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Journal

Neuroscience Letters, 485(3)

ISSN

0304-3940

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Publication Date

2010-11-01

DOI

10.1016/j.neulet.2010.09.016

Published in final edited form as:
Neurosci Lett. 2010 November 26; 485(3): 222–227. doi:10.1016/j.neulet.2010.09.016.

Neuropathology of Dementia with Lewy Bodies in Advanced Age: a comparison with Alzheimer Disease

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Abstract

Dementia with Lewy Bodies (DLB) is a common neurodegenerative disorder of the aging population characterized by α–synuclein accumulation in cortical and subcortical regions. Although neuropathology in advanced age has been investigated in dementias such as Alzheimer Disease (AD), severity of the neuropathology in the oldest old with DLB remains uncharacterized. For this purpose we compared characteristics of DLB cases divided into three age groups 70–79, 80–89 and ≥90 years (oldest old). Neuropathological indicators and levels of synaptophysin were assessed and correlated with clinical measurements of cognition and dementia severity. These studies showed that frequency and severity of DLB was lower in 80–89 and ≥90 year cases compared to 70–79 year old group but cognitive impairment did not vary with age. The extent of AD neuropathology correlated with dementia severity only in the 70–79 year group, while synaptophysin immunoreactivity more strongly associated with dementia severity in the older age group in both DLB and AD. Taken together these results suggest that the oldest old with DLB might represent a distinct group.

Keywords

Cognition; Neuropsychological assessment

INTRODUCTION

Lewy body disease is an heterogeneous group of neurodegenerative disorders of the aging population that includes Dementia with Lewy Bodies (DLB) and Parkinson's Disease [13]. In DLB, α–synuclein containing Lewy bodies (LBs) are found in cortical and subcortical

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regions and accompanied in most cases by amyloid deposition and occasional tangle formation. Advanced age is an important risk factor for DLB and Alzheimer disease (AD). Previous studies have shown that advanced age modifies the severity of the neuropathology and clinical symptoms in AD [13]. Surprisingly, in the oldest old patients with AD the density of plaques and tangles and the extent of the neuronal loss is lesser than in the younger age groups [3,6,8,12,17].

Although neuropathology in advanced age has been investigated in AD, severity of neuropathology in the oldest old with DLB remains uncharacterized. To address this we compared neuropathological features and levels of a synaptic marker (synaptophysin) in DLB and AD cases in three age groups: youngest (70–79yrs) years; middle (80–89 ys); and oldest (≥90 yrs). The results demonstrate that the frequency of DLB and severity of neuropathology is less severe in the older cases compared to younger groups and that synaptophysin immunoreactivity is more closely associated with cognitive impairment in the very elderly DLB and AD cases, suggesting that the oldest old with DLB might represent a distinct group.

METHODS

Cases

Cases selection for this retrospective study was based on neuropathological examination and determination of the diagnosis of AD and DLB. Cases were divided into three age groups (70–79 (Control n=7, DLB n=53, AD n=137), 80–89 (Control n=7, DLB n=39, AD n=197) and ≥90 years (Control n=2, DLB n=6, AD n=64)) (Table 1).

All cases were from the Alzheimer Disease Research Center (ADRC) at the University of California, San Diego (UCSD). In most cases patients received neuropsychological testing at UCSD ADRC as part of a structured annual examination[22], Blessed Information-Memory-Concentration (BIMC), Dementia Rating Scale (DRS), and Mini-Mental State Examination (MMSE) scores are reported (Supp. Tables 1 and 2). Cases included had cognitive testing performed within 12 months of death. All subjects came to autopsy between 1985 and 2006 and postmortem interval for all cases was under 12 hours. Institutional board review was obtained from the UCSD Human Research Protections Program, in accordance with the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all patients or their guardians.

