REVIEW

The Changing Landscape of Surgery for Parkinson's Disease

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ABSTRACT: Neurosurgical interventions have been used to treat PD for over a century. We examined the changing landscape of surgery for PD to appraise the value of various procedures in the context of advances in our understanding and technology. We assessed the number of articles published on neurosurgical procedures for PD over time as an albeit imprecise surrogate for their usage level. We identified over 8,000 publications associated with PD surgery. Over half the publications were on DBS. The field of DBS for PD showed a rapid rise in articles, but is now in a steady state. Thalamotomy and, to a lesser extent, pallidotomy follow a biphasic publication distribution with peaks approximately 30 years apart. Articles on gene therapy and transplantation experienced initial rapid rises and significant recent declines. Procedures using novel technologies, including gamma knife and focused ultrasound, are emerging, but are yet to have significant impact as measured by publication numbers. Pallidotomy and thalamotomy are prominent examples of procedures that were popular, declined, and re-emerged and redeclined. Transplantation and gene therapy have never broken into clinical practice. DBS overtook all procedures as the dominant surgical intervention and drove widespread use of surgery for PD. Notwithstanding, the number of DBS articles appears to have plateaued. As advances continue, emerging treatments may compete with DBS in the future. © 2017 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; pallidotomy; thalamotomy; deep brain stimulation; focused ultrasound; gamma knife

There has been tremendous evolution in the understanding and treatment of Parkinson's disease (PD) since its description two centuries ago. Pharmacological approaches to PD have always been dominant, but because of their limitations, alternative approaches began to emerge early on. A wide variety of questionable nonpharmacological interventions were considered. Parkinson himself suggested that draining blood from the neck to alleviate congestion in the brain could be used as a potential treatment.[1] Unsatisfied with available pharmacological treatments, Charcot developed a new approach, vibration therapy, after observing that the rest tremor of PD patients improved following riding in a carriage.[2] While initially promising, interest in this approach declined after Charcot's death and other treatments were examined, but none had major or sustained impact. Over the course of the late 1800s into the early to mid-1900s, the treatment of choice remained anticholinergic agents.

The limitations in efficacy of available treatments drove the emergence of surgery for PD early on. The sectioning of sensory nerves for tremor by Leriche was perhaps the first neurosurgical intervention for PD occurring more than 100 years ago.[3] An updated version of the timeline for surgery in movement disorders[4] can be described as in five partially overlapping periods: the prestereotactic era (1890-1954); the early stereotactic era (1947-1968); the latent/levodopa era (1968-1992); the ablative surgery revival era (1992-1999); and, finally, the modern/DBS era at from 1993 to the present.

Surgery for movement disorders including PD began in the early 1900s. After a brief foray of surgeries in the peripheral nervous system, the focus changed to various targets along the corticospinal tract. In the

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1940s, the team of Bucy and Case treated parkinsonian tremor by excising part of the cerebral cortex. Tremor was abolished, but at the cost of hemiparesis, preventing this approach from becoming a viable treatment.[5] Contemporarily, the first pathophysiological models of PD emerged in the 1940s and 1950s, a development that drove a growing interest in ablative surgeries of the basal ganglia. The first open procedures on the basal ganglia by pioneers like Russell Meyers had variable degrees of success, but were accompanied by high rates of morbidity and mortality.[6]

Both corticospinal and basal ganglia procedures were practiced in the 1950s. A major milestone in surgery for PD was achieved when Irving Cooper accidentally ligated the anterior choroidal artery during an attempted pedunculotomy, which resulted in an inadvertent infarction of the globus pallidus (GP) and related structures.[7] The pedunculotomy was aborted, but to Cooper's surprise, the patient's tremor and rigidity were dramatically improved. Cooper's serendipitous discovery led him to conduct this procedure on 50 patients, abolishing tremor in 65%.[8] Despite these findings, Cooper's work on choroidal artery ligation was never widely adopted because of the inconsistent benefits and high rates of complications, including hemiparesis.[9]

The invention of stereotactic neurosurgery by Horsley and Clark[10] and its adaptation to humans by Spiegel and Wycis[11] ushered the shift of surgical targets from the corticospinal tracts to deep brain targets and from open surgery to stereotactic, image-guided approaches. In 1957, unsatisfied with the results, Cooper shifted his focus from choroidal artery ligation to chemopallidectomies using procaine injection into the medial GP.[12] One patient had a particularly striking amelioration in tremor with an intended pallidotomy, but, at postmortem, was discovered to have had the lesion situated in the thalamus.[6] Cooper took advantage of this observation and shifted to the ventral lateral thalamus as his target of choice for parkinsonian tremor. Based on this also serendipitous observation and Hassler's neuroanatomical studies,[13] other surgeons followed and thalamotomy became the dominant surgical approach for PD.[14,15]

The discovery and use of L-dopa in the 1960s dramatically changed the treatment of PD. With the realization of the profound clinical benefits of L-dopa, surgery for PD entered a period of rapid decline and a moratorium or "ice age." It was only with the realization that many patients had inadequate benefit or developed adverse effects with disease progression and ongoing use of L-dopa that the opportunity to revisit surgical interventions arose in the 1980s and 1990s—the moratorium was lifted. Transplantation and, later, gene therapy were tested, and older approaches like pallidotomy and thalamotomy experienced rekindled interest. The late 1990s saw the rise of DBS surgery and, more recently, new minimally invasive tools, including gamma knife (GK) and focused ultrasound (FUS), have been examined.

It is clear that, over the course of the past century and especially since the 1980s, the landscape of neurosurgery for PD has greatly shifted. The purpose of the present study is to compile and analyze publications on the evolution of surgical approaches for PD over time. The number of publications is used as an albeit imprecise proxy for the volume of surgeries being done and the relative interest in the field for the various procedures.

Methods

We performed a generic search for all surgery related to PD. In addition, a list of established and emerging surgical therapies for PD was compiled. We examined the following topic key words: pallidotomy, thalamotomy, deep brain stimulation (DBS), gene therapy, and transplantation. Thalamotomy was further subdivided by technique, including GK and FUS thalamotomy. We included conventional (radiofrequency) as well as GK pallidotomy.

