CURRENTS OF PROGRESS: A DECADAL BIBLIOMETRIC EXPLORATION OF TDCS IN DEPRESSION RESEARCH

[1]Mei Ling Zhang, [2]Jian Wei Chen and [3]Li Xin Wang

[1]College of Traditional Chinese Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China
[2]College of Rehabilitation Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China
[3]The Third People's Hospital Affiliated to Fujian University of Traditional Chinese Medicine, Fuzhou,

Abstract: Depression, a prevalent and severe psychiatric disorder characterized by persistent low mood and diminished interest, stands as a major global health concern. The World Health Organization anticipated its ascent to the leading cause of disease burden by 2030, making it the foremost contributor to disability globally. The financial impact of depression, exacerbated by primary and secondary disability, marks it as one of the most costly medical burdens worldwide. Notably, the year 2020 witnessed a 28% surge in global major depression, particularly pronounced in COVID-19-affected nations, disproportionately affecting women and young individuals. Beyond the emotional toll, depression imposes a substantial economic burden on individuals and societies.

Traditional treatments for depression involve antidepressants, complementary medications, psychotherapy, and non-pharmacological somatic interventions. However, a significant proportion of patients exhibit inadequate response or fail to achieve remission with these conventional approaches. Shockingly, up to 70% of patients do not achieve remission with second-generation antidepressants, and adverse events are widespread, ranging from sexual dysfunction to headaches and gastroenteritis. A staggering 75.4% of patients on second-generation antidepressants experience adverse events, leading to discontinuation in 6.3-8.7% of cases. The growing concern of antidepressant addiction further complicates the landscape, necessitating a reevaluation of treatment paradigms.

Given the limitations and risks associated with pharmacological interventions, a shift towards non-pharmacological treatments for depression is gaining prominence. This is especially pertinent considering patient preferences and the increasing recognition of the drawbacks associated with medication-based approaches. As we explore alternative avenues, understanding the nuanced interplay of factors contributing to depression, its varied presentations across demographics, and the differential treatment responses becomes paramount.

This comprehensive review delves into the multifaceted dimensions of depression, emphasizing the increasing burden it poses globally. By scrutinizing the limitations of existing treatments, particularly the drawbacks of antidepressant medications, we highlight the need for innovative and effective non-pharmacological interventions. Through a critical analysis of recent developments, we aim to provide insights into emerging strategies that align with patient preferences, enhance treatment efficacy, and mitigate the adverse effects associated with traditional approaches. As we navigate the evolving landscape of depression management, embracing a holistic and patient-centered paradigm becomes imperative for improving outcomes and alleviating the substantial societal and economic impact of this pervasive mental health disorder.

1. Introduction

Depression is a common and serious psychiatric disorder, characterized by significant and persistent depressed mood and diminished interest [1]. Back in 2008, the World Health Organization ranked depression as the third leading cause of disease burden worldwide and predicted that it would rise to number one by 2030 [2]. Globally, depression is the leading cause of disability [3]. Furthermore, given the primary and secondary disability caused by depression, major depression is one of the world's most expensive medical burdens [4]. According to previous research, major depression increased by 28% globally in 2020, with a significant increase in prevalence, particularly in COVID-19-severely-affected countries, with women and young people being the most affected [5]. In short, people with depression not only suffer from the illness but also bear a huge financial burden [6].

Currently, main treatments for depression include antidepressants and other complementary medications, psychotherapy and somatic non-pharmacological treatments [7]. However, a large proportion of patients do not respond adequately or get remission after initial treatment. Data showed that approximately 40% of patients treated with second-generation antidepressants did not respond and about 70% did not achieve remission [8]. What's worse, it must be mentioned that antidepressants are usually accompanied by significant adverse events, including sexual dysfunction, headaches, gastroenteritis, etc. [9]. As shown in previous studies, up to 75.4% of patients taking second-generation antidepressants developed adverse events and 6.3-8.7% of patients discontinued medication due to these events [10]. In addition, antidepressant addiction is a serious and non-negligible problem [11]. Given the limited efficacy of medication and the significant risk events, patients with depression may prefer non-pharmacological treatment.

