Neuroimaging of Dementia with Lewy Bodies

12

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Abstract

Dementia with Lewy bodies (DLB) is the second most common form of neuro-degenerative dementia following Alzheimer's disease (AD). Despite the development of consensus diagnostic criteria, differentiating DLB from other types of dementia, such as AD, can be difficult. Several imaging studies are currently underway to differentiate DLB from other types of dementia. Magnetic resonance imaging of DLB shows preservation of the medial temporal lobe structure and predominant atrophy of subcortical structures, including the substantia innominata and dorsal midbrain, compared with AD. Decreased perfusion in the occipital lobe and relatively increased perfusion in the deep gray matter (striatum and thalamus) on single photon emission CT (SPECT) are shown to be characteristic features of DLB. MIBG myocardial scintigraphy provides a higher sensitivity and higher specificity for diagnosing probable DLB from AD than perfusion SPECT. Dopamine transporter imaging, an available technique in Japan since 2014, shows good diagnostic accuracy for DLB. The international consensus criteria for DLB (2005) incorporate abnormal imaging on dopamine transporter as a supportive feature. As idiopathic REM sleep behavior disorder (iRBD) is considered to be a prodromal stage of alpha-synucleinopathies, the above findings are observed in some patients with iRBD. This review summarizes the applications and findings from neuroimaging studies of DLB and iRBD.

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12.1   Introduction

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are the second most common causes of dementia, exceeded only by Alzheimer's disease (AD), accounting for approximately 15% of all cases at autopsy. DLB (and frequently PDD) is clinically characterized by fluctuating cognition with pronounced variations in alertness, visual hallucinations, and extrapyramidal signs [1]. Other features, such as REM sleep behavior disorder (RBD), delusions, depression, repeated falls, and syncope, are frequently observed. A recent study using comprehensive geriatric assessment demonstrated that DLB has significantly higher frequencies of minor or major problems than AD in several items, including visual function, verbal communication, medication adherence, depression, upper and lower extremity functions, history of falls, urination, and impairment of basic and instrumental activity of daily living (ADL) function [2]. These neurologic and psychotic symptoms and geriatric problems are likely to be associated with poor cognitive and functional outcomes. Indeed, we found that DLB had a greater risk of admission (or death) most commonly because of fall-related injuries and aspiration pneumonia than AD [3]. Therefore, an accurate antemortem diagnosis of DLB is important because there are differences in disease course, treatment, and management between DLB and other types of dementia. However, the diagnosis of DLB is difficult, particularly in the early stages.

Several imaging techniques have emerged as potential means of supporting the clinical diagnosis of various dementias. Magnetic resonance imaging (MRI) and positron emission tomography (PET) or single photon emission CT (SPECT) are currently being employed to differentiate DLB from other types of dementia. In addition, [^{123}I]-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, and dopamine transporter (DAT) imaging are valuable tools to identify DLB patients and to differentiate them from those with other neurodegenerative disorders [4, 5]. DLB and PDD share a similar pattern of neuroimaging studies. In this report, we review several imaging modalities to differentiate DLB from other types of dementia, particularly AD.