Searches were performed in May 2017. The Scopus database (www.scopus.com) was used to search for publications on these topics. Articles published until 31 December 2016 were included in the analysis. Search queries included the topic key words and were limited to articles and reviews in scholarly journals. Articles in languages other than English were included if they had a translated title, abstract, or keywords containing the search terms. Table 1 footnotes present the search queries used in Scopus. Duplicates and articles with incomplete author lists were identified and removed. The number of publications for each year was tallied and displayed in graphical form. The number of citations received by each article was also recorded. The citation classics (articles that received over 400 citations) representing the most cited articles in the history of PD surgery to date were compiled. These highly cited articles were also used to ascertain trends in the field of PD surgery over time.

Results

Surgery and PD

A generic search using the terms "Surgery" and "Parkinson's disease" yielded 12,021 total articles in the period of 1949-2016. The results showed a trend toward increased number of publications per year over time, with a small peak in the late 1960s and early 1970s and what appears to be a second, larger peak appearing in 2013 (Fig. 1A). Because articles

TABLE 1. Summary of publications in surgery for PD from 1949 to 2016

Search Term Used in Combination With PD	No. of Publications and Percent (%)	Year of Earliest Publication Retrieved in Scopus	Maximum No. of Annual Publications	Years of Maximum Annual Publications
Global search for surgery for PD[c]	**12,021**	1949	855	2013
Total number of neurosurgical procedure publications for PD	**8,017 (100%)**			
Pallidotomy[d]	898 (11.2%)	1958[a]	91	1999
Thalamotomy[e]	707 (8.8%)	1960[b]	40	2000
DBS[f]	4,702 (58.7%)	1987	419	2014
Gene therapy[g]	1,187 (14.8%)	1987	93	2008
Transplant[h]	468 (5.8%)	1983	24	1990, 2004
GK (pallidotomy)[i]	10 (0.1%)	1996	2	2002, 2007
GK (thalamotomy)[j]	39 (0.5%)	1991	4	2005, 2015
FUS (thalamotomy)[k]	6 (0.1%)	2013	3	2013

Summary quantifying publications on established and emerging surgical therapies for PD. Two historical publications outside the Scopus database are included in the footnotes for completeness. Search terms used are provided below. Search results were limited to articles or reviews.
[a]Although not retrieved in our Scopus search, likely the first published report of pallidotomy for PD is: Narabayashi H, Okuma, T. Procaine-Oil Blocking of the Globus Pallidus for the Treatment of Rigidity and Tremor of Parkinsonism. Proc Japan Acad 1953;29:134-137.
[b]Although not retrieved in our Scopus search, likely the first published report of thalamotomy for PD is: Hassler R, Riechert, T. Indikationen und Lokalisationsmethode der gezielten Hirnoperationen. Nervenarzt 1954;25:441-447.
[c]TITLE-ABS-KEY ("Parkinson's disease") AND ALL (surgery) AND DOCTYPE (ar OR re)
[d]TITLE-ABS-KEY (pallidotomy AND "Parkinson's disease") AND DOCTYPE (ar OR re)
[e]TITLE-ABS-KEY ("thalamotomy" AND "parkinson's disease") AND DOCTYPE (ar OR re)
[f]TITLE-ABS-KEY ("deep brain stimulation") AND TITLE-ABS-KEY ("Parkinson's disease") AND DOCTYPE (ar OR re)
[g]TITLE-ABS-KEY ("gene therapy" AND "Parkinson's disease") AND KEY (human) AND DOCTYPE (ar OR re)
[h]TITLE-ABS-KEY ("transplant" AND "Parkinson's disease") AND KEY (human) AND DOCTYPE (ar OR re)
[i]TITLE-ABS-KEY (pallidotomy AND "Parkinson's Disease" AND "gamma knife") AND NOT KEY ("thalamotomy")
[j]TITLE-ABS-KEY ("gamma knife" AND "thalamotomy" AND "Parkinson's disease") AND DOCTYPE (ar OR re)
[k]TITLE-ABS-KEY ("focused ultrasound" AND "thalamotomy" AND "Parkinson's disease") AND DOCTYPE (ar OR re)

identified using these terms included non-neurological surgery for PD, the search strategy was modified to search technique-specific surgical procedures designed to alleviate PD. The total number of articles identified using specific surgical procedure search terms and PD was 8,017 (Table 1). DBS accounted for 58.7% of all surgical papers, with pallidotomy accounting for 11.2%, thalamotomy 8.8%, gene therapy 14.8%, and transplantation 5.8%. We compiled a list of the most influential articles in PD surgery over time and identified 32 citation classics—articles that were cited over 400 times (Table 2). The greatest number of these articles (19) was in the field of DBS, with six in the transplantation field, three that described lesion surgery, two that described lesions versus DBS, one on gene therapy, and one on other topics.

Pallidotomy

Although the first published report of pallidotomy was likely the article by Narabayashi in 1953,[16] this article was not detected in our search. The earliest article identified in the pallidotomy search described mechanical pallidotomy in 17 patients in 1958.[17] The time course of pallidotomy publications (Fig. 1B) follows a bimodal distribution with an initial small spike during the 1960s and a second, much larger spike in the late 1990s. In the 1960s, there were 11 publications on pallidotomy, followed by a decline to a total of only three publications during the 1970s and 1980s. This period of low activity ended with the breakthrough publication of Laitinen in 1992, which reintroduced pallidotomy. Pallidotomy publications peaked at 91 in 1999. The peak-to-peak interval was approximately 34 years. Since this second peak, the number of annual publications on pallidotomy has declined steadily.

Thalamotomy

The likely first published report of thalamotomy was by Hassler and Riechert in 1954,[18] but this article was not captured by our search strategy that was confined to articles written in English. The first publication of thalamotomy for PD identified was a 1960 review by Krayenbühl and Yaşargil detailing safety and efficacy in contemporary cases.[15] It is evident from this review that there had been earlier publications on thalamotomy for PD, although they escaped detection by our search method. Thalamotomy publications rose to prominence initially in the late 1960s and early 1970s, reaching its first peak of 14 publications in 1974 (Fig. 1C). The annual number of publications proceeded to fall off and remain relatively low until the early 1990s. The 1990s saw a renewed interest in thalamotomy and second peak of 40 publications in 1999. The peak-to-peak interval was 26 years. The 2000s experienced variable levels of interest, but an overall downward trend.

