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Review

Insights and opportunities for deep brain stimulation as a brain circuit intervention

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Deep brain stimulation (DBS) is an effective treatment and has provided unique insights into the dynamic circuit architecture of brain disorders. This Review illustrates our current understanding of the pathophysiology of movement disorders and their underlying brain circuits that are modulated with DBS. It proposes principles of pathological network synchronization patterns like beta activity (13–35 Hz) in Parkinson's disease. We describe alterations from microscale including local synaptic activity via modulation of mesoscale hypersynchronization to changes in whole-brain macroscale connectivity. Finally, an outlook on advances for clinical innovations in next-generation neurotechnology is provided: from preoperative connectomic targeting to feedback controlled closed-loop adaptive DBS as individualized network-specific brain circuit interventions.

Highlights

Deep brain stimulation modulates neural synchrony in distributed brain networks.

Neurophysiology and neuroimaging can elucidate circuit characteristics.

Instead of anatomical landmarks, optimal circuit nodes for intervention can be defined with MRI-based connectomics and dynamic neurophysiological network measures.

Opportunities arise for preoperative network characterization, intraoperative target confirmation, and postoperative treatment optimization in spatiotemporal domains.

From human invasive recordings to connectomic circuit modulation

The human brain comprises neuronal ensembles that build intricately connected networks which exhibit synchronized activity patterns. Abnormalities in brain network synchronization may lead to brain disorders which can partially be normalized by electrical stimulation. Dynamic brain rhythms emerge from synaptic currents and neural action potential firing, to interregional coupling, to circadian cycles and sleep. Changes in rhythmic oscillatory neural activity have long been implicated in the precise control of timing of neuronal action potentials that can subserve coordinated information transfer in distributed brain networks [1]. Imbalances of oscillatory activity in brain circuits that lead to abnormal information transfer have been proposed to underlie the development of symptoms in movement disorders, such as **dystonia** (see Glossary), Tourette's syndrome and **Parkinson's disease (PD)** [2]. Therapeutic interventions, such as **deep brain stimulation (DBS)** can modulate the described pathological oscillatory circuit activity patterns and alleviate symptoms [3]. As a consequence, we should consider the circuit nature of brain disorders in order to understand the therapeutic effects of DBS. To this end, the implantation of DBS electrodes provides the unique opportunity to record deep brain activity. **Local field potentials (LFPs)** are electric currents produced by simultaneous voltage changes of thousands of synapses in direct vicinity to the target area. The resulting electrophysiological activity resembles noninvasive electroencephalography (EEG) recordings but is recorded from deep structures. Thus, LFPs from DBS electrodes can provide direct insight into neural population dynamics of affected network nodes targeted by DBS. This has enabled a systematic phenotyping of oscillatory patterns in patients undergoing DBS surgery, both in the temporal and spectral (time–frequency) domain. Invasive neurophysiology has revealed the following principles of the network effects on neural activity underlying invasive neuromodulation.

Neuromodulation can interfere with neural activity at: (i) the **microscale** comprising changes in neural plasticity and patterning of action potentials within the microcircuit [4–7]; (ii) the population **mesoscale** with synchronized membrane fluctuations of neural assemblies in defined nuclei and

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cortical regions as local field potentials [8–11]; and (iii) the systems **macroscale** with interregional synchronization and whole-brain coupling patterns of neural cortico-subcortical circuits [12–14].

This Review aims to integrate the effects of DBS observed in movement disorders into formal principles from micro- to macroscale, from invasive neurophysiology to whole-brain **connectomics**. Our review primarily focuses on disease-specific circuit alterations and their modulation with DBS. The precise synaptic mechanisms underlying DBS effects remain a topic of debate (Box 1) and are covered in more detail in other reviews [7,8,15].