12.2   MRI

MRI has shown global and subcortical atrophic changes in DLB [6]. Specifically, qualitative and volumetric MRI studies have shown less medial temporal lobe atrophy in DLB than in AD. These previous findings are consistent with recent findings of voxel-based morphometry studies. These findings are also supported by a prospective MRI study with pathological verification [7]. Using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) [8] for MRI, DLB showed significantly smaller z-score for the assessment of hippocampal atrophy than AD (Fig. 12.1). A recent study with manual tracing of hippocampal boundaries and computer-assisted post-processing showed significant tissue
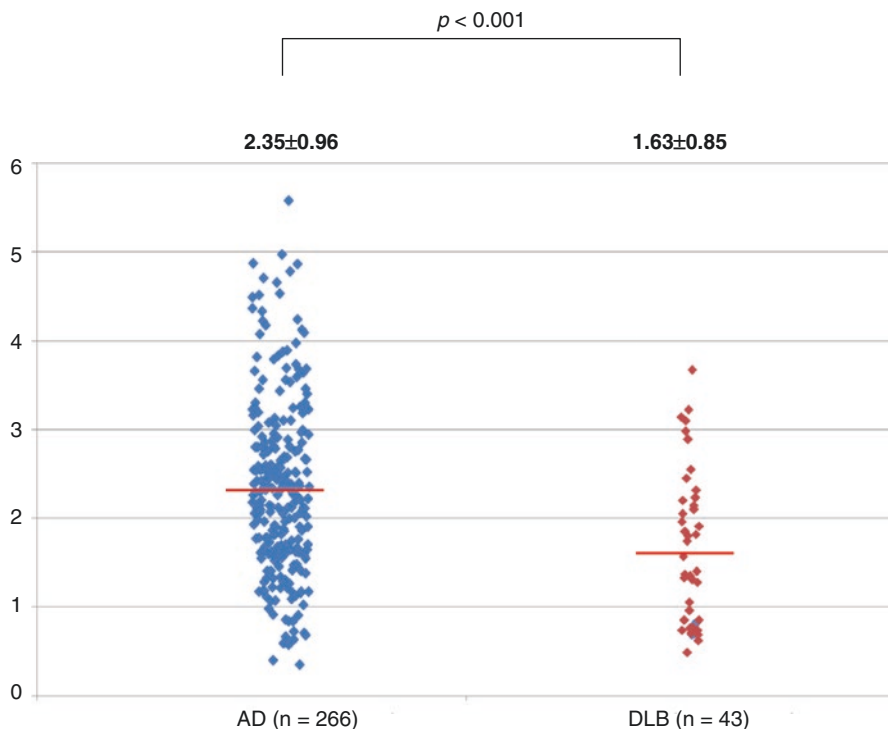
Fig. 12.1 A comparison of z-scores between AD and DLB using VSRAD

loss (10–20%) in the hippocampal subregions of DLB corresponding to the anterior portion of the CA1 field on both sides, along the longitudinal midline in the dorsal aspect within the CA2-3 field, different from the pattern of hippocampal change in AD [9]. We found that the magnetization transfer ratios (MTR) of the hippocampus were significantly higher in DLB than in AD [10]. Pathologic changes in the hippocampus, including loss of neurons, gliosis, demyelination, and axonal loss, may be associated with a decrease in the MTR. These results may reflect underlying histopathological differences with less severe neuronal degeneration in the hippocampus of DLB. Therefore, the relative preservation of the medial temporal lobe structures shows promise as a diagnostic marker in differentiating DLB from AD.

Among subcortical structures, atrophy of the substantia innominata (including the nucleus basalis of Meynert) [11] and dorsal midbrain [12] has been documented in DLB. Atrophy of these structures is supported by the pathological involvement of the areas. Atrophy of the substantia innominata is associated with cholinergic dysfunction in DLB. However, it remains unclear whether these subcortical structural changes are diagnostic markers for the identification of DLB and its differentiation from AD.

12.3 Perfusion SPECT

Perfusion SPECT studies are currently being employed in practice to differentiate between various types of dementia, as this method can reveal perfusion abnormalities that may be characteristic of different types of dementia [13]. Although the neuropathologic and neurochemical bases underlying occipital abnormalities in DLB are not yet clearly understood, functional brain imaging studies using SPECT and PET have revealed that reduced occipital metabolism and perfusion are characteristic features of DLB (Fig. 12.2). Several investigators have indicated the value of functional brain imaging studies in differentiating between DLB and AD, although there are some methodological differences, including patient selection (definite or probable cases), scanning methods (PET versus SPECT), and image analysis (conventional region of interest or statistical image analysis). In a multicenter study examining [18F]fluorodeoxyglucose (FDG) PET measures, the presence of hypometabolism in the occipital lobe discriminated DLB from AD with a sensitivity of 71% and a specificity of 95% [14]. On the other hand, the diagnostic accuracy of SPECT is relatively low, as shown by a sensitivity range of 65–85% and a specificity range of 85–87% [5]. We found that combined MMSE and perfusion SPECT studies achieved a high discrimination between DLB and AD with a sensitivity of 81% and a specificity of 85% [15].

