BJHBS

Trends and Insights into Glymphatic System Research and Alzheimer's Disease: A Bibliometric Analysis from 2014 to 2023

Raphael L. Olegário,[1,2*] Luciana Lilian L. Martini,[2] Priscila C. Teixeira,[2] Diógenes Diego de C. Bispo,[3] Felipe von Glehn,[1,4] Otávio T. Nóbrega,[1,2] Einstein Francisco Camargos[1,2]

Abstract

Introduction: Over the past decade, research on the glymphatic system has garnered increasing attention within the scientific community. This system, initially explored through animal models and magnetic resonance imaging tracer-based studies, holds potential implications for understanding neurodegenerative diseases, notably Alzheimer's disease. However, a bibliometric analysis of research related to the glymphatic system and Alzheimer's disease is lacking. Objective: Our study aimed to conduct a comprehensive analysis of the existing literature on glymphatic system research, with a particular focus on its intersection with studies of the pathology of Alzheimer's disease. By synthesizing available data, we sought to identify trends, gaps and potential avenues for future research and collaboration in this evolving field. Methods and resources: We utilized statistical techniques to analyze data obtained from the Web of Science Core Collection database. Our methodology encompassed various aspects, including frequency of publication, geographical distribution, citation networks, and thematic analysis of authors' keywords. Results and discussion: Our analysis covered a wide range of publications spanning the last decade and revealed a gradual increase in research output over time. Notably, we observed a significant level of international collaboration, underscoring the global nature of scientific inquiry in this domain. However, disparities in research capacity and collaboration were apparent, particularly among regions with limited resources. Conclusion: Our findings highlight the importance of continued interdisciplinary collaboration and exploration to advance our understanding the function of the glymphatic system and its relevance to neurodegenerative disorders. Addressing disparities in research capacity and fostering global collaboration are essential steps toward developing effective interventions for Alzheimer's disease and related conditions.

Keywords: Glymphatic System, Alzheimer's Disease, Bibliometric Analysis, Neuroscience, Neuroimaging.

1. Programa de Pós-Graduação em Ciências Médicas, Faculdade de Medicina, Universidade de Brasília. Brasília, DF, Brasil.

2. Departamento de Clínica Médica, Centro de Medicina Geriátrica, Hospital Universitário de Brasília. Brasília, DF, Brasil.

3. Unidade de Imagem Diagnóstica, Hospital Universitário de Brasília. Brasília, DF, Brasil.

4. Faculdade de Medicina, Universidade de Brasília. Brasília, DF, Brasil.

*Correspondence address:
E-mail: rlounb@gmail.com
ORCID: https://orcid.org/0000-0001-8931-9533

BJHBS, Rio de Janeiro, 2025;24(1):49-61
DOI: 10.12957/bjhbs.2024.85281
Received on 29/12/2024. Approved on 10/01/2025.

Introduction

In recent years, the glymphatic system (GS) hypothesis, which arose from a series of experiments conducted on animal models,[1–5] has gained significant momentum. Furthermore, magnetic resonance imaging (MRI) tracer-based studies have suggested a human equivalent of the GS in the brain, thus corroborating earlier findings in rodents obtained through the intrathecal administration of gadolinium-based contrast agents6. Despite ongoing debates regarding the validity of this hypothesis,[7,8] numerous studies investigating the waste clearance function of the central nervous system (CNS), including the GS, have been conducted.[9,10]

Recent literature suggests that the GS has significant implications for neurodegenerative diseases such as Alzheimer's disease (AD), in which compromised waste clearance mechanisms play a role in disease progression.[11,12] According to the classic amyloid cascade hypothesis,[13] the accumulation of β-amyloid peptide (Aβ) is an early event in AD pathogenesis. The progression of the disease, including the formation of neurofibrillary tangles containing tau protein, is a consequence of an imbalance between Aβ production and clearance.[14]

Given the growing interest within the neuroscientific community, we conducted a bibliometric analysis to assess the research landscape. With mounting evidence supporting the existence of this system in both animal[15] and human brains[16,17], our aim was to explore the extent to which research on this topic intersects with studies of AD pathology. Moreover, our work could catalyze further exploration and foster collaboration to advance our understanding of neurodegenerative diseases and develop more effective therapeutic interventions.

Previous studies have primarily focused on bibliometric analysis of the GS,[18] while our study explores the correlation between GS research and AD pathology. This distinction is crucial, because it provides novel insights into the intersection of these fields and offers a unique perspective on the relationship between GS function and neurodegenerative diseases.

