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Innovations in Deep Brain Stimulation Methodology

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ABSTRACT: Deep brain stimulation is a powerful clinical method for movement disorders that no longer respond satisfactorily to pharmacological management, but its progress has been hampered by stagnation in technological procedure solutions and device development. Recently, the combined research efforts of bioengineers, neuroscientists, and clinicians have helped to better understand the mechanisms of deep brain stimulation, and solutions for the translational roadblock are emerging. Here, we define the needs for methodological advances in deep brain stimulation from a neurophysiological perspective and describe technological solutions that are currently evaluated for near-term clinical application. © 2016 International Parkinson and Movement Disorder Society

Key Words: deep brain stimulation; basal ganglia; local field potentials; oscillations; tremor; Parkinson's disease; dystonia

Deep brain stimulation (DBS) is an established treatment for severe movement disorders such as Parkinson's disease (PD), tremor, and dystonia, leading to a significant reduction in motor deficits in the majority of patients. However, despite the often striking clinical benefits, DBS remains a complex and poorly standardized therapy requiring a high level of clinical expertise and involving a multidisciplinary and multistep procedure, along which treatment failures may occur because of inappropriate patient selection, misplacement of the stimulating electrodes, poor programming, or inadequate postoperative balancing between stimulation and pharmacological treatment.[1] Moreover, movement disorders are characterized by a highly variable clinical phenotype and fluctuating symptom severity (eg, with varying behavioral, pharmacological, or emotional states), which prompt for an individualized and dynamic treatment approach. Hence, research has focused in recent years, on how a better understanding of the pathophysiology of movement disorders and the physiological mechanisms of DBS could translate into a DBS therapy that can better adapt to individual patient needs, reduce the need for extensive clinical programming, and ultimately improve the consistency of patient outcomes.

Unfortunately, very limited technical evolution of neurostimulation devices has backed clinical success in movement disorders and rapid expansion to psychiatric indications, epilepsy, or pain. Only recently, with new competitors in the market, a race for technical device innovations has started,[2] which provides the physician with more flexible programming options (eg, Vercise; Boston Scientific, Valencia, CA) or clinical research tools (eg, ACTIVA PC+S, Medtronic; Minneapolis, MN) allowing the validation of neurophysiological concepts of neurostimulation in clinical practice.

In this review, we will briefly outline the current concepts of DBS mechanisms, define the needs for translational advances in DBS methodology, and describe the available technical solutions that may soon change our clinical practice of deep brain stimulation.

DBS Mechanisms and Resulting Translational Needs

The potential mechanisms behind DBS are varied and complex, and several hypotheses have been postulated over the years.[3-6] However, there is little doubt that DBS modulates pathological activity within central neural networks with applied electric fields and that a fundamental effect of DBS is the stimulation of axons around the electrode.[7] Although DBS is applied to brain targets consisting of mixed neural tissue

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containing other electrically excitable elements such as cell bodies, dendrites, or glia, the role of axons seems paramount because they generate action potentials at the lowest stimulation threshold.[7-9] These stimulation-induced action potentials are capable of modifying intrinsic neuronal signals within pathways of functional brain networks and possibly "eliminate" or "mask" pathological network activity.[10]

DBS has also offered the unique opportunity to directly record both multiunit activity and local field potentials (LFPs) from deep brain targets that are otherwise inaccessible and has helped to better define the nature of this disease-specific (or symptom-specific) network activity. New concepts that have emerged from this research emphasize the role of firing patterns[11] and synchronized oscillatory activity[10,12] within the thalamus-cortex basal ganglia (BG)-cortex network.