Neuropathological examination

Paraffin sections from formalin-fixed material stained with hematoxylin and eosin and thioflavin-S (TS) were used for neuropathological analysis, including assessment of plaque and tangle density in the neocortex and hippocampus as described [7,9]. In brief, TS stained sections from left midfrontal (MF), inferior parietal (IP), superior temporal (ST) neocortex and posterior level of hippocampus were examined for plaque and tangle counts. Senile plaques, both diffuse and neuritic, were counted in 100× magnification fields of maximal lesion densities from each of the 4 sections, while tangles were counted in similarly selected 400× magnification fields. Braak staging was assessed on anterior entorhinal cortex and neocortex sections [4].

Cases were subdivided into three categories via pathological analysis: non-demented age-matched controls, DLB and AD. Control cases included had very few or no plaques and no tangles. DLB diagnoses were based on pathological findings of LBs detected by immunohistochemistry with an α-synuclein antibody (Millipore, Temecula, CA) and clinical presentation of dementia, all DLB cases underwent α-synuclein immunohistochemistry for sub-classification into brainstem predominant, limbic and diffuse neocortical stages.

Analysis of α-synuclein immunoreactivity was also performed in AD cases. DLB cases had sufficient total and neuritic plaques to meet 1985 National Institute of Aging (NIA) and Consortium to Establish a Registry for AD (CERAD) criteria for probable AD. However, all cases had a Braak stage less than 4, and were classified as DLB ("mixed-DLB"). Cases having a Braak stage of 5 or 6 and displaying unequivocal AD tangle pathology are classified as AD [10]. All AD cases met CERAD and NIA criteria for diagnosis [15].

Measurement of cerebral amyloid angiopathy

Presence and severity of cerebral amyloid angiopathy (CAA) was assessed on TS preparations of MF, IP, ST and hippocampal regions. Scores from 0–4 were given to each sample reflecting increasing severity of CAA, this scoring is consistent with previous studies and work from this group [2,20].

Synaptophysin and Aβ immunoreactivity

Synaptophysin-immunoreactive terminals in the MF cortex were obtained by laser scanning confocal microscopy of vibratome sections immunostained with monoclonal synaptophysin antibody (1 μg/ml; Chemicon, Indianapolis, IN)[19]. All assessments were blind-coded and in duplicate. As previously described [21] additional immunocytochemical analysis was performed with a mouse monoclonal Aβ antibody (clone 82E1, Immunobiological Laboratories) to determine amyloid load in the basal ganglia of DLB cases.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Means were compared using the Kruskal-Wallis test for Braak scores and one-way analysis of variance (ANOVA) for all others. The Kruskal-Wallis test was followed by Dunn's multiple comparison test and ANOVA was followed by either Student Newman-Keuls or Bonferroni's multiple comparison tests, where appropriate. Pearson product moment correlations were used to determine the intragroup association of BIMC to total senile plaque (TP), neuritic plaque (NP), and neurofibrillary tangle (NFT) counts. Spearman rank order correlations were used to analyze relationships between BIMC and Braak stage.

RESULTS

The frequency of DLB is reduced in the oldest group

A total of 512 cases were included in the study (Table 1), of these, 197 (38%) were between ages 70 and 79, 243 (48%) between ages 80 and 89, and 72 (14%) were 90 and above (Supp. Table 3). Comparing youngest (70–79) and oldest (≥90) groups, the proportion of AD cases increased significantly with increasing age (69.5% as compared to 89%). In contrast, proportion of DLB cases as a percentage of all cases (DLB and AD) decreased significantly with increasing age (27% as compared to 8%) (Table 1), while 64/398 (16%) of AD cases were above 90 years, only 6/98 (6%) DLB cases were above 90 years ($\chi^2 = 5.64$; $p = 0.018$).