Basal ganglia synchrony and abnormal network synchronization as a disease mechanism

Decades of research into oscillatory **biomarkers** and pathological synchrony have uncovered important principles underlying altered oscillatory activity patterns in movement disorders [16]. Among the best characterized pathological brain rhythms is basal ganglia **beta activity** (13–35 Hz) in PD. We highlight some principles of pathological circuit synchronization as derived from studies on this pathological activity pattern. Exaggerated beta activity recorded from the basal ganglia of PD patients is considered a biomarker of the brady-/hypokinetic motor state, as it has been consistently related to the severity of motor symptoms such as bradykinesia and rigidity [9,17–19]. This relationship appears to go beyond PD, as excessive beta activity could also be shown to be related to bradykinesia as a side-effect of medication and DBS in patients with dystonia [20,21]. Even beyond pathological states, beta activity is a ubiquitous synchronization phenomenon in the mammalian brain [22], which has been described in electrophysiological recordings of healthy human subjects and invasive electrocorticography and LFPs in patients with epilepsy [23], dystonia [24,25], Tourette's syndrome [26], schizophrenia [2], and other diseases [27,28]. Thus, beta activity is not specific to PD or even pathological *per se*. The excessive beta activity in PD likely reflects a pathological alteration of a physiological and healthy synchronization phenomenon [29], speculated to be involved in dynamic brain state transitions and cognitive inhibition [30]. Rodent and nonhuman primate models of PD develop increased beta rhythmicity of local spiking of neurons (microscale) and increased amplitudes of oscillatory voltage fluctuations (mesoscale) in the striatum, pallidum, thalamus, and subthalamic nucleus (STN) [29,31,32]. Importantly, these individual structures are further coupled across nodes of the motor network

Box 1. Precise synaptic mechanisms of DBS remain elusive

DBS was empirically shown in human patients to cause synaptic depression in various target regions [4,5,67,143], but the therapeutic mechanism may rely on additional and more complex synaptic effects [7]. Depolarization block, neurotransmitter depletion, synaptic depression, ortho- and antidromic activation, collateral collision, and trans-synaptic and plasticity effects may interact and contribute to what has been described as an informational lesion in circuit communication [66]. Empirical evidence on such effects is primarily limited by the inability to characterize cell type and pathway specific synaptic responses in brain areas distant to the stimulation targets in human patients. To meet this critical gap in human neuroscience, computational modelling can inspire new testable hypotheses that can bridge micro- and macroscale [15]. A prominent example in the field of DBS is the modeling of fiber activation to try and elucidate its circuit mechanisms. Inspired by animal research, realistic computational models of axon activation have brought the excitation hypothesis to life. It proposes that high-frequency stimulation may directly activate local neurons, and even if it fails to evoke local spiking, it may excite downstream structures through efferent axonal activation [144]. This mechanism could explain some previous findings that have cast doubt on the hypothesis that the primary mechanism of DBS is limited to local inhibition [145–147]. The idea that the therapeutic effect of DBS underlies antidromic activation of cortex has been particularly impactful, but it is methodologically challenging to prove this hypothesis with available empirical human neuroscience methods. One influential nonhuman primate study demonstrated the antidromic activation of cortical neurons during subthalamic DBS [148], but the effect was not sustained over time, while clinical improvement lasted. Moreover, antidromic activation was not observed during pallidal DBS that had similar clinical effects. Recent human evidence proposed that DBS can elicit cortical evoked potentials [149,150] that can indicate the degree of alleviation of bradykinesia in PD [78]. However, ECoG and MEG/EEG recordings provide limited means to shed light on the underlying synaptic processes. In the future, pathway specific activation models that incorporate neural tissue heterogeneity, such as myelination, axonal diameters, axonal arborization and dendritic field sizes may provide precise predictions about individualized DBS effects accounting for specific brain circuits from micro- to macroscale [106,151].

