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A century of research on neuromodulation interventions: A scientometric analysis of trends and knowledge maps

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ABSTRACT

Interest in neurostimulation interventions has significantly grown in recent decades, yet a scientometric analysis objectively mapping scientific knowledge and recent trends remains unpublished. Using relevant keywords, we conducted a search in the Web of Science Core Collection on September 23, 2022, retrieving a total of 47,681 documents with 987,979 references. We identified two prominent research trends: 'noninvasive brain stimulation.' These methods have interconnected over time, forming a cluster focused on evidence synthesis. Noteworthy emerging research trends encompassed 'transcutaneous auricular vagus nerve stimulation,' DBS/epilepsy in the pediatric population,' 'spinal cord stimulation,' and 'brain-machine interface.' While progress has been made for various neurostimulation interventions, their approval as adjuvant treatments remains limited, and optimal stimulation parameters lack consensus. Enhancing communication between experts of both neurostimulation types and encouraging novel translational research could foster further development. These findings offer valuable insights for funding agencies and research groups, guiding future directions in the field.

1. Introduction

Two-thousand years ago, Scribonius Largus, the physician of the Roman emperor Claudius, suggested that applying electric currents on the cranial surface using a torpedo-fish could be a remedy for headaches (Jocks, 2013). More recently, in the 19th century, electricity from fish was also used to treat a variety of neurologic and psychiatric disorders (Kellaway, 1946). Later, in 1831, Michael Faraday introduced the concept of electromagnetic induction with the generation of a variable magnetic field by running electricity through a coil (Ziemann et al., 2008). In the late 1930s, the electroconvulsive therapy (ECT) device was invented by two neuropsychiatrists, Ugo Cerletti and Lucio Bini, as a substitute for the prior induction of seizures with Metrazol (Fink, 1984).

These developments have led to modern clinical neuromodulation, an interdisciplinary field characterized by the use of electricity to modify abnormal brain activity and, consequently, ameliorate neuropsychiatric symptoms. Its techniques can be broadly divided into noninvasive brain stimulation (NIBS), repetitive transcranial magnetic stimulation (rTMS) (Barker et al., 1985; George et al., 1995), transcranial electrical stimulation (tES), transcranial alternating current stimulation (tACS) (Antal et al., 2008), and transcranial direct current stimulation (tDCS) (Brunoni et al., 2012)), as well as convulsive therapies (such as electroconvulsive therapy (ECT) and magnetic seizure therapy (MST)). These forms of NIBS are distinct from invasive neuromodulation IBS (such as vagus nerve stimulation (VNS) (Zabara, 1992) and deep brain stimulation (DBS) (Oliveria, 2018)). rTMS and tES are performed in ambulatory settings, do not require sedation and are very well tolerated. In turn, ECT and MST are techniques that use sedation and induce seizures, and most IBS techniques are neurosurgical procedures that implant pacemakers connected to brain structures. The approval by the US Food and Drug Administration (FDA) of DBS for the treatment of Parkinson's disease in 2002 was a pivotal point in its large and rapid adoption, despite initial and controversial development in the late 1980s (Oliveria, 2018). With direct intervention in pathological neural circuits, DBS has changed the way that brain disorders are treated and understood and is considered one of the most promising therapeutic applications for clinical neuroscience (Lozano et al., 2019).

Patients with refractory neuropsychiatric disorders are treated by a interdisciplinary clinical team, including psychiatrists, neurologists, psychologists, neurosurgeons and others. Despite having similarities regarding animal models and technology development, it is unclear how well connected the field is, who the leading researchers and institutions are, and which topics are currently driving the field.

In the past two decades, the number of scientific publications on brain stimulation has increased exponentially, which has made it possible to qualitatively and quantitatively summarize this body of research in systematic reviews and meta-analyses, respectively (Razza et al., 2021). However, these evidence synthesis methods are not well suited to identify and analyze trends within knowledge domains. A novel evidence synthesis method is referred to as the "research weaving framework", as proposed by Nakagawa and colleagues, and combines bibliometrics and systematic mapping analyses (Nakagawa et al., 2019). Systematic mapping is a nascent method derived from systematic reviews, with the goal of classifying research on a broad topic. Bibliometrics is a quantitative evaluation of the structure of scientific knowledge based on citations, namely, a performance analysis. The combination of bibliometrics and systematic mapping is conducted with scientometrics analysis, with the aim of mapping scientific knowledge by analyzing performance, influence and research trends over time (Sabe et al., 2022).

Although a few bibliometric analyses have been recently published, they primarily focused on specific topics such as DBS and tDCS (Hu et al., 2017; Sun et al., 2022) or were limited to certain time periods (Zheng et al., 2020). However, a comprehensive overview of various neurostimulation techniques, examining the evolution of research across disciplines such as psychiatry, neurology, and neurosurgery, is still lacking. Therefore, we decided to conduct a comprehensive scientometric analysis of research focusing on the clinical aspects of neuromodulation interventions encompassing NIBS and IBS. Our primary objective was to evaluate how knowledge domains of brain stimulation have evolved over the past decades by retrieving co-cited reference networks. Our secondary objective was to provide a measure of the research network (countries, institutions, authors and journals) and to detect potential research gaps and limitations.

