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Global research trends on maternal separation paradigms as an early life stress model: A bibliometric analysis

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ABSTRACT

Background: Maternal separation (MS) is an early life stress model that is often studied to determine how early life stress affects brain development and psychopathological adaptation. As society has developed, public health problems have become increasingly prominent, and this research area has attracted significant attention. However, to date, there has been no systematic bibliometric study on MS. The aim of this study was to analyze the trends and frontiers in MS using bibliometrics and provide a scientific reference to researchers in the field.

Methods: Utilizing VOSviewer, CiteSpace, and Microsoft Excel, examined data obtained from the WoSCC, which encompasses the years 2002–2021.

Results: In this bibliometric study, we analyzed 6209 articles related to MS authored by 24,174 researchers across 121 countries and regions and published in 2219 journals. The United States had the most publications (2,232, 35.95%) and both the United States and the United Kingdom had the highest h-index. Institutions in the United States and France had the most published articles and citations. Keyword clustering analysis revealed associations between MS and adverse early life experiences, the hypothalamic–pituitary–adrenal (HPA) axis, stress, gene expression, and depression.

Conclusions: This bibliometric analysis highlights the current research focus on the long-term effects of MS on emotional cognition, the HPA axis, epigenetic changes, and their links to gut microbiome imbalances. Future research may expand on these findings to investigate the underlying mechanisms and broader health and societal implications of MS. These results provide a comprehensive overview of the current research landscape in MS and offer valuable insights for researchers to guide future investigations in this field.

1. Introduction

Early life is a crucial stage of neurodevelopment during which intense and stressful events can alter an individual's brain immune function and have a substantial impact on their behavioural capabilities later in life [1,2]. Negative experiences during this period can influence immune cells in the brain through various signals, ultimately modifying the individual's neurological response to stress later in life and increasing their risk of psychiatric disorders such as depression and anxiety [3].

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Maternal separation (MS) is a commonly used model of early life stress [4] that harms brain development during developmental stages. The conventional method entails the separation of rat or mouse offspring from their mother, beginning from the second postnatal day (PND2) and extending to PND14, with a 3-h daily separation interval. The littermates of the separated pups are placed in a small container filled with bedding material and kept on a temperature-controlled heating pad that is maintained at a constant temperature of 30 °C to prevent hypothermia. The control group consists of pups that are not separated from their dam and undergo normal rearing conditions. Each litter includes 5–8 pups, with a maximum of two male littermates used per experiment. Worth mentioning is that the exact design of the MS model might undergo slight variations in accordance with research aims and distinct lab stipulations. Although earlier studies primarily employed rat models for model construction, mouse models are more commonly used today. Studies have shown that rodents that experience repeated mother–infant separation have an activated neuroimmune system in early adolescence and are susceptible to depressive disorders in adulthood [5]. The MS life stress model is often used in the study of mental and digestive system diseases, such as depression and irritable bowel syndrome [6,7].

Currently, psychiatric disorders impact approximately 340 million people worldwide, often causing significant psychological distress, which seriously hinders the progress of society and the healthy development of individuals [8]. An increasing number of studies have begun to focus on the effects of adverse events in early life on psychological states in adulthood, but the mechanism of how MS induces mental state imbalance in later development has not been fully explored.

Bibliometrics which a confluence of mathematics, statistics, and linguistics, is extensively employed to detect progressions and breakthroughs across diverse disciplines [9]. However, to date, there has been no bibliometric study specifically focused on maternal separation (MS). This study intends to deliver a thorough survey of MS research standing, employing bibliometric techniques.

2. Materials and methods

2.1. Ethics statement

Since this study solely utilized scientometric information derived from the Web of Science Core Collection (WoSCC) database and did not encompass human participants, the need for Institutional Review Board (IRB) approval was waived as per applicable guidelines.

2.2. Data sources and collection

For this study, all publications were gathered using the Science Citation Index Expanded (SCIE) via WoSCC. The literature search in WoSCC was conducted on November 30, 2022, and covered a 20-year span from 2002 to 2021. The search query was defined as TS = (“maternal separation” or “maternal deprivation”) with a language restriction to English and limited to “article” and “review” types of literature. The first researcher conducted a cross-check of the included articles, and any discrepancies were resolved through a final decision made by the other researchers. The screening process is depicted in Fig. 1.

2.3. Bibliometric analysis and software

This study utilized CiteSpace and VOSviewer software for bibliometric analysis, which is a commonly used approach in scientific research that combines scientometrics and data and information visualization technology [10,11]. Burst words and co-cited references were analyzed using CiteSpace, whereas VOSviewer was utilized for the analysis of co-words, co-citations, and coupling, and to create visualizations of author collaborations, cited journals, co-occurring keywords, and density maps [12].

Microsoft Excel was used to fabricate tables exhibiting yearly patterns in publication and citation occurrences, in addition to mapping the geographical spread of publication tendencies [13].

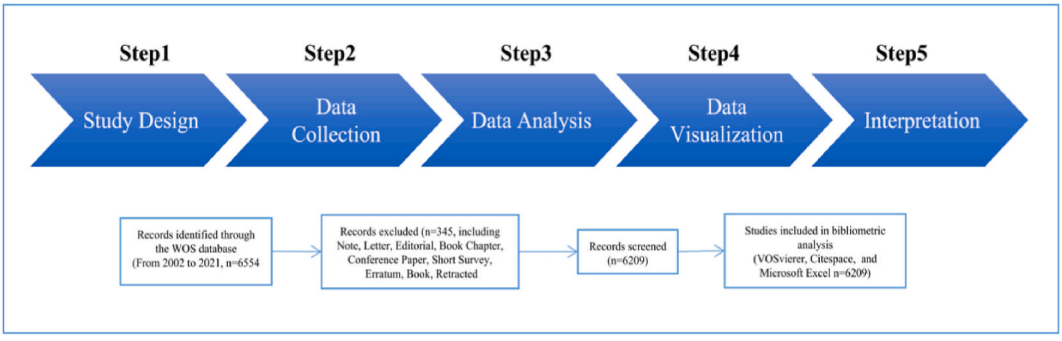

Fig. 1. Process of study selection.

3. Results

3.1. Citations and publication temporal trends

As of November 30, 2022, Web of Science identified 6209 records related to MS. Over the 20-year period from 2002 to 2021, the number of articles published on MS steadily increased (Fig. 2A). Over the last two decades, the number of publications related to MS has shown a linear increase ($R^2 = 0.9649$). Furthermore, the number of articles published in the top 10 countries has also been consistently increasing across the previous decade (Fig. 2B).

3.2. Country/region and institution characteristics

Between 2002 and 2021, researchers from 121 countries/regions conducted research on MS. Of these countries, 14 have published over 90 articles. The United States had the most publications (2,232, 35.95%), followed by the United Kingdom with 568 (9.16%), Canada with 527 (8.48%), China with 483 (7.78%), Germany with 366 (5.89%), France with 327 (5.26%), Brazil with 308 (4.96%), Italy with 284 (4.58%), Japan with 260 (4.18%), Australia with 248 (3.99%), Spain with 193 (3.10%), Sweden with 176 (2.83%), Mexico with 99 (1.59%), and Iran with 92 (1.49%), as shown in Fig. 3. In terms of total citations, the five leading countries included the United States (93,902), the United Kingdom (24,283), Canada [14,15], Germany (12,892), and China (7,377), as presented in Table 1.