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(macroscale), through coherence and phase amplitude coupling [33–35]. When investigating directionality of information flow using Granger causality analyses, cortex has reproducibly been demonstrated to precede and potentially drive beta activity in the basal ganglia [34,36]. This suggests that beta activity is either generated and transmitted from the cortex or the excitation/inhibition sequence leading to beta synchronization may reside in the global interregional circuit (macroscale) itself [37]. Notably, combined **electrocorticography (ECoG)–**LFP recordings, that characterize beta oscillations from cortex and the STN in PD patients have revealed that bradykinesia/rigidity symptoms are reflected more robustly in the subthalamic than in the cortical beta frequency signature [10]. While the basal ganglia exhibit direct increases in oscillatory power and coherence of beta activity in the PD OFF state, this increase appears to be less prominent in the cortex [38,39]. Instead, pathologically increased beta synchrony at the cortical level can be observed in the form of phase amplitude coupling, where high-frequency activity is excessively locked to the phase of the beta carrier phase [34,40]. An alteration in waveform shape of beta oscillations, with increased sharpness asymmetry has been associated with the dopaminergic OFF state in PD, which can also influence phase amplitude coupling measures [38,41]. Thus, sensorimotor cortex may constitute a necessary node of the beta network, but may not reflect the key structure that leads to pathological changes of synchrony in PD [37]. The hypodopaminergic state may reflect a vulnerability of the basal ganglia to cortical synchronization, which disrupts flexible information transfer across the cortex–basal ganglia network. Thus, the principal pathological alteration of exaggerated beta in PD may originate from global cortico-subcortical network interactions instead of a single neural cell type or nucleus. Nevertheless, pathological beta synchrony is encoded in bursts of single unit firing at the microscale, evidenced by strong time-frequency and phase-coupling relationships between the bursting and LFP signals [6].

It is important to note that the strength of beta activity is highly dependent on the present network-state at the timepoint of recording. For instance, body movements like reaching, walking or riding the bike have been shown to desynchronize beta activity along all described nodes of the motor network, including cortex, basal ganglia and thalamus [42–47]. Recent studies recording beta activity in chronic settings have described that beta activity can be modulated by everyday life events [48,49]. Finally, enhanced beta activity recorded from motor areas does not reflect the entire phenomenological spectrum of PD including nonmotor symptoms but specifically the hypokinetic rigid state [50].

The aforementioned insights can provide grounds for generalized principles of the tendency of neural circuits for pathological synchronization from the network perspective:

Pathological synchronization (i) reflects exaggerated or aberrant alterations of physiological activity; (ii) can be observed at the micro-, meso-, and macroscales; (iii) can be attributed to a imbalanced macrocircuit communication instead of local pathology; (iv) is not necessarily disease specific; and (v) can be modulated by pharmacological and neurotechnological interventions.

Beyond beta activity, low frequency oscillations in the theta/alpha band (3–12 Hz) and gamma band activity (60–90 Hz) have been described as a biomarkers in patients with hyperkinetic motor states such as dystonia and Tourette's syndrome or during levodopa-induced dyskinesia in patients with PD [26,51–54]. Low frequency (3–12 Hz) oscillations follow all the rules formalized in the previous section, as they (i) can be observed during normal movement [43]; (ii) can be identified in local firing patterns [55], but also in oscillatory activity from multiple recording locations [26,43,56], which can be coupled through coherence across nodes of the network [26,57]; (iii) cannot be attributed to local pathology; (iv) are present in multiple hyperkinetic disorders

Glossary

Beta activity (13–35 Hz): a rhythmic oscillatory brain activity pattern that can be recorded with EEG, MEG, and invasive neurophysiological recording techniques, mostly in brain regions associated with motor system. In PD, exaggerated beta activity recorded in the basal ganglia is associated with the hypodopaminergic state.
Biomarkers: in the field of DBS neurophysiology, biomarkers is commonly used to describe a brain activity pattern that carries information on specific symptoms or therapeutic effects of a neurological disorder. The most prominent neurophysiological biomarker in DBS research is the exaggerated beta activity pattern in Parkinson's disease.
Connectomics: whole-brain interrogations of functional and structural wiring diagrams of the human brain, mainly derived from functional and diffusion MRI sequences in healthy participants or patient cohorts.
Deep brain stimulation (DBS): a neurosurgical treatment for which electrodes are chronically implanted into the depth of the brain to deliver high-frequency electrical pulses to disease specific target regions.
Dystonia: a rare neurological disorder, associated with sustained or repetitive involuntary movements and abnormal posturing. DBS of the internal pallidum can be a viable treatment option for patients with complex dystonia and insufficient effect from botulinum toxin injection or medication.
Electrocorticography (ECoG): a neurophysiological recording technique where a recording electrode is placed on the brain surface, typically below the dura mater. ECoG can provide valuable information on cortico-subcortical interactions and can be used to feed machine learning models for brain signal decoding in adaptive DBS.
Local field potentials (LFPs): Deep brain electrodes can be used to record so-called LFPs directly from the brain tissue in proximity to the target region, similar to EEG in the depth of the brain.
Macroscale: distant effects such as inter-regional coupling changes, for example, when DBS in the STN leads to changes in corticothalamic coupling, as measured with fMRI.
Mesoscale: local interaction of neural ensembles, composed of thousands of neurons within a defined gray-matter