Lim et al. [16] confirmed that occipital hypometabolism and relative preservation of the posterior cingulate gyrus (cingulate island sign) differentiated DLB from AD in patients with a sensitivity of 77% and a specificity of 80%. In addition to occipital hypoperfusion, increased perfusion in the deep gray matter (striatum and thalamus) was shown to be a characteristic feature of DLB, possibly due to compensatory changes to decreased dopaminergic input to the basal ganglia [17] (Fig. 12.3).
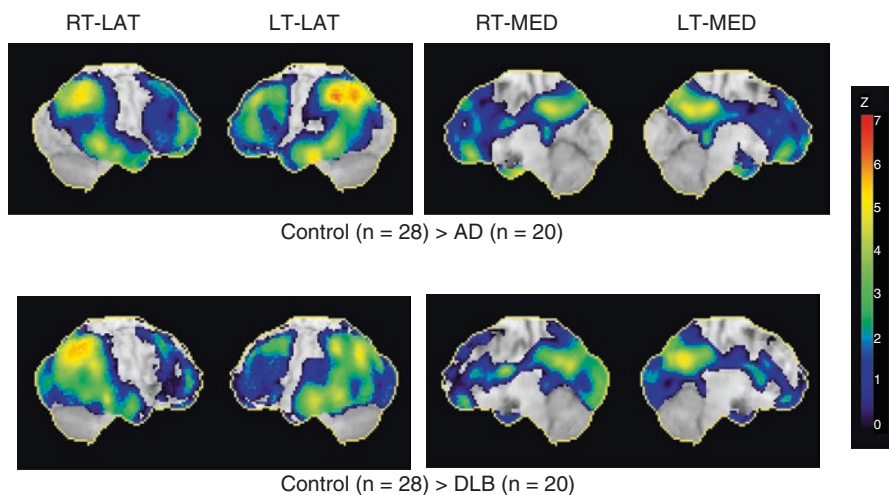

Fig. 12.2 Z-score images of AD and DLB on perfusion SPECT (3D-SSP)

AD   DLB

Temporoparietal ↓ / Occipital ↑   Occipital ↓ / Striatum ↑
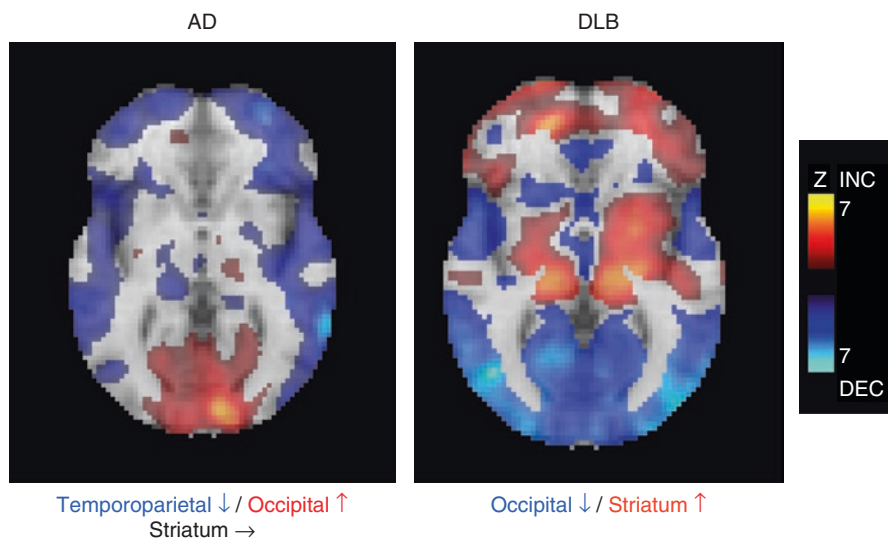   Striatum →

Fig. 12.3 Two-tail views of AD and DLB on perfusion SPECT

These additional alterations on functional brain imaging may enhance the diagnostic accuracy of DLB.

