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Technology of deep brain stimulation: current status and future directions

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Abstract

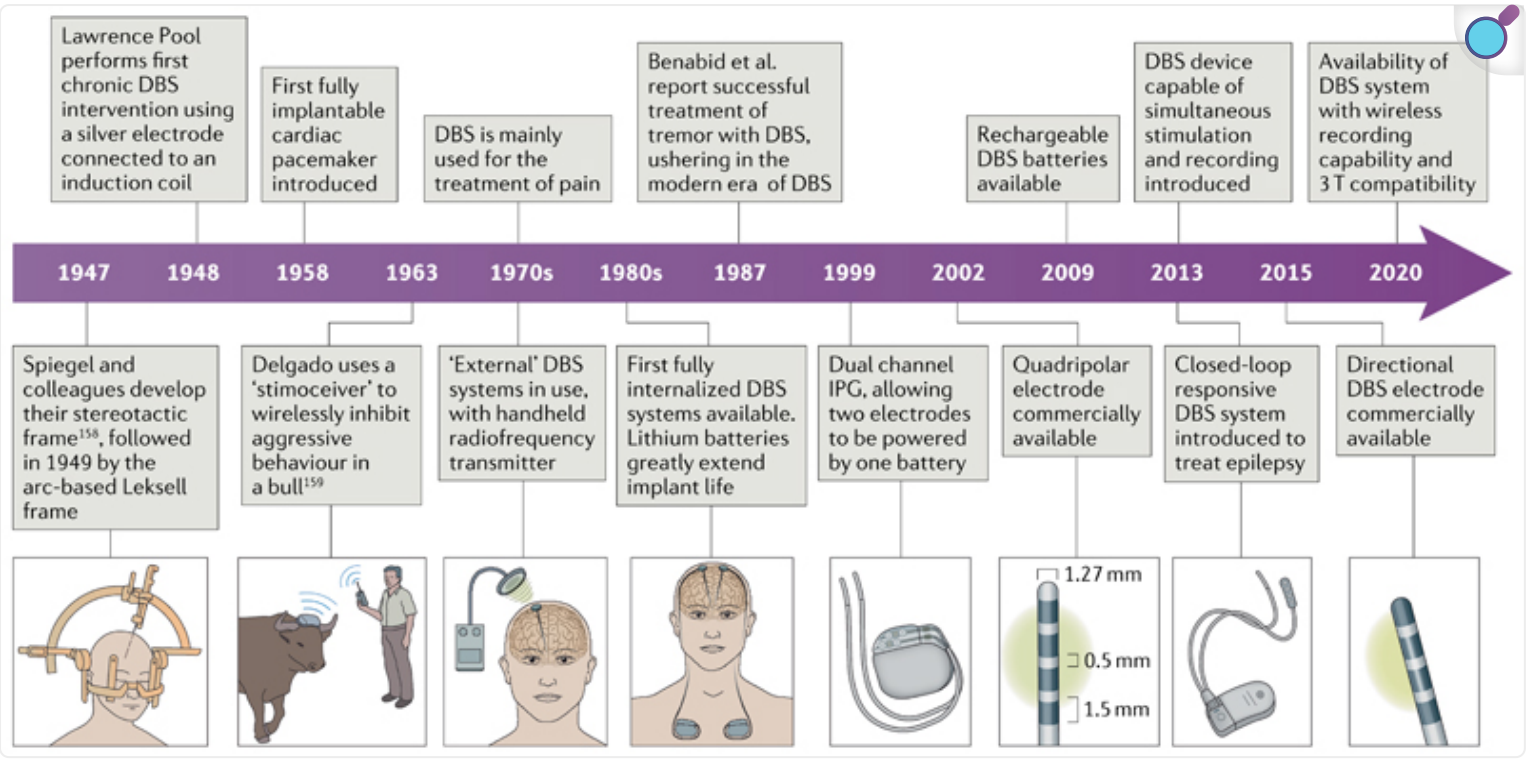
Deep brain stimulation (DBS) is a neurosurgical procedure that allows targeted circuit-based neuromodulation. DBS is a standard of care in Parkinson disease, essential tremor and dystonia, and is also under active investigation for other conditions linked to pathological circuitry, including major depressive disorder and Alzheimer disease. Modern DBS systems, borrowed from the cardiac field, consist of an intracranial electrode, an extension wire and a pulse generator, and have evolved slowly over the past two decades. Advances in engineering and imaging along with an improved understanding of brain disorders are poised to reshape how DBS is viewed and delivered to patients. Breakthroughs in electrode and battery designs, stimulation paradigms, closed-loop and on-demand stimulation, and sensing technologies are expected to enhance the efficacy and tolerability of DBS. In this Review, we provide a comprehensive overview of the technical development of DBS, from its origins to its future. Understanding the evolution of DBS technology helps put the currently available systems in perspective and allows us to predict the next major technological advances and hurdles in the field.

The opportunities to use technology to modulate or influence brain circuitry and human behaviour have increased exponentially over the past few years. These developments have spawned the field of

electroceuticals, with deep brain stimulation (DBS) being the most important and accepted treatment within this class of therapies[1]. DBS is commonly indicated for the treatment of movement disorders such as Parkinson disease (PD), tremor and dystonia, and became the standard of care for these conditions after receiving FDA and Conformité Européene (CE) approval[2–4]. In addition, DBS has been used for pain syndromes, such as neuropathic pain and cluster headache, as well as for epilepsy[5–7]. A favourable safety profile and demonstration of efficacy in several randomized controlled trials has led to increased interest in the potential application of DBS to psychiatric disorders[1]. Following a positive randomized controlled trial published in 2008, DBS for obsessive–compulsive disorder (OCD) was granted CE approval and an FDA Humanitarian Device Exemption[8,9], and DBS is currently under investigation for a wide range of other treatment-resistant conditions, including depression, Alzheimer disease, Tourette syndrome, addiction, anorexia nervosa and schizophrenia[9]. The minimally invasive character of DBS, combined with the low incidence of severe, disabling adverse effects, has expanded its potential uses and prompted studies on novel applications for conditions such as tinnitus, arterial hypertension and sleep disorders[9]. Chronic stimulation not only has direct physiological effects on brain circuits but also produces a range of cellular, molecular and neuroplastic changes[1]. Our increased understanding of the complex mode of action of DBS is leading to a more comprehensive appreciation of the effects of chronic stimulation in the nervous system.

The technology for DBS was developed by modifying cardiac pacemakers and saw little development or advancement for almost two decades following the inception of the ‘modern’ DBS era in the late 1980s (FIG. 1). Until recently, technological advancements in the field have been driven largely by limitations of DBS technology such as large battery size, limited battery life and the need for frequent battery replacements. However, the appearance of multiple manufacturers of DBS technology on the global market has sparked international competition and we are now seeing progress at an accelerated pace. In the coming years, we anticipate the implementation of new hardware designs, improved technology and refined stimulation algorithms. Advances in DBS technology will no doubt extend the scope of its application and are expected to yield additional benefits, both clinically and scientifically[10–12]. We expect these advances to lead to enhanced market penetration and a wider accessibility of DBS to the populations and patients who can benefit the most, including those in low-income nations. However, it is important to be aware of new dangers that might arise with advances in electronics and computing, such as the prospect of modulation of cognitive and decision-making processes, and the possibility of acquiring data for misuse and brainjacking [13,14].

Fig. 1. Timeline of technology development for DBS.



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DBS, deep brain stimulation; IPG, implantable pulse generator.

In this article, we review the evolution and current status of DBS technology, anticipate future advances and discuss their clinical implications. We provide a reasoned overview of new DBS electrodes and pulse generators as well as of innovations in stimulation algorithms and programming. We also discuss developments in the imaging of implanted electrodes, which has become relevant not only for practical reasons but also in understanding brain dysfunction and enhancing the efficacy of chronic neurostimulation. Finally, we address the ethical and security issues raised by new technical developments, in particular with regard to potential scenarios of misuse, including by third parties. We conclude by predicting future directions for the field of DBS technology and consider how changes in DBS will enhance the accessibility of this effective surgical technique to those patients who are most in need.

