Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Visualising the Knowledge Structure of Microglia in Alzheimer's Disease: A CiteSpace Analysis

Qi Wang[1], Xiuchu Zhang[2], Delong Wang[3], Xinyu Jiang[2], Yanyan Zhou[1], Te Zhang[4], Xueying Yang[5], Li Liu[6], Quan Li[1]

[1]Basic Theory of Traditional Chinese Medicine, College of Basic Medicine, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, 150040, People's Republic of China; [2]College of Basic Medicine, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, 150040, People's Republic of China; [3]Key Laboratory of Neurobiology of Acupuncture and Moxibustion Clinical Encephalopathy, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, 150001, People's Republic of China; [4]Department of Fourth Therapy, First Specialized Hospital of Harbin, Harbin, 150000, People's Republic of China; [5]Department of Traditional Chinese Medicine, Harbin First Specialized Hospital, Harbin, 150000, People's Republic of China; [6]Department of Cardiology, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, 150040, People's Republic of China

Correspondence: Li Liu, Department of Cardiology, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, 26 Heping Road, Xiangfang District, Harbin, 150040, People's Republic of China, Tel +86 0451-82111401, Email liuli6913@21cn.com; Quan Li, Department of Basic Theory of Chinese Medicine, Heilongjiang University of Chinese Medicine, No. 24 Heping Road, Xiangfang District, Harbin, Heilongjiang, 150040, People's Republic of China, Tel +86 0451-82195947, Email zyylq78@126.com

Purpose: Alzheimer's disease (AD) is a growing global health burden, yet effective therapies remain elusive. Microglia—the brain's resident immune cells—have emerged as key players in AD, capable of both neuroprotection and neurotoxicity. To elucidate research progress and gaps, we conducted a bibliometric analysis of global studies on "microglia and AD" from 2010 to 2025, highlighting advances beyond prior reviews.

Methods: We searched the Web of Science Core Collection for relevant publications (2010–2025). After screening and deduplication, 12,275 records were analysed with CiteSpace 6.2.R4 to generate co-citation networks, keyword clusters, citation-burst timelines, and collaboration maps at national, institutional, and author levels.

Results: Annual output rose markedly, peaking in 2022. The United States and China led the field; Harvard University, the University of California System, and the Chinese Academy of Sciences were the most prolific institutions. Influential authors included Holtzman, Heneka, Zetterberg, and Colonna. Co-citation analysis revealed three dominant knowledge clusters: microglial activation, TREM2-mediated immune responses, and neuroinflammation. Keyword evolution showed growing attention to TREM2 variants, NLRP3 inflammasome, single-cell omics, and novel imaging techniques, reflecting a shift toward microglial heterogeneity and translational research.

Conclusion: Microglia occupy a central position in AD pathogenesis through intertwined molecular pathways and dynamic functional states. Future work should refine subtype-specific roles, integrate peripheral–central immune interactions, and accelerate the translation of mechanistic insights into targeted interventions. This bibliometric overview maps collaboration patterns and emerging themes, providing a strategic guide for researchers aiming to advance microglia-focused AD therapeutics.

Keywords: microglia, Alzheimer's disease, neuroinflammation, bibliometric analysis, CiteSpace, collaboration network

Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder primarily characterized by clinical symptoms such as cognitive impairment, memory decline, and abnormal behaviors.[1,2] At present, AD has become a major public health challenge in the context of global aging, imposing a substantial burden on patients, their families, and healthcare resources worldwide.[3] Over the past few decades, considerable progress has been made in exploring the pathophysiological mechanisms of AD, especially regarding the traditional pathological hypotheses of β-amyloid (Aβ) deposition and abnormal phosphorylation of Tau protein.[4,5] However, the core mechanisms leading to neuronal dysfunction and progressive cognitive decline remain to be fully elucidated.[6]

Received: 7 February 2025
Accepted: 14 August 2025
Published: 17 September 2025

As research has advanced, the perspective of neuroimmunology has gradually entered the mainstream of this field. Microglia, the resident immune cells of the central nervous system (CNS), are regarded as "frontline defenders" that maintain neuronal homeostasis and respond to brain damage.[7,8] Early studies focused largely on the phagocytosis and clearance of Aβ by microglia, suggesting certain neuroprotective potential.[9] However, subsequent work indicated that, if microglia become overactivated or functionally dysregulated, they may release large quantities of inflammatory factors, exacerbating neuronal injury and synaptic degeneration.[10] This dual nature of "protection vs damage" makes microglia a pivotal variable in AD pathology. Moreover, recent multi-omics technologies (eg, single-cell transcriptomics, spatial omics) have further revealed the heterogeneity of microglial subpopulations and their dynamic roles in AD progression.[11,12]

Meanwhile, attention has gradually turned to specific molecular pathways and regulatory mechanisms of microglia in AD. For instance, TREM2 gene variants have been shown to be significantly associated with the risk of sporadic AD;[13] mutant TREM2 can affect the immune phagocytosis and migration capacity of microglia.[14] Additionally, activation or inhibition of the NLRP3 inflammasome has been demonstrated in multiple in vitro and in vivo models to modulate the degree of neuroinflammation and disease progression.[15] Furthermore, novel molecular or cellular therapies—such as monoclonal antibodies, immune-regulating small molecules, or gene editing technologies—have begun to exhibit potential for intervention in the preclinical and basic research stages.[16] Nevertheless, considerable limitations and challenges remain, including potential off-target effects, difficulties in delivering therapies across the blood–brain barrier (BBB), variable patient responses and the complex interplay between microglial activation states and stages of disease progression (Supplement Figure 1).

It is noteworthy that there is no unified understanding of the role of microglia during the early, middle, and late stages of AD. Some researchers contend that microglial functional decline causes inefficient clearance of Aβ, thereby accelerating disease progression; others suggest that chronic or excessive inflammatory responses significantly impair synaptic plasticity and cognitive function.[17] At the same time, from a global research collaboration standpoint, AD-related studies show a pattern of participation by multiple countries, institutions, and disciplines, with literature output and academic impact steadily rising over the past decade 131313. Systematically organizing this research surge and clarifying the key issues and future directions in the field are crucial for advancing both basic science and clinical translation.

Against this background, this study adopts bibliometric and visualization methods (using tools such as CiteSpace) to systematically review and quantitatively analyze the global research status and hot topics concerning "microglia and Alzheimer's disease". On the one hand, we employ multiple perspectives—annual publication trends, collaboration networks, keyword and co-citation clustering—to reveal the knowledge structure and evolutionary patterns of the field. On the other hand, by identifying highly cited and burst-detected references, we explore potential critical frontiers and future directions in the interplay between microglial immune functions and AD pathological mechanisms. We hope that this study offers a comprehensive literature overview for researchers newly entering the field, helps existing investigators summarize progress and seek breakthroughs, and provides substantial reference material for subsequent exploration of AD pathogenesis and the development of intervention strategies from a multidisciplinary perspective.

Method

Data Sources and Retrieval Strategy

Data for this study were obtained from the Web of Science (WoS) Core Collection database, covering the period from 1 January 2010 to 1 January 2025. To ensure a comprehensive collection of documents on "microglia and AD", the following retrieval strategy was applied.

The "Topic" field in WoS (ie TS=) was used to search within the title, abstract, author keywords and KeyWords Plus fields of each article, thereby improving both the hit rate and coverage. Various spellings and expressions of "microglia", along with "AD" and its common abbreviations and variants, were considered to maximise the retrieval scope. The final search query was as follows:

TS=((microglia OR "micro-glia" OR "micro glia*" OR "microglial cell*" OR "microglial activation" OR "microglial proliferation" OR "microglial dysfunction") AND ("Alzheimer's disease" OR "Alzheimer disease" OR "Alzheimers disease" OR Alzheimer* OR AD)).

Exporting and Screening

Based on the search query, a total of 12,313 relevant records were retrieved from the WoS database. The "Analyse Results" and "Refine Results" functions in WoS were used to restrict the language to Chinese or English, excluding publications in other languages. All retrieved records were exported locally, and duplicate entries were removed using CiteSpace. After screening and deduplication, 12,275 unique references were retained for further analysis.

Data Analysis and Visualisation

The final set of 12,275 references was subjected to visualisation analysis. All statistical and visualisation tasks were performed using CiteSpace version 6.2.R4. The protocol was registered: https://doi.org/10.17605/OSF.IO/KN35U

Results

Annual Publication Trends

As shown in Figure 1, the annual number of publications between 2010 and 2025 exhibits a clear upward trend, reflecting sustained interest in the relationship between "microglia and AD" within the academic community.

Initial Exploration Stage (2010–2014): The number of publications was relatively low but increased steadily, suggesting an emerging awareness of microglial roles in AD.

Rapid Growth Stage (2015–2019): A pronounced increase occurred, especially in 2016 and 2017, with annual outputs exceeding 600 and 700, respectively, indicating intensified research focus on neuroinflammatory mechanisms involving microglia.

Research Peak (2020–2022): Growth accelerated markedly, peaking in 2022 with over 1300 publications, highlighting breakthrough interest driven by advances in single-cell omics, clinical translation and interdisciplinary collaboration.

Steady High-Level Stage (2023–2024): The annual publication volume remained high (around 1300 per year), reflecting sustained academic and clinical attention.

