The Curious Case of Tau: Exploring the Role Tau Protein Plays in Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder marked by progressive memory loss and cognitive decline. Prior research has shown that abnormal tau protein forms neurofibrillary tangles that destabilize microtubules and interfere with synaptic signaling which weakens the neuronal communication needed for learning and memory. Studies also suggest that pathological tau disrupts calcium homeostasis, a process essential for synaptic plasticity and neuronal survival.

However, the specific mechanisms linking tau-induced calcium imbalance to deficits in synaptic signaling and memory remain unclear. There has been little evidence to fill in the gap between disruptions in calcium homeostasis caused by pathological tau and the downstream mechanisms that produce cognitive deficits. This gap is significant because calcium regulation is central to how neurons adapt and store information. Understanding this missing link may reveal new therapeutic targets. This study aims to address that gap by examining how tau-related disruptions in calcium homeostasis contribute to synaptic dysfunction and, ultimately, memory decline in individuals with AD.

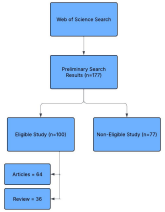
Objectives

- Utilize bibliometric tools to assess the most influential research regarding neurodegenerative diseases.
- Visualize and determine trends by creating figures from relevant bibliometric data.
- Evaluate how tau-induced disruptions in calcium homeostasis alter neuronal stability and intracellular signaling.
- Determine the relationship between tau-mediated synaptic impairment and deficits in memory related neural circuits.

Methods

We utilized a bibliometric literature review to identify the Top-100 most-cited articles in Alzheimer's disease research. We began by systematically searching scientific databases, including Web of Science (WoS), PubMed, and Scopus, for neurodegenerative disease studies and compiling a preliminary list based on citation metrics, relevance, and expert recommendations. Articles meeting our criteria were dissected and analyzed using bibliometric software (R's bibliometrix package, RI Studio) to map author networks, visualize publication patterns, and quantify research impact. The WoS (Web of Science) platform enabled detailed filtering and export of citation data, supporting robust analyses of co-authorship, journal distribution, and research trends. Visualizations were generated to highlight dominant journals and collaboration networks among lead and senior authors. We then conducted focused literature reviews of selected key papers from the Top-100 list, summarizing foundational advances in mechanisms, diagnostics, and therapeutic strategies in Alzheimer's disease. This approach ensured comprehensive coverage of the most influential research and captured evolving trends in neurodegenerative disease scholarship.

Figure 1. WOS methods.



Results

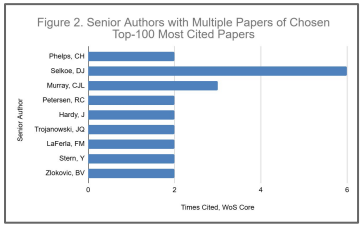


Figure 2. Senior authors with multiple top-100 cited papers. A bar chart which shows senior authors that contributed the highest number of papers to the Top-100 most cited list, a small number of authors dominate the dataset showing that highly cited research in neurodegenerative diseases is usually concentrated among a few leading researchers.

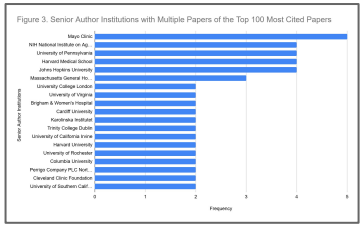


Figure 3. Senior author institutions with multiple top-100 cited papers. A bar chart which shows the institutions that produced the most highly cited papers. Large research universities and national institutes appear most frequently as a result of institutional resources and funding that may influence high-impact research. Top tier research centers drive most of the influential work in neurodegenerative disease research.