History of DBS technical innovation

The history of DBS began with its use in psychiatric disease and pain[15]. The use of subcortically implanted electrodes for therapeutic chronic stimulation was first described by Columbia University neurosurgeon Lawrence Pool. In 1948, Pool implanted an electrode into the head of the caudate nucleus in a woman with depression and anorexia and reported "favourable results" for several weeks until the wire broke[16]. In 1952, Yale neuro-physiologist José Delgado and colleagues started a programme of chronic stimulation of deep brain structures in patients with psychiatric illnesses[17]. With remarkable prescience, they invented

a so-called 'stimoceiver' that was implanted in the skull, thereby allowing remote activation of the stimulator[18]. Following the identification of 'pleasure' brain targets associated with self-stimulation via intracranial electrodes in experimental animals at McGill University, controversial Tulane University psychiatrist Robert Heath developed the technique of high-frequency (100 Hz) chronic stimulation, which he subsequently applied in the septal area of the brain to treat schizophrenia and pain[19,20].

Norwegian neurophysiologist and psychiatrist Carl Wilhelm Sem-Jacobsen and colleagues at the Mayo Clinic contributed to the development of chronic subcortical stimulation with the intent of finding the best sites for subsequent neural ablation in patients with psychiatric disorders[21]. On returning to Oslo, Sem-Jacobsen continued this technique and extended it to the treatment of patients with PD[22]. Again, the aim was to apply chronic stimulation over several weeks to identify the optimal ablation target. In parallel, Leningrad neurophysiologists Natalia Bechtereva and colleagues used a similar technique termed therapeutic electrostimulation[23,24]. Chronic stimulation was delivered repetitively over weeks or months and a lesion was eventually made at the site where stimulation yielded the best clinical results. The use of chronic stimulation without subsequent lesioning only became possible with the introduction of reliable pulse generators[25].

The development of neurostimulation owes much to the battery and implant design of cardiac pacemaker technology. Following the publication of the gate theory by Ronald Melzack and Patrick Wall in 1965 (REF.[26]), the first commercially available stimulators were applied to the treatment of pain by spinal cord stimulation (SCS). Owing to the work of Mazars[27] and Hosobushi[28], DBS targeting of the sensory thalamus soon followed, building on technology from the SCS hardware. DBS for pain became widespread in Europe but was never FDA-approved for clinical use in the USA. The implantable hardware consisted of a DBS electrode and an extension cable, powered by a radiofrequency receiver and an external transmitter driven by a 9-V battery and carried by the patient. The 1970s also saw the introduction of DBS in movement disorders to replace or complement the thalamotomies that were widely performed at the time as well as, more rarely, in psychiatric applications[29]. A rudimentary DBS design allowing closed-loop adaptive stimulation was described as early as 1980 in patients with multiple sclerosis tremor[30,31]. In this system, activation of the deltoid muscles by the patient triggered the stimulation of the thalamic and subthalamic areas, which stopped the tremor.

The modern era of DBS arrived in 1987, when a group from Grenoble published their experience with DBS for essential tremor (ET) and PD tremor[32]. Although quadripolar electrodes were already available in the 1970s, the electrodes initially used in Grenoble had only one contact at the tip and chronic stimulation was achieved through radiofrequency coupled coils. The first implantable pulse generator (IPG) for DBS, manufactured by Medtronic, had a maximal frequency of 130 Hz — the value used in most current DBS applications — and accommodated only unilateral stimulation. In 1999, the first dual-channel IPG was launched in Europe. This device delivered a current with a frequency of up to 250 Hz and, with the increasing adoption of bilateral DBS globally, particularly for subthalamic nucleus (STN) stimulation in PD, it became the most used IPG worldwide.

The next generation of DBS hardware was the Activa series, namely Activa PC and Activa RC. These devices expanded the parameter space that clinicians could use to programme DBS devices. Unlike

previous IPGs, the Activa IPG could be programmed to deliver either a constant voltage or a constant current. Additional features included the possibility to deliver different stimulation programmes in an interleaving pattern. Some of the newer IPGs were noted to have a shorter battery life than the earlier models[33,34] and the relatively large size of the implant and the need for replacement owing to battery expiration every 3–4 years led to the introduction of rechargeable IPGs.

Starting around a decade ago, new companies, including St. Jude Medical (subsequently acquired by Abbott), Boston Scientific, SceneRay, PINS, Neuropace and Aleva Neurotherapeutics, entered the DBS market with technical innovations such as segmented leads, directional stimulation, longer battery duration, more flexibility in deciding stimulation parameters and remote internet-based programming. The most recent developments include current directionality with electrode segmentation, increased parameter space for programming (in particular, shorter pulse widths (10 μs) and frequencies of up to 10,000 Hz) and advances in MRI compatibility and neural recording capabilities.

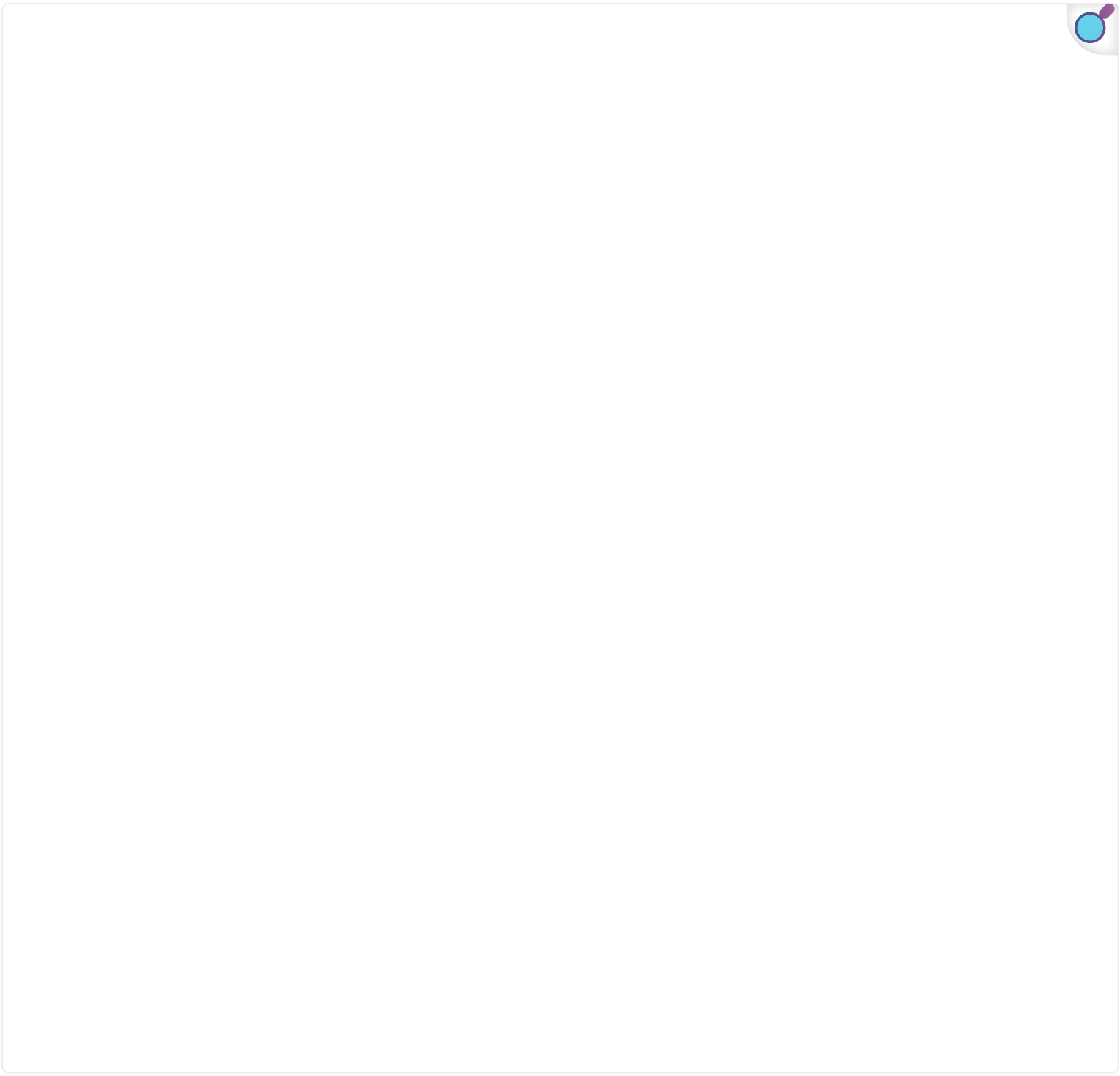
Innovation in electrode and IPG design

Electrode design

The basic principle of DBS is to use a small electrode to deliver electrical impulses to focal brain regions. The crucial characteristics of an electrode include biocompatibility, inertness, durability, stability over time, surgical feasibility, good conductivity, electrical properties, tractability, appropriate current delivery and spatial configuration. Additional considerations include MRI compatibility and the potential for sensing.