In contrast, transcranial direct current stimulation (tDCS), known for being more economical, noninvasive, well tolerated, and with fewer side effects, is widely used in clinical practice [12]. As a nonpharmacological neuroprotective measure, tDCS delivers low-intensity continuous (typically < 2mA) polarized direct current to the cerebral cortex for modulating neuronal activities [13]. In general, clinical practice for depression consists of 5 to 10 stimulation sessions per day for up to 6 weeks [14] and a current intensity of 2 mA applied for more than 20 minutes per day can be considered safe [12].

Evidence revealed that tDCS regulated emotions in patients with depression while also improving mood balance and sleep quality [15]. The dorsolateral prefrontal cortex (DLPFC) was a commonly site of interest during tDCS stimulation of depression. Besides, mountains of meta-analysis demonstrated positive results of tDCS stimulating DLPFC to alleviate depression [16-17]. After decades of exploration, tDCS had shown great potential for applications in the behavioral and cognitive sciences [18]. Particularly in antidepressant, it had gained increasing interest in recent years [19]. Yet, less attention has been paid to developments and trends in tDCS research for the treatment of depression.

In terms of the scientific community, publications from various fields were increasing rapidly and exponentially. Over the last decade, a considerable number of scholars and academic journals had been focusing on tDCS in depression. Bibliometrics is a comprehensive system that combines quantitative and qualitative analysis to reveal the information behind publications [20]. Additionally, bibliometric methods organize a large amount of information and facilitate the presentation of the current status and trends in a certain research field for new

researchers [21]. To our knowledge, previous retrospective analyses of tDCS in depression had been mainly reviews and meta-analyses [12, 22-24]. Consequently, there remains a need for a bibliometric analysis of tDCS for depression.

2. Methods

2.1. Data source and search strategy

All publications were collected from the Web of Science Core Collection (WOSCC) on 28 February 2022. WOS was considered as the appropriate database for bibliometric analysis with a comprehensive and high-quality collection of publications [25]. The query on the WOS was limited to the topic field, and the retrieval strategy was as followed: (TS=("depression" OR "depresse" OR "depressive" OR "depress")) AND TS=("Transcranial Direct Current Stimulation" OR "tDCS"), indexes= WOSCC, timespan=2013–2022. Documents only published as journal articles and reviews type were considered in this study. No language restrictions were imposed. The retrieved publications were exported as "Endnote Desktop" with "full records and cited references". After removing duplicate documents in Endnotes, the following information were extracted from the retrieved documents: year of publication, title, author, keywords, abstract, country or region, affiliation, type of literature, journal and citation count.We only accept papers written in English and without orthographic errors.

2.2. Data analysis

Bibliometric analysis is a statistical tool providing a comprehensive view of specific research areas[26]. Data including highly cited authors, journals, countries and institutions had been imported into Microsoft Excel 2016 for analysis, ranking and counting. The bar charts were created by Origin 2021, and VOSviewer software (version 1.6.18) was applied to construct and view bibliometric charts. In order to obtain accurate data, synonyms or near-synonyms of key fields were combined before running the VOSviewer software. According to the Price's Law P=0.749 $\sqrt{}$ Nmax (Nmax was the maximum number of articles published by an author), if this author had published more articles than P, he was a core author. Accordingly, author co-occurrence thresholds were set to obtain a core author network map of the literature [27]. Meanwhile, the Zip's word law was applied to identify the terms that appeared most frequently in the articles [28]. In the visual mapping, the circles represented the individual terms (keywords, countries, institutions and authors). The closer the distance between two circles, the stronger the link between the terms. Clusters of terms were distinguished by different colors. A higher frequency of items meant a larger circle, and the thickness of the line indicated the strength of the connection between the items.

3. Results

3.1. Analysis of publication output

A total of 898 articles were extracted by searching the WOSCC. One errata publication was excluded and there was no duplicate article. Of the remaining 897, 663 (73.9%) were original research documents and 234 (26.1%) were review articles. Almost the publications (884, 98.6%) were published in English, with authors from 61 different countries or regions. Articles were written by 3850 authors from 1298 organizations and were published in 337 journals.

