

## The 50 Most Cited Articles in Invasive Neuromodulation

Max Ward<sup>1</sup>, Joseph Doran<sup>1</sup>, Boris Paskhover<sup>2</sup>, Antonios Mammis<sup>1</sup>

■ **OBJECTIVE:** Bibliometric analysis is a commonly used analytic tool for objective determination of the most influential and peer-recognized articles within a given field. This study is the first bibliometric analysis of the literature in the field of invasive neuromodulation, excluding deep brain stimulation. The objectives of this study are to identify the 50 most cited articles in invasive neuromodulation, provide an overview of the literature to assist in clinical education, and evaluate the effect of impact factor on manuscript recognition.

■ **METHODS:** Bibliometric analysis was performed using the Science Citation Index from the Institute for Scientific Information, accessed through the Web of Science. Search terms relevant to the field of invasive neuromodulation were used to identify the 50 most cited journal articles between 1900 and 2016.

■ **RESULTS:** The median number of citations was 236 (range, 173–578). The most common topics among the articles were vagus nerve stimulation ( $n = 24$ ), spinal cord stimulation ( $n = 9$ ), and motor cortex stimulation ( $n = 6$ ). Median journal impact factor was 5.57. Most of these articles ( $n = 19$ ) contained level I, II, or III evidence.

■ **CONCLUSIONS:** This analysis provides a brief look into the most cited articles within the field, many of which evaluated innovated procedures and therapies that helped to drive surgical neuromodulation forward. These landmark articles contain vital clinical and educational information that remains relevant to clinicians and students within the field and provide insight into areas of expanding research.

Journal impact factor may play a significant role in determining the literary relevance and general awareness of invasive neuromodulation studies.

### INTRODUCTION

Invasive neuromodulation (IN) is an expanding surgical subspecialty that encompasses a multitude of clinical fields including, but not limited to, neurological surgery, neurology, bioengineering, and urology. IN has rapidly evolved since the preliminary experiments with implanted deep brain electrodes<sup>1</sup> and spinal cord stimulators.<sup>2</sup> and technological and procedural advancements will continue to drive the field forward. Advancements within the field are primarily conveyed to the community through contributions to the literature, and as IN moves forward it becomes important to identify significant and impactful contributions.

Bibliometric analysis is a method of identifying the most frequently cited articles within a given field, allowing objective measurement of peer recognition. This analysis has been performed on varied surgical specialties and procedures; however, the present study represents the first bibliometric analysis of IN.<sup>3-5</sup> The present study provides clinicians and students a brief overview of the field of IN for the purpose of personal and institutional education, analyzes the effect of journal impact on article citations, and highlights areas of investigational growth in the field.

### METHODS

For the present study we used the same search methodology as in Chang et al.<sup>5</sup> To determine the 50 most cited articles in surgical

#### Key words

- Bibliometric
- Motor cortex stimulation
- Neuromodulation
- Spinal cord stimulation
- Vagus nerve stimulation

#### Abbreviations and Acronyms

- CMM:** Conventional medical management  
**FBSS:** Failed back surgery syndrome  
**IN:** Invasive neuromodulation  
**MCS:** Motor cortex stimulation  
**RCT:** Randomized controlled trial  
**SCS:** Spinal cord stimulation

**VNS:** Vagus nerve stimulation

From the Departments of <sup>1</sup>Neurological Surgery and <sup>2</sup>Otolaryngology Facial Plastics and Reconstruction, Rutgers New Jersey Medical School, Newark, New Jersey, USA

To whom correspondence should be addressed: Max Ward, B.S.

[E-mail: [MaxWard94@gmail.com](mailto:MaxWard94@gmail.com)]

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Table 1. Top 50 Cited Articles