2. Methods

This study was conducted according to a protocol based on a previously published large-scale scientometric analysis (Sabe et al., 2022) that can be found in the Open Science Framework (osf.io).

2.1. Search strategy and data collection

Data were collected from the Science Citation Index Extended in the Web of Science (WOS) Core Collection database. WOS is considered one of the most suitable databases for scientometric analysis (Mongeon and Paul-Hus, 2016), as it contains the full list of references and citations of each article from 1900 – citations that are not available in PubMed or Embase – and that were extracted in tag-delimited plain text files on September 23, 2022. The search terms used were a combination of keywords and MeSH terms related to brain stimulation. To focus on clinical aspects of brain stimulation, we excluded animal studies by excluding specific keywords. The full list of search terms is reported in our protocol (osf.io).

Included publications types were 'article', 'reviews', 'editorial material 'and 'proceedings papers' with no restrictions on publication date or language. Duplicates were removed with CiteSpace.

To assess the quality of the retrieved articles, we conducted a

filtering process using statistical values with a confidence level of 95% and a confidence interval of 10%. For a dataset of 20,000 citations, we inspected 2,000 randomly selected articles with a maximum of 100 irrelevant references. Furthermore, we inspected all highly cited WOS articles, which are papers that perform in the top 1% of cited papers in the same field. Reasons for the exclusion of articles are reported in Supplementary Figure 1 and Supplementary Table 1.

2.2. Data analysis

Two different tools were used for analysis. The Bibliometrix R package (4.0.0)(Aria and Cuccurullo, 2017) was used to obtain information on authors and journals. CiteSpace is a Java application used for scientometrics. We used CiteSpace (6.1. R2)(Chen, 2006) to retrieve co-cited networks using reference, authors, institutions and countries, and co-occurrence networks with keywords as units of measures.

The citation count is the number of direct citations of a publication. Co-citation analysis extracts pairs of papers that are cited together in a source article (Small, 1973), and co-occurrence networks are the counting of paired data within a collection unit. Different metrics are used in CiteSpace to generate network analyses, with structural (betweenness centrality, modularity, silhouette score) and temporal metrics (citation burstness) as a combination of both (sigma metrics). Betweenness centrality quantifies the number of times a node acts as a bridge along the shortest path between two other nodes (Freeman, 1977). Nodes with the highest centrality tend to be at the center of networks. The modularity score (Q) is a measure of the structure of a graph, measuring the density of connections within a module or community. The Q score ranges from 0 to + 1. For Q values greater than 0.3, the cluster structure is considered significant, and higher values indicate a well-structured network. The silhouette score (S) is a metric used to calculate the goodness of a clustering technique (Rousseeuw, 1987). S scores range from -1 to +1. If the silhouette score exceeds 0.3, 0.5, or 0.7, the network is considered homogenous, reasonable, or highly credible, respectively. The generated clusters are labeled by CiteSpace based on noun phrases of the keyword lists of articles using the likelihood ratio test (p < 0.001).

Burstness is the intermittent increase and decrease in activity or frequency of an event over a specific time period. The retrieved dataset can thereby be reduced if CiteSpace detects specific time slicing by excluding empty intervals. Finally, Sigma is a metric of CiteSpace that combines burstness and betweenness centrality: (centrality +1)^{burstness} (Chen, 2006). The sigma metric estimates the influence of a node, with higher scores indicating higher influence. We report CiteSpace parameters in Supplementary Information 1.

3. Results

3.1. Analysis of publication outputs and growth trend prediction

We retrieved 47,681 documents, encompassing 987,979 references from 3,383 sources (e.g., books, journals) published between 1910 and 2022.

The earliest paper identified was an experimental study published in 1911 that examined the effect of mechanical stimulation of the vagus nerve (Robinson and Draper, 1911).

The annual scientific production only started to grow in 1990 (n = 22 per year), with exponential growth (average growth rate per year of 18.34%) reaching a peak in 2021 (n = 4069) (Supplementary Figure 2). We identified 116,310 authors with an average of 5.72 co-authors per document. The average citation per document per year was 0.6 in 1990 and increased exponentially, reaching a peak in 2014 (4.7). The average citation per document y Figure 3).

4. Analysis of clusters of research

4.1. Co-cited reference network (1990-2022)

We retrieved a co-cited reference network that gathered landmark references and clusters of research (Fig. 1). CiteSpace slicing reduced the 1901–2022 time frame to 1990–2022, excluding empty citation intervals. This co-cited reference network (1990–2022) gathered 22 clusters describing a two-tailed comet with two major trends of research on NIBS and IBS. The modularity score was significant (Q=0.842), and the mean weighted silhouette score (S=0.928) suggested highly credible clusters.

The first and oldest major trend on 'noninvasive brain stimulation' included four minor trends: ECT (clusters #12, #19, #23, #28), TMS (#1, #4, #5, #7, #14, #18, #24), transcranial direct current stimulation (tDCS) (#2, #0) and transcranial alternating current stimulation (tACS) (#13). The second major trend concerned 'invasive brain stimulation', with a trend regarding 'DBS' for Parkinson disease (#3, #6, #9, #10, #16) and various psychiatric and neurological conditions (#11, #17, #20), in parallel to a weaker trend regarding 'VNS' (#15, #8). In the last decade, both major trends of research fused into clusters that focused on evidence synthesis (#0, #4, #10, and #19). Finally, the network time map revealed that the most recently active clusters are clusters #0, #4, #6, #8, and #19 (Supplementary Figure 4).