Over the past 10 years, the number of publications on tDCS for depression had fluctuated slightly from year to year but with a positive trend. In detail, the annual number of documents issued increased marginally from 2013-2017, and significantly from 2017 to 2018, followed by zigzagging in subsequent years but maintained a large volume of issuance. The lowest number of published papers was in 2013 and 2015 (n=58), and the highest number

was in 2020 (n=177) (Figure 1). In recent years, non-invasive neurostimulation had been increasingly used in psychiatry and mental health, with tDCS for depression receiving increasing attention.
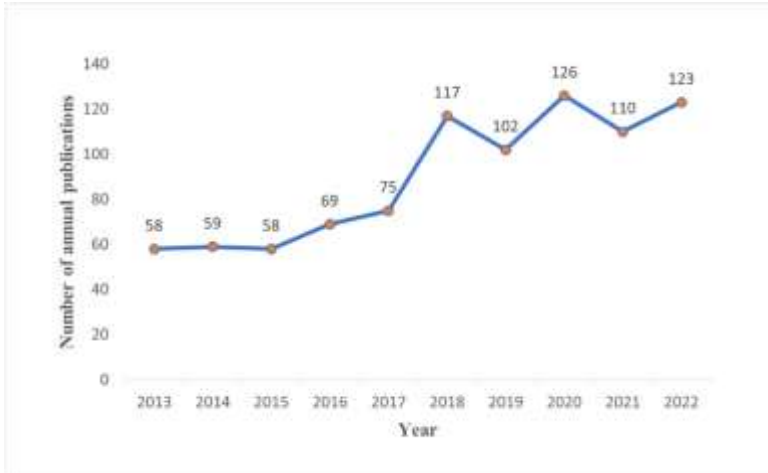

Figure 1: The number of publications on tDCS for depression from 2013 to 2022.

3.2. Analysis of Countries/Regions and Institutions

The geographical distribution of tDCS for depression was shown in Table 1. As on the whole, the publications originated in 61 different countries or regions. The United States proved to be the most productive country, with 256 articles published and the most citations (n=9376). Germany came in second place (163, 18.1%). The top two countries comprised nearly fifty percent of all articles (46.7%). Figure 2 depicted achievements of all countries in the field of tDCS in depression during the preceding decade and global collaboration among each countries were demonstrated in Figure 3. The U.S. shared the strongest international cooperation network (total link strength 339), followed by Brazil (273), Germany (163) and Canada (82). The strongest national links were between the USA and Brazil, followed by Germany and Brazil, and the USA and Germany.

Figure 2: Geographical distribution of publications on tDCS for depression from 2013 to 2022.
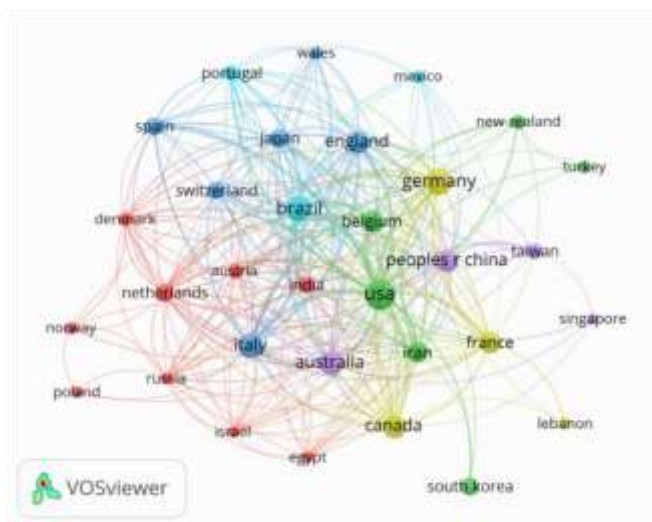
Figure 3: The collaboration network of countries.

The top 10 most productive institutions were displayed in Table 1. With 109 publications, University of São Paulo from Brazil was the institution with the most publications, and Harvard University had received the most citations (4939). Despite not publishing as many, the Spaulding Rehabilitation Hospital had received 2,677 citations, the most citations on average. Total 128 institutions published 5 or more articles and the network of institutional collaborations was shown in Figure 4. The largest number of institutions collaborated with University of São Paulo.