Rank	First Author	Title	Journal	Year	Number of Times Cited
1	Handforth	Vagus nerve stimulation therapy for partial-onset seizures—a randomized active-control trial	<i>Neurology</i>	1998	578
2	De Jonge	Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-Stat3 signaling pathway	<i>Nature Immunology</i>	2005	442
3	Vanoli	Vagal-stimulation and prevention of sudden-death in conscious dogs with a healed myocardial-infarction	<i>Circulation Research</i>	1991	431
4	Ben-Menachem	Vagus nerve-stimulation for treatment of partial seizures .1. A controlled-study of effect on seizures	<i>Epilepsia</i>	1994	350
5	Tsubokawa	Chronic motor cortex stimulation for the treatment of central pain.	<i>Acta Neurochir Suppl</i>	1991	334
6	Kumar	Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome	<i>Pain</i>	2007	325
7	Tsubokawa	Chronic motor cortex stimulation in patients with thalamic pain.	<i>Journal of Neurosurgery</i>	1993	322
8	Morris	Long-term treatment with vague nerve stimulation in patients with refractory epilepsy	<i>Neurology</i>	1999	318
9	Kemler	Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy	<i>New England Journal of Medicine</i>	2000	317
10	Rush	Vagus nerve stimulation (Vns) for treatment-resistant depressions: a multicenter study	<i>Biological Psychiatry</i>	2000	316
11	George	A randomized controlled trial of chronic vagus nerve-stimulation for treatment of medically intractable seizures	<i>Neurology</i>	1995	305
12	Li	Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats	<i>Circulation</i>	2004	304
13	North	Spinal cord stimulation for chronic, intractable pain: experience over two decades	<i>Neurosurgery</i>	1993	290
14	Garcia-Larrea	Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study	<i>Pain</i>	1999	289
15	Sackeim	Vagus nerve stimulation (Vns) for treatment-resistant depression: efficacy, side effects, and predictors of outcome	<i>Neuropsychopharmacology</i>	2001	274
16	Krahl	Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation	<i>Epilepsia</i>	1998	274
17	Cameron	Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review	<i>Journal of Neurosurgery</i>	2004	265
18	Degiorgio	Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures	<i>Epilepsia</i>	2000	259
19	Rush	Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial	<i>Biological Psychiatry</i>	2005	256
20	North	Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial	<i>Neurosurgery</i>	2005	251
21	Clark	Enhanced recognition memory following vagus nerve stimulation in human subjects	<i>Nature Neuroscience</i>	1999	250
22	Smith	Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival	<i>Journal of Clinical Oncology</i>	2002	250
23	Theodore	Brain stimulation for epilepsy	<i>Lancet Neurology</i>	2004	246

Continues

Table 1. Continued

Rank	First Author	Title	Journal	Year	Number of Times Cited
24	Harkema	Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study	<i>Lancet</i>	2011	242
25	Weiner	Peripheral neurostimulation for control of intractable occipital neuralgia	<i>Neuromodulation</i>	1999	238
26	Schmidt	Sacral nerve stimulation for treatment of refractory urinary urge incontinence	<i>Journal of Urology</i>	1999	234
27	Nguyen	Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data	<i>Pain</i>	1999	232
28	Schachter	Vagus nerve stimulation	<i>Epilepsia</i>	1998	230
29	Groves	Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects	<i>Neuroscience And Biobehavioral Reviews</i>	2005	224
30	George	Vagus nerve stimulation: a new tool for brain research and therapy	<i>Biological Psychiatry</i>	2000	221
31	Turner	Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications	<i>Pain</i>	2004	216
32	Wagenaar	Controlling bursting in cortical cultures with closed-loop multi-electrode stimulation	<i>Journal Of Neuroscience</i>	2005	210
33	Kumar	The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation	<i>Neurosurgery</i>	2008	201
34	Ben-Menachem	Vagus-Nerve Stimulation For The Treatment Of Epilepsy	<i>Lancet Neurology</i>	2002	198
35	Siegel	Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention	<i>Urology</i>	2000	197
36	Naples	A spiral nerve cuff electrode for peripheral nerve stimulation	<i>IEEE Trans Biomed Eng</i>	1988	193
37	De Ferrari	Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure	<i>European Heart Journal</i>	2011	191
38	George	A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression	<i>Biological Psychiatry</i>	2005	191
39	Magis	Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study	<i>Lancet Neurology</i>	2007	189
40	Rush	Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study	<i>Biological Psychiatry</i>	2005	188
41	Katayama	Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response	<i>Journal of Neurosurgery</i>	1998	188
42	Naritoku	Regional induction of Fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve	<i>Epilepsy Research</i>	1995	187
43	Rutecki	Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve-stimulation	<i>Epilepsia</i>	1990	184
44	Meyerson	Motor cortex stimulation as treatment of trigeminal neuropathic pain.	<i>Acta Neurochir Suppl</i>	1993	181
45	Stiller	Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats	<i>Neurosurgery</i>	1996	180