DBS electrodes consist of platinum–iridium wires and nickel alloy connectors encased in a polyurethane sheath. Platinum–iridium is chosen because of its minimal toxicity and excellent conduction properties. Several electrode configurations are currently available (FIG. 2). The standard electrode configuration is quadripolar, with four stimulating electrode contacts at the tip of the probe, which is 1.27 mm in diameter. Each cylindrical contact is 1.5 mm in length and contacts are spaced 0.5 mm or 1.5 mm apart. Such electrode configurations allow the electric field to be shaped along the *z* axis of the lead through the programming of various combinations of anodes or cathodes.

Fig. 2. DBS electrode configurations.



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a | Common electrode configurations for deep brain stimulation (DBS). Dark grey regions illustrate electrode contacts, which can be activated to deliver current. Electrode designs vary with regard to the spacing between contacts as well as the number and shape of contacts. Greater contact spacing expands the range of neural targets, whereas smaller contact spacing facilitates more precise stimulation control. **b** | Modes of stimulation, depending on the type of DBS system in use. Unipolar stimulation refers to current being directed from the battery to the contact or vice versa. Bipolar stimulation indicates current flowing between electrode contacts, with at least one functioning as an anode and one as a cathode. Interleaving stimulation refers to the alternation of

different stimulation settings. Multiple level stimulation enables multiple neural targets to be stimulated, provided that they lie along the electrode trajectory. With directional stimulation, current can be directed or 'shaped' on the basis of local anatomy or clinical symptoms.

Since 2015, the availability of directional electrodes has allowed more versatile shaping of the electric field, thereby improving the therapeutic window by enhancing efficacy and reducing adverse effects[35]. Unlike conventional DBS electrodes, which use a cylindrical configuration, directional electrodes use radially segmented contacts that allow the stimulation field to be moved in the horizontal plane or shaped using anodes and cathodes to steer the current in a particular direction (FIG. 2). The electrode and its capabilities need to be considered as a unit with the technical properties of the connected IPG. Theoretically, single-source, current-driven or voltage-driven devices allow less flexibility in the programming of electric fields than systems offering multiple independent sources connected to each electrode contact.

Despite providing enhanced capabilities owing to an increased number of available contacts, directional electrodes add complexity to surgical implantation and create challenges for programming. The limits to the benefits and feasibility of increasing contact numbers are illustrated by the Sapiens electrode. This electrode has 64 contacts, making integration with the extension cable surgically challenging and has never been used for chronic stimulation (FIG. 2). In addition, higher current amplitudes lead to loss of directionality and the ability to shape the stimulation field other than in the longitudinal direction. Improvements in programming algorithms, including a shift from trial and error to automated programming, will be important to maximize the benefits of new electrode designs.

Currently available commercial DBS systems are manufactured in a labour-intensive and cost-intensive process in which the electrodes are assembled manually. Modern production techniques, such as film printing, might increase the flexibility of electrode design and allow further miniaturization but also raise concerns about the long-term performance and safety of novel materials. The stability of impedance might be improved by techniques such as nanocoating[36,37].

Biocompatibility

After implantation, an interface between the electrode and brain tissue develops, which changes over time. In the chronic state, glial encapsulation of the electrode, protein adsorption on electrode sites and the characteristics of the ionic environment at the electrode–electrolyte interface dictate the electrical characteristics of the electrode–tissue interface[38]. A general problem with the chronic implantation of electrodes into the brain is an inflammatory foreign body reaction, which needs to be minimized if stable therapeutic responses are to be achieved with commercial deep brain electrodes[39]. Studies of chronically implanted leads have demonstrated a multinucleate giant cell-type reaction irrespective of the duration of implantation, which might be a response to the polyurethane component of the surface coating of the electrode[38]. Although these reactions require further study, the global experience to date suggests that long-term DBS is reasonably safe.

Idiopathic delayed-onset oedema surrounding the leads, presumed to be a subacute foreign body reaction to electrode implantation, has occasionally been reported. The aetiology, predisposing factors and prognosis of peri-lead oedema are still unknown but it seems to be more frequent than was originally assumed, with a substantial proportion of cases being detected on routine postoperative MRI scans[40].

IPGs and programming

Innovation in IPG technology is long overdue in the DBS field. Advances in the shaping and control of current delivery, novel waveforms and patterns, optimization of programming, energy efficiency, and miniaturization are necessary to enhance clinical outcomes, patient safety and comfort. Innovations that have been in use for some time in SCS are now being adapted to DBS. Examples include multiple independent current control, which involves the pairing of individual lead contacts with a dedicated current source, thereby allowing the precise customization of stimulation field size and shape. In addition to field shape optimization, neuromodulation for pain has benefited from the use of novel waveforms such as BurstDR and 10-kHz high frequency (HF-10) therapy[41,42]; these stimulation platforms are likely to be explored in DBS in the near future.

The optimization of programming through standardization is one of a number of different strategies that are under investigation in the field of neuromodulation. Both BurstDR and HF-10 run on standard algorithms and the sometimes cumbersome and lengthy 'art of programming' is being replaced with the ease of automation. This approach is likely to make its way to DBS programming, with the ultimate goal of developing closed feedback loops and artificial intelligence-based programming optimization. To some degree, we are already seeing automatic programming in the SCS world. For example, a teachable IPG that is available for SCS uses position data from a built-in accelerometer to toggle through and automatically select optimal pre-programmed parameters[43]. The increasingly complex implanted electrode systems will require artificial intelligence-based or computational model-based programming to achieve optimal results. A commercially available system from Boston Scientific allows clinicians to designate a desired volume of tissue activated (VTA), after which the programming software will determine the scheme for contact activation. Although physician oversight of programming will always be required and wireless DBS programming in the clinic is currently the standard approach, remote monitoring and telemetry applications as well as automated or self-programming devices are likely to appear in the future.

Improvements in current delivery will need to be accompanied by changes to IPGs that make DBS more palatable to prospective patients and physicians. These changes include miniaturization and a reduction of the charging burden. Currently, the lightest IPG for SCS is 29.1 g, whereas the typical DBS devices range from 40 g to 67 g. In addition, with renewed interest in rechargeable DBS products, the charge time and capacity fade become important. The currently available SCS IPGs charge from empty to full in 1 h and have >95% battery capacity at 9 years but these properties have yet to be translated to DBS IPGs. Energy-harvesting IPG technology has the potential to eliminate manual battery charging altogether[44].

As IPGs become smaller, we should also expect the emergence of cranial or possibly even burr hole-mounted IPGs. Such technology would eliminate the risk of wire passage and complications associated

with wire breakage but could also introduce new concerns such as cranial IPG infections.

Patient safety concerns

Patient safety is a top priority in neuromodulation. Full-body MRI-safe systems should be an attainable goal for all manufacturers in the near future. Changes to the physical implant, including the elimination of extension cables, would reduce concerns regarding the heating of DBS systems during MRI scans. The prevention of infection of implantable devices is also essential and current infection rates in patients with chronic DBS range from 5–10%[45–47]. We are already seeing the use of antibacterial envelopes to prevent cardiac pacemaker infections. Indeed, a recent randomized controlled study in people with cardiac implantable devices showed that the use of antibacterial envelopes significantly reduced infection rates[48]. The antibiotic coating of neurostimulation systems could also prevent infection and the subsequent need for explantation.

Acute hardware failure might not only result in the rebound of symptoms such as tremor or depression but might also lead to severe adverse events such as the neuroleptic-like malignant syndrome in PD[49]. The newer IPGs allow better readouts of battery capacity to determine the date for pre-emptive replacement and the use of error-detecting servomechanisms could also be considered in the future.