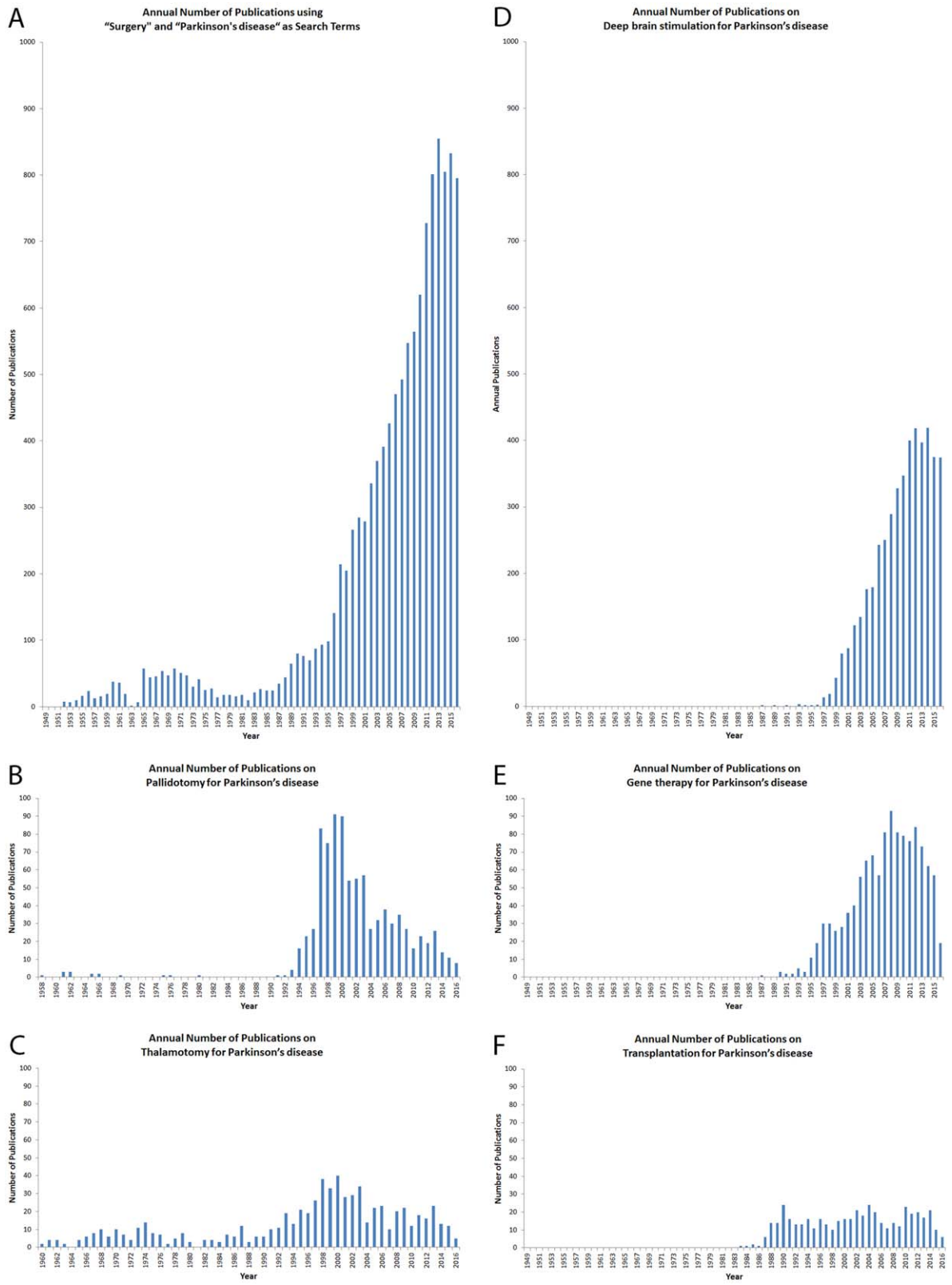

FIG. 1. Annual number of publications on established surgical therapies for PD. Annual publication data presented by surgical technique: (A) surgery, (B) pallidotomy, (C) thalamotomy, (D) DBS, (E) gene therapy, and (F) tranplantation. In (A) and (C), the y-axis scale maximum value is 1,000 versus 100 in the other panels. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2. The most influential publications in surgery for PD from 1949 to 2016

Rank	Author	Year	Title	Field	No. of Citations
1	Freed C.R. et al.[39]	2001	Transplantation of embryonic dopamine neurons for severe Parkinson's disease	Transplantation	1666
2	Krack P. et al.[40]	2003	Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease	Deep brain stimulation	1311
3	Deuschl G. et al.[41]	2006	A randomized trial of deep-brain stimulation for Parkinson's disease	Deep brain stimulation	1173
4	Obeso J.A. et al.[42]	2001	Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease	Deep brain stimulation	1028
5	Benabid A.L. et al.[43]	1991	Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus	Deep brain stimulation	991
6	Limousin P. et al.[44]	1995	Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation	Deep brain stimulation	919
7	Laitinen L.V. et al.[22]	1992	Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease	Lesioning	791
8	Lindvall O. et al.[45]	1990	Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease	Transplantation	777
9	Benabid A.L. et al.[46]	1996	Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders	Deep brain stimulation	748
10	Kordower J.H. et al.[38]	2008	Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease	Transplantation	678
11	Weaver F.M. et al.[47]	2009	Bilateral deep brain stimulation vs best medical therapy for patients with advanced parkinson disease: A randomized controlled trial	Deep brain stimulation	665
12	Rodriguez-Oroz M.C. et al.[48]	2005	Bilateral deep brain stimulation in Parkinson's disease: A multicentre study with 4 years follow-up	Deep brain stimulation	639
13	Schuurman P.R. et al.[32]	2000	A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor	Deep brain stimulation + Lesioning	622
14	Kaplitt M.G. et al.[49]	2007	Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial	Gene therapy	617
15	Benabid A.L. et al.[50]	1987	Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease	Deep brain stimulation + Lesioning	590
16	Chaudhuri K.R. et al.[51]	2009	Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment	Deep brain stimulation	588
17	Frank M.J. et al.[52]	2007	Hold your horses: Impulsivity, deep brain stimulation, and medication in Parkinsonism	Deep brain stimulation	553
18	Follett K.A. et al.[53]	2010	Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease	Deep brain stimulation	524
19	Piccini P. et al.[54]	1999	Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient	Transplantation	521
20	Freed C.R. et al.[55]	1992	Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease	Transplantation	513
21	Benabid A.L. et al.[56]	2009	Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease	Deep brain stimulation	512
22	Lozano A.M. et al.[57]	1995	Effect of GPi pallidotomy on motor function in Parkinson's disease	Lesioning	491
23	Kleiner-Fisman G. et al.[30]	2006	Subthalamic nucleus deep brain stimulation: Summary and meta-analysis of outcomes	Deep brain stimulation	484
24	Bejjani B.-P. et al.[58]	1999	Transient acute depression induced by high-frequency deep-brain stimulation	Deep brain stimulation	476
25	Kumar R. et al.[59]	1998	Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease	Deep brain stimulation	472
26	Stefani A. et al.[60]	2007	Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease	Deep brain stimulation	463
27	Madrazo I. et al.[61]	1987	Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease	Transplantation	456
28	Defer G.-L. et al.[62]	1999	Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (CAPSIT-PD)	Other	455

