis. Risk signs such as rapid eye movement sleep behavior disorder (RBD), and anosmia have been identified, and core and supportive clinical features such as cognitive fluctuations, visual hallucinations, parkinsonism, and RBD were proposed. Different biomarkers with nuclear medicine imaging, electrophysiological recording, and structural magnetic resonance imaging can help differentiate DLB from other neurodegenerative dementias, but to date, functional magnetic resonance imaging (fMRI) has not been considered as a valid biomarker. The applications of resting-state and task-related fMRI on DLB were reviewed in this study. Due to the clinical features of DLB, such as attention deficits and visual hallucinations, fMRI can observe functional connectivity differences and activity differences through well-designed stimulations between DLB and controls, making fMRI a promising technique for DLB diagnosis.

1. Introduction

After the world-famous actor Robin Williams was misdiagnosed with Parkinson's disease (PD) and died by suicide,[1] dementia with Lewy bodies (DLB) received public attention. Following Alzheimer's disease (AD), DLB accounted for 50%–60% of dementia cases at autopsy and thus was recognized as the second most common type of neurodegenerative dementia.[2]

Lewy bodies are round eosinophilic inclusions formed by pathological alpha-synuclein aggregates, and the neural inclusion of Lewy bodies is the signature of Lewy body disease.[3,4] Neuron electrical signal generation and release of neurotransmitters, such as dopamine and acetylcholine, could be interfered with by the buildup of alpha-synuclein inside the neurons.[5,6] Brain function might further worsen due to the inflammatory responses provoked by abnormal alpha-synuclein deposits in the brain.[7] The cellular function can be interfered by the abnormally folded alpha-synuclein deposits at various stages of alpha-synuclein aggregation, and eventually cause cell death.[8]

2. Risk signs, clinical feature, and biomarker of DLB

People at risk of DLB might be identified by several early clinical signs[9–11] (Table 1 left column). Genetic analysis suggested that a person's risk of developing DLB might increase due to the variations in the sequences of certain genes.[12,13] Moreover, genome-wide association studies indicated that common biological mechanisms exist among DLB, AD, and PD[13] because DLB, AD and PD share other genetic risk factors.

Clinical manifestations of Lewy body pathology include DLB, PD, and PD dementia. Clinical features (Table 1 middle column) are common among these diseases. Milder cognitive impairment also can be observed from people who eventually develop DLB[9,10] in the early stage. In elder people with the cerebrovascular disease, DLB progress may be accelerated or worsened.[14–16] Compare with people with Lewy bodies or AD alone, more rapid cognitive decline tends to be observed from people whose brains contain plaques and tangles in addition to Lewy bodies.[17,18] In the fourth consensus report for DLB diagnosis[19] the clinical features of DLB were comprehensively suggested.

The aforementioned clinical features may associate with the quality of life (QoL) of DLB patients. However, not like the other diseases such as AD,[20] no instrument was specifically developed to assess the factors leading to poor QoL for DLB patients[21] such as dysautonomia, delusion, apathy, and the presence of depression.

The ideal biomarker for DLB is one that identifies abnormally folded alpha-synuclein, which is a signature characteristic of DLB neuropathology. Researchers have been exploring the way to visualize Lewy bodies on brain imaging by binding compounds to

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Table 1
Ways to identify DLB at the different stages.

Risk signs		Clinical features		Biomarkers
Rapid eye movement (REM) sleep behavior disorder (RBD),[24] anosmia[25], autonomic dysfunction,[26] impaired color vision, family history of PD.[27,28]	→	Visual hallucinations,[29] cognitive impairment,[30,31] sleep disorders, motor symptoms,[2] autonomic symptoms.[32–35]	→	DaTscan,[36,37] MIBG myocardial scintigraphy,[38] polysomnography,[39] MRI and CT,[40–42] ^{18}F FDG PET,[43,44] electroencephalography,[45,46] ^{99m}TC-HMPAO SPECT.[47,48]

alpha-synuclein.[22,23] Several indicative and supportive biomarkers can help distinguish, differentiate, or predict the clinical course of DLB from other neurodegenerative diseases (Table 1 right column).

3. fMRI for dementia

Blood oxygen level-dependent (BOLD) contrast[49] functional MRI (fMRI) records secondary information associated with neuronal functional status in the brain,[50] and several studies suggested a potential role of resting-state fMRI in the differential diagnosis of dementias by demonstrating that different dementia syndromes might specifically affect different networks.[51] Compare to the aforementioned biomarkers listed in Table1, which directly measure the radioactivity related to the level of neurotransmitter or metabolism, the neuronal activity, and the brain structure, the result revealed from blood-oxygen level dependent by fMRI is relative indirect to the clinical observation with DLB. However, the balanced spatial and temporal resolution of fMRI allows us to compute the activity or the connectivity map with whole brain coverage, which still makes fMRI a promising candidate to differentiate DLB from the other neurodegenerative disease. Table 2 showed the demographic data of the included subjects of the following reviewed studies.

