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Editorial

Neuromodulation: Update on current practice and future developments

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During the past decades, neuromodulation has entered the clinical practice exponentially with a variety of invasive and non-invasive approaches (Table 1). Most of these treatments have shown not only that their adoption results in an improvement of quality of life (QoL) but also that a multidisciplinary approach is key to a successful implementation. Clinical implementation aside, these advanced treatments have been used to gain a better understanding of how the nervous system works in normal and pathological conditions. Not surprisingly, treatments like deep brain stimulation (DBS) are now adopted in almost all countries worldwide, with a steady growth in numbers of implanted patients [1].

Such growth is resulting in an expansion of indications and less conservative patient enrollments, also given the high level of evidence supporting that early intervention translates to greater and sustained QoL benefit [2].

In this special issue of Neurotherapeutics, we present a compilation of excellent articles that provide a comprehensive review of both approved and experimental neuromodulation therapies.

Davidson et al. [3] provide a broad overview of neuromodulation technologies, encompassing both non-invasive methods like transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial ultrasound stimulation (TUS), and surgical approaches such as deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS), which have significantly advanced the treatment of neurological disorders by enabling precise modulation of neural activity. Techniques such as TMS and tDCS are applied for both diagnostic and therapeutic purposes, leveraging their ability to induce transient or lasting changes in brain excitability to address neurological and psychiatric disorders. The authors emphasize that, as the field of neuromodulation expands, ongoing research and clinical trials are vital for optimizing these technologies for personalized medicine, enhancing their efficacy and understanding of their mechanisms in various conditions.

Durham et al. [4] review focused ultrasound stimulation (FUS) technology, highlighting its potential for enhancing drug delivery to the brain, which could significantly improve the treatment of neurological disorders. The review underscores ongoing efforts to optimize this technique and the need for further research to test its intervention across emerging neurological applications, such as Alzheimer's disease, Parkinson's disease (PD), and brain tumors; a prospect that holds great promise for improving patient outcomes.

Gouveia et al. [5] discuss neurostimulation treatments for drug-resistant epilepsy, specifically focusing on VNS, DBS, and responsive neurostimulation (RNS). These treatments, which include both open-loop and closed-loop systems, offer therapeutic options for patients who do not respond to traditional drug treatments or are not candidates for surgical resection. While VNS is the most accessible and FDA-approved for children, both DBS and RNS show promise in reducing seizure frequency in drug-resistant cases, with the need for further research to optimize these treatments and develop biomarkers for predicting treatment response.

Neudorfer et al. [6] review the evolution and current state of DBS targeting for essential tremor (ET), focusing on the controversies surrounding the optimal targets within the thalamic ventral intermediate nucleus (Vim) and the posterior subthalamic area (PSA). They discuss the historical and anatomical basis for selecting DBS targets, emphasizing the role of the cerebellothalamic tract (CTT) and the integration of modern imaging and electrophysiological techniques for improving targeting accuracy. This review suggests that while Vim has been the traditional focus for ET treatment, emerging evidence and technological advances indicate the PSA, particularly areas adjacent to or involving the CTT, may offer superior outcomes for tremor suppression, highlighting the ongoing need for refined targeting strategies to enhance DBS efficacy.

Further developing this theme, Silva et al. [7] review advances in surgical neuromodulation, mainly focusing on DBS and ablation by means of high-intensity FUS as well as their optimization through advanced imaging techniques such as diffusion MRI (dMRI) and functional MRI (fMRI). They highlight the shift toward conceptualizing therapeutic targets as nodes within specific brain networks, rather than merely anatomical structures, a paradigm facilitated by dMRI and fMRI, which have improved the precision of targeting and programming of neuromodulation therapies. Their review underscores the potential of these imaging modalities in personalizing treatment for neurological and psychiatric conditions, calling for further research to fully realize their capabilities in clinical practice.

Martinez-Nunez provide a comprehensive overview of current and emerging neuromodulation therapies for PD, focusing on their application, mechanisms, and clinical outcomes [8]. The review details various methods, including DBS, TMS, tDCS, and electroconvulsive therapy

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Table 1
The list of invasive and non-invasive neuromodulation techniques is constantly expanding.

