

REVIEW

Research Hotspots and Global Trends of Transcranial Direct Current Stimulation in Stroke: A Bibliometric Analysis

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Purpose: Transcranial direct current stimulation has been widely used in the clinical treatment of stroke. The purpose of this study was to perform a bibliometric analysis of scientific literature in this field.

Methods: Articles and reviews regarding transcranial direct current stimulation in stroke from January 01, 2004 to May 31, 2022 were identified from the Science Citation Index-Expanded of the Web of Science Core Collection database. CiteSpace 6.1.R2, Bibliometrix and the Bibliometric Online Analysis Platform were used to analyze data.

Results: A total of 905 papers were obtained, with the highest number of publications coming from the USA. The institutions and authors with the most publications were Harvard Medical School and Fregni F respectively. Nitsche MA had the most co-citations, followed by Fregni F. Neurosciences was the most fruitful research area and Brain Stimulation had the highest H-index. The research topics could be divided into three sections: mechanisms of treatment, comparison of efficacy with transcranial magnetic stimulation, clinical application of post-stroke dysfunction. The field of "walking", "strength" and "virtual reality therapy" are the future research hotspots of transcranial direct current stimulation.

Conclusion: The overall research showed a slow growth trend, and the outstanding contribution of the USA in this field cannot be ignored. Relevant researchers are suggested to focus on international collaboration and actively conduct high-quality randomized controlled clinical trials on research hotspots and frontiers in order to identify the optimal stimulation paradigm for clinical purposes. Keywords: stroke, transcranial direct current stimulation, bibliometric analysis, hotspots, frontier

Introduction

Globally, stroke is the second leading cause of death and the third leading cause of disability. Stroke, with high rate of morbidity, disability, mortality, and high economic burden not only can badly affect patients' daily function, but also imposes a significant challenge on the health care system.^{2,3} Therefore, effective rehabilitation of post-stroke dysfunction is important to improve patient' quality of life and relieve the pressure of care for them.

Transcranial direct current stimulation (tDCS) is a popular treatment for stroke patients. It regulates the excitability of post-stroke neurons mainly by applying two superficial electrodes on the scalp to generate weak direct current. 4,5 Compared to other neuromodulation methods, tDCS's advantages of safety, effectiveness, low cost, and portability make it have considerable therapeutic potential.⁶ In recent years, there has been an increasing number of researches related to tDCS treatment for stroke. Although a bibliometric analysis of tDCS in stroke⁷ had already performed, it was presented as a conference abstract with less information and did not display the current development and hot frontiers of

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its research area. Therefore, it is necessary to summarize the research progress of tDCS treatment for stroke in order to provide more comprehensive and detailed information for related researchers.

With the advent of scientific databases such as Web of Science (WOS), research data are readily available, which has contributed to the development of bibliometric research. Bibliometrics uses quantitative methods to analyze the acquired knowledge carriers, thus revealing information on countries, institutions, authors, co-citations, keywords etc. of publications and enabling discovery of the current state of research, research hotspots and future trends in a field. Policy To ensure the paper's quality and accessibility, the Science Citation Index-Expanded (SCI-E) of the Web of Science Core Collection (WoSCC) database was chosen, which is considered to be the most suitable database for conducting bibliometric analysis. Our goal was to describe the current status of tDCS in stroke, enhance understanding of its research hotspots and potential trends during the period 2004–2022, and provide useful reference guide for future researchers.

Methods

Data Source and Search Strategy

The retrieval strategy was as follows: [TS = ("stroke" OR "apoplexy" OR "brain infarction" OR "cerebral infarction" OR "hemorrhagic stroke" OR "ischemic stroke" OR "intracerebral hemorrhage" OR "intraceranial hemorrhage" OR "cerebral haemorrhage" OR "cerebral haemorrhage" OR "cerebral haemorrhage")] AND [TS = ("transcranial direct current stimulation" OR "transcranial electric stimulation" OR "tDCS" OR "transcranial DC stimulation" OR "a-tDCS" OR "c-tDCS" OR "HD-tDCS")]. In addition, we only considered the literature type of "article" and "review" types in English, excluding letter, conference abstract, editorial material, news item, book chapter, etc. The search was conducted on publications from January 01, 2004 to May 31, 2022, with a retrieval date of June 10, 2022. Two researchers (J.Z. and X.C.) performed the data collection independently, a third author (K.Z.) analyzed the data and addressed the disagreements that existed during data collection. A total of 905 relevant documents (695 articles and 210 reviews) were obtained for final analysis and saved as plain text files in "download ***.txt" format.