Methods

Methodological Design and Data Retrieval

Our data retrieval process, conducted in May 2024, involved querying the Web of Science Core Collection (WoSCC) using pre-selected Mesh terms to ensure a comprehensive coverage of the relevant literature. The search query included terms such as "Glymphatic System," "Glymphatic Pathway," "Glymphatic Pathways," "Glymphatic Clearance System," "Meningeal Lymphatic Vessels," "Meningeal Lymphatic Vessel," "Brain Perivascular Spaces," "Virchow-Robin Spaces," and "Virchow-Robin Space", combined with terms related to AD such as "Alzheimer's Diseases," "Alzheimer Diseases," "Alzheimer Dementia," "Alzheimer Type Dementia," "Focal Onset Alzheimer's Disease," "Early Onset Alzheimer Disease," and "Late Onset Alzheimer Disease" (Figure 1). To refine the dataset, we included original journal articles, reviews, and early access publications, focusing on studies published between 2014 and 2023 to capture recent advancements. We excluded articles that did not meet these criteria or were not written in English, as well as conference abstracts, editorials, letters and other non-peer-reviewed materials, thereby ensuring the integrity and scholarly rigor of our analysis. See Supplementary Material for the detailed search strategy.

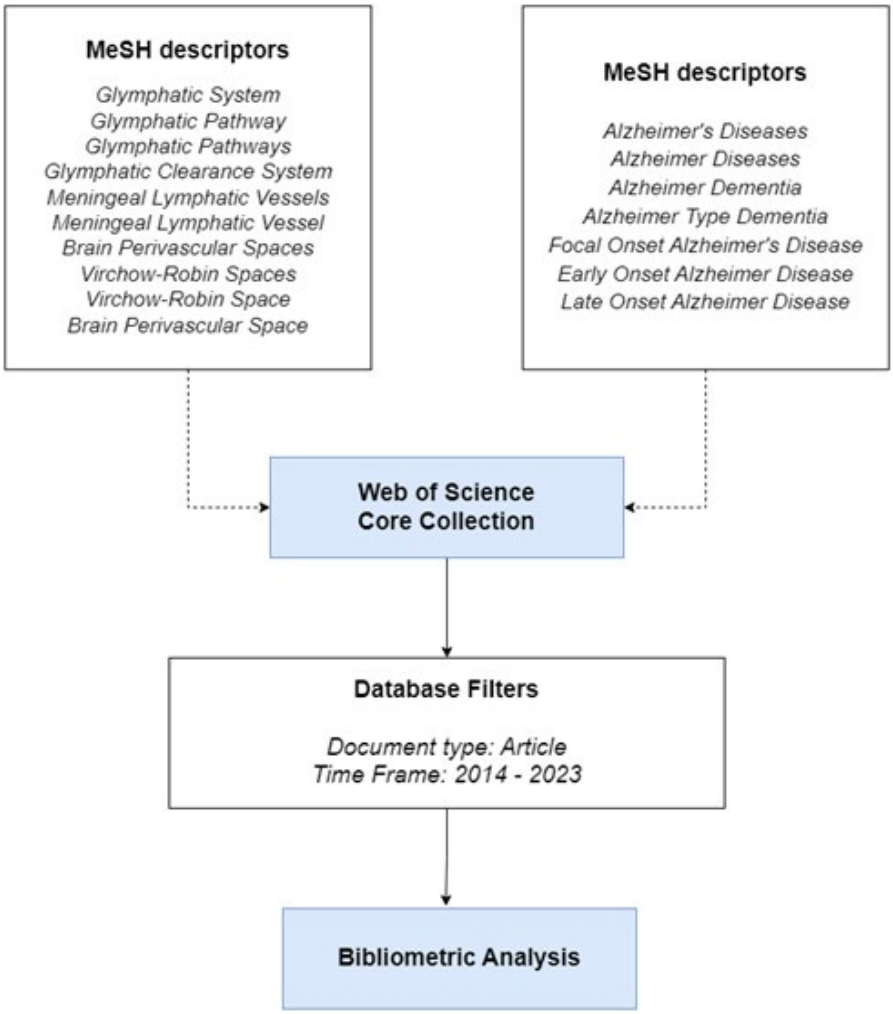

Figure 1. Methodological sequence flowchart.
Source: The authors (2024).

After data extraction, we implemented a filtration process to refine the dataset. This process included the inclusion of specific document types, such as original journal articles, reviews and early access publications, to ensure the integrity and relevance of the analysis. Temporal constraints were applied by focusing on publications from 2014 to 2023, thus capturing recent advancements and trends in the field.

We conducted a multifaceted analysis utilizing algorithms and statistical techniques to explore various dimensions of the dataset. These dimensions included frequency of publication, geographical distribution, institutional affiliations, author contributions, prevalent keywords and citation networks. Through advanced data manipulation, aggregation and clustering, we unveiled underlying patterns, correlations and insights embedded within the dataset.

