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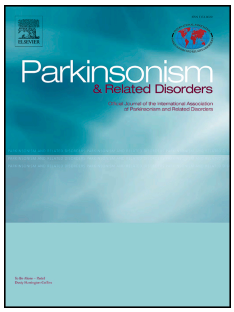

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Does attentional dysfunction and thalamic atrophy predict decline in dementia with Lewy bodies?

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ABSTRACT

Introduction: To evaluate the clinical characteristics of DLB subjects who died within 1 year of assessment compared to those who survived and investigate their patterns of *in vivo* regional thalamic atrophy using structural MRI.

Methods: Seventy subjects (35 DLB, 35 aged controls) underwent 3 Tesla T1-weighted MR scanning as well as clinical and cognitive assessments, including a computerised assessment of attention. All subjects were contacted after 12 months for reassessment.

For both hemispheres, using FSL FIRST, the thalamus was automatically segmented followed by inter-subject vertex-wise analyses involving group comparisons and behavioural correlates.

Results: There was significant bilateral atrophy in the ventral-dorsal and pulvinar regions in DLB relative to controls ($p_{corrected} < 0.05$). The DLB group was then re-categorised based on 12-month mortality data: DLB-a (n=25) and DLB-d (n=9) (a=alive, d=death within 12 months of study assessment). Compared to controls, significant attentional dysfunction and bilateral atrophy of the pulvinar, ventral and dorsal nuclei were observed in DLB-d ($p_{corrected} < 0.05$), whereas in DLB-a, atrophy was far less extensive.

Conclusions: Distinct patterns of thalamic atrophy occur in DLB that may relate to the attentional dysfunction and cognitive fluctuations that characterise this disorder. Relative to controls, the extent of attentional impairment and pattern of thalamic degeneration differ in those patients who died within 12 months of assessment, despite having an otherwise similar level of dementia severity. These findings may provide insight into the

neurobiological changes underpinning important clinical characteristics and disease heterogeneity.

1. Introduction

Dementia with Lewy bodies (DLB) is a common form of dementia in late life. It is associated with higher morbidity, mortality and a poorer quality of life when compared to Alzheimer's disease (AD) [1-3]. It is a heterogeneous condition with a proportion of people deteriorating very rapidly until death. However, we do not have a good understanding of the pathophysiological mechanisms underpinning the differing clinical features and the potential influence that they may have on disease course and patient outcomes. A shorter duration of illness has been reported in DLB compared to AD although the reasons were not clear and the difference remained significant even when factors such as age, gender and vascular risk factors were controlled for [1, 4].

Attentional dysfunction is prominent in DLB and related to cognitive fluctuations, one of the core clinical features of the disease [5]. Interestingly, a case series of six patients with DLB and rapid progression had prominent attentional deficits at presentation [6]. The neurobiological correlate of attentional function in DLB is unclear, although increased cognitive fluctuations have been reported to be associated with increased thalamic perfusion in DLB [7].

The thalamus is a key area in maintaining consciousness and is an area vulnerable to Lewy body related pathology [8]. It is an important deep brain structure, key to many sensory, motor and cognitive systems where it has received much interest in the cognitive

neurosciences [9] including examination of thalamic structure using magnetic resonance imaging (MRI). Thalamic volume and shape changes have been reported in AD [10-13], while variations in thalamic diffusion and perfusion have been shown in DLB [14-16].

We aimed to evaluate attentional function and patterns of *in vivo* regional atrophy of the thalamus using structural MRI in DLB, comparing the characteristics of DLB subjects who died within 1 year of assessment to those who survived. We hypothesised that those DLB subjects who died within a year would have greater attentional impairment (but not global cognitive impairment) at baseline as well as greater thalamic atrophy than those who survived. As an exploratory analysis, the correlation between attentional function and thalamic shape change was also examined, hypothesising that greater attentional impairment would relate to atrophy in the posterior region (pulvinar) of the thalamus.