DBS electrodes are surrounded by thousands of different axons, which can project to or from the area of implantation or simply pass by on their way to a completely different brain region. The electric field generated by DBS polarizes all the axons that are sufficiently close to the stimulating electrodes, resulting in action potentials traveling orthodromically and antidromically along the axon.[13,14] The axonal response to extracellular electrical stimulation is dictated by 3 fundamental biophysical principles: (1) the variable axonal excitability with fiber diameter, (2) the current-distance relationship, and (3) the strength-duration relationship.[7] Based on theoretical models[15,16] and experimental evidence,[17-19] including novel techniques such as optogenetics, we are starting to understand which are the target neurons for a particular DBS indication and which neural elements within the stimulation volume rather contribute to adverse effects of stimulation.

For subthalamic stimulation in Parkinson's disease, current concepts favor antidromic activation of the so-called hyperdirect pathway, which consists of axon collaterals of layer V pyramidal neurons in the motor cortex.[20] The remote effect of stimulating these axons within the subthalamic region may be a change in motor cortical activity, possibly masking or desynchronizing pathologically enhanced beta-band oscillations within the basal ganglia–thalamocortical network.[18] The goal of therapeutic DBS should be to maximize the stimulation of these target neurons while minimizing unintended activation of nontarget neurons such as corticospinal or corticobulbar fibers within the internal capsule, which may cause speech, walking, or fine motor skill impairments.[21]

The great advantage of DBS over stereotactic lesioning is the postoperative adaptability of stimulation parameters, but with new devices offering an even wider parameter space, this task has become a burden for clinicians because it relies on clinical experience and repeated testing of the patient response rather than neurophysiologically optimized technical solutions. Historically the settings, which are still used today, have been dictated by the technical properties of the available neurostimulation devices and shaped within these limits by clinical experience, but theoretical studies based on the biophysics of membrane excitability and the physical properties of the stimulation pulse have recently proposed numerous opportunities of improving device function with the goal of selectively stimulating therapeutic target neurons at the lowest energy possible. We want to discuss 5 translational needs for technological innovation of DBS in the following paragraphs and outline the emerging solutions for these needs.

Need 1: Directional Deep Brain Stimulation

Conventional DBS systems use ring-shaped electrodes, which generate an approximately spherical electrical field. In these systems programming of polarity and stimulation pulse parameters allow only limited control of the shape of the volume of tissue activated.[22] Advanced programming techniques such as multiple independent current control or interleaving, which means running 2 programs with different settings on the same lead in a temporally alternating sequence,[23] offer additional degrees of freedom in sculpting the electrical field along the longitudinal axis of a multicontact ring electrode, but do not allow to direct current within the horizontal plane.

Recently, 2 acute intraoperative studies have proven the feasibility of horizontal current steering by using novel lead designs such as segmented or multicontact electrodes[24,25] with an external stimulation device. Directed stimulation using these electrodes resulted in increased stimulation thresholds for side effects compared with standard spherical stimulation. In particular, directing current away from the internal capsule demonstrated an increase in the current threshold for contractions or dysarthria. The acute intraoperative setting, however, did not allow evaluating potential advantages in clinical efficacy when steering current into the "sweet spot" for motor symptoms of PD within the subthalamic area, which has been proposed to be the dorsolateral segment of the STN.[26,27]

A few theoretical considerations are important when moving from a segmented electrode design to a fully integrated directional DBS system — the smaller contact surface of segmented electrodes compared with ring electrodes causes increased electrode impedance and requires a higher stimulation voltage to pass the stimulation current. This is likely rendering directed stimulation less energy efficient than stimulation in conventional ring mode. Moreover, with very small contact sizes such as that planned for the 32-contact Sapiens-Medtronic lead,[24] stimulation of a single contact may well exceed the voltage compliance range of