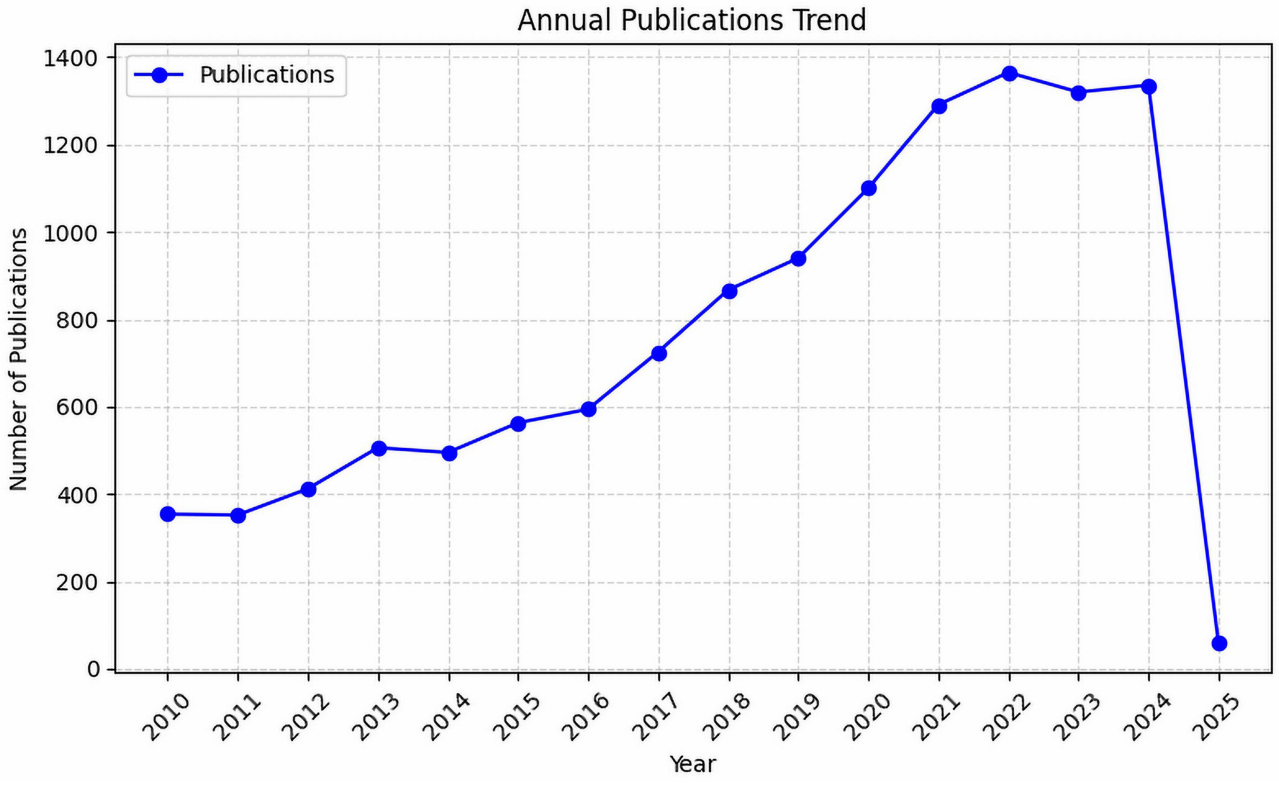

Figure 1 Annual publications from 2010 to 2025.

Incomplete Data (2025): Fewer than 100 papers were available due to early retrieval timing, resulting in partial data for the year.

National and Institutional Collaboration Networks

National Collaboration Network

As shown in Figure 2, each node's size and colour represent the publication volume and time distribution, respectively, whereas the connecting lines represent co-authorship or collaborative relationships between countries. Supplement Figure 2 presents the map of national cooperation.

The main contributing countries are the US and China. Their larger node sizes indicate they produce the most publications in this field and frequently exhibit higher centrality, functioning as "bridges" or "hubs" within the network. Other countries with substantial publication outputs include the UK, Germany, Japan, Canada and France, which have formed a pattern of joint participation across Europe, Asia and North America. The strong connection between the US and China suggests close cooperation and a high rate of international co-authorship.

European countries, such as the UK, Germany, France, Italy and the Netherlands, also demonstrate strong regional collaboration. In the Asia–Pacific region, beyond China, South Korea and India maintain moderate-scale networks, reflecting the emergence of new contributors in this research domain.

The colours of each node ring, from inner to outer, indicate the temporal distribution of publications; several countries have been active since around 2010, and their contribution has continued to grow over the past 5 years.

Although overall connectivity in the collaboration network is relatively high, regional "cluster" phenomena remain evident, highlighting the need for enhanced cross-regional collaboration.

Institutional Collaboration Network

Figure 3 illustrates the collaboration network among major research institutions in the field. Node size reflects an institution's publication volume or citation count, whereas the ring colour indicates the time distribution of publication activity. The following summary is based on the main nodes observed:

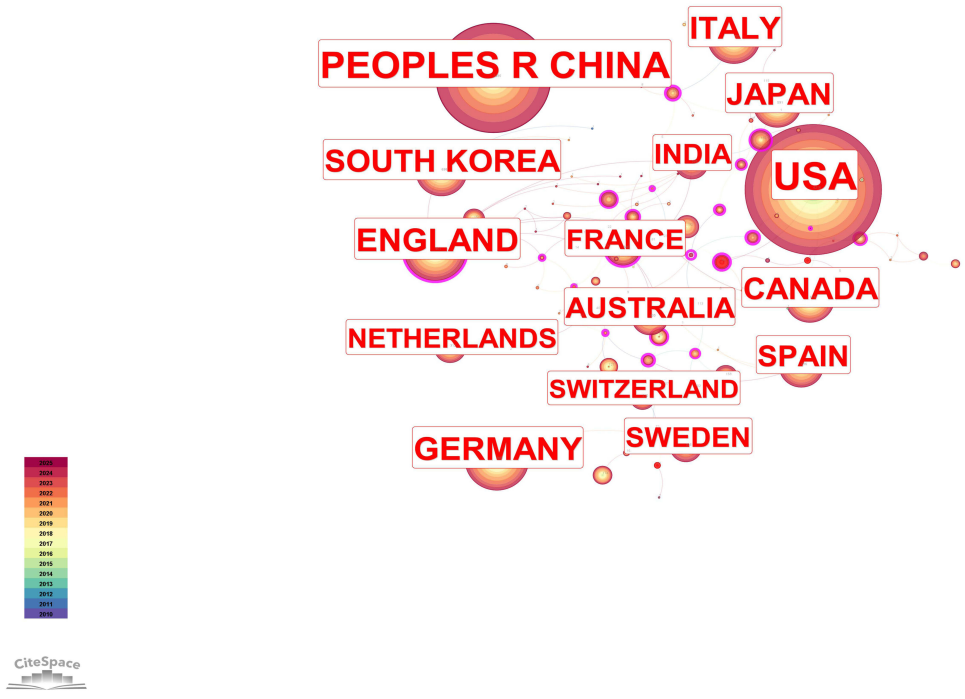

Figure 2 National collaboration network.

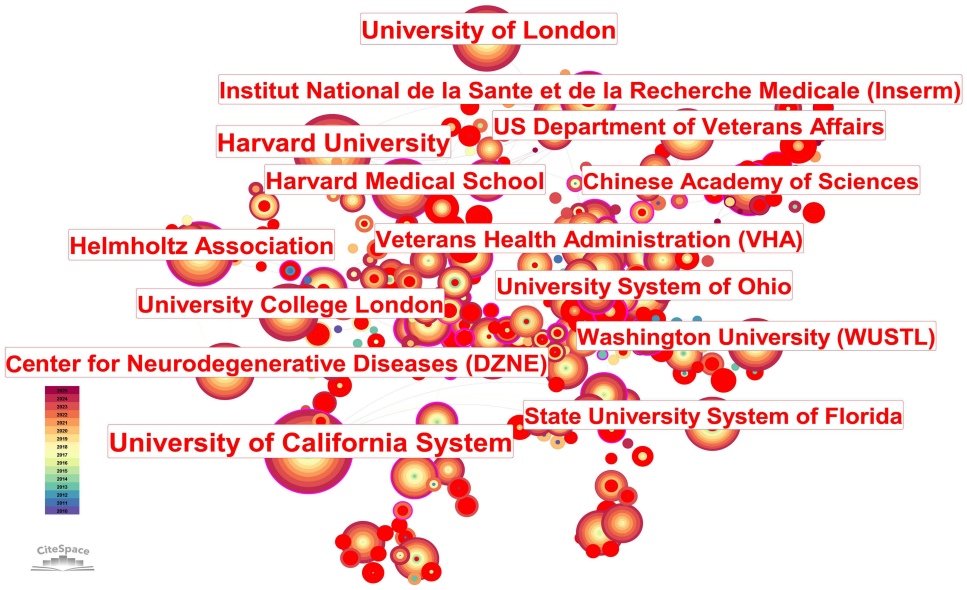

Figure 3 Institutional collaboration network.

Leading institutions include Harvard University, the University of California System, the Chinese Academy of Sciences and the University of London, all of which demonstrate significant international influence.

Collaborative relationships are primarily driven by prominent US universities and European research centres, with extensive cross-border interactions, particularly between US, European and Chinese institutions.

Specialised neurodegenerative research centres, such as Germany's DZNE, also emerge as critical nodes, underscoring the importance of focused institutions in facilitating targeted AD research.

Author Collaboration Network Analysis

Figure 4 presents active authors and their co-authorship relationships in the field of "microglia and AD". Node size generally reflects an author's publication volume or citation frequency, node colour indicates the author's active research period and lines represent co-authorship links. The analysis reveals the following:

Core authors include Colonna, Holtzman, Heneka, Haass and Bennett, all noted for high publication outputs and influential studies on TREM2 signalling pathways, Tau protein pathology and Aβ clearance.

Authors are clustered into distinct but interconnected research groups, reflecting strong cross-institutional and interdisciplinary collaboration, particularly evident in topics related to neuroinflammation and immune microenvironment regulation.

As shown in Table 1, Holtzman ranks first with 72 publications. Heneka exhibits a strong citation burst between 2020 and 2025, indicating growing recognition of his work. Zetterberg, Bennett and Haass show recent increases in citation frequency, underscoring their influential recent contributions to the field.

Supplement Figure 3 reveals the seven major keyword clusters of "microglia-Alzheimer's disease" research and their corresponding relationships with core authors in the form of a visual network, further highlighting the multidisciplinary intersection and theme evolution trend in this field.

#0 neurodegenerative diseases (rose-red diamond) is located in the center of the network, gathering high-frequency words such as "Alzheimer's disease, Parkinson's disease, oxidative stress, NF-κB", forming the backbone connecting the remaining clusters; authors such as Rivest S. can be seen next to the node, indicating its bridge role in neuroimmunology research.

#1 reactive astrocyte (lemon yellow) focuses on concepts such as "activation, inflammation, microglia-astrocyte crosstalk", showing that astrocyte activation has become an important parallel direction of microglial research.

