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Emerging technologies for improved deep brain stimulation

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Abstract

Deep brain stimulation (DBS) is an effective treatment for common movement disorders and has been used to modulate neural activity through delivery of electrical stimulation to key brain structures. The long-term efficacy of stimulation in treating disorders, such as Parkinson's disease and essential tremor, has encouraged its application to a wide range of neurological and psychiatric conditions. Nevertheless, adoption of DBS remains limited, even in Parkinson's disease. Recent failed clinical trials of DBS in major depression, and modest treatment outcomes in dementia and epilepsy, are spurring further development. These improvements focus on interaction with disease circuits through complementary, spatially and temporally specific approaches. Spatial specificity is promoted by the use of segmented electrodes and field steering, and temporal specificity involves the delivery of patterned stimulation, mostly controlled through disease-related feedback. Underpinning these developments are new insights into brain structure–function relationships and aberrant circuit dynamics, including new methods with which to assess and refine the clinical effects of stimulation.

Deep brain stimulation (DBS) is an effective treatment strategy for a wide range of neurological conditions, such as Parkinson's disease[1–4], essential tremor[5,6], and dystonia[7–10]. Prior expertise gained from surgical ablation strongly influenced the clinical use of DBS—in particular, the choice of brain regions targeted for stimulation[11,12]. Empirically chosen stimulation parameters (e.g., a 130–180 Hz stimulation frequency, a 60–90 μs pulse width, and 1–4 V stimulation intensity)[6] induce similar clinical outcomes to those observed with surgical ablation. Long-term efficacy of applying high-frequency stimulation to certain brain regions[5], together with the reversible nature of DBS and the

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Competing interests

C.M. is a shareholder in Surgical Information Sciences, Hologram Consultants, Cortics, Autonomic Technologies, Cardionomic and Enspire DBS, as well as a paid consultant to Boston Scientific Neuromodulation. C.M. has intellectual property directly related to the areas we discuss and receives royalties from Neuros Medical, Boston Scientific, Hologram Consultants and Qr8 Health. T.D. is a shareholder in Medtronic, is a consultant for Inspire Medical and Cortec Neurotechnologies, is an advisor for Nia therapeutics, and has intellectual property directly related to the areas we discuss. P.B. has intellectual property directly related to the areas we discuss. H.C. has intellectual property directly related to the areas we discuss.

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possibility of reducing the amount of drugs administered to patients with Parkinson's disease[13], has helped adoption of this electroceutical treatment, which can reduce symptoms by an average of ~40% 3–4 years after surgery[14]. Even in Parkinson's disease, however, as few as 2% of patients undergo DBS[15], potentially reflecting the invasive nature of the intervention, the high cost of treatment and limited access to, or fear of, surgery.

A critical aspect of DBS efficacy is patient selection and the choice of the appropriate target location based on patient's symptom profile, age and cognitive status[13,16–18]. These choices heavily rely on the expertise of the surgical team and vary from center to center. Surgical complications include hemorrhage, infection, skin erosion and hardware-related complications, such as stimulator failure and electrode fracture[16,19]. In addition, an important postoperative limitation of DBS is stimulation-induced side effects caused by electrical activation of the surrounding brain tissue. Up to 50% of implanted patients can experience stimulation-induced side effects, albeit not severe ones in most cases[14]. Prevalence of side effects strongly depends on the target nucleus and the anatomy and functionality of the surrounding tissue[14]. Emerging technologies such as segmented electrodes and closed-loop DBS aim to minimize these side effects.

In this Review, we provide an overview of the mechanism of DBS within the context of movement disorders and assess application of DBS for treatment of various neurological and psychiatric conditions. We discuss recent technological advancements that could improve stimulation location and timing, highlight types of signals that could be used as a biomarker, and provide an overview of how these biomarkers could be decoded to deliver closed-loop stimulation. We review studies that provide alternative stimulation strategies to state-of-the-art high-frequency DBS and explore different control policies. We highlight important considerations for therapy safety as the field moves toward treatments that continuously adapt stimulation parameters according to a disease biomarker. Finally, we review some of the upcoming technologies that could shape the neuromodulation field.

DBS mechanism and movement disorders

The similarities between the outcome observed with applying high-frequency stimulation and lesioning the same brain region led to the initial hypothesis that DBS inhibited neural activity and reduced the output of the target nucleus. This was supported by experimental evidence that showed a reduction in neural activity at the site of stimulation, potentially through the activation of inhibitory projections to the target region[20–23]. Hashimoto et al., by contrast, reported that downstream neural activity increased during high-frequency stimulation of one of the most common target nuclei used for the management of Parkinson's disease symptoms: the subthalamic nucleus[24]. This observation was corroborated by other studies that concluded that downstream neural activity was either upregulated or downregulated depending on whether the projection from the target nucleus to the downstream nucleus was excitatory or inhibitory, respectively[25–29]. Further research has demonstrated that upstream targets could similarly be affected by antidromic conduction[30,31]. Taken together, this body of work raised a paradox regarding the mechanism of DBS. An influential theoretical model capturing the effect of high-frequency stimulation on thalamic neurons suggested that stimulation could directly activate axons

traversing or adjacent to nuclei while inhibiting activity at the somata, reconciling the experimental evidence on modulation of upstream and downstream activity in the presence of a reduction in neural activity at the site of stimulation[32] (Fig. 1).

