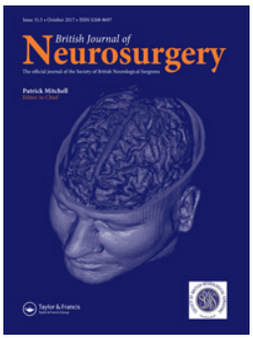

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ORIGINAL ARTICLE

Bibliometric profile of deep brain stimulation

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ABSTRACT

Objective: We aimed to identify and analyze the characteristics of the 100 most highly-cited papers in the research field of deep brain stimulation (DBS).

Methods: The Web of Science was searched for highly-cited papers related to DBS research. The number of citations, countries, institutions of origin, year of publication, and research area were noted and analyzed.

Results: The 100 most highly-cited articles had a mean of 304.15 citations. These accrued an average of 25.39 citations a year. The most represented target by far was the subthalamic nucleus (STN). These articles were published in 46 high-impact journals, with *Brain* ($n = 10$) topping the list. These articles came from 11 countries, with the USA contributing the most highly-cited articles ($n = 29$); however, it was the University of Toronto ($n = 13$) in Canada that was the institution with the most highly-cited studies.

Conclusions: This study identified the 100 most highly-cited studies and highlighted a historical perspective on the progress in the field of DBS. These findings allow for the recognition of the most influential reports and provide useful information that can indicate areas requiring further investigation.

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Bibliometrics; citation; analysis; deep; brain stimulation; stimulation targets; Parkinson's disease

Deep brain stimulation (DBS) is a neurosurgical procedure that was first described in the 1950s[1] and over the next few decades neurosurgeons tried to explore the possible therapeutic value of electrode implantation with chronic recording and stimulation in a small number of patients for numerous indications.[2] The modern era of therapeutic DBS, however, was heralded by the team of Benabid, Pollak and their colleagues in a 1987 report.[3] Over the past several decades, with the approval of the United States Food and Drug Administration (FDA), DBS has become the major growth area for the treatment of severe Parkinson's disease, essential tremor, dystonia and obsessive-compulsive disorder.[4,5] Although these applications are not yet FDA-approved, recent interest has begun to focus on the clinical application of DBS to other psychiatric and affective disorders, particularly post-traumatic stress disorder and depression, as well as epilepsy.[6–8] The exact mechanism of action of DBS remains uncertain, but the use of this technique for an increasing number of disorders has brought dramatic and lasting benefits to patients.[9]

The Institute for Scientific Information (ISI) initiated "Science Citations" as a systematic approach to evaluate the impact of scientific journals or researchers according to the number of times the work has been cited.[10] This type of analysis has been applied to the literature of various specialties and research areas.[11–15] In addition, several journals publish their own journal citation classics.[16,17] In the field of neurosurgery, an analysis of highly-cited papers dealing with functional and stereotactic neurosurgery,[18] traumatic brain injury,[19] aneurysmal subarachnoid hemorrhage,[20] and skull base procedure[21] have all been studied. Little is currently known, however, about the most frequently cited articles that are specifically related to DBS research. Therefore, the purpose of this study was to identify the 100 most highly-cited articles pertaining to DBS and related research, in an effort to reveal important contributions to the literature in this promising field.

Materials and methods

Thomson Reuter's Web of Science was queried through the Harvard Library Portal, on one specific day, June 30th, 2016, to minimize changes in citation number as much as possible, for all articles relating to DBS. Different combination of the words "DBS", "deep brain stimulation", "intracranial", "subcortical", "electrostimulator", "neurostimulator", "neuropacemaker", "brain pacemaker", "depth lead implantation" and "stimulator generator" were used and results were ranked by the number of citations. The term "cortical lead implantation" was also used as a search term in order to exclude papers dealing with implantation of neurostimulators in the cortex. Whenever possible, the full texts of these reports were mainly obtained by PubMed, EMBASE, and Medline. When full-text articles were not available, online abstracts were relied upon.

Data inclusion criteria were: (a) peer-reviewed articles on DBS research published and indexed in the Web of Science; (b) type of article: original research articles and review articles. Exclusion criteria were: (a) patents, books, manuals and non-biomedical publications, conference abstracts and case reports; (b) articles focusing on specific diseases, regardless of whether they mentioned DBS as a potential treatment.

The 100 most highly-cited articles were then identified based on the number of citations. Owing to differences in

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Supplemental data for this article can be accessed here.

Table 1. The top 10 of 100 most highly-cited DBS articles.

