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Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

Is synaptic loss a unique hallmark of Alzheimer's disease?

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ABSTRACT

Synapses may represent a key nidus for dementia including Alzheimer's disease (AD) pathogenesis. Here we review published studies and present new ideas related to the question of the specificity of synapse loss in AD. Currently, AD is defined by the regional presence of neuritic plaques and neurofibrillary tangles in the brain. The severity of involvement by those pathological hallmarks tends to correlate both with antemortem cognitive status, and also with synapse loss in multiple brain areas. Recent studies from large autopsy series have led to a new standard of excellence with regard to clinical–pathological correlation and to improved comprehension of the numerous brain diseases of the elderly. These studies have provided evidence that it is the rule rather than the exception for brains of aged individuals to demonstrate pathologies (often multiple) other than AD plaques and tangles. For many of these comorbid pathologies, the extent of synapse loss is imperfectly understood but could be substantial. These findings indicate that synapse loss is probably not a hallmark specific to AD but rather a change common to many diseases associated with dementia.

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1. Introduction

Compelling data from many sources support the hypothesis that synaptic changes play a key role in Alzheimer's disease (AD), probably contributing directly to the profound cognitive impairment that is characteristic of the disease. However, there are also key unanswered questions in the field. Here we address the issue of the specificity of synapse loss to AD. We review some of the published data with a focus on human studies. We include figures and photomicrographs to help express how non-AD brain diseases can produce synapse loss that render the understanding of AD-specific changes very challenging. Before addressing the data related to synapse loss in AD and other dementias, it is worth considering some of the recent advancements in the field.

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Nomenclature

AβPs	a-beta plaques
AD	Alzheimer's disease
ADL	activities of daily living
CAA	cerebral amyloid angiopathy
CPC	clinical-pathologic correlation
CVD	cerebrovascular disease
DLB	dementia with Lewy bodies (some studies use "DLBD" to refer to the dementia of DLB)
FTD	frontotemporal dementia (a clinical diagnosis)
FTLD	frontotemporal lobar degeneration (a pathological diagnosis)
HD	Huntington's disease
HS-Aging	hippocampal sclerosis of aging
LB	Lewy body
LBV	Lewy body variant (of Alzheimer's disease)
LN	Lewy neurites
MAPT	microtubule associated protein tau
MCI	mild cognitive impairment (aMCI—amnestic MCI)
nbM	nucleus basalis of Meynert
NCI	no cognitive impairment
NFT	neurofibrillary tangle
NP	neuritic amyloid plaque
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PiD	Pick's disease
PSP	progressive supranuclear palsy
α-SN	alpha-synuclein
TDP-43	TAR-DNA binding protein 43

2. Evolution of clinical-pathologic correlations

The question of whether or not synapse changes in AD correlate with disease severity (i.e. cognitive status) is essentially one of clinical–pathological correlation (CPC). The past decade has seen important research advancements in the area of CPC. These advancements are directly relevant to the current review and bear consideration. In recent years, better quality data and more sophisticated analyses from many different research centers have enabled new insights and more valid research conclusions. These improvements constitute a truly new standard of research excellence. Some of the features that characterize the new standard for research in this area are:

- higher-quality research cohorts incorporating a fuller spectrum of disease;
- longitudinal assessment of patients, rather than only cross-sectional analyses;
- improving clinical & neurocognitive evaluation;
- more universally applied pathological evaluation (new pathologic biomarkers have found evidence for "new" diseases as described below);
- increasingly quantitative assessment of pathological markers with less bias;
- better statistical power due to larger cohorts;
- more variables gathered and factored into quantitative correlation;
- increased focus on the full spectrum of advanced age.

These technical and infrastructural advancements have enabled the field to move past the prior stumbling blocks linked to over-dichotomization (dementia/nondemented, AD/"control"), ignoring comorbid diseases, and a general oversimplification of the concept of brain diseases among the elderly.

As a specific example of how far we have advanced in recent years, it is instructive to compare our level of insights relative to the seminal work in CPC performed by Tomlinson, Blessed, and Roth in the 1960s and early 1970s [1–3]. While these works provided breakthrough new insights at the time, there were also necessary limitations. For example, the research cohorts were relatively young (average age at death ~74 years); specific pathologic markers for AD (tau and Aβ markers) were not yet developed; and there was poor knowledge about frequently seen neurodegenerative disease comorbidities. Coupled with this was the fact that good pathologic markers for α-synuclein and TDP-43 were not available [4,5]. Knowledge of the molecular pathogenesis or markers for frontotemporal lobar degeneration (FLTD) was mostly non-existent. The patients in the classic CPC studies also had cross-sectional (not longitudinal) assessment of cognitive status, not necessarily proximal to death, and there were neither epidemiologic nor community-based cohorts to study to advanced age. The application of advanced statistical approaches with greater statistical power was still awaiting both the mathematical expertise and larger research cohorts so the more sophisticated approaches could pay off. Although the early CPC studies provided key insights, one should not remain tethered to those conclusions. New technology and approaches have enabled new insights with new basic assumptions that now can lead us forward. Among these new insights is the important realization that comorbid pathologies are the rule, rather than the exception, in the aged human brain.

3. Brain pathologies linked to aging: Prevalence and impact on cognitive status

The gold standard for describing the presence and severity of brain disease is neuropathologic evaluation. Pathology can provide insights about disease mechanisms when the molecular pathways are modeled in other experimental systems. However, pathological assessments themselves are cross-sectional (generally seen at autopsy) and relate to the visual manifestation of histochemical or immunohistochemical staining often observed at the end stage of the disease.

3.1. Multiple and comorbid pathologies in aging brain

Dementia is a significant problem worldwide especially in older individuals and a clinical condition that is expanding at a very rapid rate [6]. It consists of a variety of different clinical syndromes including Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), frontotemporal lobar degeneration (FTLD), Huntington's disease (HD), and cerebrovascular disease (CVD). Relative to younger individuals, there are alterations that are observed consistently in the aged human brain, some of which are seen in increased abundance in individuals with dementia. However, there has been substantial focus on less disease-specific brain changes such as myelinopathy, neuroinflammation, glial activation, and the oxidation of proteins, lipids, and nucleic acids [7–10]. One of the major hypotheses of the current review is that synapse changes may belong in this category, i.e. changes seen in multiple different neurodegenerative diseases. Some subtypes of those changes may in the future be proven to be restricted to specific diseases, or the aging process itself, but more work needs to be performed in those areas. By contrast, there are AD-linked brain changes such as Hirano bodies, granulovacuolar degeneration, and cerebral amyloid angiopathy