Table 1: Top 10 countries, institutions, authors with the most publications.

Country / Subject	Number of publications	Count of citations	Average citation
USA	256	9376	36.6
Germany	163	6600	40.5
Brazil	139	5231	37.6
Australia	99	3898	39.4
Italy	95	3887	40.9
Canada	82	3105	37.9
China	79	759	9.6
England	76	3070	40.4
Belgium	61	2669	43.8
France	58	3019	52.1
Institution			
University of São Paulo	109	4722	43.3
Harvard University	93	4939	53.1
Harvard Medical School	81	4573	56.5
University of Munich	69	3340	48.4
University of New South Wales Sydney	53	2676	50.5
University of Toronto	53	2606	49.2

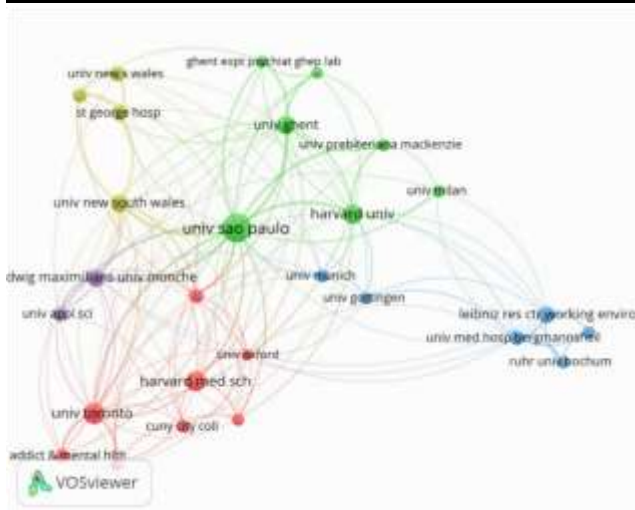|			
Black Dog Institute	51	2523	49.5
Spaulding Rehabilitation Hospital	41	2677	65.3
University of London	38	1606	42.3
Ghent university	37	1851	50.0
Author			
Brunoni, A. R.	91	4624	50.8
Padberg, F.	50	2537	50.7
Fregni, F.	47	3162	67.3
Loo, C.	46	2557	55.6
Vanderhasselt, M. A.	33	1369	41.5
Martin, D. M.	32	794	24.8
Bensenor, I. M.	31	1780	57.4
Nitsche, M. A.	27	2997	111.0
Alonzo, A.	24	1185	49.4
Lotufo, P. A.	24	1406	58.6

Figure 4: Cooperation network of organizations.

3.3. Analysis of authorship

Over the last decade, a total of 3805 authors contributed to the retrieved articles on tDCS in depression. 405 articles were dedicated by the top 10 most prolific authors, representing 45.2% of all publications. Of these, Brunoni, A.R., from University of São Paulo was the most productive author with 91 papers (Table 1). According to the Price's law (P=0.749 $\sqrt{91} \approx 7.2$), the minimum number of core author publications was 8 and 50 authors met the threshold. The core author collaborative network was obtained after filtering, as shown in Figure 5, where the authors were intensively connected to each other, with Brunoni, A. R. sharing the strongest collaborative network with researchers, followed by Padberg, F. and Bensenor, I. M. . Such a high density of relationships demonstrated that multiple stable research teams had been established.
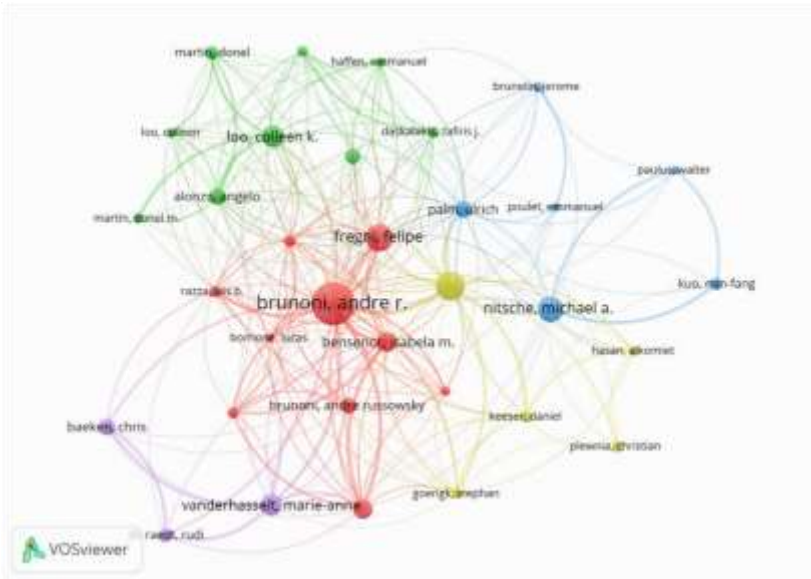
Figure 5: Cooperation network of authors.