The h-index, also known as the h-factor, is a widely used method to evaluate academic impact that is calculated based on the number of citations received by a paper or researcher. An elevated h-index corresponds to a more significant impact of the paper or researcher. The current study results indicated that the United States had the highest h-index, 138, demonstrating significant influence in MS research and widespread recognition of its publications. The findings also showed that although China had a relatively large number of publications in this field, its h-index was low [16], indicating a weak impact. This suggests a need for improvement in the quality of MS-related research in China (Table 1).

In the analysis of research institutions, a total of 4572 institutions conducted MS research. The five institutions with the highest number of publications included the University of California system (270 articles), the University of London (188 articles), Udice French research universities (160 articles), the French National Centre for Scientific Research (140 articles), and Columbia University (119 articles).

The five leading institutions by mean citations included the University of California system (58.58 citations), Columbia University (49.05 citations), the University of London (42.54 citations), the French National Centre for Scientific Research (37.01 citations), and

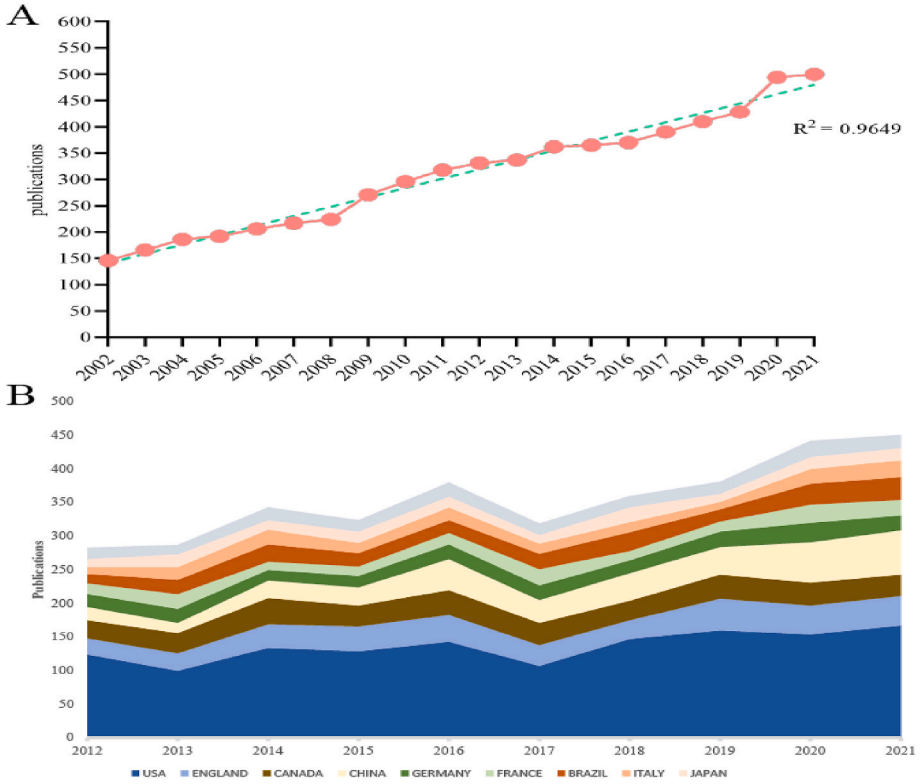

Fig. 2. Trends in publications and citations of MS research. (A) Annual trends of global publications. (B) Temporal trends of publications from the top 10 countries.

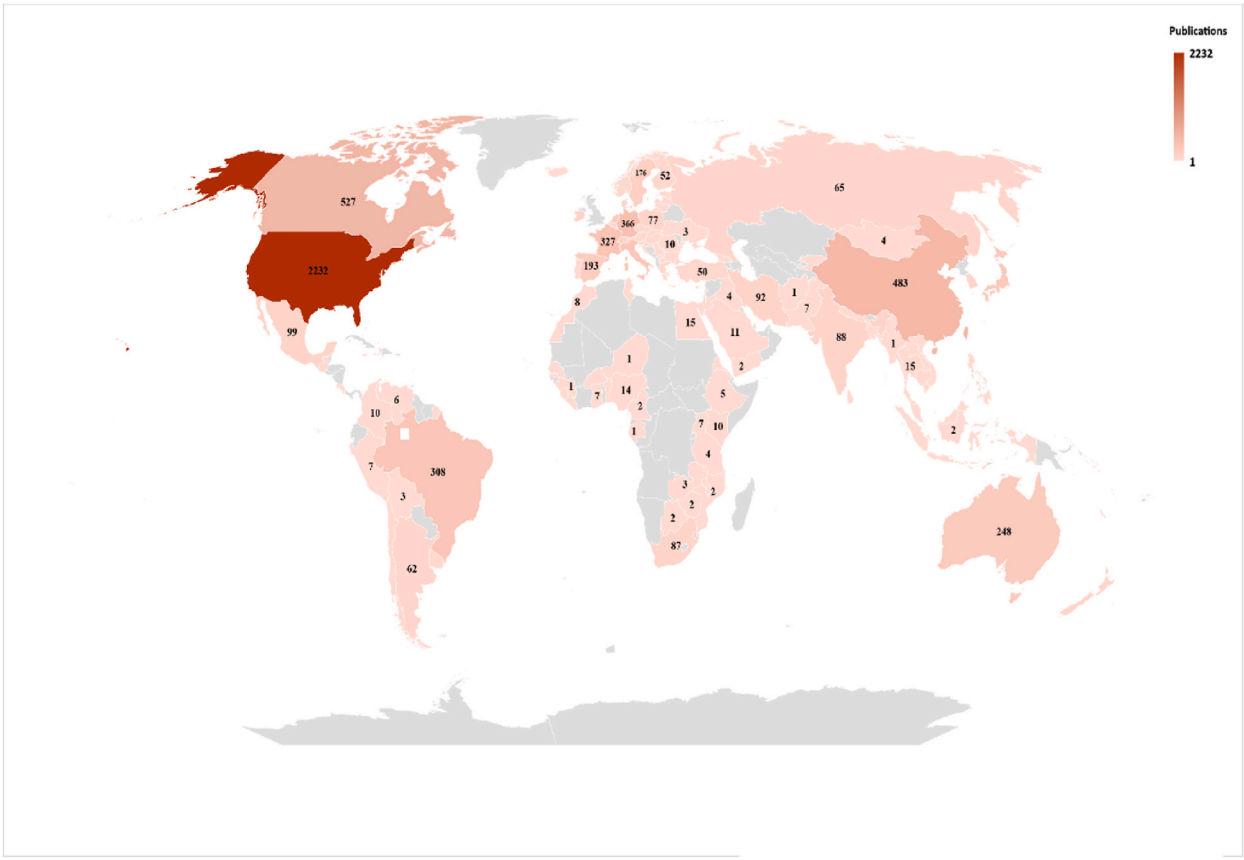

Fig. 3. Top 14 countries by publications.

Table 1
Top 10 countries by publications, citations.

Rank	Country	Publications	% of 6208	Total Citations	Average Citations	H-index
1	USA	2232	35.954	93,902	42.07	138
2	ENGLAND	569	9.166	24,283	42.68	78
3	CANADA	527	8.489	22,039	41.82	76
4	CHINA	442	7.12	7377	16.69	41
5	GERMANY	366	5.896	12,892	35.22	58
6	FRANCE	327	5.267	11,066	33.84	50
7	BRAZIL	308	4.961	6154	45.73	41
8	ITALY	284	4.575	10,513	46.98	53
9	JAPAN	260	4.188	7328	28.18	43
10	AUSTRALIA	248	3.995	7098	28.62	46

Udice French research universities (32.52 citations). The University of California system had the highest h-index (73), indicating that it significantly influences MS research.