2. Methods

2.1. Subjects, assessments and diagnosis

Thirty five individuals over the age of 60 with probable DLB [5, 17] were recruited from a community dwelling population of patients referred to local Old Age Psychiatry, Geriatric Medicine or Neurology Services. Thirty-five similar aged healthy control subjects were also recruited from relatives and friends of subjects with dementia or volunteered via advertisements in local community newsletters. The research was approved by the local ethics committee. All subjects or, where appropriate, their nearest relative, provided written informed consent. All subjects underwent clinical and neuropsychological evaluations and the clinical diagnosis of probable DLB was assigned

by independent clinical raters as previously described [18]. This included assessment for Rapid Eye Movement (REM) sleep behaviour disorder using the International Classification of Sleep Disorders-II diagnostic criteria B [19]. Assessments included the Cambridge Cognitive Examination (CAMCOG) incorporating the Mini-Mental State Examination (MMSE) [20], the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [21], Bristol ADL and Neuropsychiatric inventory. Attention was assessed with the Cognitive Drug Research (CDR) computerised assessment system and included measures of Simple Reaction Time (SRT), Choice Reaction Time (CRT) and Digit Vigilance (DigVig) [22].

2.2. MRI data acquisition

Subjects underwent T1 weighted MR scanning on a 3T MRI system using an 8 channel head coil (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands) within 2 months of the study assessment, as previously described [18]. The sequence was a standard T1 weighted volumetric sequence covering the whole brain (3D MPRAGE, sagittal acquisition, 1 mm isotropic resolution and matrix size of 240 (anterior-posterior) x 240 (superior-inferior) x 180 (right-left); repetition time (TR) = 9.6ms; echo time (TE) = 4.6ms; flip angle = 8^{o}; SENSE factor = 2). The acquired volume was angulated such that the axial slice orientation was standardised to align with the AC-PC line.

2.3. Thalamic segmentation using FIRST

Estimates of thalamic volumes were conducted using the FSL (FMRIB Software Library, ver. 5.06, http://www.fmrib.ox.ac.uk/fsl) tool FIRST. The method used shape and

intensity models of the thalamus, constructed from manually segmented T1 datasets (n=336), generating surface meshes constrained to preserve vertex number and correspondence. Using these learned models, FIRST then searches through linear combinations of shape variations to obtain the most probable surface/shape given the observed set of voxel intensities for the thalamus for each and every subject. Surfaces were then aligned to MNI125 space to enable intersubject vertex-wise analyses [23].

2.4. Statistical Analysis

For demographic and clinical data, the Statistical Package for Social Sciences software (SPSS ver. 19.0.0.1, http://www-01.ibm.com/software/analytics/spss/) was used for statistical evaluation. Continuous variables were examined for normality using the Shapiro-Wilk test and visual inspection of variable histograms and assessed where appropriate using parametric (t-tests) and non-parametric (Mann-Whitney U) tests. For categorical data, χ^2 tests were applied. A p-value of ≤ 0.05 was considered significant.

Vertex shape analysis was performed using the FSL script *first_utils* in order to assess group effects and behavioural correlates on a per-vertex basis. Regional changes in the vertices between groups were conducted using a two-sample unpaired t-test with age and total intracranial volume (TIV) as confounding variables. Exploratory multiple regression analysis was used to investigate the relationship between regional changes and behaviour in DLB with age as confounding covariate. Statistical inference was evaluated using the program *randomise* with 5000 permutations generating the appropriate statistic images.

Results were family-wise error corrected ($p \leq 0.05$) using the threshold free cluster enhancement (TFCE) method [24].

3. Results

3.1. Subjects

Table 1 shows demographic and group characteristics of healthy controls and patients with DLB. Groups were of similar age and there were more men in the DLB than control group. As expected, those with DLB had greater global cognitive and attentional impairment and higher UPDRS III scores than healthy controls.

3.2. Thalamic atrophy in DLB relative to healthy subjects

Significant bilateral atrophy in the ventral-dorsal and pulvinar regions of the thalamus was observed in DLB relative to controls (Fig. 1A, orange regions). Table 2, depicts peak significance and MNI coordinates of results.