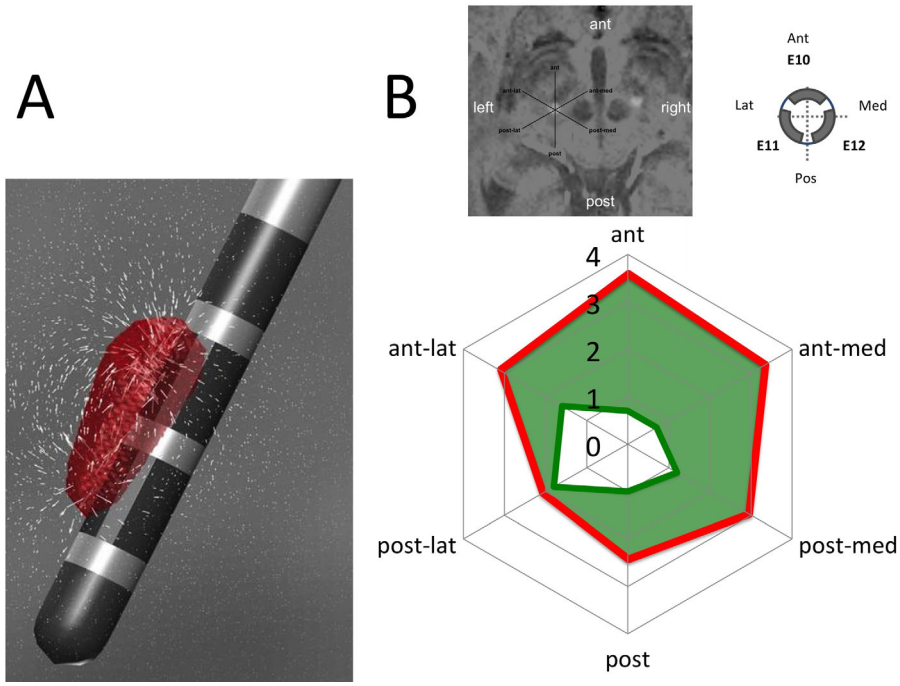

FIG. 1. (**a**) Modeling of the electrical field and volume of tissue activated generated by bipolar stimulation between contacts K2 (anode) and K5 (cathode) of a directional DBS lead (Boston Scientific Vercise). The gradient of the E-field is visualized by white arrows. The red area visualizes the volume of activated tissue. The model was created using the Lead-DBS toolbox[37] (http://www.lead-dbs.org; image courtesy of Dr. Andreas Horn). (**b**) An MRI/CT fusion displays the location of the electrode in the STN. A schematic drawing on the right displays the orientation of the segmented contacts. A monopolar review was conducted with current steering in 60-degree rotations to determine thresholds (in mA) for complete rigidity reduction and first capsular adverse effects (contraction of contralateral mouth). The clinical effect thresholds were then transferred into a polar plot to outline the current steering effects in 6 main directions. The green line connects the efficacy thresholds and the red line the adverse effect thresholds. The green area denotes the therapeutic window. Note the expanded therapeutic window when directing current in anterior and medial directions in this case. [Color figure can be viewed at wileyonlinelibrary.com]

a standard DBS battery. This problem is solved by stimulating groups of contacts simultaneously to keep the contact surface within limits. The flexible selection of these groups of contacts requires an additional electronic control circuit, a multiplexer, which may be integrated within the lead.

Because of the greater impact of impedance, a current-controlled system is preferable to a voltage-controlled pulse generator for segmented electrodes. When using a single-source stimulation device, the impedance difference between contacts will passively dictate the current distribution between multiple simultaneously active contacts and make directionality less predictable. Theoretically, a segmented electrode combined with a neurostimulator providing independent current sources for each contact would be the optimal combination for reliable current steering.

In September 2015 a novel, fully implantable neurostimulation system (Vercise PC; Boston Scientific, Valencia, CA), which combines an 8-contact directional lead and a pulse generator capable of multiple independent current source control, was introduced to the market in Europe. Clinical experience with this system is still limited, and no published controlled trial data are available. First evidence from acute monopolar review data demonstrates the feasibility of directional DBS and the expected changes in therapeutic window with horizontal steering[28] (see Fig. 1). However, future studies need to evaluate if directional DBS can improve the consistency of good DBS outcomes by compensating for variable lead placements within STN.[27]