We subsequently detail the cluster numbers, labels, cluster silhouette score (S), size (N), and mean year (Y) of co-cited articles and the articles with the highest betweenness centrality. The NIBS trend started with a relatively isolated, minor trend on ECT, with cluster #12 'ECT' (1; 74; 1993)(Sackeim, 1994), which evolved into cluster #28 'ECT/depression' (0.997;7; 1999)(Prudic et al., 1996), highlighting the efficacy of ECT for depression. This was followed by a focus on the combination of ECT with antidepressant effects of NMDA antagonists for treatment-resistant depression (TRD) #23 'ECT/ketamine' (0.997;19;2015)(Li et al., 2010), and more recently, evidence synthesis on ECT #19 'ECT/depression/evidence synthesis (0.997; 42; 2019) (Joshi et al., 2016).

The second minor trend concerned rTMS, with a similar initial focus on depression as shown in cluster #18 'NMDAr/depression' (0.998; 49; 1994)(Bliss and Collingridge, 1993), TMS mechanisms of action with #1 'TMS' (0.969; 347; 1995)(Ziemann et al., 1996), and #7 'rTMS/TRD' (0.968; 187; 2000)(Pascual-Leone et al., 1996). Exploration of rTMS application continued with #5 'rTMS/theta burst stimulation (TBS)' (0.889; 246; 2007)(Huang et al., 2005), #14 'rTMS/neuropathic pain' (0.983; 64; 2011)(Lefaucheur et al., 2014), and more recent applications, e.g., in neurosurgery #24 'preoperative nTMS/cortical mapping' (0.998; 18; 2015)(Picht et al., 2013).

The 'noninvasive brain stimulation' trend continued with two minor trends. First, tDCS with #2 'tDCS' (0.99; 326; 2010)(Nitsche et al., 2008), with the largest cluster of the network, cluster #0 'tDCS/DBS evidence synthesis' (0.882; 428; 2017)(Nitsche and Paulus, 2000), and tACS, #13 'tACS' (0.982; 68; 2015)(Helfrich et al., 2014).

The second major trend, 'invasive brain stimulation', mainly concerned the use of DBS for Parkinson's disease, with DBS of the subthalamic nucleus, cluster #3 'DBS/Parkinson's disease' (0.956; 269; 2002)(Krack et al., 2003), which continued with cluster #16 (0.972; 57; 2009)(Gradinaru et al., 2009) on the neuropathophysiology of Parkinson's disease, and several randomized controlled trials (RCTs) with #9 (0.911; 158; 2011)(Schuepbach et al., 2013). More recently, research on the use of DBS for Parkinson's disease has been very dynamic, with #6 'DBS/Parkinson disease/Magnetic innovative options Resonance-guided focused Ultrasound Surgery (MRgFUs) thalamotomy' (0.915; 226; 2018)(Horn et al., 2017). DBS has also been used for treatment-resistant depression (TRD), cluster #11 'DBS/TRD' (0.959; 125; 2000)(Mayberg et al., 2005), and for different psychiatric and neurological conditions, such as #20 'DBS/cluster headache' (0.993; 40; 2004)(Schoenen et al., 2005) and #17 'DBS/dystonia' (0.974; 52; 2006)

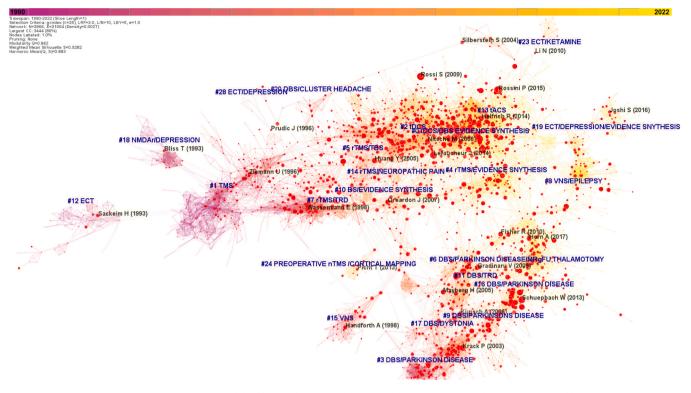


Fig. 1. Co-citation references network (1990–2022) with highlight of burstness obtained with CiteSpace. Each node represent one highly co-cited article. Nodes are organized in different clusters gathered into a network of co-citation. Nodes trims and links colors are adjusted to the average year of burst, according to a range of colors from violet (1990) to yellow (2022). The size of a node is proportional to the co-citation count. Nodes with important burstness are represented with central red dots, which diameters is proportional to the degree of burstness.

(Kupsch et al., 2006). A second and minor trend was observed regarding VNS with cluster #15 (0.996; 62; 2000)(Handforth et al., 1998) and, recently, drug-resistant partial epilepsy #8 'VNS/epilepsy' (0.965; 165; 2018)(Salanova et al., 2015).