The study indicated that the majority of the top 10 institutions in terms of citations were situated in the United States, France. This indicates that both countries are influential in the field of MS research (Table 2).

3.3. Academic partnerships

Academic exchange and collaboration among different countries/regions, institutions, and authors are crucial for enhancing the scope and perspectives of research in MS. Regarding academic collaboration in MS, we discovered that exchange and collaboration occur on multiple levels, as depicted in Fig. 4.

The VOSviewer software presents a network visualization of the interconnections between countries, institutions, and authors, with the closest relationships depicted. Fig. 4A illustrates the network of collaboration among countries/regions in the field of MS research, in which each node corresponds to a different country/region, and the size of the node represents the number of research studies

Table 2
Top 10 institutions distributed by publications.

Rank	Institution	Publications	Average Citations	H-index	Original Country
1	UNIVERSITY OF CALIFORNIA SYSTEM	270	58.58	70	United States
2	UNIVERSITY OF LONDON	188	42.54	54	England
3	UDICE FRENCH RESEARCH UNIVERSITIES	160	32.52	36	France
4	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS	140	37.01	36	France
5	COLUMBIA UNIVERSITY	119	49.05	44	United States
6	UNIVERSITY OF TORONTO	117	45.72	35	Canada
7	HARVARD UNIVERSITY	115	58.22	43	United States
8	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM	107	36.22	30	France
9	NATIONAL INSTITUTES OF HEALTH	97	68.78	41	United States
10	UNIVERSITY OF TEXAS SYSTEM	92	31.77	32	United States

published. The interconnections between nodes reflect the level of collaboration between countries/regions. Among the 66 countries/regions that have published at least five studies, the United States, the United Kingdom, Germany, and Canada exhibit the highest degree of collaboration with other countries/regions, which is in line with the countries/regions identified in Table 1 as the top performers in MS research.

In this study, we identified a cohort of 486 research institutions that have contributed a minimum of 20 research studies. and these institutions were assigned to different cooperative groups that are represented by circles/nodes of various colors.

Fig. 4B shows the 11 most cooperative groups, among which the National University of Ireland and Emory University had relatively more academic cooperation with other research institutions.

Further analysis of the authors shows that there are 24,174 authors in this field, with Cryan having the most articles (59), followed by Dinan [17] and Nylander [18] (Table 3). Among the 24,174 authors, there are 486 with more than five articles, and a cluster analysis shows 17 major collaborating groups (Fig. 4C). Among the largest collaborating groups, Cryan occupies a key position in the collaboration network, indicating that his research has involved in-depth collaboration with others.

3.4. Distribution of cited authors and Co-cited authors

Co-citations, which are typically used to identify highly cited core articles by researchers in the field, reflect the views of experts and the recognition of the co-cited authors [19]. Of the 125,828 co-cited authors we counted, 10 were cited over 500 times (Table 3), with Meaney (1206 citations, Canada), Levine (1191 citations, United States), and Hemm (990 citations, United States) receiving the most citations. This demonstrates a high regard for their research direction and findings, as illustrated in Fig. 5.

3.5. Distribution of journals

The investigation revealed that over the last two decades, a total of 2219 journals have published articles pertaining to MS, among which 10 journals have published over 70 such articles. The impact factors and quartiles of these journals were extracted from the 2021 Journal Citation Report.

The top three journals in terms of number of articles published were *Behavioural Brain Research* (IF: 3.352), *PLOS One* (IF: 3.75), and *Developmental Psychobiology* (IF: 2.531). The top three journals in terms of number of citations were *Behavioural Brain Research* (IF: 3.352), *Neuroscience & Biobehavioral Reviews* (IF: 9.0521), and *Biological Psychiatry* (IF: 12.810), all of which had more than 4500 citations (Table 4 and Fig. 6A). The top three journals in terms of co-citations were the *Journal of Neuroscience* (IF: 6.709), *Behavioural Brain Research* (IF: 3.352), and *Biological Psychiatry* (IF: 12.810) (Fig. 6B). The journals that published articles on MS and the top 10 cited journals are primarily in the Q2 and Q1 regions (Table 4). The results of this study show that these journals have the most significant influence in the field of MS.

3.6. Analysis of highly cited articles and Co-cited references

The most co-cited reference was published by Plotsky in 1993 (533 citations) [20]. This paper emphasized the importance of the early environmental factor of mother–infant separation in regulating the development of the hypothalamus system and the reactivity of the HPA axis to stress. It suggested that the rat model of mother–infant separation could promote the increase of hypothalamus corticotropin-releasing factor (CRF) mRNA level.

The second most co-cited reference was published by Liu in 1997 (455 citations) [21].

This article suggests that alterations in maternal care may impact the development of individual variations in neuroendocrine stress responses in rats. Maternal behavior also helps “program” the offspring’s hypothalamus–pituitary–adrenal gland response to stress, indicating that MS plays an essential role in offspring stress resistance.

The third most co-cited reference was published by Heim in 2001 (350 citations) [22]. The results showed that exposure to early life stress (MS) induces the long-term high activity of the corticotropin-releasing factor (CRF) system and changes in other neurotransmitter systems, resulting in increased responsiveness to stress and the susceptibility to mental disorders (Table 5). To a certain extent,

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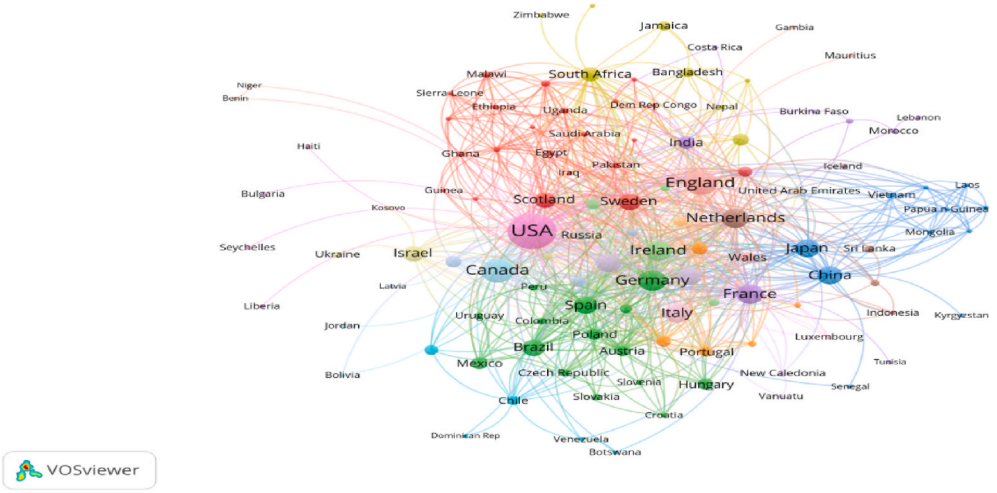