Data Analysis and Visualization

We began by retrieving data through queries in the WoSCC electronic database by use of relevant search terms and filters. Subsequently, we applied data extraction techniques to collect pertinent metadata, including publication titles, abstracts, authors, affiliations, and citation counts. This raw data was then imported into Biblioshiny,[19] a web-based platform known for its

robust data visualization capabilities and integrated with the RStudio[20] interface for advanced analytical processing.

Within Biblioshiny, we conducted a thorough analysis covering various dataset dimensions, such as frequency of publication, geographic distribution, institutional affiliations, prevalent keywords and citation networks. Employing computational algorithms and statistical methodologies, we manipulated, aggregated, and clustered data to reveal underlying patterns and insights.

To further refine and visualize our findings, we utilized Microsoft Excel 2023 for additional data preprocessing tasks and to create custom graphical representations. These visualizations, along with analytical insights, were synthesized to construct a coherent narrative, elucidating the interconnections between variables and observed trends within the dataset. Ultimately, the synthesized findings, raw data and visualizations were systematically organized and deposited into the Open Science Framework directory (DOI: 10.17605/OSF.IO/6DCU4) to facilitate peer review and knowledge dissemination within the scientific community (available at https://osf.io/6dcu4/).

Results

Outputs

From 2014 to 2023, our analysis covered a significant body of literature, comprising 1,681 documents sourced from 618 distinct publications. These documents involved the contributions of 10,940 authors, indicating extensive collaboration within the research community. The analysis identified 3,734 unique author keywords, providing insights into the breadth and depth of topics explored. International collaboration was prevalent, with 30.81% of the documents involving co-authors from different countries, which highlights the global nature of scholarly collaboration in this domain. On average, each document received approximately 29.84 citations, reflecting the impact of the research output. The annual growth rate of publications stood at -12.86%, demonstrating a dynamic and evolving landscape of research activity. Furthermore, the average age of the documents was 4.42 years, suggesting the relevance and currency of the research literature, with an average of 9.68 co-authors per document.

Annual Scientific Production

Analysis of annual trends reveals a notable progression in research output within the field from 2014 to 2023 (Figure 2). The number of articles published has generally increased over the years, which indicates a growing interest and engagement among researchers. Starting with 103 articles in 2014, the output climbed to 98 in 2015, followed by a slight decrease to 97 in 2016. The upward trajectory resumed in 2017 with 140 articles, continuing with 142 articles in 2018, 155 in 2019, and 188 in 2020. The year 2021 saw a remarkable spike, with 210 articles published, followed by 236 articles in 2022. The highest output was experienced in 2023 with 286 articles.