Advances in stimulation methods

After a long period of stasis in hardware development, over the past few years, we have witnessed an abundance of new stimulation methods, including the introduction of regulated current IPGs, novel stimulation waveform shapes and novel temporal patterns of stimulation. These technological improvements have led to a re-evaluation of stimulation algorithms and consideration of new paradigms of stimulation treatment, many of which are available but not yet sufficiently tested. Studies using blinded comparisons of different stimulation paradigms are needed to assess their clinical utility[50].

Controlled current versus controlled voltage

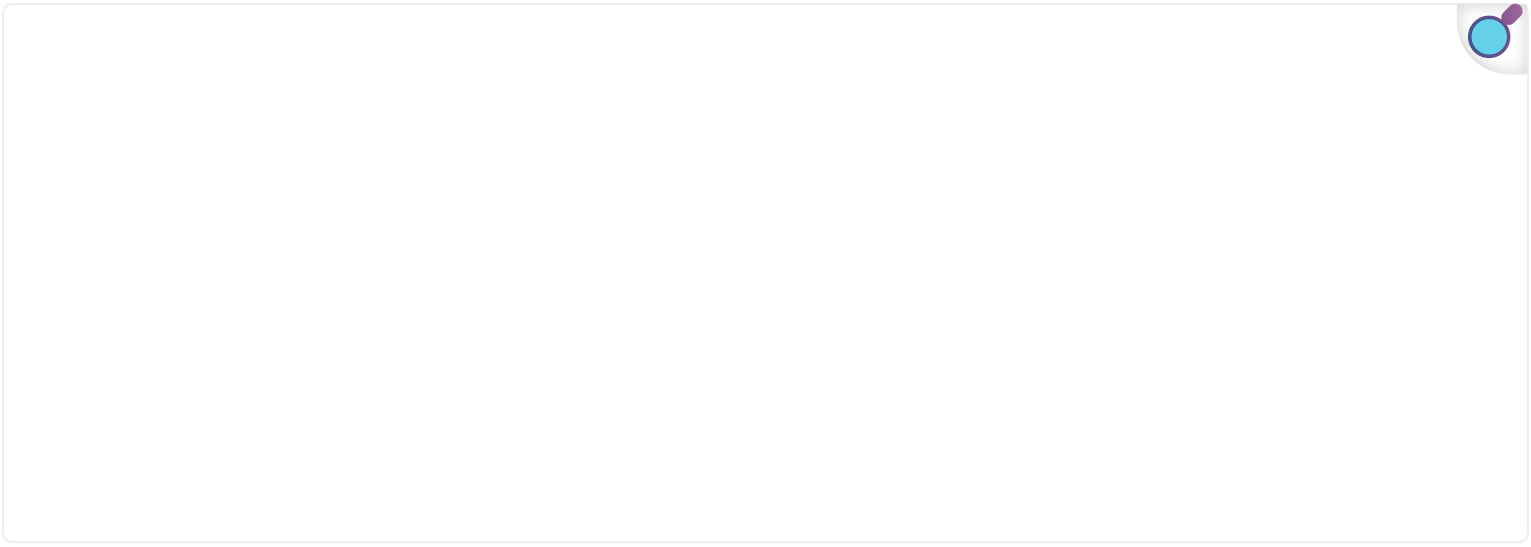
A consensus paper[51] published in 2015 highlighted the paucity of studies[52,53] comparing clinical outcomes using regulated current DBS versus regulated voltage DBS but surmised that, in the face of dynamic changes in load impedance, current DBS would be expected to produce more stable effects than voltage DBS[54]. As outlined above, the impedance of implanted DBS electrodes changes over time as a result of the inflammatory response and gliosis around the electrode[55].

Stimulation waveform shape

The stimulation waveform — that is, the shape of the stimulation current (or voltage) as a function of time — can influence the number and type of neural elements that are activated[56] and waveforms or pulses can be repeated at various interpulse intervals to create a stimulation pattern (FIG. 3). Comparisons

of different stimulation waveforms and patterns suggest that symmetric biphasic pulses produce greater suppression of PD motor symptoms than do conventional asymmetric DBS waveforms with a long-duration anodic recharge phase[57], albeit at the expense of additional battery drain. Similarly, in patients with ET undergoing thalamic nucleus ventralis intermedius (Vim) DBS, symmetric biphasic pulses produced a greater suppression of tremor than conventional asymmetric DBS waveforms[58]. At any given stimulation intensity, symmetric biphasic pulses are likely to activate a larger number of neurons than asymmetric pulses, as both the cathodic and anodic phases of the stimulus waveform can contribute to net activation[59].

Fig. 3. Stimulation waveform shapes and temporal stimulation patterns.



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In deep brain stimulation (DBS), waveform shapes are repeated at interpulse intervals to create a stimulation pattern. **a** | Conventional asymmetric biphasic DBS waveform with a short-duration cathodic phase followed by an interphase delay and a long-duration anodic (recharge) phase. **b** | Symmetric biphasic DBS waveform with equal-duration cathodic and anodic phases. **c** | Symmetric biphasic DBS waveform with zero interphase delay. **d** | Reversal of the standard pulse phase order of a symmetric biphasic DBS waveform. **e** | Regular temporal pattern of stimulation with fixed interpulse intervals (typically ~7.7 ms or ~130 Hz). **f** | Non-regular temporal pattern of stimulation with random interpulse intervals. **g** | Burst pattern of stimulation with several pulses at short interpulse intervals followed by a long interpulse interval. **h** | Stimulation pattern for coordinated reset with bursts of stimulation distributed across four different electrode contacts, with each row corresponding to the stimulation pattern delivered to each electrode contact.

Other factors that might improve the activation and entrainment of neurons include an appropriate choice of waveform polarity, reversal of the standard pulse phase order, and a gap between the two phases of charge-balanced biphasic pulses[60]. The waveform shape can also influence the desynchronizing impact of

DBS techniques in which the pulse amplitude is modulated in a closed-loop manner by linear or nonlinear delayed feedback[61–63].

Similar to early studies of Vim DBS for tremor[64], the thresholds for STN DBS to produce both adverse effects and reductions in PD motor symptoms were higher with anodic stimulation than with cathodic stimulation[65]. However, at amplitudes just below the adverse effect threshold, anodic stimulation produced a greater suppression of symptoms than cathodic stimulation.

Stimulation patterns

Increasing evidence suggests that the temporal pattern of stimulation can influence the clinical outcome after DBS[66], particularly in PD[67]. The selection of an optimal pattern creates a substantial design challenge: assessing the effects of a stimulation pattern on symptoms is difficult enough when the responses to stimulation are relatively rapid and overt, for example, in the case of tremor in ET[68] or bradykinesia in PD[69]. However, this assessment becomes exceedingly challenging in instances where the outcomes are slow to develop and cannot readily be observed such as in dystonia, where improvement of tonic symptoms is often seen only after a delay[70], or in epilepsy, where changes in seizure frequency might occur only after several months. In addition, the response to stimulation might not be stable over time as has been observed in ET. Furthermore, the range of possible temporal patterns is very large and an empirical approach to identifying the most clinically effective pattern may not be feasible. One alternative is to employ model-based optimization of the temporal pattern[71]; however, this approach requires a high-fidelity model of the relationship between the pattern of stimulation and changes in a particular symptom[67,72].

Stimulation techniques have been computationally designed to counteract the abnormal synchronization of neuronal activity[73–75]. In the presence of spike timing-dependent plasticity [76], neuronal populations display complex dynamics and can stably reside in states with strong or weak synapses and synchrony[75]. In theoretical models and simulations, desynchronizing stimulation reduces neuronal coincidence rates which, mediated by spike timing-dependent plasticity, might decrease synaptic strength[75,77,78]. Coordinated reset stimulation, which delivers brief high-frequency pulse trains through different stimulation contacts[74], might cause acute desynchronizing effects during stimulation as well as unlearning of abnormal neuronal synchrony and synaptic connectivity. Desynchronization was shown to accumulate and persist after the cessation of coordinated reset stimulation[75,77,78] and long-lasting effects were verified in both preclinical and clinical studies[79–81].