Neuromodulatory approaches	
Invasive	Non-invasive
• Brain-computer interface	• Electroconvulsive therapy
• Cochlear implant	• Functional electrical stimulation
• Deep brain stimulation	• Low-intensity focused ultrasound stimulation**
• Dorsal root ganglion stimulation	• Non-invasive vagus nerve stimulation (auricular, cervical)
• Gastric/Intestinal electrical stimulation	• Peripheral nerve stimulation*
• Motor cortex stimulation	• Transcranial alternating current stimulation
• Peripheral nerve stimulation*	• Transcranial direct current stimulation
• Peripheral subcutaneous field stimulation	• Transcutaneous electrical nerve stimulation
• Retinal stimulation	• Temporal interference stimulation
• Responsive neurostimulation	• Transcranial magnetic stimulation
• Spinal cord stimulation	• Transcranial ultrasound stimulation**
• Vagus nerve stimulation	
Possibly neuromodulatory and/or offered within the same program	
• Intrathecal drug delivery (e.g. ITB)	• Drug infusion (e.g. ketamine)
• Intraventricular drug delivery (e.g. ITB)	• Subcutaneous pump-based infusion (e.g. CSAI)
• Lumboperitoneal shunt**	
• Ventriculoperitoneal shunt**	
• Intestinal pump-based infusion (e.g. LICG)	

Abbreviations: * includes (invasive and/or non-invasive) stimulation of the nerves: trigeminal, hypoglossal, sacral, pudendal, occipital, phrenic ('diaphragm pacing') and tibial (usually percutaneous)' ** non-electrical (acoustic waves, intracranial pressure modulation); CSAI: continuous subcutaneous apomorphine infusion; ITB: intrathecal baclofen; LCIG: levodopa-carbidopa intestinal gel.

(ECT), alongside emerging approaches like Temporal Interference Stimulation and FUS. The review underscores the importance of personalized treatment strategies that consider the patient's specific symptoms, disease progression, and genetic background, aiming for a more tailored approach to manage a PD patient's complex symptomatology.

Davidson et al. [9] provide an in-depth review of the neurobiological mechanisms underpinning DBS in PD, discussing its effects at local, circuit, and neurobiochemical levels, particularly focusing on the subthalamic nucleus (STN) as a prime target. They elaborate on how DBS influences neuronal activity through direct stimulation of axons, modulation of neurotransmitter release, and impacting the surrounding microenvironment. It also affects broader neural circuits and alters oscillatory activities within the basal ganglia. The review addresses the ongoing debate on whether DBS exerts disease-modifying effects in PD, highlighting the need for robust biomarkers and large-scale prospective trials to determine its long-term impact on disease progression conclusively.

Noor et al. [10] present a comprehensive review of the mechanisms underlying DBS-evoked neural activity in the basal ganglia, particularly focusing on the STN and globus pallidus internus in PD treatment. They discuss the recent discovery of large amplitude evoked potential (EP) oscillations resulting from DBS, which provide new opportunities to understand human basal ganglia network activity. The review highlights the role of DBS-induced antidromic activation of globus pallidus externus (GPe) as a critical driver of these oscillations, suggesting a significant but previously underappreciated role for GPe in the therapeutic effects of DBS for PD and outlines the potential of DBS EPs as clinically useful electrophysiological biomarkers for confirming DBS target engagement.

Wang et al. [11] discuss the challenges and complexities of treating postural instability in PD, emphasizing the biomechanical and neural circuitry deficits that contribute to this condition. The authors also describe current therapies, including DBS and feedback-based wearable devices, in managing postural instability. They highlight the potential of implantable devices for chronic neural data collection to better understand postural control mechanisms. Their review underscores the importance of developing future neuromodulation interventions where personalized, circuit-based approaches could improve symptom control.

Sammartino and colleagues [12] discuss SCS as an established and cost-effective treatment for chronic nonmalignant neuropathic pain, focusing on its application for conditions such as post-laminectomy syndrome, peripheral neuropathy, and complex regional pain syndrome. They also highlight the specific SCS indications through case studies followed by clinical evidence that demonstrates the efficacy of SCS in reducing pain and improving quality of life in patients who have exhausted conventional treatments. The review emphasizes the need for further research to optimize SCS therapy, address challenges such as loss of efficacy over time, and explores its potential in treating other neuropathic pain syndromes, underscoring the role of SCS in the evolving landscape of pain management.

Saway et al. [13] discuss the exciting development of neuromodulation to facilitate chronic stroke recovery, focusing on their mechanisms rooted in neuroplasticity and the application of advanced techniques such as brain-computer interfaces (BCIs). The review also highlights VNS, DBS, and BCIs, emphasizing their potential to augment conventional rehabilitation efforts. The authors explore future directions in the field, including integrating artificial intelligence and wearable technologies to enhance the personalization and effectiveness of neuromodulation therapies for improving the functional recovery of stroke patients.

Finally, Ranjan et al. [14] explore DBS and FUS applications in treating psychiatric disorders, specifically obsessive-compulsive disorder (OCD), depression, and addiction. They highlight that while DBS is FDA-approved for OCD, other uses remain investigational. The authors emphasize the importance of ongoing research to optimize these neuromodulation techniques, particularly testing their safety, efficacy, and mechanisms in hopes of expanding approved applications in the future.