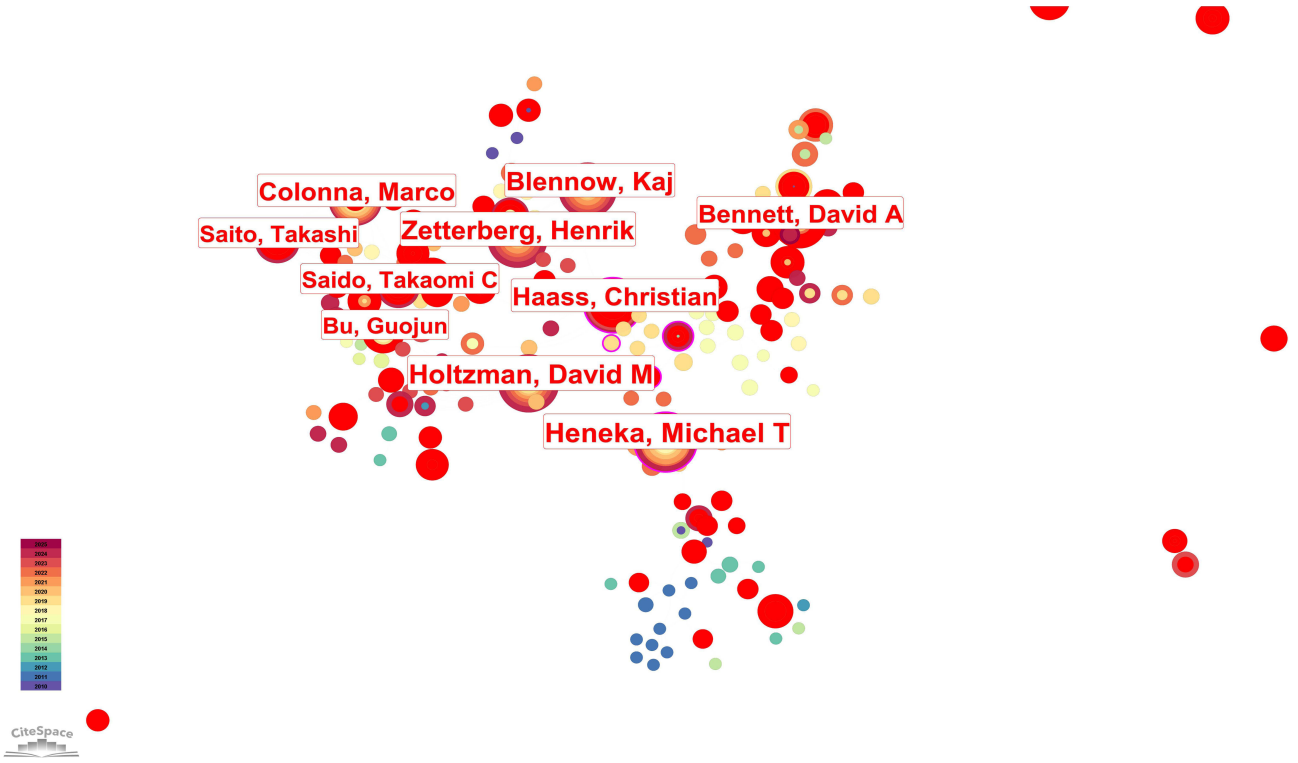

Figure 4 Author collaboration network analysis.

#2 transgenic mice (light green diamond) revolve around "microglial activation, amyloid β, mouse model", and annotates highly productive scholars such as Heneka MT and Saito T, indicating that transgenic animal models are still the core technical platform for mechanism exploration.

#3 soluble TREM2 (turquoise) links keywords such as "dementia, APOE, tau, cerebrospinal fluid", and is accompanied by authors such as Zetterberg H, Haass C, and Holtzman DM, reflecting the hot interweaving of TREM2-AD humoral markers and genetic susceptibility.

#4 synaptic plasticity (sky blue) keywords include "long-term potentiation, cognitive deficits, neurotrophic factor", highlighting the research trend of impaired synaptic plasticity and cognitive decline.

#5 cell-derived extracellular vesicle (lavender) links "pluripotent stem cells, mesenchymal stem cells, microglia-like cells", etc., pointing to the emerging application of stem cell-exosomes in inflammation regulation and regenerative therapy.

Table 1 Top 10 Authors by Publication Volume/Citation Frequency

Ranking	Author	Publication/Citation Initiation	Frequency	Burst	Begin–End
1	Holtzman, David M	2015	72	0	—
2	Heneka, Michael T	2020	66	2.84	2020–2025
3	Zetterberg, Henrik	2019	61	5.08	2021–2025
4	Bennett, David A	2019	59	3.82	2023–2025
5	Haass, Christian	2016	54	5.2	2023–2025
6	Blennow, Kaj	2016	54	3.5	2021–2025
7	Colonna, Marco	2015	51	6.38	2015–2020
8	Saito, Takashi	2019	38	5.26	2023–2025
9	Saido, Takaomi C	2019	37	5.26	2019–2023
10	Bu, Guojun	2015	31	3.92	2022–2023

#6 gut microbiota (pink ellipsoid) surrounds "nervous system, chain fatty acids, complement", showing that the gut-brain axis and microbial metabolites have become the frontier of interdisciplinary research.

Co-Citation Analysis of References

Co-Citation Network Structure

Figure 5 illustrates the co-citation network of references.[3,13,18–48] Each node represents a paper, with node size indicating citation frequency or weight, and colours - from dark to light or from inner to outer rings - showing the chronological order of publication. Major thematic clusters include "microglia activation", "neuroinflammation in AD" and "TREM2 and immune response", highlighting distinct yet interconnected research domains. Foundational papers (eg Butovsky;[49] Keren-Shaul[47]) serve as anchors within clusters, indicating their key role in shaping the current understanding of the field.

Timeline View

Figure 6 Timeline view of the co-citation network.[3,13,18–48] Nodes are key references, sized by citation frequency and coloured by publication year (legend, lower-left). Superscript Arabic numerals correspond to the reference list.

Early stage (2010–2012). The initial stage of research focused on the basic theory of neuroinflammation and the mechanism of Aβ clearance. Representative papers include Heneka[33] and Guerreiro.[30]

Middle stage (2013–2017). The "diversification" stage saw the emergence of hotspots such as TREM2 mutation, Tau protein pathology and NLRP3 inflammasome; highly cited papers such as Keren-Shaul,[47] Liddelow,[37] and Wang[24] laid a new framework for immune imbalance and synaptic damage.

Recent stage (2018–2025). With the application of cutting-edge technologies such as single-cell transcriptomics and CRISPR/Cas9, the research focus has shifted to microglial heterogeneity and precise intervention: Hansen,[45] Zhou,[40] Leng[50] and other literature show that microglial subtype-specific functions and peripheral-central immune interactions are rapidly becoming a core issue.

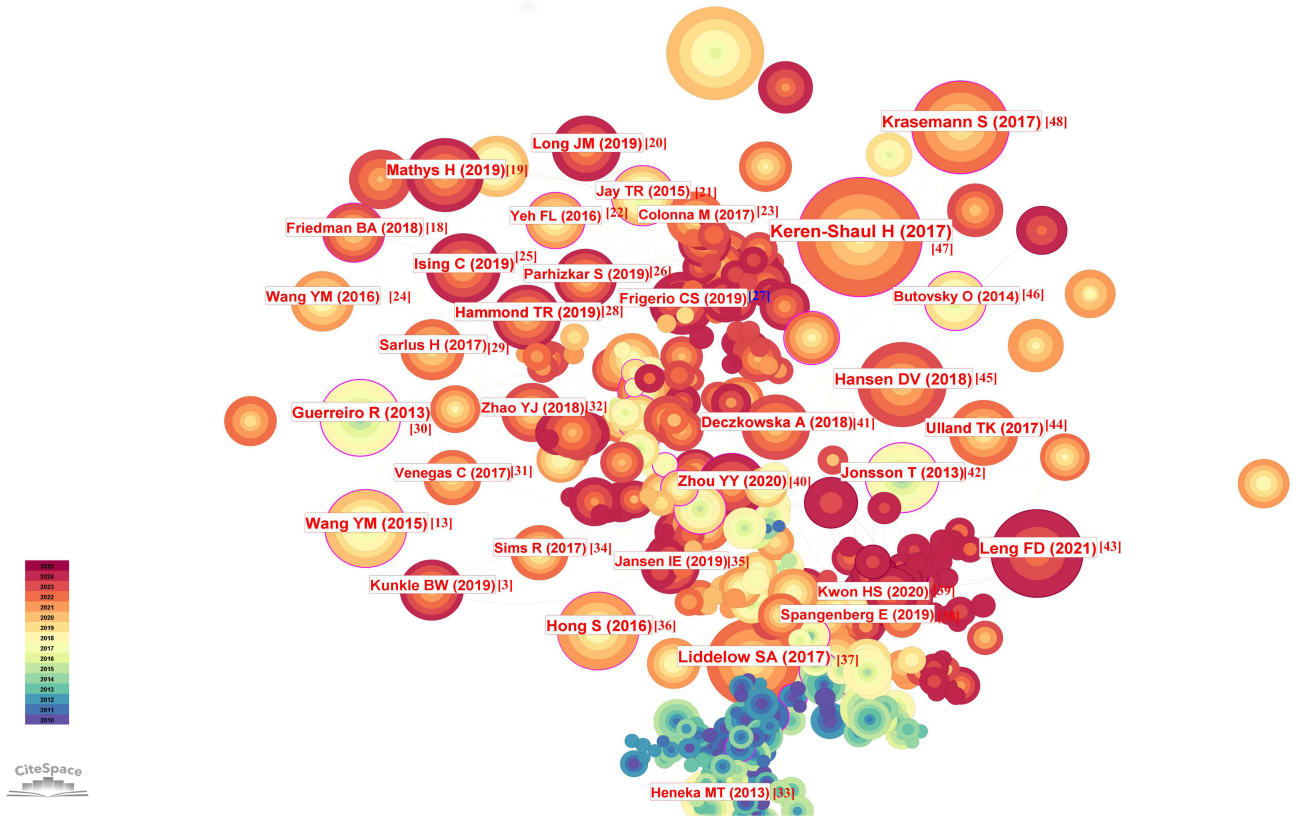

Figure 5 Reference co-citation network.