Rank	Title	Corresponding Author	Country	Year	Journal	Total citation	Annual citation
1	Deep brain stimulation for treatment-resistant depression	Mayberg HS & Lozano AM	Canada	2005	NEURON	1408	117.33
2	Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease	Krack P	France	2003	NEW ENGLAND JOURNAL OF MEDICINE	1061	75.79
3	Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus	Pollak P	France	1991	THE LANCET	863	33.19
4	A randomized trial of deep-brain stimulation for Parkinson's disease	Deuschl G	German	2006	NEW ENGLAND JOURNAL OF MEDICINE	847	77
5	Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease	Obeso JA	Spain	2001	NEW ENGLAND JOURNAL OF MEDICINE	813	50.81
6	Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders	Benabid AL	France	1996	JOURNAL OF NEUROSURGERY	659	31.38
7	Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up	Obeso JA	Spain	2005	BRAIN	497	41.42
8	A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor	Speelman JD	Netherland	2000	NEW ENGLAND JOURNAL OF MEDICINE	492	28.94
9	Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease A Randomized Controlled Trial	Weaver FM	USA	2009	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	460	57.5
10	Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons	Vitek JL	USA	2003	JOURNAL OF NEUROSCIENCE	445	31.79

time since publication, annual citations rates were also defined. Articles were selected by reading the abstract to gauge whether they were related to DBS, and the following data were abstracted from each article that met our criteria: title, year of publication, last corresponding author and his/her first institution, country of origin, journal name, number of citations, type of study, research topic and keywords of study. Statistical analysis was performed using R version 3.2.3 (Wooden Christmas-Tree). Mean and standard error (SE) were used for citations comparison, significant differences were identified using a non-parametric ANOVA analysis with an alpha level of 0.05. CiteSpace v4.0 was used to visualize the trends and patterns in DBS research.[22–24]

Results

The top 10 most highly-cited articles on DBS research are presented (Table 1), while the full list of the 100 most highly-cited articles are listed in Supplemental Materials (Table S1) in descending order by total number of citations. The 100 papers obtained a mean of 304.15 (SE 19.14) citations per article, with the top one receiving 1408 citations (Mayberg et al., 2005)[25] and the least highly-cited article receiving 168 citations (Vidailhet et al., 2007).[26] Annually, the 100 highly-cited articles received an average of 25.39 (SE 1.62) citations per paper (range, 8.56 to 117.33).

Years of publication

The years of publication in our sample ranged from 1991 to 2013 (Figure 1), with 72 studies having been published between 2000 and 2009, 17 studies before 1999, and 11 after 2010. There was a peak in the number of highly-cited studies after 2002.

Countries of origin and institutions

While the 100 articles originated in 11 different countries (Figure 2), most ($n = 29$) were from the USA, followed by France ($n = 26$), Canada ($n = 14$), Germany ($n = 11$), England ($n = 7$), Netherlands ($n = 3$) and Italy ($n = 3$). Belgium, Spain, and Switzerland each had two highly-cited studies, whereas South Korea contributed one study. Even though we placed no language restrictions on our searches, we found that all 100 studies were published in English-language journals.

These articles originated from 49 universities, hospitals, and clinics. Six institutions were responsible for three or more articles, led by the University of Toronto ($n = 13$). The six research institutions with the most highly-cited articles are listed in Figure 3.

Journal distribution and study field

The top 100 highly-cited articles were published in 46 journals, most appeared in *Brain* ($n = 10$), *followed by Neurology* and *Journal of Neurosurgery* ($n = 9$, each). *New England Journal of Medicine* ($n = 8$) is the highest impact factor journal in the list (Table 2).

Study fields

Of the 100 articles, 19 were review articles, 81 were clinical human studies covering different stimulation sites. Original articles had more average citation numbers (310.52, SE 23.17) than review articles (277.0, SE 19.52), but the difference was not significant ($P = 0.495$). Parkinson's disease (PD) received the most attention, while the subthalamic nucleus (STN) was the most preferred stimulation target (Table 3).

Figure 1. The 100 most highly-cited DBS articles appearing in journals per year.

Figure 2. Distribution of country origin for the 100 most highly-cited DBS research articles.

Keywords of DBS articles that closely cluster to "deep brain stimulation" occur in categories including "subthalamic nucleus", "basal ganglia", "limbic system", "Parkinson disease", "epilepsy" and "intracellular analysis" (Figure 4).