Data Analysis

CiteSpace6.1. R2, 64-bit (Chaomei Chen, Drexel University, USA), *Bibliometrix* (R-Tool of R-studio), the Bibliometric Online Analysis Platform (http://bibliometric.com/) were used to analyze data. The H-index and average citations (ACI) of the subject categories were extracted directly from the WoSCC database. The H-index was defined as the number of papers with citation numbered \geq H, 12,13 which can be used to assess academic achievement in a field. Impact Factor (IF) of journals were obtained from the Journal Citation Reports of 2022. The specific operation process was presented in Figure 1.

CiteSpace is a Java-based application that presents the structure, patterns and distribution of knowledge using visualization. The parameters were set as follows: Time Slicing: 2004.01-2022.05, with time slice of 1; Node Types: Chose Institution, Author, Reference, Keyword respectively; Selection Criteria: Each node chose g-index (k=25); Pruning: none of the clipping methods were selected. The nodes in the network mapping represent Institution, Author, Reference, Keyword. The frequency is indicated by the size of the circle, and the thickness between the connecting lines represents the closeness of cooperation. When the centrality is ≥ 0.1 , it is denoted by a purple circle, which means occupying an important position in the network mapping.

The R tool *Bibliometrix* of R-Studio (Version 4.2.0) was used for scientometric quantitative research. In this study, it was used to identify the country scientific production and summarize the authors' H-index and ACI.

Moreover, we obtained the annual publication counts of the top 10 countries with the highest number of publications and the international collaboration mapping from the *Bibliometric.com*.

Results

Distribution of Overall Publications

As illustrated in Figure 2A, a smooth trend of growth was presented in the period from 2004 to 2021. The maximum number of publications was posted in 2021, up to 92. In the first five months of 2022, 36 papers were published. Figure 2B showed the top 10 countries in number of publications. The USA published the most papers about tDCS in

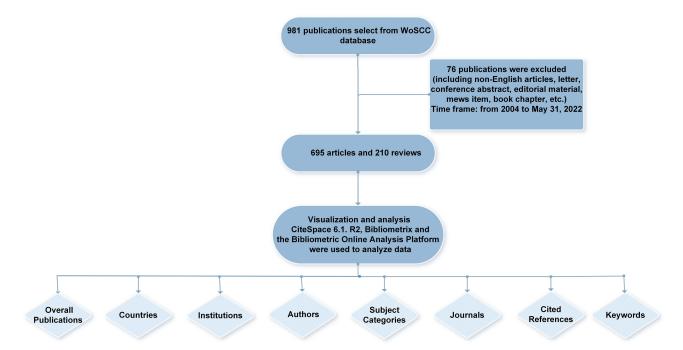


Figure I Inclusion and analysis flow chart.

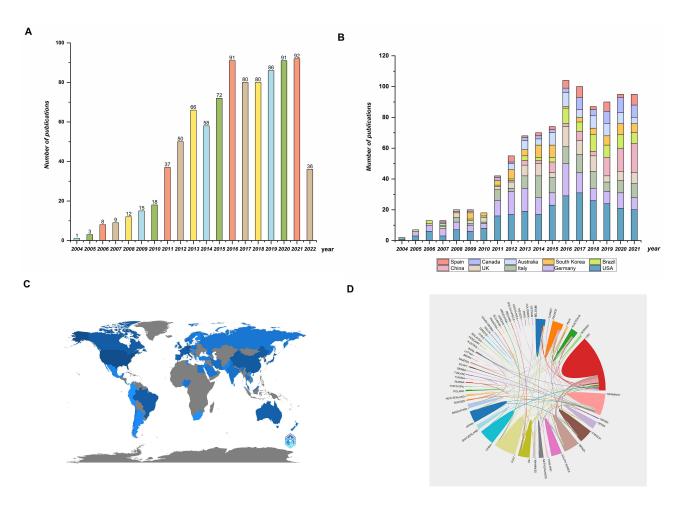


Figure 2 Publication trends and country publication, collaborative contributions (A) The annual number of publications. (B) The annual number of publications in major countries. (C) Country scientific production. (D) International collaboration among countries/regions.

stroke. Notably, China has caught up with other countries, with almost as annual publications as the USA in the last two years, though its first literature was in 2012.