https://doi.org/10.2147/JMDH.S521350

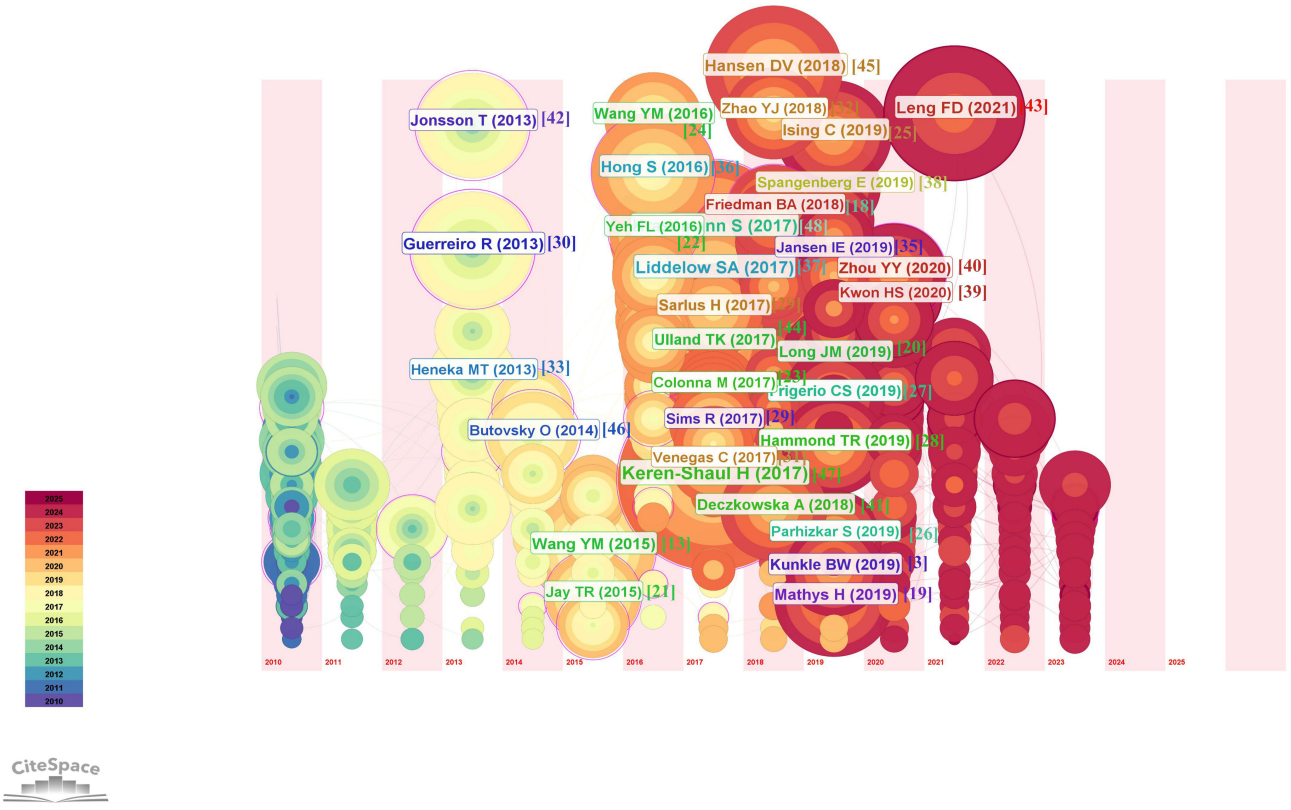

Figure 6 Timeline view of the reference co-citation network.

Highly Cited References with Citation Bursts

In addition to co-citation structures, Citation Burst detection in CiteSpace was used to identify references with significant increases in citation frequency over a defined time period. Figure 7 presents the top 25 references with the strongest citation bursts.

Burst intensity and duration: References such as Guerreiro (2013), Jonsson (2013), Heneka (2015), Keren-Shaul (2017) and Leng (2021) exhibit high burst intensities (>80), indicating that they received extensive citations during specific periods. The burst duration (Begin–End) reflects how long a paper's influence or popularity is sustained, which in some cases spans 3–5 years or more.

Research content and academic impact: Guerreiro (2013) and Jonsson (2013) focus on *TREM2* gene variation and AD susceptibility. Heneka (2015), published in *The Lancet Neurology*, offers important insights into neuroinflammation, enhancing the understanding of microglial inflammatory pathways. Keren-Shaul (2017) applies single-cell transcriptomics to microglial subtype identification, paving the way for precision medicine research. More recent references, such as Leng (2021) and Paolicelli (2022), explore immune microenvironment regulation and synaptic plasticity, reflecting the continued rapid development in this area.

Keyword Co-Occurrence and Clustering Analysis

Keyword Timeline View

Figure 8 displays high-frequency keywords along a timeline. Each diamond represents the first appearance or a period of heightened usage for a specific keyword in a given year. The size or colour may indicate the frequency or duration of activity.

Early stage (around 2010–2012): Keywords such as "central nervous system", "experimental autoimmune encephalomyelitis" and "nitric oxide synthase" are primarily associated with foundational concepts in neuroimmunity and inflammation. During this phase, microglia were primarily viewed as key mediators of CNS immune responses, with a focus on inflammation and oxidative stress.

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2010 - 2025
Ransohoff RM, 2009, ANNU REV IMMUNOL, V27, P119, DOI 10.1146/annurev.immunol.021908.132528, DOI	2009	66.88	2010	2014	
Hickman SE, 2008, J NEUROSCI, V28, P8354, DOI 10.1523/JNEUROSCI.0616-08.2008, DOI	2008	64.36	2010	2013	
Glass CK, 2010, CELL, V140, P918, DOI 10.1016/j.cell.2010.02.016, DOI	2010	74.22	2011	2015	
Guerreiro R, 2013, NEW ENGL J MED, V368, P117, DOI 10.1056/NEJMoa1211851, DOI	2013	156.1	2013	2018	
Jonsson T, 2013, NEW ENGL J MED, V368, P107, DOI 10.1056/NEJMoa1211103, DOI	2013	130.29	2013	2018	
Kettenmann H, 2011, PHYSIOL REV, V91, P461, DOI 10.1152/physrev.00011.2010, DOI	2011	86.22	2013	2016	
Heneka MT, 2013, NATURE, V493, P674, DOI 10.1038/nature11729, DOI	2013	84.87	2013	2018	
Schafer DP, 2012, NEURON, V74, P691, DOI 10.1016/j.neuron.2012.03.026, DOI	2012	62.42	2013	2017	
Griciuc A, 2013, NEURON, V78, P631, DOI 10.1016/j.neuron.2013.04.014, DOI	2013	69.57	2014	2018	
Parkhurst CN, 2013, CELL, V155, P1596, DOI 10.1016/j.cell.2013.11.030, DOI	2013	66.9	2014	2018	
Wang YM, 2015, CELL, V160, P1061, DOI 10.1016/j.cell.2015.01.049, DOI	2015	114.59	2015	2020	
Butovsky O, 2014, NAT NEUROSCI, V17, P131, DOI 10.1038/nn.3599, DOI	2014	86.92	2015	2019	
Jay TR, 2015, J EXP MED, V212, P287, DOI 10.1084/jem.20142322, DOI	2015	67.46	2015	2020	
Kleinberger G, 2014, SCI TRANSL MED, V6, P0, DOI 10.1126/scitranslmed.3009093, DOI	2014	63.48	2015	2019	
Hickman SE, 2013, NAT NEUROSCI, V16, P1896, DOI 10.1038/nn.3554, DOI	2013	62.79	2015	2018	
Heneka MT, 2015, LANCET NEUROL, V14, P388, DOI 10.1016/S1474-4422(15)70016-5, DOI	2015	187.4	2016	2020	
Heppner FL, 2015, NAT REV NEUROSCI, V16, P358, DOI 10.1038/nrn3880, DOI	2015	80.68	2016	2020	
Hong S, 2016, SCIENCE, V352, P712, DOI 10.1126/science.aad8373, DOI	2016	94.79	2017	2021	
Keren-Shaul H, 2017, CELL, V169, P1276, DOI 10.1016/j.cell.2017.05.018, DOI	2017	159.99	2019	2022	
Krasemann S, 2017, IMMUNITY, V47, P566, DOI 10.1016/j.immuni.2017.08.008, DOI	2017	96.85	2019	2022	
Liddelow SA, 2017, NATURE, V541, P481, DOI 10.1038/nature21029, DOI	2017	84.19	2019	2022	
Hansen DV, 2018, J CELL BIOL, V217, P459, DOI 10.1083/jcb.201709069, DOI	2018	75.77	2020	2023	
Leng FD, 2021, NAT REV NEUROL, V17, P157, DOI 10.1038/s41582-020-00435-y, DOI	2021	151.34	2022	2025	
Kwon HS, 2020, TRANSL NEURODEGENER, V9, P0, DOI 10.1186/s40035-020-00221-2, DOI	2020	68.21	2022	2025	
Paolicelli RC, 2022, NEURON, V110, P3458, DOI 10.1016/j.neuron.2022.10.020, DOI	2022	82.56	2023	2025	

Figure 7 Top 25 References with the Strongest Citation Bursts.

