Heliyon 10 (2024) e26377

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The role of short-chain fatty acids in central nervous system diseases: A bibliometric and visualized analysis with future directions

Ziwei Lan [a], Xiangqi Tang [a], Ming Lu [c], Zhiping Hu [a,**], Zhenchu Tang [a,b,*]

[a] Department of Neurology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China
[b] Hunan Key Laboratory of Tumor Models and Individualized Medicine, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China
[c] Hunan Provincial Key Laboratory of Neurorestoratology, The Second Affiliated Hospital, Hunan Normal University, Changsha, 410003, Hunan, China

ARTICLE INFO

Keywords:
Short-chain fatty acids
central nervous system diseases
bibliometric analysis
Hotspots
Trends
Intellectual structure
Visualization

ABSTRACT

Background: Short-chain fatty acids (SCFAs) are thought to play a key role in the microbe-gut-brain axis and involve in the pathogenesis of a variety of neurological diseases. This study aimed to identify research hotspots and evolution trends in SCFAs in central nervous diseases (CNS) and examine current research trends.

Methods: The bibliometric analysis was performed using CiteSpace, and the results were visualized via network maps.

Results: From 2002 to 2022, 480 publications in the database met the criteria. On the country level, China produced the highest number of publications, while the United States had the highest centrality. On the institutional level, University College Cork contributed to the most publications, and John F. Cryan from this university was the key researcher with considerable academic influence. The article, *the role of short-chain fatty acids in microbiota-gut-brain*, written by Boushra Dalile et al., in 2019 was the most cited article. Furthermore, the journal *Nutrients* had the maximum number of publications, while *Plos One* was the most cited journal. "Gut microbiome", "SCFAs", and "central nervous system" were the three most frequent keywords. Among them, SCFAs had the highest centrality. "Animal model" was the keyword with the highest burst strength, with the latest burst keywords being "social behavior", "pathogenesis", and "insulin sensitive". In addition, the research topics on SCFAs in CNS diseases from 2002 to 2022 mainly focused on following aspects: SCFAs plays a key role in microbe-gut-brain crosstalk; The classification and definition of SCFAs in the field of CNS; Several CNS diseases that are closely related to SCFAs research; Mechanism and translational studies of SCFAs in the CNS diseases. And the hotspots over the past 5 years have gradually increased the attention to the therapeutic potential of SCFAs in the CNS diseases.

Conclusion: The research of SCFAs in CNS diseases is attracting growing attention. However, there is a lack of cooperation between countries and institutions, and additional measures are required to promote cooperation. The current evidence for an association between SCFAs and CNS diseases is preliminary and more work is needed to pinpoint the precise mechanism. Moreover, large-scale

* Corresponding author. Department of Neurology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China.
** Corresponding author. Department of Neurology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China.
E-mail addresses: zhipinghu@csu.edu.cn (Z. Hu), ztang65@csu.edu.cn (Z. Tang).

https://doi.org/10.1016/j.heliyon.2024.e26377
Received 6 November 2023; Received in revised form 11 February 2024; Accepted 12 February 2024
Available online 19 February 2024

clinical trials are needed in the future to define the therapeutic potential of SCFAs in CNS diseases.

Abbreviations

AD	Alzheimer's disease
ASD	Autism spectrum disorder
Aβ	Amyloid β-protein
αSyn	α-synuclein
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
DM	Diabetes mellitus
EAE	Experimental autoimmune encephalomyelitis
FFAR	Free fatty acid receptor
FoxP3+	Forehead box P3
GDP	Gross domestic product
GPCRs	G protein-coupled receptors
GF	Germ-free
GABA	Gamma-aminobutyric acid
GDNF	Glial cell line-derived neurotrophic factor
HDACs	Histone deacetylases
IF	Impact factor
JCR	Journal Citation Reports
MGB	Microbe-gut-brain
MCTs	Monocarboxylate transporters
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
MS	Multiple sclerosis
NGF	Nerve growth factor
PD	Parkinson's disease
SCFAs	Short-chain fatty acids
Th cells	T-helper cells
WoSCC	Web of Science Core Collection

1. Introduction

As the fields of microbiology and neuroscience have become more intertwined in recent decades, the microbe-gut-brain (MGB) axis has been proposed [1]. Central nervous system (CNS) disorders are often associated with imbalances in the gut microbial composition [2–5]. Nevertheless, the exact mechanisms involved in the crosstalk between the gut microbiome and the brain remain unelucidated. Vagus nerve activity, the hypothalamic-pituitary-adrenal axis, modulation of the immune system, tryptophan metabolism, and bioactive metabolites produced by gut microbiota have been speculated as the potential pathways for MGB communication [6]. Among them, short-chain fatty acids (SCFAs) appear to play a key role in MGB crosstalk [7].

SCFAs are byproducts of the microbial fermentation activity in the intestines, referring to organic fatty acids with 1–6 carbon atoms, mainly including acetate, propionate, and butyrate [8]. Most SCFAs are absorbed by the intestine or metabolized by the hepatocytes, resulting in some of them entering systemic circulation [9]. Current researches suggests that SCFAs can act on brain physiology through both direct interactions and indirect effects [10,11]. SCFAs enter the CNS by binding to receptors on the blood-brain barrier (BBB) or by other passive routes, where they alter gene expression, mitochondrial function, neurotransmitter production, immune activation, and neuronal behavior [12]. Several publications have reported the association between SCFAs various CNS diseases. However, the manuscripts on SCFAs in CNS diseases lack unified generalization.

Bibliometric analysis, also named systematic scientometric review, is an approach providing a comprehensive overview of a research field with the assistance of science mapping tools [13]. This method focuses on the system and characteristics of research literature and is used to quantitatively analyze publications, visualize the knowledge structure, measure the impact of publications, and identify emerging trends [14,15]. Researchers who are new to a field may benefit from timely and comprehensive systematic reviews by understanding the intellectual landscape and by defining their research topic in an effective and concise manner. For experienced researchers, a bibliometric analysis can assist in keeping up with the latest knowledge in the area of interest [16].

With the deepening research on the role of the gut microbiota as a regulator of gut-brain axis signaling, more research has focused

on SCFAs and their biological effects on CNS diseases such as psychiatry, neurodevelopment, and neurodegenerative diseases. Researchers have found that SCFAs are involved in the pathogenesis and development of a variety of CNS diseases, and pointed out that SCFAs may have a potential therapeutic effect. Given the huge research value, studies on SCFAs in CNS diseases have been growing rapidly in recent years. The objective and overall reports on the frontier trend and hotspots of SCFAs in CNS diseases are lacking. Therefore, a bibliometric analysis of the published literature was conducted to quantify the whole picture of research related to SCFAs in CNS diseases. The purpose of our study was to provide first comprehensive bibliometric analysis of the literature on SCFAs in CNS diseases, and to provide fresh insights into the current status, emerging trends, and future prospects for scholars who have entered or are about to enter the field.

2. Materials and methods

2.1. Data collection and search strategy

A systematic literature search was conducted using the Web of Science Core Collection (WoSCC). The search strategy is described below: TS = ("short chain fatty acid" OR "short-chain fatty acid" OR "SCFA") AND (TS = neurological diseases OR TS = neurological disorder OR TS = brain injury OR TS = central nervous system disease OR TS = CNS disease OR TS = central nervous system disorder OR TS = brain disorder OR TS = CNS disorder) AND Language = (English), with a time span from 2002 to 2022. A day-long literature search and data collection were conducted on April 13, 2023 to avoid the impact of database updates. A total of 499 papers were assessed. Only original articles and reviews were obtained, and 480 records were finally obtained. The search procedure is displayed in Fig. 1. And to avoid missing the last research trend, we also search the last 5 years related publication using the same search strategy as we described above. The literature retrieval was carried out on December 23, 2023. A total of 507 publications were obtained, 302 articles and 205 reviews included. As butyrate is the most widely studied SCFAs in CNS diseases, we searched the literature related to butyrate separately. The search strategy is described below: TS = ("butyrate*") AND (TS = neurological diseases OR TS = neurological disorder OR TS = brain injury OR TS = central nervous system disease OR TS = CNS disease OR TS = central nervous system disorder OR TS = brain disorder OR TS = CNS disorder) AND Language = (English) AND Publication Date = (Last five years). The searches were conducted on December 23, 2023. A total of 374 publications were obtained, 237 articles and 137 reviews included.

2.2. Analysis tool

The WoSCC database was primarily used to analyze the annual number of publications and publication years. The CiteSpace (6.2. R2 for the two decades, and 6.2. R6 for the last 5 years) was used to visualize the research countries, institutions, authors, published journals, references, keywords and other indicators associated with the research field. The data in Citespace is organized into yearly slices, with the selection criterial set as the g-index k = 25, pruning pathfinder in each slice. In the graphs, nodes represent elements such as country, institution, author, and keyword while the size of the nodes presents the number of documents or frequency. The links

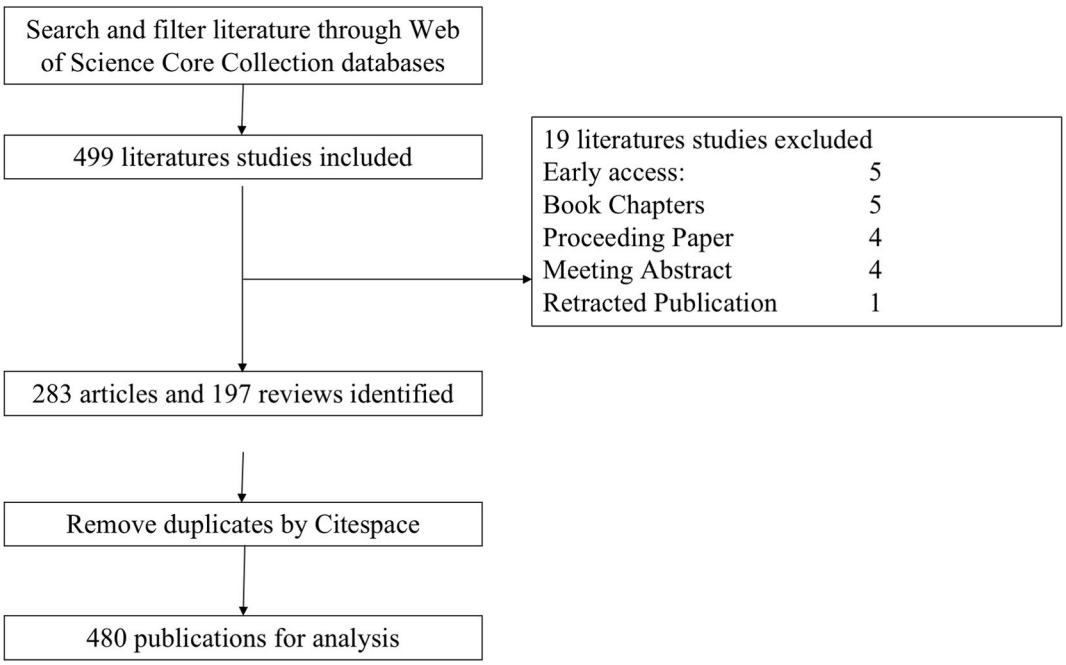

Fig. 1. Flowchart of the literature search and selection process.

represent relationships such as collaboration, co-occurrence, and co-citations. The colors of nodes and links represent the occurrence or citation years. The outside circles in purple represent the centrality higher than 0.1, which is used to evaluate the importance of nodes in network cooperation and is considered significant. The journal dual-map overlap, keyword cluster timeline, and keyword burst were also analyzed to clarify the research status and focus. The paths in dual-map overlap indicate the journal-cited relationship. A keyword burst reflects a sharp rise in interest in a particular research topic direction and is applied to uncover cutting-edge topics.

3. Results

3.1. Yearly quantitative distribution of articles

From 2002 to 2022 (December 31, 2022), there were 499 English publications related to SCFAs in neurological diseases were indexed in the WoSCC online database. After exclusion, a total of 480 publications were included in the final analysis. The variation in the number of annual publications reveals the progress and the degree of focus in this research field. As displayed in Fig. 2, the topic was hardly studied from 2002 to 2006. After 2007, the number of annual publications on SCFAs in CNS diseases showed an overall upward trend, with the exception of a decline in the number at some time points. Between 2017 and 2022, the publications on SCFA in CNS showed a rapid rise, with a total of 435 papers published, accounting for 90.63% of the total included studies. In 2022, the number of publications reached a peak of 129. The results reveal the increased focus on this topic over the past five years.

3.2. Contribution by country and institution

The global contribution to SCFA in CNS disease research was analyzed, with more than 50 countries making significant contributions. As shown in Table 1, the top five countries in terms of publication volume were China, the United States, Italy, Canada and Ireland. Fig. 3A displayed the spatial distribution map of countries. Nodes were sized based on the number of articles published, the links represented the collaboration, and the outermost purple ring represented a centrality level greater than or equal to 0.1. The United States showed the highest centrality at 0.4, followed by England (0.37) and the Netherlands (0.19). These countries were considered to play a crucial role in the area of research. In spite of China being the most prolific publisher, its global influence is not proportional to its production.

As illustrated in Table 2, University College Cork had the highest number of publications at the institutional level, followed by JiangNan University, and the University of Western Ontario. The co-institution network map had 260 nodes and 466 links, with a network density of 0.0138 (Fig. 3B), indicating that most research institutions were scattered and lacked extensive cooperation. Among the top 10 most prolific institutions, University College Cork, JiangNan University, and UDICE-French Research University all had a centrality greater than 0.1. Karolinska University from Sweden had the highest centrality of 0.24. They were circled in purple in Fig. 3B, representing that studies of SCFAs in CNS diseases conducted by these institutions may have played a crucial role in the field.