(Continued)

TABLE 2. *Continued*

Rank	Author	Year	Title	Field	No. of Citations
29	Saint-Cyr J.A. et al.[63]	2000	Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease	Deep brain stimulation	449
30	Hutchison W.D. et al.[64]	1998	Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease	Deep brain stimulation	447
31	Baron M.S. et al.[65]	1996	Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-Year results of a pilot study	Lesioning	440
32	McIntyre C.C. et al.[66]	2004	Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both	Deep brain stimulation	423

List of the most cited publications in PD surgery. Only citation classics (>400 citations) were included. Articles were categorized as: Deep brain stimulation (DBS) (19), Transplantation (6), Lesioning (3), DBS versus lesioning (2), Gene Therapy (1), and Other (1).

DBS

Benabid's landmark article on high-frequency stimulation of the ventrointermediate nucleus (VIM) in 1987 was a turning point in the use of DBS for PD. The 1990s saw a surge of publications examining DBS as a treatment for PD. The numbers grew, surpassing 100 annual publications by 2002 and reaching a maximum of 419 in 2014 (Fig. 1D).

The explosion of interest in DBS has been accompanied by high-impact publications of clinical trials. The 1990s saw the first planned investigation of VIM DBS for PD as well as the first double-blind trial of STN DBS. In the 2000s, the first clinical trial of STN DBS versus medical treatment for PD was published as well as an investigation of STN versus internal GP (GPi) DBS. Optimization of DBS treatment for PD continued in the 2010s with studies that evaluated DBS targets (STN vs. GPi) and efficacy compared to other medical treatments. Over the last 3 years (2014-2016), publications in DBS for PD appear to have remained stable at approximately 350 to 400 per year.

Gene Therapy

Since initial interest in the 1990s, there was stable growth in the number of gene therapy publications throughout the 2000s, with a maximum of 93 in 2008 (Fig. 1E). This was followed by a plateau in publications and subsequent decline toward present day. Although our search criteria specified "human" as a keyword, many of the articles identified in our search were indeed animal studies. Furthermore, the majority of studies for human gene therapy, in fact, used cell lines for in vitro or ex vivo studies and thus represented preclinical investigations. A number of clinical trials involving gene therapy have been conducted to assess improvement in striatal dopamine metabolism, delivery of neurotrophic factors, or transduction of the STN. While these strategies are promising and have a good safety record, gene therapy remains investigational.

Transplantation

The earliest publications on transplantation for PD appeared in the 1980s (Fig. 1F). Publications in this topic remained stably low, around one to two annual publications throughout the mid-1980s, but then accelerated in the 1990s. From 1988 to 2014, annual publications varied between 10 and 24, with a recent downward trend in the most recent 3 years. Beginning in the 1980s, the most commonly occurring articles were on the topic of autologous transplant of adrenal medulla catecholamine-producing cells for PD. We found 18 medullary transplant articles in the 1980s, 25 in the 1990s and two in the 2000s. The next trend was fetal cell grafts, for which there were 35 publications in the 1990s, 18 in the 2000s, and four in the 2010s. There was a sharp decline in the number of publications and citations on transplantation in the 2010s. In recent years, articles have been mainly animal studies and reviews.

Other Emerging Therapies for Parkinsonian Movement Disorders

We searched for other prominent emerging therapies for movement disorders, including GK radiosurgery and FUS surgery. A search for GK thalamotomy and PD yielded a total of 39 publications in the period of 1991-2016 (Fig. 2A). Activity in this area of research has been relatively sparse compared to work on conventional thalamotomies using radiofrequency ablation. The first case study of GK VIM thalamotomy for parkinsonian tremor uncovered by our search was published in 1993 and reported four of seven patients being relieved of their symptoms.[19] By including the term "essential tremor" in the search query, the number of publications on GK thalamotomy increased to 58. We also performed a search for GK pallidotomy with PD and found 10 publications between 1996 and 2016 with no apparent trend (Fig. 2B).

Magnetic resonance-guided FUS thalamotomy was the newest topic examined, and, accordingly, the search yielded the fewest number of publications: six articles between the years of 2013 and 2016, with a