The current consensus regarding the mechanism of DBS is that high-frequency stimulation modulates neural activity at afferent and efferent brain regions[24,33,34] to restore function[35]. For disorders characterized as oscillopathies, where patients' symptom severity is correlated with excessive rhythmic neural activity at the DBS target region and projection targets (for example, Parkinson's disease[36], essential tremor[37] and dystonia[38]), high-frequency electrical stimulation has been shown to suppress rhythmic neural activity and concurrently alleviate patients' symptoms[38,39]. A similar mechanism has been recently observed during stimulation of the anterior nucleus of the thalamus for the treatment of refractory focal seizures: stimulation was effective in desynchronizing downstream hippocampal activity only when it was applied at high frequencies[40]. This stimulation effect has been linked to a suppression of epileptic activity, highlighting a potential mechanism for stimulation efficacy comparable to those highlighted for other oscillopathies[41–43]. Indeed, evidence is emerging that oscillatory activity may also play a role in psychiatric conditions like obsessive-compulsive disorder[44,45] and Tourette's syndrome[46]. However, there is nothing to suggest that DBS exclusively acts through the overwriting of pathological oscillatory activities; aberrant, arrhythmic circuit motifs underlying symptoms, although more difficult to detect, may also be overwritten.

Beyond movement disorders

In recent years, use of DBS has been extended to the treatment of a wide range of neurological and psychiatric conditions, such as Tourette's syndrome[18,47], obsessive-compulsive disorder48–[50], major depression[51–53] and Alzheimer's disease[54,55] (Table 1). However, treatment of these disorders remains experimental, with the exception of obsessive-compulsive disorder, which is regulated under a humanitarian exemption. Two clinical trials studying the use of DBS for the treatment of major depression[53,56] have failed. Pilot results in Alzheimer's disease were similarly limited[54]. For these diseases, several critical aspects of therapy remain unresolved—in particular where, when and how stimulation should be delivered in the light of individual anatomical and pathophysiological differences. Failure to take into account these issues has arguably given rise to inconsistent clinical outcomes for the majority of the aforementioned neuropsychiatric disorders. In the upcoming sections, we review recent technical advances in the neuromodulation field that could enhance therapeutic efficacy and selectivity not only for the existing applications of DBS, but also for future applications to other medication-refractory neurological and psychiatric disorders.

Where to stimulate?

Stimulation efficacy strongly depends on the target brain region. For instance, in Parkinson's disease, delivering high-frequency DBS to the subthalamic nucleus and local fiber pathways is able to suppress all the cardinal symptoms of the disease: bradykinesia, rigidity and tremor4. In contrast, high-frequency DBS delivered to the ventrolateral thalamus reduces

tremor severity but is relatively ineffective for the management of bradykinesia and rigidity[57]. Similar considerations apply in the context of epilepsy, where complex network models are beginning to be employed to determine the most effective target location for surgical intervention[58,59].

Once a target is selected, the accuracy with which it is stimulated is critical so that the volume of tissue activated (VTA) matches, as best as possible, the target structure. Traditionally, this has been achieved first via electrode contact selection and then by manipulations of the amplitude and width of the stimulus pulse[60–62]. Electrode design is also a key determinant of the VTA during DBS. To facilitate application of DBS technology to the treatment of various neurological and psychiatric disorders, the design of the electrode should allow a flexible interface when targeting different brain regions, compensating for morphological differences and surgical variance. The traditional cylindrical DBS electrode design uses four cylindrical contacts (for example, 1.27 mm in diameter and 1.5 mm in height for the Medtronic 3387/3389 quadripolar DBS electrode). The VTA around the electrode critically depends on the number of contacts used for stimulation; return reference (i.e., monopolar versus bipolar); stimulation parameters, such as amplitude and pulse width; and properties of the tissue surrounding the electrode (i.e., isotropic—homogenous across all orientations—versus anisotropic)[63–65].

In isotropic media, stimulation delivered using cylindrical DBS electrodes gives rise to a symmetric, omnidirectional VTA around the electrode, and induced side effects can only be reduced by either minimizing the duration and stimulation intensity or changing to bipolar mode. Thus, anisotropic media affect the VTA and, in the case of cylindrical DBS electrodes, affect the symmetry of the field around the electrode. However, for certain disorders, target regions and placements minimizing the stimulation intensity may not be sufficient to reduce stimulation induced side effects. Therefore, in recent years, electrode designs that allow field steering[66] have taken center stage as an alternative to cylindrical DBS electrodes. The added precision that these electrodes afford can help improve the accuracy of lead interfacing (Fig. 2).

Segmented electrodes allow greater control over the VTA through field steering and independent control of electrode contacts. Current commercial variants achieve directionality by replacing the middle two cylindrical contacts of traditional quadripolar electrodes with three segmented electrodes, increasing the total number of programmable contacts from four to eight and allowing three radial directions of stimulation separated by 120 degrees. These segmented electrodes allow clinicians to modify side-effect thresholds and create a greater margin between symptom suppression and side-effect induction (the therapeutic window)[67–73]. Upcoming technologies, such as thin-film planar arrays, could provide further improvement to spatial specificity of stimulation and recordings acquired from disease circuits[74], through reduced contact size and increased contact numbers.