3.4. Analysis of journal

Articles of tDCS in depression were published in 337 journals. There were 211 papers in the top 10 most active journals, accounting for 45.2% of all publications in the previous decade. Brain Stimulation received the most citations (2500) (Figure 6A) with the most research published (51 papers) (Figure 6B), and it achieved the greatest impact (IF 9.184).
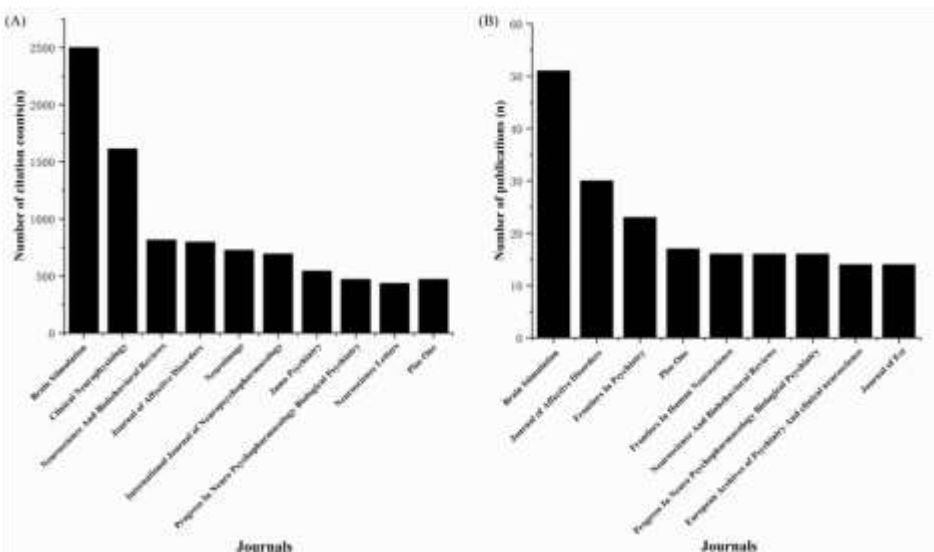

Figure 6: Plots. A. The most-cited journals on tDCS in depression from 2013 to 2022; B. the journals with the most publications on tDCS in depression from 2013 to 2022.

3.5. Analysis of the keyword co-occurrence cluster

Discipline-specific research directions and hotspots were revealed by keyword co-occurrence analysis. Based on the Zip's Law, 3108 terms ($\sqrt{3108} \approx 56$) were extracted with the help of VOSviewer, and 54 key terms met the threshold, with each term occurring more than 29 times. The keyword "tDCS" (total link strength 3505) appeared most frequently with 717 occurrences (23.1%), followed by depression (352, 11.3%), major depression (287,