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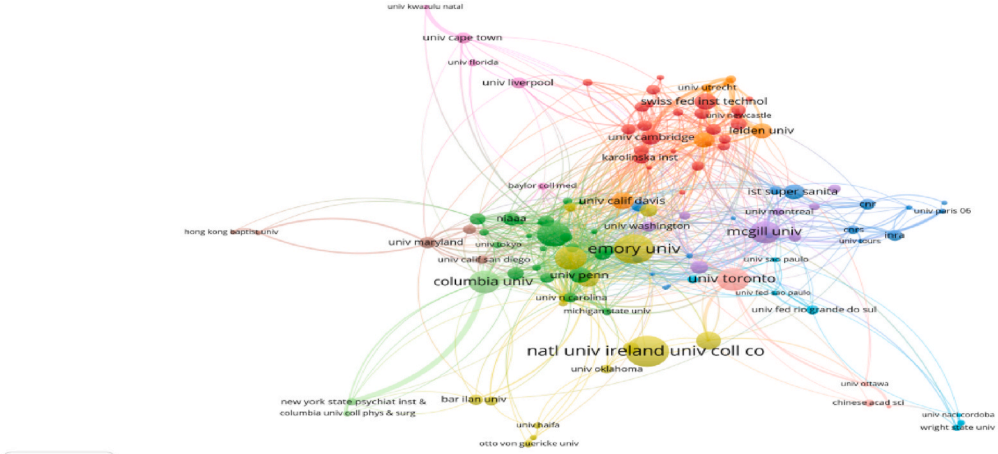

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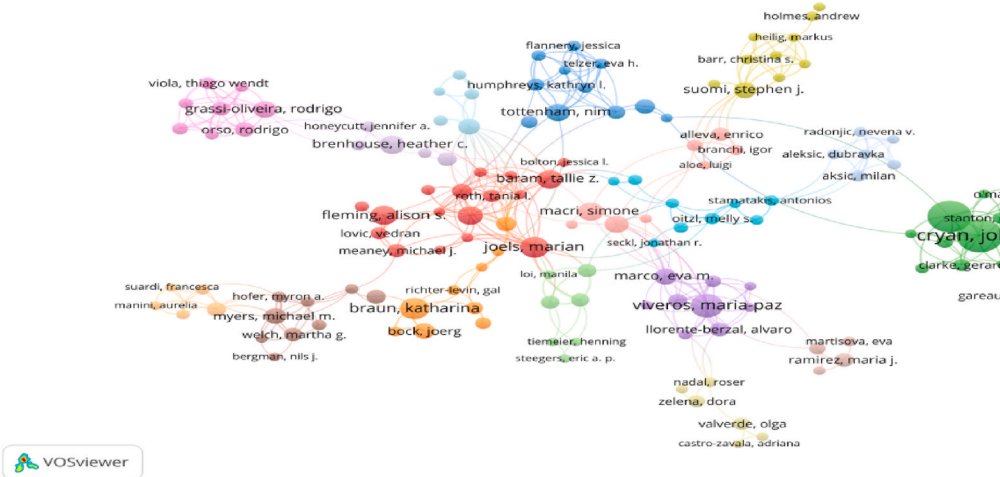

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Fig. 4. Academic collaboration between different countries/regions (A), institutions (B), and authors (C) in the MS research area.

co-citation reference clustering reflects the frontier direction or unexplored scientific topics in the research field, including emerging trends [23]. The current study showed that the clustering of co-cited references related to MS mainly focused on early environmental factors (#0, #1, #2, #5, #11), mechanism of action (#3, #4, #8), mental behavior (#7), and clinical symptoms (#6), as shown in Table 6 and Fig. 7.

Table 7 lists the top 10 most cited articles. The top article [24], was published by Cryan in 2012 (2152 citations) and suggested that the early life stress of mother–child separation can change the composition of the gut microbiota. Gut microbiota communication with the central nervous system may affect brain function and behavior through neural, endocrine, and immune pathways, ultimately playing a role in regulating anxiety, emotional cognition, and pain. The second most cited article was published by Sudo et al., in 2004 (1388 citations) [25]. This article suggested that there is bidirectional communication between the brain and the gut, with stress experiences leading to changes in gastrointestinal motility, secretions, and blood flow. In turn, such changes in gastrointestinal function are transmitted to the brain, leading to the perception of visceral events (e.g., pain). The third most cited article [26]was published by O'Mahony in 2015 (843 citations). This paper suggested that intestinal microflora can affect tryptophan metabolism and the 5-hydroxytryptamine system, emphasizing the critical role of the intestinal microflora in the development of the central nervous system. The potential of targeted therapy for the intestinal microbiota was also proposed.

3.7. The MS negative effects

Table 8 lists five negative effects of MS: impaired emotional development [14]; limited social skills [27]; developmental delays [28]; mental health problems [29]; and increased risk for drug abuse [30]. Based on further analysis of the literature in this study, the field of maternal separation and its negative effects have been widely studied in Iran.

3.8. Analysis of keywords

The keywords of the literature can reflect the research frontiers and trends in specific fields. The current study found 21,966 keywords in the literature related to maternal and infant separation, of which 198 appeared more than 50 times. After classification, five clusters were formed. The same-color nodes in Fig. 8A represent the same cluster. These clusters covered behavioural cognition, the HPA axis, stress, gene expression, depression, and other variables (Fig. 8B).

The top 25 burst words included adverse childhood experience (10.1, 2016–2021), early life stress (13.93, 2017–2021), oxidative stress (9.01, 2017–2021), abuse (9.15, 2018–2021), inflammation (8.85, 2018–2021), and health (8.95, 2019–2021), which suggests that adverse experiences early in life and the intrinsic physiological pathologies of the organism induced by them may be the frontiers and trends of future research; the words adult rat (28.82, 2002–2009), infant rat (14.98, 2002–2011), neonatal rat (9.39, 2002–2010), and long even rat (14.28, 2002–2012) suggested that the maternal separation model of rats was preferred before 2012, and the maternal separation model of rats was no longer trending after 2012 (Fig. 9). In recent years, because the reproductive cycle and generation time of mice are shorter than those of rats, mice are commonly used animal models, but according to specific experimental needs, rats are sometimes optional animal models.

4. Discussion

The early life period is a crucial stage of brain development that has an essential impact on individuals' long-term neurodevelopment and behavior [31]. Early life adversity is considered a significant risk factor for susceptibility to depression, irritable bowel syndrome, and other diseases later in life [32]. Furthermore, early life stress, such as MS, interferes with an individual's normal development, reshapes the brain's structure, and permanently affects brain function, such as immune response [33]. Most mammals are in close contact with their mother during their early life. As a result, early MS is a traumatic event for newborns that may affect adult behavior under certain conditions [34]. Some studies have revealed that enhanced maternal care can have a positive impact on offspring development following a brief period of MS. However, rodents that undergo prolonged MS show increased susceptibility to immune and stress responses in adulthood, leading to multiple behavioural abnormalities [24].

4.1. General information

Through the application of bibliometric analysis to a corpus of 6209 articles on MS retrieved from the WoSCC database, this study offers a comprehensive summary of the research topics and trends in the field and provides an overview of the current status of MS research. The analysis revealed a consistent upward trend in the annual publication and citation of articles focused on MS, which attests to the sustained interest and rapid development of MS research. The United States emerged as the top contributor to MS research, as evidenced by having the highest number of publications and total citations.

In addition, academic institutions in the United States and the United Kingdom have increased their academic cooperation with other research institutions and authors.

Our findings further showed that Cryan and Dinan have close cooperation in this field and are the most published and cited authors, suggesting that their contributions to the study of MS cannot be ignored. After an in-depth study of the literature of Cryan and Dinan,

Table 3
Top 10 authors distributed by publications, citations and co-citations.