However, increased electrode precision comes with trade-offs. The greater flexibility afforded by segmented electrodes and thin planar arrays considerably increases the degrees of freedom allowed in programming. This flexibility increases the burden on the clinical team[72] because optimal stimulation contact and parameter selection mostly rely on a process

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of trial and error. Therefore, automated or support tools for assisting clinicians in determining optimal stimulation parameters are sorely needed. For example, it has recently been shown that the use of a disease biomarker, such as heightened rhythmic neural activity, can reduce the amount of time needed for programming segmented electrodes for the treatment of Parkinson's disease[71,72]. Evoked potentials might also be useful in this regard[75]. Strategies that consider electrode location and anatomical landmarks in conjunction with individualized diffusion tensor imaging could provide additional information needed to reduce the degrees of freedom associated with programming DBS electrodes[76–78].

How and when to stimulate

In recent years, the traditional practice of continuously stimulating the brain using static stimulation parameters has shifted to the use of disease biomarkers and patient's state (for example, awake or asleep) or actions to determine how much and when to stimulate. The main motivation behind closed-loop stimulation is minimization of treatment side effects by providing only the necessary stimulation required within a certain time window, as determined from a guiding biomarker. This in turn limits any unwanted direct stimulation of nearby fiber tracts, such as those in the internal capsule responsible for many aspects of the dysarthria that may complicate stimulation of the subthalamic nucleus[79]. It has also been suggested that temporal patterning of stimulation could spare residual local physiological neural processing, as in the case of physiological bursts of beta activity in the subthalamic nucleus related to decision conflict, where DBS-driven suppression leads to motor impulsivity[80]. Similarly, adverse effects of DBS on sleep might decrease during responsive stimulation of the anterior nucleus of the thalamus for treatment of epilepsy[81]. Closed-loop stimulation could be essential not only to reverse direct side effects of stimulation, but also to minimize adverse effects due to combined pharmacological treatment, as has been explored in the context of dyskinesias observed in Parkinson's disease due to dopaminergic medication[82,83].

Closed-loop stimulation is also being investigated for the treatment of neuropsychiatric disorders, such as obsessive-compulsive disorder and Tourette's syndrome[50,84], in Tourette's syndrome, a case report of closed-loop stimulation has already been published[85]. The viability of these approaches will strongly depend on identification of reliable disease biomarkers that reflect patients' symptom severity and change with treatment[46,49]. Critically, though, closed-loop DBS has only hitherto been trialled over periods of time measured in hours, with the exception of closed-loop stimulation for pain and epilepsy management (Box 1). Thus, it remains to be seen whether the efficacy and side-effect profile of closed-loop DBS is maintained sufficiently to warrant chronic use for treatment of movement disorders and neuropsychiatric conditions. In this regard, the recent development of bidirectional implantable devices, such as the Responsive Neurostimulation system (RNS) manufactured by Neuropace[86] or the Activa PC+S manufactured by Medtronic[87], is noteworthy. In particular, Activa PC+S can serve the dual purpose of interrogating diseases for biomarkers useful for closed-loop DBS and piloting such therapy over long periods while retaining the option of defaulting to conventional stimulation.

Biomarkers for closing the loop

Various classes of signals have been used to determine when and how much to stimulate, including pathological neural activity[79,82,88–90] and peripheral measurements[91,92]. Biomarkers need not necessarily be directly related to disease mechanisms, but should correlate with the severity of disease symptoms[36,93–95] and track the response to therapeutic interventions[39,46,93,95,96]. The relevant signals may be relatively unprocessed or subject to several processing steps to extract the information of interest, with or without the aid of machine learning. Processing commonly involves spectral analysis. As will be seen below, this serves to focus on a particular pathological oscillation, but in the future, control is more likely to be based on combinations of spectral and other features[97], some with different temporal resolutions, such as phase–amplitude coupling and coherence between brain sites.

Closed-loop DBS strategies have thus far mainly focused on the treatment of common movement disorders, such as Parkinson's disease and essential tremor (Fig. 3). In these indications, two types of neural control signal have been exploited to determine when and how much to stimulate. First, the instantaneous power of rhythmic neural activity in the beta band (~20 Hz) can be tracked in the form of the local field potential at the site of stimulation[79,88–90]. This approach has the advantage of sensing and stimulating via the same electrode and therefore minimizing surgical instrumentation needed to implement closed-loop stimulation. Recordings direct from the stimulation electrode may also allow feedback through evoked activity[75]. Second, the instantaneous power of rhythmic neural activity can be tracked in the motor cortex. In the latter case, studies have focused on gamma activity (~75 Hz) in the control of dyskinesias[82] or on movement-related modulation of beta activity in the control of tremor[98]. This approach limits contamination of the feedback signal by stimulus artifact and leverages the improved signal-to-noise ratio of cortical recordings.