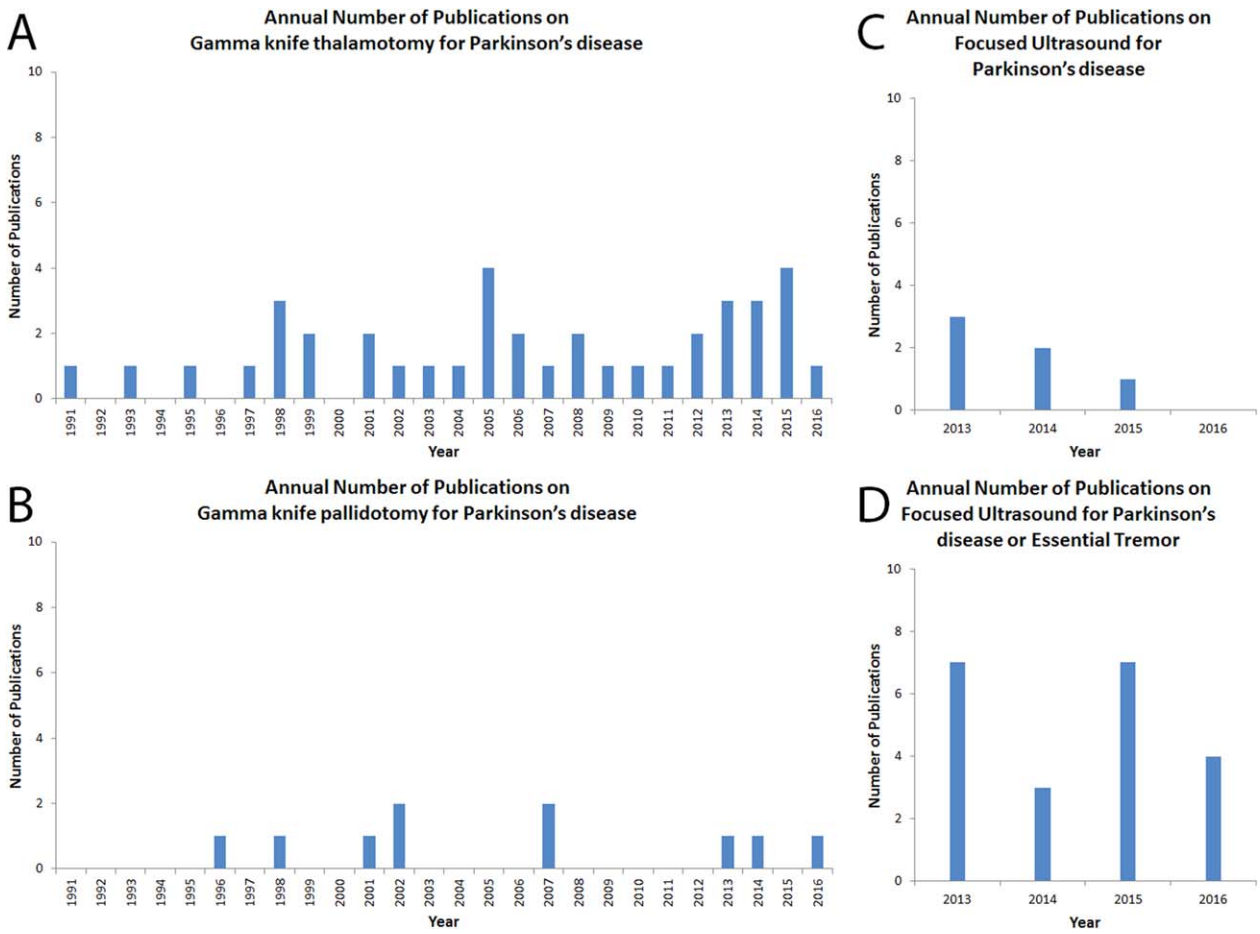

FIG. 2. Annual number of publications on emerging surgical therapies for PD. Annual publication data are presented by emerging surgical technique: (A) GK thalamotomy for PD, (B) GK pallidotomy for PD, (C) FUS thalamotomy for PD, and (D) FUS thalamotomy for PD and essential tremor. [Color figure can be viewed at wileyonlinelibrary.com]

maximum of three in 2013 (Fig. 2C). Expanding the search query to include the term "essential tremor" increased the search results to 21 with a new maximum of seven in 2015 (Fig. 2D). The first publications of FUS thalamotomy for tremor were pilot studies published in 2013. A multicenter, randomized, controlled trial of FUS thalamotomy for essential tremor with 76 subjects was published in 2016.[20]

Discussion

The Rise and Fall, Re-emergence, and Redecline of Pallidotomy for PD

While there has been an ongoing and continuous background level of activity, our data indicate that ablative surgery for PD (both pallidotomy and thalamotomy) have risen and declined not once, but twice in the last 70 years. In the early stereotactic, pre-CT (computerized tomography) era of the 1950s-1970s, medical therapy was limited and advances in stereotactic instruments made surgery safer and more reliable. Correspondingly, pallidotomy and thalamotomy procedures were widely utilized as reflected by an increasing number of related publications. The choice among these two targets was contested, but eventually shifted from the pallidum to the thalamus in the late 1960s attributed to the perceived superiority of thalamotomy for the control of tremor. Thalamotomy could be performed with small and accurate lesions that produced more consistent benefits for tremor as well as fewer complications.[15] A survey of American and Canadian neurosurgeons published in 1975 found that approximately 500 thalamotomies for movement disorders were performed annually by 74 neurosurgeons.[21] In contrast, approximately 35 pallidotomies were being done annually by only 12 neurosurgeons. Although articles concerning pallidotomy continued to be published in the 1970s, these largely involved follow-up of work from the previous decades. In the early stereotactic era, little attention was paid to the rigidity and akinesia of PD, and there were, of course, no drug-induced dyskinesias to contend with. After a period of high usage of pallidotomy and thalamotomy came a sharp fall in the 1970s. The main factor in the decline of neurosurgery for PD at that time was the introduction of L-dopa in the 1960s and the realization of its profound clinical impact.[6]

After 30 years of experience with L-dopa for PD, there was an unexpected renaissance of ablative surgery in the 1990s. This occurred as a consequence of the rediscovery and the clinical reintroduction of pallidotomy by Laitinen and his colleagues.[22] This led to renewed enthusiasm in surgery for PD and a large spike in the number of publications on pallidotomy beginning in the early 1990s (Fig. 1B), including a small number of GK pallidotomy articles (Fig. 2B). The number of articles on pallidotomy increased from 0 to over 90 per year in the decade from 1989 to 1998. In contrast to the experience of the 1950s-1970s, this time, however, pallidotomy was used not so much to treat tremor, but to treat the *off* period symptoms of PD, including rigidity, akinesia, and gait disturbances—as well as the now increasingly important problems of L-dopa-induced dyskinesias, motor fluctuations, and other medication-related adverse effects. The clinical benefits and striking amelioration of L-dopa-induced involuntary movements were documented in several highly cited papers in the 1990s (Table 2). In addition, with improved imaging in the form of CT and MRI and the introduction of microelectrode mapping, the adverse effects of pallidotomy were much reduced compared to the earlier years. Another possible contributing factor to the rapid increase in publications in the 1990s was the additional participation of non-neurosurgeons and the shift from neurosurgeon-driven programs to multidisciplinary programs with more academic opportunities. There were also a very small number of studies of GK used for pallidotomy. While some works report efficacy, others highlight a worrisome rate of adverse effects with GK pallidotomy, which may have dampened enthusiasm for this procedure.[23]