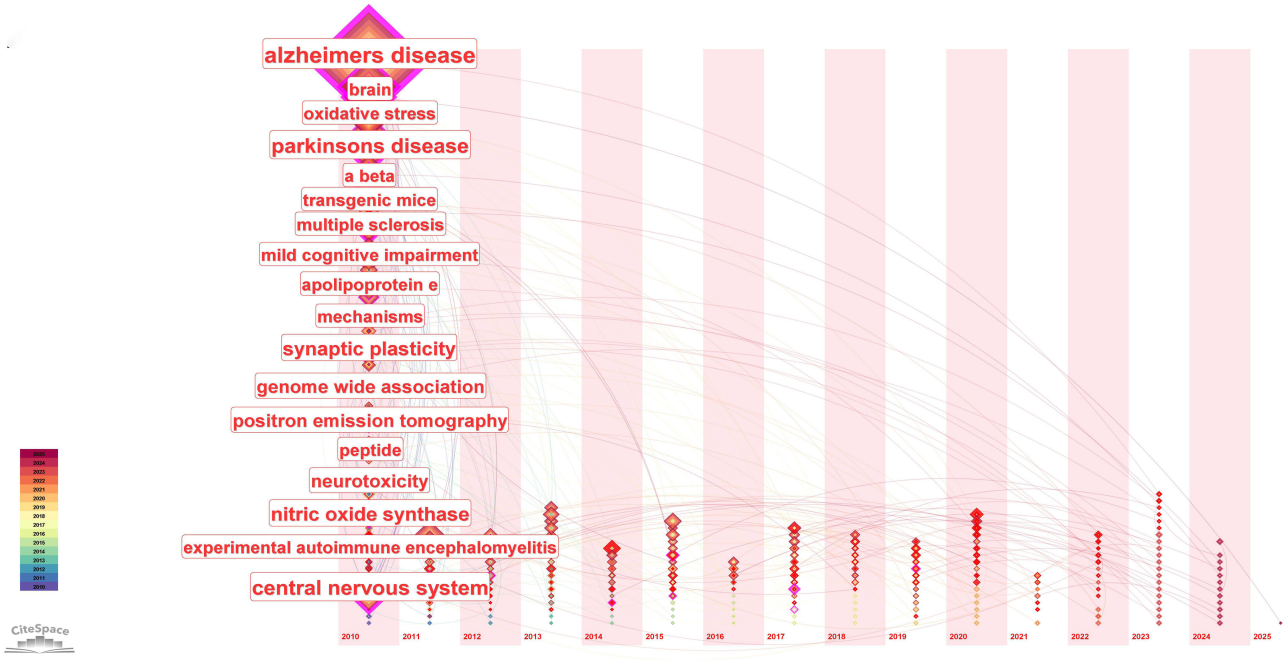

Figure 8 Keywords Timeline.

https://doi.org/10.2147/JMDH.S521350

Mid stage (2013–2017): Keywords such as "mild cognitive impairment", "transgenic mice", "apolipoprotein E" and "genome-wide association" began to emerge and increase in frequency, reflecting a shift from the singular "inflammatory hypothesis" towards genetic and molecular pathways more closely linked to AD. Terms such as "synaptic plasticity" and "mechanisms" also became more prominent, indicating a growing interest in neuron–microglia interactions and synaptic regulation.

Recent stage (2018–2025): Terms such as "oxidative stress", "A beta", "positron emission tomography (PET)", "multiple sclerosis" and "Parkinson's disease" suggest increasing cross-talk among AD, other neurodegenerative conditions and various imaging techniques. "Alzheimer's disease" remains a dominant term, indicating a continued central focus. Newly emerging clinical trials and multimodal imaging approaches (eg PET) reflect efforts to establish more precise clinical correlations between microglial function and AD pathology.

Overall, the timeline view suggests that early microglia research focused on fundamental pathology and immune function, later expanding to encompass molecular mechanisms, gene pathways and various neurodegenerative disorders, and more recently intersecting with clinical imaging and pharmacological interventions.

Keyword Clustering View

As shown in Figure 9, the clustering results generated by CiteSpace (using LLR or tf*idf algorithms) reveal several major clusters with high Silhouette values, indicating strong intra-cluster cohesion and clear differentiation among clusters. Notable large clusters include the following:

#0 BBB: Explores the BBB's crucial role in regulating central inflammation and molecular permeability. This cluster is closely associated with early AD pathology and microglial inflammatory responses that cross the barrier.

#1 multiple sclerosis: Reflects the expansion of microglial research beyond AD to include other neurodegenerative and autoimmune diseases, emphasising the broad relevance of neuroimmunological insights.

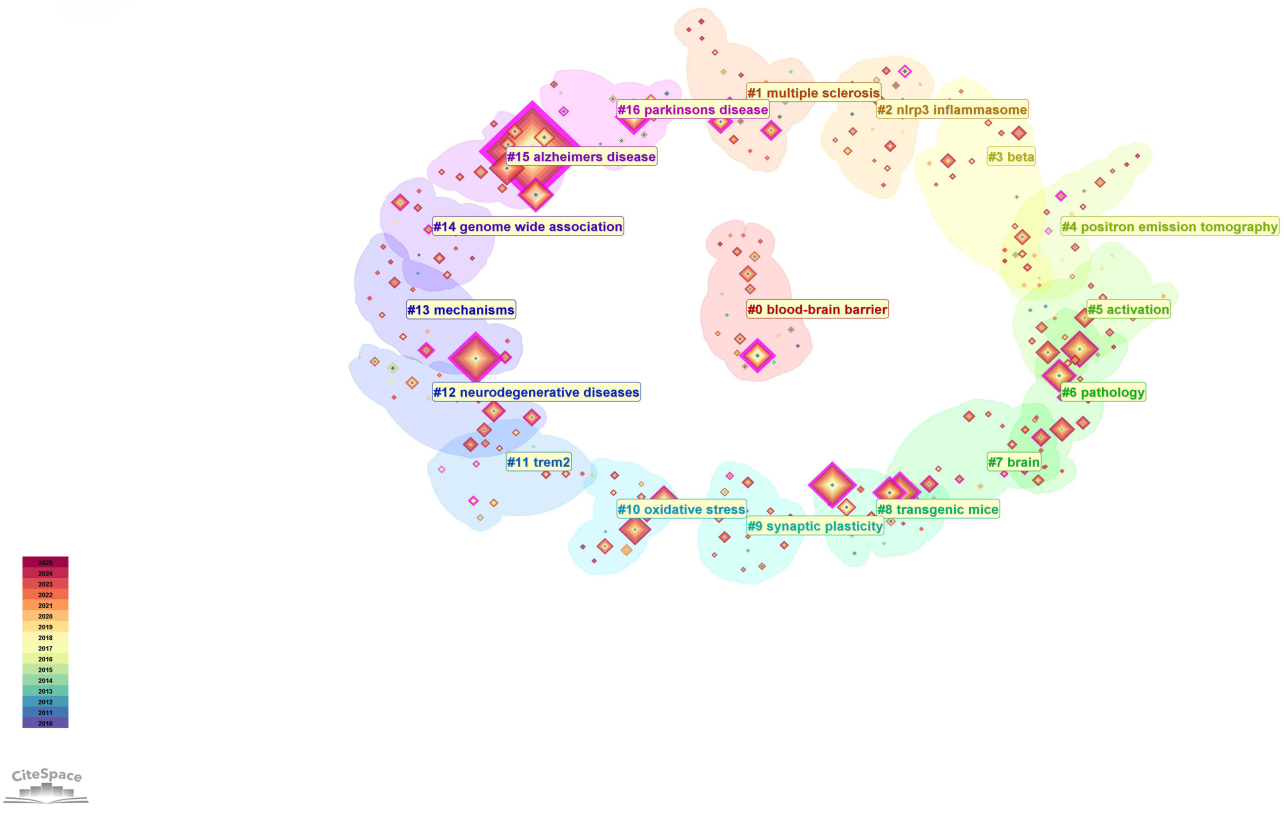

Figure 9 Keyword clustering analysis.

#2 NLRP3 inflammasome: Highlights growing interest in the relationship between the NLRP3 inflammasome and microglial activation. Inflammatory pathways involving microglia are a key mechanism in AD-related neuroinflammation and degeneration.

#8 transgenic mice and #9 synaptic plasticity: Represent the extensive use of transgenic animal models to simulate AD pathology, alongside investigations into synaptic plasticity and damage as critical factors in disease onset and progression.

#11 TREM2: A more recent hotspot cluster, indicating the association between TREM2 gene mutations, microglial dysfunction and AD pathogenesis.

#14 genome-wide association, #12 neurodegenerative diseases, #13 mechanisms, #15 Alzheimer's disease and others: These clusters focus on genome-wide association studies, broader neurodegenerative conditions, molecular mechanisms and AD pathology, serving as central areas of research in the field.

Keyword Burst Analysis

Figure 10 shows that many keywords began their burst period around 2010 (eg "in vivo", "nitric oxide synthase", "central nervous system", "microglia", "transgenic mice"), attracting widespread attention between 2010 and 2015. More

