

Opposite Effects of Senile Plaques and Neurofibrillary Tangles on Lewy Body Propagation: Analysis of 2,308 Autopsy Cases

Hiroaki Sekiya, M.D., Ph.D., Daisuke Ono, M.D., Ph.D., Dennis W. Dickson, M.D.
Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA

ABSTRACT

BACKGROUND: Lewy body disease (LBD) exhibits marked pathological heterogeneity in the anatomical distribution of Lewy bodies (LB). Although LB propagation has been extensively debated, the specific anatomical progression patterns within the cerebrum remain poorly understood. Additionally, most patients with LBD have concomitant Alzheimer disease (AD) pathology; however, how senile plaques (SP) and neurofibrillary tangles (NFT) influence LB distribution remains unclear.

METHODS: We analyzed 2,308 autopsy cases from the Mayo Clinic Brain Bank with LB in any brain region and complete LB counts across six regions (amygdala, parahippocampal cortex, cingulate cortex, frontal, temporal, parietal cortices) plus SP/NFT counts in three neocortical regions (frontal, temporal, parietal). LB were assessed by α -synuclein immunohistochemistry (20 $\times$ field), SP by Thioflavin S fluorescent microscopy (10 $\times$ field), and NFT by Thioflavin S fluorescent microscopy (40 $\times$ field). We performed kernel density estimation, SuStaln analysis (an unsupervised machine learning algorithm for disease progression modeling), Spearman correlations, partial correlations adjusting for age/sex, and multiple linear regression.

RESULTS: Kernel density plots and SuStaln analysis demonstrated a predominantly unidirectional LB progression pattern, proceeding from amygdala through parahippocampal and cingulate cortices to temporal, frontal, and parietal neocortices, in 99% of cases. Approximately 1% showed relatively amygdala-sparing patterns with early neocortical involvement. Total neocortical LB correlated positively with neocortical SP (Spearman $\rho=0.189$, $p<0.0001$) and negatively with NFT ($\rho=-0.092$, $p<0.0001$). After adjusting for age/sex, correlations strengthened (SP: $\rho=0.240$, $p<0.0001$; NFT: $\rho=-0.194$, $p<0.0001$). Multiple regression (neocortical LB $\sim$ SP + NFT + age + sex) revealed independent opposite effects: SP promoted (standardized $\beta=0.533$, $p<0.0001$) while NFT inhibited ($\beta=-0.463$, $p<0.0001$) neocortical LB accumulation, collectively explaining 27.1% of variance.

CONCLUSIONS: Although LB progression follows a stereotyped anatomical sequence, neocortical AD pathology modulates neocortical spread. High SP/NFT ratios promote diffuse neocortical LB spread, while low ratios restrict LB to limbic regions. These findings elucidate the mechanistic basis of LBD pathological heterogeneity and redefine the role of AD pathology in mixed AD-LBD cases.

METHODS

- We examined 2,308 cases from the Mayo Clinic brain bank with Lewy bodies (LB) in any brain region.
- LB was assessed by α -synuclein immunohistochemistry ($\times 20$) in 6 regions (amygdala, parahippocampal and cingulate cortices, temporal, frontal, and parietal cortices). Senile plaques (SP) and neurofibrillary tangles (NFT) were assessed by thioflavin S fluorescence microscopy (SP: $\times 10$; NFT: $\times 40$) in 3 neocortical regions (frontal, temporal, parietal).
- Statistical analyses:
 - Kernel density estimation to visualize regional LB distribution patterns
 - SuStaln algorithm^{1,2} (unsupervised machine learning for disease progression modeling) to identify LB progression subtypes
 - Spearman correlations and partial correlations (adjusted for age and sex) to assess relationships between pathological variables
 - Multiple linear regression with standardized coefficients to quantify independent effects of SP and NFT on neocortical LB burden

TABLE 1 Characteristics of patients

Characteristics	n (%)
Females	867 (38%)
Age at death	77.6 $\pm$ 8.7
APOE e4 carrier	549/1023 (54%)
Brain weight	1130 $\pm$ 170
LBD subtypes	
Brainstem-predominant	310 (13%)
Transitional	735 (32%)
Diffuse	918 (40%)
Amygdala-predominant	308 (13%)
Incidental	37 (2%)
Braak NFT stage	IV (III, VI)
Thal amyloid phase	4 (2, 5)
TDP-43 pathology	628/1823 (34%)
Small vessel disease	794 (34%)