9.2%) and motor cortex (245, 7.9%) and four clusters with different colors were identified for documents concerning tDCS in depression over the past decade. The four clusters were "Mechanisms on tDCS for depression" (cluster 1, red), "Antidepressant effects of tDCS and evidence-based medical evidence" (cluster 2, green), "Antidepressant neuro-modulatory therapies" (cluster 3, blue) and "Cognitive effects of tDCS in depression" (cluster 4, yellow) (Figure 7). Specifically, in cluster 1, the most notable keywords were tDCS, motor cortex, brain, modulation, excitability, functional connection, plasticity and mechanism. In cluster 2, the most common keywords were major depression, efficacy, meta-analysis, safety, current therapy and control trial. In cluster 3, the most repeated keywords were double-blind, rTMS, brain stimulation, treatment-resistant depression, deep brain-stimulation and theta-burst stimulation. In category 4, the most frequently mentioned keywords were depression, DLPFC, prefrontal cortex, working memory, cognitive control, attention. These results shed light on the most prominent areas and directions of tDCS in depression over the past decade.
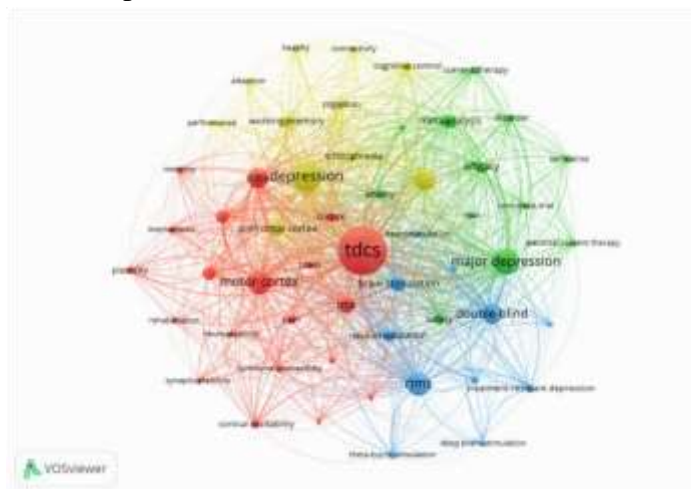

Figure 7: Cooccurrence map of keyword cluster.

4.   Discussion

To our knowledge, this is the first bibliometric study to conduct evaluation and visualization research of tDCS in depression. Focusing on the last decade of papers on tDCS in depression, this study summarized general information and research topics in this area.

A total of 897 publications from the WOS core collection were processed. In line with our research, publications had increased rapidly since 2017. Thanks to many studies evaluating the effectiveness of non-invasive brain stimulation (NIBS) for the treatment of several neurological and psychiatric conditions, positive results had led to the U.S. Food and Drug Administration approving NIBS for some of these conditions. Papers were published in 61 countries or regions. Eight of the top ten richest countries were from developed countries, with developing countries having great potential in this domain. The U.S. led the way in terms of publications (256), followed by Germany (163) and Brazil (139), with these three countries contributing around 62% of publications as the major forces. France played an irreplaceable role in the field with the tenth highest number of publications but the highest average number of citations, averaging 52.1 citations per article. Researchers in the U.S. worked with most countries including Iran, Belgium, New Zealand. Thus, together, these countries formed the largest cluster of cooperating countries. The results of the analysis of organizations demonstrated that universities were the prominent backbone of scientific research. Cooperation between organizations also features a marked

geographical dimension, as economic development determines, to a certain extent, scientific and cultural outcomes. As we all known, the strong communication between organizations facilitated the further development of the discipline.

Referring to co-authorship, Brunoni, A. R. from the University of São Paulo, Brazil, was the foremost author in the area and had a better understanding of research trends. Therefore, following their research progress and trends might help us to understand the frontiers of scholarship in the subject. For example, researchers had concentrated on the clinical efficacy of tDCS in major depressive disorder [29-30] and on

the mechanism of action of tDCS in depression [31-32]

Papers of tDCS in depression were published in 337 different journals, with the 10 most productive journals publishing 45.2% of the all. Brain Stimulation came in as one of the most authoritative journals, ranked Q1 by the JCR. Furthermore, its impact factor is the highest of the top 10 most active journals, contributing the most relevant articles, while articles originating from Brain Stimulation were the most widely cited by researchers. Generally speaking, highly cited literature predicted that it was receiving a great deal of attention in the research field. Therefore, we can keep an eye on these active journals to understand the trends of tDCS in depression.