Rank	Author	Publications	Country	Rank	Cited author	Total citations	Country	Rank	CO-Cited author	Total citations	Country
1	Cryan JF	59	Ireland	1	Cryan JF	9127	Ireland	1	Meaney MJ	1206	Canada
2	Dinan TG	57	Ireland	2	Dinan TG	8929	Ireland	2	Levine S	1191	United States
3	Nylander I	44	Sweden	3	Plotsky PM	2905	United States	3	HeimC	990	United States
4	Braun K	38	Germany	4	Nemeroff CB	2047	Ireland	4	D Liu	836	Canada
5	Kinkead R	38	Canada	5	Feldon J	1884	United States	5	Plotsky PM	776	United States
6	Viveros MP	37	Spain	6	Tottenham N	1833	Switzerland	6	McewenBS	764	United States
7	Hennessy MB	34	United States	7	Pryce CR	1781	United States	7	Pryce CR	752	Switzerland
8	Quevedo J	31	Brazil	8	Clarke G	1592	Switzerland	8	LehmannJ	696	Switzerland
9	Russell VA	31	South Africa	9	Baram, TZ	1510	Ireland	9	Ladd C	654	United States
10	Mathe AA	29	Sweden	10	Meaney MJ.	1495	United States	10	Hofer, MA	634	United States

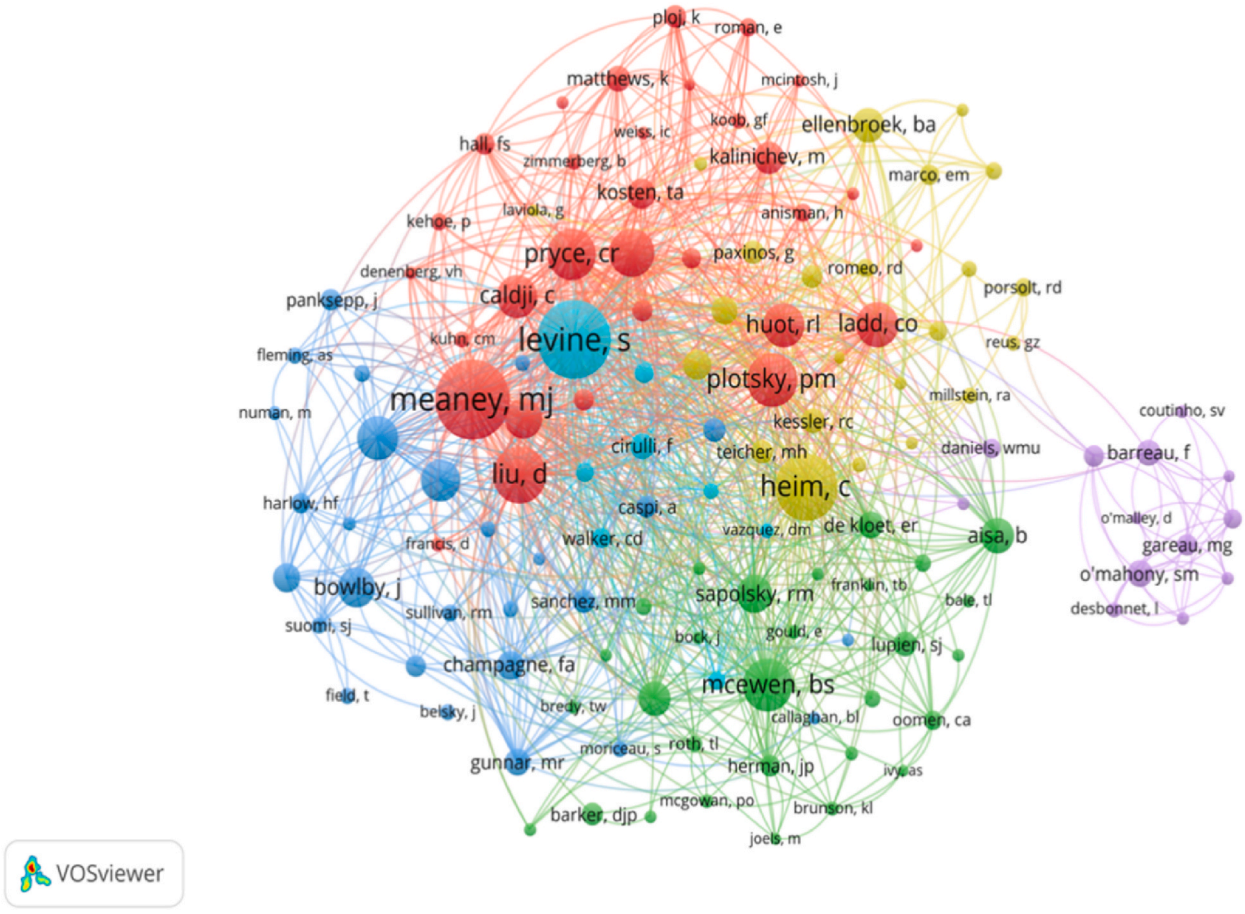

Fig. 5. VOSviewer visualization map of co-cited authors devoted to MS research.

we found that they have conducted many studies on MS and brain–gut axis dysfunction. For example, early life stress, such as MS, can lead to gastrointestinal diseases and mental illness by causing intestinal flora imbalance [34,35].

Furthermore, drugs such as flavonoids and non-flavonoid polyphenols have potential therapeutic effects on reversing MS-induced behavior and intestinal flora disorders [36]. Meaney, another highly cited author, focused on the regulation of the HPA in offspring affected by MS and the stress response in adulthood caused by a stressful early living environment [37,38].

The top 10 journals in this study were mainly distributed in the Q1 and Q2 regions. *Behavioural Brain Research* had the most publications and citations. It is also worth noting that although *PLOS One* had a high number of publications, it was cited less frequently, suggesting that the quality of literature is related to academic influence. The quality of relevant literature should be further improved.

4.2. Trends and frontiers

Based on the clustering of keywords and literature on MS, combined with burst terms analysis, the focus of current MS research is concentrated on the following six aspects.

(1) **Long-term effects of MS on mood and cognition.** As a common early life survival stress, MS typically leads to increased anxiety and depression-like behavior [39], while also causing hippocampus-dependent spatial learning and memory impairment, prefrontal cortex dysfunction (e.g., working memory, cognitive flexibility), and other problems [40,41].

(2) **Long-term effects of MS on the HPA axis.** Early life stress, such as MS, induces persistent neuroplasticity of the HPA axis by affecting the developmental trajectory of brain maturation, with broad and long-lasting effects, including neuroendocrine signal transduction, neuronal morphology and plasticity, and changes in local brain volume and functionality [42,15]. This long-term effect is related to MS-induced HPA axis overreaction, increased amygdala excitability, and impaired regulatory negative feedback function in the hippocampus and prefrontal cortex [43].

(3) **Correlation between MS and intestinal flora imbalance.** An increasing number of studies have recognized that the gut microbiota play a crucial role in maintaining homeostasis in the body, are highly sensitive to the environment, and that changes

Table 4
Top 10 journals distributed by publications and citations.