A different approach is the use of peripheral sensors for feedback, which also circumvents stimulus artifact and may prove useful for gait disturbance and tremor[91,92,99–102]. However, with this approach additional constraints need to be addressed, such as the energy expenditure associated with wireless communication between the peripheral sensor and the implanted stimulator, the security of wireless communication and the fact that information from peripheral sensors follows the development of symptoms and is therefore not predictive. Patient compliance in the wearing of peripheral sensors is another important consideration.

Decoding biomarkers for closing the loop

Applications of closed-loop DBS have mainly focused on the use of specific signal features, such as neural activity in the beta or gamma frequency bands, to control stimulation timing for a range of movement disorders. However, the exact mapping between neural activity and symptom severity remains unknown for most neuropsychiatric disorders, which necessitates the use of alternative techniques. Real-time decoding strategies could be employed to identify signal features that could be used as a proxy for the patient's symptom severity or behavioral state. Features extracted from thalamic field potentials have been used to decode onset of tremor and tremor-triggering voluntary movement in a group of patients with

essential tremor[103], while subthalamic field potentials from patients with Parkinson's disease have been successfully used to determine the amount of muscular force exerted[104]. The feature space could be different frequency bands obtained from electrophysiological recordings, derived using techniques such as wavelet transforms or fast Fourier transforms[103,104]. Important considerations for real-time implementation of such strategies are energy expenditure and processing cost of decoding algorithms. Similarly, the timescales over which signal features evolve can be a complicating factor, especially when features of interest fluctuate over vastly different time scales (for example, seconds to days).

Potential solutions for such scenarios could be (i) to use a combination of cloud computing and real-time processing utilizing implanted electronics[105] or (ii) to process signal features that are fluctuating at a slower rate using a lower sampling rate than the ones evolving at a much faster rate. Although previous examples of decoding relied on recordings from single brain regions, this may not be sufficient for most neuropsychiatric applications. For these applications, the feature space could include changes in coupling across multiple sites[106–108], providing more insight into network properties that could be leveraged to further adjust stimulation parameters, particularly when treating disorders driven by complex network architectures. Coupling across different sites could be derived from either field potentials[106,107] or field potential and single-unit activity[108] and could be based on fluctuations in activity timing (i.e., phase coupling) and/or strength (i.e., amplitude coupling). It should be noted that while the utility of single-unit activity has been demonstrated in animal experiments[109], state-of-the-art chronically implanted devices for the treatment of neuropsychiatric disorders only provide access to field potentials.

Another important consideration for decoding neural activity is the resolution of symptom severity or behavioral measures. Although symptom severity in movement disorders can be derived in real time using either peripheral sensors (for example, ones that measure tremor severity) or neural activities with a previously established relationship with symptoms, this is not feasible when, for instance, decoding patients' mood. Sparsity of behavioral measures coupled with high dimensionality of feature space have been elegantly addressed in a recent study by Sani et al., wherein the authors propose that (i) restricting the number of model parameters, (ii) limiting the number of brain regions used for decoding mood, and (iii) using a low-dimensional state space could enable decoding of mood variations while minimizing problems such as overfitting[97].

Getting away from high-frequency stimulation

Several theoretical models suggest that moving away from high-frequency stimulation to pathology- and brain-region-specific stimulation could improve the therapeutic outcome further not only by inducing long-lasting plastic changes but also by limiting the amount of energy delivered and thereby side effects. Coordinated reset is a theoretical concept put forward to desynchronize a population of neurons by delivering patterns of short pulses in a coordinated fashion across different electrode contacts[110]. Efficacy of coordinated reset together with long-lasting effects of this stimulation strategy have been experimentally shown in both MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated monkeys and a

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group of patients with Parkinson's disease, although in the latter case no control group was included[111,112].

Another influential theoretical model focuses on tailoring the stimulation pattern according to the temporal properties of the pathological neural activity in a closed-loop fashion, under the hypothesis that stimulation at a certain phase of neural activity can disrupt synchrony[113–115]. This stimulation strategy, referred to as phase-specific DBS, has been shown to be effective in acutely suppressing tremor in a group of patients with essential tremor, despite using ~40% of the total electrical energy delivered per unit time associated with conventional high-frequency DBS[91]. Like coordinated reset, this stimulation approach has the potential to minimize DBS-induced side effects by reducing the amount of energy delivered to the brain.

Control policies need not be fixed

Consideration of patient behavior, such as sleep, walking or decision making, could also further aid in determining optimal stimulation patterns. In recent electrophysiological studies, only high-frequency stimulation that was delivered at a certain period of the decision-making process impaired patients' behavior, suggesting that adapting stimulation timing according to patient behavior could limit such adverse effects[80,116,117].

In a similar vein, alternating stimulation patterns between hemispheres according to patients' walking pattern could potentially improve gait by reinforcing the physiological modulation of beta activity with stepping[118]. The timing of stimulation may also prove important during sleep, where the available evidence already suggests that even conventional high-frequency stimulation can improve or worsen patients' sleep quality according to stimulation site[81,119]. In sum, these observations highlight a potential new avenue for stimulation control: tailoring stimulation not only according to pathology and its circuit manifestations, but also according to the everyday actions and behaviors of patients.