Need 2: Novel Pulse Parameters

A simple way of modifying the charge injection into the tissue and the selectivity of DBS is a change in the duration of the current pulse. The threshold for activation of neural elements with different membrane excitability properties covaries with stimulus strength and pulse duration and is reflected by the nonlinear strength duration or chronaxie relationship. Using measures of chronaxie, we recently demonstrated that reducing pulse duration to 30 microseconds or less may be beneficial for STN-DBS because it increases the therapeutic window and helps to reduce capsular side effects of stimulation without sacrificing stimulation efficacy.[29] The presumed mechanism supported by model data is a focusing of the neurostimulation effect on smaller diameter axons close to the electrode while avoiding stimulation of distant pyramidal tract fibers when using <60-microsecond pulse durations.

Experimental data also suggest a potential benefit of shorter pulse durations for tolerance development and stimulation-induced ataxia in patients with thalamic deep brain stimulation for essential tremor,[30] but clinical studies are still pending.

Computational models suggest that changing the pulse waveform from a standard rectangular shape may offer another opportunity of improving the efficiency of DBS.[31-33] Exploring the vast parameter space of pulse parameters in clinical proof-of-concept studies is an urgent need in DBS research.

Need 3: Computational Models of Deep Brain Stimulation

Several groups have developed computational models to predict the electrical field and volume of neural tissue activation by DBS as a function of the stimulation parameter settings.[34-36] Recently, these DBS modeling efforts have focused on the integration of imaging data[37] and finite element models of the DBS electric field to make patient-specific predictions on the neural response to DBS.[38] The results are then imbedded in a 3-D graphical user interface that can run on a personal computer and assist the physician in preselecting DBS parameter settings based on a visualization of the patient-specific volume of tissue activated. One study has compared clinical outcomes generated by model-defined versus clinically defined stimulation parameter settings and found equal efficacy but a tendency for physicians to chronically overstimulate the STN based on monopolar review data, thus causing mild cognitive adverse effects.[39] This interesting observation needs to be confirmed in further clinical studies when visual programming tools become commercially available in the near future. In general, such tools are needed to reduce the programming burden of clinicians, in particular, with the introduction of directional DBS and pulse generators that offer a wider parameter space than conventional DBS systems. Moreover, computational models allow the creation of testable hypotheses about optimized ways of stimulating neural tissue and could provide valuable input into the engineering of next-generation DBS systems.[40]

Need 4: Identification of Symptom- or Disease-Specific Physiomarkers

Physiological markers of particular brain states are necessary to control adaptive neurostimulation devices, which sense pathological activity and only act when needed. This approach is straightforward in epilepsy, for which a first commercial system is available. Moreover, these biosignals could be used to identify effective contact combinations in future autoprogramming algorithms for multisegmented leads. For movement disorders physiomarkers have emerged from research using the implanted DBS electrodes by externalized leads to record LFPs and from subdural electrodes recording cortical activity (Crowell et al, 2012).

LFP Signals Related to Hypokinesia

A multitude of studies have demonstrated enhanced beta-band activity (~20 Hz) in LFP recordings from the basal ganglia of patients with Parkinson's disease (PD) withdrawn from dopaminergic medication.[41-43] Elevated beta power has been associated with bradykinesia and rigidity in PD, as it is decreased with dopaminergic treatment,[42,44,45] and its reduction correlates with clinical improvement in motor symptoms induced by levodopa[46-48] and DBS.[49,50] New-generation bidirectional devices with sensing function (PC+S, Medtronic) allow monitoring of the neuronal signal in chronically implanted patients and thus probe beta power as a reliable biomarker for adaptive DBS (aDBS; see Fig. 2).[51-53]