4.2. Co-cited reference network (2020–2022)

To further explore the latest research trends, we retrieved the reference networks from the last two years with monthly slices (2020–2022) (Supplementary Figure 5). The modularity score was significant, and the mean weighted silhouette suggested highly credible clusters (Q=0.635; S=0.871). Previous clusters on evidence synthesis were detected (clusters #0, #1, #2, #4, #5, and #6); however, more specific applications of VNS have been found, such as cluster #3 'transcutaneous auricular VNS (taVNS)' (0.956; 269; 2020)(Frangos et al., 2015), and novel small clusters delignating new frontiers to brain stimulation research were also identified, such as cluster #13 'DBS/e-pilepsy pediatric population' (0.985; 26; 2020)(Kapural et al., 2016), and cluster #10 'brain-machine interface' (0.998; 25; 2020)(Musk, 2019).

4.3. Most highly cited papers

The most cited articles according to our datasets are reported in Table 1. The three most cited papers were the Nitsche and Paulus (2000) clinical trial on excitability changes with tDCS (Nitsche and Paulus, 2000) and two clinical guidelines on the use of NIBS techniques, namely, Rossi et al. (2009) and Rossini et al. (2015) guidelines for rTMS (Rossi et al., 2009; Rossini et al., 2015). The burstness analysis proposed that for the 2020–2022 time period, the three papers with the latest and most important strength of burst were Lefaucheur, ' et al. (2014) evidence-based guidelines, Ashkan and colleagues' 2017 review on the mechanisms of DBS (Ashkan et al., 2017), and Lozano and colleagues'

review on the future direction of DBS (Lozano et al., 2019) (Table 1).

We conducted a structural variation analysis for the 2020–2022 time period focused on novel boundary-spanning connections to detect the best candidates for transformative papers (Supplementary Table 3). The three papers with the most transformative potential for the 2020–2022 network were the Rossi et al. (2021) safety and recommendations guidelines for TMS (Rossi et al., 2021), the Fregni and colleagues 2021 evidence-based guidelines on tDCS for neurological and psychiatric disorders (Fregni et al., 2021), and the Krauss and colleague review on future directions of DBS (Krauss et al., 2021).

4.4. Co-occurring authors' keyword networks

Co-occurring keywords can inform the latest trends and possibly future directions of research. We retrieved the co-occurring author's keyword networks of the last five years (2016–2022) (Fig. 2). The network presented a significant modularity score (Q=0.4738) and a highly credible weighted mean silhouette score (S=0.7193). Nine different clusters were identified: #0 'TMS' (0.695; 203; 2016), #1 'functional connectivity' (0.628; 197; 2017), #2 'DBS' (0.695; 203; 2016), #3 'microglia' (0.695; 203; 2016), #4 'ECT' (0.695; 203; 2016), #5 'VNS' (0.695; 203; 2016), #6 'spinal cord stimulation' (0.695; 203; 2016), #7 'diffusion tensor imaging' (0.695; 203; 2016), and #8 'cochlear implant' (0.695; 203; 2016). Clusters #3, #4 and #7 were less active in 2022 than other clusters. The burstness analysis proposed among the keywords with the most recent and strongest bursts of cooccurrence was 'machine learning', 'deep learning', 'neural network', 'TTMS' and 'ECT' (Supplementary Table 2).

4.5. Analysis of cooperation across countries and institutions and growth trend prediction

A total of 135 countries were identified. The three countries

Table 1

The top 10 most co-cited references.

Number of citations in the network/ Number of citations in the literature ^a	Source	Vol	Page	Title	Doi	Type of study	Related cluster in Fig. 1
950/5367	J Physiol.	15	633–9	Nitsche and Paulus (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation	10.1111/ j.1469–7793.2000. t01–1–00633.x	Clinical trial	#0
611/1983	Clin Neurophysiol	89	1071–1107	Rossini et al. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee	10.1016/j. clinph.2015.02.001	Guidelines	#4
534/4893	Clin Neurophysiol	120	2008–89	Rossi et al. (2009). The Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research	10.1016/j. clinph.2009.08.016	Guidelines	#4
452/1924	Clin Neurophysiol	125	2150-2206	Lefaucheur et al. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)	10.1016/j. clinph.2014.05.021	Guidelines	#14
446/1252	Clin Neurophysiol	128	56–92	Lefaucheur et al. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)	10.1016/j. clinph.2016.10.087	Guidelines	#0
339/1076	Clin Neurophysiol	127	1031–1048	Woods et al. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools	10.1016/j. clinph.2015.11.012	Guidelines	#0
339/1048	Brain Stimul	9	641–661	Bikson et al. (2016). Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016	10.1016/j. brs.2016.06.004	Guidelines	#0
263/1228	N Engl J Med	368	610–22	Schuepbach et al. (2013). Neurostimulation for Parkinson's disease with early motor complications	10.1056/ NEJMoa1205158	RCT	#9
262/760	Clin Neurophysiol	128	1774–1809	Antal et al. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines	10.1016/j. clinph.2017.06.001	Guidelines	#0
235/1451	Brain Stimul	5	175–195	Brunoni et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions	10.1016/j. brs.2011.03.002	Review	#4
226/1655	JAMA	301	63–73	Weaver et al. (2009). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial	10.1001/jama.2008.929	RCT	#9
222/935	J Physiol	59	1987–2000	Batsikadze et al. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans	10.1113/ jphysiol.2012.249730	Clinical trial	#0

^a Number of citations in the literature in December 2022 according to the journal where the paper was published

associated with the highest number of citations were the USA (n = 15,216), Germany (n = 5895) and the UK (N = 4415). The co-cited author's country network can inform the international collaborative network. We retrieved the 1990–2022 co-cited author's country network (Fig. 3. A). The USA is the country with the most important betweenness centrality (0.99); however, the sum of the European countries followed up to fifth place with the United Kingdom (0.23), Italy (0.22), Spain (0.20), Germany (0.18) and France (0.16). China was only in fifth place of citation counts (n = 3692); nevertheless, these citations mostly occurred since 2019 with an outstanding citation burst strength (356.86) (Supplementary Table 4). The burstness analysis revealed the start of this in the USA beginning in 1990, i.e., This is the country with the oldest citation burst.