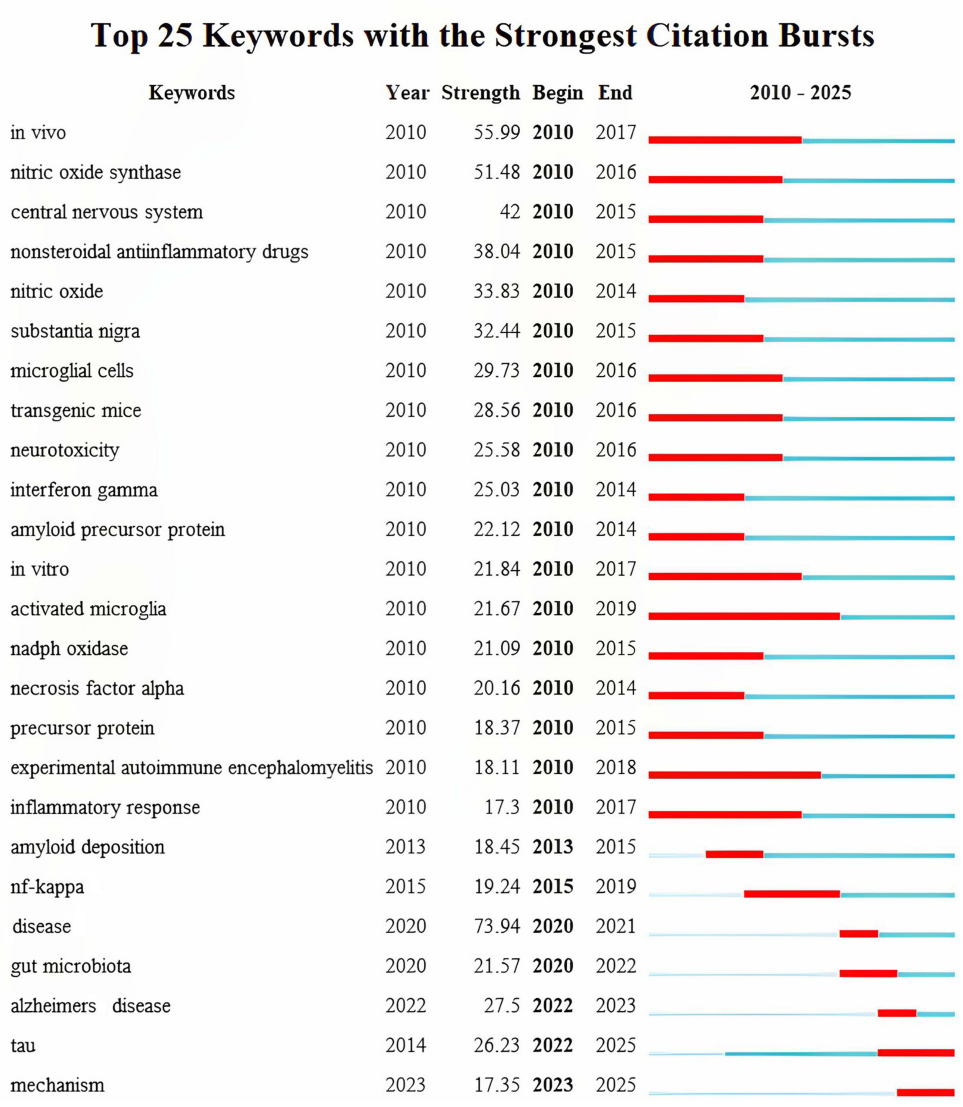

Figure 10 Top 25 Keywords with the Strongest Citation Bursts.

https://doi.org/10.2147/JMDH.S521350

recently, high-burst keywords have emerged, including "s disease" (starting in 2020), "gut microbiota" (2020), "alzheimer's disease" (2022), "tau" (2022) and "mechanism" (2023), indicating renewed research interest after 2020.

Early high-intensity bursts: "in vivo" (55.99), "nitric oxide synthase" (51.48), "central nervous system" (42).

Recent attention: "s disease" (potentially a variant or database indexing term for "AD") showed a burst strength of 73.94 (2020–2021).

Burst duration: Most keywords that began around 2010 continued until 2014–2017, reflecting their substantial impact during that period. Newly emerging terms such as "alzheimer's disease" (2022–2023), "tau" (2022–2025) and "mechanism" (2023–2025) have shown strong bursts in recent years.

Discussion

Multiple Dimensions of Accelerating Microglia Research

Our findings indicate that annual publication volume has increased significantly over the past decade, peaking between 2020 and 2022 and remaining consistently high thereafter. This surge aligns with several landmark discoveries and methodological advances, including breakthroughs in single-cell sequencing technologies that enabled unprecedented resolution of microglial subtypes, the identification of novel genetic risk factors such as *TREM2* and *APOE* variants, and major progress in understanding the mechanistic interplay between microglia, tau pathology and neuroinflammation.[51,52] In addition, the growing prevalence of AD, driven by a globally ageing population, has compelled researchers to direct more resources towards early intervention and precision therapies for neurodegenerative diseases.[53] Against this backdrop, microglia, as key mediators of CNS immune responses and microenvironmental regulation, have increasingly drawn attention from research teams and biotech enterprises alike.

International Collaboration and the Formation of Research Clusters

The national collaboration network highlights the leadership of the US and China in this field, with Europe (the UK, Germany, France) and other countries (Japan, Canada) forming another strong pillar, reflecting a multipolar global research landscape. Compared with earlier studies, the US has long held a leading position at the intersection of neuroscience and immunology, supported by agencies such as the NIH.[26] Over the past decade, China has made substantial investments through programmes such as the "973 Projects", the National Natural Science Foundation and various brain science initiatives, catalysing rapid growth in microglia- and neuroinflammation-related research.[54] European nations, supported by well-established research platforms (eg Germany's Helmholtz Association, France's Inserm and the University of London in the UK), are increasingly engaging in broader cross-regional cooperative networks with the US and China.[55]

Nevertheless, some degree of "regional clustering" remains evident, suggesting that although cross-border co-authorship has intensified, differences in academic culture and resource allocation may still pose barriers. Specifically, European and North American institutions often benefit from established funding mechanisms, robust regulatory frameworks and stable research infrastructures. In contrast, emerging research regions such as Asia–Pacific countries tend to rely more heavily on government policies and targeted funding initiatives, which may cause variability in research continuity and thematic priorities.[54,55] To address these challenges, explicit policies promoting data standardisation, open resource-sharing platforms and international collaborative frameworks should be encouraged.

Author-level analyses show that prolific and highly cited researchers - Holtzman, Heneka, Zetterberg, Haass, Colonna, among others - are recognised for their pioneering contributions to *Aβ* metabolism, *TREM2* pathways and neuroinflammatory regulation. Heneka's team contributed foundational work on the *NLRP3* inflammasome in AD,[23,56,57] which shifted the field's understanding of microglia-mediated inflammation as a therapeutic target substantially. Colonna's group systematically examined how *TREM2* gene mutations affect microglial function and AD susceptibility,[58,59] providing critical evidence for the role of innate immunity and lipid sensing in microglial activity. More recent contributors, such as Saito, Saido, Leng and Paolicelli, tend to focus on advanced methodologies (eg single-cell sequencing, spatial omics, gene editing) and emerging molecular targets (*TREM2, APOE*, tau), reflecting the field's growing reliance on interdisciplinary collaborations and innovative technologies.[60,61]

Intersection and Deepening of Microglial Mechanisms

Early studies described microglia as "protectors" responsible for clearing Aβ deposits.[62] Later, researchers recognised their dual role: they may provide neuroprotection through Aβ phagocytosis or contribute to neuronal damage when overactivated or dysfunctional, leading to chronic inflammation.[63] Between 2013 and 2015, Heneka et al emphasised inflammatory cascades as a significant contributor to AD pathogenesis, demonstrating that highly activated microglia secrete inflammatory mediators that result in synaptic injury and neurodegeneration.[33,64,65]

More recent findings further indicate that microglial phenotypes dynamically shift across the stages of AD progression. In the early stages, microglia predominantly exhibit protective profiles associated with enhanced phagocytosis and debris clearance. As the disease advances, however, prolonged pathological stimuli (eg aggregated tau, persistent amyloid) drive microglia towards a pro-inflammatory state, characterised by excessive cytokine release, impaired clearance capacity and synaptic pruning dysfunction - factors that ultimately exacerbate neuronal damage and cognitive decline.[47,66]

With the emergence of genome-wide association studies and single-cell omics, key molecular pathways involving TREM2, NLRP3 and APOE have gained prominence in AD risk research.[66,67] For example, TREM2 variants have been directly linked to altered microglial metabolism and reduced phagocytic capacity, whereas excessive activation of the NLRP3 inflammasome contributes to sustained inflammation and neuronal damage, highlighting both as critical therapeutic targets. TREM2 mutations significantly increase susceptibility to both early-onset and sporadic AD by influencing microglial phagocytosis, inflammasome activity and migration.[67,68] The chronic activation of the NLRP3 inflammasome, which is linked to chronic brain inflammation and neuronal loss, has prompted investigations into NLRP3 inhibitors and blockade strategies.[69] In addition, APOE, a key regulator of lipid metabolism and Aβ deposition, has been shown to interact with microglial activation patterns.[70]

Keyword Evolution: From Single Pathological Hypothesis to Multisystem Interactions

The evolution of keywords, from a single pathological hypothesis to a multisystem perspective, also emerges from the timeline and clustering analyses. Initially, microglia research was predominantly concerned with the Aβ-centric model. Over time, insights into genetic risk factors (eg APOE, TREM2) and inflammatory cascades (eg NLRP3 inflammasome) reshaped scientific consensus, leading to broader integrative approaches involving peripheral immunity, gut–brain axis interactions and systemic inflammation.[51,61]

Emerging research areas such as the gut–brain axis have gained prominence, driven by evidence indicating that gut microbiota dysbiosis can modulate systemic inflammatory signalling via microbial metabolites, cytokines and peripheral immune cells. These mechanisms influence microglial activation states and may ultimately alter the trajectory of AD progression.[51] Additionally, cutting-edge technologies such as CRISPR-based genome editing have begun facilitating the precise manipulation of microglia-associated genetic pathways (eg TREM2, APOE) in animal models, advancing our mechanistic understanding and therapeutic targeting potential substantially. Spatial transcriptomics has also emerged as a pivotal tool, allowing researchers to visualise spatially resolved microglial activation patterns and their interactions with amyloid plaques, tau pathology and synaptic dysfunction across disease stages.

For example, the rise of the keyword "blood–brain barrier" underscores the interplay between peripheral immunity and the CNS, as well as the crucial role of BBB permeability in disease progression.[61] Similarly, "gut microbiota" has recently become a high-burst keyword, suggesting that gut dysbiosis may influence the cerebral inflammatory environment through immunological axes.[51] Furthermore, multiple neurodegenerative diseases (eg Parkinson's disease, multiple sclerosis) share overlapping microglial activation mechanisms, drawing increased attention to cross-disease comparisons.[14] These findings suggest that future microglia-targeting strategies may incorporate not only conventional anti-Aβ or anti-inflammatory therapies but also approaches focused on gut flora regulation, systemic immune modulation and personalised genomic data.