Distribution of Countries/Regions and Institutions

A total of 56 countries and regions were involved in the publication of 905 articles and reviews. The different colors in Figure 2C represented various countries' posting numbers on the world map, with darker colors indicating higher amounts of publications. Except Africa and Northern Europe, most countries had published relevant literatures. Besides, As could be seen from Table 1, the USA (centrality = 0.45) ranked first, playing an important role in expanding knowledge to other countries. This was confirmed by Figure 2D, shown the closer contact exchanges with other countries, especially with Italy, Germany and Brazil.

Total 1278 institutions participated in the publishing of the publications. As shown in Figure 3A and Table 2, Harvard University (82) contributed the highest number of publications, followed by University Sao Paulo (32). Harvard University (0.29) also had the highest centrality, followed by Johns Hopkins University (0.28). We found that four of the top ten institutions were from the USA. In overview, the USA is ahead in this area.

Distribution of Authors and Co-Cited Authors

These 905 publications were completed and published by 3074 authors. We used the ACI, H-index and the number of publications to synthetically identify the most influential authors in the field of tDCS treatment for stroke. As seen in Figure 3B, Fregni F ranked first in the number of publications and H-index, while Cohen LG ranked first in the ACI. Fregni F works at Harvard Medical School now, who has been researching on tDCS in stroke since 2005. He has provided insights to other researchers in the treatment of different dysfunctions post stroke, experimental methods, stimulation sites, and stimulation parameters, etc. ^{16–18} The high ACI confirmed Cohen LG's academic position in the field of DCS in stroke. In particular, his publication in 2006 "Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation" was cited 1114 times. ¹⁹ This article confirmed the feasibility of tDCS in double-blind, sham-controlled randomized trials and provided strong support for subsequent related experimental studies.

As shown in Figure 3C, Fregni F had the highest centrality, who was more closely connected with other authors, such as Nitsche MA, Pascual-leone A. The centrality of the remaining authors was less than 0.1. Overall, the collaborative aspect of investigators in studies of tDCS treatment for stroke still needs to be strengthened. Co-citation authors are two or multiple authors who are simultaneously cited in one or more subsequent publications. It is another indicator to evaluate the contribution of authors.²⁰ In Figure 3D, it could be seen that Nitsche MA had the highest number of co-citations, followed by Fregni F.

Rank	Country	Year	Publications Counts	Centrality
1	USA	2004	281	0.45
2	Germany	2005	148	0.20
3	Italy	2004	107	0.29
4	UK	2006	79	0.25
5	China	2012	65	0.05
6	Brazil	2005	63	0.06
7	South Korea	2008	63	0.02
8	Australia	2007	60	0.06
9	Canada	2007	47	0.04