The core and essence of a document could be represented by keywords and keyword co-occurrence analysis could reveal the direction of research and hot spots in a particular discipline [33]. Based on the keyword co-occurrence mapping, four main research topics of tDCS in depression over the last decade were identified. In order to provide information on the most influential papers, we showed a co-citation analysis of the cited references in figure 8. It was widely recognized that papers with high centrality within each group would carry the greatest impact and there was no doubt that these papers were of significant value to the reader.
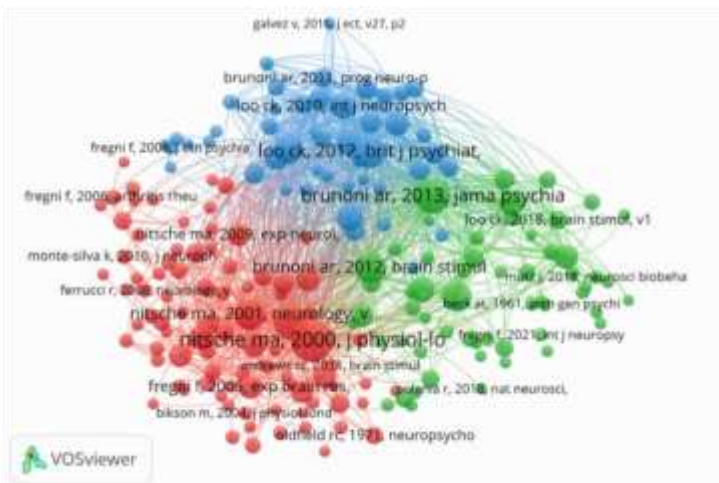

Figure 8: Co-citation analysis of the cited references.

Depression was a common disorder of the mind, with over 30 billion people suffering from it, worldwide [34]. In addition, depression caused approximately 8 million people to commit suicide each year. As a result, research into depression had never stopped. As tDCS, a NIBS technique, was gradually being studied in depth in the psychiatric and cognitive sciences, it had shown great potential in the treatment of depression. It has been established that tDCS acted on major depression mainly by activating neural activity in the left DLPFC through anodal stimulation [35] because the comparative lack of activity (i.e. prefrontal dysfunction as evidenced by reduced blood flow or glucose metabolism) in the left DLPFC of depressed patients had been confirmed in

previous studies [36]. Besides, according to evidence-based guidelines for the therapeutic practice of tDCS, there was level B evidence for the antidepressant effect of anodal tDCS stimulation on the left side of DLPFC [37]. In terms of clinical efficacy, current evidence pointed out that tDCS showed some benefits in depressed patients with drug resistance as well [38]. Interestingly, due to its non-invasive and non-adverse nature, tDCS also offered antidepressant help for children and adolescents [39-40]. At the same time, tDCS provided patients with more convenient home treatment outside of clinical situations. Additionally, safety and feasibility had proven themselves in a number of completed therapeutic trials of remotely supervised and home tDCS [41, 42]. Positive clinical outcomes had led to the development of practice guidelines for the remote use of supervised tDCS [43], which revealed that tDCS had a promising future in the field of antidepressant disorders.

5. Strengths and limitations

In a word, it was the first bibliometric study to examine tDCS in depression, providing comprehensive information on publication outputs, countries, institutions, journals, authors and keywords. The WOS was acknowledged as an important data source for bibliometric analysis and it offered a more consistent and standardized record than other databases [44]. However, the WOS, as the only data source of this study, had led to the neglect of publications from other databases, such as Scopus and PubMed, resulting in incomplete data. Secondary, article type bias was present, as we included only original articles and reviews. Publications such as conference abstracts, letters or social commentaries were excluded as the details in these publication types were often incomplete. Besides, the search for publications was conducted by taking only the subject term field, which might have missed a minority of additional papers if the important content subject concepts were not flagged. Despite these limitations, we believe that these findings provide a reliable representation of tDCS in depression.

6. Conclusions

Analyzing documents on tDCS in depression over the past 10 years, this bibliometric study provides comprehensive information on the development of research in this domain. The most influential countries, institutions, journals and author were USA, University of São Paulo, Brain Stimulation and Brunoni, A. R.. "Antidepressant effects of tDCS and evidence-based medical evidence", "Antidepressant neuromodulatory therapies" and "Cognitive effects of tDCS in depression" are current research hot topics and potential future research directions.

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