4. Resting-state fMRI for DLB

Compared with AD, DLB is associated with greater deficits in attention, visuoperceptual tasks, and working memory tasks.[29,64] Given the greater attention deficits in DLB than AD and the link between attention demand and deactivation in default mode network,[65] one would predict a decreased connectivity of default mode network in DLB than in AD.

Galvin et al.[52] selected the default network mode (DMN) as the first site to examine the functional connectivity of BOLD fMRI to compare DMN connectivity with controls without well-characterized dementia, participants with AD, and participants with DLB by using the precuneus as the seed point. The results demonstrated that in participants with DLB, the precuneus and occipital regions were less connected than in controls and patients with AD.[52,53] The precuneus and occipital regions also decreased the connectivity between the bilateral precuneus and medial prefrontal cortex, frontoparietal operculum, part of the executive control network, and primary visual cortex compared with patients with AD. Increased connectivity was also reported[52] with the putamen and inferior parietal cortex, part of the dorsal attention network.

Kenny et al.[54] observed that compared with controls, the DLB group had greater connectivity between the right posterior cingulate cortex and other brain areas; however no significant differences in hippocampal connectivity were observed. Compared with the study by Galvin et al.,[52] Kenny et al. did not discover any significant differences in precuneus or primary visual cortex connectivity between groups and did not reveal significantly less connectivity in patients with DLB compared with controls with any seed points. These findings might indicate either a frontal inhibition dysfunction of the DMN in DLB or a compensatory attempt to maintain DMN function[56] because compared with DLB, AD has a relatively greater pathological load.[54,56] Later studies from Kenny et al.[55] argued the parkinsonian features in DLB might be associated with the greater connectivity between parietal, temporal, and frontal regions and the putamen in patients with DLB compared with those with AD.

Franciotti et al.[58] isolated and characterized resting-state networks in DLB cognitive fluctuations by using functional connectivity and Granger causality together with a data-driven independent component analysis[66,67] approaches. They revealed decreased functional connectivity in patients with DLB in the right hemisphere compared with controls, and the connectivity was correlated with the severity of the cognitive fluctuations. Posterior cingulate cortex activity was higher in patients with DLB than in those with AD. The causal flow analysis indicated differences among patients with DLB and AD and controls.

Peraza et al.[59] used a graph theory approach to characterize how functional connectivity of resting-state networks are altered in patients with DLB with visual hallucinations. They revealed an association with local network measures of nodal betweenness

Table 2
Summary of demographic data of the subjects with functional MRI study.

Study	Sample	Age, year Mean (s.d.)	MMSE Mean (s.d.)
Galvin et al.[52]	DLB: 15	71.7 (9.1)	25.0 (4.4)
	AD: 35	75.3 (6.6)	24.7 (3.5)
	Control: 38	73.9 (6.6)	28.8 (1.2)
Lowther et al.[53]	DLB: 15	80.6 (6.0)	19.5 (4.2)
	AD: 13	75.5 (8.2)	21.5 (3.7)
	Control: 40	77.8 (4.5)	29.1 (1.2)
Kenny et al.[54,55]	DLB: 15	80.6 (6.0)	19.5 (4.2)
	AD: 16	77.3 (8.9)	21.1 (3.5)
	Control: 16	76.3 (8.3)	28.6 (1.3)
Peraza et al.[56]	DLB: 16	76.2 (5.7)	24.2 (3.8)
	Control: 17	77.3 (4.7)	29.1 (0.8)
Sauer et al.[57]	DLB: 9	78 (5)	23.7 (2.5)
	AD: 10	78 (6)	22.9 (3.2)
	Control: 13	71 (7)	29.5 (0.7)
Franciotti et al.[58]	DLB: 18	75 (1)	20.6 (0.5)
	AD: 18	76 (1)	20.4 (0.6)
	Control: 15	74 (2)	28.9 (0.8)
Peraza et al.[59]	DLB: 18	77.2 (6.2)	23.6 (3.9)
	AD: 19	74.7 (8.5)	22.6 (2.9)
	Control: 17	76.8 (5.7)	29.1 (0.9)
Cormack et al.[60]	DLB: 15	79.7 (8.9)	(No reported)
	PD: 21	76.0 (4.6)	
	AD: 18	79.3 (5.6)	
	Control: 10	76.2 (11.9)	
Mosimann et al.[61]	DLB: 20	77.6 (6.9)	19.4 (5.2)
	PD: 24	76.9 (5.4)	28.1 (1.4)
	PDD: 24	75.2 (6.2)	20.8 (3.8)
	AD: 23	77.8 (6.8)	20.0 (5.4)
	Control: 25	75.5 (5.9)	29.0 (1.3)
Taylor et al.[62]	DLB: 17	81.2 (5.6)	18.8 (5.1)
	Control: 19	77.6 (7.1)	29.0 (1.2)
Erskine et al.[63]	DLB: 17	81.5 (5.5)	19.0 (5.1)
	AD: 15	82.5 (9.2)	20.8 (4.4)
	Control: 19	77.6 (7.1)	29.0 (1.2)