In addition to beta power, other more complex control signals should be considered for aDBS in PD. Taking into account the temporal evolution of beta activity, studies have focused on time-variant spectral properties, spatial extent of beta-band synchronization, and long-range temporal correlations in the envelope of beta-band amplitude oscillations, revealing additional evidence for a correlation of beta oscillations and clinical state in PD.[54-56] Further, high-frequency oscillations (HFOs) recorded from the STN in PD patients in the range of 200-350 Hz are modulated with levodopa[57]; beta-HFO phase-amplitude coupling (PAC) within the STN correlates with motor impairment,[58] and beta-HFO PAC is reduced with levodopa treatment in parallel with clinical improvement.[59] More recently, pathologically enhanced coupling between beta-phase and high-gamma amplitude in the motor cortex has been described in PD using cortical electrodes, suggesting abnormal phase-amplitude interaction in the cortico-subthalamic network[60] that is reduced during DBS along with clinical improvement.[61]

LFP Signals Related to Hyperkinesia

Recordings from the BG of patients with dystonia are characterized by increased low-frequency (5-12 Hz, theta-alpha) activity,[44,62-64] irrespective of the target area of deep brain stimulation.[65] In dystonia, low-frequency activity is coherent with dystonic EMG activity, especially driving phasic EMG bursts.[62-67] A combined magnetoencephalography pallidal LFP study showed cortico-subcortical coherence in low-frequency activity between the cerebellum and pallidum that correlated with the severity of motor symptoms,[64] and DBS is known to suppress pallidal low-frequency activity in patients with predominantly phasic dystonic movements.[68] Similarly, low frequency activity was suppressed by geste antagoniste in a patient with cervical dystonia.[69] Other hyperkinetic movements such as levodopa-induced dyskinesia, myoclonus, motor tics,

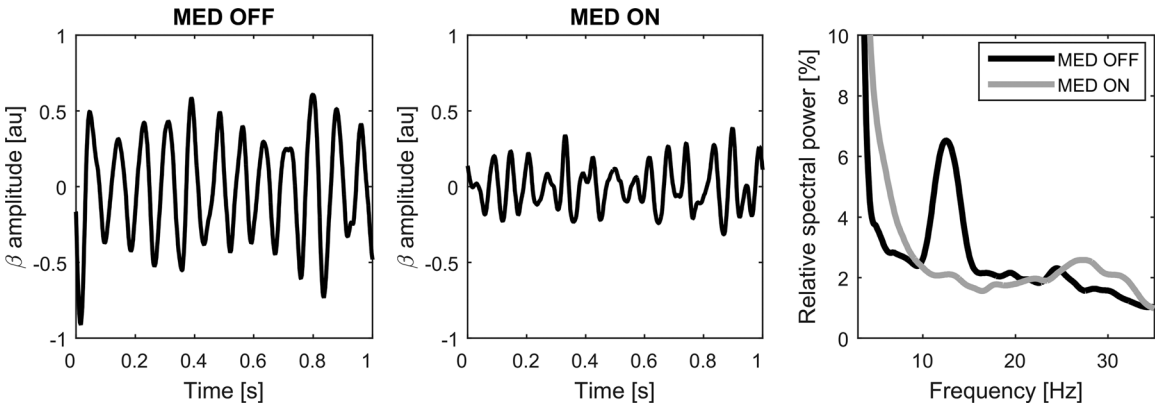

FIG. 2. Raw signal of local field potentials recorded with the ACTIVA PC+S system with and without medication off DBS 8 months after DBS surgery. Note that beta oscillation are consistently present also after long-term DBS and are suppressed by levodopa.

and hyperkinesia in Huntington's disease patients have been associated with enhanced theta-alpha activity in the BG[70-74] and/or thalamus,[75,76] supporting a link between mobile hyperkinesia and enhanced theta-alpha activity. In addition, in PD patients increased gamma band activity (60-90 Hz) occurs with levodopa-induced dyskinesia along with a reduction in beta-band activity.[70,73,77,78]

