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REVIEW

Parkinson's Disease Related Depression and Anxiety: A 22-Year Bibliometric Analysis (2000-2022)

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Background: Parkinson's disease (PD) is one of the common neurodegenerative diseases. Depression and anxiety are the most common psychiatric symptoms of PD. It is important to study the potential relationship between PD and depression or anxiety.

Aim: This study aimed to use bibliometrics to analyze the papers about parkinson's disease related depression and anxiety over the last 22 years, and to characterize the current status of research and predict future hotspots.

Methods: In the Web of Science Core Collection (WoSCC) from 2000 to 2022, documents are searched according to specific subject words. The selected literature was retrospectively analyzed and mapped using CiteSpace and Vosviewer software. We analyzed countries, institutions, journals, authors, references and keywords.

Results: A total of 7368 papers were included from 2000 to 2022, and the number of publications has shown an upward trend year by year. Movement Disorder is the journal with the highest number of publications (391 publications, 5.31%) and citations (30,549 times), with the United States (2055 publications, 27.9%) and the University of Toronto (158 publications) being the countries and institutions with the highest number of publications. The high-frequency keywords focused on "quality of life", "deep brain stimulation" and "non-motor symptoms". "Functional connectivity", "gut microbiota" and "inflammation" may be at the forefront of future research.

Conclusion: Parkinson's disease related depression and anxiety have been increasingly studied over the past 22 years. Functional connectivity, gut microbiota, and inflammation will be the subject of active research hotspots in the future, and these findings may provide new research ideas for researchers.

Keywords: Parkinson's disease, depression, anxiety, bibliometric analysis, Citespace, VOSviewer

Introduction

Parkinson's disease (PD) is a common degenerative disease of the central nervous system that involves the progressive impairment of voluntary motor control.[1] The main symptoms of PD include motor retardation, static tremors and rigidity, as well as changes in posture and gait. Some PD patients also have clinical symptoms of dysphagia and dysarthria.[2,3] These motor symptoms tend to develop gradually and worsen with age, severely reducing the quality of life for the sufferer. According to the Global Burden of Disease Study, the number of cases of PD increased 118% between 1990 and 2015, making it the fastest-growing neurological disorder in the world.[4]

There is no doubt that motor symptoms are the main clinical manifestations of PD, but non-motor symptoms such as anxiety, depression, constipation, urinary dysfunction, memory loss, pain and sleep disorders are also worthy of our attention, some of which can be almost throughout the course of PD.[5,6] Anxiety and depression are the most common and prominent affective disorders of PD,[7] with 30–35% of patients having obvious above symptoms,[8] and both of them often

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appear simultaneously in the course of the patient's disease. Depressive symptoms are considered to be the earliest non-motor symptoms of PD, and their incidence increases with age.[9] In the advanced stages of PD, about 60% of patients will have some degree of depressive symptoms.[6] Anxiety includes generalized anxiety, panic disorder, and social phobia.[10] There are many causes of anxiety and depression in people with PD, including care dependency, decline in daily activities, rapid decline in physical and cognitive abilities, and fear of exacerbation and death.[7,11–13] These affective disorders not only directly affect the quality of life of patients with PD,[14] but also accelerate the progress of the disease, which is related to the deterioration of motor symptoms.[15] These disorders are often more problematic and distressing for patients and families than the motor aspects of PD.[16] But so far, little is known about depression and anxiety disorders in PD, and management and treatment approaches are limited.[17,18]

Current research links defects in dopaminergic and non-dopaminergic function, abnormalities in brain structure and metabolism, and inflammation during the course of PD to the occurrence and progression of depression. Recent studies have suggested that inflammatory activation by gut microbiota may play a role in the pathological processes of Parkinson's disease, anxiety and depression through the brain-gut axis.[19] In neuroimaging, PET or SPECT studies have found reduced neurometabolic activity in patients with PD depression(dPD) compared to patients with PD alone or healthy controls, mainly in the frontal and striatum and subcortical or limbic regions.[20] RS-fMRI studies have found that dPD patients have increased neural activity in the prefrontal region and decreased functional connectivity between the prefrontal and limbic networks.[21] Parkinson's anxiety may be related to changes in the limbic cortico-striato-thalamocortical circuit and the fear circuit.[22] In addition, the lack of dopamine release during PD may cause some 5-HT and NE nerves to release dopamine instead, affecting anxiety-related neurotransmitter levels. That, in turn, affects anxiety-related neurotransmitter levels.[23] Treatment of Parkinson's disease and depression or anxiety can be divided into drug therapy and non-drug therapy, where non-drug therapy mainly includes deep brain stimulation, cognitive behavioral therapy,[24] transcranial magnetic stimulation,[25] and some other complementary therapies such as yoga and tai chi.

