Bibliometric and Visual Analysis of Research on the Links between the Microbiome-Gut-Brain axis and Depression

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Abstract

Background

The pathways and mechanisms underlying the associations between the gut microbiome and the brain are collectively known as the microbiome-gut-brain axis (MGBA). Depression is a common and frequent psychological and psychiatric disease. The interactions comprising the MGBA may play a role in the pathogenesis of depression. Nevertheless, the general aspects of the links between the MGBA and depression have not been systematically investigated through bibliometric analysis.

Methods

Publications from 1994 to 2022, focusing on the links between the MGBA and depression, were downloaded from the Web of Science Core Collection. HistCite, VOSviewer, CiteSpace, and the Bibliometrix Package and were used for bibliometric analysis and visualization. The main analyses we performed included collaboration network analysis, co-citation analysis, co-occurrence analysis, and citation burst detection.

Results

A total of 829 publications related to the relationship between the MGBA and depression were identified. The number of such publications has been rapidly growing since 2014. The People's Republic of China, University College Cork, and John F. Cryan were the most influential country, institute, and scholar, respectively. BRAIN BEHAV IMMUN and NUTRIENTS were the most productive and co-cited journals. Five hot topics in research linking the MGBA with depression were depression, gut microbiota, gut-brain axis, microbiota, and anxiety. Five frontier topics in the field were cytokine, maternal separation, neuroinflammation, probiotics, and vagus. The most representative and symbolic reference with the highest co-citation number was an article by Bravo J. A. et al. (2011).

Conclusions

These results provide an instructive perspective for research on the relationship between the MGBA and depression, and a timely review and analysis of research hotspots and research trends, which will promote the development of this field. Future research will focus on understanding the underlying mechanism of action of the MGBA on depression, and on elucidating microbial-based interventions and treatment strategies for depression.

Background

There are hundreds of millions of bacteria living in the human gut, generating a bacterial ecosystem that affects many physiological functions of the host. As early as the mid-nineteenth century, pioneering research on the brain-gut connection suggested that secretions from the digestive tract and other related organs are strongly influenced by emotions or the senses. In the 1920s, Walter Cannon emphasized the role of the brain in regulating intestinal function and disease, such as the common brain-gut disease irritable bowel syndrome (IBS) and functional bowel disease[1]. Information exchange between the brain and the gut occurs through the gut-brain axis. Therapeutic strategies targeting the gut-brain axis have proven effective to be used for future treatment practices in psychiatric medicine[2]. The two systems connected by the gut-brain axis respond to each other through the enteric nervous system (ENS) and the central nervous system (CNS). Another route between the gut and the brain is the vagus nerve, which transmits information on the state of the body's organs to the CNS. From 2007, when the National Institutes of Health (NIH) took the lead in proposing the Human Microbiome Project, to the official launch of the “National Microbiome Project” by the White House in 2016, many successful studies have enabled a quantitative analysis of the components of the gut microbiome and microbial metabolism. Of special interest are studies using next-generation sequencing technology and metagenomic research, bioinformatics, modern neuroimaging, and computational biology[3–5]. With the development of this field, the concept of the gut-brain axis has been further expanded to that of the microbiota-gut-brain axis (MGBA). Current research focuses on the specific physiological and pathological mechanisms that link the MGBA with depression.

Depression is a common mental disorder with clinical manifestations of long-term depression, slow thinking, loss of interest, and in severe cases, suicidal behavior. More than 350 million people worldwide are reported to suffer from depression, which is projected to become the number one global burden of disease by 2030[6]. The gut microbiota affects not only the physiological functions of the gastrointestinal tract but also the function and behavior of the brain through the MGBA (Fig. 1)[7]. The mechanisms underlying the role of the MGBA in the occurrence and development of depression involve mainly inflammatory responses, monoamine neurotransmitters, brain-derived neurotrophic factors, and the hypothalamic-pituitary-adrenal (HPA) axis[8, 9]. Sim K. et al.[10] found that fecal microbiota transplantation (FMT) from patients with depression into germ-free (GF) rats induced depression-like behavior in the rats. Currently, depression is treated mainly with drugs. However, the onset of antidepressant treatment is often delayed and has a good curative effect only in 70% of the patients. To improve the curative effect of drug therapies and overcome drug resistance, the development of methods for treating depression by targeting gut microbes, for example, by taking probiotics, FMT, or healthy eating, has become the focus of new research[11].

Regarding the increased interest in research on the mechanisms of depression from the perspective of the MGBA, there have been many reviews summarizing the relevant literature, but estimates of the general situation and research trends in the fields of MGBA and depression have not been analyzed. Bibliometric analysis, a series of analytical methods for evaluating and quantifying information in the literature, has been applied in many fields of research to identify core researchers, institutions, and countries, and the collaborative relationships between them. Keyword co-occurrence analysis, co-citation analysis, and keyword burst analysis reflect global research trends and hot topics. Therefore, it is necessary to understand the current status of research on the relationship between the MGBA and depression on a global scale.

Methods

Data Source and Search Strategy

We conducted a literature search on the Web of Science Core Collection (WoSCC) from the date of their inception to March 6, 2022. We used the key terms“microbiome-gut-brain axis” and its synonyms, the search formula was as follows: (1) (Brain-Gut Axis OR Axis, Brain-Gut OR Brain Gut Axis OR Gut and Brain Axis OR Gut-Brain Axis OR Axis, Gut-Brain OR Gut Brain Axis OR Brain and Gut Axis OR Microbiota-Gut-Brain Axis OR Axis, Microbiota-Gut-Brain OR Microbiota Gut Brain Axis OR Brain-Gut-Microbiome Axis OR Axis, Brain-Gut-Microbiome OR Brain Gut Microbiome Axis OR Microbiome-Gut-Brain Axis OR Axis, Microbiome-Gut-Brain OR Gut Brain Microbiome Axis OR Microbiome-Brain-Gut Axis OR Axis, Microbiome-Brain-Gut OR Microbiome Brain Gut Axis OR Microbiota-Brain-Gut Axis OR Axis, Microbiota-Brain-Gut OR Microbiota Brain Gut Axis) and (2) (Gut microbiome OR Gut microflora OR Gut microbiota OR Gut flora OR Intestinal microbiome OR Microbiome microbiota OR Intestinal microflora OR Intestinal flora) and (3) (depression OR depressions OR depressed OR despondent OR gloomy OR depressive OR antidepressant OR antidepressants OR Depressive Symptoms OR Depressive Symptom OR Symptom, Depressive OR Symptoms, Depressive OR Emotional Depression OR Depression, Emotional OR depressive disorder OR major depressive disorder) .The article language was set to English. In order to avoid deviations from data updates, all the above operations were performed within 1 day, and on March 6, 2022. Indexes = SCI-EXPANDED, IC Timespan = 1994–2022. As a result, 829 records were obtained.

Eligibility Criteria and Data Collection

The document types included in the study were only articles and reviews. Meeting abstracts, editorial materials, and proceedings papers, among others, and were excluded. Duplicate studies were also removed artificially. All the information, including the number of papers and citations, titles, authors, affiliations,countries, keywords, journal, publication year, and references,were collected for bibliometric analysis.

Analytical Tools

In this study, HistCite (version 12.03.17)[12], VOSviewer (version 1.6.16)[13], CiteSpace (version 5.7.R5)[14], and the Bibliometrix 4.1.0 Package[15] (https://www.bibliometrix.org) based on the R language were used to perform the bibliometric analysis.

Table 1
Document types for documents on MRI research on acupuncture

Rank	Type	Counts	TLGS	TGCS
1	Article	478	3024	18176
2	Review	323	1771	16727
3	Article;Book Chapter	8	113	729
4	Review;Early Access	7	0	31
5	Article;Early Access	5	0	1
6	Review;Book Chapter	5	26	490
7	Article;Proceesings Paper	3	0	100

Results

Overall Distribution, Annual Publications, and Document Type

A total of 829 publications related to research on the relationship between MGBA and depression were retrieved from WoSCC, including 478 articles and 323 reviews (Table 1, Fig. 2). Total global citation score (TGCS) and total local citation score (TLCS) were used to assess publication quality and impact. The number of published works in the literature each year is shown in Fig. 2. As can be seen in this figure, although the number of studies fluctuated slightly from 2009 to 2022, the overall number increased gradually and reached a peak in 2021. In particular, the number of published works in the literature fluctuated continuously from 2014 to 2021. According to the analysis of annual production and growth rate, research on the links between the MGBA and depression first appeared in 2009 by S. M. O'Mahony, who described the correlation between the gut-brain axis and depression earlier than researchers in other parts of the world, proposing that early-life stress leads to alterations in the gut-brain axis and is, therefore, an important parameter to consider when studying potential mechanistic aspects of stress-related disorders, including depression and IBS. This article was published in the journal BIOLOGICAL PSYCHIATRY. During the early stage, the total number of publications on the relationship between the MGBA and depression was less than 10 per year. However, a gradual increase in the number of published papers became apparent since 2014. By 2019, the increase in the number of published papers reached a steady state. The period from 2014 to 2019 can be classified as the growth period, and the period from 2020 to 2021 as the mature stage. During the growth period, the total number of published articles on the relationship between the MGBA and depression was less than 100 articles per year, but it increased at an average rate of 21.5 articles per year, with an average annual growth rate of 33.94%. During the mature stage, the total number of papers on the topic was more than 100 per year, with an average annual growth of 40 papers and an average annual growth rate of 19.37%. It is expected that the number of published papers will reach 283 by 2022.