Safety and future-proofing

As we transition from the laboratory to clinical use of advanced DBS technologies, care should be taken regarding patient safety and sustained stimulation efficacy[120]. Many of these considerations are captured in the ISO guidance 60601-1-10, essential requirements for physiologic control systems. One example for both segmented leads and adaptive algorithms is the setting of safe boundaries for stimulation. For field steering, controls should be used to ensure that a safe charge density is applied. For adaptive algorithms, upper and lower boundaries for stimulation intensity should be fixed on the basis of clinical assessment, and any algorithm's stimulation updates limited to this predetermined safe zone of operation[120].

Another safety procedure is to define a fallback mode. For directional leads, the ability to revert to ring mode (the most common setting) and provide 'classical' stimulation is an important risk-mitigation approach. For adaptive systems, an open-loop stimulation at predetermined parameters should be made readily available to the patient to ensure sustained stimulation efficacy in case of an unforeseen limitation of the closed-loop approach. These

concepts have been demonstrated in several investigational studies for Parkinson's disease and essential tremor[82,98].

The future

DBS is undergoing a renaissance as it evolves from a 'reversible lesion' to a targeted prosthesis that dynamically and accurately restores brain function. For accuracy, spatial selectivity is enhanced through higher resolution electrodes; for dynamics, we are on the verge of a paradigm shift away from monotonic high-frequency stimulation toward temporal patterning informed by dynamics in neural circuits and symptoms. These developments push us ever closer to the goal of individualized therapy that tracks clinical state. However, more sophisticated control requires a greater understanding of pathophysiology to allow the development of useful biomarkers and, where necessary, biomarker combinations to dictate stimulation. Similarly, control algorithms should mature while maintaining tractability. Most of all, at every point in the development journey, we must remain open to alternative non-invasive[121,122] or minimally invasive electrical and other interventions[123,124], when and if these compete in terms of efficacy.

In the near future, technology trends in the broader landscape, such as the 'Internet of Things', will further help support the adoption of new technologies. These trends include both automation and information processing, as well as device miniaturization. For example, the use of rechargeable systems and secure telemetry allows continuous wireless upload of data with marginal impact on device longevity. The increased data uploads will allow more continuous patient assessments and more complex control on multiple timescales using off-the-body local and distributed cloud computing systems. At the same time, such a system lends itself to integration of data from peripheral sensors, the output of which may be fed into machine-learning methods to provide summaries that aid decision-making and prevent clinicians from being overloaded with too much information. A prototype for this style of control has been recently published in a canine model of epilepsy, in preparation for investigational studies in human[105]. Modern circuit technology also allows firmware to be rewritten in the device. Firmware upgrades 'future-proof ' the implant and allow patients to benefit from enhancements in adaptive algorithms[82,125]. The ability to update algorithms is especially important for rechargeable systems, which might last more than a decade.

All of these methods require care in security and risk management to ensure patient safety and minimize the threat of malicious hacks. Guidance from regulators is helping to inform more robust device architectures[126]. In addition, the continued focus on miniaturization will drive innovations in device design and surgical techniques. In the past few years, cardiac pacemakers without leads have been developed that can be implanted through endovascular techniques. This new design minimizes complication rates while maintaining basic therapy functionality[127]. Similar techniques are being explored for neuromodulation, whereby electrodes implanted through less invasive vascular routes might provide access to the nervous system without the necessity of cranial burr holes and tissue-disrupting lead insertion[128]. All of these existing technology trends are expected to cross-pollinate with brain stimulation and further advance the field. These advancements could potentially reduce the invasive nature of DBS surgery and minimize the risk of infection in hospital settings.

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In the longer term, it is likely that brain stimulation therapies will be further disrupted by advancing technology, much as DBS originally disrupted ablation procedures. New mechanisms to actuate the nervous system with optogenetics or other cell-specific targeting approaches could greatly refine the ability to modulate and control neural circuits. Although technical limitations on transfection efficiency remain, improvements in opsin quality[129] and the adoption of gene therapies in clinical trials[130] are removing some barriers to translation[131]. At the other extreme, minimally invasive methods such as transcranial ultrasound are enabling 'non-invasive' ablation of neural circuits, such as those in the thalamus for tremor[124], and the field is now expanding to explore real-time modulation of cortical and subcortical circuits[132–134]. These approaches might one day provide the many of benefits of DBS without the requirement of cranial surgery; the physical implementation of an ambulatory ultrasound system is an active area of technology development. Technology might also provide a means to improve the specificity of an implant, with substantially less invasiveness, using hybrid methods that combine implantable and wearable systems. For example, distributed ultrasound-linked 'neural dust' might provide a means to distribute energy and sensing capability across broad networks with minimal physical impact, enabling a scale of neural interfacing that is hard to replicate with physically tethered leads[135,136]. Hybrid methods might also include access from the periphery[137].

Laser thermal ablation and radiosurgery provide an ablationbased alternative to DBS, which could be used in combination with magnetic resonance imaging guidance to increase targeting accuracy. Critically, these therapies are more cost effective than DBS without compromising therapy efficacy when unilateral targeting would suffice for controlling disease symptoms[138–140]. The main limitation of all ablation-based alternatives, however, remains laterality of the treatment. The vagal nerve system is currently used for the treatment of epilepsy and is being explored for stroke rehabilitation. As our understanding of interactions between the peripheral and central nervous system increases[141,142], we expect there to be less of a dichotomy in treatment approaches, which will further motivate distributed neural interfaces.