Continues

Table 1. Continued

Rank	First Author	Title	Journal	Year	Number of Times Cited
46	Matzel	Sacral spinal nerve stimulation for faecal incontinence: multicentre study	<i>Lancet Neurology</i>	2004	180
47	Henry	Therapeutic mechanisms of vagus nerve stimulation	<i>Neurology</i>	2002	178
48	Reilly	Peripheral nerve stimulation by induced electric currents: exposure to time-varying magnetic fields	<i>Med Biol Eng Comp</i>	1989	175
49	Hassouna	Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety	<i>Journal of Urology</i>	2000	174
50	Burns	Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients	<i>Lancet</i>	2007	173

neuromodulation, we accessed the Web of Science “all databases” search function on July 2016 that contains articles from international journals between the years 1900 and 2016. Search terms included Spinal cord stimulation, Motor cortex stimulation, Vagus nerve stimulation, Sacral nerve stimulation, Peripheral nerve stimulation, Occipital nerve stimulation, Cranial nerve stimulation, Intrathecal drug delivery, Dorsal root ganglion stimulation, and Trigeminal nerve stimulation. “Deep Brain Stimulation” was excluded, as a previous bibliometric study had already analyzed this topic.<sup>4</sup> Articles that specifically discussed topics relevant to surgical neuromodulation were selected. Articles that only minimally addressed surgical neuromodulation, including clinical guidelines and field overviews, were excluded, as they were mainly cited for reasons unrelated to neuromodulation. Each article was reviewed for its number of citations, first author, year of publication, journal of publication, impact factor of the journal, subject matter, and level of evidence. Impacts factors were obtained using the Journal Citation reports database. We used categorization as described by the Oxford Centre for Evidence-based Medicine to determine the level of evidence for clinical articles, which include randomized controlled trials (RCTs) (level I), nonrandomized controlled or prospective cohort trials (level II), retrospective cohort studies (level III), case series (level IV), and expert opinions or observational articles (level V).

## RESULTS

The 50 most cited articles relating to surgical neuromodulation were identified and contained a combined 12,641 citations (Table 1). These articles were cited a median of 236 times (range, 173–578) and published between 1988 and 2011 (Table 2). Most of these articles were published between 2000 and 2009 ( $n = 26$ ). The most articles were published in the *Biological Psychiatry* ( $n = 5$ ) and *Epilepsia* ( $n = 5$ ), followed by *Lancet Neurology* ( $n = 4$ ), *Neurology* ( $n = 4$ ), *Neurosurgery* ( $n = 4$ ), and *Pain* ( $n = 4$ ) (Table 3). The average journal impact factor for these articles was 11.59 (range, 1.81–72.41) and the median impact was 5.57. The average impact factor for the top 10 articles was 15.1 and 10.74 for the bottom 40, although this difference is not significant ( $P = 0.5$ ). Subject matter within the top 50 articles included vagus nerve stimulation (VNS) ( $n = 24$ ), spinal cord stimulation (SCS)

( $n = 9$ ), motor cortex stimulation (MCS) ( $n = 6$ ), sacral nerve stimulation ( $n = 4$ ), peripheral nerve stimulation ( $n = 3$ ), occipital nerve stimulation ( $n = 2$ ), closed loop stimulation ( $n = 1$ ), and intrathecal drug delivery systems ( $n = 1$ ) (Table 4). Of the 50 articles, 9 presented findings from translational research (4 related to VNS, 2 related to peripheral nerve stimulation, 2 related to SCS, and 1 related to closed loop stimulation). Five of the articles were literature reviews. The remaining 36 articles presented clinically obtained information, most of which focused on utilization of VNS or SCS. The majority of these articles ( $n = 19$ ) provided level I, II, or III evidence to support their claims (Table 5).

## DISCUSSION

### Overview of Invasive Neuromodulation

This is the first bibliometric analysis performed on literature pertaining to the overall field of invasive neuromodulation. The articles identified within this study provide an overview of some of the most pivotal developments in the field and highlight areas of potential growth. Although each of these articles are worthy of lengthy discussion, we have chosen to highlight the most highly cited article pertaining to each of the 4 most common technologies (Table 4) to provide a brief overview of the IN literature.