Clinical Implications and Future Outlook

Based on the aforementioned evidence, interventions targeting microglial function are gradually advancing into translational research. Examples include monoclonal antibodies, *TREM2* agonists or inhibitors, and *NLRP3* inhibitors, some of which have shown promise in preclinical or early-phase clinical trials.[71,72] Nevertheless, several challenges remain:

Subtype specificity: Microglia exhibit functional diversity across different disease stages or brain regions, necessitating refined approaches to identify and regulate specific subtypes.[73]

Peripheral–central immune interplay: Changes in BBB permeability and the migration of peripheral immune cells may influence therapeutic efficacy.[74]

Potential risks and failures: The clinical translation of microglial therapies faces considerable challenges, such as off-target immune modulation, potential neurotoxicity and disappointing outcomes in early-phase clinical trials, emphasising the need for cautious, stepwise clinical development strategies.[75]

Personalised therapy: Ongoing trials targeting TREM2-specific patient populations (eg AL002, a TREM2-activating antibody trial) represent tangible applications of precision medicine, aiming to tailor therapies based on individual genetic risk profiles.[76]

Recently reported clinical trials have highlighted both promise and caution. For example, the monoclonal antibody AL002, which targets TREM2 activation, is currently undergoing Phase II clinical evaluation to assess efficacy in genetically stratified patient populations. Likewise, small-molecule inhibitors targeting the NLRP3 inflammasome pathway (eg MCC950 and related compounds) have demonstrated significant reductions in neuroinflammation and cognitive deficits in preclinical models. However, translating these promising results into clinical settings presents challenges, including concerns around safety profiles and pharmacokinetic optimisation.[73] Thus, careful patient stratification, rigorous safety monitoring and adaptive trial designs are critical components in the successful clinical development of microglia-targeted therapies.

Hence, more systematic preclinical studies and extensive multicentre clinical trials are needed to determine whether regulating microglial function can provide safe and meaningful therapeutic benefits across different stages of AD. Multidisciplinary and international collaborations remain crucial, enabling the integration of foundational science with advanced methodologies and leveraging multicentre cohorts and multidimensional databases to build a more robust evidence base. Future clinical research should prioritise the development of standardised biomarker criteria for microglial activation and treatment response, thereby supporting the design of more targeted and effective clinical interventions.

Limitations and Future Prospects of This Study

Although this study employs bibliometric analysis based on the WoS database and covers a broad scope, certain limitations remain due to database update frequency, language filters and possible omissions. Specifically, the exclusive use of the WoS Core Collection may introduce database bias, potentially excluding relevant grey literature, conference proceedings and preprints that may contain emerging data or preliminary findings not yet formally published. Additionally, limiting the search to English-language publications may further restrict comprehensiveness by overlooking important non-English-language studies, particularly those published in other major research languages. The data for 2024–2025 are still subject to ongoing indexing, which may lead to partial trend representation.

Moreover, bibliometric analysis provides only a quantitative snapshot of research hotspots and trajectories. A deeper understanding of underlying mechanisms and clinical relevance requires continued original experimental work and clinical trials.

Overall, research on microglia and AD is rapidly expanding into a broader neuroimmune and cross-system regulatory domain. By integrating multiple technological layers, such as genomics, proteomics, immunomics and pharmacology, future breakthroughs in the prevention and treatment of neurodegenerative diseases appear likely. Future bibliometric studies should consider incorporating multiple databases, grey literature, preprints and non-English-language publications to offer a more comprehensive and representative view of the evolving research landscape.

Conclusion

Recent advances underscore the critical role of microglia in AD pathogenesis, spanning multiple molecular pathways, diverse functional states and complex interactions between central and peripheral immunity. Unlike previous bibliometric analyses that primarily described quantitative trends, this study uniquely integrates citation network dynamics with thematic evolution, revealing how specific discoveries and methodologies (eg single-cell sequencing, TREM2 signalling, gut microbiome research) have reshaped the research landscape and influenced patterns of collaboration.

Clinically, the growing understanding of microglial heterogeneity and immune regulation presents novel therapeutic opportunities, such as targeting TREM2 signalling or modulating peripheral inflammation through microbiota-based interventions. However, considerable challenges remain, including the need to ensure subtype specificity, reduce off-target effects and address variability in therapeutic responses caused by genetic and environmental factors.

Future research should aim to clarify the mechanisms underlying microglia–peripheral immune interactions, systematically assess microbiome-based strategies and rigorously validate these approaches through multicentre clinical trials. Strengthened international collaboration, supported by standardised frameworks for data sharing and methodological harmonisation, will be vital to accelerate the translation of microglia-targeted research into meaningful clinical outcomes.

Funding

1. National Natural Science Foundation of China Youth Fund (82405220); 2. Heilongjiang Natural Science Foundation Project (LH2022H070); 3. China Postdoctoral Science Foundation Project (2021M701128); 4. Heilongjiang Postdoctoral Research Project (LBH-Z20193); 5. Heilongjiang Traditional Chinese Medicine Research Project (ZHY2022-108); 6. Heilongjiang University of Chinese Medicine Research Fund Project (2019MS31).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Chen D, Miao S, Chen X, et al. Regulated necrosis in glaucoma: focus on ferroptosis and pyroptosis. *Mol Neurobiol*. 2024;61(5):2542–2555. doi:10.1007/s12035-023-03732-x
2. Yegla B, Foster T. Effect of systemic inflammation on rat attentional function and neuroinflammation: possible protective role for food restriction. *Front Aging Neurosci*. 2019;11. doi:10.3389/fnagi.2019.00296
3. Sims R, Van Der Lee SJ, Naj AC, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat Genet*. 2017;49(9):1373. doi:10.1038/ng.3916
4. Fang YQ, Wang J, Yao L, et al. The adhesion and migration of microglia to β-amyloid (Aβ) is decreased with aging and inhibited by Nogo/NgR pathway. *J Neuroinflammation*. 2018;15(1). doi:10.1186/s12974-018-1250-1
5. Das R, Balmik AA, Chinnathambi S. Melatonin reduces GSK3β-mediated tau phosphorylation, enhances Nrf2 nuclear translocation and anti-inflammation. *ASN Neuro*. 2020;12(1). doi:10.1177/1759091420981204
6. Cazarin CA, Dalmagro AP, Gonçalves AE, et al. Usnic acid enantiomers restore cognitive deficits and neurochemical alterations induced by $A\beta^{1-42}$ in mice. *Behav Brain Res*. 2021;397:112945. doi:10.1016/j.bbr.2020.112945
7. Cavanagh C, Colby-Milley J, Bouvier D, et al. βCTF-correlated burst of hippocampal TNFα Occurs at a very early, pre-plaque stage in the TgCRND8 mouse model of Alzheimer's disease. *J Alzheimers dis*. 2013;36(2):233–238. doi:10.3233/JAD-122131
8. Song J, Choi SM, Kim BC. Adiponectin regulates the polarization and function of microglia via PPAR-γ signaling under amyloid β toxicity. *Front Cell Neurosci*. 2017;11. doi:10.3389/fncel.2017.00064
9. Kim SM, Mun BR, Lee SJ, et al. TREM2 promotes Aβ phagocytosis by upregulating C/EBPα-dependent CD36 expression in microglia. *Sci Rep*. 2017;7:11118.
10. Goswami P, Afjal MA, Akhter J, et al. Involvement of endoplasmic reticulum stress in amyloid $\beta^{(1-42)}$-induced Alzheimer's like neuropathological process in rat brain. *Brain Res Bull*. 2020;165:108–117. doi:10.1016/j.brainresbull.2020.09.022
11. Nagata K, Hashimoto S, Joho D, et al. Tau accumulation induces microglial state alterations in Alzheimer's disease model mice. *eNeuro*. 2024;11(12):ENEURO.0260–24.2024. doi:10.1523/ENEURO.0260-24.2024
12. Walker JM, Orr ME, Orr TC, et al. Spatial proteomics of hippocampal subfield-specific pathology in Alzheimer's disease and primary age-related tauopathy. *Alzheimers Dement*. 2024;20(2):783–797. doi:10.1002/alz.13484
13. Wang YM, Cella M, Mallinson K, et al. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. *Cell*. 2015;160(6):1061–1071. doi:10.1016/j.cell.2015.01.049
14. Filipello F, Morini R, Corradini I, et al. The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. *Immunity*. 2018;48(5):979. doi:10.1016/j.immuni.2018.04.016
15. Zhao XY, Yin L, Wu Y, et al. Manganese induces neuroinflammation via NF-κB/ROS NLRP3 pathway in rat brain striatum and HAPI cells. *Mol Cell Toxicol*. 2019;15(2):173–183. doi:10.1007/s13273-019-0021-0
16. Jadhav SP. MicroRNAs in microglia: deciphering their role in neurodegenerative diseases. *Front Cell Neurosci*. 2024;18. doi:10.3389/fncel.2024.1391537
17. Monasor LS, Müller SA, Colombo AV, et al. Fibrillar Aβ triggers microglial proteome alterations and dysfunction in Alzheimer mouse models. *eLife*. 2020;9:e54083.
18. Friedman BA, Srinivasan K, Ayalon G, et al. Diverse brain myeloid expression profiles reveal distinct microglial activation states and aspects of Alzheimer's disease not evident in mouse models. *Cell Rep*. 2018;22(3):832–847. doi:10.1016/j.celrep.2017.12.066
19. Mathys H, Davila-Velderrain J, Peng Z, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*. 2019;570(7761):332. doi:10.1038/s41586-019-1195-2