2007

Spain

Table I The Top 10 Countries Based on the Total Number of Publications

10

0.04

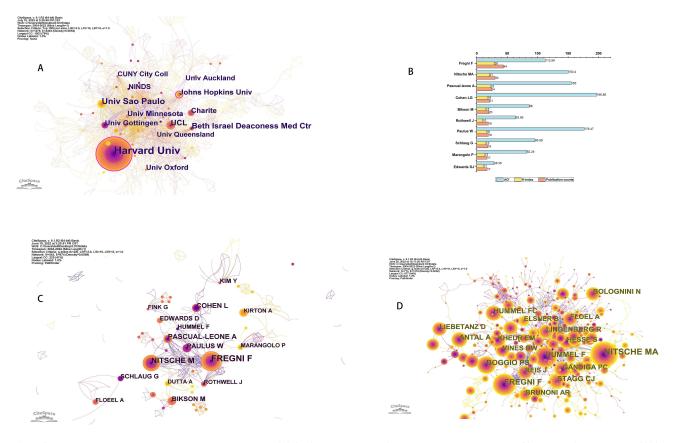


Figure 3 Institutions and authors posting, collaborative contributions (A) CiteSpace visualization of the institutions associated with tDCS treatment for stroke during 2004–2022. (B) The publication counts, H-index, and ACI of the top 10 authors associated with tDCS treatment for stroke during 2004–2022. (C) CiteSpace visualization of the authors associated with tDCS treatment for stroke during 2004–2022. (D) CiteSpace visualization of the co-citation authors associated with tDCS treatment for stroke during 2004–2022.

Distribution of Subject Categories

The top 10 subject categories on tDCS in stroke, including publication counts, open access, citations, ACI and H-index, were demonstrated in Figure 4A. Among the top 10 discipline categories, Neurosciences ranked the largest number of publications (508), open access papers (295), citations (26,071), and the highest H-index (79). Neuroimaging had the highest number of citations per paper of 27.22.

Distribution of Journals

In total, 249 journals appeared in this research area, according to statistics. The top 10 most active tDCS-related journals published 29.17% of the total publications (n=905; Table 3; Figure 4B). Frontiers in Human Neuroscience (47) published

Table 2 The top to comportating institutions in the confidence for our order									
Rank	Institution	Country	Publications Counts	Centrality					
1	Harvard University	USA	82	0.29					
2	University of Sao Paulo	Brazil	32	0.08					
3	Beth Israel Deaconess Medical Center	USA	24	0.05					
4	University College London	UK	23	0.07					
5	Johns Hopkins University	USA	20	0.28					
6	University of Minnesota	USA	19	0.12					
7	Charite	Germany	18	0.03					
8	University Oxford	UK	18	0.05					
9	University of Gottingen	Germany	18	0.04					
10	University of Auckland	New Zealand	16	0.05					

Table 2 The Top 10 Collaborating Institutions in tDCS Treatment for Stroke

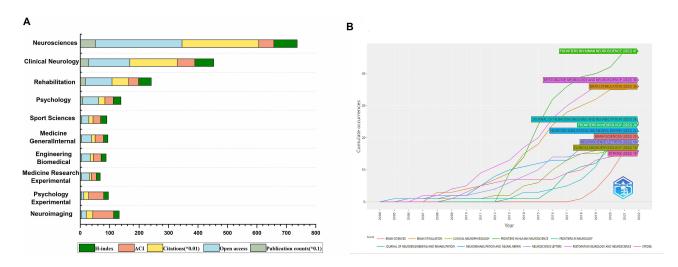


Figure 4 The top 10 scientific categories and journals in tDCS treatment for stroke (A) The Publication counts, Open access, Citations, ACI and H-index of the top 10 subject categories of WOSCC associated with tDCS treatment for stroke during 2004–2022. (B) Cumulate occurrences in the top 10 journals of tDCS treatment for stroke during 2004–2022.

the most publications, Restorative Neurology and Neuroscience (38) ranked second, followed by Brain Stimulation (36). In addition, Brain Stimulation has the highest H-index (26), followed by the second highest IF in the top ten journals, located in the Q1 as well as the second highest number of citations.

Distribution of Cited References

Using CiteSpace to study the co-citation network of the literature, it is possible to explore the development and research frontiers of a discipline.²¹ The color in Figure 5 ranged from brown to green, indicating that the time was from far to near. As could be seen from the co-occurrence figure on the left, the article published by Lindenberg R in 2010 was the most co-cited, which used a sham-controlled randomized trial to confirm the effectiveness of bi-hemispheric transcranial direct current stimulation combined with physiotherapy on motor function in chronic stroke, before which the efficacy of bilateral stimulation had not been studied in the literature.²² In addition, there was no obvious highly centralized articles in the figure. Cluster analysis of the citing papers yielded the 18 clusters in the figure on the right, which represented the forward direction of research as time progresses. Initially, researchers focused on the feasibility of tDCS for stroke