Analysis of Country

Overall, these 829 references were published in 58 countries. The global article productivity is presented in Fig. 3 using VOSviewer. For better visualization, we only selected countries with more than 5 published articles (33). Each node represents a country, and the size of the node is proportional to the number of published articles. Connections between nodes represent collaborations, with wider connections denoting tighter collaborations. The list of the top 5 countries is presented in Table 2. The People's Republic of China had the most publications (n = 192; 16%), followed by the United States of America (USA) (n = 122; 14.71%), Canada (n = 87; 10.49%), Ireland (n = 85; 10.25%) and Italy (n = 53; 6.4%). Canada had the highest centrality (0.45).

The top 5 countries in terms of total link strength were USA (122), which had the highest connectivity, followed by Canada, China, Germany, Ireland, and Italy. In addition, The TGCS of Ireland (cited 12,405 times) was the highest, followed by the United States (cited 8,369 times), Canada (cited 6,643 times), China (cited 4,269 times), and Italy (cited 1,402 times).

Table 2
Top 5 countries and institutions which performed Between the MGBA with depression research.

Rank	Country/region	Frequency	Centrality	TLCS/TGCS	Total link strength	Institution(Country)	Frequency
1	Peoples R China	192	0.35	746/4269	54	University College Cork(Ireland)	64
2	USA	186	0.16	851/8369	122	McMaster University(Canada)	41
3	Canada	87	0.45	911/6643	98	Chongqing Medical University(China)	19
4	Ireland	85	0.30	2003/12405	54	University College Cork National University of Ireland(Ireland)	19
5	Italy	53	0.55	121/1402	43	Chiba University(Japan)	18

Analysis of Institution

Nearly 1156 institutions made contributions to research linking the MGBA with depression. To obtain a better visualization, we used VOSviewer to depict institution collaboration networks from only 14 institutions, which had at least 10 documents published (Fig. 4). Each node represents an institution, and the size of the node is proportional to the number of published articles. Connections between nodes represent collaborations, and wider connections represent tighter collaborations. The list of the top 5 institutions is presented in Table 2. University College Cork has published the largest number of studies (n = 64), followed by McMaster University (n = 41), Chongqing Medical University (n = 19), University College Cork National University of Ireland (n = 19), Chiba University (n = 18), Deakin University (n = 16), University of California Los Angeles (n = 14), Medical University of Graz (n = 14), University of Toronto (n = 13), University of Melbourne (n = 11), and Chinese Academy of Sciences (n = 11). Cooperation between institutions was relatively high and was divided into three institutional clusters. The cooperation groups led by the McMaster University of Canada showed the closest cooperation with other institutions, and had the highest centrality (0.33).

The timeline of articles published by each institution was visualized using VOSviewer. We expect that by 2020, Chinese research institutes, in particular, Fudan University, Southern Medical University, Sichuan University, Jining Medical College, and Northwest A&F University, will pay more attention to research linking the gut-brain axis with depression.

Analysis of Authors

An author map, generated using VOSviewer, is presented in Fig. 5, showing 60 research authors that had at least 5 published articles. Each node represents an author, and the size of the node is proportional to the number of published articles. Connections between nodes represent collaborations and a wider connection denotes a tighter collaboration. Table 3 shows the top 10 authors who have published articles related to research linking the MGBA to depression. These are professional authors from China, Ireland, Canada, and Japan, who are active in the field, and their partnerships can be seen in an analysis of author collaborative networks using VOSviewer. Four clusters were formed, each containing authors with long-term relationships. Of the top 10 authors, the three most productive were John F. Cryan, Timothy G. Dinan, and Gerard Clarke from Ireland University College Cork, followed by Peng Xie, Peng Zheng, and Hong Wei from Chongqing Medical University of China, Kenji Hashimoto from Chiba University, and J. A. Foster and J. Bienenstock from Canada McMaster University. As can be seen from the publication year of the first article, John F. Cryan and Timothy J. Dinan from the Alimentary Pharmabiotic Centre collaborated to publish this article on their MRI research on acupuncture. So far, they have been engaged in research in this field for nearly 20 years (2009–2022)[16]. In 2011, J. Bienenstock published a paper in collaboration with John F. Cryan, showing that probiotics (*Lactobacillus rhamnosus*, JB-1) had a direct effect on stress-induced corticosterone levels and related behavioral and physiological responses, while no neurochemical or behavioral effects were observed in mice with vagus nerve severance. The vagus nerve has been identified as the main regulatory component of communication between bacteria exposed to the gut and brain.

Table 3
Top-10 authors who performed MGBA with depression research.

Rank	Author	Frequency	Citations	Total link strength	TLCS	TGCS	Country	Institution
1	Cryan,john f	73	9307	143	1943	11857	Ireland	University College Cork
2	Dinan,timothy g	62	8801	129	1822	10853	Ireland	University College Cork
3	Clarke,gerard	31	3341	73	905	4669	Ireland	University College Cork
4	Stanton,catherine	19	495	55	45	573	Ireland	University College Cork
5	Hashimoto K	18	2587	55	305	1282	Japan	Chiba University
6	Xie,peng	16	307	14	305	1282	China	Chongqing Medical University
7	Foster JA	13	2085	8	389	2122	Canada	McMaster University
8	Zheng p	11	148	43	237	1023	China	Chongqing Medical University
9	Bienenstock j	10	238	22	451	2684	Canada	McMaster University
10	Wei,hong	10	284	42	231	924	China	Chongqing Medical University

A Sankey diagram of the city-institution-author contact map shows that the main association bands are University College Cork-Cryan, Ireland, China-Chongqing Medical University -Xie, Peng, United States -University of Pittsburgh-Rinaman L from the Department of Neuroscience, Canada -McMaster University-Foster JA, Australia - Deakin University- Berk M.

Analysis of Journals and Co-cited Journals

All articles in research linking the MGBA to depression were published in 345 journals, 40 of which had published more than 5 articles (Fig. 6). About 45.83% of all articles were published in these journals. The h-index is a measure of productivity and the impact of a researcher who has published h articles cited at least h times each[17]. The 5 journals with the highest productivity are shown in Table 4. The first most productive journal was BRAIN BEHAV IMMUN (published 34 articles, cited 1929 times), followed by NUTRIENTS (published 30 articles, cited 564 times), FRONT PSYCHIATRY (published 21 articles, cited 659 times), and PROG NEURO-PSYCHOPH (published 17 articles, cited 246 times), and J AFFECT DISORD (published 15 articles, cited 505 times). Among them, the average impact factor (IF) was 5.399. The IF from Thomson Reuters indicates the impact of journals, referring to the number of citations of a given journal in a specific year[18].

Table 4
Top-5 journals and co-cited journals related to MGBA with depression research.

Rank	Journals	Frequency	TLCS	TGCS	IF(2021)	H-index	co-cited journals	citations	total link strength
1	Brain behavior and immunity	34	299	1929	7.217	17	brain behavior and immunity	1929	263
2	Nutrients	30	0	564	5.717	9	nutrients	564	212
3	Frontiers in psychiatry	21	0	659	4.157	10	frontiers in psychiatry	659	170
4	Progress in neuro-psychopharmacology & biological psychiatry	17	3	246	5.067	8	progress in neuro-psychopharmacology & biological psychiatry	246	181
5	Journal of affective disorders	15	190	505	4.839	7	journal of affective disorders	505	161

Figure 7 presents the 76 journals that were co-cited at least 200 times. The top five co-cited journals were BRAIN BEHAV IMMUN, NUTRIENTS, FRONT PSYCHIATRY, PROG NEURO-PSYCHOPH, and J AFFECT DISORD (Table 4). Among them, BRAIN BEHAV IMMUN had the highest citation rate.

Research Hotspots

A research hotspot refers to a large number of interconnected papers or topics discussed in a certain period of time. Cited authors, co-occurring keywords, and cited references can be used to investigate current research hotspots.

Analysis of Co-cited Authors

The map of co-cited authors is presented in Fig. 7. For better visualization, we included only authors who were cited at least 100 times (44). The top 5 co-cited authors are shown in Table 5. T. G. Dinan ranked first, followed by J. F. Cryan, L. Desbonnet, P. Bercik, and J. R. Kelly. Among them, T. G. Dinan had the highest total connection strength.

T. G. Dinan, J. F. Cryan, L. Desbonnet, and J. R. Kelly came from University College Cork, Cork, Ireland.

Among them, T. G. Dinan and J. F. Cryan were from the Department of Psychiatry and Neurobehavioural Science. L. Desbonnet was from the Alimentary Pharmabiotic Centre.

1. P. Bercik was from McMaster University, Hamilton, Canada, Department of Medicine, Farncombe Family Digestive Health Research Institute.

2. J. R. Kelly was from APC Microbiome Institute, University College Cork.

Table 5
Top-5 co-cited Author related to MGBA with depression research.

Rank	co-cited Author	Frequency	Country	Institution	Total link strength
1	Dinan,TG	574	Ireland	University College Cork	9956
2	Cryan, JF	506	Ireland	University College Cork	7566
3	Desbonnet, L	480	Ireland	University College Cork	9877
4	Bercik, P	442	Canada	McMaster University	8521
5	Kelly, JR	404	Ireland	University College Cork	6548

Analysis of Co-occurring Keywords

The map of co-cited keywords is presented in Fig. 8A. We extracted 3191 keywords at data collection. Keyword co-occurrence clustering roughly divided these keywords into nine clusters, which are shown in different colors: Cluster 1 refers to related diseases, with primary keywords being “Alzheimer's disease”, “bipolar disorder”, and “autism”. Cluster 2 refers to communication links, with primary keywords being “blood-brain barrier”, “CNS”, “short-chain fatty acids” (SCFAs), and “gut-brain axis”. Cluster 3 refers to intervention, with primary keywords being “probiotics”, “bacterial translocation”, and “diet”. Cluster 4 refers to research on mechanisms linking the MGBA with depression, with primary keywords being “activation” and “responses”. Cluster 5 refers to burden of disease, with primary keywords being “anxiety-like behavior” and “quality of life”. Table 6 shows the top 10 co-cited keywords. Analysis of co-occurrence frequency revealed that “depression” showed the maximum frequency (398), followed by “gut microbiota” (291), “gut-brain axis” (242), “microbiota” (220), and “anxiety”(216). Among them, “depression” had the highest connectivity (2539).