Thalamotomy: Back to the Future

Thalamotomy experienced similar rises and falls as did pallidotomy, although of lesser magnitude. It is estimated that by the mid-1970s, more than 70,000 patients worldwide were treated with thalamotomy.[24] After the mid-1970s, the number of publications declined. The most prominent reason for this decline appears again to be attributed to the popularity of L-dopa therapy. In a 1983 article, Tasker and colleagues considered other possible factors that diminished the use of thalamotomy, including the realization that it does not stop disease progression and that there are relatively narrow patient populations that stand to benefit from it.[25]

The rediscovery of pallidotomy in the early 1990s increased interest in surgery for PD—all boats rise with the tide—and was likely a major contributor to the rising interest in thalamotomy, with the number of articles on thalamotomy peaking in 1999 (Fig. 1C). Another source of publications on thalamotomy in the 1990s and later came from the application of minimally invasive approaches, including GK (Fig. 2A) and FUS (Fig. 2C,D). Gamma-radiation lesions had been attempted to treat movement disorders in the 1960s at a time when target visualization relying on pneumoencephalography was largely unsatisfactory. With the advent of CT scans and MRI, GK thalamotomy became a more viable option.

The first trial of GK thalamotomy for parkisonian tremor was published in 1993 and found modest results. Later, a larger trial with 34 patients also yielded mixed results; only 24% of patients had their tremor completely abolished while the rest had varying efficacy, including 10.5% failing to have any improvement.[26] A year later, an open-label MR-guided GK thalamotomy trial of 154 patients (102 with parkinsonian tremor and 52 with essential tremor) reported more convincing results; 88% of PD patients were tremor free at long-term follow-up.[27] Despite the improving results, a report emerged that raised the alarm about complications associated with the procedure.[23] Between 2000 and 2015, there were nine studies of GK for intractable tremor yielding positive results and conferring low complication rates; however, none of them were randomized, controlled trials.[28] Overall, the long latency response to treatment, concerns of the delayed long-term effects of ionizing radiation, and lack of controlled double-blind data likely contributed to the lack of widespread adoption of GK procedures for PD.

We also investigated the current landscape of MR-guided FUS thalamotomy. Given that it is only in its infancy, publications on this technique are only recently appearing (Fig. 2C,D). This procedure shares similarities with GK thalamotomy, particularly that it does not require opening the skull. Important differences, however, include the immediate effects of FUS, allowing intraoperative adjustment of lesion size and location. More time will have to pass to determine the impact and role of this technique in the treatment of PD.

DBS

The second decline in popularity of pallidotomy and thalamotomy was a direct consequence of the introduction and widespread adoption of DBS (Fig. 1D). A review by Rascol and colleagues compiled the number of Pubmed citations for "pallidotomy" and "deep brain stimulation" for the decades from 1950 to 2010. They found that 1991-2000 saw a 2:1 ratio of citations for pallidotomy versus DBS; however, in 2001-2010, citations for DBS accelerated to become greater than 10 times those for pallidotomy.[29] The record of safety and efficacy of DBS for PD[30] makes it unsurpassed as the current technique of choice for PD surgery.

There are a number of reasons for the shift away from ablative surgeries toward DBS. DBS is

reversible—no permanent lesion is made. DBS allows for adjustment and optimization of stimulation parameters, whereas ablation can only be modified by further ablation. Adverse effects related to lesions are permanent. Adverse effects related to stimulation are reversible. The efficacy of lesional and stimulation procedures, however, can be similar. For example, several studies have shown that both thalamotomy and thalamic DBS control tremor, but DBS has a lower risk of complications.[31,32] Where DBS differentiates itself is in reducing the incidence and severity of adverse effects, particularly for bilateral procedures. It is this improved profile of safety that has been driving the choice of DBS over ablative alternatives. Another factor that may play a large role in the popularization of DBS and other approaches is the strong advocacy and marketing from industry. Alternative approaches, such as lesioning with radiofrequency techniques, have little or no voice.

Since its introduction, there have been a large number of DBS trials with a variety of different targets demonstrating efficacy that is superior to medical therapy alone in carefully selected patients. Since the U.S. Food and Drug Administration approval of DBS for PD in the United States in 2002, DBS device manufacturers estimate that some 150,000 DBS procedures have been performed worldwide, predominantly for PD. That being said, DBS is not without limitations, including (1) a relatively high cost; (2) the need for programming of stimulation parameters; (3) the adverse effects that can be associated with stimulation; and (4) the ongoing risks of breakage, battery depletion, device malfunction, and infection with implanted hardware.

Our search for DBS for PD publications revealed that the number of articles peaked in 2013 and has since decreased slightly. This is consistent with the field being at a mature, steady-state level. DBS will likely remain the dominant technique for the foreseeable future. Despite its success, however, many questions remain. Issues of patient and target selection (thalamus, pedunculopontine nucleus, STN, or GPI) remain active. A major area for the future will be developing a better understanding of the mechanism of action of DBS. The impact of recent advances in DBS technology, including MRI compatibility, directional leads, facilitation and optimization of programming, and closed loop stimulation, have not yet had a major imprint on the landscape of PD publications.

False Starts in Gene Therapy and Transplantation

Throughout the 1990s and early 2000s, the number of publications for gene therapy grew to a maximum in 2009 (Fig. 1E), but much of this growth occurred in the basic science literature as clinical trials struggled to demonstrate efficacy.[33] Overall, the interest in gene therapy in the PD community was has been modest. Several factors may have contributed to this phenomenon, including the (1) significant regulatory hurdles to overcome, which contribute to the complexity of the therapy; (2) lack of or the limited benefits of gene therapy demonstrated to date; (3) superior clinical benefits achievable with other therapies, which have raised therapeutic expectations; and (4) uncertainty about long-term effects on gene expression and safety.