Tremor-Related Signals

Levodopa-induced modulation in STN LFP beta activity does not correlate with tremor suppression in PD,[46] but periods of tremor have been related to reduced beta power in the cortex and STN.[79] Conversely, low gamma-band suppression was observed during DBS-induced tremor reduction.[80] Specific tremor-associated activity has been detected in the tremor network in PD patients using invasive and noninvasive recordings,[81] showing coupling to EMG at single and double tremor frequencies.[82-84] These findings suggest a direct relationship between the synchronization of cerebral oscillations and tremor manifestation, which would allow feedback-controlled stimulation techniques based on phase cancellation.[85]

Need 5: Novel Stimulation Patterns Selectively Suppressing Disease-Specific Brain Activity

The concept of adaptive stimulation is based on feedback-controlled stimulation, in which the stimulation is either discontinued or adjusted in amplitude in relation to a continuously sensed biosignal that is indicative of the current clinical state. These feedback signals could involve either direct sensing of the clinical symptom such as tremor using accelerometer or recording of surrogate neuronal activity.

Closed-Loop Neurostimulation

One proposed mechanism of continuous high-frequency DBS is the suppression of abnormally synchronized oscillatory activity within the motor cortico–basal ganglia network.[10] Even though suppression is highest at those contacts with the largest amount of abnormal oscillatory activity,[49,86] suppression of other frequencies that might be more relevant for information coding (such as gamma-band activity)[87,88] cannot be excluded and may account for DBS-induced side effects like deficits in verbal fluency[89] or motor slowing.[90,91] aDBS using signals that reflect the individual modulation of motor symptoms over time will allow stopping stimulation during asymptomatic periods.

Closed-loop stimulation has been probed by only a few groups using different techniques for feedback control so far. First, in nonhuman primates Rosin and colleagues recorded neuronal spike activity from the ipsilateral primary motor cortex to trigger pallidal DBS, providing the first evidence for successful aDBS.[92] Efficacious reduction in bradykinesia with aDBS was obtained with an 80-millisecond delay between the cortical spike activity and pallidal high-frequency stimulation, possibly because of phase interference of aDBS with abnormal network activity. A trigger in the DBS target area might be more suitable for surgical approach, and population activity might be a more stable biosignal.

In their landmark article,[93] Little et al described the first application of unilateral aDBS in 8 PD patients under laboratory conditions. Here, Peter Brown's group has taken the results from a multitude of previous studies to the next level, closing the loop for DBS by using local STN beta-band activity as a feedback signal for adaptive stimulation. Specifically, filtered STN beta activity is tracked online, and an individual threshold is set for each patient triggering aDBS. Surprisingly, unilateral aDBS was even more effective, by 27%, than conventional chronic unilateral stimulation, and at the same time, stimulation time was reduced by 56%. One additional interesting aspect was the progressive reduction in stimulation time with aDBS over the 10-minute cycle, suggesting adaptive network

changes over time with ongoing suppression of beta activity. In their follow-up study, the same authors have shown similar effects for aDBS on limb and axial motor symptoms when applied bilaterally over longer periods in 4 patients.[94] Importantly, in 2 patients tested during levodopa challenge, aDBS was triggered less frequently during the ON period, indicating that it follows the clinical state and thus may prevent the occurrence of dyskinesia. However, the comparison with conventional chronic DBS is missing for this group of patients.

Alberto Priori's group recently reported a single subject result using a portable aDBS device in a freely moving PD patient who was stimulated for up to 2 hours ON and OFF levodopa.[95] In this setup the amplitude of stimulation is adapted during aDBS triggered by STN beta-band power and adjusted each second. The patient showed similar improvement in axial motor symptoms during walking but improved bradykinesia and less dyskinesia during aDBS compared with conventional DBS, providing further evidence for a potential advantage of aDBS in effectiveness of stimulation with fewer side effects. However, the overall effects of stimulation were very small, and additional studies are needed to corroborate these findings.