Rank	Journal	Publications	% of 2219	IF (JCR2021)	JIF quartile	Journal	Total Citations	IF (JCR2021)	JIF quartile
1	*BEHAVIOURAL BRAIN RESEARCH*	206	3.318	3.352	Q2	*BEHAVIOURAL BRAIN RESEARCH*	7423	3.352	Q2
2	PLOS ONE	163	2.626	3.752	Q2	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	5652	9.0521	Q1
3	*DEVELOPMENTAL PSYCHOBIOLOGY*	135	2.175	2.531	Q3	*BIOLOGICAL PSYCHIATRY*	5186	12.810	Q1
4	*PSYCHONEUROENDOCRINOLOGY*	96	1.546	4.693	Q2	*PSYCHONEUROENDOCRINOLOGY*	4995	4.693	Q2
5	*NEUROSCIENCE*	92	1.482	3.708	Q3	*PLOS ONE*	4896	3.752	Q2
6	*PHYSIOLOGY & BEHAVIOR*	91	1.466	3.742	Q1	*NEUROSCIENCE*	4741	3.708	Q3
7	*APPLIED ANIMAL BEHAVIOR SCIENCE*	76	1.224	2.569	Q1	*NEUROPSYCHOPHARMACOLOGY*	3470	8.294	Q1
8	*BRAIN RESEARCH*	72	1.16	3.610	Q3	*DEVELOPMENTAL PSYCHOBIOLOGY*	3354	2.531	Q3
9	*HORMONES AND BEHAVIOR*	72	1.16	3.492	Q2	*JOURNAL OF NEUROSCIENCE*	2931	6.709	Q1
10	*INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE*	72	1.16	2.540	Q3	*BRAIN RESEARCH*	2872	3.610	Q3

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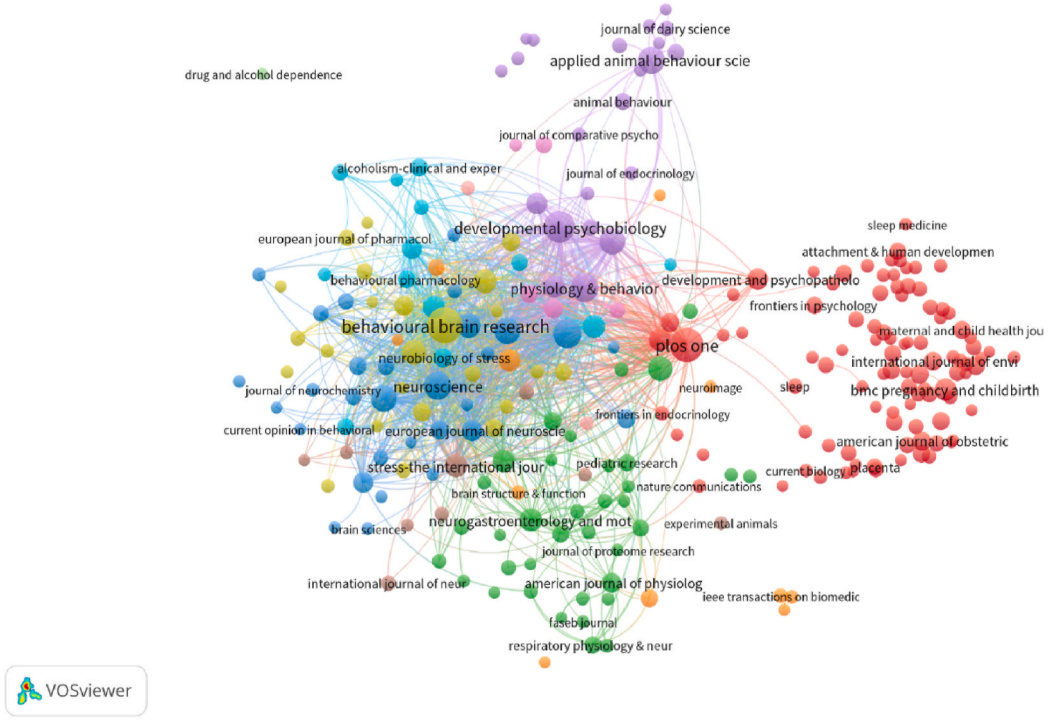

VOSviewer

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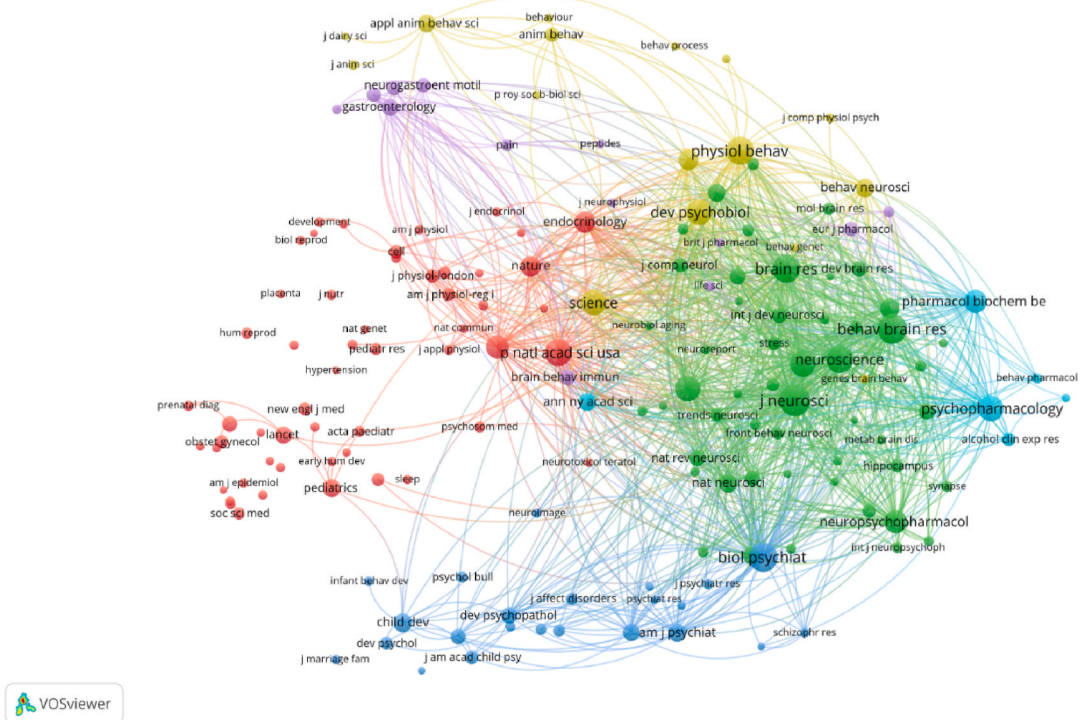

VOSviewer

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Fig. 6. VOSviewer visualization map of most commonly cited journals related to MS research. (A) Co-citation network of journals. (B) Co-cited network of journals.

Table 5
Top 10 co-cited reference.

Rank	Author	Title	Source	Citations
1	Plotsky *Pm* (1993)	Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats	Brain Res Mol Brain Res	533
2	D Liu (1997)	Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress	Science	455
3	Heim C (2001)	The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies	Biol Psychiatry	350
4	Meaney MJ (2001)	Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations	Annu Rev Neurosci	298
5	Huot Rl (2001)	Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment	Psychopharmacology	297
6	Weaver ICG (2004)	Epigenetic programming by maternal behavior	Nat Neurosci	291
7	LehmannJ (2000)	Long-term biobehavioral effects of maternal separation in the rat: consistent or confusing?	Rev Neurosci	276
8	Wigger A (1999)	Periodic maternal deprivation induces gender-dependent alterations in behavioural and neuroendocrine responses to emotional stress in adult rats	Physiol Behav	268
9	Aisa B (2007)	Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats	Psychoneuroendocrinology	265
10	Ladd CO (2000)	Long-term behavioural and neuroendocrine adaptations to adverse early experience	Prog Brain Res	264

Table 6
Major clusters of co-cited references.