Comparison of the cognitive impairment scores in advanced age in DLB and AD cases

Analysis of cognitive impairment using BIMC, MMSE and DRS was available in most cases across the age group of 70–79 years (Control n=7, DLB n=42, AD n=98), 80–89 years (Control n=7, DLB n=39, AD n=131) and ≥90 years (Control n=2, DLB n=3, AD n=34) (Supp. Table 3). In DLB, there were no significant differences in cognition among the groups (Supp Table 1). In AD, the oldest cases (≥90) had lower BIMC scores than the youngest (70–79) (Supp Table 2), suggesting less severe dementia in the ≥90 group at death. There were no differences in the cognitive performance in the AD cases (Supp Table 2).

Comparison of the neuropathological indices in advanced age DLB and AD cases

The unimpaired control groups had an average brain weight at 70–79 and 80–89 years of age of 1200 grams and in the oldest group (≥90) of 1100 grams. The control unimpaired cases included for this study had only occasional amyloid deposits, but had no neocortical NP or tangles and the Braak stage was 0–1. In the DLB oldest (≥90) group, brain weight was significantly lower than the average in either of the two younger groups (Supp Table 1). To account for gender effects cases were stratified by gender, males had a significantly greater brain weight than females (Fig.1a). In the oldest AD group, brain weight was also significantly lower than the average in either of the two younger groups (Supp Table 2). Males had a significantly greater brain weight than females in the 70–79 and 80–89 age groups (Fig.1b); there was no gender difference in brain weight in the ≥90 age group. Considering gender separately, male brain weight decreased with increasing age (Fig.1b), while there was no trend in female brain weight with age (Fig.1b).

In DLB, no differences in Braak score (Supp Table 1), plaque number or amyloid angiopathy were observed among the groups (Table 2). Fewer neocortical tangles were observed in the oldest DLB group (≥90 year old (y/o)) compared to younger groups (Table 2). Braak score was significantly lower in the oldest AD group compared to the two younger groups (Supp Table 2). Consistently, NFTs in the neocortex significantly decreased with increasing age in most brains regions (Table 2). Although TP counts did not differ between groups, NP counts were significantly lower in the oldest group (Table 2). CAA did not differ among the AD groups in any region examined (Table 2).

Analysis of presynaptic terminals was performed in the frontal cortex of a subset of the cases for which suitable tissues were available ((70–79 (Control n=7, DLB n=16, AD n=28), 80–89 (Control n=7, DLB n=14, AD n=197) and ≥90 years (Control n=2, DLB n=0, AD n=15) (Supp. Table 3)). Comparing all groups of DLB and AD cases to non-demented controls, the number of synaptophysin-immunolabeled nerve terminals was approximately 30–40% lower in cases than in controls (Fig.1c). Levels of synaptophysin did not vary significantly with age for either DLB or AD cases (Fig.1c).

Cortical LB pathology is less severe but amyloid load in the basal ganglia is comparable in older DLB cases

Analysis of LB pathology was performed with an antibody against α-synuclein in a subset of cases across age groups for which suitable tissue was available ((70–79 (Control n=7, DLB n=16, AD n=28), 80–89 (Control n=7, DLB n=14, AD n=31) and ≥90 years (Control n=2, DLB n=3, AD n=15) (Supp. Table 3))

The localization of α-synuclein immunoreactivity was used to assign each DLB case a LB pathology type - brainstem-predominant, limbic, or diffuse neocortical, in order of increasing pathological severity[18] (Fig. 1d). In the youngest group (70–79, n = 17), 11 cases (65%) were diffuse neocortical, with the remaining 6 (35%) evenly divided between limbic and brainstem-predominant. In the middle group (80–89, n = 11), 7 cases (64%) were brainstem-predominant, the remaining 4 (36%) evenly divided between diffuse neocortical and limbic. Finally, in the oldest group (≥90, n = 3), all cases were brainstem-predominant (Fig. 1d). Although these cases were brainstem-predominant, they presented clinically with dementia and did not meet criteria for the pathological diagnosis of AD. There was a significant difference in proportion of diffuse neocortical, limbic, and brainstem-predominant cases among the three groups ($\chi^2 = 11.42$; $p = 0.02$), with each subsequent age group displaying progressively less severe LB pathology (Fig.1d). Since previous studies have proposed a contribution of amyloid deposition in the basal ganglia to the impairments in patients with DLB [14,16] levels of Aβ load in the putamen were compared across the age

groups. We found Aβ immunoreactive diffuse and mature plaques in 82% (14 of 17 cases) of the 70–79 y/o group; in 81% (9 of 11 cases) of the 80–89 y/o group and in 66% (2 of 3 cases) of the ≥90 y/o.

