

# Deep brain stimulation: An overview of history, methods, and future developments

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## Abstract

Deep brain stimulation has already revolutionised the clinical management of treatment-resistant movement disorders and offers novel treatment options for an increasing range of neurological and psychiatric illnesses. In this article, we briefly review the history of deep brain stimulation, particularly focusing on the last 50 years, which have seen rapid development in the safety and efficacy of deep brain stimulation. We then discuss the current state of the art in deep brain stimulation, focusing on emerging indications and recent technological advances that have improved the field. Finally, we consider the future developments in technology, technique, and research that will impact deep brain stimulation; particularly focusing on closed-loop stimulation techniques and emerging techniques such as optogenetics, cybersecurity risk, implantation timing, and impediments to undertaking high-quality research.

## Keywords

Deep brain stimulation, neuromodulation, history, future advances, cybersecurity, movement disorders

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## Introduction

Deep brain stimulation (DBS) has revolutionised treatment of movement disorders over recent decades, providing remarkable relief to patients with Parkinson's disease (PD) and other profoundly debilitating disorders. The rise of DBS has provided a clear example of successful translation from basic neurophysiological research into clinical practice and offers a prospect of exciting future developments in neuromodulatory treatments. To mark the 50th anniversary of the *Brain and Neuroscience Advances* (BNA), we will look back over the recent history of DBS to assess the foundations of modern clinical practice, discuss the state of the art in the field, and speculate as to the challenges and opportunities facing the field over the coming 50 years.

DBS is the implantation of electrodes into deep brain regions for the purpose of modulating neural function in order to treat neurological/psychiatric conditions. The electrodes are implanted using stereotactic techniques and are attached to an implantable pulse generator (IPG), which is typically placed subdermally below the clavicle (Figure 1). A modern IPG contains a battery along with electronic components that deliver electrical stimulation and can be externally controlled by patients or clinicians. Stimulation parameters such as frequency, pulse width, and voltage need to be altered to achieve maximum efficacy.

The precise physiological mechanisms of DBS are not yet fully understood, but it is generally believed to work via excitation and/or inhibition of neuronal cell bodies local to the electrode

and of axons passing nearby. Low-frequency stimulation appears to generally excite nearby neurons, whereas high-frequency stimulation can reduce local activity and thereby induce a reversible functional lesion. However, this simplistic view of the mechanism of action has been challenged in recent years, and it is likely that a more complete understanding will facilitate improved DBS treatments in Herrington et al. (2016; Figure 1).

## The history of DBS

### Early history

The roots of modern DBS stretch back to the early experimental endeavours in brain stimulation that took place in the late 19th century. A detailed discussion of these events can be found in Schwab and Hamani (2008), but, briefly, developments in stimulation of the cerebral cortex of animals laid the foundations of cortical functional localisation as we know it today. The first

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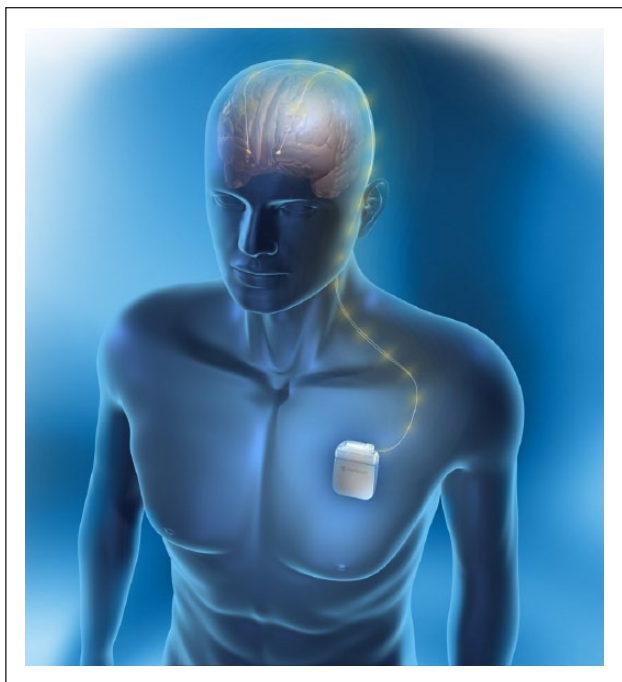
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**Figure 1.** Diagram of implanted DBS system (courtesy of Medtronic, inc. (used with permission)).

stereotactic frame was developed in the early 1900s, enabling experimentation in stimulation of deeper brain regions.