Table 3 The Top 10 Journals in tDCS Treatment for Stroke

Rank	Journal	Publications Counts	Total Citations	ACI	H-index	IF	JCR
I	Frontiers in Human Neuroscience	47	1462	31.11	22	3.473	Q2
2	Restorative Neurology and	38	1749	46.03	25	2.976	Q3
	Neuroscience						
3	Brain Stimulation	36	2401	66.69	26	9.184	QI
4	Journal of Neuroengineering and	24	558	23.25	11	5.208	QI
	Rehabilitation						
5	Frontiers in Neurology	24	188	7.83	8	4.086	Q2
6	Neurorehabilitation and Neural	22	1524	69.27	17	4.895	QI
	Repair						
7	Brain Sciences	20	74	3.70	4	3.333	Q3
8	Neuroscience Letters	19	801	42.16	12	3.197	Q3
9	Clinical Neurophysiology	18	2619	145.50	13	4.861	Q2
10	Stroke	16	1108	69.25	11	10.170	QI

Abbreviations: ACI, Average Citation; IF, Impact Factor; JCR, Journal Citation Reports.

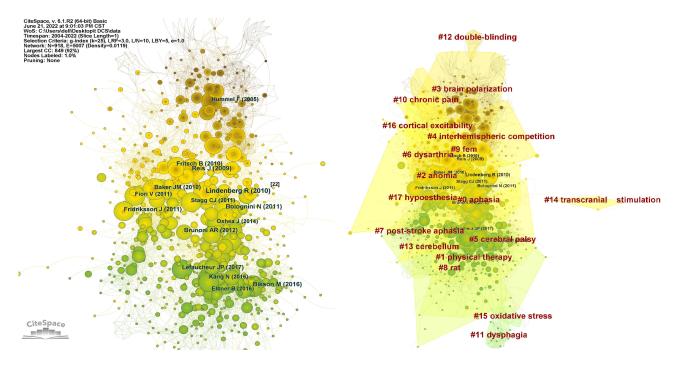


Figure 5 CiteSpace visualization of the co-cited references associated with tDCS treatment for stroke during 2004–2022. Left figure: Co-occurrence Diagram of Co-cited references. Right figure: Cluster Diagram of Co-cited references.

rehabilitation and how it could improve the mechanisms of stroke. Later, post-stroke aphasia and the cerebellum (the site of stimulation) were the hot topics, especially post-stroke aphasia. Recently, dysphagia and physical therapy have become more prominent, along with researchers also have developed widespread interest in oxidative stress.

Burst detection of the literature resulted in a total of 20 bursts (Figure 6). We found that the study presented by Hummel et al (22.31, 2005, Brain)²³ had the highest bursts strength with its focus on hand motor function in chronic stroke patients. Meinzer M (9.78, 2016, Brain),³ Rocha S (8.25, 2016, Disability and Rehabilitation),²⁴ Marangolo (8.25, 2016, Journal of Cognitive Neuroscience)²⁵ have been highlighted since 2016 to date. Notably, all three papers were clinical experimental studies, two of which focused on aphasia, and one on chronic upper limb dysfunction in stroke patients.

Distribution of Keywords

Keywords are the condensation and extraction of the article's content, which best represents the topic of the article. Scholars usually use high-frequency keywords to reflect the hot issues in the research field.²⁶ At this stage, keywords with similar meanings, such as "transcranial direct current stimulation", "direct current stimulation", and "dc stimulation" were combined together. The left of Figure 7 depicted the final merged keyword co-occurrence map. In this analysis, excluding "transcranial direct current stimulation", "stroke", "noninvasive brain stimulation" and "recovery", the main keywords was transcranial magnetic stimulation (TMS) (frequency = 376, centrality = 0.03), followed by excitability (299, 0.02), human motor cortex (292, 0.06), motor recovery (132, 0.05), modulation (124, 0.09), plasticity (123, 0.06), upper limb (100, 0.10), chronic stroke (72, 0.11), randomized controlled trial (64, 0.09), theta burst stimulation (57, 0.06). TMS was present most frequently while chronic stroke had the highest centrality, indicating that chronic stroke was at a key position in the network and showed the most impact.