These emerging and promising results indicate the potential of temporal patterns to achieve an enhanced efficiency of stimulation and prolong symptom relief through the control of plasticity.

Adaptive DBS and closed-loop systems

The possibility of regulating DBS over time according to one or more feedback signals has attracted considerable interest in recent years. This approach, which we term ‘adaptive DBS’, encompasses

responsive, adaptive and closed-loop control modes[82,83]. The development of adaptive DBS is primarily motivated by the potential for improved efficacy and reduced risk of adverse effects. A simple example is position-adaptive SCS treatment for pain, whereby feedback from an accelerometer automatically adjusts the stimulation voltage according to positional changes in the electrode with respect to its target[43]. However, in most applications, feedback relates directly or indirectly to the dynamic state of the nervous system. Although a mechanistic relationship between the feedback signal and neural dysfunction is not essential, causally relevant signals have the advantage that they can change before symptoms emerge, potentially allowing predictive rather than reactive symptom management. To date, adaptive DBS has been studied mainly in PD, tremor and epilepsy but is increasingly being explored in other conditions such as Tourette syndrome[82,84].

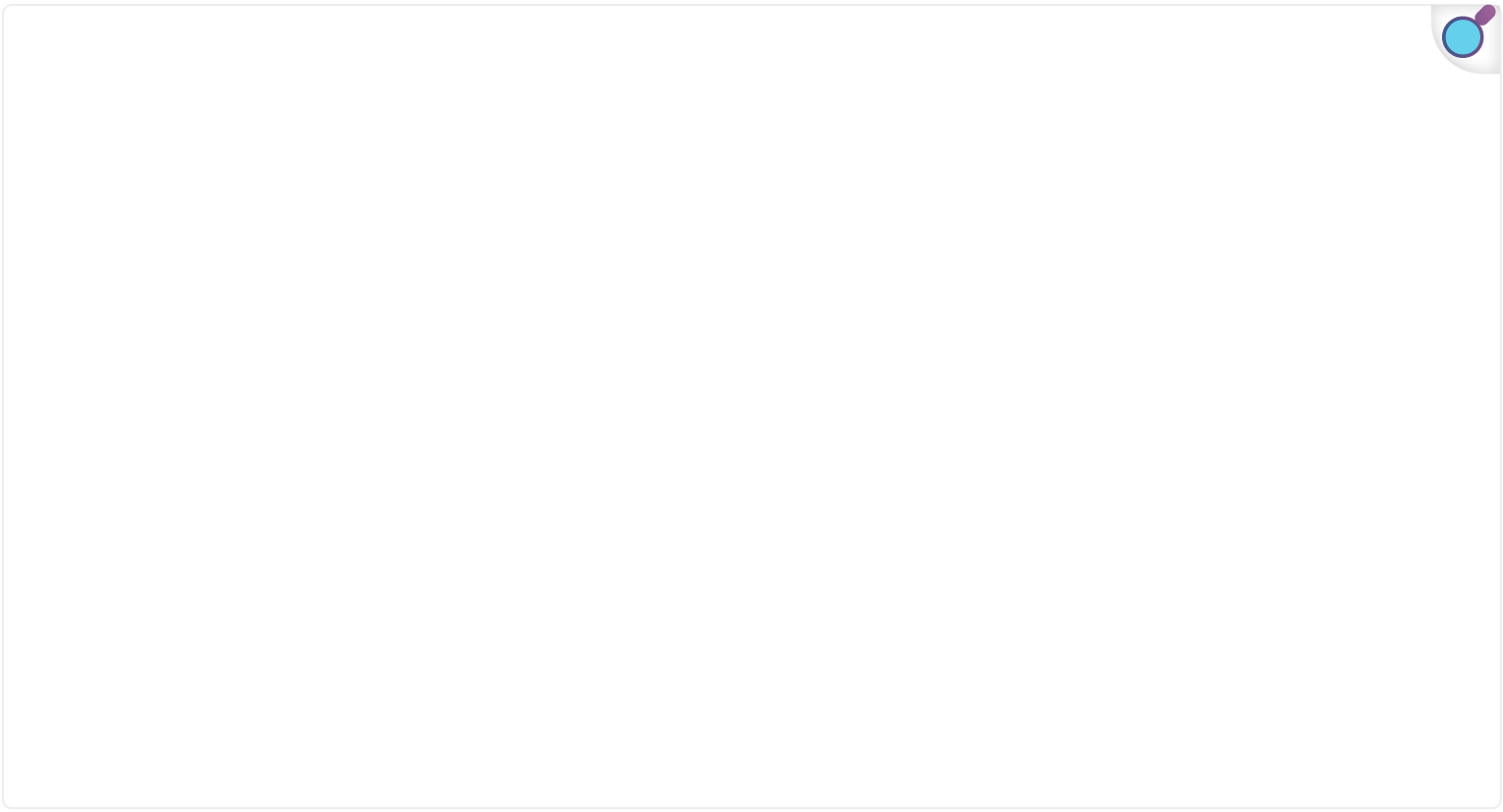
Local field potentials (LFPs) recorded from contacts of implanted electrodes have revealed differences in power spectra in various disorders[85–91] (TABLE 1). Adaptive DBS in PD has focused on LFP feedback in the beta frequency range as a correlate of bradykinesia and rigidity[87,88] and on gamma activity, picked up from a cortical strip electrode, as a marker of dyskinesia[85] (FIG. 4). Beta activity recordings can be smoothed over many seconds[88] or processed to retain rapid fluctuations in the signal[87]. The heavily smoothed signal predominantly tracks the dynamics related to drug therapy and captures motor on–off state changes. The use of this form of feedback to drive DBS can reduce power requirements by ~50% and has been shown to reduce on-state dyskinesias[92].

Table 1. Neural biomarkers of local field potentials.

Neural biomarker	Recording site	Disease	Main uses	Refs
Gamma (~70 Hz) activity	Cortex	Parkinson disease	Feedback signal related to dyskinesia for adaptive DBS	85
Beta (~20 Hz) activity	Cortex	Essential tremor	Triggering stimulation in response to movement in adaptive DBS	86
Beta (~20 Hz) activity	Subthalamic nucleus or globus pallidus internus	Parkinson disease	Feedback signal related to bradykinesia–rigidity for adaptive DBS; localizing signal for contact selection in programming	87,88,89
Theta (~7 Hz) activity	Subthalamic nucleus or globus pallidus internus	Dystonia	Feedback signal related to muscle spasms for adaptive DBS	90
Event-related resonance activity (~260 Hz)	Evoked potentials from subthalamic nucleus stimulation	Parkinson disease	Localizing signal for contact selection in programming	91

DBS, deep brain stimulation.

Fig. 4. Adaptive DBS in Parkinson disease.



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a | Stimulating and recording from the deep brain stimulation (DBS) electrode. When the patient is in the off-levodopa phase, which is characterized by slow movements and muscle stiffness, the local field potential activity at the electrode contacts contains prominent oscillations at ~20 Hz (beta activity). The amplitude of these oscillations varies over time and high-frequency DBS is delivered whenever an amplitude threshold is crossed. An alternative approach is to deliver DBS with an intensity that is proportional to the beta amplitude. **b** | Stimulating DBS electrode and recording from an electrocorticographic (ECOG) electrode strip overlying the motor cortex. When the patient is on levodopa and dyskinetic, the ECOG activity picked up by the strip electrode contains prominent oscillations at ~70 Hz (gamma activity). The amplitude of these oscillations is monitored and DBS is stopped or reduced when an amplitude threshold is crossed. STN, subthalamic nucleus.

Alternatively, beta feedback can be processed to capture the bursting nature of spontaneous beta activity. This strategy is based on growing evidence that these bursts, particularly when prolonged and elevated in amplitude, mediate bradykinesia and rigidity[89,93]. In this application, the detection of longer-duration bursts triggers or increases stimulation to terminate these bursts. This approach also achieves a 50% reduction in power requirements and reduces adverse effects on speech in comparison with conventional continuous stimulation[87,94,95]. It has also achieved better control of bradykinesia and rigidity than adaptive DBS based on smoothed beta feedback[88] but the control of dyskinesia has not been objectively

confirmed. An alternative approach to control dyskinesia is to detect rapid changes in finely tuned gamma activity at the cortical level, where its amplitude is larger and more easily distinguished from stimulation artefacts than in other areas of the brain[85].