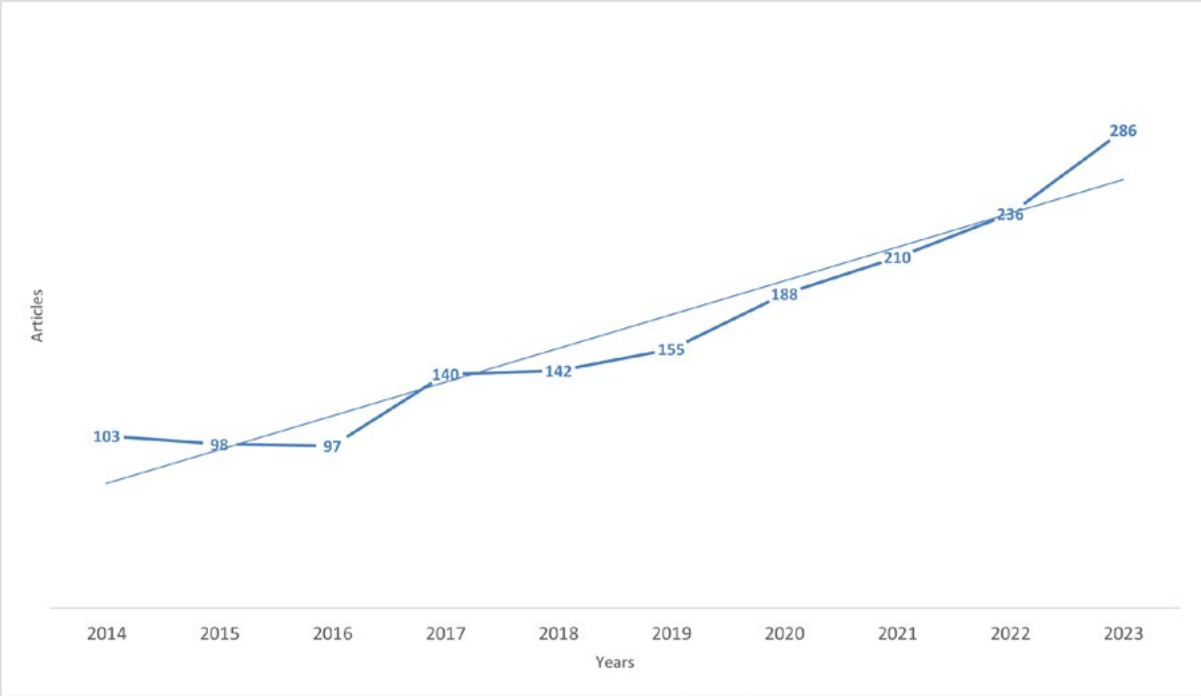

Figure 2. Annual scientific production from 2014 to 2023 as a function of the number of articles published.
Source: The authors (2024).

Citation Report

Based on the citation report obtained directly from WOSCC, we identified the contribution of the publishers to the evolving discourse surrounding the GS and AD (Figure 3). These publications have garnered considerable attention within the neuroscientific community, with a total of 28,158 citing articles identified. After taking into account self-citations, this number decreases slightly to 27,164, indicating the robust influence of the research output beyond its immediate sphere. Notably, researchers have cited these publications 50,140 times, demonstrating the significant impact they have had on advancing knowledge in the field. Excluding self-citations, the total number of citations stands at 43,292, with an average of 29.83 citations per item. Moreover, the H-index, a metric that quantifies the productivity and impact of a researcher's publications, is calculated at 97. This highlights the scholarly significance and influence of research conducted in this field. These statistics underscore the enduring relevance and impact of contributions to this critical area of scientific inquiry.

Most Relevant Affiliations

The analysis of affiliations reveals the institutions that have made significant contributions to research in the field. Leading this list is Columbia University with 153 articles, showcasing its prominent role in the advancement of knowledge in this area. Following closely are Washington University with 144 articles and Zhejiang University with 138 articles, indicating their substantial contributions to the field. The University of Rochester also stands out with 129 articles. Other notable contributors include Boston University with 123 articles, the University of Washington with 113 articles, and the University of Edinburgh with 105 articles. Additionally, institutions such as Oregon Health and Science University, with 104 articles, the University of Copenhagen, with 92 articles, and Rush University, with 91 articles have demonstrated noteworthy involvement. Each of these institutions has significantly contributed to the body

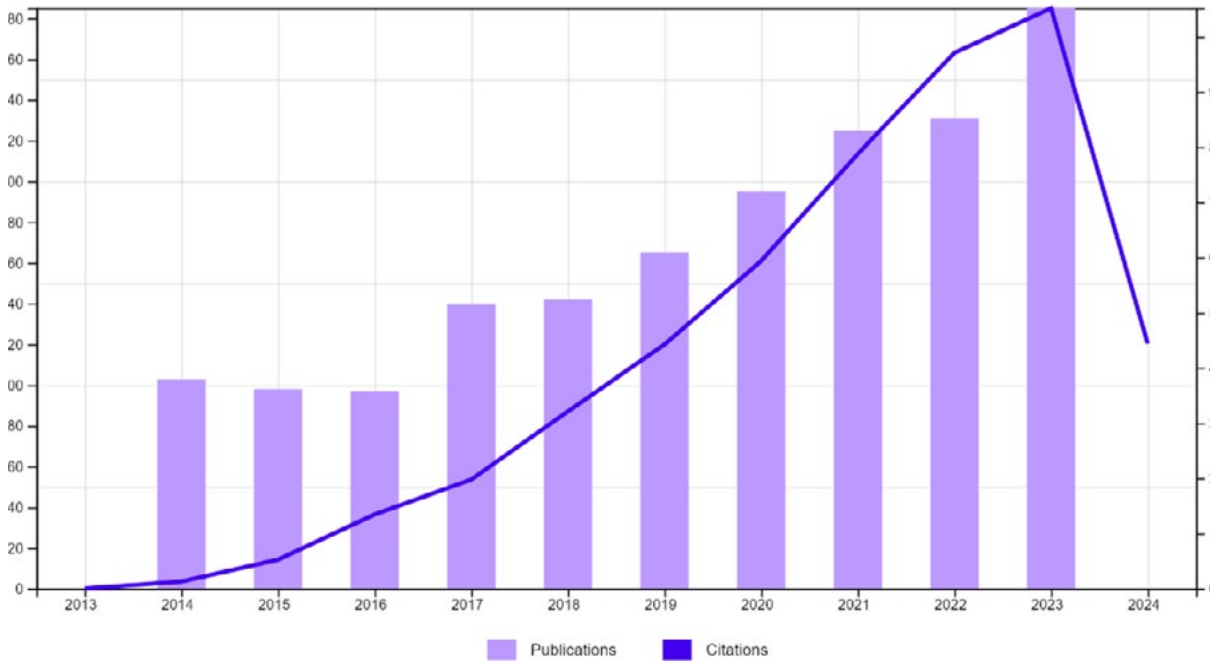

Figure 3. Annual scientific production from 2014 to 2023 as a function of publications and citations.
Source: The authors (2024).

of research. These findings underscore the collaborative efforts of institutions worldwide in advancing our understanding of this critical area of scientific inquiry.