3.3. Analysis of journals and co-cited journals

Analyzing the distribution of published sources helps identify core journals. All studies concerning SCFA in CNS disease were published in 272 different journals and the top 10 prolific journals are displayed in Table 3. *Nutrients* had the highest number of

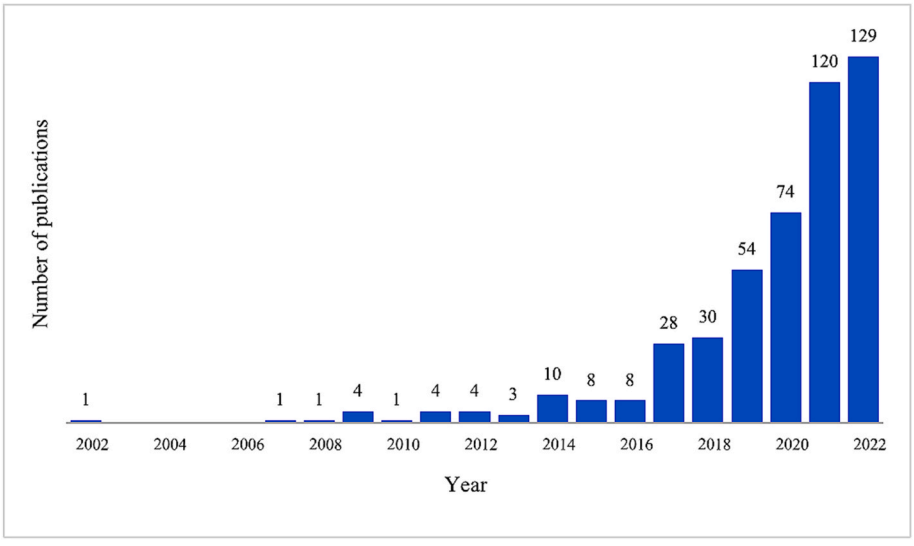

Fig. 2. Global trend of annual publications related to SCFAs in CNS disease from 2002 to 2022.

Table 1
Top 10 countries/regions in terms of publications and centrality.

Rank	Country/Region	Count (%)	Rank	Country/Region	Count	Centrality
1	China	139 (28.96)	1	United States	109	0.4
2	United States	109 (22.71)	2	England	14	0.37
3	Italy	35 (7.29)	3	Netherlands	17	0.19
4	Canada	30 (6.25)	4	Italy	35	0.11
5	Ireland	26 (5.42)	5	Canada	30	0.11
6	Germany	26 (5.42)	6	Brazil	10	0.1
7	Japan	25 (5.21)	7	Australia	18	0.09
8	India	20 (4.17)	8	Germany	26	0.08
9	Australia	18 (3.75)	9	Sweden	14	0.08
10	Netherlands	17 (3.54)	10	Saudi Arabia	9	0.08

publications, with a total of 23 papers, followed by *Frontiers in Microbiology, Frontiers in Immunology*, and *International Journal of Molecular Sciences*. *Gut Microbes* had the highest impact factor (IF), with an IF of 9.434. Nine of the 10 journals had an IF over five and eight were in the Q1 Journal Citation Reports (JCR) division. In order to evaluate the interdependence and cross-relationship among journals, the co-citation of journals was analyzed. As shown in Table 3, despite having only 7 publications in *Plos One*, it ranked first in total citations (334 citations), followed by *Proceedings of the National Academy of Sciences of the United States of America* (330 citations) and *Cell* (323 citations).

The aim of the dual-map overlap analysis is to present patterns of scientific assemblages on the basis of a global scientific literature map. Fig. 4 showed a dual-map concerning SCFA in CNS disease published between 2002 and 2022. All colored curves originate from the left map (citing journals) to the right (cited journals), representing the path of the citation links. There is one major citation path in the current map, indicating that papers published in Molecular/Biology/Immunology are always cited by Molecular/Biology/Genetics.

3.4. Author analysis

Co-citation analysis of authors aims to identify influential authors and potential collaborations in the field. About three thousand authors had contributed to SCFA in CNS disease since 2002. The ten most prolific authors and most cited authors are listed in Table 4. The co-author network was composed of 380 nodes and 781 links, the nodes in Fig. 5A represented authors, and the lines represented the collaborative relationships. Apparently, only a small number of links appeared on the co-author network map, indicating little collaboration between different researchers in this research field. The network of cited authors, depicted in Fig. 5B, comprises 691 nodes and 2181 links. Only three of the 691 co-cited authors had more than 100 citations. John F. Cryan, a researcher from the University College Cork in Ireland, published the maximum number of manuscripts and had the most citations. His research in SCFAs in CNS disease mainly focused on neurodevelopment, neurodegenerative and mental disorders.

3.5. Analysis of cited references

Highly-cited articles indicate a hotspot and depth of research in a field, as reflected by their citation frequency and influence. Fig. 6A displays a network visualization map of cited references. Table 5 lists the top 5 references in terms of citation frequency and centrality on SCFAs in CNS disease. The most cited article was *The role of short-chain fatty acids in microbiota-gut-brain*, published in *Nature Reviews Gastroenterology & Hematology,* written by Boushra Dalile et al., in 2019, with 67 citations [6]. The second most cited article was a review written by John F. Cryan entitled "*The role of short-chain fatty acids in microbiota-gut-brain communication*" with 62 citations [10]. The total number of citations of the top 5 references was close to 300. The article published in *Biochimica et biophysica acta* by Sa'ad H. Al-Lahham et al., in 2010 was the article with the highest centrality [17].

Burst detection was considered as a tool to identify research frontiers or research trends that have emerged over time. The references with the strongest citation burst were explored using CiteSpace software, and the top 25 references were shown in Supplementary Fig. 1. The references with citation burst first appeared in 2014, and the burst was attributed to a publication in 2013 [18]. The article entitled "*Host microbiota constantly control maturation and function of microglia in the CNS*", which was published by *Nature Neuroscience*, had the strongest citation burstiness (2017–2020, strength 15.33) [19]. And the latest references with citation bursts were all published in *Cell*, appearing in 2019 and 2020 respectively, and the citation bursts are still ongoing [20,21].

As an additional step, to take a closer look at these co-citations, we performed a clustered network analysis. Publications sharing many citations tend to be homogeneous. After selecting the "show the largest connected component only " node, 10 major clusters were generated (Fig. 6B): #0 (molecular mechanism), #1 (translational research), #2 (autism spectrum disorder), #3 (multiple sclerosis), #4 (rat), #5 (key regulator), #6 (propionic acid), #7 (Parkinson's disease), #8 (systematic review), and #11 (metabolic tinkering).

3.6. Analysis of keywords

Keywords analysis is an effective way to investigate the structure of scientific knowledge to identify research frontiers and development trends. Fig. 7 shows the keyword co-occurrence network. Table 6 demonstrates that the top 10 high-frequency keywords

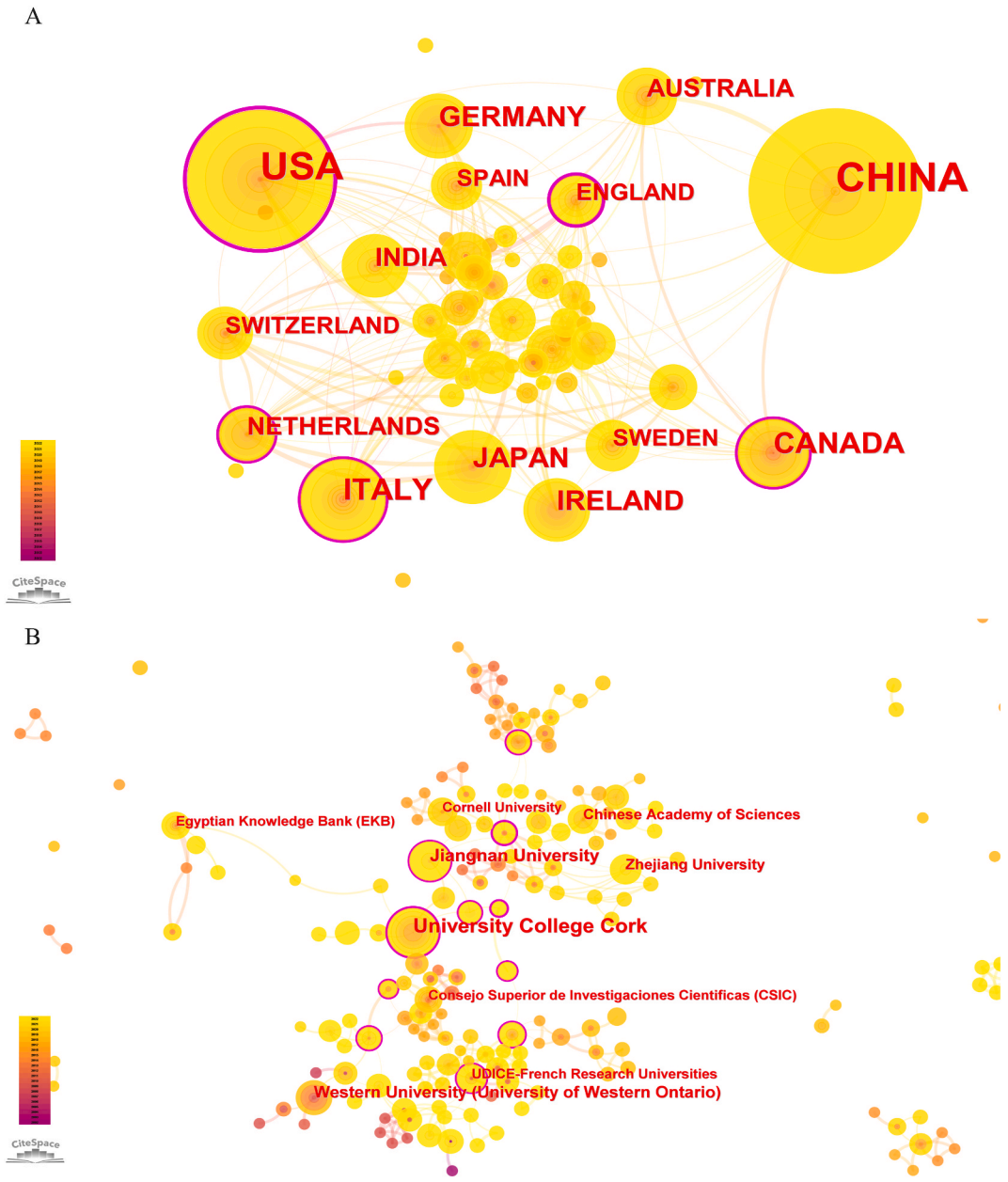

Fig. 3. Visual maps of publications over (A) countries/(B) institutions studying SCFAs in CNS disease. Each node represents a(n) country/institution, and node size indicates the number of publications. The connection between the nodes represents a co-occurrence relationship. And nodes with purple round mean high betweenness centrality (≥0.1).

on this topic were "gut microbiome", "SCFAs", "central nervous system", "gut brain axis", "butyrate", "inflammation", "Parkinson's disease (PD)", "disorder", "expression", "autism spectrum disorder (ASD)", and "Alzheimer's disease (AD)". Among them, "SCFAs" showed the highest centrality of 0.21, which shared "bridge" effects in the keyword co-occurrence map with "central nervous system" (0.16), and "expression" (0.13).

Keyword cluster refers to clustering network based on keywords with similar research topics, focusing on revealing the main themes. Cluster connotations were identified by the most frequent title word in the article. A total of twelve clusters were generated as shown in Fig. 8. It intuitively reflected the developmental path and phased hotspot of SCFA in CNS disease research from the time dimension. On this basis, in order to clarify the association of SCFAs with CNS diseases, we divided these clusters into four categories according to the commonality of research hotspots, as shown in Table 7. Fig. 9 displays the top 15 keywords with the strongest citation burst, showing the development of the hot topics. Red lines indicate timeframes for keyword bursts. "valproic acid", "Animal model", and "histone deacetylase inhibitor" appeared in the earliest research and had taken an important position for a long time. The latest

Table 2
Top 10 institutions in terms of publication volume.

Rank	Institutions	Country	Centrality	Publications
1	University College Cork	Ireland	0.21	22
2	JiangNan University	China	0.14	14
3	University Of Western Ontario	Canada	0.03	12
4	ZheJian University	China	0.07	8
5	Chinese Academy of Sciences	China	0.08	8
6	UDICE-French Research University	France	0.12	7
7	Cornell University	USA	0.03	7
8	Consejo Superior de Investigaciones Cientificas	France	0.06	7
9	The Egyptian Knowledge Bank	Egypt	0.03	7
10	Ruhr University Bochum	Germany	0.00	6

Table 3
The top 10 prolific journals and cited journals.

Rank	Journal	Count (%)	JCR	IF (2021)	Rank	Cited-Journal	Count	IF
1	Nutrients	23 (4.79)	Q1	6.706	1	Plos One	334	3.752
2	Frontiers In Microbiology	16 (3.33)	Q1	6.064	2	Proceedings Of The National Academy Of Sciences Of The United States Of America	330	12.779
3	Frontiers In Immunology	14 (2.92)	Q1	6.208	3	Cell	323	66.850
4	International Journal Of Molecular Sciences	14 (2.92)	Q1	5.324	4	Nature	319	24.274
5	Food & Function	8 (1.68)	Q2	5.152	5	Scientific Reports	318	4.996
6	Gut Microbes	7 (1.46)	Q1	9.434	6	Gut	256	31.793
7	Frontiers In Neuroscience	7 (1.46)	Q1	6.317	7	Science	256	63.714
8	Frontiers In Nutrition	7 (1.46)	Q1	6.59	8	Brain Behavior and immunity	255	19.227
9	Frontiers In Cellular And Infection Microbiology	7 (1.46)	Q1	6.073	9	Nutrients	233	6.706
10	Plos One	7 (1.46)	Q2	3.752	10	Gastroenterology	224	33.883

JCR: Journal Citation Reports; IF: impact factor.

