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Pathoanatomical Correlations of Amyloid Plaque Distribution in Cortical and Subcortical Structures

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Abstract

Amyloid plaque distribution in Alzheimer's disease exhibits pronounced regional specificity across cortical and subcortical brain structures, reflecting underlying patterns of neural connectivity and differential tissue vulnerability. This study aimed to investigate the pathoanatomical correlations of amyloid deposition using combined macroscopic assessment, histological examination, and quantitative morphometric analysis. Cortical regions—especially temporal and parietal association areas—demonstrated the highest plaque burden, with a characteristic laminar preference for layers II–III and V–VI. Subcortical nuclei displayed heterogeneous involvement, with the basal forebrain and amygdala showing early and prominent plaque accumulation, whereas the thalamus and striatum were affected to a lesser degree. Morphometric evaluation and three-dimensional reconstruction revealed coordinated anatomical gradients consistent with trans-synaptic propagation models, highlighting the role of interconnected neural pathways in the spread of amyloid pathology. Differences in plaque morphology between cortical and subcortical regions further emphasized region-specific microenvironmental influences. These findings underscore the value of integrated pathoanatomical approaches for improving the understanding of Alzheimer's disease progression and refining diagnostic and staging criteria.

Keywords: Alzheimer's disease; amyloid plaques; cortical structures; subcortical nuclei; pathoanatomy; β-amyloid; histology; morphometry; neural pathways; neurodegeneration; brain connectivity; plaque morphology.

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and is characterized by progressive neurodegeneration associated with the accumulation of β-amyloid (Aβ) plaques and tau pathology. Despite decades of research, the topographic distribution and structural consequences of amyloid deposition in cortical and subcortical regions remain incompletely understood. Recent advances in neuropathology and neuroimaging have highlighted that amyloid pathology is not uniformly distributed but follows specific anatomical patterns that correlate with clinical severity and cognitive decline [1]. However, significant variability in plaque localization across individuals complicates diagnostic interpretation and staging.

Over the past five years, the integration of high-resolution histopathology, three-dimensional tissue clearing, and advanced neuroimaging modalities has enabled more precise mapping of amyloid deposits in both cortical association areas and deep subcortical nuclei. These approaches have shown that amyloid accumulation often begins in cortical regions with high metabolic demand and extensive connectivity, later involving subcortical structures such as the basal forebrain, thalamus, and striatum [2]. Nevertheless, the structural and functional impact of these region-specific

distributions remains an active area of investigation, especially given that amyloid deposition does not always correlate directly with neuronal loss or symptom severity.

A major challenge in current research is the discrepancy between amyloid plaque burden visualized using PET imaging and the detailed micromorphological patterns revealed in postmortem tissue. While amyloid PET provides valuable whole-brain visualization, it lacks the spatial resolution to distinguish between plaque subtypes or their exact laminar and nuclear localization. Conversely, neuropathological studies offer high precision but cannot capture dynamic changes over time. This methodological gap limits our understanding of how cortical versus subcortical amyloid deposition contributes to network dysfunction and cognitive decline in AD [3].

In addition, recent studies have emphasized the importance of examining the interplay between amyloid plaques and non-neuronal components of the brain, including astrocytes, microglia, and vascular structures. Emerging evidence suggests that amyloid deposition in subcortical regions may disrupt neuromodulatory systems, particularly cholinergic pathways originating in the basal forebrain, which are crucial for attention and memory. Such findings underscore the need for a more integrated pathoanatomical analysis that considers cellular and regional context, rather than plaque burden alone [4]. Despite significant progress, unanswered questions remain regarding the factors that shape amyloid distribution patterns and their differential impact across brain regions.

Given these gaps, a systematic investigation of pathoanatomical correlations of amyloid plaque distribution in cortical and subcortical structures is essential. Understanding these correlations can provide deeper insights into disease progression, facilitate more accurate staging, and support the development of targeted therapeutic interventions. This topic remains highly relevant in contemporary neuropathological research, as precision mapping of amyloid pathology is critical for improving diagnostic accuracy and advancing personalized approaches to Alzheimer's disease.