Scientific Production and Impact by Country

The analysis of scientific production and impact in the field by country reveals a comprehensive view of global research efforts and their influence. Leading the list is the United States, with a staggering 3,578 publications, reflecting its profound contribution to advancing knowledge in this area. The United States also leads in citations, with a total citation count of 21,975 and an average of 46.00 citations per article, underscoring its significant influence in the field.

China follows closely with 1,723 publications, demonstrating its substantial engagement in research endeavors related to the topic. China also has a significant citation impact, with 4,825 total citations and an average of 16.60 citations per article, highlighting its emerging role as a major contributor to scientific discourse in this area.

The United Kingdom and Japan also made notable contributions, with the United Kingdom accounting for 527 publications and Japan with 569 publications. The United Kingdom has a total of 2,428 citations and an average of 41.20 citations per article, while Japan has 2,131 citations and an average of 17.50 citations per article. Germany, with 433 publications, has 818 total citations and an average of 13.40 citations per article.

Other notable contributors include France, with 449 publications and 2,148 total citations (35.20 average per article), Italy, with 438 publications and 1,135 total citations (17.20 average per article), and South Korea, with 482 publications and 1,465 total citations (19.00 average per article).

Countries such as the Netherlands, Spain, Canada, Sweden, and Australia also demonstrate significant impact and reach in scientific production and citations, illustrating a robust and

interconnected global scientific community actively contributing to advancements in understanding and addressing neurological disorders such as AD.

World Map of Collaboration by Country

The collaboration network analysis reveals a staggering 245 unique collaborations between countries, underscoring the global reach of research efforts in the field (Figure 4). Among these collaborations, prominent partnerships include those between the USA and China (61 collaborations), the USA and Denmark (45), and the USA and Canada (42). In addition, the United Kingdom has engaged in collaborative research with a multitude of countries, notably Germany (24 collaborations), Canada (23), and Spain (22). Other significant collaborations involve other partnerships of the USA, particularly with the United Kingdom (52 collaborations) and Australia (28). These collaborations highlight the importance of international cooperation in advancing scientific understanding and fostering innovation in the study of neurodegenerative diseases.

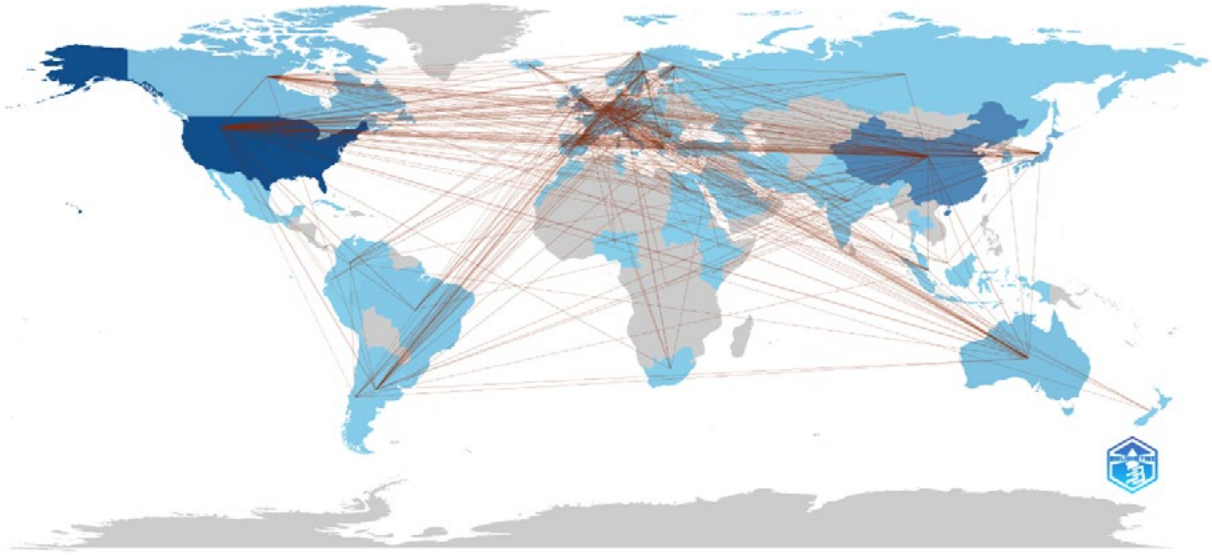

Figure 4. World map of collaboration by country.
Source: The authors (2024).