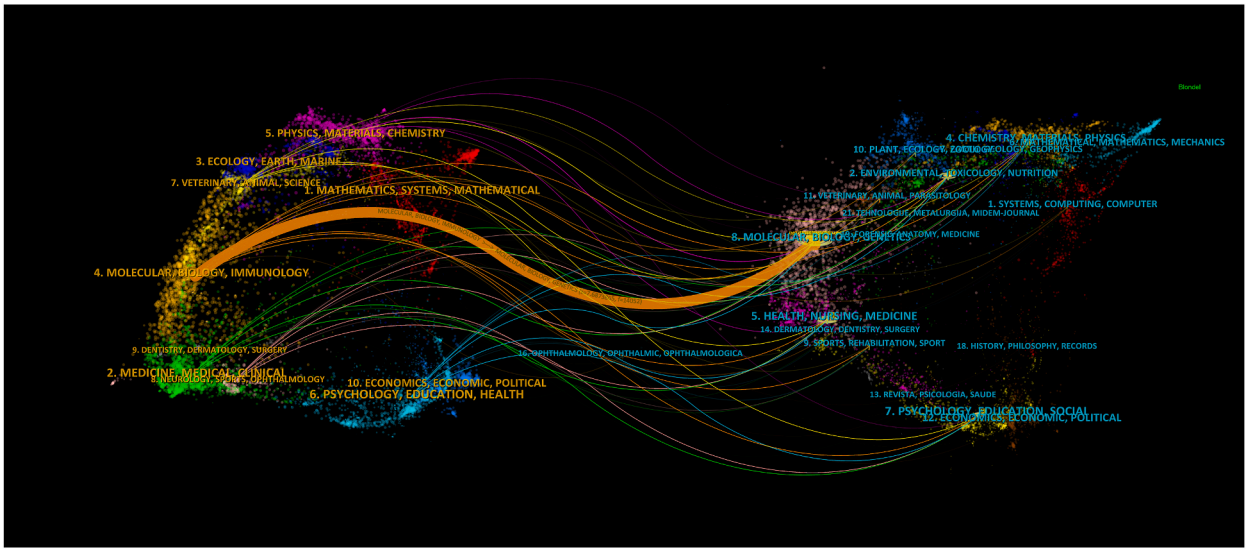

Fig. 4. The dual map overlay of journals contributed to publications on the application of SCFAs in CNS disease from 2002 to 2022. All the orange path showed articles in the research fields of molecular/biology/immunology are more likely to cite articles in the field of molecular, biology, genetics.

Table 4
The top 10 prolific authors and cited authors.

Rank	Author	Institution (country)	Publications	Rank	Cited Author	Institution (country)	Citation Counts	Centrality
1	Jonh F. Cryan	University College Cork (Ireland)	20	1	Jonh F. Cryan	University College Cork (Ireland)	151	0.03
2	Timothy G. Dinan	University College Cork (Ireland)	13	2	Daniel Erny	University of Freiburg (Germany)	124	0.01
3	Derrick F. Macfabe	Universuty Of Western Ontario (Canada)	10	3	Timothy G. Dinan	University College Cork (Ireland)	100	0.06
4	Gerard Clarke	University College Cork (Ireland)	8	4	Viorica Braniste	Karolinska Institutet (Sweden)	96	0.06
5	Wei Chen	Jiangnan University (China)	8	5	Timothy R. Sampson	Emory University (USA)	90	0.02
6	Jianxin Zhao	Jiangnan University (China)	8	6	Premysl Bercik	McMaster University (Canada)	83	0.03
7	Klaus-Peter Ossenkopp	Universuty Of Western Ontario (Canada)	8	7	Javier A. Bravo	Pontificia Universidad Catolica de Valparaiso (Chile)	82	0.03
8	Zhigang Liu	Northwest A&F University (China)	6	8	Roman M. Stilling	University College Cork (Ireland)	80	0.13
9	Xuebo Liu	Northwest A&F University (China)	6	9	Haiyin Jiang	Zhejiang University (China)	78	0.03
10	Gang Wang	Jiangnan University (China)	6	10	Jessica M. Yano	University of California (USA)	78	0.01

burst keywords included “social behavior”, “pathogenesis”, and “insulin sensitive”.

3.7. Analysis of research topics in past 5 years

Published researches in the field of SCFAs in CNS diseases continues to increase year by year. To keep up with research trends and hotspots, we used the Citespace software to analyze references and keywords in this area over the past five years. In addition, as “butyrate" was one of the top 10 keywords with the highest frequency between 2002 and 2022, we separately explored the research hotspots of butyrate in CNS diseases from 2018 to 2023.

The top 5 most cited SCFAs-related articles in the CNS field during last 5 years were listed in Supplementary Table 1. Among the 5 highly cited references, a paper entitled “*The role of short-chain fatty acids from gut microbiota in gut-brain communication*" published in *Frontiers in endocrinology was a newly emerging highly cited reference* [22]. As shown in Fig. 10A, the latest publications in the field of SCFAs in CNS diseases mainly focused on physical exercise, energy balance, Parkinson’s disease, multiple sclerosis, and autism spectrum disorder. Moreover, combined with the top 5 highly cited references (Supplementary Table 2) and timeline view of references (Fig. 10B) in the field of butyrate in CNS disease in past 5 years, we identified that the research topics in this field were mainly based on the involvement of butyrate in MGB crosstalk and the relationship between butyrate and CNS diseases.

Over the past 5 years, 305 keywords have been discovered in the field of SCFAs in CNS diseases. The top 10 high-frequency keywords were essentially the same as they were from 2002 to 2022 (Supplementary Table 3). As shown in Fig. 11A, a total of eleven clusters generated, in the following order: “sepsis-associated encephalopathy”, “upcoming role”, “promising psychobiotics”, “regulating gut microbiota”, “neuropsychiatric disorder”, “Parkinson’s disease”, “autism spectrum disorder”, “multiple sclerosis”, “risk factor”, “microbiological therapy”, and “rodent model”. After classifying these clusters (Table 8), it was found that compared with the keyword clusters from 2002 to 2022, the hotspots in the past five years have increased the attention to the therapeutic potential of SCFAs in the CNS diseases. Furthermore, 262 keywords were found in the research area of butyrate in CNS diseases, and the top 10 keywords based on occurrence were displayed in Supplementary Table 4. A keyword timeline graph was generated based on eleven keywords clusters (Fig. 11B). And as presented in Table 9, these keywords clusters could also be grouped into four categories.

4. Discussion

4.1. General information

Based on the data from the WoSCC, from 2002 to 2022, a total of 480 articles were published in 254 academic journals by 2997 authors from more than 50 countries/regions. The increasing trend of publications reflected the growing interest in SCFAs in CNS diseases. As presented in Fig. 2, there are roughly three stages were observed in the publication trend: the embryonic stage (2002–2006), the phase of fluctuation (2007–2016), and the development stage (2017–2022). The overall trend of publications was consistent with a previous bibliometric analysis involving gut microbiome and neuroscience [23]. These findings indicate that the relationships between CNS diseases and gut microbiota and its products in humans are being increasingly studied, and a large amount of literature on this topic will likely be generated in the coming years. Furthermore, the number of articles published in 2022 showed no significantly increase from 2021, which might be attributed to the relative stagnation of research in most fields during the COVID-19 pandemic. During that time, the scientific community shifted its focus.

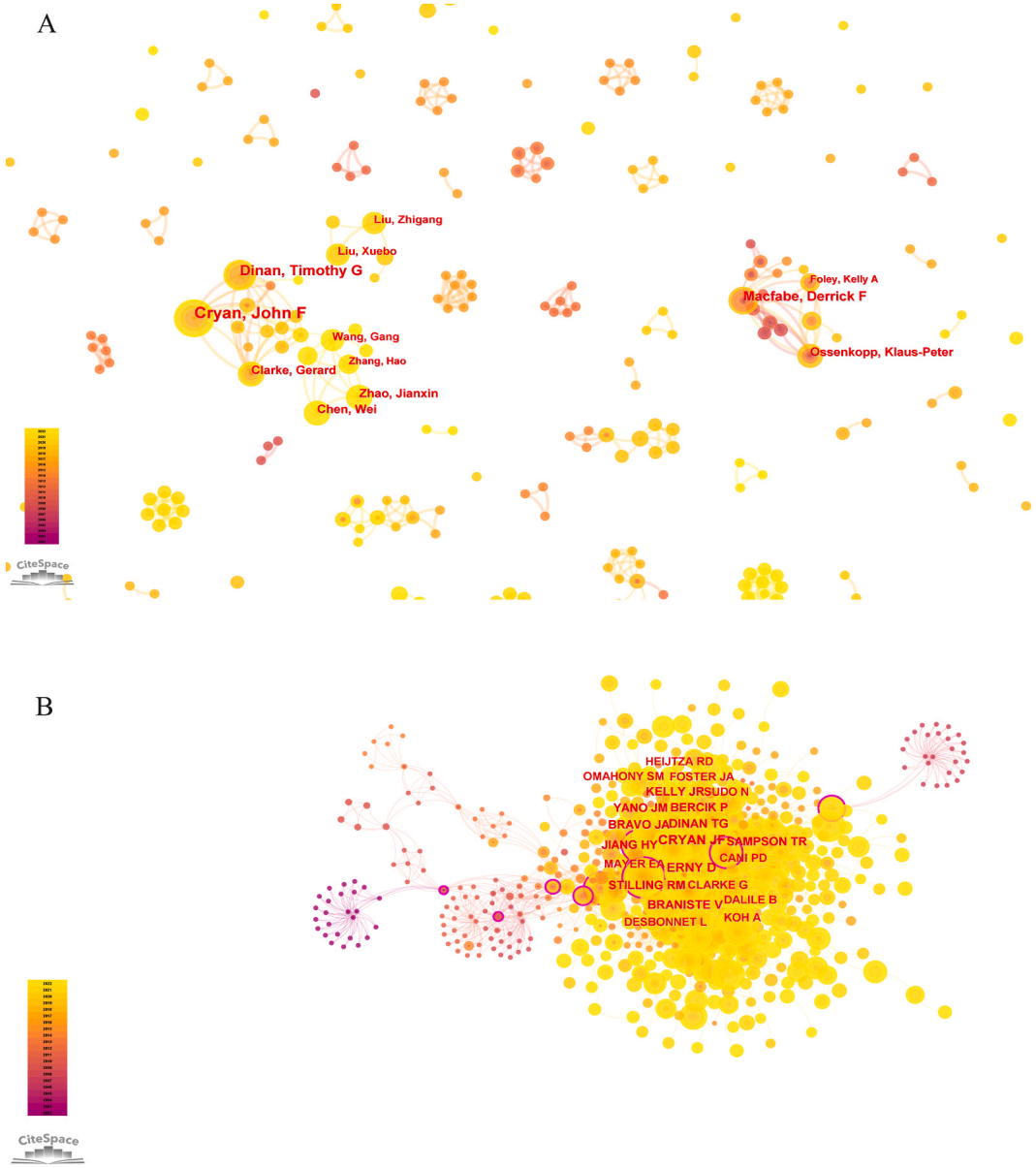

Fig. 5. Visual analysis of authors. Collaboration network of co-authors (A) and network visualization map of cited authors (B). The nodes in the map represent authors/cited authors. The lines between nodes represent the collaborative/co-citation relationships. The purple ring represents centrality (≥0.1).

Analyzing the literature source, the highest number of articles were published by China, followed by the United States. More than half of the total number of publications originated from these two countries. We considered the reasons as the following: On the one hand, the gross domestic product (GDP) is closely related to scientific research output, and China and the United States both have high GDPs. Countries with rapid economic growth are expected to allocate more funds to promote research [24]. On the other hand, the second phase of the Human Microbiome Project on the MGB axis launched by the National Institutes of Health in 2013 and the Microbiome Program hosted by the Chinese Academy of Sciences in 2017 have provided significant financial support [25]. These projects have increased academic interest in gut microbiota and its products, including SCFAs. Besides, countries with high centrality have a bridging effect in the global cooperation network [26]. The United States is undoubtedly the leader in this field, with the highest centrality and the second largest number of publications. It is also because the United States has the most exchanges and cooperation with other countries (Supplementary Fig. 2). As displayed in Fig. 3A, China has a lower centrality compared with Western countries, which means China should pay more attention to strengthening cooperation and enhancing international influence. To alleviated this situation, Chinese researchers need to cultivate advanced thinking such as critical thinking and innovative thinking in the process of future research.

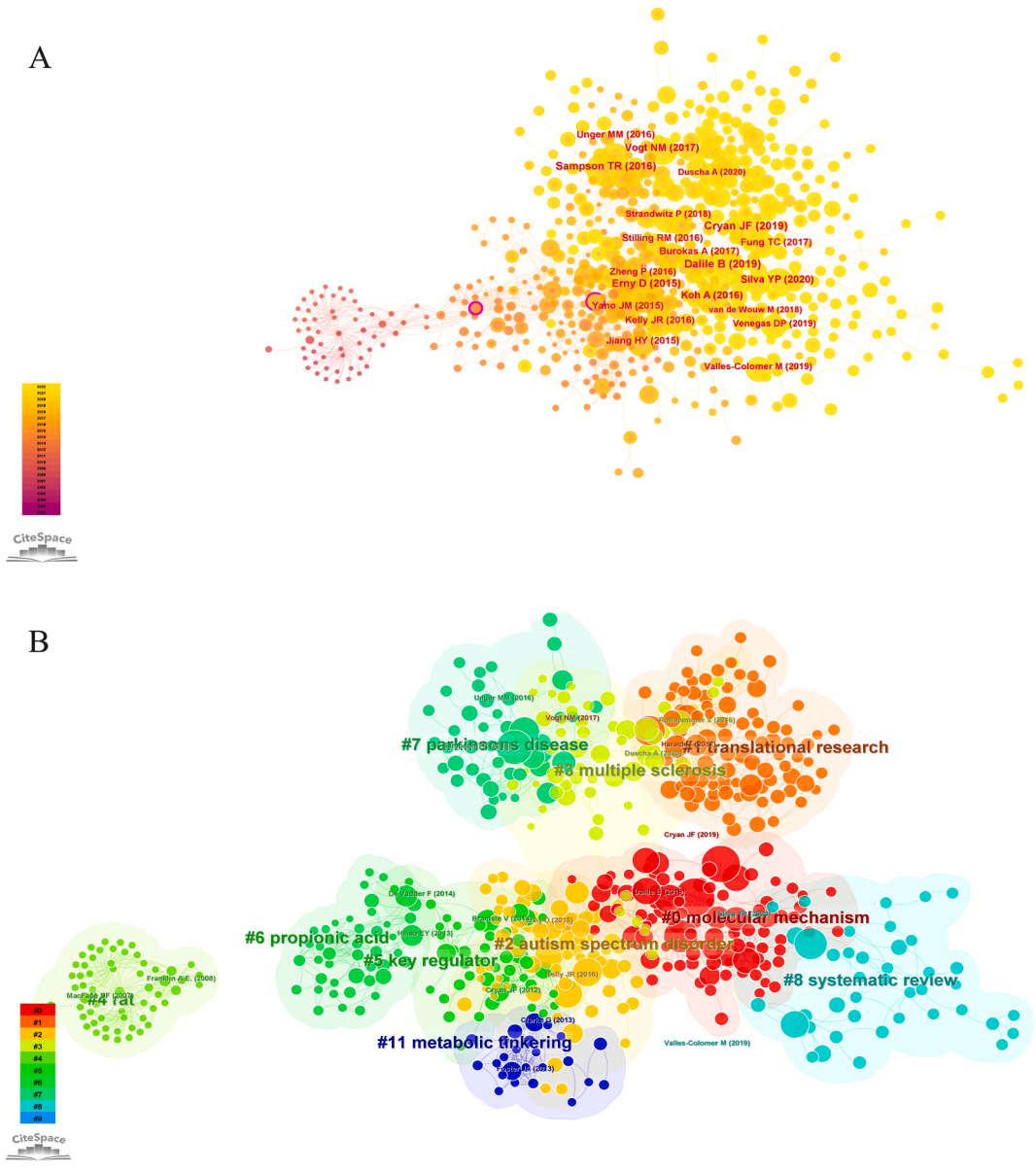

Fig. 6. Visual analysis of references co-citation network (A) and references clustering network (B).

