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The convergence of neuromodulation and brain–computer interfaces

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Neuromodulation and brain–computer interfaces are rapidly evolving fields with distinct origins but with the shared goal of improving the lives of people with neurological and psychiatric disorders or injuries. Their increasing technological overlap provides new opportunities for collaborative work and rapid progress in neurotechnology.

For decades, implanted electrical neuromodulation systems have been a critical component of the clinical care pipeline for patients with neurological disorders. The widespread clinical availability of deep brain stimulation (DBS) and spinal cord stimulation systems has provided an important technical pathway for advancing chronic device-based neuromodulation research with implantable neurostimulation devices. The identification of disease-relevant electrophysiological neural biomarkers (for example, beta-band oscillatory activity in the subthalamic nucleus, and interictal epileptiform discharges) demonstrated the potential to improve therapy via adaptive systems. This presented a challenge: the field needed human-use investigational devices that combined intracranial sensing capabilities with established stimulation-based therapies in a chronic and implantable research platform. In addressing this challenge, early implantable research tools were developed within existing clinical neuromodulation devices as the foundation, with the addition of an expanded hardware, firmware and software package to support research investigating the use of sensing to enhance therapies. The behaviour of sensing-enabled neuromodulation devices can range from triggering stimulation on the basis of neural activity (for example, the NeuroPace brain-responsive neurostimulation (RNS) system triggers stimulation in response to epileptic discharges) to closed-loop systems that regulate pathological circuits through continuous stimulation adjustments to keep a biomarker within healthy limits using principles of feedback (for example, adaptive DBS (aDBS) methods investigated with the Medtronic Activa PC+S and Summit RC+S systems adjust stimulation on the basis of measurements of spectral band-power). The evolution from RNS to aDBS represents the continuous improvement of neurotechnology and its ability to create a real-time, bi-directional interface between the brain and the device. These technological advances have led to new insights into essential tremor[1], Parkinson's disease[2], epilepsy[3] and Tourette syndrome[4], among other disorders. Many of these studies required research agreements with manufacturers, but the recent commercial availability of neurostimulators with 'on-label' brain-sensing capabilities, such as the Medtronic Percept PC, is facilitating their investigational use.

Intracortical brain–computer interfaces (iBCIs) have a technological pedigree different from that of neuromodulation systems: iBCIs evolved from research platforms that were used to understand and interpret neural activity, rather than to modulate it. In 2006, a groundbreaking example of a chronically implanted human iBCI demonstrated decoding of neural signals from nearly 100 neurons of the motor cortex, which enabled a patient with tetraplegia from spinal cord injury to control a computer cursor and perform rudimentary actions with prosthetic and robotic devices[5]. Rapid progress in analytical tools has improved iBCI-based prosthetic control and communication interfaces[6]. Access to human motor cortical data has led to more-complete mathematical models of brain activity and dynamics, which in turn have improved the stability and longevity of iBCI-based effector control. Traditionally, the complexity of iBCI systems has required substantial technical support for everything from physical device connection to algorithm calibration, observation for clinical safety, and disconnection. Although wireless systems[7] and self-calibrating algorithms[6] have partially addressed these issues, home use of an iBCI remains limited to participants enrolled in clinical trials and still requires trained support staff.

Shared goals, challenges and opportunities

Despite substantial differences in the challenges that confront the iBCI and aDBS fields, there are also illustrative similarities that demonstrate how such challenges can be more effectively and efficiently met by active collaboration between the fields. One example is the unsolved challenge of maintaining therapy stability in the face of electrophysiological changes related to disease progression, circadian rhythms or normal variations in the physical and mental state of the patient. A second example is the pursuit of reliable closed-loop neural stimulation, a familiar DBS feature that has new parallels in iBCIs, such as the use of cortical microstimulation to provide sensory feedback for enhanced prosthetic performance[8]. A shared goal is to provide intuitive, stable closed-loop control of the relevant effector, whether a cursor on a computer screen, a communication interface, an assistive prosthetic device or a tremor of the hand.

Early DBS systems provided few parameters for clinicians to tune: stimulation amplitude, pulse width and frequency. Early leads had few contacts, and frequency was typically set to the canonical 'functional lesion' high-frequency-stimulation (for example, 130-Hz) values. In-clinic device-programming sessions focused on amplitude adjustments until the desired effect (such as reduction in tremor or rigidity) was observed and the patient was sent home. However, the indication space has grown, and the initial adjustment of therapy parameters can differ considerably between diseases and patients. For example, in epilepsy and neuropsychiatric illnesses, the process of tuning the therapy may last weeks to months because the clinical readout of efficacy (improvement in seizure frequency, mood or pain) is sparse or slow to respond