Bibliometrics is a quantitative method that can analyze the published works (such as books, journal articles, etc.) and their related contents (such as abstracts, keywords, citations, etc.), and use statistical data to describe or show the relationship between the published works. It can also be used to describe and analyze changes and advances in a discipline or research field.[26] Although bibliometrics has some limitations, it cannot be denied that it is currently an effective and objective tool for understanding research activities.[27] In this study, for the first time, we performed bibliometric and visual analysis of parkinson's disease related depression and anxiety using the VOSviewer and CiteSpace, which can quantitatively explore the contributions of authors, countries, institutions and their cooperative relationships.[28,29] Not only that, but we can also use bibliometrics software to analyze keywords in the articles included, identify research hotspots in the field, and predict research trends for future periods. These informations can help subsequent researchers to understand the current state of research in this area more easily.

Method

Data Source

Articles about PD related depression and anxiety were searched from the Web of Science Core Collection (WoSCC) from 2000 to 2022. The search strategies are as follows: topic = (depressive disorder or depression or anxiety) and (Parkinson); language (English) and literature type (paper or review paper); publication date range "2000-01-01" and "2022-11-01"; A total of 7368 articles were retrieved. Plain text files are chosen to export the Full Record and Cited Reference. After extraction, the data retrieved from WoSCC were downloaded and transferred to CiteSpace and VOSviewer software for bibliometric analysis. The retrieval strategy used in this study is illustrated in Figure 1.

Data Analysis Method

CiteSpace (version 5.8.R3) and VOSviewer software (version 1.6.18) were used for co-occurrence analysis and visual graph drawing, and the resulting data was imported into Microsoft Excel 2019 for graph generation. Nodes and lines are the main content of the visualization map, where each node represents an analyzed element such as author, institution, journal, etc. Links help us to understand the co-occurrence and co-citation relationships between nodes. In general, the

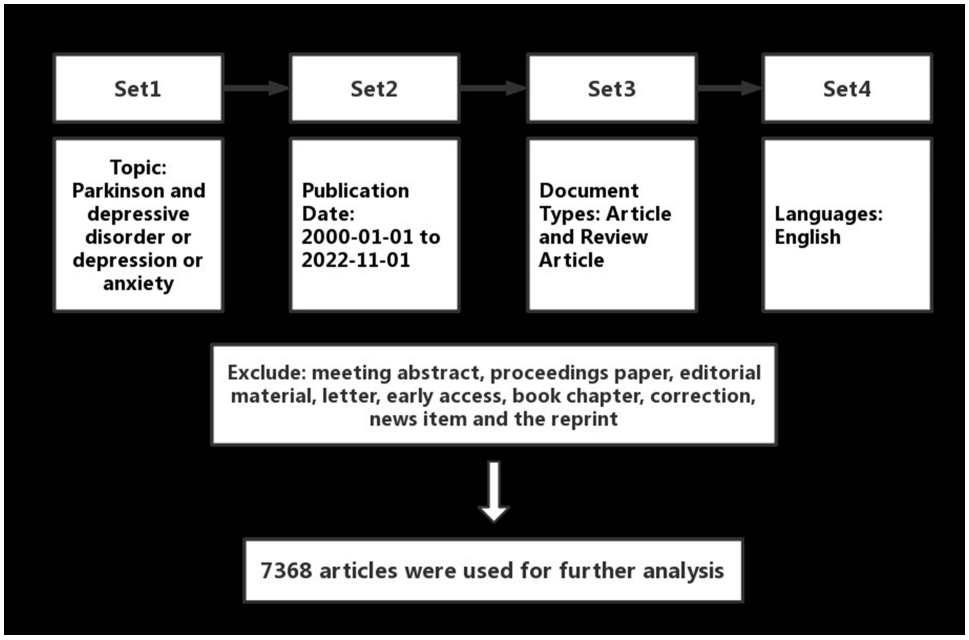

Figure 1 Flow chart of literature collection.

larger the number of nodes, the higher the frequency, and the number and thickness of links between nodes indicates the strength of the relationship between nodes. Centrality is a metric that measures the importance of nodes in a network. The more shortest paths pass through the node, the stronger the centrality of the node. When a node centrality > 0.1, this node is often considered as a turning point in a field.

Result

Distribution of Annual Publications

A total of 7368 articles about PD related depression and anxiety were searched between 2000 and 2022. As shown in Figure 2, no related papers were published between 2000 and 2002. In 2003, Nesrin Gökhan et al published an article entitled "1-N-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazolines: synthesis and evaluation as MAO inhibitors" in Arch Pharm, introducing a new prison compound showing antianxiety, antidepressant activity and potential therapeutic