3.3. Attentional impairment as an indicator of disease vulnerability

The DLB group was then re-categorised based on 12-month survival data: DLB-a and DLB-d (a=alive, d=death within 12 months of study assessment) (Table 3). Groups were comparable in age and estimated disease duration. Measures of global cognition, motor parkinsonism, neuropsychiatric features and normalised total hippocampal volumes (obtained from a previous imaging study of dementia [25]) were also similar. Furthermore, prescription of cholinesterase inhibitors, number or prescribed medications and history of vascular comorbid conditions were not significantly different between

groups. Attention was more impaired in the DLB-d group and reached statistical significance for the vigilance task.

3.4. Thalamic atrophy in DLB as an indicator of disease vulnerability

Compared to controls, significant bilateral atrophy of the pulvinar, ventral and dorsal regions were observed in DLB-d (Fig. 1C, orange areas), whereas in DLB-a, atrophy was much less extensive, affecting the bilateral dorsal-lateral and right ventral lateral nuclei regions (Fig. 1B). Patterns did not significantly differ between DLB-d and DLB-a ($p_{corrected} > 0.05$).

3.5. Attentional impairment correlates with thalamic shape change in DLB

Exploratory linear regression analysis revealed that atrophy in the region of the left pulvinar and ventral lateral nucleus was associated with impaired attentional function in DLB ($P_{TFCE\text{-}uncorrected} < 0.05$).

4. Discussion

The main study findings included: (1) 26% of DLB subjects died within 12 months of assessment; (2) this group (DLB-d) had greater attentional but not global cognitive impairment; (3) DLB was characterised by thalamic atrophy in the ventral, dorsal and pulvinar regions of the thalamus and (4) relative to controls, thalamic degeneration was more extensive in the DLB-d group.

DLB is a heterogeneous condition. There are substantial differences between people with DLB in their disease course, response to treatment and also vulnerability to infection and neuroleptic medications. However, the reasons for these differences are unclear and there are currently no clinically defined sub-groups. A shorter duration of illness has been reported in DLB compared to AD [1]. Furthermore, a more rapidly progressive DLB sub-type has been previously suspected; however, features that may predict this have not been examined.

Attentional impairment is more common in DLB than AD, and is associated with cognitive fluctuation, one of the core clinical features of the disease [5]. Using the CDR computerised attentional battery, we found that the DLB-d group had more impaired attention which reached statistical significance for the digit vigilance task; whereas other clinical measures including motor function, neuropsychiatric symptoms and vascular risk factors were similar. In an exploratory logistic regression analysis that included age and gender, digit vigilance standard deviation was found to be a significant predictor of mortality ($p<0.05$). This suggests the possibility of a more vulnerable DLB sub-group although conclusions were somewhat limited by the small sample size.

The neurobiological correlate of attentional dysfunction in DLB is unclear. However, the thalamus is a key area in maintaining consciousness and is an area vulnerable to Lewy body related pathology. The association observed between fluctuation and increased thalamic perfusion in DLB highlights its potential importance in the underlying pathological process [7]. Furthermore, one model of attentional function suggested that

the alerting task (vigilance) involved the thalamic areas [26, 27]. Thalamic atrophy in DLB included the internal medullary lamina region, part of the thalamus which is implicated in the maintenance of attention. It contains key intralaminar nuclei including the centromedian-parafasicular complex (CMPf) which, with the nucleus reticularis, forms part of the reticulo-thalamo-cortical activating system, highlighting their importance in consciousness. Interestingly, a pathological study in Parkinson's disease (PD), a disease closely related to DLB, reported selective neuronal loss in the CMPf complex [28]. An MRI study of the thalamus in 18 PD subjects reported that whilst there were no differences in volume compared to healthy control subjects, there was bilateral shape change along the dorsal surface, which possibly represented degeneration of the CMPf complex. The pulvinar, located in the posterior thalamic region is thought to be involved in sensory attentional orienting with projections to the posterior parietal structures. We found atrophy in this region with relative sparing of medial aspects of the thalamus, which was in contrast to dorsal-medial thalamic shape change reported in AD [12]. Moreover, attention (choice reaction time standard deviation) correlated with regional change in the left posterior and dorsal-lateral thalamic regions suggesting that these areas may be important in understanding the neurobiological change underpinning attentional dysfunction and cognitive fluctuation in DLB.