Cluster ID	Cluster label	Size	*S*-value	Mean (year)
#0	early life adversity	311	0.889	2018
#1	early life programming	247	0.806	2008
#2	long-lasting change	231	0.941	2003
#3	epigenetic mechanism	172	0.88	2013
#4	gut microbiota	107	0.904	2014
#5	maternal deprivation	84	0.944	2012
#6	irritable bowel syndrome	57	0.948	2008
#7	making sense	37	0.938	2018
#8	pituitary-adrenal axis	36	0.976	2002
#11	perinatal environment	11	0.996	2006

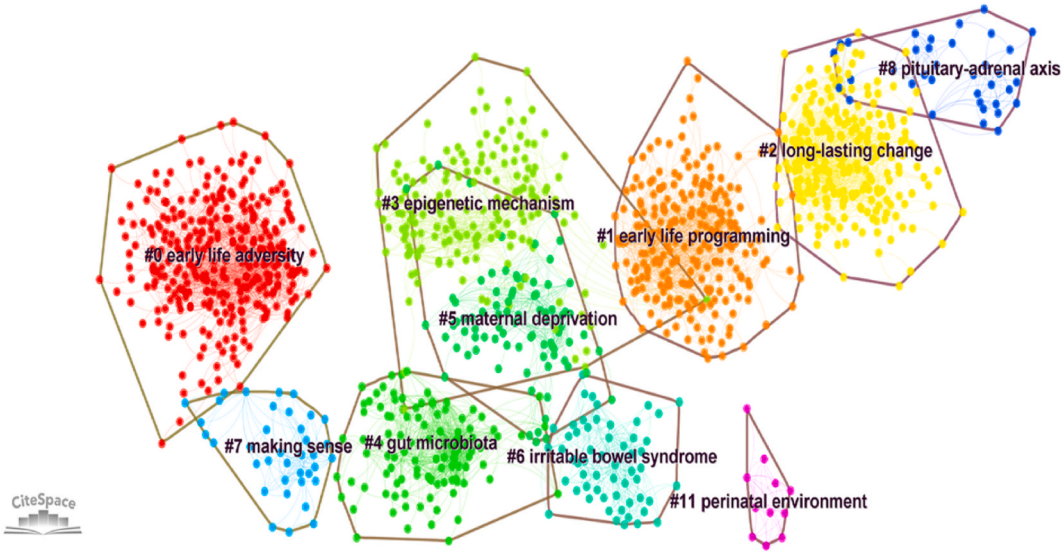

Fig. 7. CiteSpace visualization map of major clusters of co-cited references.

Table 7
Top 10 cited papers.

Rank	Author	Title	Source	Citations
1	Cryan JF (2012)	Mind-Altering Microorganisms: The Impact Of The Gut Microbiota On Brain And Behavior	*NATURE REVIEWS NEUROSCIENCE*	2152
2	Sudo N (2004)	Postnatal Microbial Colonization Programs The Hypothalamic-Pituitary-Adrenal System For Stress Response In Mice	*JOURNAL OF PHYSIOLOGY-LONDON*	1388
3	O'Mahony SM (2015)	Serotonin, Tryptophan Metabolism And The Brain-Gut-Microbiome Axis	*BEHAVIOURAL BRAIN RESEARCH*	843
4	Walker SP (2011)	Child Development 1 Inequality In Early Childhood: Risk And Protective Factors For Early Child Development	*LANCET*	812
5	Messaoudi M (2011)	Assessment Of Psychotropic-Like Properties Of a Probiotic Formulation (Lactobacillus Helveticus R0052 And Bifidobacterium Longum R0175) In Rats And Human Subjects	*BRITISH JOURNAL OF NUTRITION*	764
6	O'Mahony SM (2009)	Early Life Stress Alters Behavior, Immunity, And Microbiota In Rats: Implications For Irritable Bowel Syndrome And Psychiatric Illnesses	*BIOLOGICAL PSYCHIATRY*	708
7	Mayer EA (2015)	Gut/Brain Axis And The Microbiota	*JOURNAL OF CLINICAL INVESTIGATION*	701
8	Franklin TB (2010)	Epigenetic Transmission Of The Impact Of Early Stress Across Generations	*BIOLOGICAL PSYCHIATRY*	681
9	Fone KCF (2008)	Behavioural And Neurochemical Effects Of Post-Weaning Social Isolation In Rodents - Relevance To Developmental Neuropsychiatric Disorders	*NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS*	596
10	Desbonne L (2010)	Effects Of The Probiotic Bifidobacterium Infantis In The Maternal Separation Model Of Depression	*NEUROSCIENCE*	541

Table 8
The negative effects of MS.

Rank	Negative Effects	References
1	Impaired emotional development [14]	Intergenerational effects of maternal separation on cognitive abilities of adolescent rats
2	Limited social skills [27]	Social withdrawal in children moderates the association between parenting styles and the children's own socioemotional development
3	Developmental delays [28]	Oxytocin mitigated the depressive-like behaviors of maternal separation stress through modulating mitochondrial function and neuroinflammation
4	Mental health problems [29]	Trigonelline through the Attenuation of Oxidative Stress Exerts Antidepressant- and Anxiolytic-Like Effects in a Mouse Model of Maternal Separation Stress
5	increase risk for drug abuse [30]	Effects of maternal separation on nicotine-induced conditioned place preference and subsequent learning and memory in adolescent female rats

in composition (imbalance) can lead to the creation of various disease states, including irritable bowel syndrome, obesity, depression, and autism [16,44]. Changes in the diversity and richness of the gut microbiota due to early life survival stress, represented by MS, are apparent, but little is known about the specific mechanisms. Interestingly, using different but complementary gut microbiota as interventions (including fecal transplantation, probiotics, and prebiotics) can have a therapeutic effect on MS-induced anxiety and depression-like emotions [45,18], which provides a potential treatment option for intervention in psychiatric disorders. However, there is still a lack of large-scale clinical studies.

(4) **MS is involved in epigenetic changes.** Multiple investigations have revealed that MS can induce epigenetic alterations in rodent. For example, MS may cause DNA methylation associated with depression, stress, mood, and other genes [46], including BDNF, glucocorticoid receptor, corticotrophin-releasing hormone, and arginine vasopressin [47–49]. In addition, the early stress of MS exerts enduring effect on the transcriptional regulation of histone modification factors. Seo et al. [50] found that MS induced a significant decrease in the acetylation levels of BDNF protein, exon I mRNA, and histone H3; a significant increase in the mRNA levels of DNMT1 and DNMT3a; a decrease in the acetylation levels of histone H3 and H4 at BDNF promoter IV; and an increase in the mRNA levels of MECP2 and HDAC5 at BDNF promoter IV. MS can also regulate non-coding RNA [51]. In addition, Bondar et al. [52] found that early-life MS in mice led to heightened vulnerability to social defeat stress during adulthood. Furthermore, they observed enduring alterations in gene expression, splicing patterns, and the H3K4me3 epigenetic landscape across the prefrontal cortex. This study is of great importance, as it not only expands the depth of research on epigenetic changes induced by maternal separation but also enhances our understanding of the impact of maternal separation on the genome-wide distribution of the active chromatin marker H3K4me3.

(5) **The effects of MS on structural and functional changes in brain volumes and its cytoarchitecture.** MS may lead to a reduction of the size of certain brain areas, including the cingulate gyrus, and amygdala [53,54]. Furthermore, MS may cause changes in the function of brain regions, such as emotional regulation and cognitive control [55]. Several studies have also found that MS may alter the structure of brain cells, such as the number and density of synapses, morphology, and number of neurons [56,57].