The most cited article in VNS, published by Handforth et al<sup>6</sup> in 1998, was a randomized controlled double-blind trial to investigate the efficacy of high frequency VNS when compared WITH low frequency active-control stimulation for treatment of partial-onset seizures. The investigators found that high frequency stimulation produced a 28% average reduction in seizure frequency compared

Table 2. Time Period That Generated Most Cited Articles

Decade	Number of Articles
1980–1989	2
1990–1999	20
2000–2009	26
2010–current	2

**Table 3. Journals with Most Cited Articles**

Journal	Number of Articles
<i>Biological Psychiatry</i>	5
<i>Epilepsia</i>	5
<i>Lancet Neurology</i>	4
<i>Neurology</i>	4
<i>Neurosurgery</i>	4
<i>Pain</i>	4
<i>Journal of Neurosurgery</i>	3
<i>Acta Neurochir Suppl</i>	2
<i>Journal of Urology</i>	2
<i>Lancet</i>	2
<i>Circulation</i>	1
<i>Circulation Research</i>	1
<i>Epilepsy Research</i>	1
<i>European Heart Journal</i>	1
<i>IEEE Trans Biomed Eng</i>	1
<i>Journal of Clinical Oncology</i>	1
<i>Journal of Neuroscience</i>	1
<i>Med Biol Eng Comp</i>	1
<i>Nature Immunology</i>	1
<i>Nature Neuroscience</i>	1
<i>Neuromodulation</i>	1
<i>Neuropsychopharmacology</i>	1
<i>Neuroscience and Biobehavioral Reviews</i>	1
<i>New England Journal of Medicine</i>	1
<i>Urology</i>	1

with 15% in the control group. They conclude that VNS represents a safe and effective additive option in the nonpharmacologic management of patients with refractory partial onset seizures.

The most cited article in MCS, authored by Tsubokawa et al<sup>7</sup> in 1991, is the earliest recorded use of MCS for the treatment of central pain. Although thalamic stimulation was thought to be effective for treating deafferentation pain, secondary to peripheral lesions, it was considered ineffective for pain of central origin. This prompted the investigation of stimulation of other brain regions, including the motor cortex, in 12 patients with deafferentation pain secondary to central lesions. A total of 8 of the 12 patients achieved effective pain relief after a full year. Five of those patients reported complete pain relief, and the other 3 reported partial pain relief.

The Prospective Randomised Controlled Multicentre Trial of the Effectiveness of Spinal Cord Stimulation (PROCESS), the most cited article in SCS, was authored by Kumar et al<sup>8</sup> in 2007 and is a RCT investigating the efficacy of SCS and conventional medical management (CMM) when compared to CMM alone for patients

with failed back surgery syndrome (FBSS). One hundred patients with FBSS and predominantly leg pain were randomized into either the SCS plus CMM group or the CMM group. The primary outcome measured, >50% pain relief, was achieved by 48% of patients with SCS and only 8% of patients with CMM. In addition, the SCS group had significantly more improvements in quality of life, functional capacity, and satisfaction of treatment. Although this was not the first RCT to investigate SCS for FBSS,<sup>9</sup> it compared SCS to a more realistic control group, used more number patients, and more of the population achieved the primary outcome.

The most cited article on sacral nerve stimulation is the first RCT<sup>10</sup> investigating it for urinary urge incontinence. Patients were randomized to either delayed control or stimulation group and at 6 months controls were crossed over to the stimulation group. The investigators found significant reductions in daily incontinence episodes, severity of incontinence, and the number of absorbent pads used per day within the stimulation group compared with the control group. Criticisms of the trial have included the inadequate explanation of the randomization process and the unexplained omission of 20% of the sample population from the analysis.<sup>11</sup> It was later reported by the Blue Cross and Blue Shield Association that the exclusion was due to inadequate follow-up, although this was never mentioned in the study.

#### The Effect of Impact Factor

Interestingly, the Handforth et al<sup>6</sup> study was not the first double-blind RCT to investigate VNS for partial-onset seizures. The fourth most cited article on this list, published by Ben-Menachem et al<sup>12</sup> in *Epilepsia* in 1994, was the first double-blind RCT to investigate VNS for partial-onset seizures. Although they also report statistically significant reductions in seizure frequency within the high frequency compared with the low frequency group, the article has been cited nearly half as many times as Handforth et al,<sup>6</sup> despite being published 4 years earlier. Interestingly, the impact factor of *Neurology*, where Handforth et al<sup>6</sup> published their manuscript, is 8.268, nearly twice that of *Epilepsia*. Although it is true that the later study includes more patients and provides global evaluation scores, the earlier article should still be cited at least as often as early pilot data. It could be argued that the earlier article had a reduced number of citations due to its 3-part publishing choice, as there are 641 total citations for all 3 articles