Introduction of X-ray pneumoencephalography in 1947 vastly improved surgeons' ability to localise targets, particularly with the later development of detailed stereotactic atlases. The 1950s saw the introduction of lesioning as treatment for tremor – stereotactic techniques were used to ablate the ventrolateral or ventroanterior nuclei of the thalamus, with intraoperative electrical stimulation and recording being employed to localise targets. This work was extended by Albe Fessard et al. (1963), who first reported that high-frequency (~100–200 Hz) electrical stimulation of the ventral intermediate thalamic nucleus could substantially alleviate Parkinsonian tremor (Albe Fessard et al., 1963). Implantable spinal cord stimulators first introduced by Shealy and colleagues in 1967 also moved the field closer to the modern use of chronically implanted DBS systems.

### *The last 50 years*

Research into early forms of DBS was curtailed by the development of levodopa treatment in the late 1960s, which proved highly effective for alleviating most Parkinsonian symptoms. In comparison to the seemingly miraculous efficacy of levodopa, the risk and expense inherent in implantation of DBS was unjustifiable in most physicians' minds. Combined with the ongoing public reaction against deeply concerning aspects of prefrontal leucotomy psychosurgery, DBS and stereotactic neurosurgery in general stagnated.

Despite this lack of enthusiasm among many researchers and clinicians, some work did continue. DBS continued to see limited use in the treatment of intractable chronic (Hosobuchi et al., 1973), with Medtronic, Inc. (Minneapolis, MN, USA) releasing

the first commercially available fully implanted DBS systems in the mid-1970s for this purpose. Other research groups were investigating use of thalamic DBS for treating disorders of consciousness, reporting some degree of success at increasing patients' level of arousal.

By the 1980s, it was clear that using levodopa will not result the miracle cure that it was initially thought to be; Parkinsonian patients developed resistance after years of treatment along with side effects such as dyskinesias. Meanwhile, implantable medical device technology had been improving to the point that chronically implanted devices such as spinal cord stimulators and cardiac pacemakers were routine. At the same time, understanding of the neurophysiological basis of movement disorders was improving rapidly; perhaps the most important theoretical advance was the development by Albin, DeLong, and colleagues of a coherent model of basal ganglia functional anatomy and its relation to movement (Albin et al., 1989).

This model was heavily influenced by primate experiments throughout the 1980s, in particular those utilising the N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinsonism (Burns et al., 1983). Further evidence supporting the model was provided by metabolic studies utilising radiolabelled 2-deoxyglucose, as pioneered by Crossman and colleagues, which revealed the subthalamic nucleus (STN) to be overactive in the Parkinsonian brain (Mitchell et al., 1989). Concurrently, teams led by Benabid and Blond and Siegfried had been experimenting with the use of high-frequency DBS as an alternative to thalamic lesioning for patients with advanced PD, each independently reporting their results in 1991 (Schwalb and Hamani, 2008) demonstrating the first implementations of modern DBS.

The early 1990s also saw publication of further primate data, supporting the value of the STN as a surgical target based on the MPTP nonhuman primate (NHP; Aziz et al., 1991). This work was quickly translated into clinical practice and the first report of STN-DBS appeared in Pollak et al. (1993), indicating efficacy in treating PD motor symptoms. Similarly, the internal globus pallidus (GPi) was identified as a viable target for DBS as an alternative to pallidal ablation (Siegfried and Lippitz, 1994). By the end of the decade, clinical use of DBS was started to become widespread in the treatment of Parkinsonian disorders.

## **The state of the art**

### *Indications*

Since the introduction of STN and GPi DBS for PD, more than 100,000 patients worldwide have received the procedure. Both stimulation targets have proven to be highly effective at treating a range of PD symptoms, with STN-DBS tending to be more effective at reducing medication intake and GPi-DBS being preferable in terms of minimising psychiatric illness (Liu et al., 2014).