Co-occurrence network with thematic map (Authors' keywords)

The co-occurrence network analysis based on authors' keywords reveals distinct thematic clusters that contribute to our understanding of the GS and AD (Figure 5). Among the identified clusters, the most prominent include "glymphatic system," "Alzheimer's disease," and "dementia," indicating their pivotal roles in connecting other keywords within the network. Notably, the "perivascular spaces" cluster exhibits dense connections among keywords within this group. In addition, keywords such as "magnetic resonance imaging," "tau" and "aging" demonstrate significant importance in the network structure. Moreover, keywords like "cerebrospinal fluid," "magnetic resonance," and "meningeal lymphatic vessels" remain integral components of the thematic network, contributing to the comprehensive understanding of the etiology and pathophysiology of AD. This analysis provides insights into the interconnectedness of key concepts and themes within the research literature, thus facilitating further exploration and investigation in this critical field.

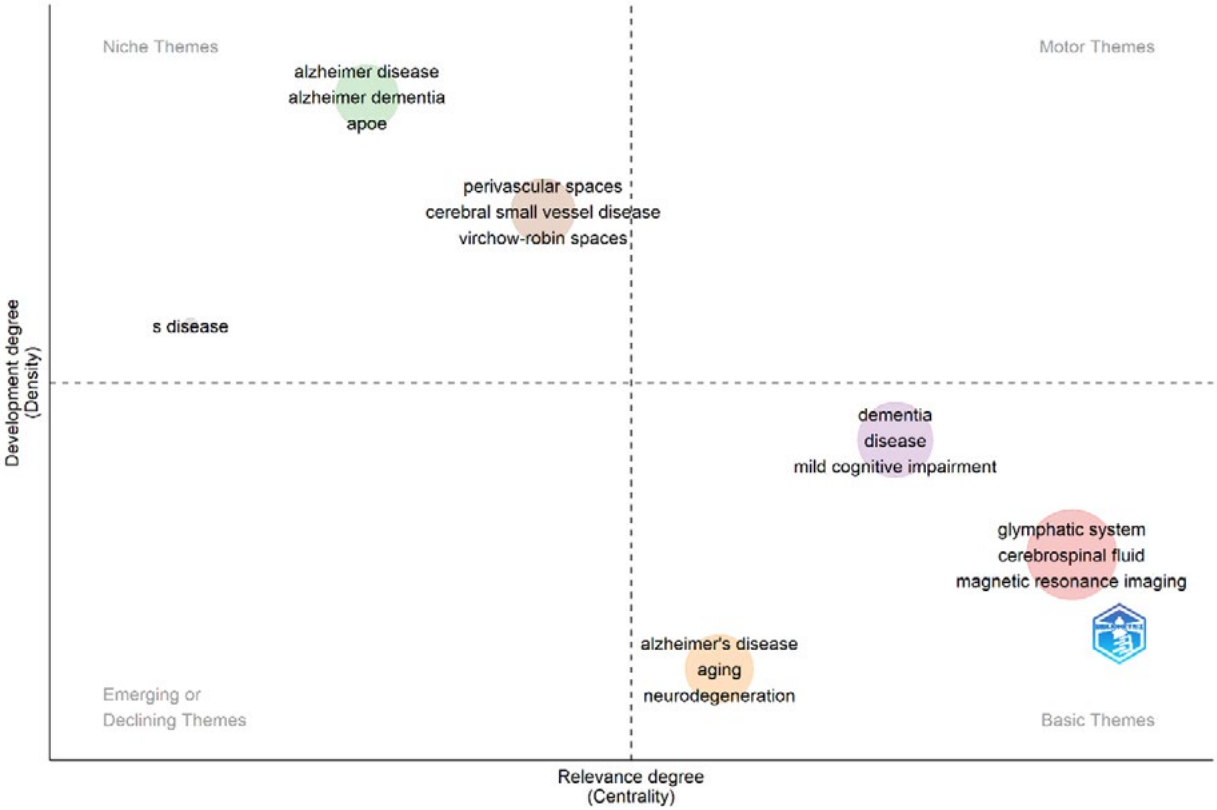

Figure 5. Co-occurrence network with thematic map (Author's keywords).
Source: The authors (2024).