A number of recent reports have investigated α-synuclein in relation to AD pathology [1,24], in this study we observed LB-like inclusions in the amygdala of 45% of the AD cases examined, however no LBs were identified in the neocortex of these cases.

Relationship between dementia and neuropathological indices in older DLB and AD cases

Linear regression analysis was performed to investigate the relationship between cognitive impairment and neuropathological markers. For DLB, Braak stage did not correlate with cognition as indexed by BIMC for the 70–79 or the 80–89 age groups (Table 3). However it is worth noting that 12 out of the 30 DLB cases had a Braak stage of 4 that could contribute to some extent to the cognitive alterations. NFT counts in the hippocampus were associated with BIMC in the youngest group, whilst NFT in the MF and IP cortex were better associated with BIMC in the middle group (Table 3, Fig.2a, b). NP counts in the hippocampus associated with BIMC in the youngest group while in the 80–89 group this was only observed in the MF cortex (Table 3). Synaptophysin levels associated best with BIMC in the 80–89 y/o group (Table 3; Fig.2c, d).

In AD, Braak stage positively associated with BIMC in all three groups (Table 3). NFT counts in the neocortex and hippocampus associated with BIMC in the 70–79 and 80–89 age groups; in the oldest group (≥90), NFT counts related to BIMC only in the temporal cortex and hippocampus (Table 3, Fig.2e–g). NP counts in the neocortex and hippocampus associated with BIMC in the 70–79 and 80–89 age groups; in the ≥90 group, NP counts associated with BIMC only in the IP cortex (Table 3). In contrast, synaptophysin levels strongly associated with BIMC in the oldest (≥90) group but to a lesser extent in the younger groups (Table 3; Fig.2h–j).

DISCUSSION

Characterization of DLB in advanced age has not been investigated; in the present study we demonstrate that DLB neuropathology, as in AD, is age-dependent, with oldest subjects (≥90 years) manifesting less severe α-synuclein pathology than younger counterparts. We found that with increasing age, DLB cases represent an ever-smaller fraction of all dementia cases while AD cases were more uniformly distributed across ages. The lower proportion of DLB cases in older groups may be due to the rapid progression of DLB [11,23] and patient death before reaching older ages.

Cognitive impairment in older DLB cases was similar to younger groups and there was limited or no difference in the severity of plaque and tangle pathology across the age groups. In AD, dementia and neuropathology were both less severe in the ≥90 group compared to younger counterparts. This is consistent with studies showing that advanced age in AD is associated with a less severe cognitive impartment, lower Braak stage and fewer neuritic plaques and NFTs[3]. Moreover, the magnitude of the neuronal loss in AD centenarians is significantly lower than that reported for younger AD cases[6]. In our patients, severity of AD pathology strongly associated with cognitive impairment in the 70–79 and 80–89 age groups, but not in patients over 90, instead, synaptophysinimmunoreactivity significantly associated with BIMC in the ≥90 age group compared to younger counterparts. This is consistent with a recent study in 90+ AD patients showing that levels of synaptophysin in the frontal cortex were the strongest correlate of MMSE score [13].

Cerebrovascular pathology also contributes to dementia in the elderly and the impact of cerebrovascular pathology on dementia has been reported [5]. Case selection at the ADRC, who refer cases with a history of cerebral infarction elsewhere, limits these cases in our patient population therefore this study was directed at DLB and AD pathology rather than vascular pathology.