How neuromodulation is challenging the present and shaping the future of healthcare

With very few exceptions, centers offering neuromodulatory treatments are nowadays organized within the classic framework of hospitals' operations, whereby different departments (neurology, neurosurgery, psychiatry, etc.) collaborate while maintaining distinct space and personnel allocation. The existence of multiple therapeutic options emphasizes the need for a center to centralize the decision making process related to the selection of the *right* candidate for the *right* procedure (e.g., ketamine infusion or rTMS before ECT in a depressed patient). Therefore, any tertiary center should be able to offer alternative treatments, including non-invasive or less-invasive options. Furthermore, existing DBS data indicate that the rate of complications reduces over time in individual centers [15] and that academic and large centers tend to have better overall outcome [16].

The fast pace of technological advances requires dedicated expertise, and the field is now ready for a change in the paradigm whereby – similar to the well-established role of the functional neurosurgeon – there should be a new specialist with expertise in the selection and management of patients treated with neuromodulatory treatments; e.g., a 'functional' neurologist. Establishing this emerging subspecialty, as well as educational and training curricula for students, residents, and postgraduate fellowships that are necessary for the accreditation of certain training programs, has been highlighted as a priority by many experts in the field. This was indeed the goal of the recent Brain Stimulation Subspecialty Summit, which took place over September 14–15, 2023, hosted by the Brigham & Women's Hospital and the Harvard Faculty Club, in Boston, Massachusetts. The meeting was attended by 54 physicians and/or scientists representing psychiatry, psychology, neurology, neurosurgery, and partners from neuroscience, industry, professional societies, and training accreditation bodies.

A unified approach to neuromodulation agnostic to disease has other advantages. From a clinical point of view, some targets can be used to treat multiple conditions at the same time, as the case of a patient with post-traumatic Tourettism and drug-resistant seizures in whom DBS of the centromedian nucleus was chosen, given data supporting that such target could improve *both* problems [17]. From an experimental standpoint, other indications can inspire novel targets and/or stimulation paradigms. This is the case of SCS (an established treatment for pain management) for freezing of gait [18]. Another example is VNS, classically used for seizure management but also recently approved for depression, with a pipeline of new indications, including PD-related gait disorders. Interestingly non-invasive devices for VNS are also approved for migraine management and could potentially be used to predict the outcome of implantable VNS for newer indications.

Lastly, neuromodulation has clearly shown how interdisciplinarity is key to success well before it was an established need in contemporary medicine (Fig. 1). Beyond neurologists, psychiatrists and neurosurgeons, Table 2 offers a partial list of other contributors and practitioners whose expertise adds value to the field of neuromodulation.

In summary, the comprehensive compilation of articles in this special issue of Neurotherapeutics underscores the evolving landscape of neuromodulation therapies, ranging from established to experimental techniques, for treating a broad range of neurological and psychiatric conditions. The reviews collectively highlight the pivotal role of several technologies in advancing treatment paradigms through precise neural activity modulation, offering hope for conditions previously deemed intractable. All the included articles emphasize the critical need for ongoing research to optimize these interventions, develop robust biomarkers for treatment response, and explore novel applications. Moreover, the potential of integrating advanced imaging techniques and personalized, circuit-based approaches promises to improve therapeutic outcomes. The exploration into neuromodulation's disease-modifying capabilities, especially in conditions such as PD, highlights a future where neuromodulation therapies could revolutionize patient care. This special issue aims to serve as a cornerstone for future research and development in the neuromodulation space, inspiring new investigations and collaborations that will push the boundaries of what is possible in neurotherapeutics.

Fig. 1. Profs. Pierre Pollak (neurologist), Abdelhamid Benazzouz (neurophysiologist) and Alim Louis Benabid (neurosurgeon), celebrating 30 years of subthalamic DBS in Grenoble, France, June 2023.

Table 2
Beyond neurologists, psychiatrists and neurosurgeons, many other professionals can contribute to a successful implementation of interdisciplinarity neuromodulation program.

Expertise	Role
Biomedical engineers, computational scientist	Discovery and commercialization of novel devices and stimulating algorithms
Ethicist	Design of studies and clinical dilemmas
Geneticist	Prognosis of surgery, i.e. 'surgicogenomics' (visanji et al., 2022)
Kinesiologist	Objective evaluation of gait, balance and other motor disturbances.
Neuropathologist	Analysis of biopsies taken during surgery
Neurophysiologist	Neuronal recordings during surgery or by means of externalized wires or non-invasive LFP recording.
Neuroradiologist	Anatomical or DTI-based targeting, aggregated or individualized analysis of VTA to provide heatmaps of efficacy and assist neuroimaging-based programming (e.g. DBS).
Psychologist	Assessment and intervention around the psychosocial changes introduced by life-changing interventions, e.g. functional neurological disorders
Rehabilitation scientists and physiotherapists	Maximizing the benefits of the gained mobility.

Abbreviations: DBS: deep brain stimulation, DTI: diffusion tensor imaging (tractography), LFP: local field potential, VTA: volume of tissue activated.

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