University College Cork (Ireland) was the most influential and productive institution. Among the top ten most productive institutions in the field of SCFAs in CNS diseases, only one was in the United States. This suggested that institutions in the United States were decentralized and lacked cooperation. John F. Cryan, a researcher from University College Cork, was the most prolific author and had the highest citations. As displayed in Table 4, two of the top three prolific authors and cited authors worked at University College Cork, suggesting that the University College Cork taking the leading position in this field. The research team, represented by John F. Cryan and Timothy G. Dinan, focused on the mechanisms by which SCFAs affect brain function and behavior [27–29]. They implemented animal experiments to demonstrate that SCFAs can alleviate the changes brought about by psychosocial stress, opening a new avenue in the field of nutritional neuropsychopharmacology and playing an important guiding role [30]. Although China was the most productive country, the global influence of Chinese scholars was relatively low, which could be related to the later entry of Chinese academics into the field. Hence, in order to promote the development and prosperity of SCFAs in CNS diseases, solid cooperation should be established between institutions and researchers is highly recommended.

In the journal analysis, the most prolific journal was *Nutrients* and the most cited journal was *Plos One*. A majority of relevant studies were published in Q1/Q2 journals with a strong international reputation, as shown in Table 3. Among these journals, *Gut Microbes* had the highest IF of 9.434, while other journals had an IF between 3.352 and 6.706. These results indicate that the link between SCFAs and CNS diseases has appealed to many scholars and its research value has been acknowledged. However, high-impact papers are

Table 5
Top 5 references in terms of citation frequency and centrality.

Rank	Frequency	References	Author and publication year	Rank	Centrality	References	Author and publication year
1	67	The role of short-chain fatty acids in microbiota-gut-brain communication.	Boushra Dalile (2019)	1	0.16	Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms.	Sa'ad H. Al-Lahham (2010)
2	62	The Microbiota-Gut-Brain Axis.	John F. Cryan (2019)	2	0.11	Microbiota is essential for social development in the mouse.	Lieve Desbonnet (2014)
3	54	Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease.	Timothy R. Sampson (2016)	3	0.09	Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders.	Elaine Y. Hsiao (2013)
4	53	Host microbiota constantly control maturation and function of microglia in the CNS.	Daniel Erny (2015)	4	0.08	Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice.	Aurelijus Burokas (2017)
5	49	From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites.	Ara Koh (2016)	5	0.08	Role of the microbiota in immunity and inflammation.	Yasmine Belkaid (2014)

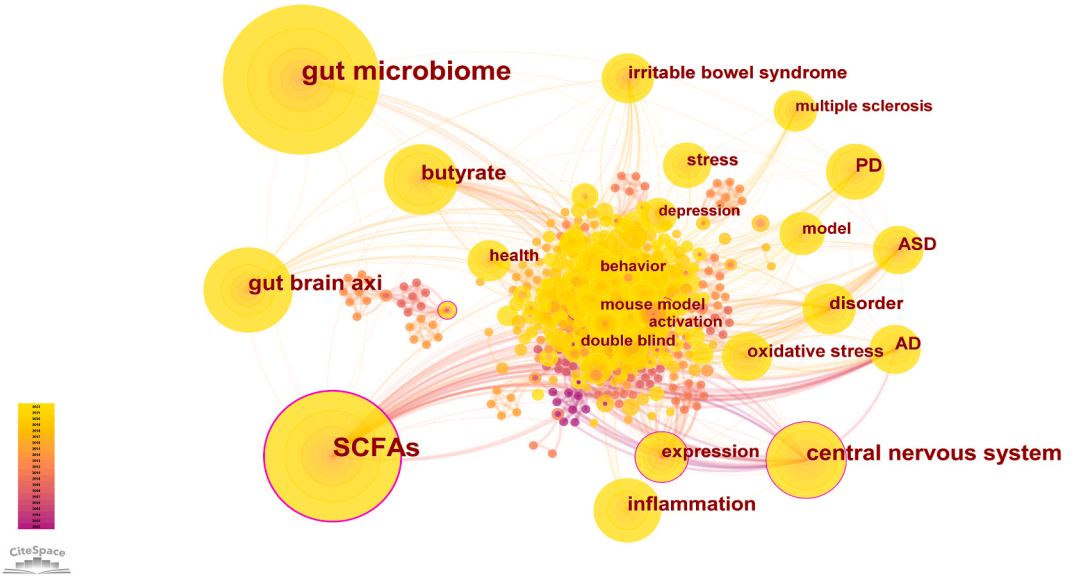

Fig. 7. Co-occurrence Analysis of keywords. Each node represents a keyword, and node size indicates the number of occurrences. The connection between the nodes represents a co-occurrence relationship. The top ten co-occurrence keywords are "gut microbiome" (316), "SCFAs" (249), "central nervous system" [101], "gut brain axis" [99], "butyrate" [74], "inflammation" [61], "PD" [47], "disorder" [40], "expression" [39], "ASD" [38], and "AD" [38]. Note: ASD: autism spectrum disorder; AD: Alzheimer's disease; PD: Parkinson's disease; SCFAs: short-chain fatty acids.

challenging to publish. In accordance with the dual-map analysis, the journals in Table 3 were mainly focused on the molecular, biology, and other comprehensive fields.

The number of citations is an indicator that can assess the impact of a scientific publication, which reflects the contribution of an article to the area of concern [31]. A review of the highly cited literature allows a comprehensive understanding of the knowledge structure in the field of SCFAs in CNS disease research. Combining the results of Table 5 (2002–2022) and Supplementary Table 1 (2018–2023), the top 5 cited references were published between 2015 and 2020, including four reviews and two animal experiment articles. The most cited reference was published in *Nature Reviews Gastroenterology & Hematology in* 2019. This review summarized the current understanding of the potential of SCFAs to mediate MGB interactions and discussed the relationship between SCFAs and psychobiological processes [6]. Another review written by John F. Cryan et al. published in *Physiological reviews* was the second most cited reference, which provided a comprehensive overview of the MGB axis and what still needs to be understood in developing a microbiota-based treatments [10]. Timothy R. Sampson et al. published in *cell in 2016,* ranked in the top 5 highly cited articles in terms of citation frequency, indicating that the gut dysbiosis was involved in the pathogenesis of PD and was a risk factor for PD [21].

Table 6
The top 10 keywords in terms of frequency.

Rank	keywords	Count	Centrality
1	gut microbiome	316	0.04
2	SCFAs	249	0.21
3	central nervous system	101	0.16
4	gut brain axis	99	0.06
5	butyrate	74	0.07
6	inflammation	61	0.02
7	PD	47	0.06
8	disorder	40	0.06
9	expression	39	0.13
10	ASD/AD	38	0.07

ASD: autism spectrum disorder; AD: Alzheimer's disease; PD: Parkinson's disease; SCFAs: short-chain fatty acids.

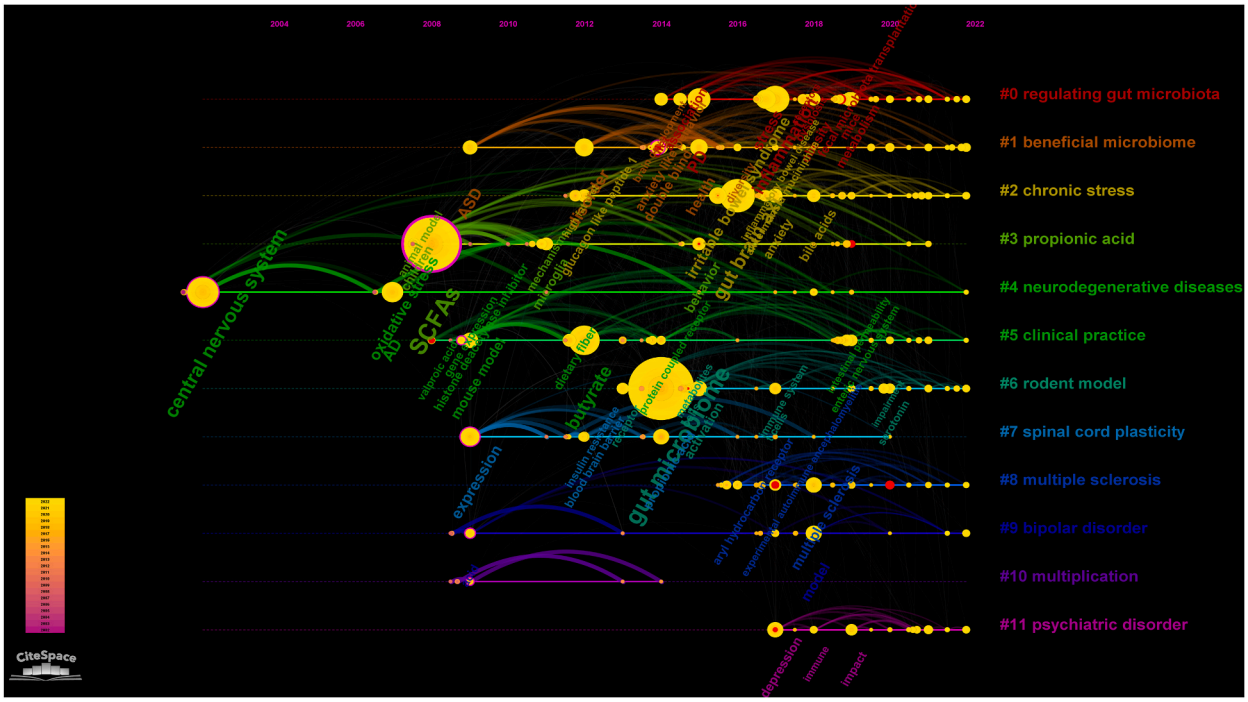

Fig. 8. Keyword cluster timeline analysis. Each node represents a keyword, and the size of the node was closely related to the number of occurrences. Nodes with purple circles stated the existence of significant turning points in scientific knowledge, i.e., higher centrality. Note: ASD: autism spectrum disorder; PD: Parkinson's disease; SCFAs: short-chain fatty acids.

Table 7
The Keywords cluster analysis of SCFAs in CNS diseases research.

Category	Cluster ID	Year (mean)	Top keyword	Research hotspots
I	#0	2018	regulating gut microbiota	SCFAs play a key role in microbe-gut-brain crosstalk
	#1	2016	beneficial microbiome	
	#10	2011	multiplication	
II	#3	2014	propionic acid	The classification and definition of SCFAs in the field of CNS.
III	#2	2017	chronic stress	Several CNS diseases that are closely related to SCFAs research
	#4	2012	neurodegenerative diseases	
	#8	2019	multiple sclerosis	
	#9	2016	bipolar disorder	
	#11	2019	psychiatric disorder	
IV	#5	2015	clinical practice	Mechanism and translational studies of SCFAs in the CNS diseases
	#6	2017	rodent model	
	#7	2015	spinal cord plasticity	

CNS: central nervous system; SCFAs: short-chain fatty acids.

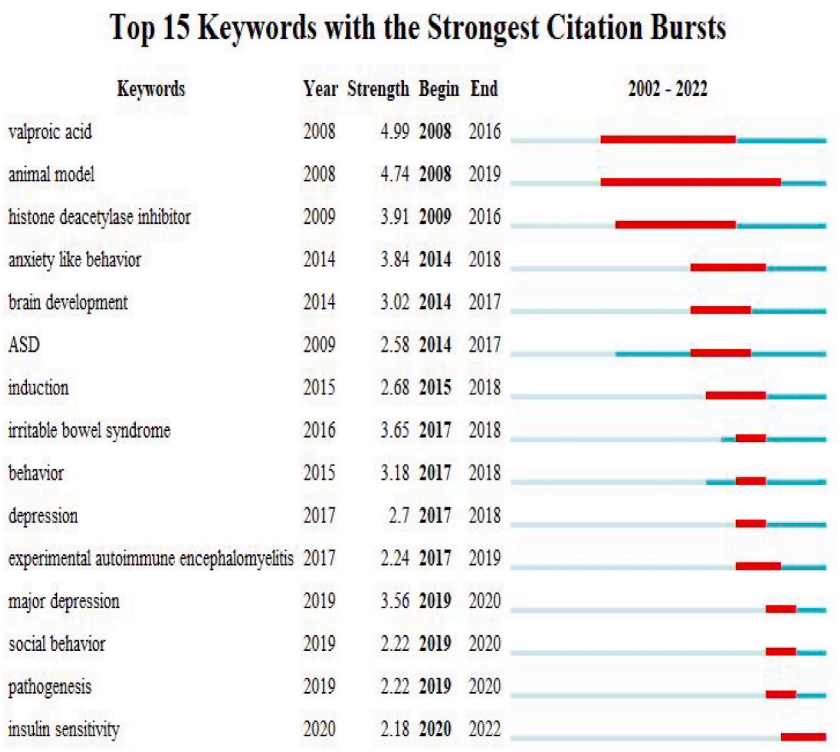

Fig. 9. The top 15 keywords with the strongest citation bursts. The red bands indicate the duration of burst. Note: ASD: autism spectrum disorder.