Discussion

DBS is a neuromodulation technique that targets specific structures in the brain. With both technological and conceptual advances, the field of DBS has grown exponentially during the past decade. In 2012, Lipsman and Lozano defined the top 100 highly-cited studies in stereotactic and functional neurosurgery.[18] Of them, 13 studies were specific to DBS, with treatment of movement disorders representing the largest proportion of papers with 31 total studies. In our study, we identified the 100 most highly-cited articles focusing specifically on DBS. Although older publications have more years to accumulate citations and are therefore often overrepresented in top 100 lists, our analysis showed a peak in the number of studies after 2002. In that year, STN and GPi stimulation were approved by the FDA for PD treatment. Apart from FDA approval of thalamic DBS for essential tremor and PD-related tremor in 1997, this 2002 peak correlates well with a major trend in clinical movement disorders treatment practice to refer patients for DBS. This likely accounts for why the 2000s was the most productive period for DBS research.

The country of origin for the papers we identified is most frequently the USA; furthermore, half of the corresponding institutions are located in the USA. While this is similar to other fields of neurosurgery research,[19–21] the dominant position of the USA is less prominent in our list than in other studies. Our list includes a larger proportion (71%) of international articles, reflecting the diversity of countries contributing to DBS research.

Brain, Neurology, and *Journal of Neurosurgery, three high impact journals,* published most of the highly-cited articles. The coverage of these journals spans across neuroscience, neurology,

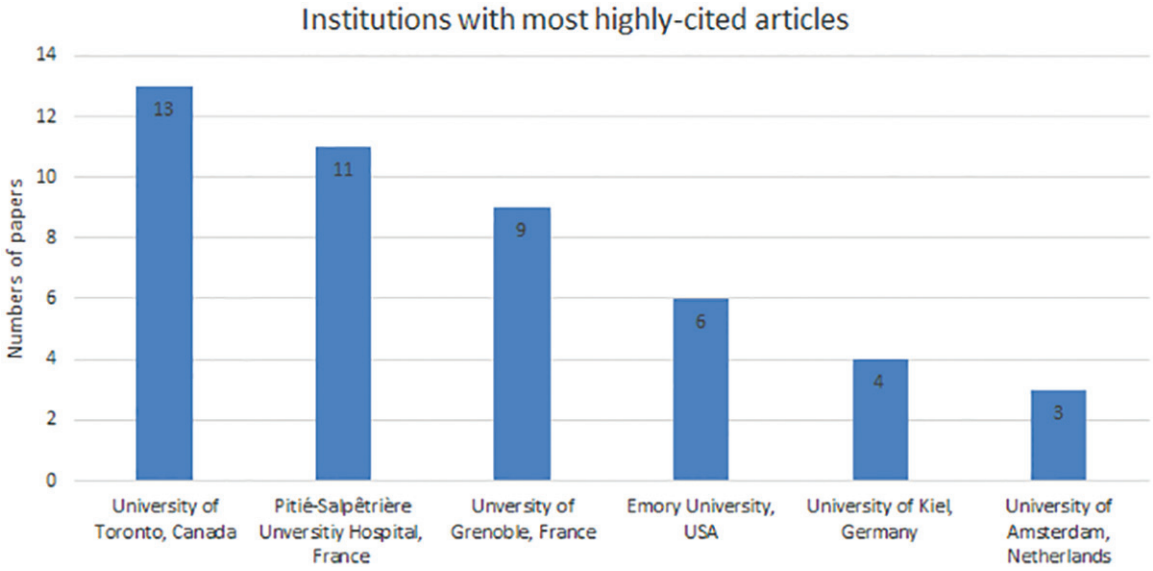

Figure 3. Corresponding institutions (including the affiliated hospitals) contributing the most highly-cited DBS research articles.

Table 2. The journals in which the more than two highly-cited DBS articles were published. The journal impact factor was based on thomson reuters web of knowledge journal citation reports ranking (2015).

Rank	Journal	Num.	IF
1	*BRAIN*	10	9.196
2	*JOURNAL OF NEUROSURGERY*	9	3.737
2	*NEUROLOGY*	9	8.286
4	*NEW ENGLAND JOURNAL OF MEDICINE*	8	55.873
4	*LANCET NEUROLOGY*	8	21.896
6	*ANNALS OF NEUROLOGY*	5	9.977
6	*MOVEMENT DISORDERS*	5	5.68
8	*BIOLOGICAL PSYCHIATRY*	4	10.255
8	*JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY*	4	6.807
10	*EPILEPSIA*	3	4.571
10	*NEUROSURGERY*	3	3.62
10	*ARCHIVES OF NEUROLOGY*	3	7.419

IF: impact factor.

and neurosurgery, and they are also flagship journals in their own specialties, respectively. It is noteworthy that DBS has broad applicability and relevance to multiple disciplines, and neuroscientists, neurologists and neurosurgeons all made great contributions. Furthermore, highly-cited DBS studies tended to cluster in broadly applicable, typically higher impact publications, such as *NEJM* and *Lancet Neurology*.