Taken together, feedback-controlled aDBS was shown to be effective for the treatment of the main motor symptoms in PD and at the same time could possibly reduce side effects induced by conventional high-frequency continuous stimulation such as dyskinesia. Currently, it is not yet applicable for clinical routine, but available stimulators with sensing function (PC+S) will pave the way for aDBS, especially by detailed exploration of brain signals suitable for feedback control. The current proof-of-principle studies have shown the potential application of feedback-controlled adaptive stimulation, but some critical issues remain: enhanced beta-band activity is not consistently found in all PD patients[49] and may not be disease specific.[96] A direct correlation between beta power OFF medication and motor impairment in PD has recently been demonstrated, but the analysis required large patient groups.[49,58] The latter may imply a lack of a strong causal relationship between STN LFP beta-band activity and motor symptoms in PD. Nevertheless, as beta activity reflects the modulation in motor state in PD patients, it could still serve as a feedback signal for aDBS. The downside of using a control signal from the DBS implanted area is also the large stimulation-induced artifact that needs to be filtered out, thereby limiting available contacts for LFP recordings to those adjacent to the contact used for DBS in a specific bipolar configuration.

The current approach is accomplished under laboratory conditions without considering motor network changes during movement that is known to reduce beta-band activity. Likewise speech, other activities of daily living or the stun effect shortly after electrode implantation may influence oscillatory activity in the target area. Moreover, external custom-made stimulators have been used that deliver pulses that have a configuration and pulse width different than those used in conventional DBS. Electrophysiological consequences of these different stimulation forms on the motor network remain elusive. Before applying aDBS in clinical routine, the complex system for sensing, filtering, smoothing, and thresholding beta power would need to be miniaturized for implantable systems. To use threshold crossing of beta power for triggering stimulation is the first major step toward feedback-controlled systems for DBS; however, future application may be based on more complex biosignals using multiple LFP features or spiking activity from cortical and subcortical sources, as discussed above.

A different approach using peripheral sensing of tremor-related limb acceleration as a feedback signal for aDBS was recently applied in 5 tremor-dominant PD patients.[97] In this setup, resting tremor was measured by a wearable sensor (LG G-watch), and stimulation amplitude was adjusted using the Nexus-D system (Medtronic) according to the tremor amplitude, leading to even more effective tremor suppression compared with standard chronic DBS, whereas stimulation time was significantly reduced.

A more complex approach for tremor suppression is based on the specific phase relationship between the neuronal tremor-related oscillatory activity and the aDBS burst that should reduce tremor amplitude by phase cancellation.[85] So far, modulation of tremor amplitude has been shown with this approach under laboratory conditions with specific configuration of stimulation parameters such as longer pulse widths. For future systems a combination of peripheral biosignals and neuronal activity to control aDBS may allow accounting for the different motor symptoms in PD.

Novel Stimulation Patterns

Coordinated reset stimulation (CR) is an alternative approach to reset abnormally synchronized brain signals that has been proposed by Peter Tass and his group based on extensive computational modeling[98] and in vitro data.[99] CR works without a feedback signal by providing a patterned stimulation through multiple contacts of a lead, which are supposed to desynchronize the phase of ongoing oscillatory activity. Behavioral effects of CR have been tested in the MPTP monkey model[100] and a proof-of-concept study in PD patients.[101] Both studies demonstrated incremental clinical improvement in motor symptoms after short (1- to 2-hour) periods of CR over several days. Interestingly, the effects were outlasting the stimulation periods, suggesting a plastic change in

network activity. However, the clinical value is difficult to assess because the patient study was not blinded and did not control for intercurrent medication effects, and chronic effects have not been tested.

Novel stimulation devices may allow overcoming the physical limitations of continuous high-frequency stimulation and testing alternative stimulation patterns, which, based on computational modeling, animal work or human neurophysiology could have sustained plastic effects on disease-specific network dysfunction.

Conclusions

After more than 2 decades of clinical empiricism, a better understanding of DBS mechanisms from physiological research is now being translated into novel technical solutions. More flexible devices will help to test the vast parameter space of DBS in humans and to develop a safer and more effective therapy. ■

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