**Table 4. Subject Matter of Most Cited Articles**

Topic	Number of Articles
Vagus nerve stimulation	24
Spinal cord stimulation	9
Motor cortex stimulation	6
Sacral nerve stimulation	4
Peripheral nerve stimulation	3
Occipital nerve stimulation	2
Closed loop stimulation	1
Intrathecal pump	1

**Table 5.** Evidence Level for Clinical Studies

Evidence Level	Number of Articles
I	15
II	1
III	3
IV	14
V	3

combined.<sup>12-14</sup> However, when you remove the duplicates that occurred when a single manuscript cited more than 1 of the 3 articles the true number of citations is 438, which is still 140 less citations than the study published in *Neurology*.

The case report published by Harkema et al<sup>15</sup> presents the use of SCS combined with intense training to restore some function to a 23-year-old complete T1 paraplegic man. The investigators discuss how they used central pattern recognition in the spine to train this patient to functionally stand and step using SCS in lieu of signals from the brain. The article, published in *The Lancet* (impact factor, 44) has been cited 242 times despite being both the only case report and the most recently published article on the list. Case reports, although useful, are generally considered to be the least reliable source of clinical information. In this case, the article's high impact was likely due to a combination of the high interest in improvements to spinal cord injury management, and the extraordinarily high impact factor of *The Lancet*.

Impact factor represents the average number of citations for articles within a journal and, although it is meant to provide some measure of journal prevalence, it has become an arbitrary and ineffective measure of academic journals, providing no real information as to the quality of the journals or the articles within them.<sup>16</sup> Despite this, there appears to be a very real effect of impact factor on the literary relevance of articles, represented by the number of citations an article receives. Whether this is due to volume of readership, institutional subscription choices, or pure bias toward articles in higher impact journals is beyond the scope of this study. For the year 2016 the Journal Citation Reports Database indexes the impact factor of 6260 journals. Of these only 1246 (20%) have an impact of at least 4, and only 776 (12%) have an impact of at least 5. In contrast 18 of the 25 journals (72%) that we identified had impact factors >4 and 15 (60%) had impact factors

>5. Although deep brain stimulation was not included in the overall analysis, we identified the top 5 articles in this category as cited a combined 5388 times, nearly half the combined total of the top 50 articles within this study, with a mean of 1077 citations (range, 698–1663). Three of the articles were published in *New England Journal of Medicine*, one in *Neuron*, and one in *Journal of Neurosurgery*, averaging an impact factor of 47.

Of course, it is possible that high impact factor journals exclusively publish studies that are worthy of increased recognition, thus leading to increased citation; however, we believe that these data suggest that studies published in “lower impact,” but more in-scope, journals are simply less likely to receive the recognition they deserve. The quality of an article should not be determined by the impact factor of the journal it is published in, and impact factor may actually be stifling the investigational and clinical landscape it is meant to assist.

Newer neuromodulation therapies, including dorsal root ganglion stimulation, burst wave technology, and HF10 stimulation did not make the list. This is likely because they have not had time to fully penetrate the clinical landscape, leading to lower levels of citation within the literature. We predict that as neuromodulation continues to prove clinically effective, the impact of articles investigating these therapies will increase as well.

Bibliometric analysis provides an objective measure of peer recognition within a given field. This allows insight into influential articles that helped to shape the direction of routine clinical practice. Within the field of IN, we have discussed articles that influenced the development of procedures including VNS, MCS, SCS, and sacral nerve stimulation. Identified articles most commonly focused on VNS (US Food and Drug Administration approved in 1997), despite the fact that SCS was approved almost 10 years earlier (1989) and is noted to be the most common IN procedure by the International Neuromodulation Society. This is likely because VNS has been investigated for clinically prevalent indications, including heart failure, depression, and seizure control, whereas SCS, MCS, peripheral nerve stimulation, and occipital nerve stimulation are primarily (although not exclusively) therapies for pain control, which has historically (and recently) been a controversial topic in the medical and regulatory communities. The increasing evidence of clinical effectiveness in neuromodulation for pain and the negative regulatory outlook surrounding traditional pharmacologic pain management make this a uniquely appropriate time for clinicians and institutions to seek funding for neuromodulation studies.<sup>17</sup>

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