Further analysis of thalamic shape change revealed that the DLB-d group had more extensive regional atrophy than the DLB-a group in comparison to healthy controls. Areas affected included posterior, ventral and dorsal regions and very little change was observed in the DLB-a group. Differences between these subgroups did not reach

statistical significance and may have been due to the unbalanced and relatively small samples. However, the more extensive thalamic atrophy observed may be an important marker of disease severity in DLB and warrants further investigation. It is not clear whether attentional impairment in DLB may contribute to rapid decline and mortality through, for example, fall-related injuries or whether it heralds an important DLB sub-type, vulnerable to rapid progression or possibly neuroleptic sensitivity reactions, characterised by greater thalamic degeneration. A large prospective longitudinal study is needed to address this.

Study strengths include: a well characterised DLB group, 3T MRI dataset and validated imaging methodologies. The cause of death for the DLB-d group is not known. However, DLB groups were similar in terms of their global cognition, duration of illness, vascular risk factors and overall disease burden at initial assessment. The reliance on clinical diagnosis was a limitation, as with all ante-mortem imaging studies as well as the relatively small sample characterising the DLB-d group. However, methods of diagnosis were robust and clinical scales used are well validated, where these methods has been shown to have high specificity in autopsy confirmation studies [29].

This was the first study to identify regional patterns of thalamic atrophy in DLB compared to healthy subjects. Such patterns in DLB may also relate to the attentional dysfunction and cognitive fluctuations that characterise this disorder. The extent and pattern of degeneration appear to differ in those patients who died within 12 months of assessment, despite having an otherwise similar level of dementia severity. These

findings may provide insight into the neurobiological changes underpinning important clinical characteristics and disease heterogeneity in DLB.

Author roles

R. Watson: Co-designed the study, interpreted the results and co-wrote the manuscript.

S. Colloby: Co-designed the study, carried out all image and data analyses and co-wrote the manuscript.

A. Blamire: Reviewed the manuscript and secured project funding.

K. Wesnes: Developed the attentional battery and reviewed the manuscript.

J. Wood: Conducted all attentional and cognitive assessments of patients and reviewed the manuscript.

J. O'Brien: Reviewed the manuscript and secured project funding.

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Table 1 Demographic and group characteristics.

Table 2 Peak significance of surface results. Table depicts voxel significance ($P_{TFCE\text{-}corr}$), extent (k) and MNI coordinates.

Table 3 Demographic and group characteristics of DLB subgroups based on survival data.

Fig. 1. Significant regional atrophy of the thalamus (orange areas) in DLB (A), DLB-a (B) and DLB-d (C) relative to healthy older controls. (L=Left, R=Right, A=Anterior, P=Posterior).

Table 1 Demographic and group characteristics.

	Controls	DLB	Statistic, p value
n	35	35	
Gender (m: f)	20: 15	27: 8	$\chi^2 = 3.2, 0.08$
Age (yrs)	76.7 ± 5.2	78.4 ± 6.9	$t_{68} = 1.1, 0.3$
MMSE	29.1 ± 1.0	20.3 ± 5.3	**$t_{68} = 9.7, <0.001$**
CAMCOG	97.3 ± 3.8	67.7 ± 15.3	**$t_{68} = 11.2, <0.001$**
NPI total	Na	21.5 ± 17.1	
UPDRS III	2.0 ± 1.9	26.0 ± 10.7	**$U_{70} = 1225.0, <0.001$**
SRT_{mean}	319.5 ± 71.5	692.3 ± 592.1	**$t_{68} = 7.0, <0.001$**†
SRT_{SD}	64.4 ± 24.2	308.8 ± 569.3	**$t_{68} = 4.8, <0.001$**†
CRT_{mean}	516.7 ± 92.4	1104.5 ± 737.9	**$t_{68} = 8.8, <0.001$**†
CRT_{SD}	98.8 ± 29.4	477.1 ± 665.3	**$t_{68} = 7.9, <0.001$**†
$Digit\_Vig_{mean}$	424.3 ± 50.5	608.3 ± 109.9	**$t_{68} = 9.3, <0.001$**†
$Digit\_Vig_{SD}$	62.0 ± 20.4	133.3 ± 47.5	**$t_{68} = 8.6, <0.001$**†
ChI use (y: n)	Na	30: 5	