The aim of the study was to investigate the pathoanatomical correlations of amyloid plaque distribution in cortical and subcortical brain structures using contemporary histological and morphometric approaches.

2. Methods

The study was based on a combined macroscopic, histological, and morphometric examination of human brain material obtained from individuals with clinically and neuropathologically confirmed Alzheimer's disease. Brain specimens were collected in accordance with ethical standards and institutional approval, ensuring the absence of traumatic lesions, large-vessel strokes, or coexisting neurodegenerative diseases that could confound the anatomical assessment. After fixation in 10% neutral buffered formalin, the cerebral hemispheres were sectioned in the coronal plane to obtain standardized cortical and subcortical blocks, with particular attention to association cortices, limbic structures, basal forebrain nuclei, thalamus, and striatum.

Macroscopic evaluation included assessment of regional cortical thickness, gyral atrophy, ventricular enlargement, and visible plaque clusters using both gross inspection and stereomicroscopy. Standardized photographic documentation was performed for subsequent topographic correlation. Tissue blocks were then dehydrated, paraffin-embedded, and sectioned at 4–6 μm thickness for histological analysis. Hematoxylin–eosin staining was used for general structural assessment, while Congo red, Thioflavin-S, and immunohistochemistry with antibodies against β-amyloid (Aβ1–42 and Aβ1–40) were employed to identify and classify amyloid plaques.

Micromorphological analysis focused on plaque type (diffuse, neuritic, cored), density, laminar distribution in the cortex, and nuclear localization in subcortical regions. Digital whole-slide scanning was performed using a high-resolution slide scanner, allowing quantitative analysis of plaque burden with morphometric software. Automated and semi-automated segmentation algorithms were applied to calculate plaque density per mm², plaque size distribution, and spatial clustering patterns. Inter-rater reliability was ensured through independent evaluation by two neuropathologists, with discrepancies resolved by consensus.

To explore pathoanatomical correlations, histological data were aligned with macroscopic topographic maps using 3D reconstruction methods. Anatomical regions were defined according to standard neuroanatomical atlases, enabling cross-comparison of cortical layers and subcortical nuclei. Statistical analysis included assessment of regional differences in plaque burden,

correlation analysis between cortical and subcortical involvement, and evaluation of spatial progression patterns consistent with contemporary models of Alzheimer's disease pathology. All analyses were conducted using validated morphometric and statistical software packages.

3. Results

Macroscopic examination revealed regionally heterogeneous involvement of cortical and subcortical areas by amyloid pathology. Cortical regions with the most pronounced atrophic changes included the temporal and parietal association cortices, followed by the posterior cingulate and superior frontal areas. In several specimens, discrete clusters of whitish granular deposits corresponding to dense-cored plaques were visible on the cortical surface and within deep cortical layers. Ventricular enlargement and thinning of the entorhinal cortex were consistent findings, supporting advanced neurodegenerative involvement.

Histological analysis confirmed abundant amyloid deposition across all examined specimens, with marked variability in plaque density and morphology between cortical and subcortical structures. In neocortical regions, plaques were predominantly neuritic and cored, exhibiting strong Thioflavin-S fluorescence and intense immunoreactivity for Aβ1–42. Plaques demonstrated a clear laminar preference, with highest concentrations observed in layers II and III, followed by layers V–VI. Diffuse plaques were present in all cortical areas but were most prominent in the frontal and temporal lobes. Quantitative morphometry showed significantly higher plaque density in association cortices compared with primary sensory regions.

In subcortical structures, amyloid deposition exhibited distinct topographic patterns. The basal forebrain, particularly the nucleus basalis of Meynert, showed high concentrations of diffuse and immature plaques, whereas the thalamus and striatum contained fewer but more compact deposits. Amyloid accumulation within the hippocampal formation was concentrated in the subiculum and CA1 sector, with relative sparing of CA3 and the dentate gyrus. Notably, the amygdala displayed mixed plaque morphology, including both cored and diffuse plaques, suggesting an intermediate position in the progression of amyloid pathology.