Adaptive DBS for tremor is being explored using LFP activity recorded from the STN, cortical surface or thalamus or using one or more electromyographic or kinematic sensors on the body for feedback[86,96–98]. Features extracted from LFPs have been used to decode the onset of tremor and, in the case of ET, tremor-triggering voluntary movement[86,96,99].

Though exciting, the application of adaptive DBS in movement disorders is at an early stage and the efficacy and adverse effect profiles remain to be determined in patients with chronic implants. In addition, it remains to be seen whether feedback control can be too selective in some patients, necessitating the use of two or more control loops for different symptoms. Such an approach might prove necessary in the few patients with PD who develop breakthrough tremor during adaptive beta-based DBS for bradykinesia and rigidity[100]. Opportunities to develop more sophisticated adaptive DBS approaches based on computational modelling are also arising.

In the epilepsy field, considerable experience has been gained with the NeuroPace responsive neurostimulation (RNS) system, which includes a cranium-implanted pulse generator connected to one or two recording and stimulating depth and/or cortical strip electrodes placed at previously identified seizure foci. The pulse generator provides short-term stimulation in response to the detection of abnormal electrocorticographic activity that precedes a possible clinical seizure. This stimulation approach is reported to reduce the frequency of partial-onset seizures and is well tolerated and acceptably safe[101]. In 2019, the RNS system was combined with stimulation of the anterior nucleus of the thalamus with the aim of extending the use of the system to refractory multifocal or generalized epilepsy[102]. Indeed, an adaptive approach might help ameliorate the frequent arousals from sleep that are experienced with conventional stimulation of this target[103]. Another development has been the tachycardia-based seizure detection algorithm implemented in the AspireSR system, which allows automatic top-up vagal nerve stimulation during seizures[104,105].

Despite excitement about the prospect of dynamic interfacing with the brain to control symptoms, position-adaptive SCS for pain and RNS for epilepsy are the only approaches that have made substantial inroads into clinical practice so far. This situation is likely to change in the near future as flexible bidirectional devices for chronic implantation become more widely available, allowing chronic trials of novel adaptive approaches with rescue in the form of standard DBS as necessary as well as long-term recording of neurophysiological signals for machine learning of the precise correlations between neural activity and symptom severity across a variety of diseases. Another area of increasing interest is implantation and recording from more than one brain site in individual patients[106], thereby ameliorating the effects of stimulation artefacts and enabling network-related rather than single-site feedback control[85,107]. Feedback control is also likely to expand to include multiple signals related to the neural and physical state, supported by more sophisticated control algorithms. These advances could be facilitated by the development of local and distributed cloud computing systems[108] and firmware upgrades to allow ‘future-proofing’ of implants[109].

DBS imaging and stimulation modelling

Over the past decade, advances in neuroimaging have improved DBS target visualization and lead localization (FIG. 5). These developments have informed both surgical targeting and postoperative DBS programming. Novel imaging methods have also led to a better understanding of the mechanisms of action of DBS.

Fig. 5. DBS neuroimaging.

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a | Postoperative neck and chest X-rays showing an implanted deep brain stimulation (DBS) system with electrodes and extension wires (left image) and the implantable pulse generator implanted over the chest area (right image) **b** | Novel MRI visualization techniques, including quantitative susceptibility mapping (QSM) and fast grey matter acquisition T1 inversion recovery, have improved the visualization of subcortical structures. QSM coronal slice shows the subthalamic nucleus (outlined) — the most commonly targeted structure in Parkinson disease. **c** | Ultra-high-field preoperative MRI is increasingly used in surgical planning and research. T1-weighted axial slice intrathalamic nuclei (labelled in the right-hand image). **d** | On the basis of MRI metallic artefacts associated with DBS electrodes (shown on T2-weighted coronal image and axial image (arrowheads) on the left), the electrodes can be localized and reconstructed in 3D using specialized software. CT scans can also be used for electrode localization. DBS settings, including active contact, voltage, pulse width and impedance, can be used to estimate the electric field (white arrows, right image) surrounding the DBS electrodes. Heuristic assumptions or axonal cable models can be used to estimate the volume of tissue activated (VTA, red, right image). **e** |

The VTA can be used in connectivity analyses informed by metrics such as resting-state functional MRI (top left) and diffusion-weighted, imaging-based tractography (bottom left) to determine the effects of DBS on distributed brain regions. CeM, central medial nucleus; CM, centromedian nucleus; IC, internal capsule; MD, mediodorsal nucleus; MTT, mammillothalamic tract; PuM, medial pulvinar nucleus; PuL, lateral pulvinar nucleus; VA, ventral anterior nucleus; VLA, ventral lateral anterior nucleus; VLP, ventral lateral posterior nucleus; VPL, ventral posterolateral nucleus. Part **a** is adapted with permission from REF.[152], Boutet, A. et al. *Radiology* (2019) **293**, 174–183, Radiological Society of North America. Part **b** is adapted with permission from REF.[110], Liu, T. et al. *Radiology* (2013) **269**, 216–223, Radiological Society of North America. Part **c** is adapted with permission from REF.[115], Elsevier. Part **e** is adapted with permission from REF.[137], Wiley.

Some DBS targets are poorly visualized on the brain MRI scans that are routinely acquired for surgical planning. For instance, although the STN is visible on T2-weighted sequences, its ventral border towards the substantia nigra is often difficult to delineate. The internal medullary lamina separating the globus pallidus internus and externus is not visible on routine T1-weighted sequences. To address these limitations, higher field strengths and novel sequences have been developed to improve the visualization of DBS targets[110]. For example, quantitative susceptibility mapping applied to gradient-echo sequences is highly sensitive to iron and provides striking improvements in STN visualization[111] (FIG. 5). Similarly, the fast grey matter acquisition T1 inversion recovery sequence was introduced to enhance the visualization of subcortical structures[112] and is specifically optimized to visualize the globus pallidus internus and substructures of the thalamus[113]. Diffusion-weighted imaging is also gathering interest as a targeting tool focusing on white matter tracts, particularly for ET treatment[114]. Ultra-high-field (UHF) MRI at 7 T also holds promise for improving target visualization. For example, the intrathalamic nuclei can be seen with UHF MRI[115,116], which is a notable advantage when planning DBS surgery for tremor (FIG. 5). STN borders can also be better appreciated on UHF MRI than on conventional MRI[117,118]. A fundamental limitation of UHF MRI is an increased susceptibility to distortion artefacts, especially in the centre of the brain, which requires careful distortion correction.

Electrode localization is paramount to confirm adequate targeting and to define the neural substrates that are responsible for clinical outcomes. The reconstruction of precise electrode placements relative to surrounding anatomical structures is particularly important with the rise in popularity of segmented and directional leads because clinicians must decide how to steer the current during programming[119]. Several software tools have been introduced for this purpose[113,120–123], and algorithms that reconstruct electrode localization from CT and MRI scans have been developed[121,124–126]. Furthermore, algorithms were created and validated to reconstruct the orientation of segmented leads[127]. Electrode localization is particularly important as evidence suggests that the segmented contacts of directional DBS leads often show large deviations from their intended implantation orientation[119].

Retrospective group-level analysis of precise electrode locations in multiple patients provides an opportunity to further our understanding of DBS mechanisms of action[128]. Group-level analyses have been made possible by several recent advances in neuroimaging: first, the precise co-registration of patients' brains onto an average brain template (for example, by non-linear normalization to the Montreal

Neurological Institute brain template)[129]; second, accurate DBS electrode localization;[113] and third, estimation of the VTA[130–132]. Large sample sizes can be used in group-level analyses to estimate robust 'sweet spots' or optimal connectivity profiles that could be useful to predict outcomes in future patients. Probabilistic maps of clinical outcomes and efficacious networks can be computed with clinically weighted contact locations or VTAs to pinpoint the most effective neuroanatomical substrates across a large cohort of patients. Of note, the VTA is a visual approximation that is inferred from a model-based theoretical concept and its validity depends on the model used. In addition, estimation of the VTA ignores local impedance changes and intrinsic dynamics of neuronal populations.