Psychotic symptom clusters in DLB appear to relate to spatially distinct perfusion deficits. Nagahama et al. [18] found that visual hallucinations concord with parietal and occipital association cortices perfusion deficits and delusional misidentifications to perfusion deficits of the limbic-paralimbic structures. Increased thalamic and decreased inferior occipital perfusion may be related to fluctuations in consciousness [19].

12.4   MIBG Myocardial Scintigraphy

MIBG myocardial scintigraphy is a useful, noninvasive technique for estimating local myocardial sympathetic nerve damage not only in primary heart disease but also in synucleinopathies, such as PD, DLB, and REM sleep behavior disorder (RBD) (Fig. 12.4). MIBG scintigraphy has been performed mainly on Japanese cohorts. A number of studies have shown reduced MIBG uptake (heart-to-mediastinum ratio) in DLB patients compared with AD and normal controls. A review from Sinha et al. [5] showed that MIBG myocardial scintigraphy yielded a high sensitivity (range, 83–100%) and a high specificity (range, 82–100%) for diagnosing DLB. MIBG scintigraphy was more sensitive in detecting DLB than occipital hypoperfusion on SPECT [20]. We investigated the role of MIBG scintigraphy in the differential diagnosis of dementia in 96 dementia patients in our Memory Clinic, including 32 with DLB, 9 with PDD, 40 with AD, and 24 with other types of dementia. The overall sensitivity to
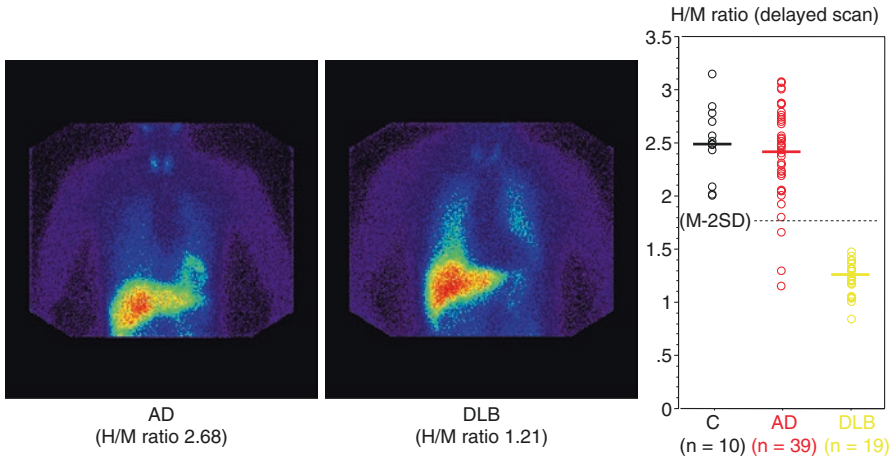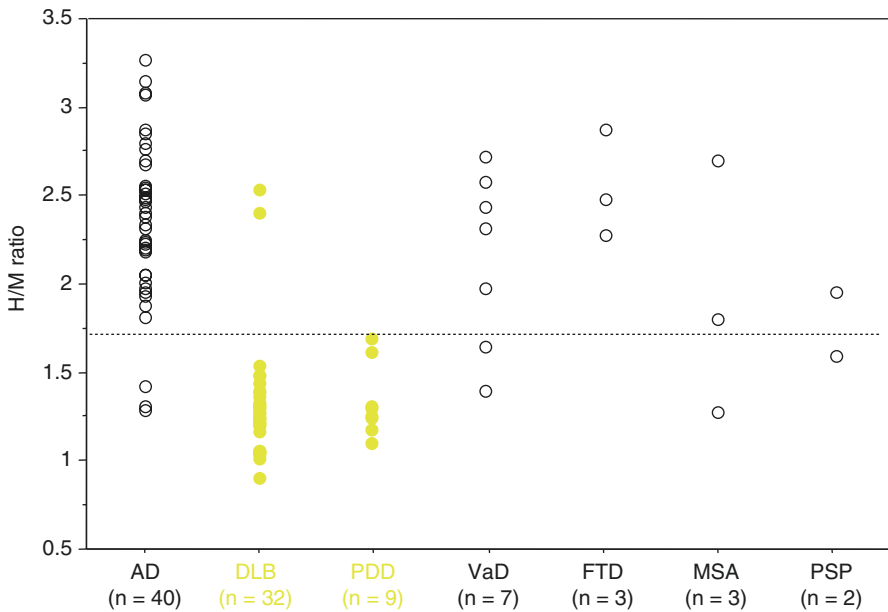
Fig. 12.4 MIBG myocardial scintigraphy