Values expressed as Mean ± 1 SD.

MMSE = Mini mental state examination, CAMCOG = Cambridge cognitive examination, NPI = Neuropsychiatric inventory, RBD= REM sleep Behaviour disorder, UPDRS III = Unified Parkinson's disease rating scale (section III), SRT = Simple reaction time, CRT = Choice reaction time, Digit_Vig = Digit Vigilance.

† Performed on transformed data.
Bold text denotes statistical significance.

Table 2 Peak significance of surface results. Table depicts voxel significance ($P_{TFCE\text{-}corr}$), extent (k) and MNI coordinates.

	Voxel-level ($P_{TFCE\text{-}corr}$)	Extent (k)	MNI Coordinates (x,y,z) (mm)
Controls vs. DLB	0.002	1842	-6, -18, -3
	0.002	2020	9, -17, -3
Controls vs. DLB_a	0.02	178	-3, -20, -2
	0.04	152	-7, -7, 13
	0.03	138	-20, -24, -1
	0.04	78	-16, -14, 3
	0.02	235	10, -17, 17
	0.01	228	5, -20, -2
	0.02	134	18, -14, 4
	0.04	17	23, -27, 3
Controls vs. DLB_d	0.006	1726	-2, -4, 1
	0.004	2092	5, -22, -1
DLB vs. CRT_{SD}	0.02	185	-16, -13, 5
	0.03	84	-10, -34, 7
	0.03	24	-4, -23, -1

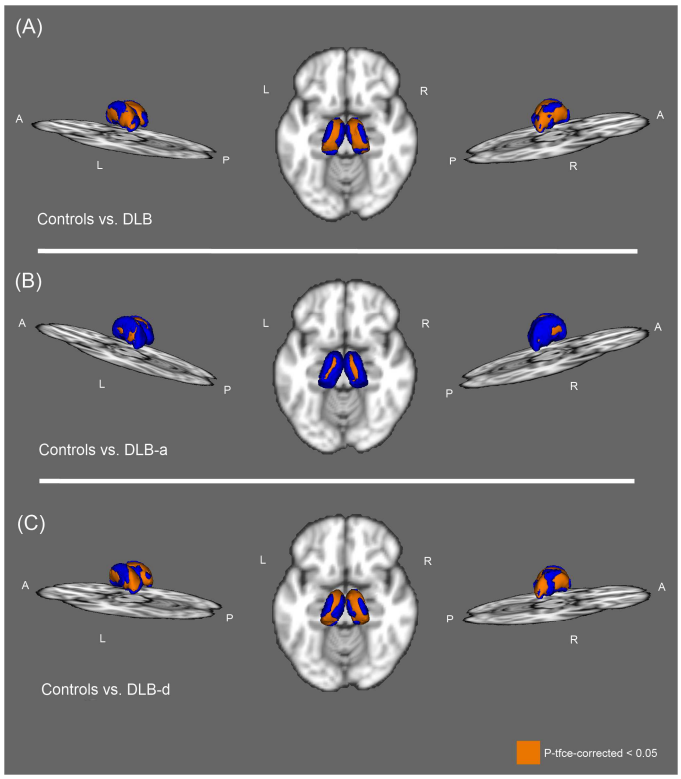
Table 3 Demographic and group characteristics of DLB subgroups based on survival data.