Similarly, another article also published in *cell*, written by Ara Koh et al. also had a high number of citations. This work concluded the process by which SCFAs are synthesized, are distributed, and contribute to host physiology [32]. It is worth noting that these two articles published in *cell* are still in burstiness, indicating that the corresponding topics have gained sustained attention in recent years (Supplementary Fig. 1). Besides, the article entitled "*Host microbiota constantly control maturation and function of microglia in the CNS"* by Daniel Erny et al. was the first research to identify that the gut microbiota can be involved in the maturation and maintenance of microglia in the CNS. More importantly, this study provided a critical foundation for the ongoing exploration of MGB in the brain's innate immune system and had the strongest citation burstiness [33]. In addition, an article by Ygor P. Silva et al. was highly cited after its publication in 2020. This study reviewed the knowledge of the involvement of SCFAs in MGB interactions, and emphasized that exploring the neuro-immunoendocrine function of SCFAs could help to develop new therapeutic targets for CNS diseases [22]. And the article with the highest centrality during 2002–2022 was published in 2010 and was written by Sa'ad H. Al-Lahham et al., which reviewed the biological effects of propionic acid in fatty acid metabolism, glucose metabolism, anti-inflammation, insulin sensitivity, and satiety. In general, according to the results of the references analysis, the knowledge structure of SCFAs-related researches in CNS diseases could be roughly divided into two categories, as follows: [1] the involvement of SCFAs in MGB interactions; [2] the effects of SCFAs on CNS diseases (including pathogenesis and therapeutic potential).

4.2. Hotspots and frontiers

During this era of information explosion, it is important for researchers to keep up with trends and hot topics. Bibliometrics analysis allows the identification of hot topics in an academic field via co-occurrence keyword analysis and visualize the evolution trend of hot issues via the timeline view [26]. In the keyword analysis, the top 3 frequent keywords from 2002 to 2023 were "gut microbiome", "SCFAs" and "central nervous system". From 2002 to 2022, as shown in Fig. 9, the burst keywords detection found that "animal model" had the highest burst strength, which suggested that the mechanism exploration based on animal models was crucial for the in-depth study of SCFAs in CNS diseases. With the advances in economic and social development, there has been an increasing focus on the social behavior and mental health. Despite several current studies linking SCFAs levels with depressive-, anxiety- and stress-related behaviors, the study designs were heterogenous and yielded conflicting results [6,30]. Therefore, the impact of SCFAs on social behavior will remain a research hotspot in the future. Globally, diabetes mellitus (DM) is the fastest-growing metabolic disease. According to genome-wide association reports, specific gut microbes are associated with metabolic pathway variants in type 2 DM [34]. As the most extensively studied metabolite of gut microbiota, SCFAs have been widely recognized for their ability to regulate the proliferation of pancreatic β cells and insulin secretion [35]. Since DM can cause primary and secondary damage to CNS function, such as cognitive deficits and cerebrovascular disease [36], the effect of SCFAs on insulin sensitivity has also been investigated in CNS diseases. Furthermore, combined the results of Fig. 8 (2002–2022) and Fig. 11A (2018–2023), we separately divided these clusters into

Fig. 10. Timeline distribution of references co-citation clusters related to SCFAs in CNS disease (A) and butyrate in CNS diseases (B) in the past 5 years.

4 categories based on the commonality of research hotspots. As listed in Table 7, the research topics on SCFAs in CNS diseases from 2002 to 2022 mainly focused on following aspects: [1] SCFAs play a key role in microbe-gut-brain crosstalk; [2] The classification and definition of SCFAs in the field of CNS; [3] Several CNS diseases that are closely related to SCFAs research; [4] Mechanism and translational studies of SCFAs in the CNS diseases. Compare categories presented in Table 8 (2018–2023) with Table 7 (2002–2022), we found that the hotspots over the past 5 years have gradually increased the attention to the therapeutic potential of SCFAs in the CNS diseases. And these findings are consistent with the results of reference analysis.

According to the reference analysis and keyword analysis, we summarized hotspots of SCFAs in CNS diseases as follows.

5. Short-chain fatty acid

SCFAs are gut microbes derived metabolites, of which more than 95% consists of acetate, propionate, and butyrate. Two signal transduction mechanism, the activation of G protein-coupled receptors (GPCRs) and the inhibition of histone deacetylases (HDACs), mediate the function of SCFAs. Among GPCRs, GPR43 and GPR41, which have been renamed free fatty acid receptor 2 (FFAR2) and FFAR3, and GPR109A, also known as HCAR2, are expressed in a wide variety of cells, including CNS cells [37]. These GPCRs have been shown to act as receptors for SCFAs and play crucial roles in the regulation of metabolism, immunity and inflammation [38]. HDACs are epigenetic enzymes essential for gene regulation [39]. N-butyric acid was first shown to be an HDACs inhibitor, providing early

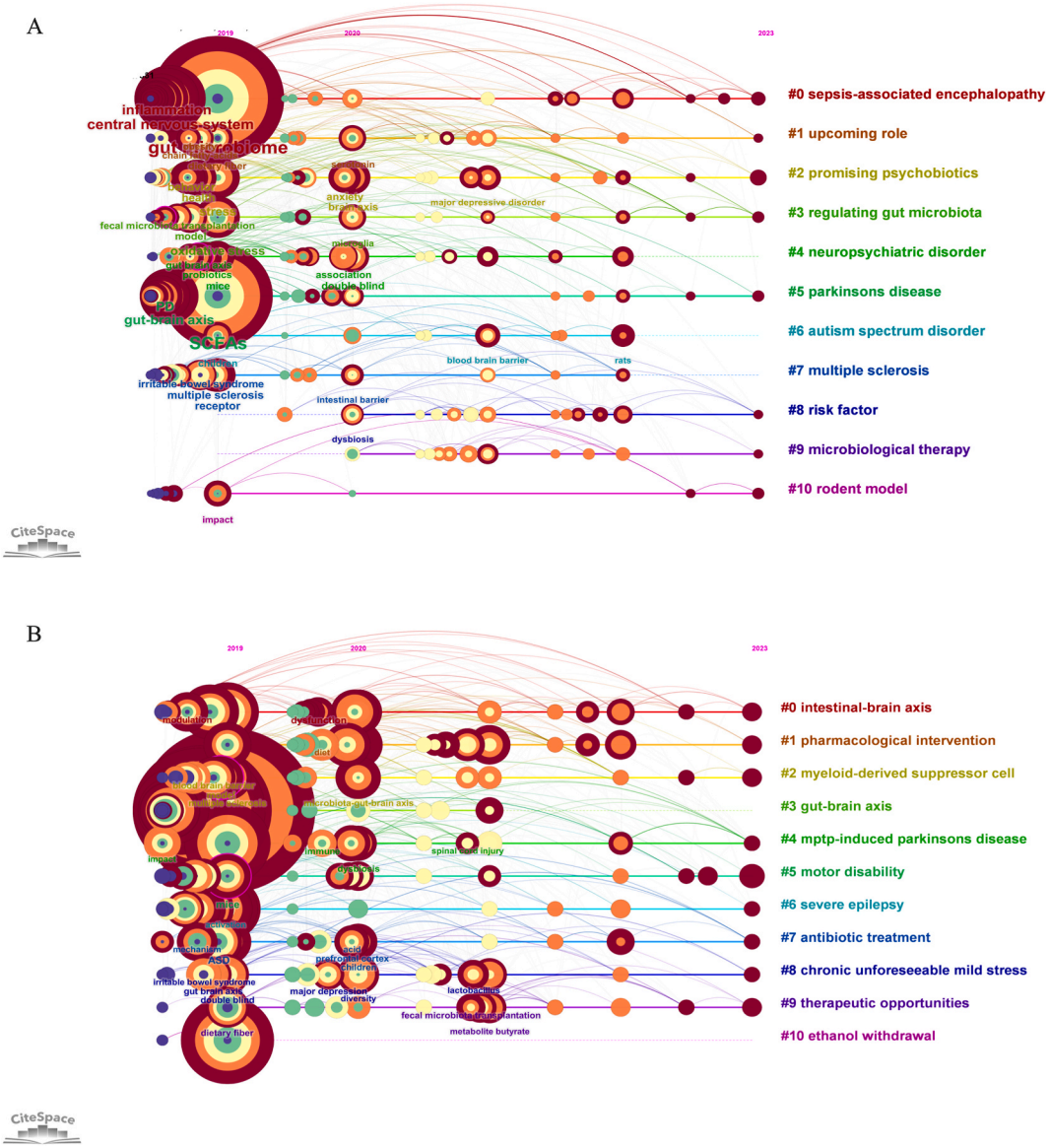

Fig. 11. Timeline view of keywords cluster analysis related to SCFAs in CNS disease (A) and butyrate in CNS diseases (B) in the past 5 years.

Table 8
The Keywords cluster analysis of SCFAs in CNS diseases research in the last 5 years.

Category	Cluster ID	Top keyword	Research hotspots
I	#3	regulating gut microbiota	SCFAs play a key role in microbe-gut-brain crosstalk
II	#10	rodent model	Mechanism of SCFAs in CNS diseases
	#8	risk factor	
III	#0	sepsis-associated encephalopathy	Several CNS diseases that are closely related to SCFAs research
	#4	neuropsychiatric disorder	
	#5	parkinsons disease	
	#6	autism spectrum disorder	
	#7	multiple sclerosis bipolar disorder	
IV	#1	upcoming role	Therapeutic potential of SCFAs in CNS diseases
	#2	promising psychobiotics	
	#9	microbiological therapy	

CNS: central nervous system; SCFAs: short-chain fatty acids.

Table 9
The Keywords cluster analysis of butyrate in CNS diseases research in the last 5 years.

Category	Cluster ID	Top keyword	Research hotspots
I	#0	intestinal-brain axis	Butyrate plays a key role in microbe-gut-brain crosstalk
	#3	gut-brain axis	
II	#2	myeloid-derived suppressor cell	Mechanism of butyrate in CNS diseases
	#7	antibiotic treatment	
III	#4	mptp-induced parkinsons disease	Several CNS diseases that are closely related to butyrate
	#5	motor disability	
	#6	severe epilepsy	
	#8	chronic unforeseeable mild stress	
	#10	ethanol withdrawal	
IV	#1	pharmacological intervention	Therapeutic potential of butyrate in CNS diseases
	#9	therapeutic opportunities	

CNS: central nervous system.

evidence that SCFAs can regulate systemic function via inhibiting HDACs activation [40]. By inhibit HDACs activity, SCFAs could alter gene expression in cells and therefore participate in the progression of disease.

Most SCFAs are absorbed by colonocytes after production, and only a tiny fraction (acetate 36%, propionate 9%, butyrate 2%) can reach the systemic circulation and peripheral tissues to regulate the physiological function of target cells or provide energy for them. It was reported that cerebrospinal fluid concentrations of acetate, propionate, and butyrate have been reported in ranges of 0–171 μM, 0–5 μM, and 0–2.8 μM, respectively [41]. Butyrate, as the most well studied of the three SCFAs in MGB, was also listed as one of the top 10 high-frequency keywords. Hence, we explored the research hotspots of butyrate in CNS diseases in the past 5 years through reference analysis and keywords analysis. As listed in Supplementary Table 2, the top 3 most cited references in butyrate-related research coincided with the results described above. Two additional highly cited articles were published in *Nature microbiology* and *The Journal of physiology*, respectively. One of them studied the correlation between microbiome features and host quality of life, as well as depression, by investigating a large cohort of microbiome population cohort. A result of this study mentioned that butyrate-producing *Faecalibacterium* and *Coprococcus* were associated with higher quality of life indicators [42]. Another highly cited reference was an animal experimental article, which suggested that SCFAs supplementation may moderate behavioral deficits caused by psychosocial stress [30].

Combined with the results of reference analysis and keywords analysis, we found that the knowledge framework of butyrate-related research in CNS diseases was basically the same as that of SCFAs-related research. At present, the hotspots in the field of butyrate in CNS diseases mainly focus on the effect of butyrate on MGB crosstalk and the link between butyrate and CNS diseases, especially psychiatric disorders.

6. SCFAs and MGB axis

In 1997, FFAR3 was found to be highly expressed in the rat brain tissues [43]. Later research confirmed that FFAR3 was expressed in brain endothelial cells [44]. Activation of FFAR3 results in propionate directly initiating a gut-brain neural circuit [45]. In addition, severe microglia malformation was observed Ffar2$^{-/-}$ mice, reminiscent of microglia in germ-free (GF) mice [33]. Besides, HDACs have been shown to be involved in various CNS diseases, including neurodegenerative diseases and a range of neuropsychiatric diseases [46,47]. Evidence shows SCFAs can function as HDAC inhibitors in animal models of CNS diseases, exhibiting neuroprotective and neuro-regenerative properties [48]. These findings indicate that SCFAs may affect CNS by binding to GPCRs or inhibiting HDACs activity. Although the crosstalk between gut and CNS has only been studied for a short time and the underlying mechanism has not been elucidated, it is speculated that SCFAs play a key role in the MGB axis.

Due to the high expression of the monocarboxylate transporters (MCTs) on endothelial cells, SCFAs can cross the BBB and act on the brain [49–51]. Moreover, a decreased expression of tight junction protein was observed in GF mice, resulting in increased BBB permeability. This phenomenon can be reversed by treating GF mice with SCFA-producing bacteria [52]. Similarly, the SCFA propionate was shown to protected BBB from deleterious inflammatory and oxidative stress [53]. This suggested that SCFAs are involved in regulating BBB function and maintaining its integrity.

SCFAs are able to affect immune cells and modulate the immune response, thereby reducing inflammation. SCFAs alter neutrophil recruitment by regulating the production of inflammatory cytokines via HDAC inhibition and inducing neutrophil chemotaxis via activating FFAR2 [54]. These bacterial metabolites affect the maturation and the ability to produce pro-inflammatory cytokines of monocytes, macrophages and DCs [55]. Additionally, SCFAs can also modulate T-cell activation and effector response. By inhibiting histone acetylation, SCFAs direct promote T cells differentiation into T-helper (Th) cells via boosting mTOR activation, or indirectly promote the transformation of naive T cells into forehead box P3 (FoxP3^{+}) regulatory T cells rather than IFN-γ+ T cells via acting on DC cells [56,57]. Microglial cells are essential to the development, innate immunity, and homeostasis of the CNS. They are involved in synaptogenesis, axonal regeneration, neuronal survival and the regulation of inflammatory responses in the CNS [58,59]. Erny et al. observed that the microglia cells of GF mice were global defects and the defective microglia can be restored by SCFAs [33]. Physiological micromolar concentrations of the SCFA mixture can reduce the levels of cytotoxins and cytokines that are secreted by the stimulation of THP-1 microglia-like cells [60]. Several studies reported that butyrate has the ability to decrease microglia activation

and exhibit a strong anti-inflammatory effect in vivo and in vitro [61–64]. Obviously, SCFAs are candidate mediators of gut microbiota affecting systemic inflammation and central neuroimmune function.