Morphometric analysis demonstrated robust region-specific differences in plaque burden. Cortical plaque density strongly correlated with subcortical involvement, especially within the basal forebrain and limbic structures, supporting the concept of anatomically interconnected vulnerability. Three-dimensional reconstruction of histological sections confirmed spatial clustering of plaques along major cortico-subcortical pathways, including projections between the temporal cortex and amygdala, as well as between the prefrontal cortex and thalamus. This anatomical pattern was consistent across specimens and corresponded to previously proposed models of trans-synaptic amyloid propagation.

Comparative evaluation of plaque morphology revealed that cored plaques were more abundant in cortical association areas, while diffuse plaques dominated in early-affected subcortical nuclei. Morphometric metrics such as mean plaque diameter, total plaque area, and clustering index showed statistically significant differences between cortical and subcortical regions. Inter-rater agreement for plaque classification exceeded 90%, confirming methodological reliability. Collectively, these findings demonstrate that amyloid plaque distribution follows distinct anatomical gradients and correlates with both cortical laminar architecture and subcortical nuclear organization.

4. Discussion

The findings of this study demonstrate that amyloid plaque distribution in Alzheimer's disease follows distinct and anatomically meaningful gradients across cortical and subcortical structures. Consistent with contemporary models of disease progression, the highest plaque burden was observed in association cortices, particularly within the temporal and parietal lobes, while subcortical regions exhibited more variable involvement. The strong laminar preference for layers II–III and V–VI suggests that amyloid accumulation preferentially targets regions with dense synaptic connectivity and high metabolic activity, supporting the hypothesis that plaque deposition is closely linked to network-level vulnerability rather than uniform tissue susceptibility.

Subcortical structures displayed a heterogeneous pattern of amyloid involvement, with the basal forebrain and amygdala showing early and prominent deposition. These findings reinforce the concept that degeneration of cholinergic pathways—particularly those arising from the nucleus basalis of Meynert—may not simply accompany cortical pathology but actively modulate its progression. The relatively sparse but structurally

significant plaques found in the thalamus and striatum further indicate that subcortical nuclei are affected in a region-specific manner that reflects their connectivity with heavily burdened cortical regions.

The morphometric data highlighted meaningful correlations between cortical plaque density and subcortical involvement, suggesting coordinated pathological spread along established neural pathways. The results align with emerging evidence supporting trans-synaptic propagation mechanisms, whereby amyloid pathology progresses through anatomically linked networks. The 3D reconstructions provided additional support by demonstrating plaque clustering along major cortico-subcortical projection systems. Such pathway-oriented distribution ptterns underscore the importance of incorporating anatomical connectivity into models of Alzheimer's disease progression.

Importantly, the study also revealed a distinct divergence in plaque morphology between cortical and subcortical regions. The predominance of compact cored plaques in the cortex versus diffuse plaques in many subcortical nuclei may reflect region-specific microenvironmental factors, including differences in glial activation, extracellular matrix composition, or local neuronal architecture. These differences have diagnostic implications, as plaque subtypes contribute differently to neuroinflammation, synaptic dysfunction, and tissue remodeling. Understanding these morphological nuances is essential for improving the interpretation of histopathological findings and enhancing the accuracy of correlations with neuroimaging biomarkers.

Overall, the results provide strong evidence that amyloid distribution is neither random nor uniformly progressive, but instead reflects a complex interplay between anatomical connectivity, regional susceptibility, and microenvironmental factors. Such insights enhance our understanding of the structural underpinnings of Alzheimer's disease and highlight the importance of integrating macroscopic anatomy, histology, and morphometric techniques to achieve a more complete picture of amyloid pathology.

5. Conclusion

Amyloid plaque distribution in Alzheimer's disease demonstrates clear, anatomically organized patterns across cortical and subcortical regions. Cortical association areas exhibit the highest plaque burden, while subcortical nuclei show region-specific and connectivity-dependent involvement. Morphometric correlations and 3D reconstructions indicate that amyloid propagation aligns with established neural pathways, supporting network-based models of disease spread. Differences in plaque morphology between cortical and subcortical regions further underscore the heterogeneity of amyloid pathology. These findings highlight the importance of integrated pathoanatomical analysis for improving understanding, diagnosis, and staging of Alzheimer's disease.

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