Success in PD has spurred development of DBS as a treatment for a plethora of other conditions, some of which have achieved widespread clinical adoption, but most remain niche and/or investigational. Aside from PD, essential tremor and dystonia are the most widely accepted indications for DBS (Kocabicak et al., 2015), with substantial bodies of evidence supporting its efficacy. Other disorders for which DBS shows

**Table 1.** DBS indications.

Indication	Target(s)	Status
Parkinson's	Subthalamic nucleus	Well-established
	Internal globus pallidus	
Essential tremor	Ventral intermediate thalamus	Not widely implemented, still under investigation
Dystonia	Internal globus pallidus	
Parkinson's	Pedunculopontine nucleus	
	Zona incerta	
Essential tremor	Zona incerta	Very limited investigation, largely hypothetical
Pain	Periaqueductal and periventricular grey matter	
	Ventral posterolateral and posteromedial thalamus	
	Anterior cingulate cortex	
OCD	Anterior limb of internal capsule	
	Medial thalamus	
Tourette's	Internal globus pallidus	
Epilepsy	Hippocampus	
Depression	Subgenual cingulated	
	Nucleus accumbens	
Cluster headache	Posterior hypothalamus	Very limited investigation, largely hypothetical
Addiction	Nucleus accumbens	
Anorexia	Nucleus accumbens	
Obesity	Nucleus accumbens	
Alzheimer's	Fornix	
	Ventromedial prefrontal cortex	
Huntington's	Internal globus pallidus	

OCD: obsessive-compulsive disorder.

promise include chronic pain, obsessive-compulsive disorder (OCD), epilepsy, and depression. More speculatively, addiction, anorexia, obesity, Tourette's, and Alzheimer's are all being discussed and limited trials are being undertaken. Table 1 shows the anatomical targets being utilised for each indication.

### Technology

Implant design has advanced substantially over recent years. During the 1980s, a typical DBS system consisted of an implanted radiofrequency receiver coil attached to electrodes, with an external battery device providing power transdermally via induction. Modern designs, however, universally include integrated batteries; these can be primary cell designs with a battery that must last several years or rechargeable designs that have become more widely available recently, enabling transdermal recharging and hence longer IPG life. Battery life is highly dependent on the stimulation parameters required and, hence, the indication. Stimulation for PD requires less charge delivered than stimulation for dystonia, for example, resulting in dystonic patients usually requiring more frequent IPG replacement and/or recharging.

The IPG itself is typically a titanium case with a protrusion of biocompatible polymer where the electrodes can be plugged in. The largest component within the case is the battery. Charge from the battery is controlled by electronics that deliver current to the electrodes at a specified frequency, pulse width, and voltage or amperage.

All modern IPGs contain a radiofrequency antenna so that external programming devices can be used to set the stimulation

parameters, as well as for monitoring impedance and editing stored data. Typically, one programming device is designed for clinicians to use and features the full range of controls, and another is given to patients and features fewer settings, often restricted by settings that can be altered by the clinician programming device. Increasingly, these devices are taking the form of 'apps' on consumer-grade mobile devices such as smartphones and tablets, instead of purpose-built devices. Most IPGs use proprietary radio communication protocols, although recently consumer-grade protocols such as Bluetooth are being utilised in order to facilitate interoperability of devices.

Charge is delivered via transcranial electrodes, which typically feature multiple electrode contacts. During programming, the active contact can be changed, delivering energy to slightly different locations, enabling limited fine-tuning of the stimulation location. A major recent development is the implementation of 'directional' or 'segmented' electrodes – these consist of multiple separate electrode contacts arranged around the circumference of the electrode, which can deliver the charge simultaneously. This enables more precise control over the volume of neural tissue that is activated, thereby allowing for minor deviations from the intended implant trajectory to be corrected and for small variations in individual anatomy to be compensated for.

### Future opportunities and pitfalls

DBS has already proven to be an exciting and effective tool for treating a range of conditions, but there is good reason to believe that the field is only beginning to realise its full potential.

Targeted stimulation has the potential to be far more precise than pharmacological approaches to neurological disorders. Conversely, however, such a powerful technological approach to modulation of brain function will inevitably come with the risk of serious negative outcomes if implemented poorly.