One final area for consideration is how other cell types might figure into optimizing therapy. The role of glia and astrocytes in neural computation is still ambiguous, but could provide another degree of freedom for modulating neural circuit activity. In sum, the rate of technology development coupled with the unknowns of clinical neuroscience make the future hard to predict, but the large burden of neurological disorders motivates new innovations.

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Box 1

FDA-approved closed-loop stimulation strategies

Chronic use of closed-loop electrical stimulation has been shown to be effective and safe for the management of pain and epilepsy.

Closed-loop spinal cord stimulation for pain.

Applications in this indication have been motivated by the observation that effective stimulation parameters varied according to patients' posture[151,152]. In the Medtronic RestoreSensor system, stimulation parameters are adaptively adjusted according to patients' posture as measured via a triaxial accelerometer integrated into the implanted stimulator. The mapping between effective stimulation settings and patients' posture is determined in an open-loop fashion. This mapping is then used to automatically adjust stimulation according to changes in patients' posture to ensure that stimulation efficacy is retained throughout the day[148,149]. By contrast, in the Saluda Evoke SCS system, compound action potentials evoked by spinal cord stimulation are sensed and interpreted to achieve continuous stimulation efficacy. The preferred evoked action potential amplitude is determined in a patient-specific manner and assessed continuously following each stimulation pulse. Stimulation intensity is then adaptively either increased or reduced to sustain effective recruitment of dorsal column fibers[150].

Closed-loop stimulation for epilepsy.

This area has been motivated by the observation that brief electrical stimulation is effective in terminating afterdischarges observed as a result of cortical stimulation[153]. In the RNS Neurostimulator system, cortical stimulation is delivered to the seizure focus when epileptic electrocorticographic activity is detected. Several options are provided for detecting epileptic electrocorticographic activity. These algorithms rely on detection of (i) rhythmic electrocorticographic activity in a specific frequency band, (ii) certain changes in the instantaneous electrocorticographic activity with respect to neural activity observed over a longer period of time, and (iii) the overall increase in electrocorticographic signal power[154–157]. Critically, it has been suggested that the total duration of stimulation could be reduced to fewer than 5 min from 24 h when the stimulation is delivered in a closed-loop fashion[153].

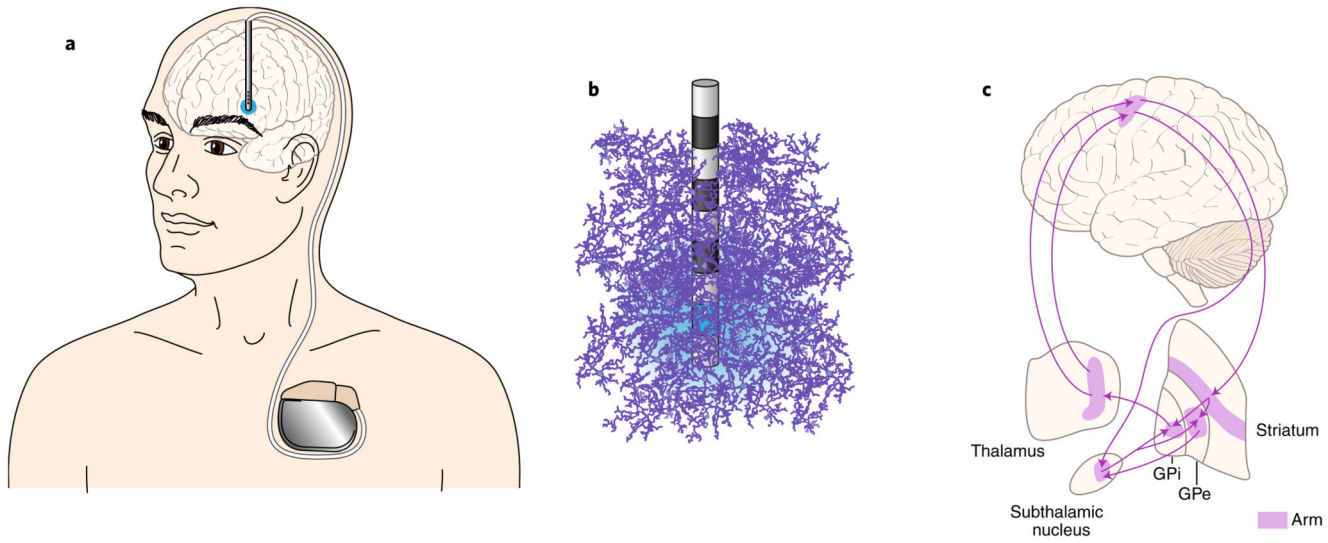

Fig. 1. Deep brain stimulation.