Such methods have enabled direct relationships to be established between electrode placement (and stimulation location) and clinical improvement in PD[133–137], dystonia[138–140], ET[141,142] and OCD[143] (FIG. 5). This work has led to the emergence of sweet spots — that is, optimal surgical and stimulation targets — that have direct and statistically significant relationships with clinical outcomes. For instance, studies by several different groups worldwide have converged on an optimal target for the treatment of PD[144].

In addition to defining brain areas implicated in clinical outcomes, the inclusion of information about functional or structural connectivity has led to the concept of network-based or tract-based targets[137,145,146]. For example, modulation of targets structurally connected to the supplementary motor area was shown to be associated with clinical improvement in PD[137]. The connection profiles could be further differentiated according to symptoms: connectivity from the active contact within the STN to the supplementary motor area explained bradykinesia and rigidity improvement, whereas the alleviation of tremor was associated with connectivity to the primary motor cortex[134]. Differential connectivity was also associated with discrete tremor improvement in ET[141]. Structural connectivity between the active contact within the Vim and the hand regions of the primary motor cortex (and the cerebellum) was associated with improvement in hand tremor, whereas connectivity-mediated modulation of head regions led to improvement in head tremor[141].

Connectivity might play an even greater role in psychiatric surgery, for which the targets are not yet universally agreed. The establishment of efficacious connectivity profiles could aid the refinement and adjustment of surgical targets[143,147,148]. A 2019 report demonstrated direct relationships between clinical improvement and connectivity profiles of DBS electrodes in patients with OCD[143]. The authors identified a subregion within the anterior limb of the internal capsule that was associated with good clinical improvement. Importantly, a second study showed that the proximity of the electrode to a white matter bundle coursing through this subregion and connecting to the STN was predictive of efficacy of the anterior limb of the internal capsule or STN DBS in two OCD patient cohorts[149]. This last example demonstrates how different DBS targets used to treat the same disease can potentially modulate a common tract or network, thereby alleviating a similar set of symptoms.

As we have discussed in this section, retrospective studies exploring the relationships between stimulation location and clinical outcomes can yield useful information regarding the mechanisms of action of DBS. However, prospective data acquisition in patients undergoing DBS (for example, functional MRI with DBS turned on) could provide a more direct in vivo insight into the neural changes induced by

DBS. To date, the prospective acquisition of functional neuroimaging data in patients with fully internalized and active DBS has been limited by the inherent risks of exposure of active implantable medical devices to the magnetic fields in MRI scanners[150]. Generally, these studies were hampered by MRI acquisition restrictions (for example, magnet strengths of no more than 1.5 T) owing to safety guidelines. However, recent investigations have shown safe and feasible acquisition of functional MRI using 3 T (with a body transmit coil) in large cohorts of patients with DBS systems[50,151,152], enabling a broader range of functional neuroimaging data acquisition and opening the door to a new field of neuromodulation research.

DBS in a connected world

The advantages offered by integrating electronics with the human nervous system are substantial. The ability to collect extensive datasets from large numbers of patients undergoing DBS is likely to have a positive impact on both patient care and the development of neuromod-ulation platforms but also raises concerns over safety, privacy and security.

Improvements in technology as well as the introduction of wireless connectivity to interact with monitoring and programming devices and the incorporation of commercial platforms into the systems, create a real risk of failure of device security[14,153]. In his considerations on 'posthuman capitalism', contemporary philosopher Slavoj Zizek outlined and summarized some of the potential dangers of misusing various types of brain–machine interfaces[154]. In particular, the concept of directly coupling neural circuits with software on digital devices could bear unforeseeable risks. The hacking of digital technology and programmes has entered new dimensions over the past few years and, in the age of the 'Internet of things', technology dysfunction caused by "distributed denial of service" attacks has become a reality[155]. As suggested in a 2019 article in *The Economist*, "a connected world will be a playground for hackers"[156].

Hacking has reached the level of global social and political manipulation and data from chronic neural recordings made available via cloud technology, in particular from limbic and cognitive-associative circuitries, could potentially be misused not only to 'optimize' emotional and cognitive states but also to establish new forms of social control. Although such 'neurosecurity' threats are still mostly theoretical, we believe that a discussion of these issues should be initiated before they become apparent. Brainjacking, a term coined by Pycroft, is a potentially serious threat that warrants early discussion before any real-world harms occur[14]. As a result of the paucity of work specifically addressing neurosecurity and brainjacking, several areas of ethical consideration and consultation might prove fruitful together with greater investment in security measures.

Various ways of attacking neurostimulation systems can be envisaged. Simply draining the battery or switching off the device could cause rebound symptoms or tissue damage or attacks might be targeted to specific indications, leading to motor impairment, increased pain, altered impulse control or unpleasant emotions. The philosophical implications of exerting control over another human being in this manner

could be profound and deserve further analysis. The legal and economic implications may also be substantial given the expected proliferation of neurotechnology in the coming years.

Ongoing discussion and study of these threats among clinicians and industry is important to minimize the risks. Clinicians should educate themselves about the basics of information security and be mindful of the risks of brainjacking when evaluating faulty implants or caring for high-profile patients. Hospital staff should also be aware of social engineering techniques used by attackers to gain privileged information and should have at least a basic understanding of how to minimize neurosecurity risks. Patients should have some degree of awareness of particularly risky behaviours to avoid, although any discussion of this topic should avoid undue alarm and emphasize, at least at the present time, the extremely low probability of an individual patient being targeted by an electronic attack.

The history of both information security and medicine has amply demonstrated that prevention is better than cure and the best approach is to apply lessons to neurosecurity while the situation remains tractable; the necessary developments include codes of best practice for neurosecurity tailored to both the devices and the indications[157]. Close cooperation between stakeholders, such as clinicians, patients and device manufacturers, is paramount but should allow flexibility to enable device development.

Conclusions and future directions

Our understanding of the brain network circuit malfunctions that lead to clinical manifestations of neurological and psychiatric diseases is increasing, with these insights informing novel DBS hardware design and stimulation methods. We envisage a future in which neuromodulation will be safer, less invasive, and more accurate and efficacious, and will be applied to a greater proportion of patients for whom other forms of treatment have proved insufficient. In particular, we anticipate advances in electrode design, IPG capabilities, and programming and stimulation methods (Box 1; FIG. 6). Sophisticated imaging techniques will improve the identification of brain targets, validate target engagement and confirm the attainment of the desired physiological circuit effect of stimulation. However, as with other powerful and life-changing technologies, ethical, privacy and security safeguards are of the utmost importance and must be considered in parallel with technological progress to avoid unintended consequences.

Box 1. Anticipated advances in deep brain stimulation technology.

Improvements in electrode and IPg design

- Miniaturization and cranialization
- Large-scale production and modernized production techniques to reduce cost
- Multiple power sources within implantable pulse generators (IPGs) to enable multiple independent current control
- Improved battery life, recharging capacity or energy harvesting

Increased safety

- Improved MRI compatibility with ≥3 T systems
- Antibiotic impregnation to reduce infection
- Protection from hacking, including 'brainjacking'

optimized stimulation

- IPGs with multiple independent power sources to enable multiple independent current controls
- Increased control over waveform shape (for example, symmetric biphasic pulses for tremor)
- Use of varying interpulse intervals or coordinated reset (brief high-frequency pulse trains from different contacts)