Fig. 12.5 Diagnostic accuracy for DLB and PDD using MIBG myocardial scintigraphy

positively identify patients with Lewy body disease (including DLB and PDD) was 95%, and the specificity to differentiate them from patients with other types of dementia was 87% [21] (Fig. 12.5). There was no correlation between MIBG scintigraphy and disease severity or duration of DLB. Although it is important to note that reduced MIBG uptake has also been reported in patients with

cardiac disorders, diabetes mellitus, and some medications, this technique is also a powerful tool in the differential diagnosis between DLB/PDD and other types of dementia.

12.5 Dopamine Transporter (DAT) Imaging

Imaging with specific SPECT ligands for dopamine transporter (FP-CIT and beta-CIT) provides a marker for presynaptic nigrostriatal degeneration. DAT scan has been clinically available for patients with DLB and PD in Japan since 2014. DAT imaging is abnormal in PD and DLB, reflecting nigrostriatal degeneration, but not in AD, indicating a useful method in the differentiation between DLB and AD. In our preclinical study of DAT imaging, a 4.1 cutoff score of specific binding ratio yielded a sensitivity of 92% and a specificity of 84% for diagnosing probable DLB from AD (Fig. 12.6). A large multicenter study demonstrated a sensitivity and specificity of abnormal DAT scans in diagnosing probable DLB from AD of 78% and 90%, respectively [22]. DAT imaging results were in agreement with autopsy diagnosis in the vast majority of cases (7 of 8 DLB and 12 of 12 non-DLB) and were more precise than clinical diagnosis [23]. FP-CIT SPECT is also reliable in confirming cases of clinically possible DLB, supporting the inclusion of reduced DAT uptake as a suggestive feature of DLB in the International Consensus Criteria [24].
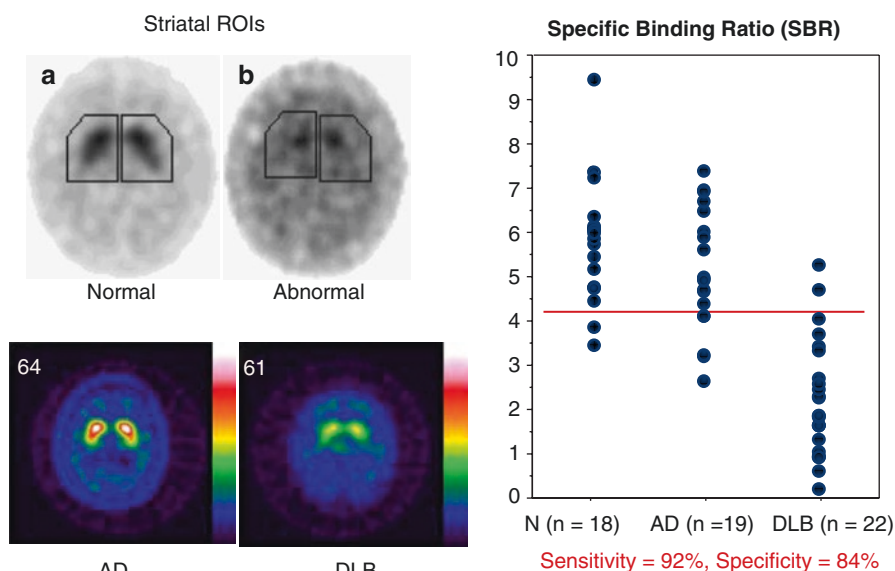