We report that advanced age in DLB is associated with less severe LB neuropathology than younger counterparts, that the proportion of DLB cases in all dementia cases decreases with age and that while traditional neuropathological lesions (NFTs and NPs) associate with cognitive impairment in younger (70–89 years) AD patients, synaptophysin immunoreactivity correlates better with cognitive impairment in older (≥90) DLB and AD patients. Taken together, these results suggest that DLB has a similar clinical presentation across age groups, but less severe LB pathology in the very elderly while the 90+ AD cases might represent a neuropathologically distinct subgroup.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Work supported by NIH grants AG5131 and 18440.

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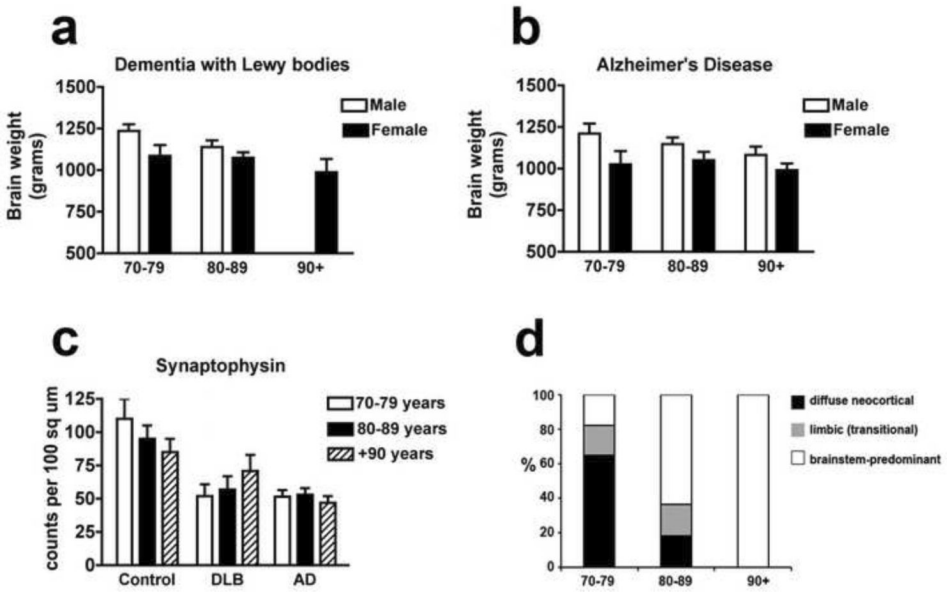

Figure 1. Neuropathological indices in DLB and AD

(a) Brain weight in Dementia with Lewy Bodies (DLB) and (b) Alzheimer disease (AD) patients. (c) Synaptophysin immunoreactivity in the frontal cortex of control, DLB and AD cases. (d) Breakdown of LB type (brainstem-predominant, limbic [transitional], or diffuse neocortical).