### *Novel technologies*

Perhaps the most obvious way in which DBS will develop is through incremental improvements in implant design, continuing a trend that has been proceeding since implantable neurostimulation devices were invented. Improved battery life comes with advances in chemical engineering; lower power microprocessor design enables more complex stimulation programmes. Some of these gradual advances will enable paradigm shifts in IPG technology, such as the historical leap from transdermal induction-powered stimulation to fully implanted battery-powered IPGs, while some will merely refine existing IPG designs.

Current DBS systems rely on stimulation parameters pre-set by a clinician (or, within limits, the patient), which remain static until manually altered. In ‘Closed-loop’ or ‘adaptive’ DBS (aDBS), the stimulator records local neural activity as well as stimulating. The local field potentials (or other physiological signals) can then be fed back to dynamically alter and optimise stimulation parameters. Clinical implementation of aDBS has so far been limited due to a range of challenges to optimising each component of the feedback (Krook-Magnuson et al., 2015), but the approach promises substantial benefits in the future. Proof-of-concept clinical testing using beta-frequency oscillations in the basal ganglia as a control signal, expanding earlier work on NHPs, suggests greater efficacy at treating PD than conventional DBS, while reducing power (Little et al., 2013).

Another important emerging theme in IPG design is increased networking with other devices. Already cardiac implants integrate with base stations that communicate wirelessly with the implanted medical device (IMD) and transmit telemetry data to clinicians over the Internet. This technology allows for fast diagnosis of emerging problems detected by the IMD, response to IMD failures, and fewer clinical visits for calibration or monitoring. It is likely that similar systems will be developed for DBS, especially once aDBS is widespread and enables remote monitoring of pathological neural activity. This networking may take place via applications running on consumer hardware such as smartphones and tablets. Increased networking of IPGs does, however, increase the cybersecurity risk inherent in wirelessly communicating electronic devices. Dedicated attackers could cause considerable harm to patients if they were able to access existing IPGs. As the complexity and prevalence of DBS increase, this risk is only likely to get worse without increased manufacturer and clinician (Pycroft et al., 2016).

Looking further ahead, DBS may begin to transition beyond electrical stimulation in isolation. Optogenetics, that is, modulation of neural activity using light to stimulate neurons transfected with light-sensitive receptors, shows obvious promise as a tool for clinical use in DBS. In animal models, this technology has been demonstrated to be capable of modulating circuits involved in pathological processes, including Parkinson’s, and could provide a practical method of stimulating deep-brain circuits in the future (Chow and Boyden, 2013). However, currently, there are many hurdles to overcome, both in terms of designing a safe and

effective viral vector and overcoming the engineering challenges involved in delivering light to regions deep inside (relatively opaque) brain tissue without causing thermal injury.

A major disadvantage of DBS as currently implemented is the necessity of inserting an electrode through the scalp, skull, and brain, with all the hazards this entails. This may not be a problem indefinitely as several emerging neuromodulatory technologies offer the potential for augmenting or supplanting traditional electrical DBS with alternative stimulation modalities. Focused ultrasound has been demonstrated to be effective at modulating cortical activity on macaques, as validated by behavioural and functional magnetic resonance imaging (fMRI; Yang et al., 2018), and it may become a viable means of modulating deep brain regions in human patients (Kubanek, 2018). Transcranial electromagnetic fields are quite well established as a means of noninvasively modulating superficial brain activity, but recent in-vivo research suggests that temporally interfering electromagnetic fields could be used to affect deep brain (Grossman et al., 2017).

### *Developments in surgical technique*

In addition to development of improved technology, there are several opportunities for future refinement of DBS through changes in its application.

Improvements may be found in simultaneous stimulation of multiple targets. Currently, the majority of patients receive stimulation targeting just a few sites, with electrodes placed unilaterally or bilaterally, but additional electrodes are occasionally implanted with the intent of managing future degradation in the patient’s condition or addressing specific symptoms not treated by the first set of electrodes. In future, patients may increasingly benefit from implantation of several electrodes with the intent of treating multiple symptoms at once or synergistically treating one symptom via multiple mechanisms. Some existing IPGs are capable of stimulating at up to two different frequencies simultaneously; future devices may allow different stimulation parameters to be established for each electrode contact.