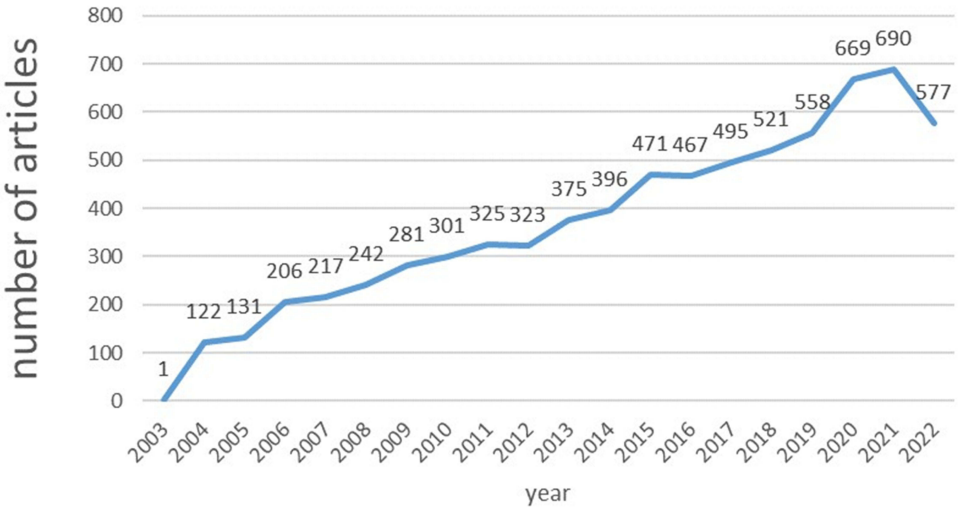

Figure 2 Number of original articles on the treatment of PD related depression and anxiety per year from 2003 to 2022.

properties for PD in vitro.[30] The number of annual articles increased steadily from one in 2003 to 579 in 2022, and the annual output peaked at 690 articles in 2021. Overall, researchers' enthusiasm for PD related depression and anxiety continues unabated. Annual publications can shed light on the trends and significance of academic topics, and the steady increase in the annual output of articles over the past 22 years indicates that related topics are receiving increasing attention from researchers.

National and Regional Distribution

Statistical analysis showed that 546 institutions from 143 countries and regions published articles related to PD related depression and anxiety. Figure 3 shows the top 10 most productive countries based on affiliation of newsletter authors. The United States has the largest number of publications (2055, 27.9%), followed by China (844, 11.5%) and the United Kingdom (617, 8.4%). As can be seen in the Figure 4. On a global level, associated research staff are collaborating and sharing experiences.

Institution Distribution

The Citespace software was used to analyze the number of articles published by the organization, and the results are shown in Figure 5. The five largest nodes correspond to the five research institutions with the largest number of articles. Of these, the research institutions with the largest number of articles are UnivToronto from Canada, the two from the United States are UnivPenn and UnivFlorida, and Kings College London and UCL are located in the United Kingdom. The top 10 research institutions are all universities or colleges, so we can see that universities are the significant players in this field.

The top 10 research institutions in the field of PD related depression and anxiety as shown in Table 1. The organization that published the most articles was Univ Toronto of Canada, with 158 articles. However, Kings Coll London has a higher centrality than Univ Toronto.

Major Contributing Authors

Citespace software was used to analyze the number of articles published by the authors, and the results are shown in Figure 6. In the data we have included, a total of 682 researchers are engaged in this field, of which Daniel Weintraub becomes the most prolific researcher in this field with 75 articles produced. Pablo Martinez Martin and Michael S Okun were second and third. From Figure 6, we find that the collaboration between authors in this field is very close. The top 10 published researchers are shown in Table 2.

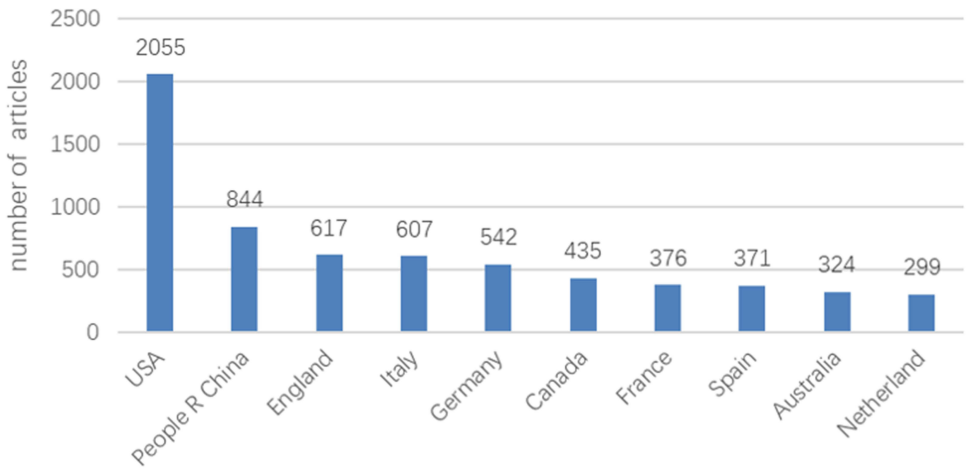

Figure 3 Top 10 countries with the largest number of publications.