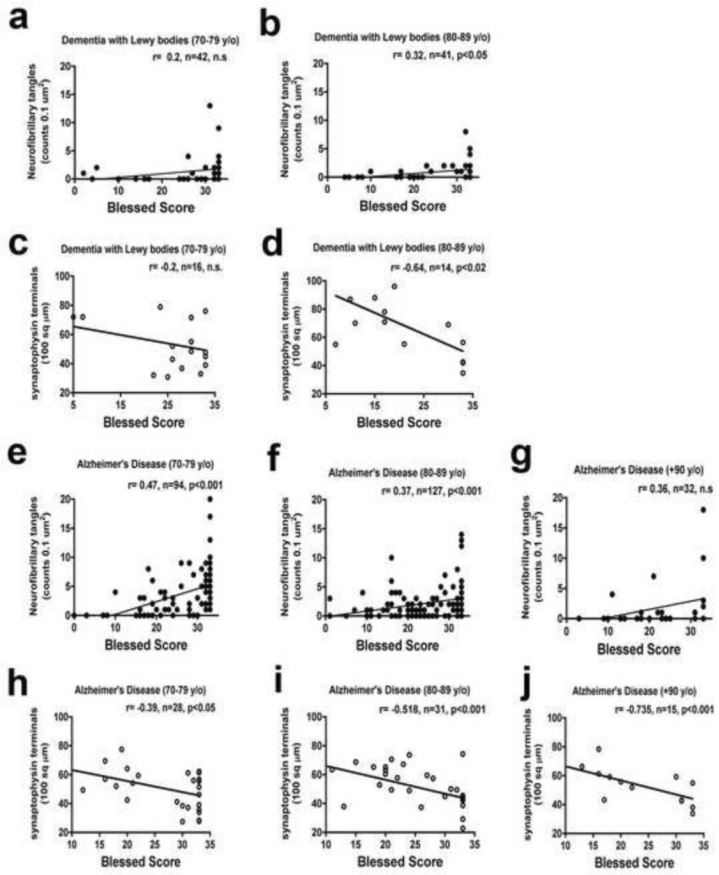

Figure 2. Correlation between neurofibrillary tangles, synaptic integrity and cognition in DLB and AD

Correlation between: (a) neurofibrillary tangles and BIMC in DLB patients in 70–79 and (b) 80–89 age groups (c) synaptophysin immunoreactive terminals and BIMC in DLB patients in 70–79 and (d) 80–89 age groups (e) neurofibrillary tangles and BIMC in AD patients in 70–79, (f) 80–89 and (g) ≥90 age groups (h) synaptophysin-immunoreactive terminals and BIMC in AD patients in 70–79, (i) 80–89 and (j) ≥90 age groups.

Table 1

Demographic Characteristics

Age Group	Final diagnosis	n=	Age	Gender (F/M)
70–79	Control	7	75 ± 3	3/4
	DLB	53	76 ± 3	19/34
	AD	137	75 ± 3	51/86
80–89	Control	7	85 ± 3	2/5
	DLB	39	84 ± 3	18/21
	AD	197	84 ± 3	120/77
90+	Control	2	94 ± 4	1/1
	DLB	6	96 ± 6	6/0
	AD	64	94 ± 4	45/19
TOTAL	-----	512	-----	265/247

AD = Alzheimer disease; DLB = dementia with Lewy bodies

Table 2

Neuropathological Variables across Brain Regions

	DEMENTIA WITH LEWY BODY			ALZHEIMER'S DISEASE		
	70–79 (n=42)	80–89 (n=39)	90+ (n=3)	70–79 (n=98)	80–89 (n=131)	90+ (n=34)
REGION	NEUROFIBRILLARY TANGLES					
MF	1.2 ± 2.6	0.9 ± 1.6	0 ± 0#	3.8 ± 3.9	2.2 ± 2.6+	1.7 ± 3.7#
IP	1.5 ± 2.8	1.9 ± 2.5	0.7 ± 0.6+	5.6 ± 4.7	14.5 ± 13.4+	2.0 ± 3.8+
ST	2.8 ± 5.9	2.6 ± 3.5	1.3 ± 0.6#	7.4 ± 6.1	5.8 ± 6.0*	3.8 ± 4.7#
HP	6.1 ± 9.9	8.4 ± 9.8	8 ± 5.3	14.8 ± 12.8	14.5 ± 13.4	16.6 ± 14.7

	TOTAL PLAQUES					
MF	37.4 ± 14.5	40.5 ± 12.4	45.3 ± 8.1	43.5 ± 10.8	43.0 ± 11.2	42.8 ± 9.4
IP	34.8 ± 13.6	40.1 ± 11.6	35.3 ± 5	43.8 ± 10.4	13.8 ± 7.6	41.4 ± 10.4
ST	30.3 ± 13.4	36.4 ± 13.6	26.7 ± 10.6	40.9 ± 11.6	39.6 ± 11.0	36.5 ± 14.6
HP	11.5 ± 9.7	13.6 ± 8.5	13.7 ± 4	15.2 ± 8.3	13.8 ± 7.6	11.4 ± 8.1