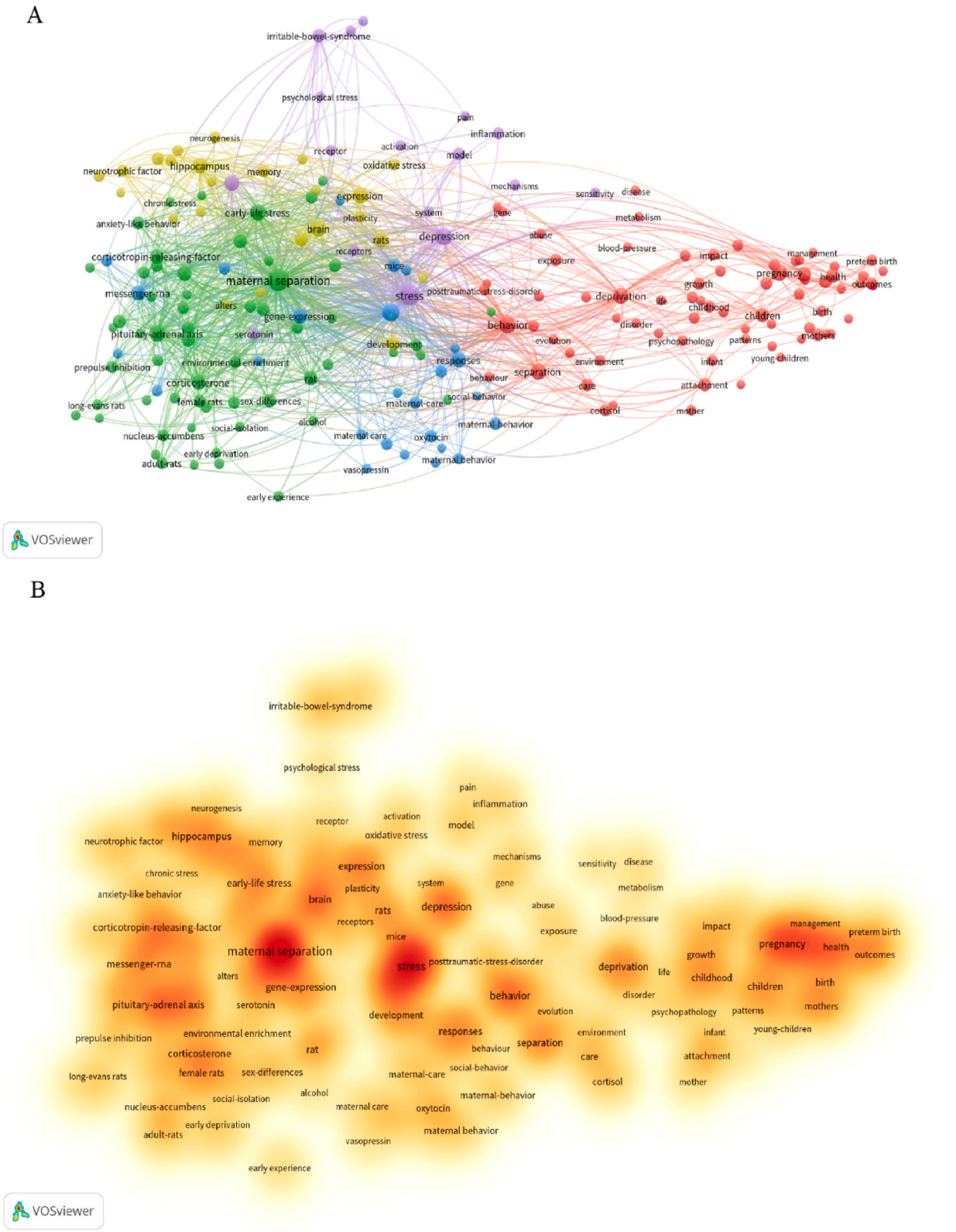

Fig. 8. Analysis of all keywords in studies related to MS research. (A) VOSviewer visualization map of co-occurring keywords. (B) The density map of keywords. (The closer the keyword node color is to red, the higher the frequency of its co-occurrence is.)

Keywords	Year	Strength	Begin	End	2002-2021
adult rat	2002	28.82	2002	2009	
early experience	2002	17.56	2002	2010	
infant rat	2002	14.98	2002	2011	
paraventricular nucleus	2002	14.56	2002	2009	
corticotropin releasing factor	2002	13.97	2002	2009	
response	2002	12.74	2002	2005	
messenger rna	2002	12.32	2002	2008	
adrenocortical response	2002	11.64	2002	2008	
neonatal rat	2002	9.39	2002	2010	
prenatal diagnosis	2002	8.16	2002	2010	
neonatal handling	2002	9.79	2003	2007	
long evans rat	2002	14.28	2004	2012	
neuroendocrine response	2002	9.58	2006	2010	
pituitary adrenal axi	2002	9.2	2006	2010	
long lasting change	2002	10.26	2007	2012	
forced swimming test	2002	8.91	2010	2015	
early maternal deprivation	2002	9.27	2012	2016	
separation anxiety	2002	9.27	2015	2019	
adverse childhood experience	2002	10.1	2016	2021	
management	2002	8.66	2016	2019	
early-life stress	2002	13.93	2017	2021	
oxidative stress	2002	9.01	2017	2021	
abuse	2002	9.15	2018	2021	
inflammation	2002	8.95	2018	2021	
health	2002	8.85	2019	2021	

Fig. 9. Top 25 keywords with the strongest citation bursts.

(6) **The effect of MS on stress reactivity.** MS has a wide range of effects on stress response, including neuroendocrine response, autonomic nerve response, and neuroelectrophysiological response, which may cause abnormal cortisol level, heart rate variability (HRV), event-related potentials (ERP), and other related indicators [17,58].

5. Limitations and strengths

The present investigation is the first bibliometric examination to delve into the burgeoning subject of MS and furnish an inclusive knowledge graph. In comparison to conventional reviews, our findings present more instinctive proof regarding research emphases and trends in various dimensions. Unavoidably, our study has several limitations. First, the study only included literature published up to November 30, 2022, and new studies published after this date may impact the understanding of current research directions and the emergence of new trends in the field. Second, relying on a single database, the WoSCC may have resulted in the exclusion of relevant research found in other large medical databases such as Scopus, PubMed, and Embase, While WoSCC is widely acknowledged as the predominant reference database employed in scientometric research. Third the documents incorporated into the WoSCC database are in a state of constant flux. Some newly published, high-caliber articles may have been overlooked due to the need for higher co-citation counts. In summary, our bibliometric investigation lays a robust groundwork for researchers engaged in MS-related studies.

6. Conclusions

This study analyzes the research on MS published in the past 20 years. Our findings summarize the regional distribution, journal distribution, article citation, prominent authors, regional cooperation, keywords, reference clustering of relevant literature, and the negative effects of MS in the field of MS.

MS, serving as a model of early life stress, holds importance in examining the impacts of early life hardship on neural development and psychopathological adaptability. However, the specific mechanisms of its effects on psychopathology have not yet been clarified. Epigenetics and alterations in the brain–gut axis are likely to be the trends and frontiers of future research in this field. The early adverse experience of MS will attract global attention in terms of its impact on human health and the public safety of society.

This study offers enduring support to those investigating the domain of MS, particularly early-career researchers, by providing them with a comprehensive understanding of global trends and research directions in MS.

Author contribution statement

Xiaoying Meng, Binghao Bao and Guangxin Yue: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

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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

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