For institutions, 645 different institutions were identified. The three most cited institutions were Harvard University (n = 1882), University of California (n = 1667), and University of Toronto (n = 1472). We focused on the last five-year collaborative networks to retrieve the most recent dynamics. We therefore retrieved the 2016–2022 co-cited authors' institutions network (Fig. 3. B) that presented a significant modularity score (Q=0.4) and a highly credible mean weighted silhouette score (n = 0.786). Eight different clusters were identified. The largest cluster was USA network #0. Although being the fifth largest cluster, Chinese network #5 was placed relatively outside of the European and American collaborative networks. The top three institutions

with the greatest centrality scores were Harvard University (167.09; 1998), the National Institute of Neurological Disorders and Stroke (52.19; 1991), and the National Institute of Mental Health (4.13; 1994) (Supplementary Table 4). The burstness analysis revealed that the three institutions with the latest strength of burst were Nagoya University (8.47; 2020), Nantong University (8.15; 2020) and Sorbonne University (8.15; 2020) (Supplementary Table 2).

4.6. Analysis of co-authorship networks

A total of 116,310 authors with a mean of 5.72 co-authors per article were found in our dataset. The co-authorship network connects authors that share the authorship of a paper, informing the individual's body of research and the global collaborative network. We extracted the co-author collaborative network of the last five years (2016–2022) (Supplementary Figure 6). The modularity score was significant (Q=0.747), and the weighted mean silhouette score indicated highly credible clusters (S=0.928). Nineteen different clusters were regrouped in a single network, gathering co-authors around the same topic of research, such as cluster # 'functional connectivity', which gathers mostly Chinese authors, and #2 'Parkinson disease' with European and American researchers.

The burstness analysis indicated that the three co-authors with the most recent and important strength of burst were Zhang Chencheng

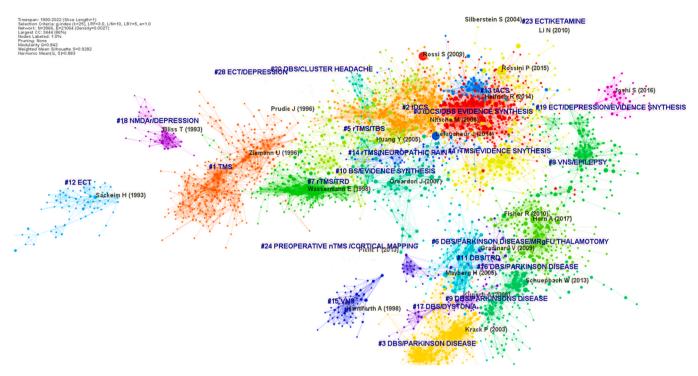


Fig. 2. Co-citation references network (1990–2022) with highlight of clusters obtained with CiteSpace. The two major research trends are delimited with distinct colors, orange for 'non-invasive brain stimulation' trend, green for the 'invasive brain stimulation' trend. The position of the node (article) corresponds to the year of publication. The size of a node is proportional to the number of times the node has been co-cited. For each cluster, a single color is attributed.

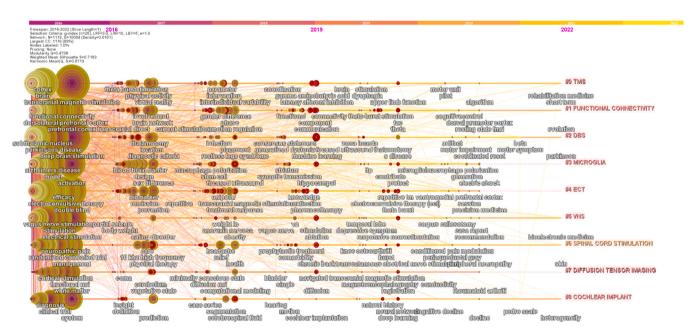


Fig. 3. Timeline visualization of co-occurring author's keywords networks (2016–2021). Each node refers to a highly co-occurring keywords. Nodes diameters and links thickness are proportional to the burstness of keywords co-occurrence. Each retrieved cluster gathers node on different horizontal time lines according to the mean year of co-occurrence.

(9.53; 2020; DBS), Sun Bo-Min (8.55: 2020; stereotactic neurosurgery), and Wang Qiang (7.68; 2020; neuromodulation techniques).