Table 6
Top-10 co-cited Keywords related to MGBA with depression research.

Rank	Keywords	Frequency	Total link strength	Rank	Keywords	Frequency	Total link strength
1	Depression	298	2539	6	Stress	185	1235
2	Gut microbiota	291	1735	7	Brain	160	1043
3	Gut-brain axis	242	1489	8	Probiotics	154	1125
4	Microbiota	220	1363	9	Intestinal microbiota	150	999
5	Anxiety	216	1451	10	inflammation	137	1327

Cluster analysis revealed 9 clustering results (Table 7). The cluster modularity Q was 0.4067, and the mean silhouette value was 0.7322. The modularity Q and mean silhouette are two important evaluation indicators in cluster analysis. A Q value higher that 0.3 indicates that the clustering structure is statistically significant. A mean silhouette value higher than 0.5 indicates that the clustering results are convincing. The timeline of clustering showed that “gut-brain axis” and “inflammatory bowel disease” were keywords representing the most important areas of research linking the MGBA to depression, whereas “anorexia nervosa” was the keyword associated with an emerging hotspot in this research topic (Fig. 8B).

Table 7
Keyword cluster analysis of MGBA with depression research.

Cluster ID	Size	Sihouette	Mean year	Top terms
#0	79	0.501	2015	Gut-brain axis
#1	73	0.472	2018	Inflammatory bowel disease
#2	62	0.565	2016	parkinson
#3	55	0.507	2017	acid
#4	47	0.504	2017	Immune system
#5	24	0.853	2011	gut-brain axis
#6	22	0.823	2015	Gut microbiome
#7	21	0.772	2016	Major depression
#8	20	0.865	2015	Anorexia nervosa

We conducted a thematic evolution analysis on keywords, and found that the initial stages of research linking the MGBA to depression was mainly focused on topics represented by the keywords “irritable bowel syndrome” and “response”. However, with the development of the research field, the main research hotspot has gradually evolved toward areas characterized by keywords such as “CNS”, “dysbiosis,” “depression”, “corticotropin releasing factor”, and “intestinal microbiota”. As the research field has matured for nearly four years, the main research hotspot has further evolved toward topics associated with the keywords

“fecal microbiota”, “neuroinflammation”, “SCFAs”, “probiotics”, and “Parkinson’s disease”, which have gradually attracted the attention of scholars, as shown in Fig. 9C.

Keyword bursts may indicate frontier topics or emerging trends[19]. Representative keyword bursts among the top 20 keywords with the strongest citation bursts are shown in Table 8. The green line represents the time period from 2009 to 2022, while the periods of each keyword burst are plotted by the red line. The strength values reflect the citation frequency. We found that the keyword with the highest strength burst was “irritable bowel syndrome”. In addition, “cytokine” was the latest keyword, which emerged in the last 2 years.

Table 8
Representative burst keywords among top 20 references with the strongest citation bursts.

Keywords	Year	Strength	Begin	End	2009–2022
irritable bowel syndrome	2009	10.424	2014	2017	
intestinal microbiota	2009	9.4116	2014	2016	
anxiety like behavior	2009	9.1911	2010	2017	
brain gut axi	2009	8.2015	2009	2017	
central nervous system	2009	6.6385	2012	2018	
mice	2009	5.9429	2016	2018	
obesity	2009	5.6276	2015	2017	
maternal separation	2009	4.7754	2009	2017	
infection	2009	4.374	2010	2017	
lactobacillus helveticus	2009	4.367	2014	2015	
brain development	2009	3.7593	2017	2019	
corticotropin releasing factor	2009	3.6825	2010	2016	
cognition	2009	3.4971	2010	2017	
immune system	2009	3.466	2015	2018	
psychological stress	2009	3.2971	2014	2017	
bacterial translocation	2009	3.2862	2015	2018	
functional gastrointestinal disorder	2009	3.2321	2013	2014	
system	2009	3.1443	2009	2015	
microbiome	2009	3.0994	2017	2018	
cytokine	2009	3.0638	2017	2020	

Analysis of Co-cited References

A total of 4,4298 references were generated from 829 records to perform an analysis of co-cited references. The map of co-cited keywords is presented in Fig. 9A. The 10 most cited references included 9 research articles and 1 review (Table 9). Most articles focused on the correlation between intestinal flora and the MGBA in the pathogenesis and pathophysiological mechanisms of depression.

Table 9
Top 10 cited references related to MGBA with depression research.

Rank	Co-cited references	Co-cited counts	First author	Year	IF	Journal	Institutions/country
1	Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. doi:10.1073/pnas.1102999108	298	Bravo JA,	2011	11.205	Proc Natl Acad Sci U S A	University College Cork, Cork, Ireland
2	Altered fecal microbiota composition in patients with major depressive 4 disorder.doi 10.1016/j.bbi.2015.03.016	284	Jiang hy	2015	7.217	Brain Behav Immun	Zhejiang University, China
3	Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice.doi:10.1113/jphysiol.2004.063388	258	Sudo N	2004	5.182	The Journal of physiology	Kyushu University,Fukuoka,Japan
4	Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. doi:10.1038/nrn3346	249	Cryan JF	2012	34.870	Nat Rev Neurosci	University College Cork, Cork, Ireland
5	Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism.doi:10.1038/mp.2016.44	220	Zheng P	2016	15.992	Mol Psychiatry	Chongqing Medical University, Chongqing, China
6	Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. doi:10.1016/j.jpsychires.2016.07.019	211	Kelly JR	2016	4.791	J Psychiatr Res	University College Cork, Cork, Ireland
7	Normal gut microbiota modulates brain development and behavior. doi:10.1073/pnas.1010529108	203	Diaz Heijtz R	2011	11.205	Proc Natl Acad Sci U S A	Karolinska Institutet, Sweden
8	Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects.doi:10.1017/S0007114510004319	189	Messaoudi M	2011	3.781	Br J Nutr	Vandoeuvre-le`s-Nancy, France
9	The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner.doi:10.1038/mp.2012.77	188	Clarke G	2013	15.992	Mol Psychiatry	University College Cork, Cork, Ireland
10	Hestad K, Avershina E, et al. Correlation between the human fecal microbiota and depression. doi:10.1111/nmo.12378	183	Naseribafrouei A	2014	3.598	Neurogastroenterol Motil	Hedmark University College, Hamar, Norway

The most cited article was written by J. A. Bravo, who reported that *Lactobacillus rhamnosus* (*L. rhamnosus*, JB-1) regulates emotional behavior and central γ-aminobutyric acid (GABA) receptor expression in mice through the vagus nerve. Moreover, vagus nerve stimulation (VNS) has been described as a successful treatment for depression, further demonstrating the importance of the vagus nerve in behavioral regulation (co-cited 298 times).

Subsequently, Jiang H. Y. et al. proposed that stress can cause "leaky gut" and plays a role in the gut-brain axis. They observed that social stressors significantly altered the relative abundance of bacteria, particularly when microbiota were assessed immediately following the stressor exposure (cited 284 times).

The third article, published in 2004 by Sudo N. et al, investigated HPA gland responses to stress by comparing GF, pathogen-free (SPF), and gnotobiotic mice, and suggested that the symbiotic microflora can influence the postnatal development of HPA stress response in mice (cited 258 times).

The fourth article, published in 2012 by Cryan J. F. et al., is a review of the literature on the effects of the gut microbiota on the brain and behavior, including the communication between the microflora and the brain through immune, neural, and endocrine pathways, the effects of the gut microbiota on the gut-brain axis in health and disease, and how the microflora communicates with the gut-brain axis in anxiety, depression, and cognitive diseases (cited 249 times).

The last article, published in 2016 by Zheng P. et al., compared the gut microbiota of depression patients and healthy people using 16S rRNA gene sequencing and found changes in the relative abundance of Firmicutes, Actinobacteria, and Bacteroidetes. Additionally, it showed that transplantation of "depressed microbiota" from patients into GF mice led to depression-like behavior, in contrast to transplantation of "healthy microbiota" from healthy individuals. That demonstrated that the gut microbiota can physiologically induce depression-like behavior in mice and contribute to depression-like behavior by altering the host metabolism (cited 220 times).

Table 10
references cluster analysis of MGBA with depression research.

Cluster ID	Size	Sihouette	Mean year	Top terms
#0	136	0.923	2018	Brain-gut-axis
#1	130	0.974	2007	Maternal separation
#2	95	0.937	2009	Post-genomics diagnositics
#3	87	0.763	2013	Neuropsychiatric disorders
#4	71	0.953	2008	psychobiotics
#5	61	0.937	2010	bifidobacteria
#6	49	0.953	2010	Fear conditioning
#7	48	1	2009	microflora
#8	33	1	2010	irritable bowel syndrome
#9	23	1	2010	recolonisation
#10	20	1	2009	gluten
#11	13	1	2009	vagus
#12	4	1	2018	Depression-like behaviors

Table 11
Representative burst references among top 20 references with the strongest citation bursts.