DBS is typically a treatment of last resort due to the non-trivial risks associated with surgery. For certain indications, however, this view could be counterproductive as optimal outcomes may be dependent on early intervention. A recent randomised blinded multi-centre trial investigated use of DBS in PD patients with a mean disease duration of only 7.5 years, instead of the more typical mean duration of ~11–14 years before DBS, compared with medication only (Schuepbach et al., 2013). The authors report significant improvements in clinical condition compared with medication only, and improvements in both motor symptoms and quality-of-life measures were comparable to those reported elsewhere in later stage DBS implants, indicating that early-stage DBS implantation may provide additional years of higher quality living for patients. This study suggests that it may be valuable to implement DBS earlier in PD, before pharmacoresistance develops, although this must be weighed against the probable necessity for subsequent IPG reimplantations incurring greater morbidity (a risk that can be lessened with rechargeable IPGs, as discussed below). Similarly, early DBS implantation has also been recommended in childhood dystonia by investigators who found a strong inverse correlation between disease duration and positive clinical outcomes (Lumsden et al., 2013).



Improvements may also be found in the preoperative planning stage. Optimal electrode placement is crucial to good clinical outcomes, but can be confounded by inter-individual variation in neural tract organisation. Therefore, use of magnetic resonance imaging (MRI) tractographic techniques such as diffusion tensor imaging to determine individual patients' connectivity may provide a useful basis for surgical planning (Calabrese, 2016). Research into connectomic approaches to DBS planning is ongoing, providing increasing evidence for the viability of tractographic planning as a means of improving electrode localisation (Riva-Posse et al., 2018; See and King, 2017). Though these studies are often hampered by small participant numbers, there is good reason to be optimistic about future developments in connectomically informed preoperative planning.

### Research challenges

For all its promise, DBS faces several prominent challenges to its development and widespread adoption. An in-depth discussion of the complexities of these issues is beyond the scope of this chapter, but they are worth mentioning briefly as potential impediments to the future of DBS.

As discussed in the history section, the development of modern DBS has been heavily reliant on animal models, and future developments will likewise require use of nonhuman in-vivo experimentation. Primates, particularly macaques and to a lesser degree marmosets, have enabled development of animal disease models very closely mirroring human movement disorders, thanks to the similarity between human and NHP (Kringelbach et al., 2007). However, this similarity brings with it substantial ethical responsibilities on the part of researchers, as well as political challenges in the form of regulatory agencies and animal rights activists, and more financially burdensome husbandry costs in comparison with rodent-based research.

Successfully translating research into widespread clinical use is impeded by difficulty in designing suitable clinical trials. Blinding is particularly challenging in DBS research as, for many targets, patients are acutely aware of the stimulation being on or off. Many of the desired clinical effects are reliant on stimulating above the threshold of conscious awareness, so stimulating below that threshold may lead to false negatives due to a lack of clinical efficacy that would be present at higher stimulation levels. For targets where patients are not aware, however, performing well blinded trials is easier than with traditional ablation surgeries, as stimulators can be switched on and off at will without performing sham surgery.

Financial cost also provides an impediment to DBS research and widespread clinical adoption. The hardware itself is expensive, as are the surgery and follow-up appointments, meaning that large-scale trials can be hard to secure funding for. Lack of large-scale trial data makes funding bodies reluctant to pay for patients to undergo DBS, resulting in fewer patients to study. This expense issue is particularly problematic in the developing world, where very few people can afford the hardware and treatment costs despite a high prevalence of movement disorders and other conditions that may be amenable to DBS treatment. Further development of low-cost IPGs would help ameliorate this problem, although the lack of surgical facilities and expertise may still be a limiting factor.

## Conclusion

As we develop a deeper understanding of the neurophysiological mechanisms underlying various disorders, it is possible to successfully target an increasing variety of structures for electrical modulation via DBS. Further advances in fundamental neuroscience, along with other fields of science and technology, will likely expand the clinical role of DBS. An unusually clear connection between basic science, clinical research, and clinical practice is evident in DBS, making it particularly interesting from both a humanitarian and a scientific perspective. There are potential pitfalls ahead, as with any developing area of science, but DBS holds substantial promise and there is good cause to believe that the next 50 years of advancement will bring even greater benefits than those seen over the last 50 years.