a, The electrodes and pulse generators are permanently implanted, self-contained systems. Electrodes can be implanted in one or both hemispheres of the brain, depending on the laterality of the symptoms. The electrode(s) implanted in the brain are connected to the pulse generator implanted in the chest. **b**, Traditional DBS electrodes consisted of four contacts (black cylinders), where typically a single contact was used to deliver stimulation. The most common surgical target for the treatment of Parkinson's disease is the subthalamic nucleus, which contains ~250,000 neurons, depicted in blue, and is much denser in reality than shown here. (Adapted with permission from ref. [158].) **c**, DBS enables wide-scale network modulation of the basal ganglia and cortex. This is because these structures are coupled into loops. There are many such overlapping loops, but here, for schematic purposes, a loop controlling the arm is illustrated. GPe, globus pallidus externa; GPi, globus pallidus interna. (Reprinted from ref. [143], *Neurobiol. Dis.* **38**, C. C. McIntyre & P. J. Hahn, Network perspectives on the mechanisms of deep brain stimulation, 329–337, copyright 2010, with permission from Elsevier.).

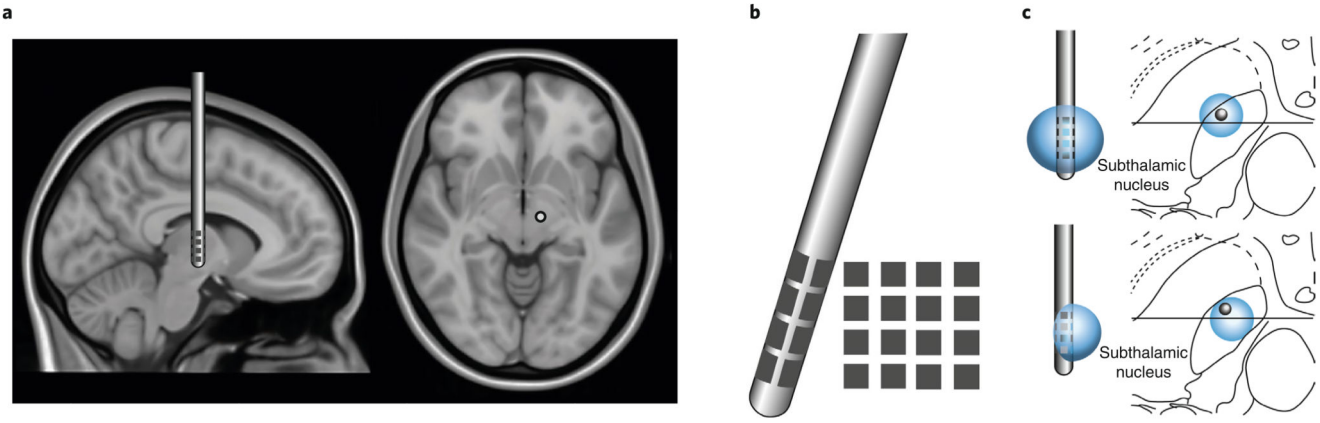

Fig. 2. Field steering.

a, Schematic DBS electrode shown on magnetic resonance imaging scans targeting the subthalamic nucleus. Perioperative imaging is essential and intraoperative imaging desirable in the accurate placement of electrodes. **b**, Prototype research electrodes have been developed with higher densities of smaller contacts. **c**, These are designed with the intention of providing finer control of the electric field (blue volume). The top panel illustrates the spherical field predominating when a complete ring of contacts is activated to mimic the field derived with conventional DBS. On the right, the electrode and electric field are superimposed on a brain atlas. The electrode is in the target, the subthalamic nucleus, but the electric field extends outside of this, risking side effects. The lower panel illustrates the shaping of the electrical field that is possible when a subset of contacts is simultaneously activated. Now the field is limited to the subthalamic nucleus. (Adapted from ref. [144]; atlas image adapted with permission from G. Schaltenbrand & W. Wahren, *Atlas for Stereotaxy of the Human Brain* 2nd edn, Thieme, 1977.).