Our co-word frequency cluster analysis revealed that the areas of most interest in the field of DBS are PD and its related stimulation targets including STN, basal ganglia, and the limbic system. As the primary clinical use of DBS has been PD, the work related to PD made up the vast majority of cited studies ($n = 45$). Advanced PD has become the best studied and most common indication for DBS and a variety of targets have been utilized. Of the 45 studies, 38 related to STN stimulation and 14 related to GPi, which confirms that these areas are the two most common targets for DBS, both of which are components of the cortico-basal ganglia-thalamo-cortical loop.[27] Stimulation of these sites has been associated with significant improvements in the cardinal motor signs of PD, including tremor, bradykinesia, and rigidity.[4]

Five studies in our list disclosed stimulation of the ventral intermediate nucleus (Vim) of the thalamus is highly effective for the treatment of tremor, especially in patients with PD-related tremor or in essential tremor patients. However, Vim stimulation lacks significant positive effect on the rigidity, bradykinesia, and gait and postural disturbances associated with PD.[28] This reason may explain why the majority of PD patients are treated with interventions in the STN or GPi, as these targets allow for improvement in all the cardinal features of PD. In contrast, Vim DBS has unequivocal functional benefits in patients with essential tremor.[29]

DBS also offers the attractive potential to directly modulate the affective brain circuitry which may underly some neuropsychiatric illnesses. Our study revealed reports proposing four different DBS targets for depression. For instance, on our list, the most highly-cited study of treatment-resistant depression, published in *Neuron* in 2006, with corresponding authors Dr. Mayberg and Dr. Lozano at the University of Toronto, described the application of chronic DBS to the subgenual cingulate white matter and how it could effectively reverse symptoms in treatment-resistant depression. This article was also ranked first in the annual citations list, with 129.4 citations per year.

As the field obtains a better and more thorough understanding of the pathophysiology of neurologic and psychiatric disorders, newer and more specific targets are being tested with varying success, including those relating to obsessive-compulsive disorder, Tourette's syndrome, epilepsy, cluster headaches, and Alzheimer's disease.[30–34] Nevertheless, while the results have largely been positive, unfortunately, no large scale randomized controlled trials have been performed and evidence in this area is limited to small case series at best.[35] In addition, at present, the electric field generated by DBS is applied indiscriminately to all the neural elements surrounding the electrode; this can sometimes result in undesirable adverse effects. Furthermore, the mechanism of action of DBS is not well understood and remains a research priority, so a better understanding of basic concepts should be encouraged and development of new techniques that permeate into clinical practice are needed to make DBS a more versatile and successful therapeutic option.

Our study has several limitations common to all bibliometric analyses. First, as older studies have more time to accumulate citations,[36] articles that were published more recently will have a shorter exposure to the medical community.[37] Thus, comparing raw citation counts for articles published from different time periods is problematic. We have attempted to adjust for this through the use of annual citation rate analysis for each

Table 3. Number of highly-cited DBS clinical articles by category and stimulation targets.

Category	No.	Target	No.
Parkinson's Disease (PD)	45	Subthalamic Nucleus (STN)	25
		Globus Pallidus (GPi)	3
		STN OR Gpi	7
		STN VS Gpi	4
		Pedunculopontine nucleus (PPN)	3
		PPN AND STN	1
		Caudal Zona Incerta (cZI) vs STN	1
		Ventroposterolateral Pallidum	1
Depression	6	Subgenual Cingulate Region	2
		Nucleus Accumbens (NAcc)	2
		Subcallosal Cingulate Gyrus (SCG)	1
		Ventral Internal Capsule (VC) OR Ventral Striatum (VS)	1
Tremor (including PD, ET, dystonias, MS)	6	Thalamic Nucleus Ventralis Intermedius (Vim)	6
Obsessive-Compulsive Disorder (OCD)	5	VC OR VS	3
		NAcc	1
		STN	1
Generalized Dystonia	5	Globus Pallidus (GP)	5
Epilepsy	4	Anterior Nucleus of Thalamus (ANT)	4
Alzheimer's Disease	1	Fornix/Hypothalamus	1
Chronic Cluster Headache	1	Ventroposterior Hypothalamus	1
Tourette's Syndrome	1	Centromedian-Parafascicular Complex (Ce-Pf) of the thalamus AND/OR Gpi	1
Intractable Pain	1	Periventricular gray matter(specific sensory thalamic nuclei) OR Internal Capsule	1
Traumatic Brain Injury	1	Central Thalamus	1