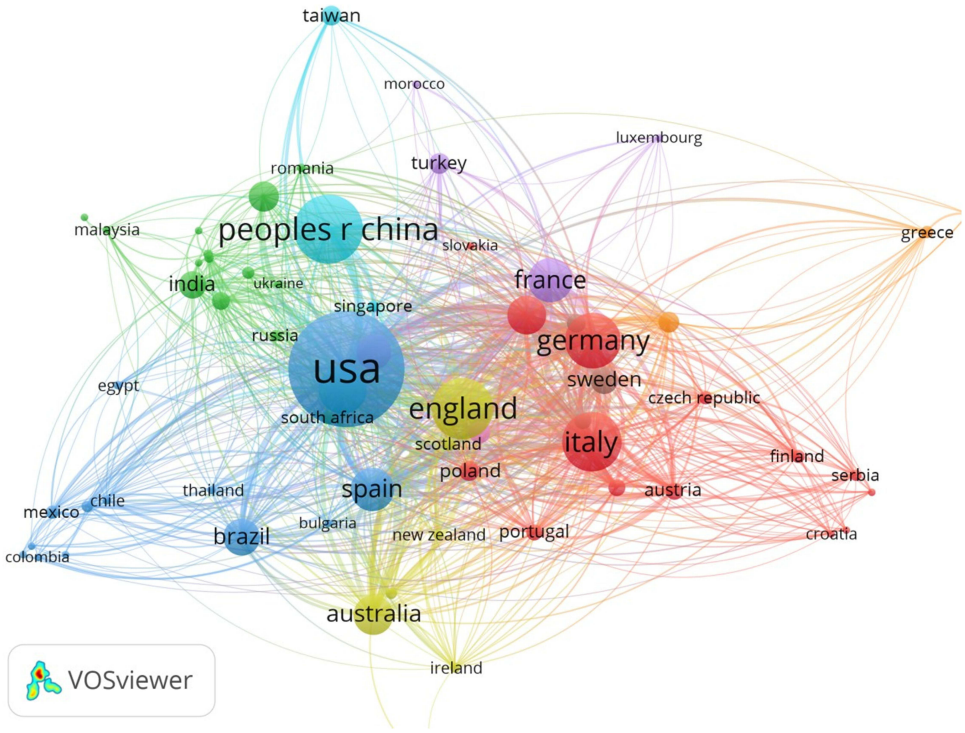

Figure 4 Network Visualization of countries and regions. The size of the colored nodes indicates the number of published articles. Node connections indicate the strength of the relationship between countries.

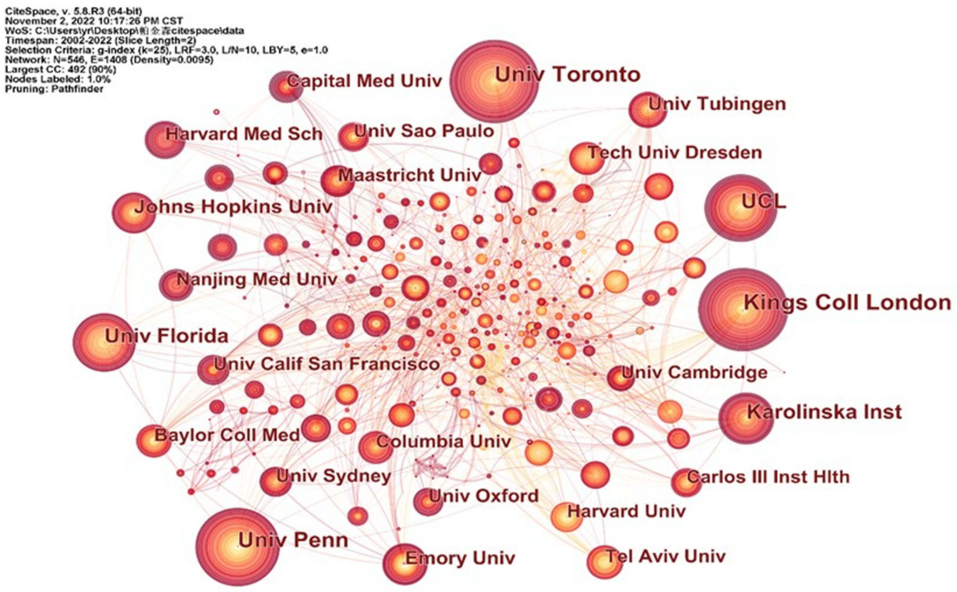

Figure 5 The number of articles published by the organization. Upper left text, shows the relevant data, where "N" in "network" denotes the number of nodes, and the 546 nodes shown in the figure represent 546 research institutions and "E" denotes the number of connections between the 546 institutions shown in the diagram. The larger the number of nodes, the higher the output of the corresponding institution, and the more connected lines, the closer the relationship between the institutions.

Distribution of Journals

A total of 1533 academic journals have published articles on PD related depression and anxiety. The top 10 journals are listed in Table 3. The largest number of articles published by "Movement disorders" (391 publications, 5.31%), followed by "Parkinsonism & Related disorders" (349 publications, 4.74%) and "Journal of neurology" (138 publications 1.87%).

Table 1 Top 10 Institutions with the Largest Number of Publications

Ranking	Institution	Frequency	Centrality
1	Univ Toronto	158	0.04
2	Kings Coll London	151	0.1
3	Univ Penn	145	0.06
4	UCL	129	0.02
5	Univ Florida	112	0.04
6	Karolinska Inst	102	0.05
7	Johns Hopkins Univ	84	0.04
8	Emory Univ	79	0.04
9	Univ Tubingen	71	0.04
10	Tel Aviv Univ	69	0.04

The most frequently cited journals are Movement Disorders, Parkinson's & Related Disorders, and Neurology. The analysis was carried out using the visualization software VOSviewer and the results are shown in Figure 7. Movement Disorders could be considered the most influential journal in the field of PD related depression and anxiety.