4.7. Analysis of co-cited journals

We found 2792 journals in our dataset. The three journals with the most important and most recent growth of publications were Clinical Neurophysiology (n = 927), Brain Stimulation (n = 875), and Journal of ECT (n = 829) (Supplementary Figure 7). Furthermore, the journals

with the most citations were Neurology (n = 18,740), Journal of Neuroscience (n = 18,108), and Brain (n = 18,071). The author's journal co-citation network can inform on the most suitable journals for publication. This network (1990–2022) presented significant modularity (Q=0.6649) and a highly credible silhouette score (S=0.8341) and gathered 11 clusters (Supplementary Figure 8). The most central and largest cluster was cluster #0 'brain stimulation journals', which gathered impactful neurology journals. Smaller clusters were also emerging on novel topics, cluster #10 'biomedical engineering journals' and #11

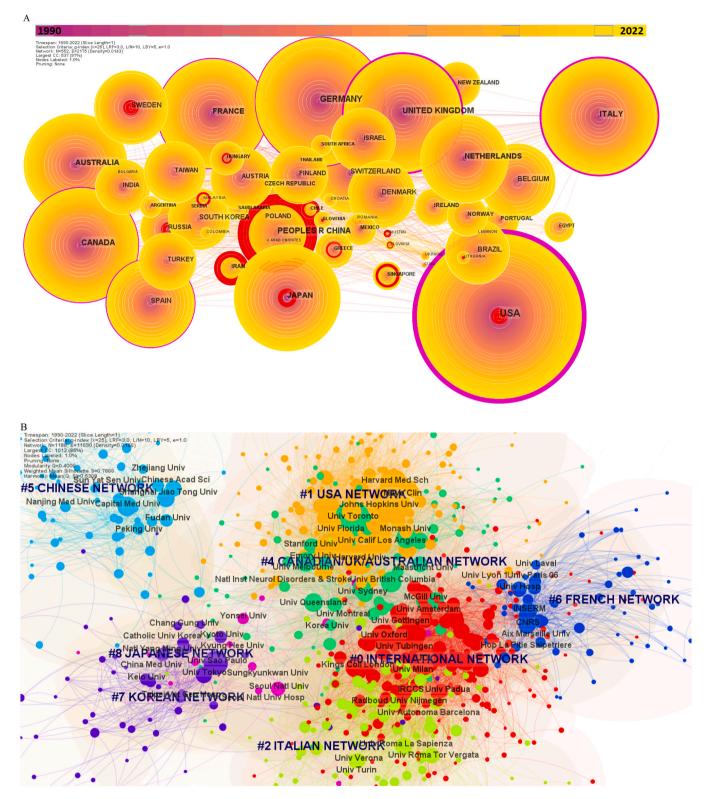


Fig. 4. Network of co-authors' countries with highlight of burstness (1990–2022) (A) and co-authors' institutions network with highlight of the cluster (1990–2022).

'computer science journals'.

The burstness analysis revealed that the three journals presenting the most recent strength bursts were Scientific Reports (908; 2019), Frontiers in Neuroscience (568.23; 2019), and Frontiers in Neurology (421.7; 2019).

5. Discussion

This comprehensive scientometric analysis included 47,681 documents, encompassing almost a million references that were published over the past century and mainly in the last 30 years. This broad synthesis allowed us to retrace the history of research on neuromodulation techniques and uncover the most influential research trends. Furthermore, the most prominent papers, journals, and authors were identified, which can also be used in grant proposals and inform policy-makers and funding agencies.

5.1. Research trend dynamics, future of research

The co-cited reference network exposes a gradual deployment of clusters that follows the different degrees of maturity and body of evidence. ECT has been studied since the 1940 s and formed the first identified cluster (#12). TMS was developed in the 1980 s (#1), whereas modern methods of tES (tACS and tDCS) were developed after 2000 (#2, #13). However, new variants of these techniques, such as theta-burst stimulation and tACS, were only clinically investigated in the 2010 s (#0). The same pattern is found for invasive neuromodulation with VNS (#15) to DBS (#16). Of note, both ECT and VNS present a renewed interest with newly formed clusters (#8 'VNS/epilepsy', #23 'ECT/ketamine'). Furthermore, as found in many scientometric studies conducted in psychiatry (Cortese et al., 2022; Sabe et al., 2022), networks are marked by similar patterns reflecting the development of distinct research fields: neuroimaging between 1990, evidence synthesis by 2000, and more recently with innovative research methods (e.g., machine learning, deep learning). Of note, the two major research trends on invasive and NIBS start to converge by 2010, which might lead to more translational research.

The latest research trends focus on very specific and innovative applications of neurostimulation, with taVNS, that could potentially be combined with ear-EEG to modulate attention as a closed-loop portable NIBS (Ruhnau and Zaehle, 2021). Moreover, DBS application for epilepsy in pediatric populations might represent a breakthrough in improving access to treatment options for this specific population. In addition, the detection of a cluster on spinal cord stimulation – although this technique has existed for more than 30 years for brain stimulation – indicates the maturation of evidence with the recent conduction of several RCTs on chronic pain (Deer et al., 2018).

One final cluster holds many promise for the use of brain-machine interfaces to restore sensory and motor function, with a focus on scalability and miniaturization (Musk, 2019)(e.g., nanoelectronic probes for glial scar–free neural integration).