20. Long JM, Zhong G, Wang C, et al. TREM2 attenuates Aβ1-42-mediated neuroinflammation in BV-2 cells by downregulating TLR signaling. *Neurochem Res*. 2019;44(8):1830–1839. doi:10.1007/s11064-019-02817-1
21. Jay TR, Hirsch AM, Broihier ML, et al. Disease progression-dependent effects of TREM2 deficiency in a mouse model of Alzheimer's disease. *J Neurosci*. 2017;37(3):637–647. doi:10.1523/JNEUROSCI.2110-16.2016
22. Yeh FL, Hansen DV, Sheng M. TREM2, microglia, and neurodegenerative diseases. *Trends Mol Med*. 2016;23(6):512–533. doi:10.1016/j.molmed.2017.03.008
23. Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Ann Rev Immunol*. 2017;35(1):441–468. doi:10.1146/annurev-immunol-051116-052358
24. Wang YM, Ulland TK, Ulrich JD, et al. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. *J Exp Med*. 2016;213(5):667–675. doi:10.1084/jem.20151948
25. Ising C, Venegas C, Zhang S, et al. NLRP3 inflammasome activation drives tau pathology. *Nature*. 2019;575(7784):669. doi:10.1038/s41586-019-1769-z
26. Parhizkar S, Arzberger T, Brendel M, et al. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. *Nat Neurosci*. 2019;22(2):191. doi:10.1038/s41593-018-0296-9
27. Frigerio CS, Wolfs L, Fattorelli N, et al. The major risk factors for Alzheimer's disease: age, sex, and genes modulate the microglia response to Aβ plaques. *Cell Rep*. 2019;27(4):1293. doi:10.1016/j.celrep.2019.03.099
28. Hammond TR, Manek R, Kerr BJ, Macauley MS, Plemel JR. Regulation of microglia population dynamics throughout development, health, and disease. *Glia*. 2019;69(12):2771–2797. doi:10.1002/glia.24047
29. Sarlus H, Heneka MT. Microglia in Alzheimer's disease. *J Clin Invest*. 2017;127(9):3240–3249. doi:10.1172/JCI90606
30. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. *N Engl J Med*. 2013;368(2):117–127. doi:10.1056/NEJMoa1211851
31. Venegas C, Heneka MT. Danger-associated molecular patterns in Alzheimer's disease. *J Leukoc Biol*. 2017;101(1):87–98. doi:10.1189/jlb.3MR0416-204R
32. Zhao YJ, Wu X, Li X, et al. TREM2 is a receptor for β-amyloid that mediates microglial function. *Neuron*. 2018;97(5):1023. doi:10.1016/j.neuron.2018.01.031
33. Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*. 2013;493(7434):674. doi:10.1038/nature11729
34. Huang KL, Marcora E, Pimenova AA, et al. A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease. *Nat Neurosci*. 2017;20(8):1052. doi:10.1038/nn.4587
35. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet*. 2019;51(3):404. doi:10.1038/s41588-018-0311-9
36. Hong S, Dissing-Olesen L, Stevens B. New insights on the role of microglia in synaptic pruning in health and disease. *Curr Opin Neurobiol*. 2016;36:128–134. doi:10.1016/j.conb.2015.12.004
37. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481–487. doi:10.1038/nature21029
38. Spangenberg E, Severson PL, Hohsfield LA, et al. Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model. *Nat Commun*. 2019;10(1). doi:10.1038/s41467-019-11674-z
39. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener*. 2020;9(1). doi:10.1186/s40035-020-00221-2
40. Zhou YY, Song WM, Andhey PS, et al. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. *Nat Med*. 2020;26(1):131. doi:10.1038/s41591-019-0695-9
41. Deczkowska A, Keren-Shaul H, Weiner A, et al. Disease-associated microglia: a universal immune sensor of neurodegeneration. *Cell*. 2018;173(5):1073–1081. doi:10.1016/j.cell.2018.05.003
42. Thomas J, Garg ML, Smith DW. Dietary supplementation with resveratrol and/or docosahexaenoic acid alters hippocampal gene expression in adult C57Bl/6 mice. *J Nutr Biochem*. 2013;24(10):1735–1740. doi:10.1016/j.jnutbio.2013.03.002
43. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3):157–172. doi:10.1038/s41582-020-00435-y
44. Ulland TK, Song WM, Huang SC-C, et al. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell*. 2017;170(4):649. doi:10.1016/j.cell.2017.07.023
45. Hansen DV, Hanson JE, Sheng M. Microglia in Alzheimer's disease. *J Cell Biol*. 2018;217(2):459–472. doi:10.1083/jcb.201709069
46. Butovsky O, Jedrychowski MP, Moore CS, et al. Identification of a unique TGF-β–dependent molecular and functional signature in microglia. *Nat Neurosci*. 2014;17(1):131–143. doi:10.1038/nn.3599
47. Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*. 2017;169(7):1276–1290.e1217. doi:10.1016/j.cell.2017.05.018
48. Krasemann S, Madore C, Cialic R, et al. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. *Immunity*. 2017;47(3):566–581.e569. doi:10.1016/j.immuni.2017.08.008
49. Butovsky O, Weiner HL. Microglial signatures and their role in health and disease. *Nat Rev Neurosci*. 2018;19(10):622–635. doi:10.1038/s41583-018-0057-5
50. Leng LG, Yuan Z, Pan R, et al. Microglial hexokinase 2 deficiency increases ATP generation through lipid metabolism leading to β-amyloid clearance. *Nat Metab*. 2022;4(10):1287. doi:10.1038/s42255-022-00643-4
51. Huang Y, Wu J, Zhang H, et al. The gut microbiome modulates the transformation of microglial subtypes. *Mol Psychiatry*. 2023;28(4):1611–1621. doi:10.1038/s41380-023-02017-y
52. Fadul MM, Garwood CJ, Waller R, et al. NDRG2 expression correlates with neurofibrillary tangles and microglial pathology in the ageing brain. *Int J Mol Sci*. 2020;21(1):340. doi:10.3390/ijms21010340
53. Daini E, Secco V, Liao WJ, Zoli M, Vilella A. A regional and cellular analysis of the early intracellular and extracellular accumulation of Aβ in the brain of 5XFAD mice. *Neurosci Lett*. 2021;754:135869. doi:10.1016/j.neulet.2021.135869
54. Zhang ZH, Wu Z, Zhu X, et al. Hydroxy-safflor yellow A inhibits neuroinflammation mediated by $A\beta^{1-42}$ in BV-2 cells. *Neurosci Lett*. 2014;562:39–44. doi:10.1016/j.neulet.2014.01.005

55. Chen Y, Holtzman DM. New insights into innate immunity in Alzheimer's disease: from APOE protective variants to therapies. *Trends Immunol*. 2024;45(10):768–782. doi:10.1016/j.it.2024.08.001
56. Heneka MT. ApoE4 makes microglia trem^{2}bling. *Neuron*. 2023;111(2):142–144. doi:10.1016/j.neuron.2022.12.032
57. Zetterberg H. Cerebrospinal fluid biomarkers for Alzheimer's disease: current limitations and recent developments. *Curr Opin Psychiatr*. 2015;28(5):402–409. doi:10.1097/YCO.0000000000000179
58. Colonna M, Wang YM. TREM2 variants: new keys to decipher Alzheimer disease pathogenesis. *Nat Rev Neurosci*. 2016;17(4):201–207. doi:10.1038/nrn.2016.7
59. Ulland TK, Colonna M. TREM2-a key player in microglial biology and Alzheimer disease. *Nat Rev Neurol*. 2018;14(11):667–675. doi:10.1038/s41582-018-0072-1
60. Wu XT, Saito T, Saido TC, Barron AM, Ruedl C. Microglia and CD206$^+$ border-associated mouse macrophages maintain their embryonic origin during Alzheimer's disease. *eLife*. 2021;10. doi:10.7554/eLife.71879
61. Ito S, Yagi R, Ogata S, et al. Proteomic alterations in the brain and blood-brain barrier during brain Aβ accumulation in an APP knock-in mouse model of Alzheimer's disease. *Fluids Barriers CNS*. 2023;20(1). doi:10.1186/s12987-023-00466-9
62. Cascella R, Conti S, Tatini F, et al. Extracellular chaperones prevent Aβ^{42}-induced toxicity in rat brains. *Biochim Biophys Acta-Mol Basis Dis*. 2013;1832(8):1217–1226. doi:10.1016/j.bbadis.2013.04.012
63. Crehan H, Liu B, Kleinschmidt M, et al. Effector function of anti-pyroglutamate-3 Aβ antibodies affects cognitive benefit, glial activation and amyloid clearance in Alzheimer's-like mice. *Alzheimers Res Ther*. 2020;12(1). doi:10.1186/s13195-019-0579-8
64. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol*. 2014;14(7):463–477. doi:10.1038/nri3705
65. Heneka MT, Carson MJ, Khoury JE, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5
66. Wang XZ, Zhu M, Hjorth E, et al. Resolution of inflammation is altered in Alzheimer's disease. *Alzheimers Dement*. 2015;11(1):40–50. doi:10.1016/j.jalz.2013.12.024
67. Yao HL, Coppola K, Schweig JE, et al. Distinct signaling pathways regulate TREM2 phagocytic and NFκB antagonistic activities. *Front Cell Neurosci*. 2019;13. doi:10.3389/fncel.2019.00457
68. Pocock J, Vasilopoulou F, Svensson E, Cosker K. Microglia and TREM2. *Neuropharmacology*. 2024;257:110020. doi:10.1016/j.neuropharm.2024.110020
69. Lee E, Hwang I, Park S, et al. MPTP-driven NLRP3 inflammasome activation in microglia plays a central role in dopaminergic neurodegeneration. *Cell Death Differ*. 2019;26(2):213–228. doi:10.1038/s41418-018-0124-5
70. Litvinchuk A, Suh JH, Guo JL, et al. Amelioration of Tau and ApoE4-linked glial lipid accumulation and neurodegeneration with an LXR agonist. *Neuron*. 2024;112(12):2079. doi:10.1016/j.neuron.2024.05.021
71. Liang GF, Lee YZ, Kow ASF, et al. Neuroprotective effects of Gypenosides: a review on preclinical studies in neuropsychiatric disorders. *Eur J Pharmacol*. 2024;978:176766. doi:10.1016/j.ejphar.2024.176766
72. Li HX, Zhao HY. Determination of bifurcation parameters and complex dynamics in Alzheimer's disease model. *Discrete Contin Dyn Syst -Ser B*. 2024;30(5):1617–1657.
73. Borrego-écija S, Pérez-Millan A, Antonell A, et al. Galectin-3 is upregulated in frontotemporal dementia patients with subtype specificity. *Alzheimers Dement*. 2024;20(3):1515–1526. doi:10.1002/alz.13536
74. Bairamian D, Sha S, Rolhion N, et al. Microbiota in neuroinflammation and synaptic dysfunction: a focus on Alzheimer's disease. *Mol Neurodegener*. 2022;17(1). doi:10.1186/s13024-022-00522-2
75. Friedman LG, McKeehan N, Hara Y, et al. Value-generating exploratory trials in neurodegenerative dementias. *Neurology*. 2021;96(20):944–954. doi:10.1212/WNL.0000000000011774
76. Long H, Simmons A, Mayorga A, et al. Preclinical and first-in-human evaluation of AL002, a novel TREM2 agonistic antibody for Alzheimer's disease. *Alzheimers Res Ther*. 2024;16(1). doi:10.1186/s13195-024-01599-1