	NEURITIC PLAQUES					
MF	21.7 ± 15.8	20.1 ± 12.4	28.5 ± 12	33.7 ± 15.3	28.8 ± 15.5*	21.5 ± 14.4+§
IP	24.2 ± 17.2	22.1 ± 12	29.5 ± 1	35.6 ± 15.6	10.4 ± 5.9#	21.9 ± 15.4+§
ST	18.8 ± 14.3	16.9 ± 10.9	11.5 ± 2.1+	28.1 ± 15.3	22.3 ± 12.4#	17.0 ± 13.0+
HP	7.1 ± 7.9	7.8 ± 6.5	9.5 ± 9.2	11.3 ± 6.4	10.4 ± 5.9*	7.7 ± 7.8*

	CEREBRAL AMYLOID ANGIOPATHY					
MF	1.1 ± 1.3	1.7 ± 1.4	1.0 ± 1.7	1.5 ± 1.4	1.8 ± 1.4	1.6 ± 1.3
IP	1.2 ± 1.3	1.3 ± 1.4	1.3 ± 1.2	1.1 ± 1.3	1.0 ± 1.2	1.4 ± 1.4
ST	0.9 ± 1.2	0.9 ± 1.2	0.7 ± 1.2	0.8 ± 1.2	1.1 ± 1.3	1.0 ± 1.3
HP	0.9 ± 1.2	0.9 ± 1.3	0.3 ± 1.6	0.8 ± 1.2	1.0 ± 1.2	0.7 ± 1.2

MF = mid-frontal; IP = inferior parietal; ST = superior temporal; HP = hippocampus.

*P < 0.05 from 70–79

#P < 0.01 from 70–79

[+] $P < 0.001$ from 70–79

[§] $P < 0.05$ from 80–89

Table 3

Correlation Coefficients between BIMC and Neuropathological Markers

	DEMENTIA WITH LEWY BODY		ALZHEIMER'S DISEASE		
	70–79 (n=42)	**80–89 (n=39)**	**70–79 (n=98)**	**80–89 (n=131)**	**90+ (n=34)**
Braak	0.262 (ns)	0.278 (ns)	0.60 (0.0001)	0.47 (0.0001)	0.66 (0.0001)
LSCM (syn)	−0.20 (ns)	−0.64 (0.02)	−0.22 (ns)	−0.47 (0.02)	−0.83 (0.0005)

Region	NEUROFIBRILLARY TANGLES				
MF	0.232 (ns)	0.329 (0.03)	0.47 (0.0001)	0.37 (0.0001)	0.36 (ns)
IP	0.254 (ns)	0.342 (0.02)	0.47 (0.0001)	0.43 (0.0001)	0.38 (0.03)
ST	0.197 (ns)	0.217 (ns)	0.53 (0.0001)	0.32 (0.0004)	0.49 (0.005)
HP	0.302 (0.04)	0.07 (ns)	0.34 (0.0009)	0.29 (0.0009)	0.47 (0.007)

	NEURITIC PLAQUES				
MF	0.149 (ns)	0.317 (0.04)	0.33 (0.003)	0.3 (0.002)	0.33 (ns)
IP	0.256 (ns)	0.214 (ns)	0.26 (0.02)	0.33 (0.0006)	0.46 (0.01)
ST	0.193 (ns)	0.251 (ns)	0.24 (0.04)	0.29 (0.002)	0.27 (ns)
HP	0.311 (0.04)	−0.103 (ns)	0.26 (0.02)	0.29 (0.004)	0.18 (ns)

BIMC = Blessed Information-Memory-Concentration; LSCM = laser scanning confocal microscopy; syn = synaptophysin; MF = mid-frontal; IP = inferior parietal; ST = superior temporal; HP = hippocampus; ns = not significant; P values in parentheses