Discussion

General Overview

In recent years, the increase in research efforts has underscored the significance of the GS within the neuroscientific community. Studies over the past decade have elucidated its role as a kind of "lymphatic system" in clearing metabolic waste and regulating water transport in the brain and the CNS21. While these findings are based on experiments conducted on animal models and studies utilizing MRI tracer-based techniques, the precise significance of the GS in waste clearance mechanisms within the CNS remains a topic of ongoing debate. This uncertainty is compounded by variations in imaging protocols,[22] including contrast agent injection protocols,[23] acquisition time points for dynamic contrast-enhanced scanning, and the specific anatomical structures targeted for measuring glymphatic flow.[24]

Our bibliometric analysis aimed to synthesize the research landscape, in particular the nexus between GS research and studies of AD pathology. However, despite our efforts, we encountered challenges in delineating clear correlations and drawing definitive conclusions. Methodologically, while we employed statistical techniques, the limitations of relying on the selected electronic database became apparent. The data retrieved, while extensive, may only partially capture the breadth and depth of research in this complex domain. Therefore, the interpretation of the findings is subject to caution.

Annual trends revealed a steady increase in research output, yet questions persist regarding the quality and rigor of these studies. Citation analysis, while indicating impact, also rais-

es concerns about self-citations and potential biases in citation practices. Furthermore, our analysis revealed an almost complete absence of low-income countries at the forefront of GS studies, despite the estimated higher number of individuals with dementia in such places. This disparity highlights issues of accessibility and resource allocation in global research endeavors.

The collaboration network analysis hinted at global cooperation in GS and AD research but also exposed gaps and disparities in research collaboration, particularly in regions with limited resources or restricted access to cutting-edge technology. The disparity in research capacity between low and high-resource countries, coupled with the prevailing global trend in health research, is a matter of concern. Therefore, the necessity for research collaboration between these two groups is crucial.[25] Thematic analysis of author's keywords provided some insights but also highlighted the fragmentary nature of research efforts, comprising disparate clusters that lacked cohesive integration.

Furthermore, it has been speculated that impaired GS function contributes to the progression of neurodegenerative disorders and emerges as a pivotal factor in their etiology.[26] While research linking the GS to AD is notable, the exploration of potential influences from other pathological processes, such as Parkinson's disease and other forms of dementia, remains limited.[27] This observation underscores the need for further investigation to broaden our understanding of the intricate interplay between the GS function and various neurological disorders.

Implications for clinical practice and clinical research

The discovery of the GS carries profound implications for both clinical practice and research in AD, which is characterized by the accumulation of toxic protein aggregates, such as Aβ plaques and tau tangles, within the brain.[28] Importantly, the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) act as significant impediments to the clearance of these pathological proteins, exacerbating the progression of the disease14. Understanding the pivotal role of the GS in waste clearance from the brain opens avenues for innovative strategies to enhance drug delivery and facilitate the removal of toxic proteins associated with Alzheimer's.[29] Leveraging this system as a pathway for drug administration could significantly enhance the efficacy of therapeutics by bypassing traditional barriers that hinder their access to the brain. Furthermore, in clinical practice, the adoption of glymphatic-targeted therapies could transform the treatment landscape for Alzheimer's patients, offering more effective and precisely targeted treatment options that could lead to improved outcomes and enhanced quality of life.

As individuals age, the natural decline in glymphatic flow and clearance activity becomes increasingly evident, contributing to various health issues30. Research indicates a significant association between this decline and disrupted sleep patterns, such as insomnia and sleep apnea.[31] In addition, neurological disorders marked by cognitive decline, such as AD and other forms of dementia, have been linked to impaired glymphatic function.[14] Understanding these associations can have profound implications for clinical medical practice. Interventions to preserve or enhance the glymphatic function may offer novel therapeutic avenues for addressing sleep disorders and cognitive decline in aging populations. Moreover, monitoring glymphatic activity could potentially serve as a biomarker for early detection and monitoring of neurological diseases, facilitating timely interventions and improving patient outcomes.

Chronic nighttime insomnia and heightened daytime sleepiness are hallmark symptoms of AD[32,33] and are often correlated with the severity of cognitive decline. However, the exact

contribution of disrupted sleep patterns to either triggering the onset of AD or emerging as symptomatic of the disease remains elusive and warrants further inquiry, particularly in clinical research settings.[34] Notably, levels of soluble Aβ in the brain's interstitial fluid fluctuate daily in conjunction with the natural sleep-wake cycle.[35] Furthermore, sleep deprivation has been shown to markedly increase susceptibility to Aβ plaque formation, as observed in studies involving both animal models and human subjects.[36,37] Understanding the relationship between sleep disturbances and AD pathogenesis is crucial for developing effective therapeutic strategies. Insights into how sleep quality influences the accumulation of pathological proteins in the brain can inform interventions to mitigate the risk of AD development or slow its progression. Moreover, unraveling the mechanisms underlying the link between sleep deprivation and Aβ plaque formation could lead to novel approaches for preventing or treating AD-related cognitive decline.