We also examined transplantation for PD. The earliest publication that our search rendered was from 1983 (Fig. 1F), although studies of transplantation in animal models of PD had been performed since the 1970s.[34] Although promising results were reported with the first medullary transplants, they did not show sustained benefit. Transplantation of fetal neural tissue came to prominence as interest in medullar transplants declined. Favorable findings in animal studies led to open clinical trials, some with positive findings. For example, a 1996 trial with fetal cell transplantation in 22 patients found significant improvements in motor and daily life outcomes, allowing the reduction of medication in most of them.[35] A recent postmortem follow-up in a patient who had received a transplant 24 years before revealed that grafted fetal neurons were indeed capable of surviving and integrating into the recipient brain in the long term.[36] Despite the positive effects, major limitations were identified that ultimately held the procedure back: (1) a scarcity of availability of fetal tissue; (2) ethical considerations accompanying its use; (3) the negative blinded clinical trials of transplantation for PD; and (4) the occurrence of dyskinesias associated with the procedure.[37] In addition, certain studies point to host- versus graft-induced neurodegenerative phenomena in the transplanted cells.[38] While still being investigated, transplantation is not in current clinical use for the treatment of PD. With clinical results of DBS as a benchmark, there is less incentive to develop transplantation surgery and a corresponding recent downward trend in transplantation publications today.

Limitations

The aim of this study was to provide a view of neurosurgery for PD over the past century. We wanted to examine the ever-changing state-of-the-art of techniques at the disposal of neurosurgeons and ask why certain procedure have come, gone, or persisted. This bibliometric approach is practical, but is not without limitations. Our method of searching for terms in the title, abstract, and key words was prone to both false positives and false negatives. We found instances of articles not picked up by the search for a variety of technical reasons—for example, the journal was not included in the searched database or the use of

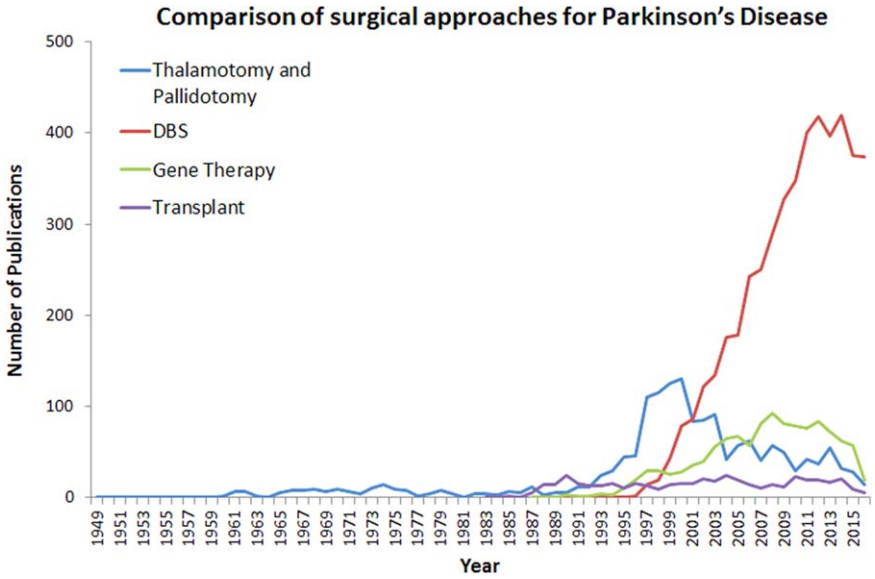

FIG. 3. Comparison of surgical approaches for PD. Trends in annual publications for ablative surgical techniques, DBS, gene therapy, and transplantation for PD from 1949 to 2016 are presented. Data for pallidotomy and thalamotomy (including GK and FUS procedures) were combined.

synonyms or alternative phrasing that was not included in the search query (e.g., pallidectomy versus pallidotomy). Scopus, unlike PubMed, does not have a built-in function to differentiate human versus animal studies; hence, a large number of false positives. In addition, the coverage of Scopus itself could have had an influence on our results. Until recently, Scopus coverage only extended to 1996, but it has now expanded to earlier years. We did, however, notice that some important articles from the 1960s and earlier were not identified by our search. Scopus, on the other hand, also provides citation counts, something that is not available with PubMed. In addition, we used the number of publications as a proxy for the level of activity or enthusiasm for a particular surgical procedure. This, by necessity, is a crude estimate and does not take into account a number of important variables, including the large number of centers who perform surgery but do not publish their results, socioeconomic factors influencing the choice of procedure, geographical differences in the propensity for publishing the results of surgery, and the time lag between procedures and publications. These limitations aside, we believe that, on the whole, our results are representative of the body of work in the field of neurosurgery for PD and how this field has changed over time.

Conclusion

The landscape of neurosurgery for PD and other movement disorders has changed dramatically over the past century (Fig. 3). Some techniques were borne out of sound rationale, others serendipitously; some were facilitated by novel technology, whereas others re-emerged after decades of lost interest. The advancement of ablative approaches was greatly facilitated by the invention of stereotaxis and dominated early on until the advent of L-dopa. After a period of dormancy in the 1960s-1980s, there was a renaissance of neurosurgery for movement disorders fueled by improvements in imaging, targeting, radiosurgery, and an emerging interest in transplantation and gene therapy. In the modern era, DBS has dominated because of its important advantages over ablative therapies. Gene therapy and transplantation showed initial promise, but so far have largely not held up in clinical trials. Other procedures like GK and FUS thalamotomy are still in their infancy and will continue to be investigated. If the past is any indication, with technical improvements and better understanding, the future will likely hold ongoing revisits of past techniques and the development of yet to be described novel procedures to treat PD. ■

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References

1. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med 2011;1:a008862.
2. Goetz CG. Jean-Martin Charcot and his vibratory chair for Parkinson disease. Neurology 2009;73:475-478.
3. Leriche R. Ueber chirurgischen Eingriff bei der Parkinsonschen Krankheit [On surgical interventions for Parkinson's disease]. Neurol Centralbl 1912;13:1093-1096.
4. Gildenberg PL. The history of surgery for movement disorders. Neurosurg Clin N Am 1998;9:283-294.
5. Bucy PC, Case TJ. Tremor. Physiologic mechanism and abolition by surgical means. Arch Neurol Psychiatry 1939;41:721-746.
6. Guridi J, Lozano AM. A brief history of pallidotomy. Neurosurgery 1997;41:1169-1180; discussion, 1180-1163.