The right of Figure 7 depicted the 9 keyword clusters based on the log-likelihood ratio (LLR) algorithm. To further detail the research content and better capture the research hot spots, the 9 clusters were divided into 3 sections, including pathogenesis (#0 excitability, #8 motor cortex), comparative efficacy (#2 transcranial magnetic stimulation), and clinical application (#1 cerebral palsy, #3 major depression, #5 aphasia, #6 visuospatial neglect, #7 ischemic stroke). This was similar to the keyword co-occurrence analysis results.

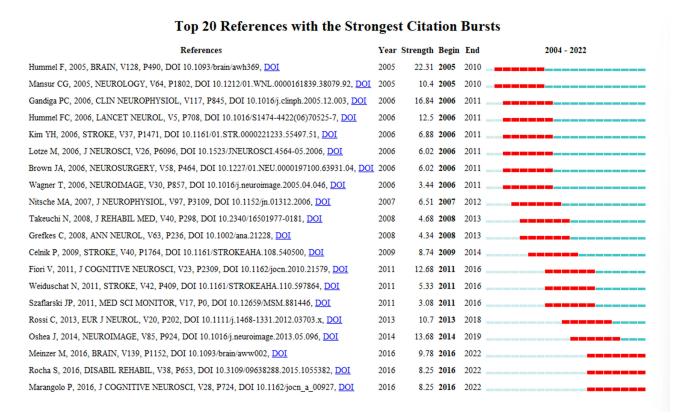


Figure 6 Burstiness analysis of co-cited references associated with tDCS treatment for stroke during 2004–2022.

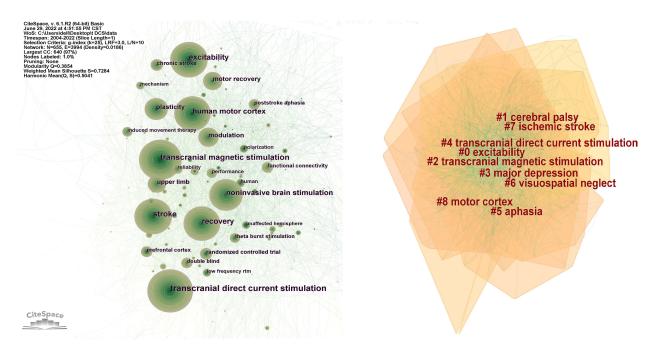


Figure 7 CiteSpace visualization of the keywords associated with tDCS treatment for stroke during 2004–2022. Left figure: Co-occurrence Diagram of Keywords. Right figure: Cluster Diagram of Keywords.

Top 20 Keywords with the Strongest Citation Bursts

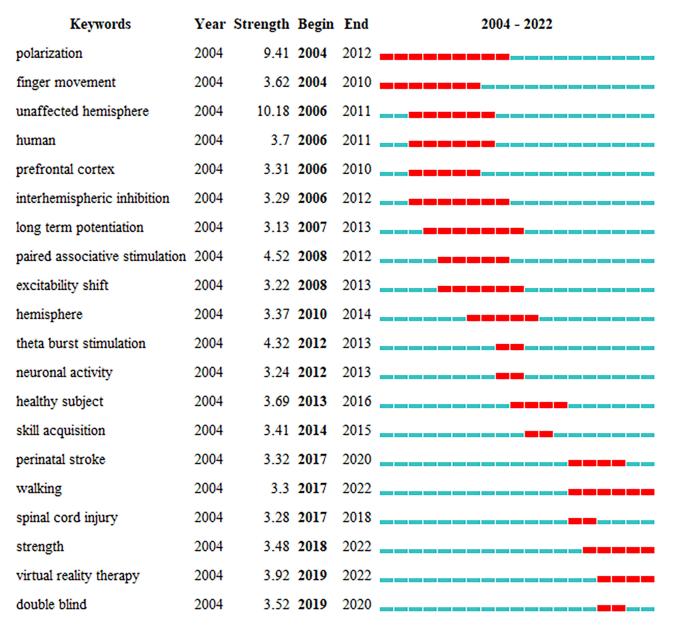


Figure 8 Burstiness analysis of keywords associated with tDCS treatment for stroke during 2004–2022.