Analysis of Co-Citation References

The top 5 cited papers as shown in Table 4. Of the 5 cited papers, three of them are from "Movement Disorders". Non-motor features of PD is the highest cited article, published in 2017 by Anthony H V Schapira in Nat Rev Neurosci. This article reviews the effects of non-motor symptoms of PD on disease progression and quality of life and presents the neuroanatomical and neuropharmacological mechanisms responsible for these symptoms.[31]

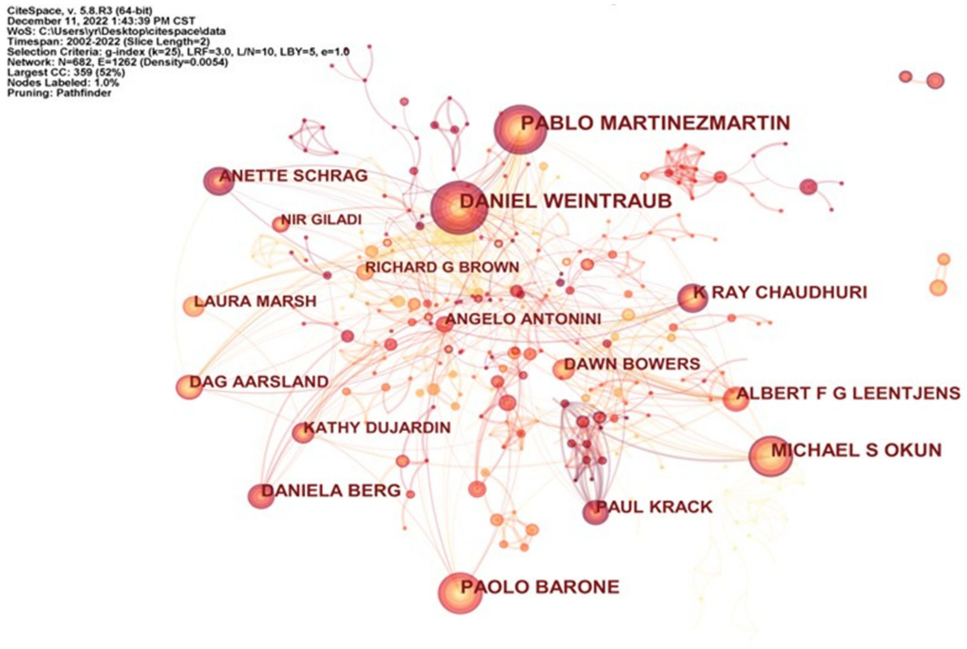

Figure 6 The number of articles published by the authors. Each node in the figure represent the an author, and links between two nodes represents a collaboration between two authors on the same article. Size of node is positively correlated with the number of articles published by authors, and the more lines between two nodes, the more connected the authors are.

Table 2 Top 10 Authors with the Largest Number of Publications

Rank	Author	Frequency	Centrality
1	Daniel Weintraub	75	0.1
2	Pablo Martinez Martin	72	0.12
3	Michael S Okun	50	0.03
4	Paolo Barone	49	0.05
5	Kray Chaudhuri	40	0.1
6	Daniela Berg	39	0.03
7	Albert F G Leentjens	38	0.06
8	Paul krack	37	0.04
9	Anette Schrag	33	0.01
10	Li Zhang	33	0.01

Table 3 Top 10 Journals with the Largest Number of Articles

Rank	Journal	Frequency	Citations	Total Link Strength	IF (2021)
1	Movement Disorders	391	30,549	406,575	9.698
2	Parkinsonism & Related Disorders	349	12,151	313,571	4.402
3	Journal Of Neurology	138	5667	194,747	6.682
4	PLoS One	137	4217	115,725	3.752
5	Journal Of The Neurological Sciences	132	4940	155,259	4.553
6	Journal Of The Neurological Sciences	119	1536	134,243	5.520
7	Frontiers in Neurology	116	1313	115,912	4.086
8	Parkinsons Disease	114	1744	143,645	3.170
9	Neurology	106	11,958	120,049	12.258
10	Journal Of Neurology Neurosurgery And Psychiatry	102	8654	108,551	13.654

Keywords Analysis

Keywords for PD related depression and anxiety are shown in Figure 8. The use of VOSviewer reflects research hotspots in different time periods and can predict future development trends. Excluding subject words related to retrieval