5.2. Clinical relevance of neuromodulation interventions and public mental health policies

The significant growth of evidence synthesis contributed to the generation of hallmark papers that impulse research and layout public mental health policies. Although the initial history of ECT is very controversial, it was the first neurostimulation intervention to receive US Food and Drug Administration (FDA) approval in 1976 on the basis of long-standing prior experience. ECT presents significant effects on resistant and disabling forms of depression and schizophrenia supported by extensive scientific data (Prudic et al., 1996) but has also greatly benefited thousands of patients with severe forms of other conditions. Consistent with these findings, ECT currently holds the highest popularity and expectation index among neuromodulation interventions (Tran et al., 2019). Similarly, DBS sparked controversy during its development in the late 1980 s by Alim Benabid (Oliveria, 2018) and was the second intervention to receive approval from the FDA in 1996. DBS approved for essential tremor and severe tremor in Parkinson's disease (FDA, 1997) followed approval for advanced forms of Parkinson's disease in 2002 (FDA, 2002a) and for refractory focal epilepsy in 2017 (FDA, 2018a). The 2002 DBS approval for the treatment of Parkinson's disease was a pivotal point in its large and rapid adoption. Nevertheless, DBS is only available to a small number of patients with refractory/resistant diseases. Thousands of patients benefited from rTMS approval in 2008 as a treatment to alleviate symptoms of mildly treatment-resistant depression, and in 2018 (McClintock et al., 2018), rTMS was further approved for obsessive-compulsive disorder (FDA,

2022). More recently, RCTs have been conducted to evaluate and define home-based tDCS for major depressive disorder (Cappon et al., 2021), as tDCS still needs to be regulated and approved in clinical practice based on adequate RCTs. Other promising neuromodulation interventions have recently been approved as the Stanford Accelerated Intelligent Neuromodulation Therapy (Cole et al., 2020).

5.3. Maturity and body of evidence

Although the two major research trends on invasive and NIBS start to converge by 2010 with a particular focus on evidence synthesis, the most co-cited articles mainly focus on guideline papers for the major trend on NIBS and more on RCTs for DBS, reflecting distinct maturity and a body of evidence (Table 1). Indeed, while the development of evidence has greatly improved in recent decades, with numerous RCTs being conducted and several of these techniques being approved and/or showing level A evidence (Table 2), the level of evidence differs for each neuromodulation intervention and for each mental disorder. For instance, there is a stronger evidence base for treating resistant depression with rTMS than for treating resistant hallucinations in schizophrenia. Furthermore, although we have several RCTs for specific populations, the selection criteria used by the authors vary across studies. Of note, most individual studies included small sample sizes and are underpowered. Moreover, for most neuromodulation interventions, there is no solid consensus regarding optimal stimulation parameters, cumulative doses, and even neural targets for some disorders. These

Table 2

FDA approval of neurostimulation interventions.

Year	Neurostimulation interventions	FDA approval or current evaluation
IBS		
1996	DBS	VIM-DBS for essential tremor and severe
		tremor in PD (FDA, 1996)
1997	VNS	Adjunctive therapy in reducing the frequency
		of seizure in pharmaco-resistant epilepsy (FDA, 2017)
2002	DBS	DBS for dystonia and treatment of advanced PD (FDA, 2002b)
2005	VNS	VNS for resistant depression
2024	DBS	Possible future evaluation of DBS for refractory
(?)		depression
NIBS		
1976	ECT	Regulated through "the premarket notification" as an intermediate and low risk device (USC, 1976)
2008	rTMS	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode (Demitrack et al., 2010)
2013	rTMS	Treatment of chronic pain and migraine
2015	Deep TMS	For treatment-resistant depression and MDD (
2010	beep mie	Levkovitz et al., 2015)
2018	ECT	Reclassification of ECT devices, for use in
		treating catatonia or a severe major depressive
		episode (MDE) associated with major
		depressive disorder (MDD) or bipolar disorder
		(BPD) in patients age 13 years and older who
		are treatment-resistant or who require a rapid
		response due to the severity of their psychiatric
2018	Deen TMC	or medical condition (FDA, 2018b) Treatment of OCD (FDA, 2018c)
2018	Deep TMS TBS	TBS for the treatment of MDD (FDA, 2018c)
2018	Deep TMS	Treatment of smoking addiction (Zangen et al.,
2020	Deep TWB	2021)
2022	iTBS	Stanford Accelerated Intelligent
		Neuromodulation Therapy (SAINT TM
		neuromodulation system) for MDD (Cole et al., 2020)
2024	tDCS	Future evaluation of define home-based tDCS
(?)		for major depressive disorder

limitations raise important conceptual questions. For example, should clinical relevance estimation be based on changes in clinical scales, and how large should a change be to be considered clinically meaningful? Moreover, the mechanism of action of neuromodulation interventions is to modify neuronal plasticity, connectivity and networks; therefore, specific symptoms (e.g., hallucinations, impulsivity, apathy) could be more appropriate therapeutic targets than diagnostic categories (Tracy and David, 2015). To address these concerns, various techniques are used to evaluate the impact of neuromodulations interventions, such as the functional near-infrared spectroscopy (Husain et al., 2020) or machine-learning (Li et al., 2022). Furthermore, ongoing research is focused on identifying the neuroanatomical substrates to optimize clinical responses (Elias et al., 2020).