Figure 8 showed the top 20 keywords with the strongest bursts from 2004 to 2022. Research on the burgeoning words "walking", "strength", "virtual reality therapy" have continued up to date. To some extent, they may be the future research trends.

Discussion

A General Upward Trend in the Number of Publications on tDCS in Stroke

In this study, we presented the research results of tDCS in stroke in the years of 2004–2022. The numbers of publications showed an overall increasing trend since 2004 (Figure 2A). Until 2016 onwards, the growth in annual publications has no changed much. It is worth noting that the relative lack of growth in the number of articles does not represent a decline in

research enthusiasm, but may be related to the long time-consuming clinical trials leading to the lack of output of research papers.

Uneven Distribution of Countries, Institutions, and Authors of Publications on tDCS in Stroke

Eight of the top ten publishers are from developed countries, with only Brazil and China as developing countries. The USA is the top publishing country and also has the highest neutrality (Figure 2C; Table 1). Developed countries, such as the USA, spend more money on health care, possess advanced medical facilities and attract higher quality researchers. Therefore, the superior conditions make the number of publications in developed countries higher than in developing countries. This is also evidenced by the fact that four of the top ten institutions are located in the USA (Table 2), and by the presence of Fregni F, who works at Harvard Medical School, is the author with the highest number of publications (Figure 3B). In addition, as shown in Figure 2D, most collaborations in this field are concentrated in the USA, which is consistent with the prominent contribution of the USA. Although the pressure and burden of stroke is higher in China than in Brazil, international exchanges and collaborations in China are not as close as in Brazil. None of the top 10 institutions are from China, while University of Sao Paulo from Brazil ranked the second place with 32 articles. In general, the distribution of publications in the field of tDCS in stroke by countries, institutions and authors is extremely unbalanced, with few results and collaborations in many countries/regions. We suggest that countries/regions with low collaboration rates, such as China, should pay more attention to international collaboration and understand the direction of research of authors and institutions with more publications and collaborations, so as to learn from each other and find opportunities for cooperation.

Multidisciplinary Research Areas in tDCS Treatment for Stroke

According to the subject categories of tDCS for stroke articles (Figure 4A), Neurosciences (508) was the most fruitful research area, followed by Clinical Neurology (275) and Rehabilitation (170). The top 10 subject categories also included Psychology, Sport Sciences, Engineering Biomedical, and Neuroimaging, among others. The distribution of subjects indicates that tDCS in stroke is a complex clinical problem requiring multidisciplinary interventions and future researchers can join forces to conduct multidisciplinary cross-sectional studies to promote disciplinary integration and development.

Relatively High Quality of Literature on tDCS in Stroke

In terms of authoritative journals, Frontiers in Human Neuroscience contributed the greatest number of published papers, Clinical Neurophysiology had the highest ACI, and Brain Stimulation had the highest H-index of journals. With Q1 accounting for 40% of the top 10 journals, the quality of publications related to tDCS treatment for stroke is generally at a high level. High-quality papers not only help researchers to establish the theoretical basis, but also provide strong evidence for the clinical application of tDCS in stroke. Therefore, researchers can pay more attention to the dynamics of the top-ranked journals.

Three Research Hotspots in tDCS Treatment for Stroke

Research hotspots in the field of tDCS in stroke research were identified by summarizing the co-cited reference and keyword results (Figures 5 and 7). The research hotspots were described in the following three aspects: mechanisms of treatment, comparison of efficacy with TMS and clinical application of post-stroke dysfunction.

Studies on the mechanisms from a molecular and cellular perspective have attracted the interest of researchers. Rasoul Kaviannejad et al²⁷ showed the use of tDCS could modulate neuroinflammatory and oxidative stress pathways in global cerebral ischemia-reperfusion.²⁸ In addition, tDCS has been reported to increase cellular activity, promote the secretion of brain-derived neurotrophic factor, and affect the release of γ -aminobutyric acid or glutamic acid, etc.^{29,30} Subsequent researchers can explore the mechanism of tDCS regulation with the help of more advanced techniques such as imaging

technology, infrared spectroscopy or combined EEG, in order to provide a more convincing theoretical basis for clinical treatment.