RESULTS 1

FIGURE 1 Kernel density estimation plots

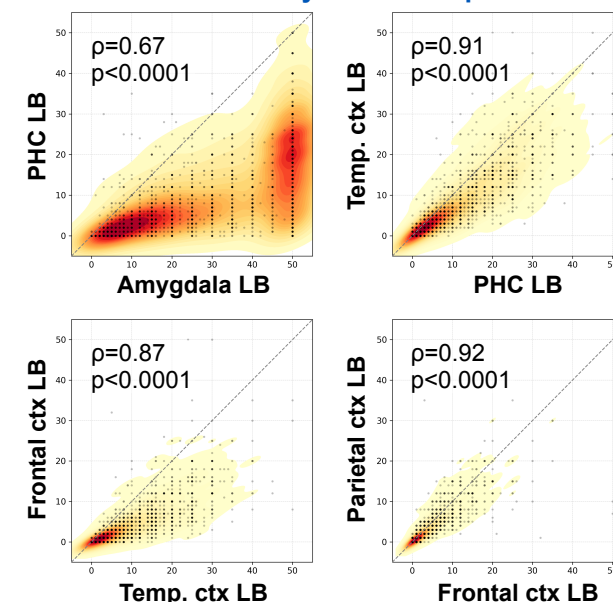


FIGURE 2 SuStaln analysis (three subtypes)

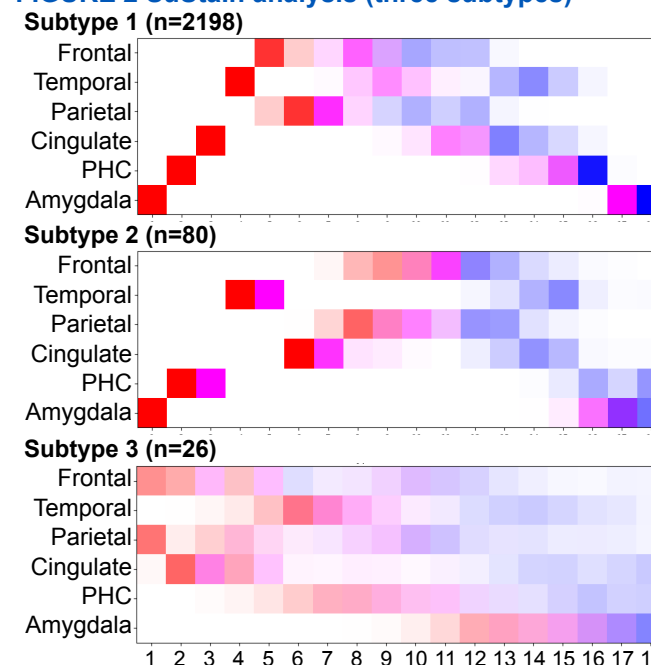
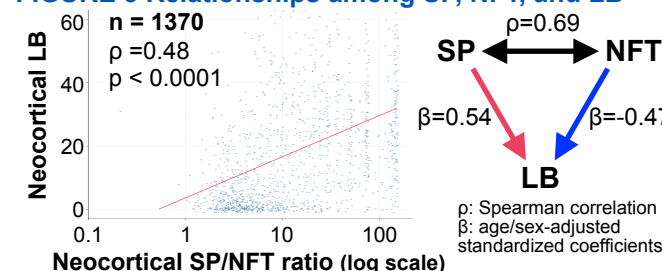


FIGURE 3 Relationships among SP, NFT, and LB



DISCUSSION

- LB pathology followed a predominantly unidirectional progression (amygdala $\rightarrow$ parahippocampal and cingulate cortices $\rightarrow$ neocortices) in 99% of cases, consistent with the Braak/Beach staging system^{3,4}.
- A minority ($\sim 1\%$) showed a relatively amygdala-sparing pattern (SuStaln subtype 3) with early neocortical involvement, which may correspond to the "cerebral type" LBD⁵.
- Despite a positive correlation between SP and NFT ($\rho=0.69$), they exerted opposite effects on neocortical LB burden: SP promoted while NFT inhibited LB accumulation.
- Previous studies have suggested synergistic interactions between AD and LB pathology⁶⁻⁸; however, our findings indicate that NFT exerts an inhibitory rather than a facilitatory effect on LB spread.
- These results suggest that the neocortical SP/NFT ratio acts as a "gatekeeper," determining whether LB pathology spreads from limbic to neocortical regions.

CONCLUSION

- LB pathology follows a stereotyped unidirectional progression, modulated by concomitant AD pathology.
- SP and NFT exert independent, opposing effects on neocortical LB spread, suggesting that the neocortical SP/NFT ratio determines the extent of LB propagation beyond limbic regions.

REFERENCES

- Young AL, et al. *Nat Commun.* 2018;9:4273.
- Sekiya H, et al. *Ann Neurol.* 2026;99:989-1000.
- Braak H, et al. *Neurobiol Aging.* 2003;24:197-211.
- Beach TG, et al. *Acta Neuropathol.* 2009;117:613-634.
- Yokota O, et al. *Neuropathology.* 2007;27:21-35.
- Clinton LK, et al. *J Neurosci.* 2010;30:7281-7289.
- Bassil F, et al. *Neuron.* 2020;105:260-275.
- Pan L, et al. *Brain.* 2022;145:3454-3471.