These questions are pertinent, considering that although these interventions have proven to be effective in the short term across multiple mental disorders and on multiple outcomes (Hyde et al., 2022; Rosson et al., 2022), the effect sizes obtained, the duration of effects, the replication, and the reliability of various techniques are still limited (Terranova et al., 2019). As such, the application of rTMS requires considerable expertise; however, most considered studies have not used MRI-based neuronavigation. More high-quality RCTs with clear inclusion criteria, including arms with different stimulation parameters, could improve the level of evidence. For neuromodulation interventions other than rTMS, the level of evidence is even thinner or stimulates intense debate, such as with ECTs, which need more high-quality RCTs, although the comparison of ECTs to placebo is not appropriate (CADTH, 2015; Meechan et al., 2022). Although the current evidence base is weak, important hopes lie in tDCS research, which is less expensive than rTMS and easy to apply (Fregni et al., 2021). Finally, evidence is still sparse regarding VNS and trigeminal nerve stimulation for depression, with mostly open unmasked trials being conducted thus far.

Another important aspect of clinical practice is the cost-effectiveness of these interventions for patients with treatment-refractory conditions (McLoughlin et al., 2007; Zemplényi et al., 2022; Zhao et al., 2018). For instance, DBS is seen as a cost-effective treatment strategy for advanced PD (Pietzsch et al., 2016) but not necessarily for depression (Widge et al., 2018). Nevertheless, these interventions remain highly expensive and are still mostly only accessible in Western countries and are very poorly covered by health insurance. The financial burden and fear of adverse effects are the main key reasons to limit the use of neurostimulation interventions.

6. Limitations

Different limitations impact this scientometric analysis. The most important limitation is linked to the nature of gathered data, from only one database, WOSCC. Indeed, for most databases, full text and citation analyses are not available. Furthermore, the combination of different databases is currently not possible considering digital object identifier errors between databases, which affect the accuracy of determined coverage differences (Pranckute, 2021).

Moreover, the use of citation-related indicators in scientometric analysis can be a potential source of different biases, such as citation bias, where the probability of being cited depends on the outcome of a study (Jannot et al., 2013). Another frequent bias is citation distortions, where unfounded authority can emerge due to distorted social citations with important co-citation, establishing unfounded scientific claims as fact (Greenberg, 2009). Although a retrieved network can deliver an accurate picture of a research network, different limitations must be acknowledged, such as the limitation of most co-cited articles in the co-citation network. Another limitation related to our own field of research is that papers on DBS trends might be less likely to be co-cited, with a more limited amount of publication compared to the NIBS trend, in particular, due to ethical issues in DBS treatment and research (Muñoz et al., 2020). the fact that citations of a publication typically peak from one to three years after the publication, the most recent impacting papers or trends could have been missed.

7. Conclusion

The field of neuromodulation interventions is rapidly expanding and remains controversial, somewhere between hopes for innovative therapies to alleviate treatment-refractory symptoms and the reality of adverse effects and financial burden of some interventions. This scientometric analysis produced a snapshot of the history of research on neuromodulation interventions, the current knowledge domains and the latest emerging trends. In the last decade, the two major research trends identified on NIBS and IBS share citations, and the potential future research trends concern specific and innovative applications of neurostimulation, such as taVNS, DBS application in a pediatric population, spinal cord stimulation, and brain-machine interface. Despite these preliminary findings of some interventions being promising, the current evidence base is still heterogeneous. In clinical practice, the approval process by the FDA remains dawdled on evidence-based proofs, and ethical and legal concerns persist with regard to potential misuse or overuse. This work may be useful for determining future research topics that can be integrated into grant proposals.

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CRediT authorship contribution statement

Conceptualization: Michel Sabe and Marco Solmi. Methodology: Michel Sabe, Chaomei Chen and Marco Solmi. Formal analysis and Investigation: Michel Sabe, Chaomei Chen and Marco Solmi. Writing – original draft: Michel Sabe. Writing – review and editing: Chaomei Chen, Adi Sulstarova, Joshua Hyde, Emmanuel Poulet, André Aleman, Jonathan Downar, Valerie Brandt, Luc Mallet, Othman Sentissi, Michael A. Nitsche, Marom Bikson, André Russowsky Brunoni, Cortese Samuele, Marco Solmi. Supervision: Marco Solmi & Chaomei Chen.

Declaration of Competing Interest

Marco Solmi has received honoraria/has been a consultant for Abbvie, Angelini, Lundbeck and Otsuka. Michael A. Nitsche is a member of the scientific advisory board of Neuroelectrics. Andre R Brunoni holds a small equity of FlowNeuroscience and has been scientific advisor of the company between 2016 and 2018. He also receives research grants from the São Paulo Research State Foundation (19/06009–6) and the Academy of Medical Sciences (NAFR 12/1010) and in-kind support from MagVenture and SoterixMedical. Othman Sentissi has received advisory board honoraria from Otsuka, Lilly, Lundbeck, Sandoz, and Janssen in an institutional account for research and teaching. André Aleman, Luc Mallet, Jonathan Downar, Marom Bikson, Valerie Brandt, Chaomei Chen, Adi Sulstarova, Emmanuel Poulet, Joshua Hyde, Samuele Cortese and Michel Sabe report no conflicts of interest.

Data Availability

The data used in the analyses of this manuscript are available upon request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105300.

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