References	Year	Strength	Begin	End	2009–2022
CRYAN JF, 2012, NAT REV NEUROSCI, V13, P701,	2012	30.8942	2014	2017	
BRAVO JA, 2011, P NATL ACAD SCI USA, V108, P16050	2011	28.2491	2012	2016	
VALLES-COLOMER M, 2019, NAT MICROBIOL, V4, P623	2019	27.2793	2020	2022	
CRYAN JF, 2019, PHYSIOL REV, V99, P1877	2019	25.9844	2020	2022	
JIANG HY, 2015, BRAIN BEHAV IMMUN, V48, P186	2015	24.2247	2017	2020	
HEIJTZA RD, 2011, P NATL ACAD SCI USA, V108, P3047	2011	23.7043	2012	2016	
BERCIK P, 2011, GASTROENTEROLOGY, V141, P599	2011	23.2511	2012	2016	
CLARKE G, 2013, MOL PSYCHIATR, V18, P666	2013	21.8028	2013	2018	
NEUFELD KM, 2011, NEUROGASTROENT MOTIL, V23, P	2011	21.4406	2012	2016	
MESSAOUDI M, 2011, BRIT J NUTR, V105, P755	2011	20.4606	2010	2016	
NASERIBAFROUEI A, 2014, NEUROGASTROENT MOTIL, V26, P1155	2014	18.5353	2016	2019	
FOSTER JA, 2013, TRENDS NEUROSCI, V36, P305	2013	18.2802	2015	2018	
TILLISCH K, 2013, GASTROENTEROLOGY, V144, P1394	2013	16.6016	2014	2018	
BERCIK P, 2011, NEUROGASTROENT MOTIL, V23, P1132	2011	16.4808	2012	2016	
HSIAO EY, 2013, CELL, V155, P1451	2013	16.3341	2014	2018	
RUDZKI L, 2019, PSYCHONEUROENDOCRINO, V100, P213	2019	15.3998	2020	2022	
DESBONNET L, 2010, NEUROSCIENCE, V170, P1179	2010	15.2387	2010	2015	
GAREAU MG, 2011, GUT, V60, P307	2011	14.7524	2010	2016	
COLLINS SM, 2012, NAT REV MICROBIOL, V10, P735	2012	14.3558	2014	2017	
BAILEY MT, 2011, BRAIN BEHAV IMMUN, V25, P397	2011	14.3149	2011	2016	

We subsequently constructed a visualization network of cited references and performed a cluster analysis. A total of 13 clusters were found (Table 10; Fig. 9B). The modularity Q was 0.4587 and the mean silhouette value was 0.8617, with each cluster having a mean silhouette value higher than 0.5, indicating reasonable cluster quality. The terms found included “vagus”, “gluten”, “maternal separation”, and “recolonisation”. Furthermore, we visualized the timeline of the clusters (Fig. 9C). We found that “maternal separation” is an early-field topic in research linking the MGBA to depression. However, the current hotspots are “gut-brain axis”, and “depression-like behaviors”. Finally, we conducted a reference burst. Table 11 shows the most representative reference bursts among the top 20 references with the strongest citation bursts. We found that the articles from Cryan J.F. et al. (2012) had the highest burst strength, and articles from

2019 have had a strong citation burst in recent years. In addition, an article from M. Valles-Colomer introduced associations between the neuroactive potential of the human gut microbiota and quality of life and depression. This topic has aroused research interest in recent years[20].

Discussion

In this study, we analyzed the main knowledge domain and emerging trends in research linking the MGBA to depression using bibliometric analysis. Some landmark articles were also identified using this analysis (Fig. 10). We analyzed a total of 829 publications found in WoSCC, and we present a comprehensive overview of the worldwide hotspots and trends in research linking the MGBA with depression over the past three decades. The retrieval years were from 1994 to 2022, but the first relevant literature appeared in 2009.

Our analysis revealed the rapid growth in the number of publications since 2014 and the close international scientific cooperation in this field. The People's Republic of China, University College Cork, and John F. Cryan were the most influential country, institute, and scholar, respectively. China was the most productive country (192 published articles, cited 4,267 times), with Chongqing Medical University being the main representative institute. The team of Peng Xie from this institution contributed the most publications, with the latest research focus being on proteomics research of the gut-brain axis in a gut microbiota-dysbiosis model of depression, which found that protein changes of the gut-brain axis were involved in energy metabolism and inflammatory responses[21]. Ireland is the most cited country, with 4 of the top 5 co-cited authors coming from this country, with the University College Cork being the main representative (64 published articles, cited 7,334 times). John F. Cryan is a leader at this institution, who has devoted his work to the study of the links between the MGBA and depression for nearly 20 years. His latest research supported the development of lifestyle-oriented adjunct therapies for depression, including physical activity and special diets. Modulation of the composition of the immune system and gut microbiota in combination with traditional antidepressants is a promising treatment option[22, 23].

Journal analysis and co-cited journal analysis can identify the most popular journals for scholars in the field and help researchers select appropriate journals for article submission. BRAIN BEHAV IMMUN and NUTRIENTS were the most productive and co-cited journals. Most leading-edge results and major breakthroughs in the research field of MGBA-depression connections have been published in these 2 journals. The BRAIN BEHAV IMMUN journal focuses mostly on psychobehavioral research, such as neuroimmunity, depression, and anxiety, and in recent years, on the vagus nerve, the pathway through which neuro-immune signals travel from the gut to the brain[24, 25]. Work published there also poses new questions and suggests new research directions, such as the idea that the normal gut microflora is important for maintaining a normal immune response, as well as a balanced intestinal mucosa, by inducing the natural immune defense of the host and inhibiting pathogen adhesion to mucosal cells. FMT can improve depression-like behaviors induced by chronic unpredictable mild stress. Such anti-depression effects were associated with the suppressed activation of glial cells and the NLRP3 inflammasome in the brain[26]. Although a clinical study [27] has reported that FMT intervention improved depressive symptoms, the possibility of symptom recurrence following FMT may be very high, and afterwards, the FMT microflora may affect the activity of the vagus nerve, causing nerve inflammation, and resulting in worse nervous and mental symptoms. To date, no studies have examined the effects of post-FMT vagus blocking in human patients to investigate the combined efficacy of FMT and vagus blocking; therefore, it may be interesting to explore this new treatment for depression. On the other hand, the journal NUTRIENTS focuses mainly on the effect of diet on anxiety and depression. An article published in NUTRIENTS found that dietary regulation of the gut microbiota is a new method to relieve mood disorders[28]. The widespread use of magnetic resonance imaging (MRI) provides an ideal way to study gut-brain interactions *in vivo*. The gut microbiota is involved in myelin formation of prefrontal cortex neurons and participates in the development of the amygdala and the hippocampus. Eating patterns that have positive effects on mental health facilitate the growth of beneficial bacteria, while limiting the growth of the pathogenic flora, and they affect the permeability and inflammatory status of the intestinal barrier. Thus, diet is an important variable in the relationship between the bowel and neurological disease[29].

The results of our analysis on keyword co-occurrence indicated frontier topics or emerging trends[19], including depression, the gut-brain axis, and anxiety. Furthermore, many keywords associated with areas of research related to MGBA-depression connections have appeared in recent years, including IBS, Parkinson's disease, and anorexia nervosa. We found that the keyword "gut-brain axis" appeared in 2009 and the keyword "IBS" had the highest burst strength. The study of the effects of the gut microbiome on behavior and neurobiology, known as the MGBA, began with observations on patients with IBS[30]. IBS is characterized by abdominal pain and changes in bowel habits. Although the exact etiology of IBS remains unknown, multiple pieces of evidence suggest that inflammation and cytokine imbalance may be a potential etiology of IBS[31]. Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, characterized by tremors and bradykinesia [32], and its main pathological features are the loss of substantia nigra dopaminergic neurons and the formation of Lewy bodies [33]. Stolzenberg et al. found that the expression of α-synuclein in the enteric nerves of the upper gastrointestinal tract in PD patients was positively correlated with the degree of intestinal wall inflammation [34]. α-Synuclein is transferred to the CNS via the vagus nerve, leading to the development of PD. Approximately 80% and 75% of patients with anorexia nervosa suffer from major depression and anxiety, respectively, and anorexia nervosa patients with psychiatric comorbidities have a higher mortality rate than patients without such comorbidities[35, 36]. The HPA axis plays an important role in the pathogenesis of anorexia nervosa[37]. Matsuwaki T et al.[39] intraperitoneally injected lipopolysaccharide (LPS), an *Escherichia coli* metabolite, into IL-1 receptor-knockout mice, and observed that the HPA axis was activated and the mice exhibited anorexia.

With the development of research on the links between the gut-brain axis and depression, some emerging research topics are gradually attracting the attention of researchers, such as "neuroinflammation", "cytokines", "corticotropin-releasing factor", and "central nervous system". Research has revolved around the role of the MGBA in the development and progression of depression. Li et al. [40] transplanted the microbiota of chronic unpredictable mild stress (CUMS) mice into GF mice and found that the levels of interferon -γ (IFN-γ) and tumor necrosis factor -α (TNF-α) in the hippocampus of mice were significantly increased, accompanied by an upregulation of indoleamine 2, 3-dioxygenase 1 (IDO1). Studies have shown that the gut microbiome regulates the levels of proinflammatory cytokines in the hippocampus and exacerbates depression-like behavior through a dysfunctional MGBA. More than 50% of depressed patients have dysregulated negative feedback control of the HPA axis, resulting in increased levels of corticosterone (CORT) and adrenocorticotropic hormone (ACTH) [41]. Under stress, the impaired function of the HPA axis in GF rats can be improved by transplantation of a normal gut microbiome [42]. Probiotics

have a positive effect on depression-like behavior by changing the activity of the HPA axis. Mice treated with *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 not only showed improvement of depression-like behaviors, but also had significantly reduced plasma CORT levels [43]. Neurotransmitters such as GABA, norepinephrine, and dopamine, and metabolites of intestinal microorganisms may directly affect CNS function by activating the stress circuit through down-down signals such as the vagus nerve pathway[44].