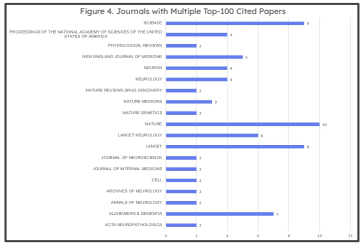


Figure 4. Journals with multiple top-100 cited papers. A bar chart which shows the names of journals that have the Top-100 most cited papers. The journal with the most Top-100 cited papers is *Nature*, a leading multidisciplinary science journal, with *Science*, a world-leading multidisciplinary, research journal, and *Lancet*, a leading medical journal, closely behind.

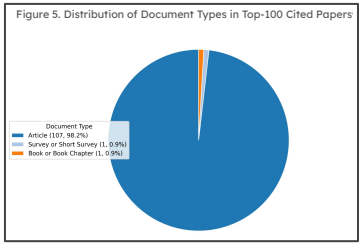


Figure 5. Distribution of document types in top-100 cited papers. A pie chart showing the types of papers included in the Top-100 most cited articles. Almost all of the publications are original research articles with a few being reviews or book chapters, indicating that original studies tend to have the greatest impact in this research area.

Discussion

According to our "Senior Author Institutions with Multiple Papers of Top-100 Most Cited Papers," most of the top cited articles are institutions that are related to health in general. However, it looks like most of research is focused within the journals of "J. Am. Geriatrics Society" and "Alzheimer's & Dementia", with "Alzheimer's & Dementia" being higher, according to the "Journal Impact Factor vs. Frequency in Top-100 Papers." From our research, we have seen how the slow buildup of Aß can lead to tau creation, inflammation, neuronal loss, and synapses not working properly (Selkoe & Hardy, 2016). Changes in the gene that are responsible for the "tau protein" lead to "frontotemporal dementia with parkinsonism", however, with big changes in the tau, it is not enough to cause "the amyloid plaques characteristic of AD" (Hardy & Selkoe, 2002, pp. 353-356). It is important to note that tau, along with beta-amyloid protein, are "biomarkers" that show the "pathology of AD" (Albert et al., 2011, pp. 270-279). Additionally, oligomers of amyloid-ß being soluble and small are mainly responsible for driving Alzheimer's Diseases, along with other neurodegenerative disorders and diseases, with them negatively impacting the plasticity, synaptic signaling, memory, and learning (Haass & Selkoe, 2007). This shows that amyloid-ß and problems in synaptic signaling can have a connection with one another. Moreover, it is suggested by LaFeria that Aß can cause tau pathology and neurodegeneration (Oddo et al, 2003).

Conclusion

Our bibliometric analysis of the top 100 most cited papers in Alzheimer's disease (AD) research revealed several key patterns in scientific influence and mechanistic understanding of AD. Highly cited work is concentrated among a small number of senior authors and top research institutions, emphasizing the importance of collaboration networks and well funded research environments in driving impactful discoveries. Across these important studies, a consistent theme emerged: abnormal tau and beta amyloid interactions disrupt calcium homeostasis, synaptic signaling, and ultimately the neural circuits responsible for memory. The literature strongly pushes forward the idea that soluble beta amyloid oligomers initiate downstream tau pathology, which contributes to inflammation, structural instability, and impaired synaptic plasticity. Together, these findings highlight a converging mechanism in which tau mediated calcium imbalance serves as a link between molecular pathology and cognitive decline. On a broader scale our study underscores how research priorities, which are shaped by influential authors, journals, and institutions guide the scientific community's understanding of AD mechanisms and potential treatments. These patterns suggest that future breakthrough discoveries may emerge from sustained interdisciplinary collaboration, improved data sharing practices, and increased time spent in early stage mechanistic research. The consistent emphasis on calcium dysregulation, synaptic dysfunction, and biomarker development also indicates a direction for therapeutic innovation. For future research, experimental studies should directly test how tau driven calcium imbalance alters specific synaptic pathways, especially those involved in long term potentiation and memory encoding. Future work should also include refining early diagnostic markers that track both beta amyloid and tau pathology simultaneously, improving early detection. Lastly, replicating this analysis across multiple decades or including global data sources could reveal how AD research trends evolve over time and identify unexplored yet high potential scientific directions.

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