7. Cooper IS. Surgical occlusion of the anterior choroidal artery in parkinsonism. Surg Gynecol Obstet 1954;99:207-219.
8. Cooper IS. Surgical alleviation of Parkinsonism; effects of occlusion of the anterior choroidal artery. J Am Geriatr Soc 1954;2:691-718.
9. Das K, Benzil DL, Rovit RL, Murali R, Couldwell WT. Irving S. Cooper (1922-1985): a pioneer in functional neurosurgery. J Neurosurg 1998;89:865-873.
10. Horsley V, Clarke RH. The structure and functions of the cerebellum examined by a new method. Brain 1908;31:45-124.
11. Spiegel EA, Wycis HT, Marks M, Lee AJ. Stereotaxic apparatus for operations on the human brain. Science 1947;106:349-350.
12. Cooper IS, Bravo G. Chemopallidectomy and chemothalamectomy. J Neurosurg 1958;15:244-250.
13. Hassler R. [Cerebellar projections to the midbrain and thalamus in man]. Dtsch Z Nervenheilkd 1950;163:629-671.
14. Speakman TJ. Results of thalamotomy for Parkinson's disease. Can Med Assoc J 1963;89:652-656.
15. Krayenbuhl H, Wyss OA, Yasargil MG. Bilateral thalamotomy and pallidotomy as treatment for bilateral Parkinsonism. J Neurosurg 1961;18:429-444.
16. Narabayashi H, Okuma, T. Procaine-oil blocking of the globus pallidus for the treatment of rigidity and tremor of parkinsonism. Proc Japan Acad 1953;29:134-137.
17. Sanchez Juan J. [Experience with mechanical pallidotomy in therapy of Parkinson's disease]. Rev Clin Esp 1958;68:155-160.
18. Hassler R, Riechert, T. Indikationen und Lokalisationsmethode der gezielten Hirnoperationen [Indications and localization methods for targeted brain surgery]. Nervenarzt 1954;25:441-447.
19. Rand RW, Jacques DB, Melbye RW, Copcutt BG, Fisher MR, Levenick MN. Gamma Knife thalamotomy and pallidotomy in patients with movement disorders: preliminary results. Stereotact Funct Neurosurg 1993;61(Suppl 1):65-92.
20. Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2016;375:730-739.
21. Gildenberg PL. Survey of stereotactic and functional neurosurgery in the United States and Canada. Appl Neurophysiol 1975;38:31-37.
22. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 1992;76:53-61.
23. Okun MS, Stover NP, Subramanian T, et al. Complications of gamma knife surgery for Parkinson disease. Arch Neurol 2001;58: 1995-2002.
24. Pereira EA, Aziz TZ. Surgical insights into Parkinson's disease. J R Soc Med 2006;99:238-244.
25. Tasker RR, Siqueira J, Hawrylyshyn P, Organ LW. What happened to VIM thalamotomy for Parkinson's disease? Appl Neurophysiol 1983;46:68-83.
26. Duma CM, Jacques DB, Kopyov OV, Mark RJ, Copcutt B, Farokhi HK. Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: a five-year experience. J Neurosurg 1998;88:1044-1049.
27. Young RF, Jacques S, Mark R, et al. Gamma knife thalamotomy for treatment of tremor: long-term results. J Neurosurg 2000; 93(Suppl 3):128-135.
28. Higuchi Y, Matsuda S, Serizawa T. Gamma knife radiosurgery in movement disorders: Indications and limitations. Mov Disord 2017;32:28-35.
29. Rascol O, Lozano A, Stern M, Poewe W. Milestones in Parkinson's disease therapeutics. Mov Disord 2011;26:1072-1082.
30. Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord 2006;21(Suppl 14):S290-S304.
31. Tasker RR. Deep brain stimulation is preferable to thalamotomy for tremor suppression. Surg Neurol 1998;49:145-153; discussion 153-144.
32. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 2000;342:461-468.
33. Bartus RT, Weinberg MS, Samulski RJ. Parkinson's disease gene therapy: success by design meets failure by efficacy. Mol Ther 2014;22:487-497.
34. Perlow MJ, Freed WJ, Hoffer BJ, Seiger A, Olson L, Wyatt RJ. Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 1979;204:643-647.
35. Kopyov OV, Jacques D, Lieberman A, Duma CM, Rogers RL. Clinical study of fetal mesencephalic intracerebral transplants for the treatment of Parkinson's disease. Cell Transplant 1996;5:327-337.
36. Li W, Englund E, Widner H, et al. Extensive graft-derived dopaminergic innervation is maintained 24 years after transplantation in the degenerating parkinsonian brain. Proc Natl Acad Sci U S A 2016;113:6544-6549.
37. Brundin P, Barker RA, Parmar M. Neural grafting in Parkinson's disease: problems and possibilities. Prog Brain Res 2010;184:265-294.
38. Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 2008;14:504-506.
39. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344:710-719.
40. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925-1934.
41. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
42. Deep-Brain Stimulation for Parkinson's Disease Study Group, Obeso JA, Olanow CW, et al. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345:956-963.
43. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991;337:403-406.
44. Limousin P, Pollak P, Benazzouz A, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91-95.
45. Lindvall O, Brundin P, Widner H, et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 1990;247:574-577.
46. Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84:203-214.
47. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 2009;301:63-73.
48. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 2005;128(Pt 10):2240-2249.
49. Kaplitt MG, Feigin A, Tang C, et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet 2007;369:2097-2105.
50. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50:344-346.
51. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009;8:464-474.
52. Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007;318:1309-1312.
53. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010;362:2077-2091.
54. Piccini P, Brooks DJ, Bjorklund A, et al. Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient. Nat Neurosci 1999;2:1137-1140.
55. Freed CR, Breeze RE, Rosenberg NL, et al. Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease. N Engl J Med 1992; 327:1549-1555.
56. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8:67-81.

57. Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 1995; 346:1383-1387.

58. Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med 1999;340:1476-1480.

59. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 1998;51:850-855.

60. Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130(Pt 6):1596-1607.

61. Madrazo I, Drucker-Colin R, Diaz V, Martinez-Mata J, Torres C, Becerril JJ. Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. N Engl J Med 1987;316:831-834.

62. Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14:572-584.

63. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 2000; 123(Pt 10):2091-2108.

64. Hutchison WD, Allan RJ, Opitz H, et al. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 1998;44:622-628.

65. Baron MS, Vitek JL, Bakay RA, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 1996;40:355-366.

66. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 2004;115:1239-1248.