According to reference co-citation network analysis, interesting research themes included “gut-brain axis”, “maternal separation”, “post-genomics diagnositics”, “vagus”, and “psychobiotics”, which formed an important basis for studies in this field. Maternal separation (MS) has been developed as a model for inducing stress and depression in studies using rodents[45]. Probiotic bacteria have antidepressive effects, and are presently considered as psychobiotics with preventive and therapeutic potential for the treatment of neurological and neurophysiological disorders[46]. *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacteria* are known as the "three healthy beneficial bacteria". Liao J. E. et al. found that *Lactobacillus paracasei* PS23 reduced early-life stress abnormalities in a maternal separation mouse model[47]. *Lacticaseibacillus paracasei* NK112 mitigated *Escherichia coli*-induced depression and cognitive impairment in mice by regulating IL-6 expression and the BDNF-TrkB signal pathway[48]. Tian P. J. et al. proposed that *Bifidobacterium brevis* CCFM1025 regulated the gut microbiome and tryptophan metabolism, having antidepressant effects[50, 51]. The vagus nerve plays an important role in the gut-brain axis interaction. Bravo J. A. et al[16]. found that after the administration of *Lactobacillus rhamnosus* in healthy mice, anxiety- and depression-like behaviors were reduced in the mice, and the expression of GABA receptors in the brain changed. However, these effects of *Lactobacillus rhamnosus* were significantly reduced after vagus nerve resection.

In recent years, increasing attention is paid to some emerging research fields. Many studies have shown that traditional Chinese medicine can improve depression symptoms by regulating the gut microbiota. Xiaoyaosan improves depressive symptoms by modulating the gut microbiota and inhibiting the overactivation of the NLRP3 inflammasome in the colon[52]. Kaixinsan alleviated depressive symptoms by modulating the gut-brain axis, improving the intestinal microenvironment and inhibiting neuroinflammation and activation of the HPA axis in the brain of CUMS model mice[53]. Baihe Jizihuang Decoction attenuated CUMS-induced depression-like behavior by regulating BDNF and intestinal flora disorder through the [54]gut-brain axis. In addition, Yu et al. found that paeoniflorin can be converted into benzoic acid by the intestinal flora and enter the brain through the blood-brain barrier, where it exerts an antidepressant effect[55]. Sun et al. found that schisandrin could alleviate the disturbance of the intestinal flora in depressed mice, change SCFA, and reduce the level of pro-inflammatory factors[56]. It is worth mentioning that the VNS is a non-drug treatment, which constitutes an FDA-approved somatic treatment for treatment-resistant depression (TRD), and can produce clinically significant antidepressant effects (12). Anatomical studies suggest that the ear is the only place on the surface of the human body where there is afferent vagus nerve distribution. A non-invasive transcutaneous vagus nerve stimulation (taVNS) method has been developed. In 2013, HEI conducted the first taVNS clinical trial for depression, which was found to have antidepressant effects and could be used as an alternative treatment[57]. Subsequent studies have found that taVNS can regulate the gastrointestinal, immune, and endocrine systems through the MGBA, rendering it an effective depression treatment[58]. Subsequently, Rong P. et al. observed that this therapeutic mechanism may be related to the modulation of brain default mode network (DMN). The reward and salience networks seem to be closely related[59, 60].

Although we do not fully understand the interaction between the MGBA and depression, a number of tools and animal models can help narrow the gap in our understanding of the MGBA. Numerous studies over the past decade have demonstrated that targeting the gut microbiome improves depressive symptoms, and as research continues, the field is shifting to the biological basis for such neurobiological effects. FMT is a technique establishing a donor-like microbiome in the recipient's gastrointestinal tract, and can generate strong inferences about the causal relationship between the gut microbiome and host outcomes. The GF animal model can further help us understand the relationship between microbes and the host. In addition, the flexibility and relevance of antibiotics make them a very valuable tool for studying the MGBA. The emergence of brain imaging techniques has provided conclusive evidence of a link between the gut and the activation of key brain networks. Metabolic models of the microbiome use experimental data, and their ability to generate big data can provide valuable insights into MGBA interactions.

Our research has some limitations. First, publications were retrieved only from the WoSCC database, and although we enriched the search strategy as much as possible, we cannot guarantee that all relevant articles were identified. Second, in some cases, different keywords may have the same meaning, for example, "brain-gut axis” and “gut-brain axis” or "intestinal flora” and “gut microbiota”. Thus, bias may still exist despite our normalization. Third, the conclusions obtained in this study using visualization and analysis software such as citespace and VOSviewer require further analysis in the future.

Conclusions

This study comprises a bibliometric and visual analysis of research linking the MGBA with depression in the field of depression over the past three decades. The number of publications has been rapidly increased since 2014. The mechanism of action of probiotics is the current focus of research in this field, whereas “cytokines”, “vagus”, “FMT”, and “gluten” are potential hotspots linking the MGBA with depression, which require more focus. However, “Parkinson’s disease”, “IBS”, and “anorexia nervosa” were identified as associated with areas of this field. In addition, related research on the treatment of depression with traditional Chinese medicine compounds and monomers is also being performed. However, most of the studies on the relationship between the MGBA and depression rely mainly on animal experiments, and some of the conclusions obtained have not been verified in clinical trials. More clinical studies are needed to fill this gap.

Future research will focus on understanding the underlying mechanisms linking the MGBA to depression and elucidating microbial intervention and treatment strategies for depression. Therefore, our timely review and analysis of the hotspots and research trends may promote the development of this field.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

Competing interests

All authors declare that they have no conflicts of interest.

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Authors' contributions

J-LF conceived and designed this experiment.This article was written mainly by YM and PX.YL ,CL-G and JF-S conducted the data analysis. All authors have read and approved the final article.

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Figures

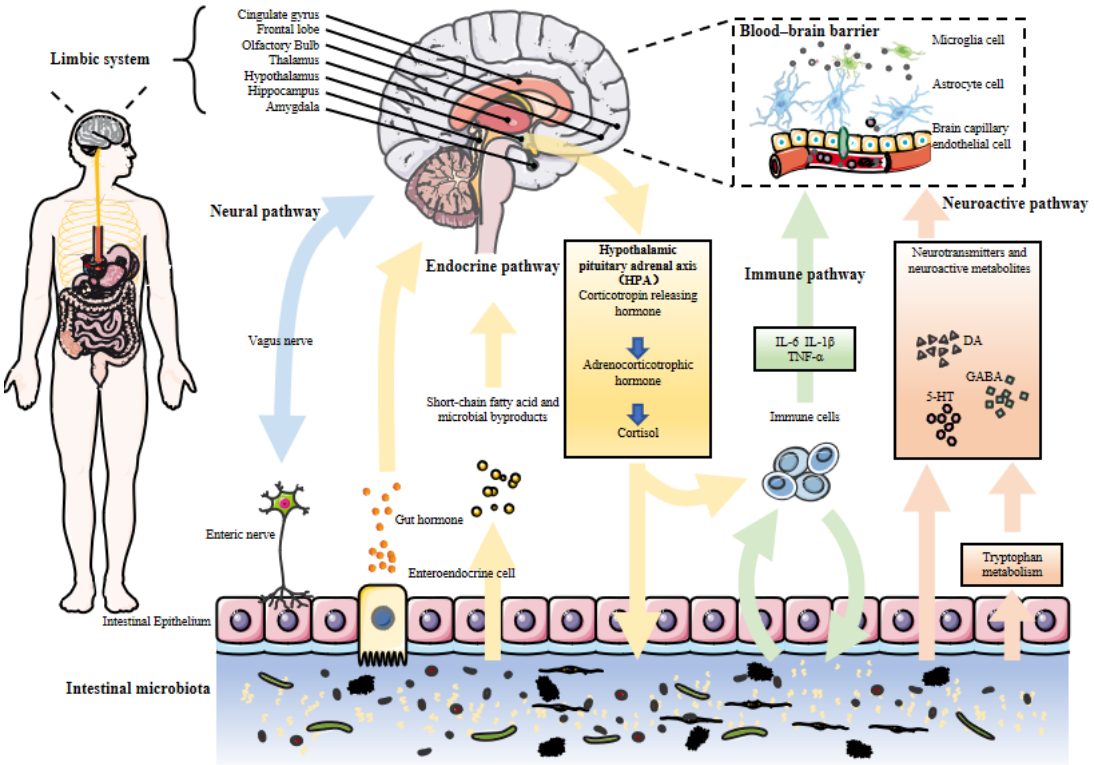


Figure 1

Pathways involved in bidirectional communication between the gut microbiota and the brain. (The microbiota-gut-brain axis involves the nervous system, endocrine system and immune system. When exposed to external stress, the HPA axis regulates the secretion of cortisol, which can affect immune cells and

change the intestinal permeability and barrier function. Intestinal flora can interact with brain through spinal cord, afferent nerve of vagus nerve and internal nerve of intestinal neuron itself. Endocrine pathway affects central nervous system activity by regulating intestinal endocrine cells and microbial metabolites; Immune pathway, immune cytokines and tryptophan metabolites secreted by intestinal epithelial cells produce neurotransmitters, and neuroactive metabolites affect brain structure and function through the blood-brain barrier)