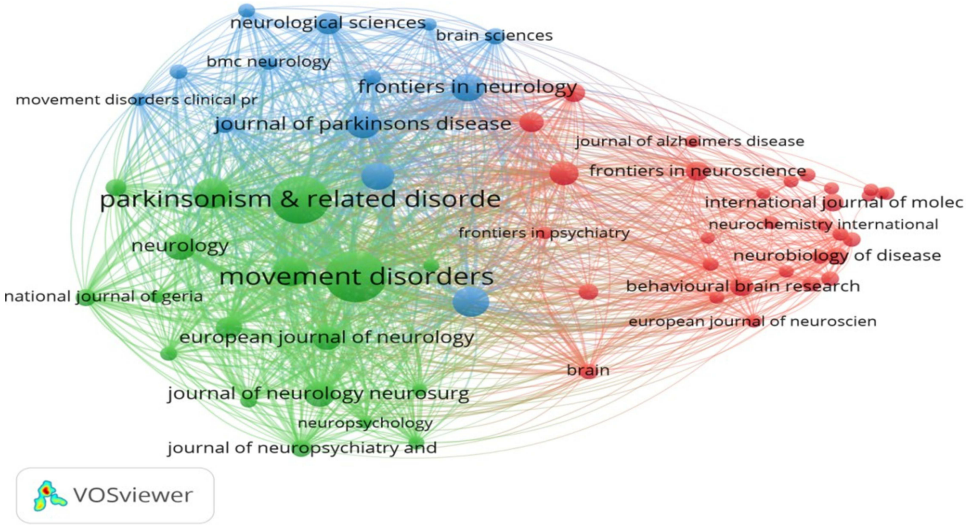

Figure 7 Periodical publication volume. Each node represents a journal, and the links between nodes indicate the frequency of cooperation of these journals. The larger the node, the higher the publication frequency of the journal.

Table 4 The Top 5 Papers Cited Most Frequently

Rank	Article Title	Representative Author	Journal	IF (2021)	Publication Year	Times Cited
1	Non-motor features of Parkinson disease	Anthony H V Schapira	Nature Reviews Neuroscience	38.755	2017	126
2	A systematic review of prevalence studies of depression in Parkinson's disease	Jennifer S A M Reijnders	Movement Disorders	9.698	2008	115
3	Systematic review of levodopa dose equivalency reporting in Parkinson's disease	Claire L Tomlinson	Movement Disorders	9.698	2010	112
4	MDS clinical diagnostic criteria for Parkinson's disease	Ronald B Postuma	Movement Disorders	9.698	2015	109
5	Parkinson's disease	Lorraine V Kalia	Lancet	202.731	2015	105

strategies, we can find multiple occurrences of quality of life, Alzheimer's disease, dementia, non-motor symptoms, deep brain stimulation, dopamine, and cognitive impairment.

"Highly explosive keywords" refers to keywords that are frequently quoted within a certain period of time. We can predict the research frontier according to the keyword distribution of the strongest citation outbreaks. Citespace was used to analyze high explosive keywords from 2000 to 2022. Subthalamic nucleus stimulation is the keyword with the longest duration of explosion (2004–2015). Functional connectivity, gut flora, and inflammation are important keywords that continue to this day and are likely to be the focus and frontier of future research in this area. As is shown in Figure 9.

Discussion

The aim of this paper is to perform a bibliometric study of PD related depression and anxiety over the last 22 years. Our study has important implications for students, researchers in the field.

The leading position of the United States in this field is solid. Of the 7368 articles we included, the United States topped the list with 2055 in absolute terms, roughly equal to the combined output of China, Britain and Italy. Among the

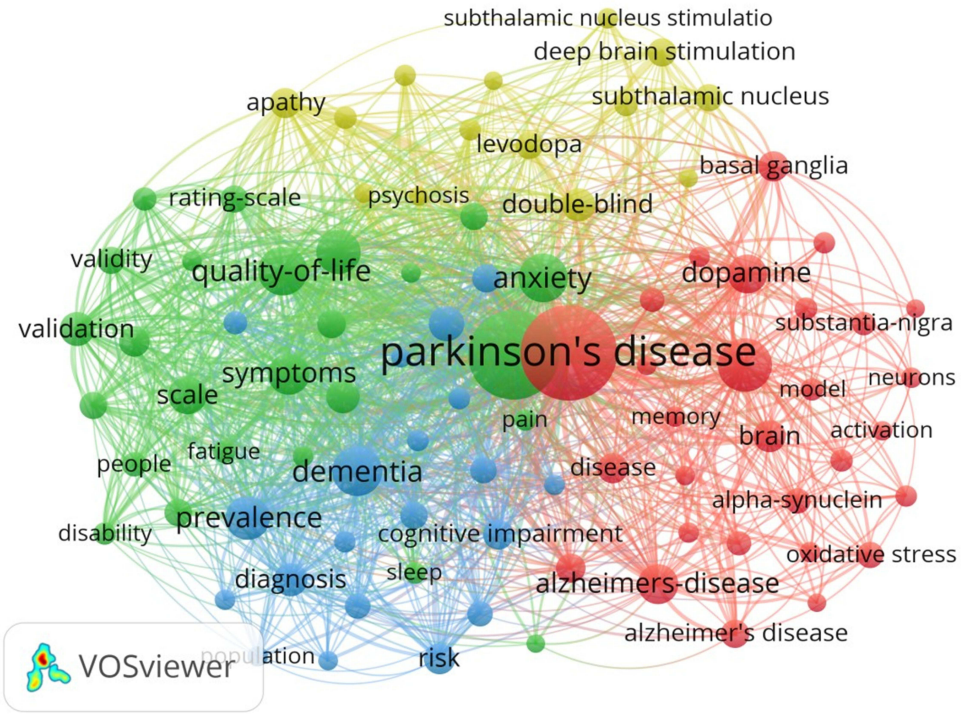

Figure 8 Frequency of co-occurring keywords. The more nodes corresponding to the keyword, the higher the frequency of this keyword in the previous study.