Measuring the function of the GS in clinical settings poses significant challenges, particularly due to the limitations inherent in MRI technology. MRI provides a non-invasive method to visualize and potentially quantify the dynamics of fluid movement within the brain,[38] which is crucial for assessing the GS. However, the resolution of this technology may not fully capture the microscale fluid movements that are essential for a detailed understanding of glymphatic functionality. Moreover, the slow and subtle nature of glymphatic flow, combined with the potential discrepancies introduced by contrast agents used in some MRI studies, complicates the accurate detection and quantification of glymphatic activity.

Furthermore, the variability in physiological conditions among individuals, such as differences in age, circadian rhythms and neurological health, adds another layer of complexity to the standardization of measurement protocols across diverse patient populations. Analyzing MRI data to correlate fluid dynamics with glymphatic function requires sophisticated techniques and models, posing a barrier in routine clinical practice.[39] Despite these challenges, MRI remains one of the most promising tools for the study of the GS due to its non-invasive nature and the amount of information it can provide. Continued research and technological developments are expected to enhance the sensitivity and specificity of MRI techniques for more effective glymphatic assessment in the future.

Recommendations for Future Research

Several key areas warrant further exploration in the field of GS research and its implications for AD. Firstly, future studies should focus on elucidating the mechanistic underpinnings of the relationship between disrupted glymphatic function and AD pathogenesis. This includes studying the molecular pathways involved in regulating glymphatic flow and clearance activity, as well as how alterations in these processes contribute to the accumulation of pathological proteins such as Aβ and tau.

Furthermore, conducting longitudinal studies to understand the temporal dynamics of glymphatic dysfunction in the context of AD and other neurodegenerative diseases is crucial. These studies, which would involve tracking glymphatic activity in individuals at different stages of cognitive decline, could offer valuable insights into the role of glymphatic dysfunction as a predictive biomarker for AD onset and progression. In addition, exploration of the potential therapeutic interventions that modulate glymphatic function to prevent or decelerate the progression of AD could have a significant impact on the field.

In addition, given the complex interplay between the glymphatic function, sleep disturbances and cognitive decline, interdisciplinary approaches involving neurology, sleep medicine and geriatrics are essential for advancing our understanding of these relationships. Collaborative efforts between researchers from different disciplines can facilitate the development of comprehensive treatment strategies that target both glymphatic dysfunction and sleep disturbances in AD patients.

Among these areas, neuropsychology plays a critical role. Analyzing cognitive abilities through comprehensive cognitive testing can significantly contribute to tracking, identifying and deepening our understanding of the relationships between the GS and AD.[40,41] The application of scales and neuropsychological tests has proven instrumental in investigating cognitive declines and their progression.

Expanding on these recommendations, future research should also explore the impact of lifestyle interventions, such as exercise and dietary modifications, on glymphatic function and AD pathogenesis. Research on how lifestyle factors influence glymphatic activity and cognitive outcomes could provide valuable insights into the development of personalized preventive strategies for individuals at risk of AD.

In addition, the role of advanced neuroimaging techniques, such as MRI and positron emission tomography (PET), is crucial in providing non-invasive methods for assessing the glymphatic function *in vivo*. Integrating these imaging modalities with biomarker analyses and clinical assessments could enhance our ability to diagnose and monitor glymphatic dysfunction in AD patients, ultimately informing the development and evaluation of targeted therapeutic interventions.

Conclusion

Our study sheds light on the evolving landscape of glymphatic system research and its relevance to Alzheimer's disease. International collaboration and key publications are driving advancements in understanding AD pathology. Future research should elucidate the link between disrupted glymphatic function, sleep disturbances and the progression of AD. Interdisciplinary approaches are crucial for the development of effective treatment strategies. This analysis informs future research directions and underscores the importance of addressing neurodegenerative diseases.

Acknowledgements

We gratefully acknowledge the financial support provided by the Coordination for the Improvement of Higher Education Personnel (CAPES), Brazil (Grant No. 88887.841787/2023-00), the Foundation for Research Support of the Federal District (FAPDF), Brazil (Project No. 00193-00002602/2022-69, Grant No. #623/2022), and the Foundation for Scientific and Technological Enterprises (FINATEC), Brazil (Notice DPG/UnB 005/2024).

Conflict of interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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