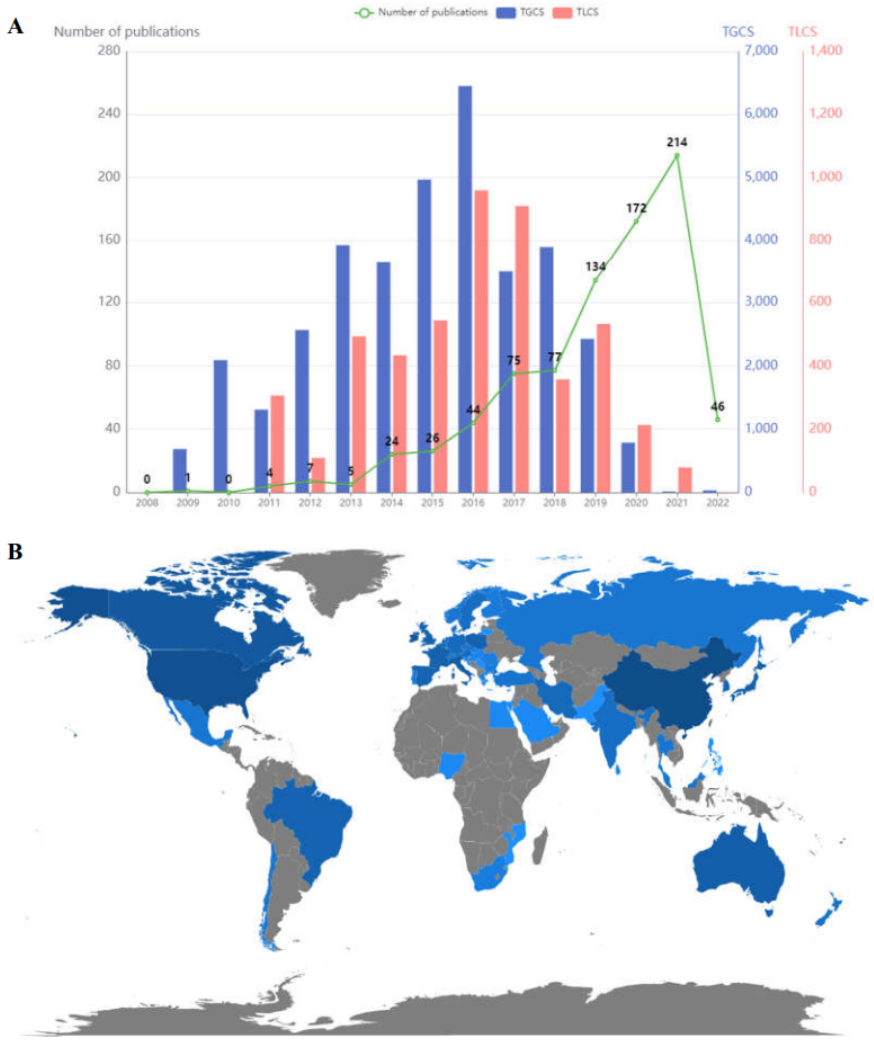


Figure 2

Overall Distribution of publication outputs on MGBA with depression research. (A) Global annual output trends, TGCS and TLCS; (B) Geographical distribution of global output; TGCS, TLCS and growth rate in annual publications.

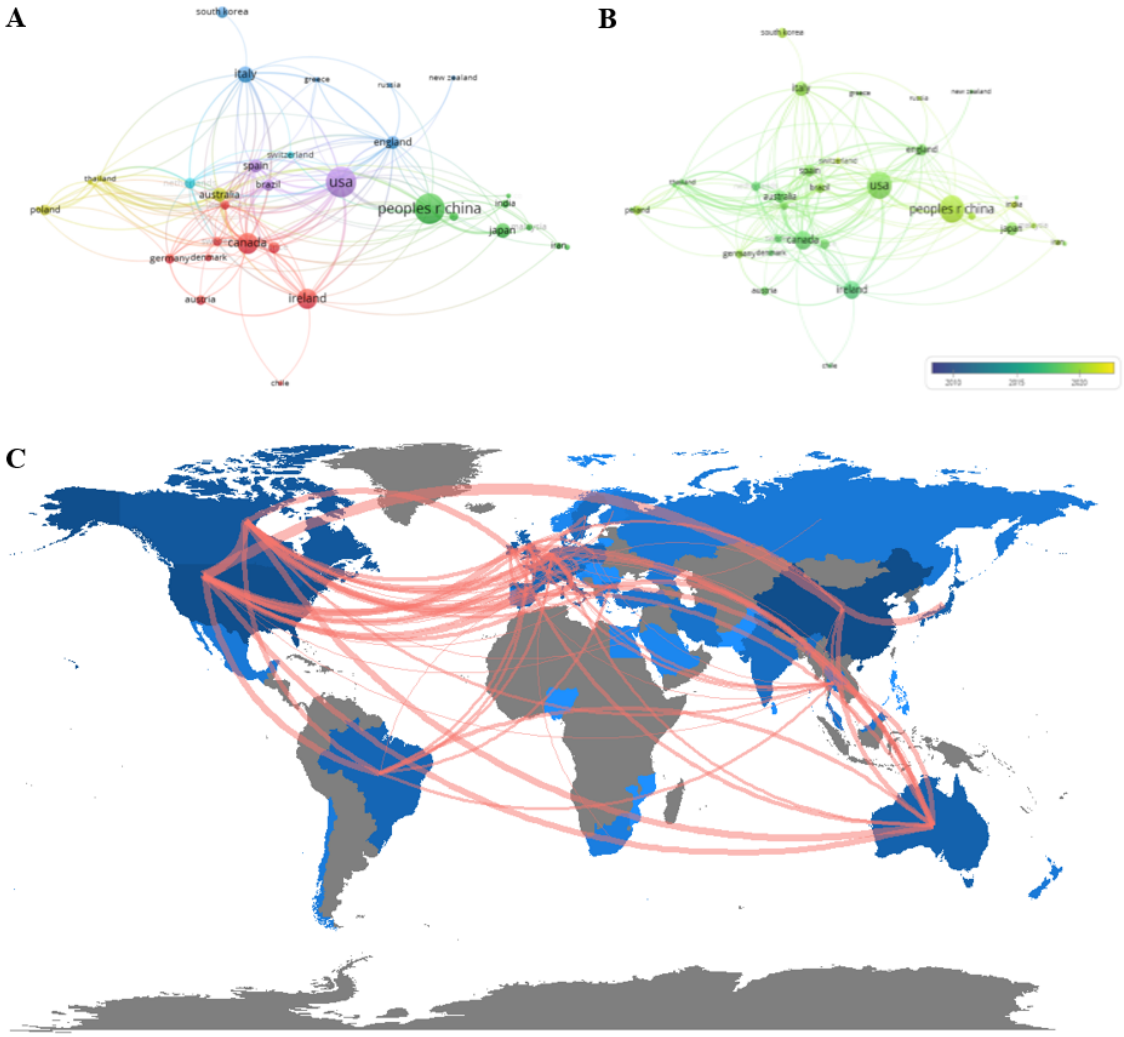


Figure 3

Leading countries on MGBA with depression research(A)Visual cluster analysis of cooperation among countries (B) Timeline visualization of cooperation among countries(C) Geographical distribution of global output.