TMS is also frequently used in clinical practice. Compared to tDCS, TMS is able to induce cortical neurons firing to generate action potentials and make it easier to establish clinical treatment protocols. However, it is a bulky device with high treatment costs and a high incidence of adverse effects. In addition, tDCS is more likely to be used in double-blind or sham-controlled studies. Most of the current comparisons of efficacy are derived from reviews between the two, and no direct guidelines have reported recommendations related to the use of post-stroke dysfunction. One study has demonstrated the effectiveness of low-frequency TMS combined with anodal tDCS stimulation protocols in motor recovery in subacute stroke patients. Future studies could be conducted to compare the efficacy or to combine the two to identify more beneficial treatment protocols to develop a patient-tailored approach.

Post-stroke motor dysfunction has been widely studied in early stages because of its high incidence.³⁴ A metaanalysis³⁵ showed that tDCS was effective in improving both upper and lower limb function, especially beneficial for the recovery of upper extremity function in chronic stroke patients. However, a study revealed no advantage of tDCS in improving upper limb motor deficits, 36 which was also shown in another study to have no additional effect on gait training.³⁷ The contradictory results were also found in post-stroke aphasia. The guidelines reported some beneficial results using anodal tDCS over Broca's and Wernicke's areas, cathodal tDCS on the right homologue of Broca's area, or a bilateral hemispheric stimulation of both inferior frontal gyri. However, the level of evidence was not sufficient to guarantee the efficacy or therapeutic potential of any protocol.⁴ There were inconsistencies in experimental methods, period of intervention, stimulation parameters, and degree of clinical impairment in stroke among different investigators, hence the variation in results. Future researchers could actively conduct large multicenter, high-quality randomized controlled clinical trials to determine the optimal stimulation paradigm and standardize medical terminology to avoid multiple replications of the same problem. Cerebral palsy, post-stroke depression, and visuospatial neglect are also hot topics of research. The available studies suggest that the use of tDCS is beneficial for the recovery of motor function in children with cerebral palsy, but its stimulation parameters still need further study. The main challenges of the application include few clinical trial studies, unknown economic benefits, the need to carefully assess children's tolerability and lack of specific guidelines. Investigators should fully consider relevant pediatric issues in subsequent studies with the aim of better advancing research progress.

Three Research Trends in tDCS Treatment for Stroke

Understanding the research frontiers is beneficial for researchers to grasp the development trend and promote the growth of a discipline. This study was divided into two phases by analyzing the highlighting keywords (Figure 8): 2004–2013, 2014–2022. The first phase focused on the mechanism of tDCS in stroke and the second phase was concerned with the practical application of tDCS, including experimental methods, stimulation parameters, and clinical applications combined with adjunctive techniques. Among them, researchers have continued to study burgeoning words such as "walking", "strength", and "virtual reality therapy" to date, and "virtual reality therapy" has the highest bursts strength. It can be predicted that future studies may continue to explore in depth the combined application with other techniques, the optimal stimulation parameters of tDCS, and the efficacy for rehabilitation of lower limb dysfunction.

Conclusion

This study used visualization to analyze the relevant literature in the field of tDCS in stroke in the WoSCC database, objectively presenting the hotspots and trends for the development of studies. The overall research tended to grow slowly, while the USA and Harvard Medical School are the countries and institutions with the highest number of publications and collaborative communication. The outstanding contribution of the USA in this field cannot be neglected. Additionally, the hotspots of interest for researchers center on the mechanisms of treatment, comparison of efficacy with TMS and clinical application of post-stroke dysfunction. The research fervor for "walking", "strength" and "virtual reality therapy" will continue. Overall, the research situation of tDCS in stroke is unlimited potential. The main limitation in this study was that only relevant literature from the WoSCC database was included.

Data Sharing Statement

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

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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 declare no conflicts of interest in this work.

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