Apart from affecting microglia, based on the active involvement of SCFAs in supplying energy to cells and cell signaling [65], these microbial metabolites may influence neuronal function. In mice, acetate has been shown to alter the levels of the neurotransmitters glutamate, glutamine, and gamma-aminobutyric acid (GABA) in the hypothalamus and increased anorectic neuropeptide expression [66]. Propionate and butyrate can regulate tyrosine hydroxylase mRNA levels, which is important for the synthesis of noradrenaline, adrenaline, and dopamine [67]. SCFAs may modulate peripheral levels of serotonin and ultimately regulate brain function [6]. Neurotrophic factors associated with the growth, survival, and differentiation of neurons and synapses, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF), also have been reported to be modulated by SCFAs [68,69]. Furthermore, physiologically relevant levels of SCFAs can increase human neural progenitor cell growth rate and induce more mitosis [70].

Collectively, SCFAs can cross the BBB and may have a directly impact on the brain by strengthening the integrity of the BBB, modulating neurotransmission and bioactivator, influencing immune response, and affecting levels of neurotrophic factors.

7. SCFAs and CNS diseases (Supplementary Table 5)

7.1. Experimental autoimmune encephalomyelitis (EAE)/multiple sclerosis (MS)

In order to understand the mechanisms of CNS autoimmunity, the EAE model has been developed and is currently the most commonly used model for studying MS [71]. MS is a chronic autoimmune-mediated CNS disease with a strong neurodegenerative component characterized by demyelination and axonal damage. The immunological changes in EAE/MS involving immune cell infiltrates, such as Th1/Th17 $CD4^+$ T cells, B lymphocytes, macrophages, and monocytes, and decreasing in $CD8^+$ T cells, $CD4^+$ $CD25^+$FoxP3+ Treg cells, and impaired Treg function [72]. The possible connotation of gut dysbiosis in MS was first investigated in EAE by application of GF mice or antibiotic treatment, suggesting that it may play a role in the pathogenesis of MS [73]. Certainly, the changes of SCFAs in MS patients in association with an altered gut microbiota. And accumulating reports have indicated that SCFAs may participated in the development and disease course of MS. Acetate levels were decreased in MS patients and inversely correlated with proinflammatory biomarkers [74,75]. Propionate levels in serum and feces samples of MS patients were significantly reduced compared with healthy controls, particularly after the first relapse. And the propionate levels positively corrected with the frequency of T follicular regulatory cells [75,76]. The amount of butyrate was reduced in body fluid specimens from MS patients [77]. In addition, the fecal SCFAs level in MS patients was positively correlated with the proportion of Treg cells, and there may be a correlation between SCFAs and disease duration and age of onset in untreated MS patients [77,78].

There have also been studies suggesting that SCFAs may have potential therapeutic effects in MS due to their potential anti-inflammatory and immunomodulatory effects. Based on studies in EAE, SCFAs may attenuate demyelination and alleviate the disease severity by mechanisms that may be related to the reduction of Th1 and Th17 cells, the promotion of Treg cell differentiation, and the promotion of anti-inflammatory cytokine secretion [79]. In congruence with these findings, Alexander Duscha et al. reported that propionate intake increased the expression of Treg-cell-inducing genes in the gut. Two weeks of propionate supplementation in MS patients increased the Treg/Th17 cell ratios, and continued supplementation for three years was associated with a reduction in the annual rate of relapse and an improvement in clinical and pathological characteristics [76]. Therefore, SCFAs can be a treatment option for managing MS.

7.2. Parkinson's diseases

PD is a progressive neurodegenerative disease characterized by bradykinesia and resting tremor. The aggregation of α-synuclein (αSyn) is considered to be the main pathogenic factor of PD, which tends to affect dopaminergic neurons. Since the common occurrence of gastrointestinal manifestations in PD patients, researchers have focused on the relationship between gut microbiota and the development of PD. In our studies, the term "Parkinson's disease" appeared frequently in the reference analysis and keyword analysis, indicating that the effect of SCFAs on PD is a research hotspot in the field and will continue in the future. The role of SCFAs in PD remains controversial. Sampson et al. reported that gut microbes were required to elicit pathophysiological changes in an αSyn-overexpressed mouse model of PD, and elimination of gut microbiota antibiotic treatment improved the condition. Administration of the SCFAs mixture promoted neuroinflammation and motor deficits in αSyn-overexpressed mouse [21]. This is inconsistent with most subsequent research, revealing a significant reduction in the number of colonic SCFA-producing bacteria, as well as a reduction in fecal SCFAs concentrations [80–82]. The decrease of SCFA producing bacteria may predict the accelerated progression of PD [83]. And the reductions in fecal SCFAs are correlated with the age of PD onset [84]. Existing studies of plasma SCFAs concentration changes in PD patients have conflicting results, probably due to different experimental settings and detection methods, but they all suggest that plasma SCFAs concentration is related to the clinical severity of PD [9,85,86].

As expected, SCFAs have also been shown to have therapeutic potential in PD, with studies related to butyrate predominating. In 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced PD mice, butyrate supplementation could prevent dopaminergic degeneration and reduce overactivation of microglia, thereby alleviating behavioral impairments. The underlying mechanism was associated with stimulating colonic GLP-1 secretion and inhibiting HDAC activation [87,88]. And butyrate was reported to rescue dopaminergic neurons by alleviate transcriptional deregulation and DNA damage induced by αSyn [89]. Furthermore, in an in vitro cell model of PD, propionate was found to promote cell survival of dopaminergic neurons and increase gene expression levels of

tyrosine hydroxylase [90].

7.3. Alzheimer's disease

AD is an irreversible neurodegenerative disease that causes loss of memory and cognition. The neuropathological features of AD mainly include accumulation of amyloid β-protein (Aβ) and hyperphosphorylated tau protein. Increasing studies have demonstrated that SCFAs might be involved in the key pathological processes underlying AD. Decreased SCFA levels were found in both brain and feces of AD mice [91]. Lack of SCFAs accelerated memory deficits in 5xFAD mouse model of AD [92]. In clinical studies, a recent study found that acetate concentrations were reduced in the serum of AD patients and were associated with a high risk of AD [93]. Marizzoni et al. reported a correlation between brain amyloid deposition levels and SCFAs concentrations in AD patients [94]. And compared to patients with mild cognitive impairment, the expression of SCFAs was lower in AD patients [95]. This finding suggested that these metabolites were gradually altered with disease progression and were significantly associated with cognitive impairment, suggesting their important role in AD.

Despite the current discouraging drug discovery in AD, several lines of evidence indicated that SCFAs may have a therapeutic effect in the disease. Acetate was confirmed to have an anti-inflammatory effect in AD model mice via upregulation of FFAR3 and suppression of the ERK/JNK/NF-κB pathway [96]. A latest study revealed that administration of SCFAs in App^{NL-G-F} AD mice reduced the Aβ burden, affected the microglia phenotype and improved the integrity of the BBB by regulating tight junctions [97]. Similarly, in another study, administration of SCFAs for nine months mitigated Aβ deposition, tau hyperphosphorylation, and cognitive impairment in AD mice. The authors proposed that SCFA supplementation could modulate neuroenergetics, that is, promote glutamate-glutamine shuttle to resist oxidative damage in neurons [98].

7.4. Autism spectrum disorder

Autism spectrum disorder (ASD) is a genetically heterogeneous neurodevelopmental disorder characterized by socio-communicative deficits, and repetitive and restricted interests. Transplantation of gut microbiota from ASD patients resulted in ASD-relevant behavioral deficits in mice. It also induced alternative splicing of ASD-related genes in the mice brain [99]. Changes in fecal SCFA levels in patients with ASD are controversial. Some studies have shown that children with ASD have significantly lower levels of SCFAs than healthy controls [100,101]. However, opposite results have also been reported. Several studies have revealed that the fecal SCFAs levels were significantly increased in children with ASD. The KEGG analysis suggested that functions related to butyrate production were overexpressed in ASD patients [102]. And the fecal propionate concentration was positively correlated with the severity of ASD [103]. Propionate disturbs neural patterning during the stage of neural development, leading to abnormalities in neural structure, excessive proliferation of glial cells, and increased inflammation, and can induce behavioral effects of relevance to ASD [104,105]. On the contrary, previous research has demonstrated that butyrate can improve ASD-like symptoms by inhibiting HDCAs [106].

7.5. Sepsis associated encephalopathy

Sepsis associated encephalopathy (SAE) is a common complication of sepsis typically characterized by cognitive dysfunction. In the keyword analysis of the past 5 years the most prominent cluster was named "sepsis-associated encephalopathy" (Fig. 11A), indicating that SAE is an emerging research hotspot and a future research trend in the field of SCFAs in CNS disease. Both the number of SCFAs-producing bacteria and the levels of SCFAs were reduced in SAE mice [107,108]. Zhang et al. divided SAE mice into light SAE and severe SAE based on mortality and time of death. Compared to severe SAE mice, light SAE mice had higher butyrate levels. And butyrate reduced the high oxidative stress levels in the hippocampus of SAE mice and improved the survival rate of SAE mice [109]. In addition, it has been reported that SCFA treatment could alleviate behavioral and cognitive dysfunction in SAE mice by reducing neuroinflammation and improving BBB integrity [110,111].

7.6. Other CNS diseases

The gut microbiota has recently received a wide range of attention as a potential risk factor in stroke [112]. Researchers are increasingly finding that gut microbiota may affect risk factors for stroke, such as hypertension, atherosclerosis, and diabetes [113,114]. The levels of SCFAs are negatively correlated with the severity of ischemic stroke, and SCFA supplementation may provide neuroprotection and improve outcomes [115–117]. A recent study has shown that fecal microbiota transplantation can alleviate cognitive decline and depression-like behavior in rats with chronic cerebral hypoperfusion by regulating intestinal flora and increasing the level of SCFAs [118]. Epilepsy is the fourth most common neurological disease and new antiepileptic drugs are constantly being developed. The latest research illustrated that both propionate and butyrate can attenuate mitochondrial disruption and neurological impairments in an epilepsy mouse model [119,120].

8. Treatment strategies and future trends

In recent years, there has been a rapid growth in the understanding of the role of SCFAs in various neurological conditions. SCFAs exerts neuroprotective effects mainly through the following mechanisms: improving BBB integrity, inducing T cell differentiation,

restoring microglia function, regulating inflammatory and immune responses, preventing neuronal death, and regulating neuroenergetics. However, the results on the application of SCFAs in CNS diseases are still heterogeneous. One reason for these findings might be that in some cases SCFAs were used in mixtures, while in others single SCFAs were used. The dosage of single SCFAs, the proportion of mixture SCFAs, and the duration of treatment could also contribute to differences in results. Therefore, future researches should be conducted under the same conditions to clarify the exact role of SCFAs on the CNS diseases. In addition, studies on the therapeutic effect of SCFAs were mostly based on animal experiments and preclinical trials. It should be noted that animal models cannot perfectly mimic human disease phenotypes and gastrointestinal microbiome, which may lead to unsuccessful translation of experimental results to humans. Future studies on the role of SCFAs in CNS diseases should attempt to employ animal models that adequately mirror the human gastrointestinal microbiome, such as pigs and chimpanzees. Furthermore, the design of clinical experiments in this field should be longitudinal, not just cross-sectional. Prospective and larger cohorts regarding the short- and long-term effects of SCFAs on CNS diseases are needed to complement in the future.

9. Strengths and limitations

Our study has several unique advantages. This is the first study that quantitatively analyzed the publications on SCFAs in CNS diseases, which provides a comprehensive guidance for scholars concerned with this research field, thereby improving their scientific research level and capabilities. The bibliometric tool applied in this paper is CiteSpace, which is widely used in the bibliometric field, so our data analysis process is likely to be objective. Through journal analysis, reference analysis and keyword analysis, we can identify appropriate journal names, hotspots, emerging trends, and unsolved issues, which will help researchers develop targeted research programs and effectively address the challenges faced within this research domain. Nevertheless, the limitations of the study should be acknowledged. First, the database chosen for analysis in this paper is the WOS data as it is considered to be the largest and most accurate biomedical database. Although bibliometric analysis guidelines recommend that it is preferable to use a single database, literature from other databases may be missed. Second, our search term mainly focused on " central nervous system disease" and its derivatives, rather than on one of its categories (e.g., vascular disease, neurodegenerative disease). The range of diseases is too broad to describe the details of each disease with precision. Third, due to constant updates to the database, some discrepancies may exist between the number of literature we obtained and the actual number of literature. Besides, only publications in English were included, whereas publications in other languages were excluded. In addition, this study consisted solely of original articles and reviews, and the collected literature was of variable quality.

10. Conclusion

In this study, 480 articles from the WoSCC database were used for bibliometric analysis to systematically evaluate the research on SCFAs in CNS diseases. The research shows that China has the most publications, while Western institutions and scholars, represented by University College Cork and John F. Cryan, are more influential in this research field. SCFAs can act on CNS and play multiple roles in CNS diseases. This field is gradually attracting the attention of many scholars and will remain a research hotspot in the next decade. Clearly, the current evidence for an association between SCFAs and CNS diseases is preliminary and more work is needed to pinpoint the precise mechanism. Several studies have shown the therapeutic benefits of SCFAs in animal models and preclinical trials, but further research is needed to probe whether the proportions and the concentrations of SCFAs have different effects. In addition, prospective and larger cohorts regarding the short- and long-term effects of SCFAs on CNS diseases are also required.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author (ZP H and ZC T) upon reasonable request.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82271367), and the Research Project of Changsha Municipal Natural Science Foundation (No. kq2208320).

CRediT authorship contribution statement

Ziwei Lan: Writing – original draft, Methodology, Formal analysis, Data curation. **Xiangqi Tang:** Writing – review & editing, Supervision. **Ming Lu:** Writing – review & editing, Supervision. **Zhiping Hu:** Writing – review & editing, Project administration, Conceptualization. **Zhenchu Tang:** Writing – review & editing, Visualization, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Home for Researchers editorial team (www.home-for-researchers.com) for the language editing service.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26377.