centrality and node degree.[59] Specifically, positive and negative nodal betweenness centrality for the putamen and the left postcentral gyrus, and positive and negative node degree for the putamen and the left postcentral gyrus were revealed, respectively. Compared with AD, small-worldness was increased in DLB, a consequence of which may be network regularization arising due to a relative loss of long-range connections. The degree of cognitive impairment and fluctuations in DLB were associated with network alterations. Peraza et al.[56] performed in another study of secondary analyses on DLB visual hallucinations and observed that a number of resting-state networks in DLB were functionally disconnected compared with controls. The NPI hallucination score was associated with the sensory-motor and left frontoparietal networks. These results might provide evidence for cognitive fluctuations in DLB depending upon involving attention systems and distributed subcortical and cortical networks.

5. Task-related fMRI for DLB

Sauer et al.[57] revealed stronger activation in DLB compared with AD in the superior temporal sulcus (STS) during the motor tasks by conducting visual stimuli of color, motion and face paradigms. This observation suggested that activation changes in the STS might predict macroscopic atrophy because of neuronal loss at an early stage. It is vital to find patients with DLB has higher motion-related activation in STS than in AD as it reduces the possibility that nonspecific effects such as failure to engage in the task or fatigue caused a higher level of visual cortex (V5) activation in DLB and deficits in motion-task reaction time. The DLB group performed equivalently to AD groups in this task contrasted with a study in which patients with DLB exhibited poorer performance in pop-out tasks.[60] In the face task, performance accuracy and ventral occipitotemporal activation were observed between DLB and AD. A lost of lateral activation was produced and a trend in reaction time data towards a performance deficit, which was consistent with the result from a visual motion processing deficit in DLB patients in a random dot task, which patient required to discriminate the velocity of a group of random dot motion.[61]

Two studies have examined the perception of moving stimuli[62,63] by using the same sample of patients with DLB to conduct different analyses. Decreased middle temporal and V5 activation in response to motion stimuli in the DLB group was observed by a region of interest analysis.[62] Among DLB, AD, and control groups no correlation was noted between the lateral geniculate nucleus BOLD signal and visual hallucination indices.

Table 3 summarized the aforementioned comparison differences between DLB and AD. While studies were devoted to reveal the functional connectivity differences using resting-state fMRI by difference strategies, a noteworthy thing is that only visual stimulation was utilized to reveal the BOLD contract difference with task-based fMRI. The reason of using visual stimulation to differentiate DLB from AD is because the notable deficit of DLB patients on a range of visual perceptual, attention and working memory tasks compare to AD patients.[57]

6. Conclusion

In this study, we reviewed the current understanding of DLB, including its pathology, risks, and the clinical features. With increasing investigations addressing different aspects of DLB, different biomarkers with high specificity and sensitivity are being proposed to more accurately distinguish between DLB and other neurodegenerative diseases such as AD. Most of the biomarkers for DLB are in functional nuclear medicine imaging; however, fMRI, which has been used to study human primary and cognitive function in the brain, might be another promising biomarker tool. Task-related and resting-state fMRI have been used to investigate patients with DLB with different clinical features. The significance of these differences is not fully understood; however, evidence suggests that patterns of connectivity and activation to a particular stimulation may provide

Table 3
Functional MRI differences between DLB and AD.

Resting-state	Seed-based	<Precuneus>[52] DLB > AD • R. Putamen • L. Inferior parietal sulcus	DLB < AD • L. Medial prefrontal gyrus • R. hippocampus • R. frontoparietal operculum • L. & R. visual cortex
		<Putamen>[55] DLB > AD • L. Pre-, and post-central gyrus • L. inferior parietal region • L. transverse temporal region	
	ICA and Granger causality (GC)[58]	DLB > AD • Low frequency fluctuation power of frontal, parietal, and PCC • PCC involving in GC • PCC →L. SFS • PCC → L. LPC • R. MFG → R. LPC	DLB < AD • L. LPC → R. LPC • R. LPC → R. IPL • R. IPL → R. SFS
	Graphic theory[59]	DLB > AD • Global efficiency • Normalized clustering coefficient • Node degree in temporal and R. frontal lobe • Nodal clustering coefficient in temporal and R. occipital pole	DLB < AD • Short, middle, and long averaged connectivity strength • (Normalized) characteristic path length • Node degree in parietal and occipital lobe • Nodal clustering coefficient in frontal, parietal, and occipital lobe
Task-based	Visual stimuli[57]	DLB > AD • STS for the motion task	

distinct functional findings across different dementia etiologies. Diagnostic accuracy in distinguishing between AD and DLB could be improved by combining biomarkers in a multimodal approach together with the simultaneous fMRI study[68] and provide information on multisystem involvement and mixed pathology.

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