Fig. 12.6 DAT imaging

DAT imaging has demonstrated superior diagnostic accuracy for DLB compared with brain perfusion SPECT and FDG-PET. A recent clinical study has revealed that DAT imaging and MIBG scintigraphy showed similar diagnostic accuracy in differential diagnosis between DLB and other dementias [25]. However, DAT imaging fails to discriminate PD/DLB from other parkinsonian syndromes because reduced striatal dopamine uptake has been shown in progressive supranuclear palsy, multiple system atrophy, and corticobasal syndrome. The impact of concurrent vascular pathology in striatal DAT binding has not yet been determined. Despite the caveat and the limited diagnostic potential to differentiate between different synucleinopathies, the European Federation of Neurological Societies (EFNS) guidelines also recommend the use of DAT scan to differentiate between DLB and AD as the only imaging test to reach the level A category of evidence [26].

12.6 Structural and Functional Changes in Idiopathic RBD (iRBD)

RBD is a type of parasomnia characterized by a loss of normal skeletal muscle atonia during REM sleep and prominent motor activity while dreaming. RBD occurs either as an idiopathic disease or in association with neurodegenerative diseases, particularly alpha-synucleinopathies. Recent studies have demonstrated several neuropsychological impairments in iRBD patients, such as visuospatial construction dysfunction, executive dysfunction, memory disturbance, smell testing abnormalities, reduction of striatal presynaptic dopamine transporters, and reduced MIBG uptake. Since these findings are characteristic features of alpha-synucleinopathies, including PD and DLB, iRBD may be a prodromal stage of alpha-synucleinopathies.

There have been few studies examining structural and functional brain changes in iRBD patients. We investigated structural brain changes using voxel-based MRI morphometry in iRBD patients. Compared with the 18 age-matched controls, 20 iRBD patients had significant gray matter volume reduction in the anterior lobes of the right and left cerebellum, tegmental portion of the pons, and left parahippocampal gyrus [27]. Recently, Scherfler et al. [28] showed significant decreases in fractional anisotropy in the tegmentum of the midbrain and rostral pons and increases in mean diffusivity within the pontine reticular formation in iRBD patients. These studies provide in vivo evidence suggesting that structural lesions of the brain stem are responsible for the occurrence of iRBD. In our SPECT study, a decreased perfusion was shown in the parieto-occipital lobe (precuneus), limbic lobe, and cerebellar hemispheres in iRBD patients, as is commonly observed in patients with alpha-synucleinopathies, including DLB and PDD [29] (Fig. 12.7). In addition, a longitudinal study demonstrated more decreased perfusion in the parieto-occipital lobe in the second SPECT than in the first study in iRBD patients [30], although none of the patients showed any neurological deficits, including extrapyramidal and cerebellar signs, visual hallucinations, or neuropsychological impairments, during the study (Fig. 12.8). Therefore, iRBD may be a progressing neurodegenerative disorder, even though neurological and neuropsychiatric impairments have not been shown.
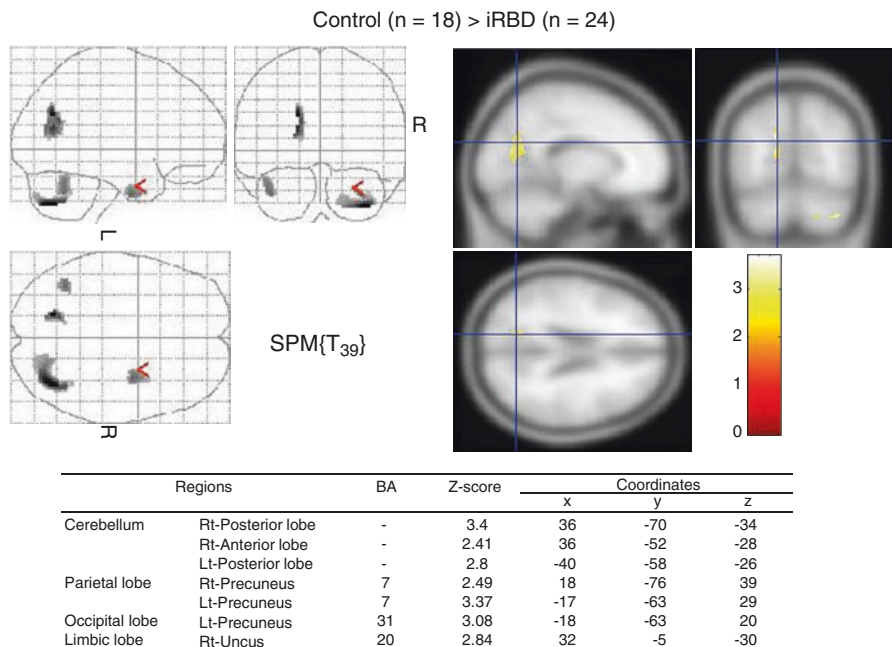
Control (n = 18) > iRBD (n = 24)