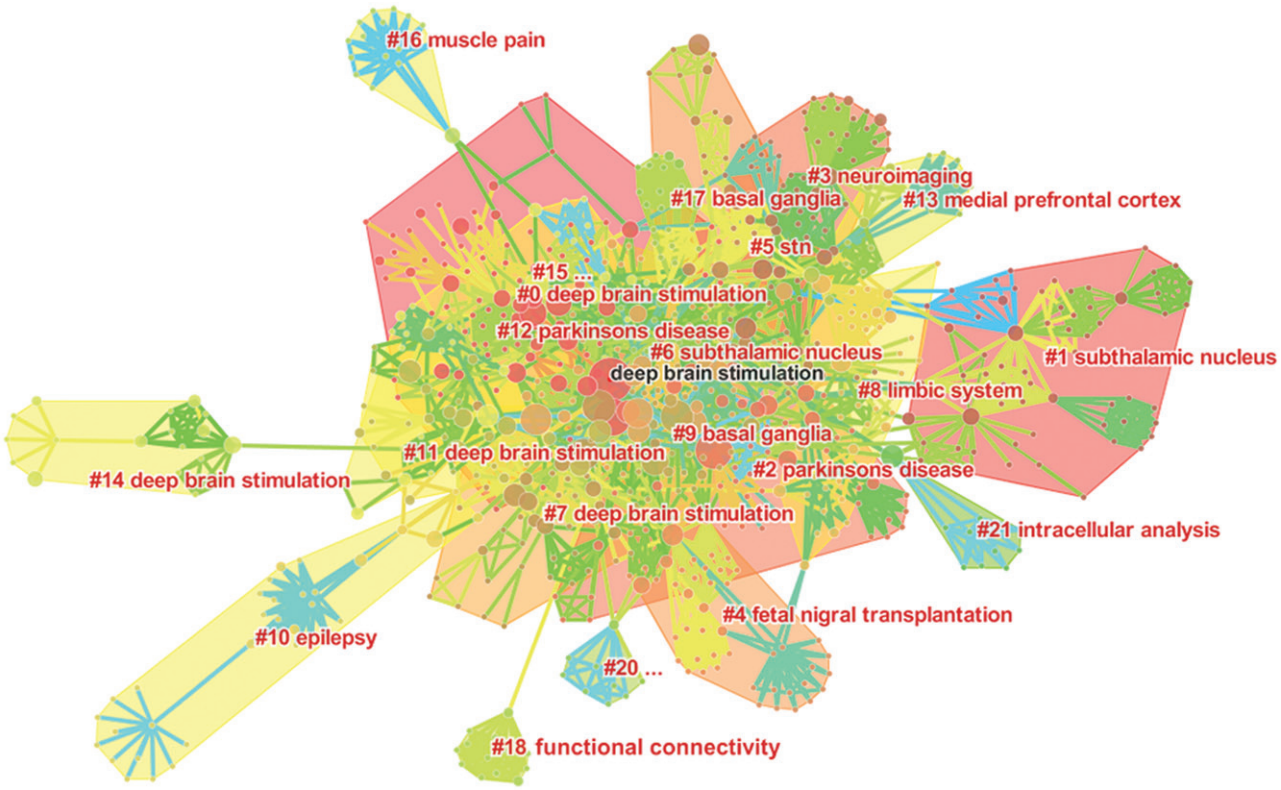

Figure 4. Visualization analysis of co-keywords burst terms in DBS research articles retrieved from the Web of Science using CiteSpace.

paper. Second, although we attempted to be as inclusive as possible, it is possible that other relevant highly-cited articles were missed in the form of conference proceedings or other publication mechanisms. Third, the most cited articles were all published in English-language journals, and it is known that language barriers are known to create a bias in citation rates as authors are more likely to cite articles in their own language.[38,39] Fourth, factors potentially influencing citation rates, such as journal and author self-citation and how many years the journals have been in existence were not considered.[40] Last, it should be acknowledged that the citation number of an article does not directly reflect its quality[41] as evidenced by some papers that were remarkable and had cornerstone effects at the early stage of DBS history but due to a lack of citations were not included in our list.

Conclusions

Our analysis provides a review of landmark papers published in the field of DBS research. These 100 highly-cited articles reflect

the major advances and popular topics in the field of DBS. Our list can help distinguish incremental from transformational studies and provides insights into priorities and trends in DBS research that could serve as a source for future research directions.

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