Adaptive or closed-loop designs

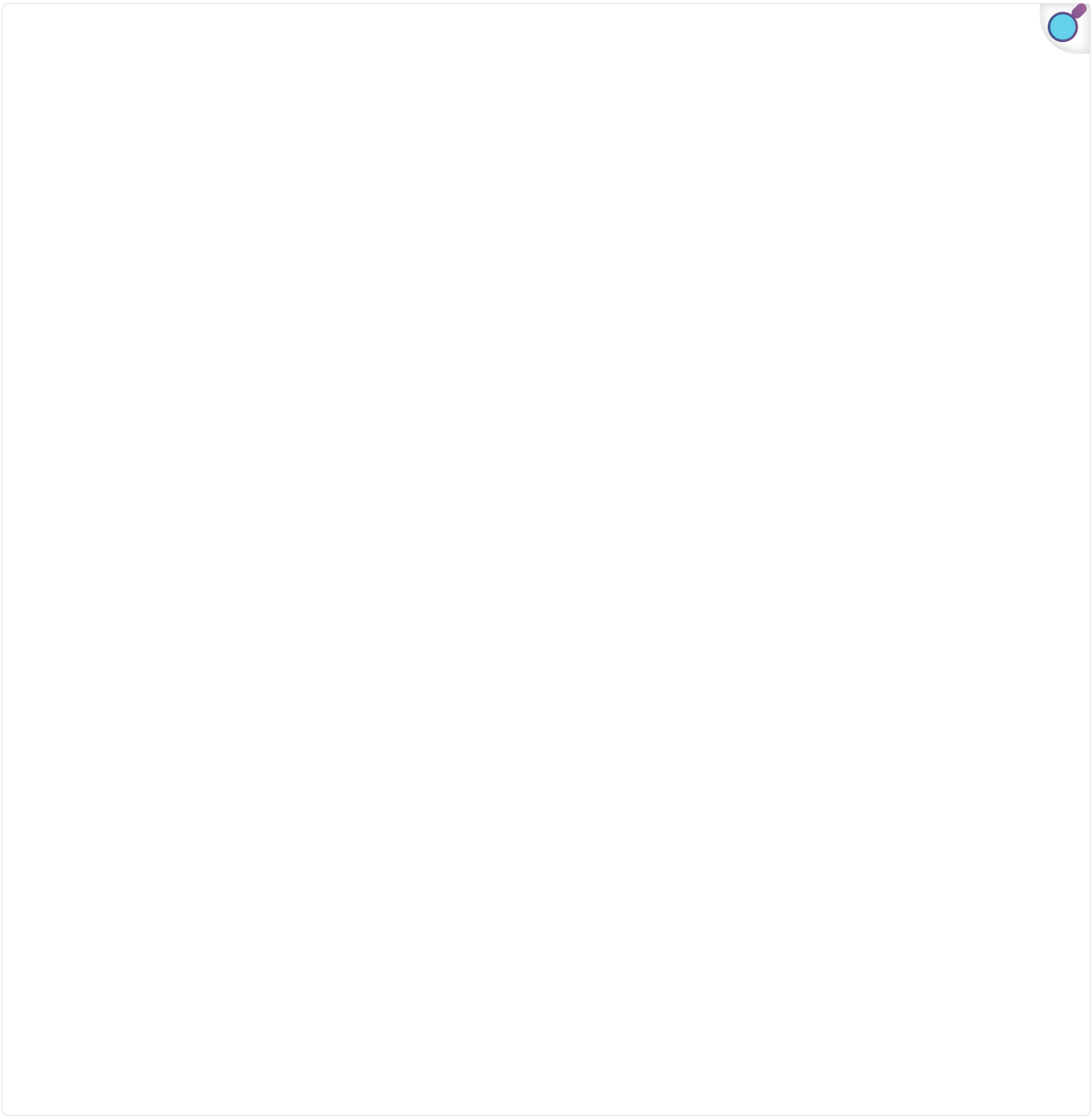
- Stimulation modulated by body position (gyroscopes) or motion (accelerometer) Response to local field potential power spectra (for example, beta for rigidity or gamma for dyskinesia) or seizure activity
- Electromyographic recording for motor feedback
- Integration of multiple feedback and stimulation sites
- Use of artificial intelligence techniques to fine-tune programming

Neuroimaging advances to improve targeting

- Enhanced anatomical resolution through specialized sequences (for example, quantitative susceptibility mapping) or ultra-high-field (7 T) MRI
- Improved automatic electrode reconstruction and segmentation with image-processing software

- Identification of ‘sweet spots’ from large retrospective imaging studies Enhanced deep brain stimulation programming through prospective functional imaging (for example, functional MRI) to identify optimal ‘neural signatures’

Fig. 6. Future visions for DBS.



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a | A typical currently available deep brain stimulation (DBS) configuration **b** | A predicted future DBS configuration.

Key points.

- Deep brain stimulation (DBS) is a neurosurgical procedure that allows targeted circuit-based neuromodulation and is commonly used for the treatment of movement disorders such as Parkinson disease, tremor and dystonia.
- Innovations in the field of cardiac pacemakers have enabled pulse generators for DBS to evolve from external devices to small rechargeable, implantable devices.
- With directional DBS leads, the current can be directed or shaped to personalize stimulation to individual anatomical structures.
- Closed-loop DBS systems simultaneously record and stimulate neural activity, allowing the stimulation to be adjusted according to disease-specific neural biomarkers.
- Open-access software can be used to localize DBS electrodes and, on the basis of the stimulation parameters, to model the volume of tissue activated around the electrodes, shedding light on key neurocircuitry elements.
- As DBS systems become compatible with wireless networks, remote programming by physicians will become possible but privacy issues will also need to be addressed to prevent misuse, including ‘brainjacking’.

Brainjacking

The unauthorized control of an implanted brain device, theoretically through Bluetooth or wireless internet technology.

Gate theory

Theory describing the 'gating' of pain signals, whereby the transmission of non-painful stimuli can block or override painful signals at the level of the spinal cord.

Quadripolar electrodes

Deep brain stimulation (DBS) electrodes configured with four equally spaced contacts — the most commonly used DBS electrode configuration.

Radiofrequency coupled coils

Early deep brain stimulation systems powered the delivery of stimulation using an implanted radiofrequency receiving coil. These systems evolved and were replaced by the modern-day battery-coupled pulse generators.

Implantable pulse generator

(IPG). A battery, typically implanted below the clavicle and connected via subcutaneous extension cables to intra-cranial electrodes. The iPg generates and transmits electrical impulses at a specified frequency, amplitude and pulse width.

Parameter space

The available combinations of voltage, current, pulse width, contact selection, current shape and stimulation pattern when programming a deep brain stimulation device.

Segmented leads

Deep brain stimulation electrodes with multiple different contacts through which current can be transmitted.

Electrode contacts

Non-insulated regions near the distal tip of an electrode from which electrical impulses are transmitted.

Waveforms

The shapes of the electrical impulses transmitted from a deep brain stimulation contact, most often represented in 2D as a function of voltage or current over time.

Volume of tissue activated

(VTA). The estimated spatial extent of the electric field surrounding an activated deep brain stimulation contact at a given stimulation parameter setting.

Energy-harvesting

Having the capability to capture energy from the surrounding environment, including from thermal, vibratory, electromagnetic and acoustic sources.

Biphasic pulses

electrical impulses consisting of both a positively and a negatively charged component. During each stimulus, a reversal between cathodic and anodic stimulation occurs.

Cathodic and anodic

During stimulation, an electrode contact can function as a cathode (or current sink) or as an anode (source of current) relative to the implantable pulse generator or to other electrode contacts.

Spike timing-dependent plasticity

Concept by which the timing of presynaptic and postsynaptic excitatory potentials affects the overall synaptic strength.

Neuronal coincidence rates

The incidence of temporally overlapping presynaptic and postsynaptic excitatory potentials.

Power spectra

In the context of local field potentials, it refers to the strength or intensity of the electric field based on frequency, commonly categorized as delta (1–3 Hz), theta (4–8 Hz), alpha (4–9 Hz), beta

(15–30 Hz) and gamma (>30 Hz).

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Footnotes

Author contributions

All authors contributed to all aspects of manuscript preparation.

Competing interests

J. K. K. is a consultant for Medtronic and Boston Scientific. P. B. is a consultant for Medtronic. W. M. G. is the Director, Chief Scientific Officer and share owner of Deep Brain Innovations, LLC. He also receives royalty payments for licensed patents on temporal patterns of deep brain stimulation. M. I. H. has received travel expenses and honoraria from Boston Scientific for speaking at meetings. A. H. was supported by the German Research Council (DFG grant 410169619) and reports lecture fees from Medtronic and Boston Scientific unrelated to the present work. P. A. T. works as a consultant for Boston Scientific Neuromodulation. J. V. works as a consultant to Boston Scientific, Medtronic, and Newronika and has received honoraria for lectures from Boston Scientific and Medtronic as well as research grants from Boston Scientific and Medtronic. A. M. L. has served as a consultant for Boston Scientific, Medtronic, Aleva, and Abbott and is a co-founder of Functional Neuromodulation. All other authors declare no competing interests.

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