Regions		BA	Z-score	Coordinates		
				x	y	z
Cerebellum	Rt-Posterior lobe	-	3.4	36	-70	-34
	Rt-Anterior lobe	-	2.41	36	-52	-28
	Lt-Posterior lobe	-	2.8	-40	-58	-26
Parietal lobe	Rt-Precuneus	7	2.49	18	-76	39
	Lt-Precuneus	7	3.37	-17	-63	29
Occipital lobe	Lt-Precuneus	31	3.08	-18	-63	20
Limbic lobe	Rt-Uncus	20	2.84	32	-5	-30

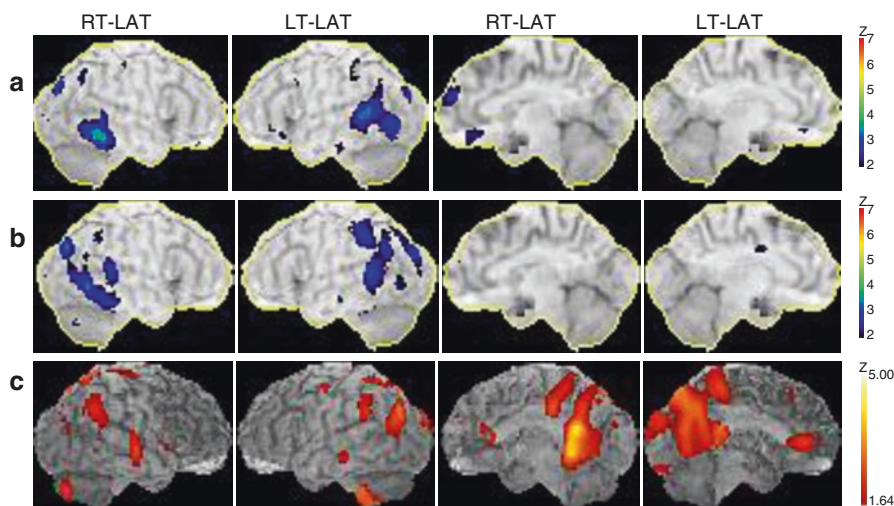**Fig. 12.7** SPM analysis of perfusion SPECT in iRBD

Fig. 12.8 Longitudinal perfusion changes in iRBD. Three-dimensional views of decreased studies showed regional perfusion on first SPECT (**a**) and second SPECT (**b**) of iRBD patients (n = 8, mean age 71 ± 3 years) compared with normal controls (n = 18, mean age 70 ± 8 years). The mean interval was 23 ± 9 months. Three-dimensional views of decreased perfusion on second SPECT compared with first SPECT of iRBD patients (**c**)

Conclusion

On neuroimaging studies, DLB is characterized by (1) preservation of medial temporal lobe structures on MRI, (2) occipital hypoperfusion and relatively striatal hyperperfusion on SPECT, (3) reduced cardiac MIBG uptake, and (4) reduced dopamine transporter in the striatum. These techniques are valuable tools to identify DLB patients and to differentiate DLB from other neurodegenerative disorders such as AD. In the near future, synuclein imaging methods would be available for use in clinical practice, similar to the development of amyloid and tau imagings in AD.

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