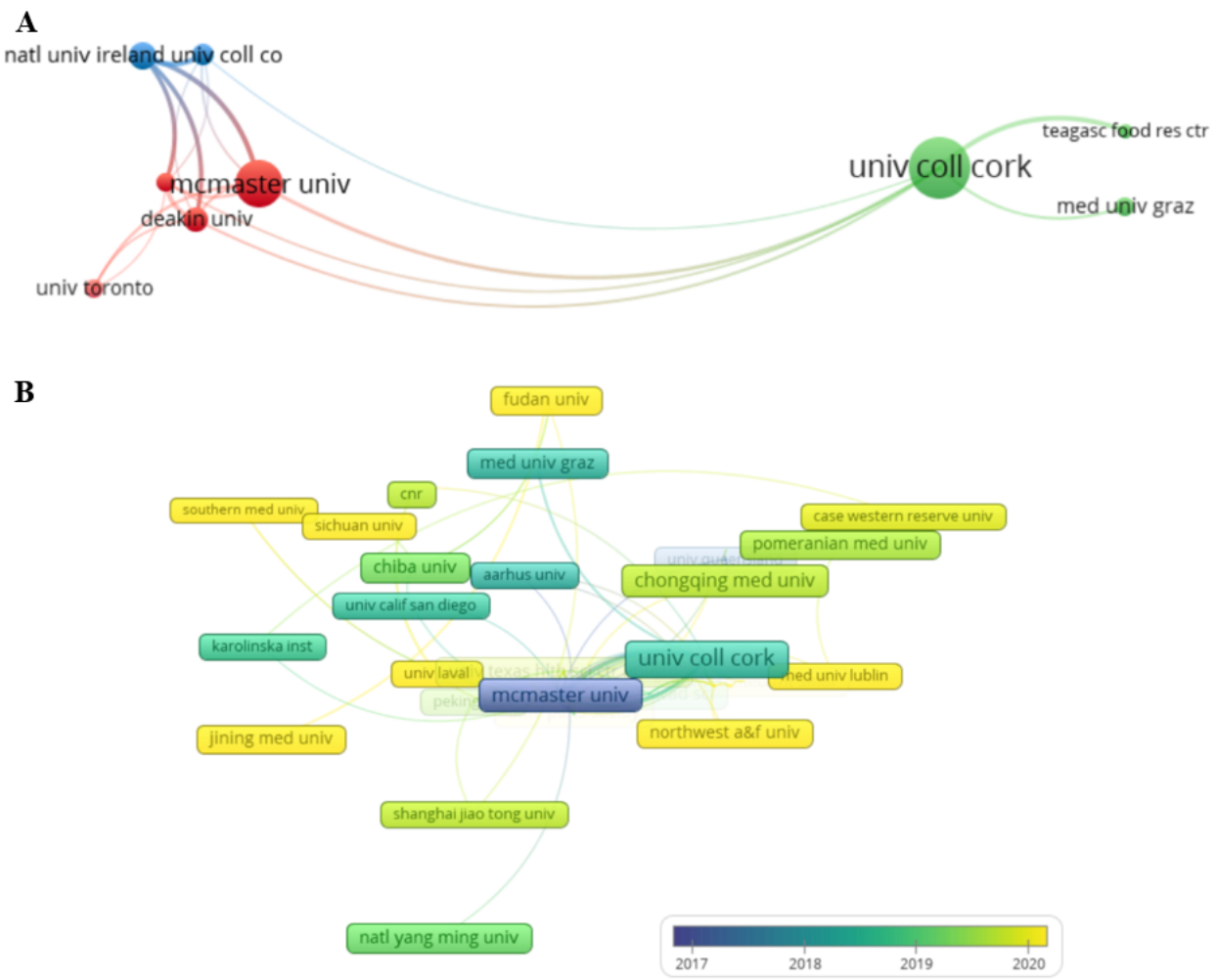


Figure 4

Visualization of active institutions analysis. (A) Map of active institutions on MGBA with depression research;(B) Timeline visualization of cooperation among institutions.

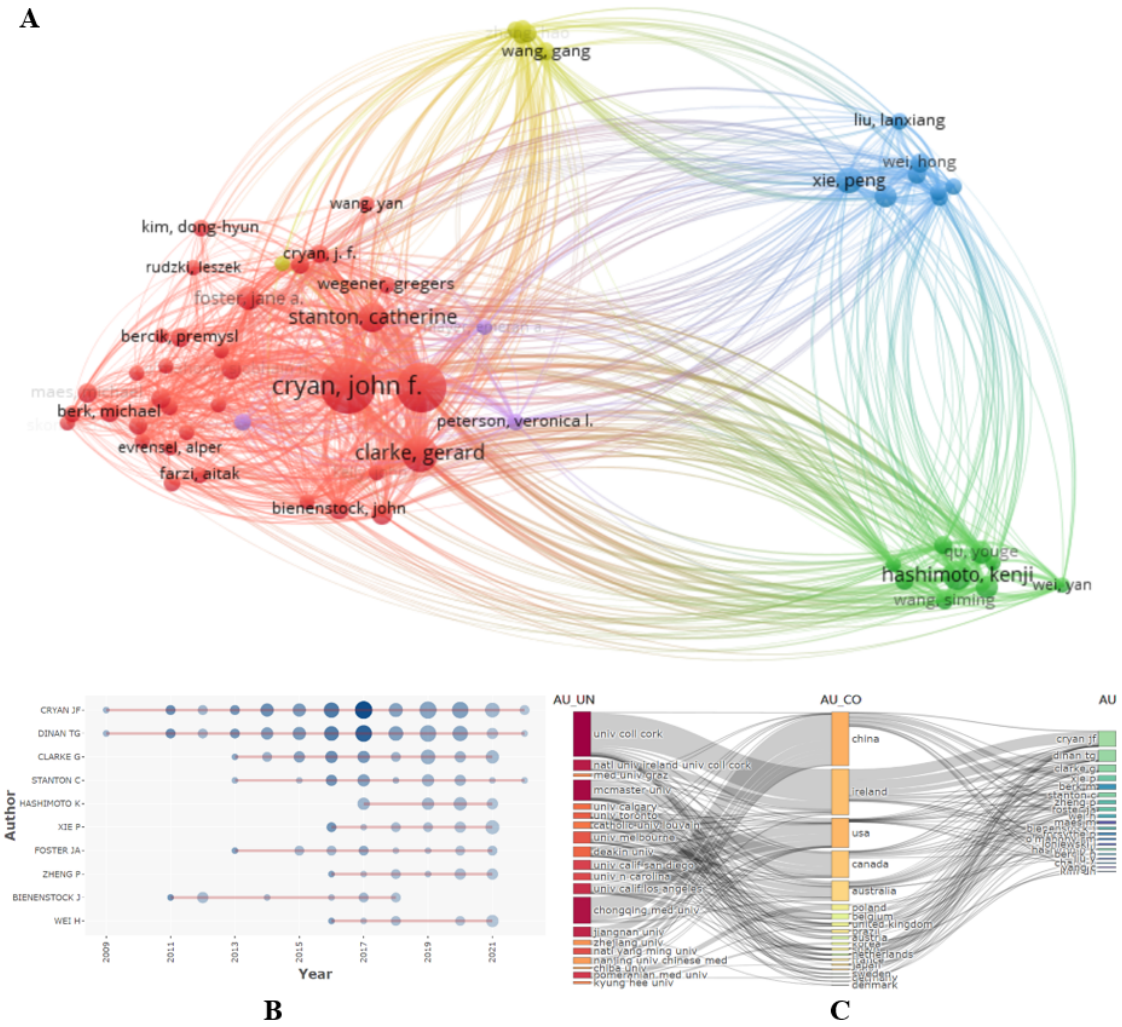


Figure 5

Visualization of active authors analysis. (A) Map of active authors in MGBA with depression research; (B) Timeline distribution of the top 10 most productive authors. (C) Sankey diagram of the City-Institution-Author Contact Map.

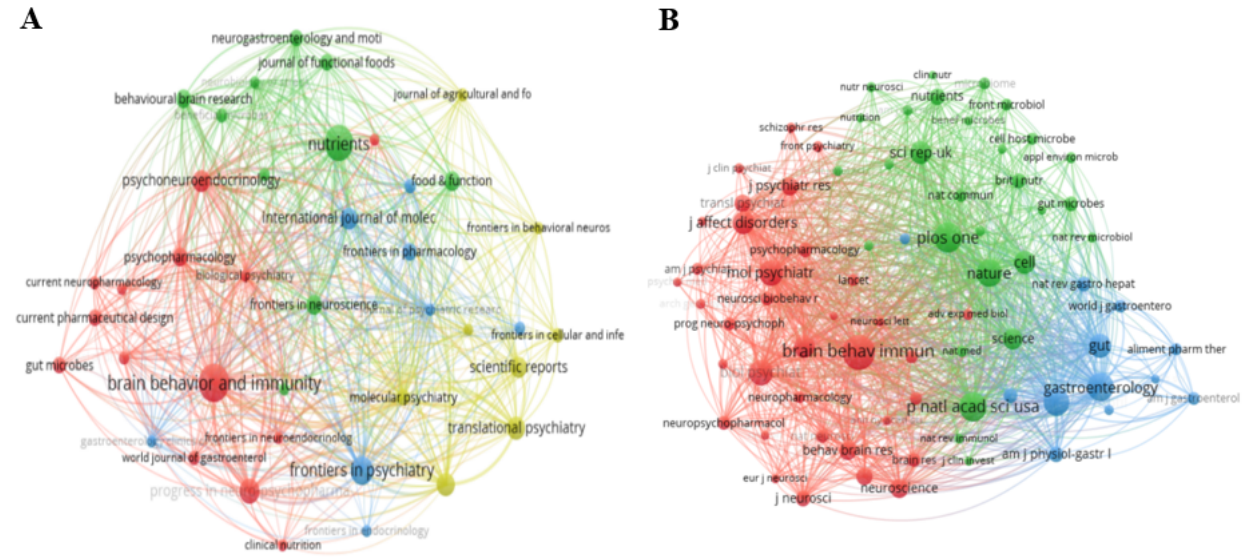


Figure 6

Map of core journals (A) and co-cited journals (B) related to MGBA with depression research.

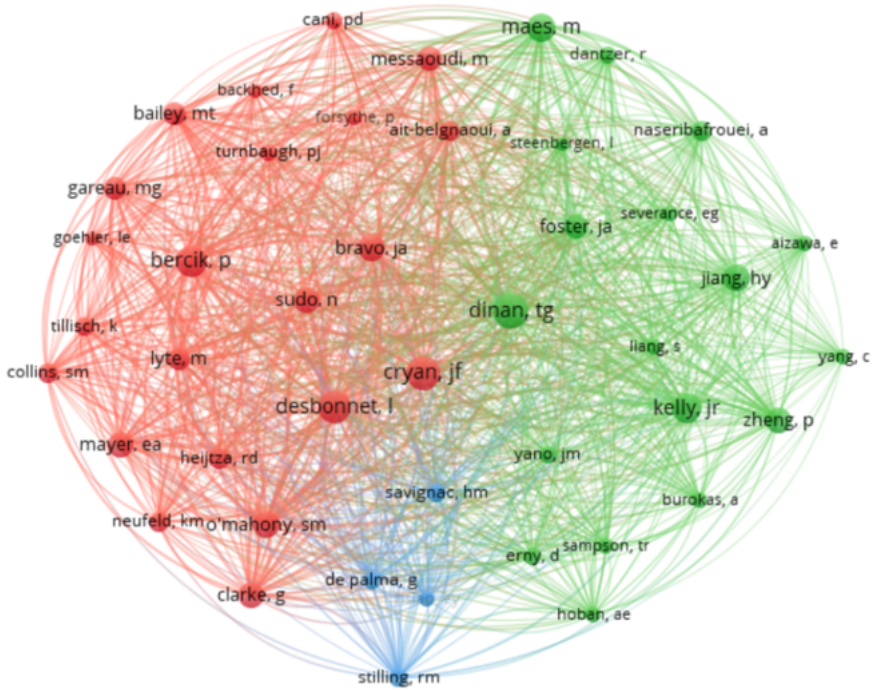


Figure 7

Map of co-cited authors related to MGBA with depression research.