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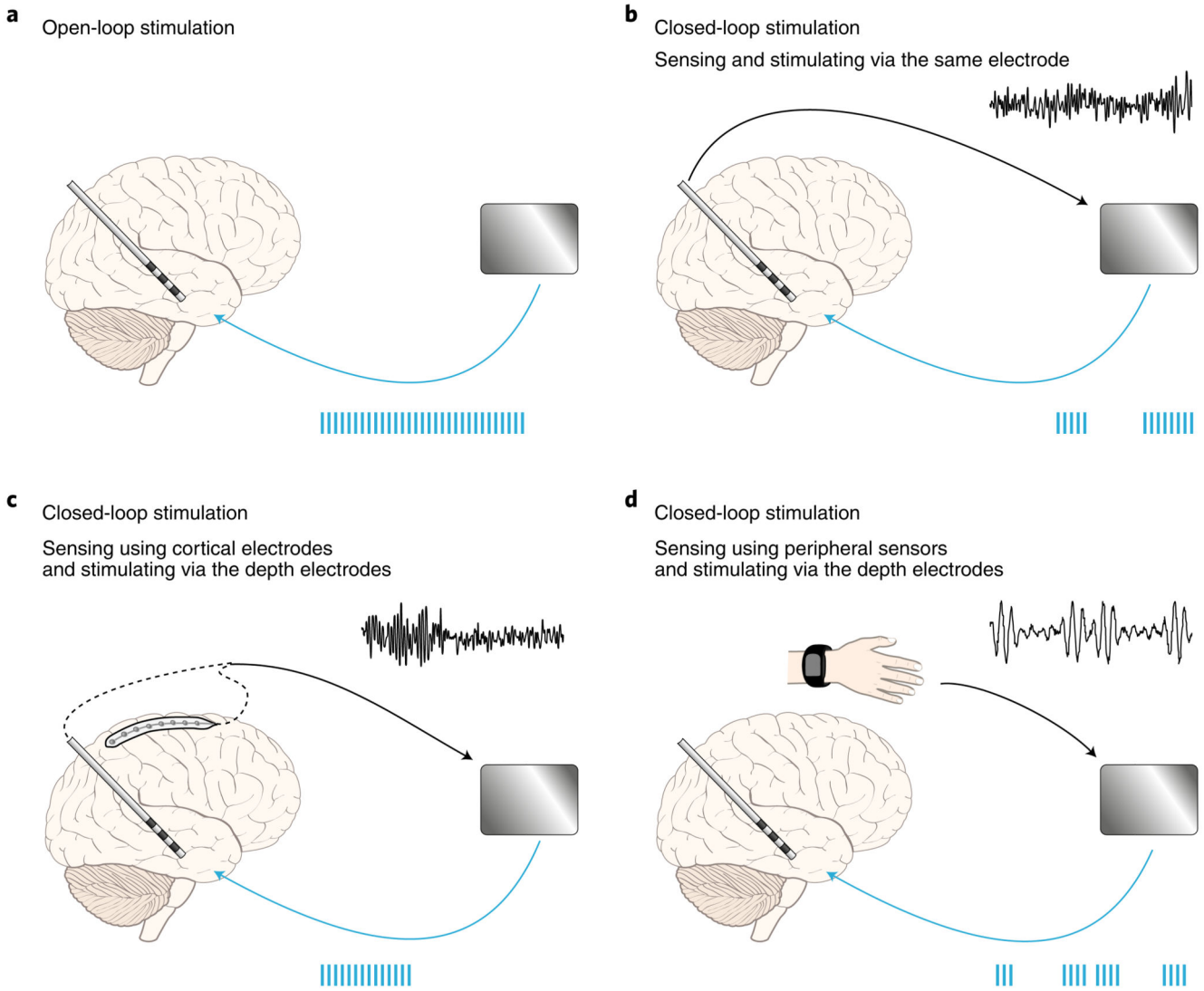

Fig. 3. A comparison of different stimulation strategies.

a comparison of different stimulation strategies. **a**, Stimulation timing and parameters are not automatically adjusted according to a disease biomarker, although the clinician will fine-tune stimulation during follow-up visits (usually twice a year). **b**, Local field potentials sensed using depth electrodes are continuously used to automatically determine stimulation timing or intensity. Stimulation is delivered via the same depth electrodes. **c**, Cortical signals sensed using an electrocorticography array are continuously used to automatically determine stimulation timing or intensity. Stimulation is delivered across the depth electrodes, creating a spatial separation between sensing and stimulation sites. **d**, Peripheral signals obtained from noninvasive measurement devices, such accelerometers and/or electromyography, are used to automatically determine stimulation timing or intensity. As in **c**, this allows a separation between sensing and stimulation sites and therefore minimizes the impact of stimulation artifacts. The gray box represents a computing device and could be an implantable pulse generator, a computer or cloud-based computing. The computing device is

used to process signals and extract features such as the intensity of neural activity in a certain frequency band or phase–amplitude coupling to control stimulation timing and parameters.

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Table 1
A summary of established and experimental DBS targets

Disorder	Target brain region	DBS approach	Refs.
Parkinson's disease	Subthalamic nucleus Globus pallidus (internal) Ventrolateral thalamus Pedunculopontine nucleus	Continuous high-frequency stimulation	2–4,13,14
		Closed-loop DBS	79,82,88–90
Essential tremor	Ventrolateral thalamus	Continuous high-frequency stimulation	5,6,57
		Closed-loop DBS	91,98,100,101
Dystonia	Globus pallidus (internal)	Continuous high-frequency stimulation	7–10
Epilepsy	Centromedian thalamus Anterior thalamic nucleus Seizure foci	Intermittent 20-Hz stimulation	43
		High-frequency stimulation (continuous or cyclic mode)	81,145
		Closed-loop DBS	86,146
Pain	Spinal cord Periventricular or periaqueductal gray matter Sensory thalamus Internal capsule	Continuous low- or high-frequency stimulation	147
		Closed-loop stimulation	148–150
Obsessive compulsive disorder	Subthalamic nucleus Nucleus accumbens Anterior limb of the internal capsule Ventral capsule or ventral striatum Inferior thalamic peduncle	Continuous high-frequency stimulation	44,45,48,49
Major depression	Subcallosal cingulate Ventral capsule or ventral striatum	Continuous high-frequency stimulation	51–53,56
Tourette syndrome	Globus pallidus (internal) Centromedian–parafascicular	Continuous high-frequency stimulation	46,47
		Closed-loop deep brain stimulation	85
Alzheimer's disease	Fornix	Continuous high-frequency stimulation	54,55