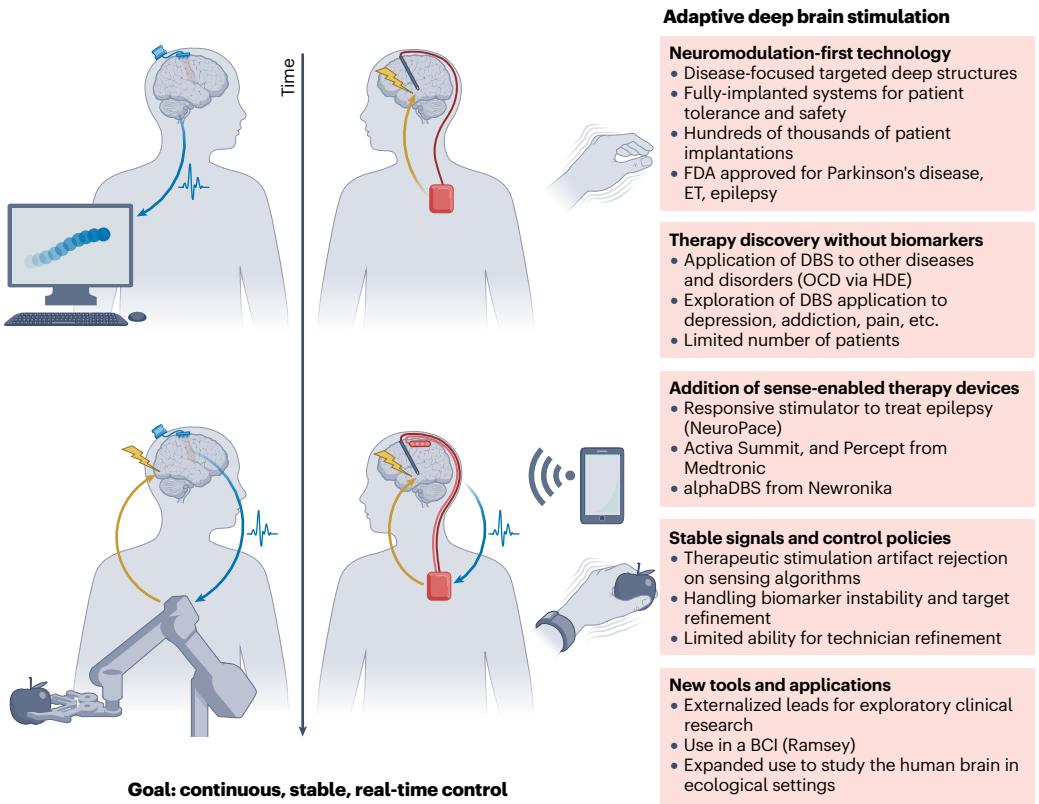

Fig. 1 | Parallel developments of the brain–computer interface (BCI) and adaptive deep brain stimulation (aDBS) fields. Tools evolved along what may be the same axis, but from opposite ends and converging on the mutual goal of continuous, stable, real-time control of effectors (for example, prosthetic limbs, neuromodulation, speech prostheses, and external computer interfaces). DBS, deep brain stimulation; ET, essential tremor; HDE, humanitarian device exemption; OCD, obsessive–compulsive disorder.

to stimulation changes. As sense-enabled DBS devices have become available, with closed-loop stimulation capability anticipated (for example, the ADAPT trial: ClinicalTrials.gov, NCT04547712), establishing clinical therapeutic control is becoming more complex. In addition, the increased sophistication of aDBS algorithms requires extensive in-clinic tuning of parameters, which necessitates substantial clinical and technical resources. On-board calculation of neural signatures (for example, in-band power) may be a trivial mathematical operation, but the criteria for determining thresholds on which to classify state changes and thus trigger corresponding therapeutic parameter changes are far more nebulous. The technical challenges facing the field of neuromodulation are thus as pragmatic as they are scientific: manually tuned patient-specific neural classifiers can be effective at improving therapy, but most clinicians will lack the time or resources to deploy aDBS without tools for automated configuration (Fig. 1).

Similarly, iBCIs face their own translational technical challenges, given the expertise needed to deploy assistive iBCIs. High system complexity has enabled the discovery of new biomarkers and has produced exciting prosthetics and communication demonstrations. Furthermore, the sophisticated processing system common in a high-performance iBCI enables real-time processing of hundreds of cortical signals at high temporal and spatial resolution. These processing techniques can include performance-stabilizing adaptive signal normalization, auto-updating decoder calibration, state-of-the-art machine learning algorithms, dynamic interfaces to multiple assistive technologies, and speech and language models. However, this complexity also limits the translatability of BCI systems into standard of care. Moreover, the lack of commercially available, FDA-approved clinical iBCI systems necessitates a long regulatory path from early feasibility data to eventual commercialization. In this context, the existence of simple clinical neuromodulation devices has been critical in the development of an ecosystem consisting of research payloads and iterative algorithms within the framework of established, common indications (such as Parkinson's disease) that are covered by insurers. The field of BCIs is currently working towards 'reduced-complexity', purpose-driven systems that target a defined patient group and therapeutic benefit. A minimally viable product that can establish the use of clinical BCIs within the therapeutic care pipeline will aid in establishing regulatory frameworks and accelerating innovation in a more economically sustainable manner.

New strategies are beginning to leverage commercial DBS or DBS-like platforms to explore iBCIs; for example, using DBS sensing-enabled devices off-label in human patients as an implantable part of the BCI system[9], or using an endovascular lead with a sensing-enabled chest-implanted system to create a neuroprosthesis device for patients with severe paralysis[10]. Both systems use local field potentials as control signals for a BCI; these potentials are well-characterized signals more extensively studied in sense-enabled DBS systems.

Conclusion

As new methods of interfacing with the nervous system are rapidly developing, it is tantalizing to consider the potential advances in neurotechnology in the next decade. However, it is equally important to consider the ecosystem required for the development of these devices. Widespread clinical (non-research) use of aDBS and BCI platforms is important for economic viability, but premature over-standardization of the platforms may impede progress while the user needs and technological requirements are still under discovery. Both aDBS systems and BCI systems aim to achieve long-term therapeutic benefit but approach the challenge from distinct ends of the complexity spectrum. Although neuromodulation devices began with simplicity and are struggling with increasing complexity, BCI systems began with complexity and

are struggling to simplify methods for clinical use. These fields can inform each other, and as the technological overlap increases, the distinction between neuromodulation and BCI becomes increasingly irrelevant.

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Competing interests

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