### Declaration of conflicting interests

Prof. Tipu Aziz has undertaken paid consultancy work for Boston Scientific, Medtronic, and St Jude Medical. The other authors have no conflicts of interest to report.

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## References

- Albe Fessard D, Arfel G, Guiot G, et al. (1963) Characteristic electric activities of some cerebral structures in man. *Annales de chirurgie* 17: 1185–1214.
- Albin RL, Young AB and Penney JB (1989) The functional anatomy of basal ganglia disorders. *Trends in Neurosciences* 12(10): 366–375.
- Aziz TZ, Peggs D, Sambrook MA, et al. (1991) Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Movement Disorders* 6(4): 288–292.
- Burns RS, Chiueh CC, Markey SP, et al. (1983) A primate model of parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proceedings of the National Academy of Sciences of the United States of America* 80(14): 4546–4550.
- Calabrese E (2016) Diffusion tractography in deep brain stimulation surgery: A review. *Frontiers in Neuroanatomy* 10: 45.
- Chow BY and Boyden ES (2013) Optogenetics and translational medicine. *Science Translational Medicine* 5(177): 177ps5.
- Grossman N, Bono D, Dedic N, et al. (2017) Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 169(6): 1029–1041.
- Herrington TM, Cheng JJ and Eskandar EN (2016) Mechanisms of deep brain stimulation. *Journal of Neurophysiology* 115(1): 19–38.
- Hosobuchi Y, Adams JE and Rutkin B (1973) Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Archives of Neurology* 29(3): 158–161.
- Kocabicak E, Temel Y, Höllig A, et al. (2015) Current perspectives on deep brain stimulation for severe neurological and psychiatric disorders. *Neuropsychiatric Disease and Treatment* 11: 1051–1066.
- Kringelbach ML, Jenkinson N, Owen SLF, et al. (2007) Translational principles of deep brain stimulation. *Nature Reviews Neuroscience* 8(8): 623–635.
- Krook-Magnuson E, Gelin JN, Soltész I, et al. (2015) Neuroelectronics and biooptics: Closed-loop technologies in neurological disorders. *JAMA Neurology* 72(7): 823–829.
- Kubaneck J (2018.) Neuromodulation with transcranial focused ultrasound. *Neurosurgical Focus* 44: E14.

- Little S, Pogosyan A, Neal S, et al. (2013) Adaptive deep brain stimulation in advanced Parkinson disease. *Annals of Neurology* 74(3): 449–457.
- Liu Y, Li W, Tan C, et al. (2014) Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease. *Journal of Neurosurgery* 121(3): 709–718.
- Lumsden DE, Kaminska M, Gimeno H, et al. (2013) Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. *Developmental Medicine & Child Neurology* 55(6): 567–574.
- Mitchell IJ, Clarke CE, Boyce S, et al. (1989) Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 32(1): 213–226.
- Pollak P, Benabid AL, Gross C, et al. (1993) Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Revista de neurologia* 149(3): 175–176.
- Pycroft L, Boccard SG, Owen SLF, et al. (2016) Brainjacking: Implant security issues in invasive neuromodulation. *World Neurosurgery* 92: 454–462.
- Riva-Posse P, Choi KS, Holtzheimer PE, et al. (2018) A connectomic approach for subcallosal cingulate deep brain stimulation surgery: Prospective targeting in treatment-resistant depression. *Molecular Psychiatry* 23(4): 843–849.
- Schuepbach WMM, Rau J, Knudsen K, et al. (2013) Neurostimulation of Parkinson's disease with early motor complications. *New England Journal of Medicine* 368: 610–622.
- Schwab JM and Hamani C (2008) The history and future of deep brain stimulation. *Neurotherapeutics* 5(1): 3–13.
- See AAQ and King NKK (2017.) Improving surgical outcome using diffusion tensor imaging techniques in deep brain stimulation. *Frontiers in Surgery* 4: 54.
- Siegfried J and Lippitz B (1994) Bilateral chronic electrostimulation of ventroposterolateral pallidum: A new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery* 35(6): 1126–1129; discussion 1129–1130.
- Yang PF, Phipps MA, Newton AT, et al. (2018) Neuromodulation of sensory networks in monkey brain by focused ultrasound with MRI guidance and detection. *Scientific Reports* 8: 7993.