References

[1] K.G. Margolis, J.F. Cryan, E.A. Mayer, The microbiota-gut-brain Axis: from motility to mood, Gastroenterology 160 (5) (2021) 1486–1501.
[2] M. Farshbafnadi, E. Agah, N. Rezaei, The second brain: the connection between gut microbiota composition and multiple sclerosis, J. Neuroimmunol. 360 (2021) 577700.
[3] B.J.H. Verhaar, H.M.A. Hendriksen, F.A. de Leeuw, A.S. Doorduijn, M. van Leeuwenstijn, C.E. Teunissen, et al., Gut microbiota composition is related to AD pathology, Front. Immunol. 12 (2021) 794519.
[4] J. Luo, Y. Chen, G. Tang, Z. Li, X. Yang, X. Shang, et al., Gut microbiota composition reflects disease progression, severity and outcome, and dysfunctional immune responses in patients with hypertensive intracerebral hemorrhage, Front. Immunol. 13 (2022) 869846.
[5] A.J. McGuinness, J.A. Davis, S.L. Dawson, A. Loughman, F. Collier, M. O'Hely, et al., A systematic review of gut microbiota composition in observational studies of major depressive disorder, bipolar disorder and schizophrenia, Mol. Psychiatr. 27 (4) (2022) 1920–1935.
[6] B. Dalile, L. Van Oudenhove, B. Vervliet, K. Verbeke, The role of short-chain fatty acids in microbiota-gut-brain communication, Nat. Rev. Gastroenterol. Hepatol. 16 (8) (2019) 461–478.
[7] K.J. O'Riordan, M.K. Collins, G.M. Moloney, E.G. Knox, M.R. Aburto, C. Fulling, et al., Short chain fatty acids: microbial metabolites for gut-brain axis signalling, Mol. Cell. Endocrinol. 546 (2022) 111572.
[8] C. Gonzalez-Bosch, E. Boorman, P.A. Zunszain, G.E. Mann, Short-chain fatty acids as modulators of redox signaling in health and disease, Redox Biol. 47 (2021) 102165.
[9] C. Shin, Y. Lim, H. Lim, T.B. Ahn, Plasma short-chain fatty acids in patients with Parkinson's disease, Mov. Disord. 35 (6) (2020) 1021–1027.
[10] J.F. Cryan, K.J. O'Riordan, C.S.M. Cowan, K.V. Sandhu, T.F.S. Bastiaanssen, M. Boehme, et al., The microbiota-gut-brain Axis, Physiol. Rev. 99 (4) (2019) 1877–2013.
[11] Y. Dong, C. Cui, The role of short-chain fatty acids in central nervous system diseases, Mol. Cell. Biochem. 477 (11) (2022) 2595–2607.
[12] R. Mirzaei, B. Bouzari, S.R. Hosseini-Fard, M. Mazaheri, Y. Ahmadyousefi, M. Abdi, et al., Role of microbiota-derived short-chain fatty acids in nervous system disorders, Biomed. Pharmacother. 139 (2021) 111661.
[13] M. Koo, Systemic lupus erythematosus research: a bibliometric analysis over a 50-year period, Int. J. Environ. Res. Publ. Health 18 (13) (2021).
[14] J. Long, Y. Zhang, X. Liu, M. Pan, Q. Gao, Exosomes in the field of neuroscience: a scientometric study and visualization analysis, Front. Neurol. 13 (2022) 871491.
[15] Y. Shi, Z. Zhao, H. Tang, S. Huang, Intellectual structure and emerging trends of white matter hyperintensity studies: a bibliometric analysis from 2012 to 2021, Front. Neurosci. 16 (2022) 866312.
[16] C. Chen, M. Song, Visualizing a field of research: a methodology of systematic scientometric reviews, PLoS One 14 (10) (2019) e0223994.
[17] S.H. Al-Lahham, M.P. Peppelenbosch, H. Roelofsen, R.J. Vonk, K. Venema, Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms, Biochim. Biophys. Acta 1801 (11) (2010) 1175–1183.
[18] E.Y. Hsiao, S.W. McBride, S. Hsien, G. Sharon, E.R. Hyde, T. McCue, et al., Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders, Cell 155 (7) (2013) 1451–1463.
[19] D. Erny, A.L. Hrabě de Angelis, D. Jaitin, P. Wieghofer, O. Staszewski, E. David, et al., Host microbiota constantly control maturation and function of microglia in the CNS, Nat. Neurosci. 18 (7) (2015) 965–977.
[20] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Bäckhed, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites, Cell 165 (6) (2016) 1332–1345.
[21] T.R. Sampson, J.W. Debelius, T. Thron, S. Janssen, G.G. Shastri, Z.E. Ilhan, et al., Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease, Cell 167 (6) (2016) 1469, 1480 e12.
[22] Y.P. Silva, A. Bernardi, R.L. Frozza, The role of short-chain fatty acids from gut microbiota in gut-brain communication, Front. Endocrinol. 11 (2020) 25.
[23] J. Yang, Y. Deng, Y. Cai, Y. Liu, L. Peng, Z. Luo, et al., Mapping trends and hotspot regarding gastrointestinal microbiome and neuroscience: a bibliometric analysis of global research (2002-2022), Front. Neurosci. 16 (2022) 1048565.
[24] G. Shi, J. Zhou, K. Huang, F.F. Bi, Trends in global amyotrophic lateral sclerosis research from 2000 to 2022: a bibliometric analysis, Front. Neurosci. 16 (2022) 965230.
[25] H. Wang, T. Long, J. You, P. Li, Q. Xu, Bibliometric visualization analysis of microbiome-gut-brain Axis from 2004 to 2020, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 28 (2022) e936037.
[26] J. Zhang, L. Song, J. Jia, W. Tian, R. Lai, Z. Zhang, et al., Knowledge mapping of necroptosis from 2012 to 2021: a bibliometric analysis, Front. Immunol. 13 (2022) 917155.
[27] C. Torres-Fuentes, A.V. Golubeva, A.V. Zhdanov, S. Wallace, S. Arboleya, D.B. Papkovsky, et al., Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling, Faseb. J. 33 (12) (2019) 13546–13559.
[28] S. Spichak, T.F.S. Bastiaanssen, K. Berding, K. Vlckova, G. Clarke, T.G. Dinan, et al., Mining microbes for mental health: determining the role of microbial metabolic pathways in human brain health and disease, Neurosci. Biobehav. Rev. 125 (2021) 698–761.
[29] R.M. Stilling, M. van de Wouw, G. Clarke, C. Stanton, T.G. Dinan, J.F. Cryan, The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochem. Int. 99 (2016) 110–132.
[30] M. van de Wouw, M. Boehme, J.M. Lyte, N. Wiley, C. Strain, O. O'Sullivan, et al., Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations, J. Physiol. 596 (20) (2018) 4923–4944.
[31] Y. Ding, D. Chen, X. Ding, G. Wang, Y. Wan, Q. Shen, A bibliometric analysis of income and cardiovascular disease: status, Hotspots, Trends and Outlook, Medicine (Baltim.) 99 (34) (2020) e21828.

[32] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Backhed, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites, Cell 165 (6) (2016) 1332–1345.
[33] D. Erny, A.L. Hrabe de Angelis, D. Jaitin, P. Wieghofer, O. Staszewski, E. David, et al., Host microbiota constantly control maturation and function of microglia in the CNS, Nat. Neurosci. 18 (7) (2015) 965–977.
[34] N.G. Vallianou, T. Stratigou, S. Tsagarakis, Microbiome and diabetes: where are we now? Diabetes Res. Clin. Pract. 146 (2018) 111–118.
[35] L. Liu, J. Zhang, Y. Cheng, M. Zhu, Z. Xiao, G. Ruan, et al., Gut microbiota: a new target for T2DM prevention and treatment, Front. Endocrinol. 13 (2022) 958218.
[36] Z.G. Li, A.A. Sima, C-peptide and central nervous system complications in diabetes, Exp. Diabesity Res. 5 (1) (2004) 79–90.
[37] S. Azam, M.E. Haque, M. Jakaria, S.H. Jo, I.S. Kim, D.K. Choi, G-protein-coupled receptors in CNS: a potential therapeutic target for intervention in neurodegenerative disorders and associated cognitive deficits, Cells 9 (2) (2020).
[38] J. Tan, C. McKenzie, M. Potamitis, A.N. Thorburn, C.R. Mackay, L. Macia, The role of short-chain fatty acids in health and disease, Adv. Immunol. 121 (2014) 91–119.
[39] J. King, M. Patel, S. Chandrasekaran, Metabolism, HDACs, and HDAC inhibitors: a systems biology perspective, Metabolites 11 (11) (2021).
[40] M.G. Riggs, R.G. Whittaker, J.R. Neumann, V.M. Ingram, n-Butyrate causes histone modification in HeLa and Friend erythroleukaemia cells, Nature 268 (5619) (1977) 462–464.
[41] K.J. O'Riordan, M.K. Collins, G.M. Moloney, E.G. Knox, M.R. Aburto, C. Fülling, et al., Short chain fatty acids: microbial metabolites for gut-brain axis signalling, Mol. Cell. Endocrinol. 546 (2022) 111572.
[42] M. Valles-Colomer, G. Falony, Y. Darzi, E.F. Tigchelaar, J. Wang, R.Y. Tito, et al., The neuroactive potential of the human gut microbiota in quality of life and depression, Nat Microbiol 4 (4) (2019) 623–632.
[43] J.A. Bonini, S.M. Anderson, D.F. Steiner, Molecular cloning and tissue expression of a novel orphan G protein-coupled receptor from rat lung, Biochem. Biophys. Res. Commun. 234 (1) (1997) 190–193.
[44] A.J. Brown, S.M. Goldsworthy, A.A. Barnes, M.M. Eilert, L. Tcheang, D. Daniels, et al., The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids, J. Biol. Chem. 278 (13) (2003) 11312–11319.
[45] F. De Vadder, P. Kovatcheva-Datchary, D. Goncalves, J. Vinera, C. Zitoun, A. Duchampt, et al., Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits, Cell 156 (1–2) (2014) 84–96.
[46] V. Kumar, S. Kundu, A. Singh, S. Singh, Understanding the role of histone deacetylase and their inhibitors in neurodegenerative disorders: current targets and future perspective, Curr. Neuropharmacol. 20 (1) (2022) 158–178.
[47] S. Bahari-Javan, A. Maddalena, C. Kerimoglu, J. Wittnam, T. Held, M. Bahr, et al., HDAC1 regulates fear extinction in mice, J. Neurosci. 32 (15) (2012) 5062–5073.
[48] A. Fischer, F. Sananbenesi, A. Mungenast, L.H. Tsai, Targeting the correct HDAC(s) to treat cognitive disorders, Trends Pharmacol. Sci. 31 (12) (2010) 605–617.
[49] R.W. Mitchell, N.H. On, M.R. Del Bigio, D.W. Miller, G.M. Hatch, Fatty acid transport protein expression in human brain and potential role in fatty acid transport across human brain microvessel endothelial cells, J. Neurochem. 117 (4) (2011) 735–746.
[50] R. Kekuda, P. Manoharan, W. Baseler, U. Sundaram, Monocarboxylate 4 mediated butyrate transport in a rat intestinal epithelial cell line, Dig. Dis. Sci. 58 (3) (2013) 660–667.
[51] N. Vijay, M.E. Morris, Role of monocarboxylate transporters in drug delivery to the brain, Curr. Pharmaceut. Des. 20 (10) (2014) 1487–1498.
[52] V. Braniste, M. Al-Asmakh, C. Kowal, F. Anuar, A. Abbaspour, M. Tóth, et al., The gut microbiota influences blood-brain barrier permeability in mice, Sci. Transl. Med. 6 (263) (2014), 263ra158.
[53] L. Hoyles, T. Snelling, U.K. Umlai, J.K. Nicholson, S.R. Carding, R.C. Glen, et al., Microbiome-host systems interactions: protective effects of propionate upon the blood-brain barrier, Microbiome 6 (1) (2018) 55.
[54] H.G. Rodrigues, F. Takeo Sato, R. Curi, M.A.R. Vinolo, Fatty acids as modulators of neutrophil recruitment, function and survival, Eur. J. Pharmacol. 785 (2016) 50–58.
[55] R. Correa-Oliveira, J.L. Fachi, A. Vieira, F.T. Sato, M.A. Vinolo, Regulation of immune cell function by short-chain fatty acids, Clin Transl Immunology 5 (4) (2016) e73.
[56] J. Park, M. Kim, S.G. Kang, A.H. Jannasch, B. Cooper, J. Patterson, et al., Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway, Mucosal Immunol. 8 (1) (2015) 80–93.
[57] A. Gurav, S. Sivaprakasam, Y.D. Bhutia, T. Boettger, N. Singh, V. Ganapathy, Slc5a8, a Na+-coupled high-affinity transporter for short-chain fatty acids, is a conditional tumour suppressor in colon that protects against colitis and colon cancer under low-fibre dietary conditions, Biochem. J. 469 (2) (2015) 267–278.
[58] A. Vidal-Itriago, R.A.W. Radford, J.A. Aramideh, C. Maurel, N.M. Scherer, E.K. Don, et al., Microglia morphophysiological diversity and its implications for the CNS, Front. Immunol. 13 (2022) 997786.
[59] H.S. Kwon, S.H. Koh, Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes, Transl. Neurodegener. 9 (1) (2020) 42.
[60] T.J. Wenzel, E.J. Gates, A.L. Ranger, A. Klegeris, Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells, Mol. Cell. Neurosci. 105 (2020) 103493.
[61] Y. Yamawaki, N. Yoshioka, K. Nozaki, H. Ito, K. Oda, K. Harada, et al., Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice, Brain Res. 1680 (2018) 13–38.
[62] R. Patnala, T.V. Arumugam, N. Gupta, S.T. Dheen, HDAC inhibitor sodium butyrate-mediated epigenetic regulation enhances neuroprotective function of microglia during ischemic stroke, Mol. Neurobiol. 54 (8) (2017) 6391–6411.
[63] P. Wang, Y. Zhang, Y. Gong, R. Yang, Z. Chen, W. Hu, et al., Sodium butyrate triggers a functional elongation of microglial process via Akt-small RhoGTPase activation and HDACs inhibition, Neurobiol. Dis. 111 (2018) 12–25.
[64] J. Huuskonen, T. Suuronen, T. Nuutinen, S. Kyrylenko, A. Salminen, Regulation of microglial inflammatory response by sodium butyrate and short-chain fatty acids, Br. J. Pharmacol. 141 (5) (2004) 874–880.
[65] A.V. Oleskin, B.A. Shenderov, Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota, Microb. Ecol. Health Dis. 27 (2016) 30971.
[66] G. Frost, M.L. Sleeth, M. Sahuri-Arisoylu, B. Lizarbe, S. Cerdan, L. Brody, et al., The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism, Nat. Commun. 5 (2014) 3611.
[67] B.B. Nankova, R. Agarwal, D.F. MacFabe, E.F. La Gamma, Enteric bacterial metabolites propionic and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neurotransmission, in PC12 cells–possible relevance to autism spectrum disorders, PLoS One 9 (8) (2014) e103740.
[68] T. Barichello, J.S. Generoso, L.R. Simoes, C.J. Faller, R.A. Ceretta, F. Petronilho, et al., Sodium butyrate prevents memory impairment by Re-establishing BDNF and GDNF expression in experimental pneumococcal meningitis, Mol. Neurobiol. 52 (1) (2015) 734–740.
[69] R.B. Varela, S.S. Valvassori, J. Lopes-Borges, E. Mariot, G.C. Dal-Pont, R.T. Amboni, et al., Sodium butyrate and mood stabilizers block ouabain-induced hyperlocomotion and increase BDNF, NGF and GDNF levels in brain of Wistar rats, J. Psychiatr. Res. 61 (2015) 114–121.
[70] L.L. Yang, V. Millischer, S. Rodin, D.F. MacFabe, J.C. Villaescusa, C. Lavebratt, Enteric short-chain fatty acids promote proliferation of human neural progenitor cells, J. Neurochem. 154 (6) (2020) 635–646.
[71] S. Glatigny, E. Bettelli, Experimental autoimmune encephalomyelitis (EAE) as animal models of multiple sclerosis (MS), Cold Spring Harb Perspect Med 8 (11) (2018).
[72] F. Chu, M. Shi, Y. Lang, D. Shen, T. Jin, J. Zhu, et al., Gut microbiota in multiple sclerosis and experimental autoimmune encephalomyelitis: current applications and future perspectives, Mediat. Inflamm. 2018 (2018) 8168717.
[73] H. Wekerle, Brain autoimmunity and intestinal microbiota: 100 trillion game changers, Trends Immunol. 38 (7) (2017) 483–497.