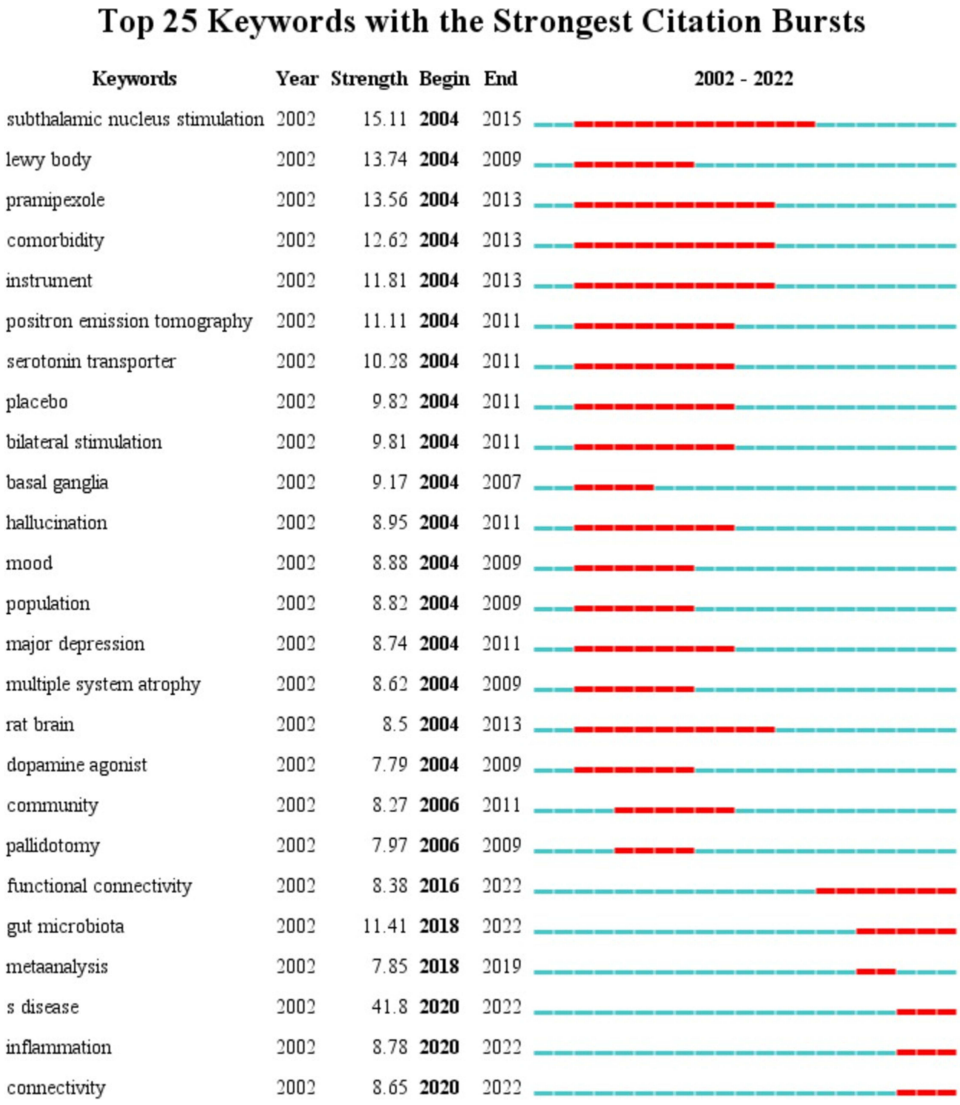

Figure 9 Top 25 keywords with the strongest citation bursts. Citation bursts can identify popular topics, which is sudden appearance of a keyword within a short period of time or a sharp increase in its frequency indicates that scholars are highly concerned with the relevant topic.

top 10 research institutions by output, four are located in the United States, namely Univ Penn, Univ Florida, Johns Hopkins Univ and Emory Univ. Among the top 10 journals published, there are three journals in the United States, namely, "Movement Disorders" (No. 1), "PLoS One" (No. 4) and "Neurology" (No. 9).

Among the first 23 articles frequently cited, there are two articles with a centrality of more than 0.1, which are "Apathy in PD: clinical features, neural substrates, diagnosis, and treatment" (Frequency=73, Centrality=0.15) in No. 16 and "A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease" (Frequency=66, Centrality=0.11) in No. 23. In the article, Javier Pagonabarraga team reviews the symptoms, neuroanatomy, and neuropharmacology of Parkinson's apathy, and expressed optimism about the use of dopaminergic drugs to improve the emotional and behavioural aspects of motivation, and for cholinesterase inhibitors to treat the cognitive aspects of apathy.[32] I.H. Richar team conducted a randomized, double-blind, placebo-controlled trial of selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI) in the treatment of PD depression. Results showed that both investigational drugs were significantly more effective than placebo on a number of depression scales and did not show any significant side effects or worsening of PD motor function. Emotional subscale scores, but not overall QOL, improved with both medications.[33]