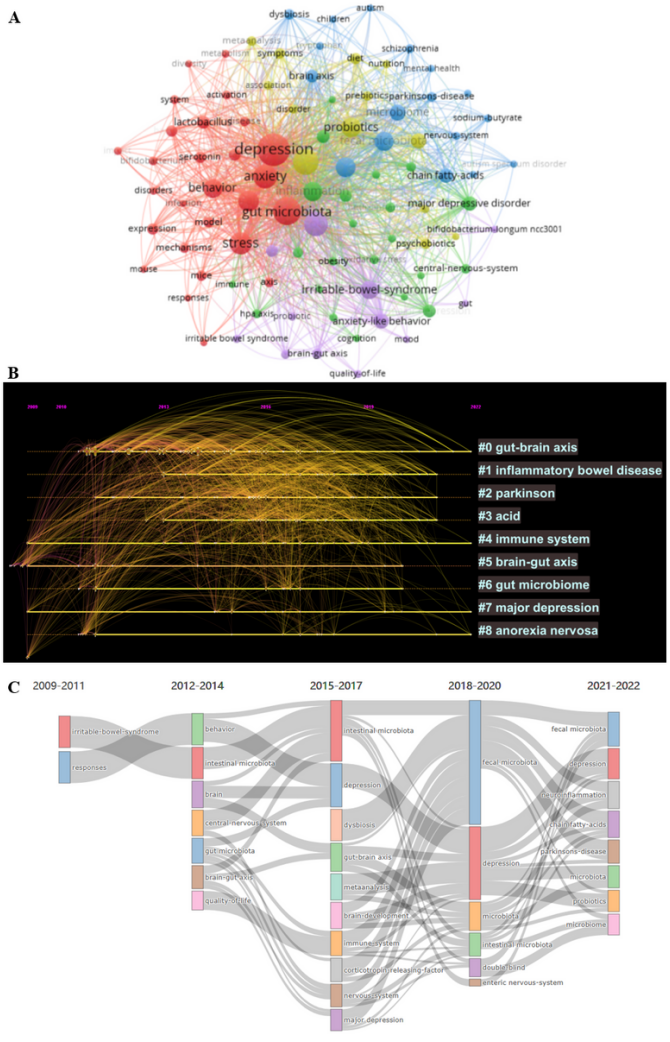
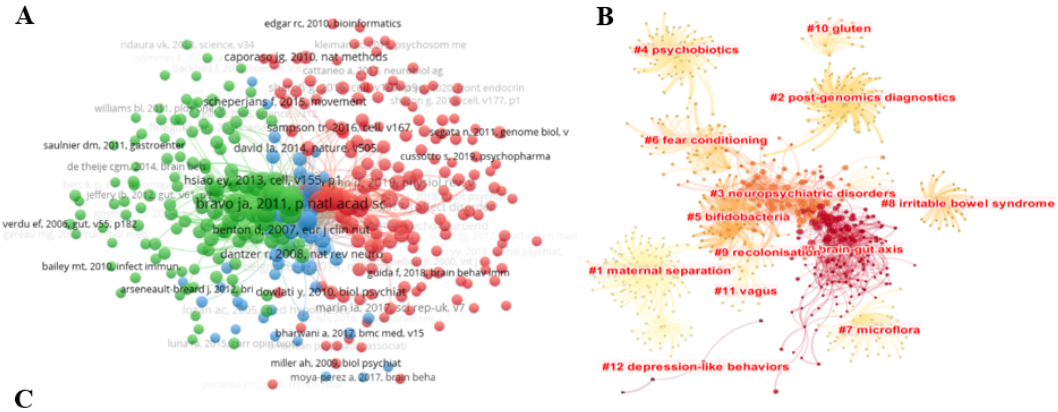


Figure 8

Map of co-cited Keywords related to MGBA with depression research. (A) The network map of keywords. (B) Timeline distribution of cluster analysis of keyword; (C) Sankey diagram of the keywords evolution.



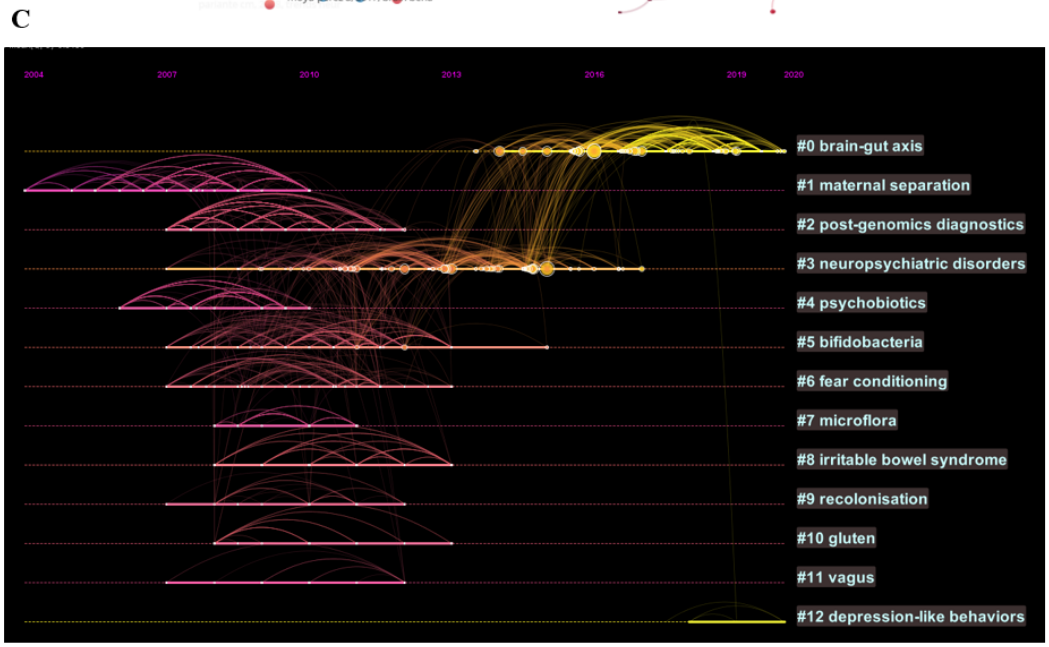


Figure 9

Visualization of co-cited reference analysis. (A) The network map of Co-cited references; (B) Cluster Analysis of Co-cited References; (C) Timeline distribution of the clusters.

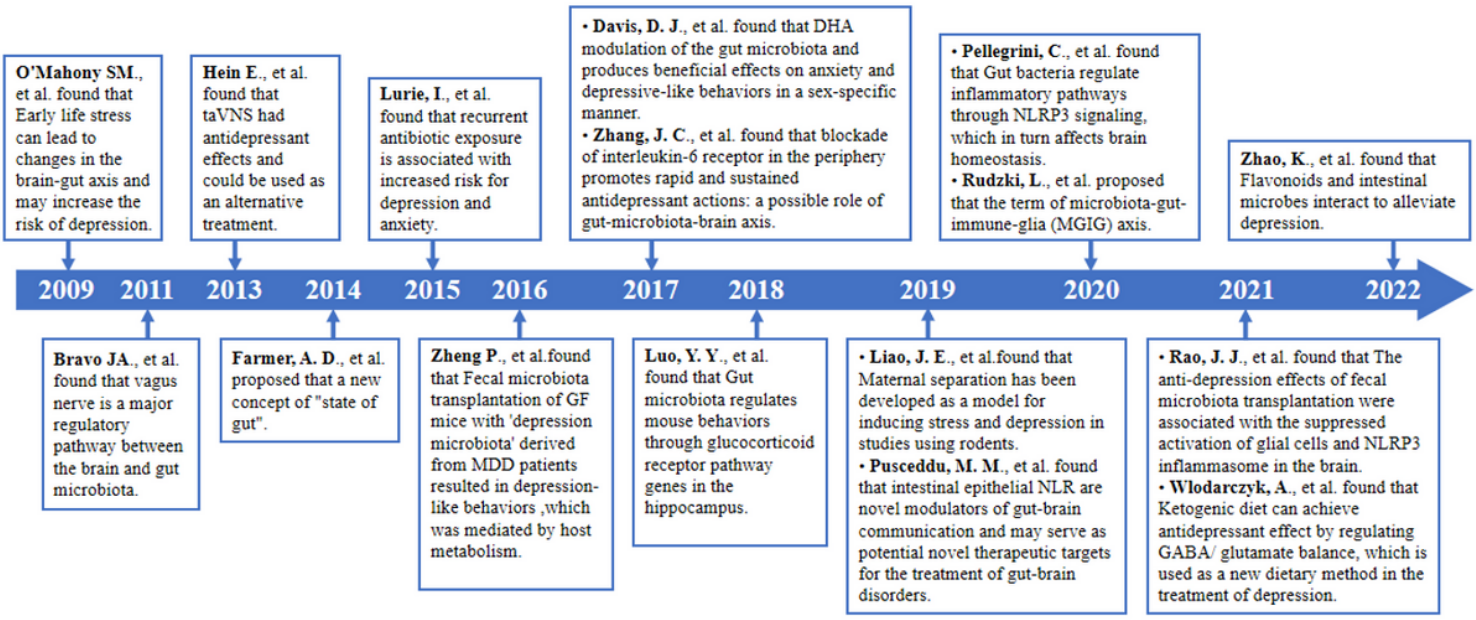


Figure 10

Timeline of part of landmark achievements in MGBA with Depression research.