[74] A. Olsson, S. Gustavsen, T.D. Nguyen, M. Nyman, A.R. Langkilde, T.H. Hansen, et al., Serum short-chain fatty acids and associations with inflammation in newly diagnosed patients with multiple sclerosis and healthy controls, Front. Immunol. 12 (2021) 661493.
[75] S. Trend, J. Leffler, A.P. Jones, L. Cha, S. Gorman, D.A. Brown, et al., Associations of serum short-chain fatty acids with circulating immune cells and serum biomarkers in patients with multiple sclerosis, Sci. Rep. 11 (1) (2021) 5244.
[76] A. Duscha, B. Gisevius, S. Hirschberg, N. Yissachar, G.I. Stangl, E. Eilers, et al., Propionic acid shapes the multiple sclerosis disease course by an immunomodulatory mechanism, Cell 180 (6) (2020) 1067, 1080 e16.
[77] Q. Zeng, G. Junli, X. Liu, C. Chen, X. Sun, H. Li, et al., Gut dysbiosis and lack of short chain fatty acids in a Chinese cohort of patients with multiple sclerosis, Neurochem. Int. 129 (2019) 104468.
[78] M.I. Dominguez-Mozo, S. Perez-Perez, N. Villarrubia, L. Costa-Frossard, J.I. Fernandez-Velasco, I. Ortega-Madueño, et al., Herpesvirus antibodies, vitamin D and short-chain fatty acids: their correlation with cell subsets in multiple sclerosis patients and healthy controls, Cells 10 (1) (2021).
[79] F. Golpour, M. Abbasi-Alaei, F. Babaei, M. Mirzababaei, S. Parvardeh, G. Mohammadi, et al., Short chain fatty acids, a possible treatment option for autoimmune diseases, Biomed. Pharmacother. 163 (2023) 114763.
[80] M.M. Unger, J. Spiegel, K.U. Dillmann, D. Grundmann, H. Philippeit, J. Burmann, et al., Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls, Parkinsonism Relat. Disorders 32 (2016) 66–72.
[81] Z.D. Wallen, M. Appah, M.N. Dean, C.L. Sesler, S.A. Factor, E. Molho, et al., Characterizing dysbiosis of gut microbiome in PD: evidence for overabundance of opportunistic pathogens, NPJ Parkinsons Dis 6 (2020) 11.
[82] S. Vascellari, V. Palmas, M. Melis, S. Pisanu, R. Cusano, P. Uva, et al., Gut microbiota and metabolome alterations associated with Parkinson's disease, mSystems 5 (5) (2020).
[83] H. Nishiwaki, M. Ito, T. Hamaguchi, T. Maeda, K. Kashihara, Y. Tsuboi, et al., Short chain fatty acids-producing and mucin-degrading intestinal bacteria predict the progression of early Parkinson's disease, NPJ Parkinsons Dis 8 (1) (2022) 65.
[84] V.T.E. Aho, M.C. Houser, P.A.B. Pereira, J. Chang, K. Rudi, L. Paulin, et al., Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease, Mol. Neurodegener. 16 (1) (2021) 6.
[85] S.J. Chen, C.C. Chen, H.Y. Liao, Y.T. Lin, Y.W. Wu, J.M. Liou, et al., Association of fecal and plasma levels of short-chain fatty acids with gut microbiota and clinical severity in patients with Parkinson disease, Neurology 98 (8) (2022) e848-e858.
[86] G. Wu, Z. Jiang, Y. Pu, S. Chen, T. Wang, Y. Wang, et al., Serum short-chain fatty acids and its correlation with motor and non-motor symptoms in Parkinson's disease patients, BMC Neurol. 22 (1) (2022) 13.
[87] Y. Hou, X. Li, C. Liu, M. Zhang, X. Zhang, S. Ge, et al., Neuroprotective effects of short-chain fatty acids in MPTP induced mice model of Parkinson's disease, Exp. Gerontol. 150 (2021) 111376.
[88] J. Liu, F. Wang, S. Liu, J. Du, X. Hu, J. Xiong, et al., Sodium butyrate exerts protective effect against Parkinson's disease in mice via stimulation of glucagon like peptide-1, J. Neurol. Sci. 381 (2017) 176, 181.
[89] I. Paiva, R. Pinho, M.A. Pavlou, M. Hennion, P. Wales, A.L. Schutz, et al., Sodium butyrate rescues dopaminergic cells from alpha-synuclein-induced transcriptional deregulation and DNA damage, Hum. Mol. Genet. 26 (12) (2017) 2231–2246.
[90] F. Ostendorf, J. Metzdorf, R. Gold, A. Haghikia, L. Tönges, Propionic acid and fasudil as treatment against rotenone toxicity in an in vitro model of Parkinson's disease, Molecules 25 (11) (2020).
[91] L. Zhang, Y. Wang, X. Xiayu, C. Shi, W. Chen, N. Song, et al., Altered gut microbiota in a mouse model of alzheimer's disease, J Alzheimers Dis 60 (4) (2017) 1241–1257.
[92] Y. Zhou, L. Xie, J. Schroder, I.S. Schuster, M. Nakai, G. Sun, et al., Dietary fiber and microbiota metabolite receptors enhance cognition and alleviate disease in the 5xFAD mouse model of alzheimer's disease, J. Neurosci. 43 (37) (2023) 6460–6475.
[93] M. Cui, Y. Jiang, Q. Zhao, Z. Zhu, X. Liang, K. Zhang, et al., Metabolomics and incident dementia in older Chinese adults: the Shanghai Aging Study, Alzheimers Dement 16 (5) (2020) 779–788.
[94] M. Marizzoni, A. Cattaneo, P. Mirabelli, C. Festari, N. Lopizzo, V. Nicolosi, et al., Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in alzheimer's disease, J Alzheimers Dis 78 (2) (2020) 683–697.
[95] L. Wu, Y. Han, Z. Zheng, G. Peng, P. Liu, S. Yue, et al., Altered gut microbial metabolites in amnestic mild cognitive impairment and alzheimer's disease: signals in host-microbe interplay, Nutrients 13 (1) (2021).
[96] J. Liu, H. Li, T. Gong, W. Chen, S. Mao, Y. Kong, et al., Anti-neuroinflammatory effect of short-chain fatty acid acetate against alzheimer's disease via upregulating GPR41 and inhibiting ERK/JNK/NF-kappaB, J. Agric. Food Chem. 68 (27) (2020) 7152–7161.
[97] J. Xie, A. Bruggeman, C. De Nolf, C. Vandendriessche, G. Van Imschoot, E. Van Wonterghem, et al., Gut microbiota regulates blood-cerebrospinal fluid barrier function and Aβ pathology, EMBO J. 42 (17) (2023) e111515.
[98] Y. Sun, H. Zhang, X. Zhang, W. Wang, Y. Chen, Z. Cai, et al., Promotion of astrocyte-neuron glutamate-glutamine shuttle by SCFA contributes to the alleviation of Alzheimer's disease, Redox Biol. 62 (2023) 102690.
[99] G. Sharon, N.J. Cruz, D.W. Kang, M.J. Gandal, B. Wang, Y.M. Kim, et al., Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice, Cell 177 (6) (2019) 1600, 18.e17.
[100] Y. Wang, N. Li, J.J. Yang, D.M. Zhao, B. Chen, G.Q. Zhang, et al., Probiotics and fructo-oligosaccharide intervention modulate the microbiota-gut brain axis to improve autism spectrum reducing also the hyper-serotonergic state and the dopamine metabolism disorder, Pharmacol. Res. 157 (2020) 104784.
[101] S. Liu, E. Li, Z. Sun, D. Fu, G. Duan, M. Jiang, et al., Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder, Sci. Rep. 9 (1) (2019) 287.
[102] L. Coretti, L. Paparo, M.P. Riccio, F. Amato, M. Cuomo, A. Natale, et al., Gut microbiota features in young children with autism spectrum disorders, Front. Microbiol. 9 (2018) 3146.
[103] J. He, X. Gong, B. Hu, L. Lin, X. Lin, W. Gong, et al., Altered gut microbiota and short-chain fatty acids in Chinese children with constipated autism spectrum disorder, Sci. Rep. 13 (1) (2023) 19103.
[104] L.S. Abdelli, A. Samsam, S.A. Naser, Propionic acid induces gliosis and neuro-inflammation through modulation of PTEN/AKT pathway in autism spectrum disorder, Sci. Rep. 9 (1) (2019) 8824.
[105] M.M. Meeking, D.F. MacFabe, J.R. Mepham, K.A. Foley, L.J. Tichenoff, F.H. Boon, et al., Propionic acid induced behavioural effects of relevance to autism spectrum disorder evaluated in the hole board test with rats, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 97 (2020) 109794.
[106] C. Cristiano, E. Hoxha, P. Lippiello, I. Balbo, R. Russo, F. Tempia, et al., Maternal treatment with sodium butyrate reduces the development of autism-like traits in mice offspring, Biomed. Pharmacother. 156 (2022) 113870.
[107] H. Liao, H. Li, H. Bao, L. Jiang, J. Du, Y. Guo, et al., Short chain fatty acids protect the cognitive function of sepsis associated encephalopathy mice via GPR43, Front. Neurol. 13 (2022) 909436.
[108] V.V. Giridharan, J.S. Generoso, L. Lence, G. Candiotto, E. Streck, F. Petronilho, et al., A crosstalk between gut and brain in sepsis-induced cognitive decline, J. Neuroinflammation 19 (1) (2022) 114.
[109] H. Zhang, J. Xu, Q. Wu, H. Fang, X. Shao, X. Ouyang, et al., Gut microbiota mediates the susceptibility of mice to sepsis-associated encephalopathy by butyric acid, J. Inflamm. Res. 15 (2022) 2103–2119.
[110] J. Liu, Y. Jin, Y. Ye, Y. Tang, S. Dai, M. Li, et al., The neuroprotective effect of short chain fatty acids against sepsis-associated encephalopathy in mice, Front. Immunol. 12 (2021) 626894.
[111] Z. Li, F. Zhang, M. Sun, J. Liu, L. Zhao, S. Liu, et al., The modulatory effects of gut microbes and metabolites on blood-brain barrier integrity and brain function in sepsis-associated encephalopathy, PeerJ 11 (2023) e15122.
[112] X. Zeng, X. Gao, Y. Peng, Q. Wu, J. Zhu, C. Tan, et al., Higher risk of stroke is correlated with increased opportunistic pathogen load and reduced levels of butyrate-producing bacteria in the gut, Front. Cell. Infect. Microbiol. 9 (2019) 4.
[113] B.J.H. Verhaar, A. Prodan, M. Nieuwdorp, M. Muller, Gut microbiota in hypertension and atherosclerosis: a review, Nutrients 12 (10) (2020).

[114] S. Sanna, N.R. van Zuydam, A. Mahajan, A. Kurilshikov, A. Vich Vila, U. Võsa, et al., Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases, Nat. Genet. 51 (4) (2019) 600–605.
[115] R. Chen, Y. Xu, P. Wu, H. Zhou, Y. Lasanajak, Y. Fang, et al., Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota, Pharmacol. Res. 148 (2019) 104403.
[116] Z. Zhou, N. Xu, N. Matei, D.W. McBride, Y. Ding, H. Liang, et al., Sodium butyrate attenuated neuronal apoptosis via GPR41/Gbetagamma/PI3K/Akt pathway after MCAO in rats, J. Cerebr. Blood Flow Metabol. 41 (2) (2021) 267–281.
[117] R. Sadler, J.V. Cramer, S. Heindl, S. Kostidis, D. Betz, K.R. Zuurbier, et al., Short-chain fatty acids improve poststroke recovery via immunological mechanisms, J. Neurosci. 40 (5) (2020) 1162–1173.
[118] W. Xiao, J. Su, X. Gao, H. Yang, R. Weng, W. Ni, et al., The microbiota-gut-brain axis participates in chronic cerebral hypoperfusion by disrupting the metabolism of short-chain fatty acids, Microbiome 10 (1) (2022) 62.
[119] D. Li, X. Bai, Y. Jiang, Y. Cheng, Butyrate alleviates PTZ-induced mitochondrial dysfunction, oxidative stress and neuron apoptosis in mice via Keap1/Nrf2/HO-1 pathway, Brain Res. Bull. 168 (2021) 25–35.
[120] Y. Cheng, Q. Mai, X. Zeng, H. Wang, Y. Xiao, L. Tang, et al., Propionate relieves pentylenetetrazol-induced seizures, consequent mitochondrial disruption, neuron necrosis and neurological deficits in mice, Biochem. Pharmacol. 169 (2019) 113607.