According to the results of high-frequency keyword analysis, quality of life (QOL) is an important concern for PD related depression and anxiety. The assessment of quality of life for people with PD is also an assessment of the impact of the disease and the effectiveness of the intervention.The evaluation is based on three main aspects: quality of life (QOL), health-related quality of life (HRQOL) and perceived health status (HS). As a neuropsychiatric disorder, people with Parkinson's often have to deal with both mental and physical effects. These groups of symptoms severely affect the quality of life of people with PD. A systematic review of quality of life in people with PD indicated that the most commonly used general measurement tool was SF-36, while PDQ-39 was the most commonly used disease-specific tool.[34] BrendaL et al argue that quality of life seems to depend more on psychosocial issues than on physical issues.[35] Depressive symptoms are an important factor in the quality of life of people with PD.[36,37] What can be done to improve the quality of life for people with PD? Resistance training may be a good option, as it improves both motor and non-motor symptoms in PD patients,[38,39] and was also validated in a randomized controlled trial of older patients with PD.[40] Tai Chi, a traditional Chinese technique, can alleviate balance disorders in patients with mild to moderate PD, improve exercise ability and reduce falls, thus improving patients' quality of life.[41,42] In addition, physical and mental exercise and music therapy are also worthy of attention.[43,44]

Deep brain stimulation is one of the effective methods to treat Parkinson's disease, and the subthalamic nucleus (STN) is the preferred target of deep brain stimulation. It has been shown in recent studies that this procedure can effectively improve PD motor symptoms. For example, a randomized trial has shown that deep brain stimulation of the subthalamic nucleus improves PD motor symptoms by 40 to 60%.[45] It is also beneficial for sleep and pain symptoms.[46,47] Other studies have shown that deep brain stimulation can also improve PD depression.[48] However, the adverse effects of deep brain stimulation on non-motor symptoms in PD patients should not be overlooked. Some patients show a decline in cognitive function, which may be associated with connectivity between the stimulation site and a specific brain network previously implicated in lesion-induced memory impairment.[49] There are also some patients patients experience behavioral changes such as depression, anxiety or mania after receiving stimulation.[50] However, Karsten Witt et al argue that while some patients experience cognitive decline and anxiety after stimulation of the subthalamic nucleus, this does not reduce the effect of deep brain stimulation on improving the quality of life of PD patients.[51]

Functional connectivity of the brain has become one of the most influential concepts in modern cognitive neuroscience.[52] With the help of RS-fMRI, FilippiM found that PD patients had functional connectivity changes involving the dopaminergic cortico-striatum and limbic-striatum loops. In previous studies, intrinsic dysfunction within the dorsolateral prefrontal cortex in PD patients has been observed,[53,54] as well as abnormal functional connectivity in the amygdala, which is closely associated with depressive mood.[21,55] Therefore, we speculate that RS-fMRI techniques may help us find new breakthroughs in the field of PD related depression and anxiety.

The two pathological features of PD are loss of dopaminergic neurons in the substantia nigra, misfolding and abnormal aggregation of α-synuclein (α-syn) in the form of Lewy Body and Lewy Neurite.[56,57] Under physiological conditions, α-syn is heavily expressed in CNS and ENS neurons and is involved in the regulation of neurotransmission.[58] In pathological conditions, alpha-SYN plays a crucial role in neuroinflammation by triggering and/or enhancing microglial activation.[59] Changes in the gut microbiome associated with intestinal inflammation may cause alpha-SYN misfolding.[60] Furthermore, the initiation of the innate immune system by the microbiome residing in the gut may enhance the inflammatory response to α-syn.[61] As well as gut microbiota can influence brain function by modulating serotonergic, noradrenergic, dopaminergic, glutamatergic, and gabaergic neurotransmission.[62] These neurotransmitters are important in the pathogenesis of anxiety and depression.

To the best of our knowledge, this is the first study to use CiteSpace and VOSviewer to perform bibliometric analysis and visualize hot spots, co-citation references, and collaborations between authors, countries, and institutions for depression and anxiety associated with Parkinson's disease. However, our study still has some limitations. Due to the limitations of the visualization software and search strategy, we only analyzed English studies in the WoSCC database, so our results may not be comprehensive enough to apply to the analysis and study of non-English articles. In follow-up studies, we will include data from more different databases to make the results more comprehensive and complete.Then,

since CiteSpace and Vosviewer are software for quantitative analysis, this study lacks qualitative analysis methods, which we will make up for in future studies.

Conclusions

This bibliometric-based review summarizes advances in PD related depression and anxiety extracted from the WoSCC between 2000 and 2022. We use Citespace and Vosviewer for visualization analysis. By analyzing countries/regions, institutions, and journals, we believe that the United States has a leading position in this research field. We believe that future research objectives should be keyword-based. Through the analysis of keywords, we find that "quality of life" and "deep brain stimulation" have a higher frequency. Based on the analysis of burst keywords, we predict that "brain functional connectivity", "gut microbiota" and "inflammation" will continue to be hot topics in the field of PD related depression and anxiety for some time to come, which suggests that we can seek new ideas from these aspects in the subsequent research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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