	DLB_a	DLB_d	Statistic, p value
n	26	9	
Gender (m: f)	19: 7	8: 1	$\chi^2 = 0.9, 0.3$
Age (yrs.)	78.3 ± 7.5	78.6 ± 5.2	$t_{33} = 0.2, 0.9$
MMSE	19.9 ± 5.7	21.7 ± 3.8	$t_{33} = 0.9, 0.4$
CAMCOG	66.2 ± 16.2	72.1 ± 11.7	$t_{33} = 1.0, 0.3$
NPI total	20.2 ± 15.6	25.4 ± 21.9	$U_{35} = 109.5, 0.7$
Bristol ADL	17.9 ± 9.8	19.0 ± 9.2	$t_{33} = 0.3, 0.8$
SRT_{mean}	683.5 ± 547.3	716.8 ± 739.3	$t_{33} = 0.2, 0.9^{\dagger}$
SRT_{SD}	261.6 ± 365.3	439.8 ± 954.0	$t_{33} = 0.03, 1.0^{\dagger}$
CRT_{mean}	1065.9 ± 672.0	1211.7 ± 934.7	$t_{33} = 0.9, 0.4^{\dagger}$
CRT_{SD}	410.4 ± 512.9	662.3 ± 992.0	$t_{33} = 1.3, 0.2^{\dagger}$
$Digit\_Vig_{mean}$	577.2 ± 113.5	677.5 ± 62.1	$\mathbf{t_{33} = 3.5, 0.002}^{\dagger}$
$Digit\_Vig_{SD}$	118.7 ± 42.6	165.9 ± 43.1	$\mathbf{t_{33} = 2.8, 0.01}^{\dagger}$
Duration of illness (months)	42.0 ± 19.1	36.8 ± 25.4	$t_{33} = 0.6, 0.5$
ChI use (y: n)	22: 4	8: 1	$\chi^2 = 0.1, 0.8$
RVH (% yes)	81 (21/26)	89(8/9)	$\chi^2 = 0.3, 0.6$
CF (% yes)	92 (24/26)	89 (8/9)	$\chi^2 = 0.1, 08$
RBD (% yes)	69 (18/26)	33 (3/9)	$\chi^2 = 3.6, 0.06$
UPDRS III	27.0 ± 10.4	22.9 ± 11.6	$t_{33} = 1.0, 0.3$
DaTSCAN[‡] (yes: no)	19: 7	3: 6	
History of:			
IHD (% yes)	27 (7/26)	11 (1/9)	$\chi^2 = 0.9, 0.3$
T2DM (% yes)	12 (3/26)	11 (1/9)	$\chi^2 = 0.001, 1.0$
Hypertension (% yes)	31 (8/26)	33 (3/9)	$\chi^2 = 0.20, 0.9$
Hypercholesterolemia (% yes)	38 (10/26)	11 (1/9)	$\chi^2 = 2.3, 0.1$
Atrial Fibrillation (% yes)	8 (2/26)	0 (0/9)	$\chi^2 = 0.7, 0.4$
No. of medications			
5 or less	11	6	
More than 5	15	3	
Total hippocampal volume[*]	0.30 ± 0.06	0.27 ± 0.06	$t_{33} = 1.3, 0.2$

Values expressed as Mean ± 1 SD.

RVH = Recurrent visual hallucinations, CF = Cognitive fluctuation, RBD = REM sleep behaviour disorder, DaTSCAN = Dopaminergic SPECT imaging, IHD = Ischaemic heart disease, T2DM = Type 2 diabetes mellitus, No. of medications = Index of medical comorbidity.

[†]Performed on transformed data.
[‡]Individuals with DaTSCAN imaging were all rated as 'positive'.
[*] Total (right + left) expressed as % of total intracranial volume.
Bold text denotes statistical significance.



Highlights

- Thalamic atrophy relate to attentional dysfunction and fluctuations in DLB.
- Atrophy pattern differed in patients who died within 12 months of assessment.
- Results characterise changes underpinning disease symptoms and heterogeneity.