and thus not disease specific [58,59]; and (v) can be modulated through intervention, that is, medication or DBS [57]. Equally noteworthy is the phenomenon of narrowband, finely -tuned or entrained gamma synchronization in cortex and STN. Traditionally, subthalamic and cortical gamma oscillations have been observed after levodopa intake and have been associated with dyskinesia [60,61], but recently a more complex picture has emerged. Finely tuned gamma activity was found even in the dopaminergic OFF state [62], while entrainment of gamma band activity through DBS was proposed as an additional DBS mechanism associated with PD motor sign alleviation [53,63]. Beyond the traditional gamma frequency band, high frequency oscillations at ~250 Hz have been another research focus and were reported to be shifted towards higher frequencies to ~350 Hz after levodopa intake in PD [64]. The neurophysiological foundation of these higher frequency activity patterns is less characterized, but a recent study suggests that cortical gamma band oscillations can synchronize local spiking in the STN during motor control [65]. Thus, at least some of the formalized principles stated previously can also generalize to this frequency band. More studies leveraging the unique intraoperative access to single-unit activity [4] or capitalizing on long-term recordings with sensing enabled implants [10] are required to understand the circuit interaction and local activity patterns related to these higher frequency synchronization phenomena.

structure, such as a subcortical nucleus or a cortical brain region.
Microscale: we use the term microscale to depict mechanisms associated with local synaptic activity of single neurons, e.g. within a specific brain region, such as the subthalamic nucleus.
Parkinson's disease: – Parkinson's disease is a neurodegenerative neural systems disorder associated with a loss of dopaminergic innervation to the striatum. Substitution of dopaminergic agents and subthalamic deep brain stimulation are effective treatments for advanced Parkinson's disease.

Modulating oscillatory circuits with DBS

DBS offers the unique opportunity to record neuronal network activity and its modulation directly in awake patients via implanted electrodes, thus providing insights into the underlying pathophysiology of movement disorders and the mechanisms of neuromodulation. These observations are of great clinical interest as they allow the integrative conceptualization of clinical therapeutic effect and neural circuit response that is needed to develop personalized adaptive stimulation systems [58]. Recent technological advancements allow chronic sensing of neural population activity during high-frequency stimulation, directly in the target area [9,10,60]. In Parkinson's disease and dystonia, it was shown that DBS can suppress pathological synchrony, when stimulation is clinically effective [19,57].

The effects of high-frequency stimulation can be formalized across scales (Figure 1) and are to be interpreted as integrative interdependent processes: (i) microscale: neural cell firing or spiking activity is perturbed; (ii) mesoscale: pathological oscillatory synchronization is disrupted; and (iii) macroscale: interregional coupling is modulated and rebalanced.

The exact neural effects depend on the inherent characteristics of the target area and the applied stimulation mode. To elaborate, we focus on subthalamic DBS for PD as the best-characterized neurostimulation technique. Here, electrode leads with stimulation contacts are implanted directly into the STN and rectangular electrical pulses of ~60 μs length are applied repetitively at high frequencies (~130 Hz) directly to the neural tissue. The precise mechanism of DBS is unknown (Box 1) and many complex interactions have been proposed to underlie its therapeutic efficacy, such as depolarization block, synaptic depression, ortho- and antidromic activation, collateral collision and trans-synaptic effects – which in summary may contribute to an informational lesion in circuit communication [7,66]. At the microscale, human single unit recordings during DBS show signs of synaptic depression and consequently inhibition of the target neurons resulting in periods of outright arrest of neural firing (silent periods) [4], which can predict the clinical efficacy of DBS in PD patients [67]. At the mesoscale and in parallel or as a consequence, the pathologically exaggerated parkinsonian beta rhythm is suppressed with DBS [9,19]. This suppression can be recorded through the same DBS lead, through which the stimulation is applied. There is a dose–response relationship of stimulation amplitude and beta suppression, with the level of beta suppression being correlated with the motor symptom alleviation in PD [9,19]. At the

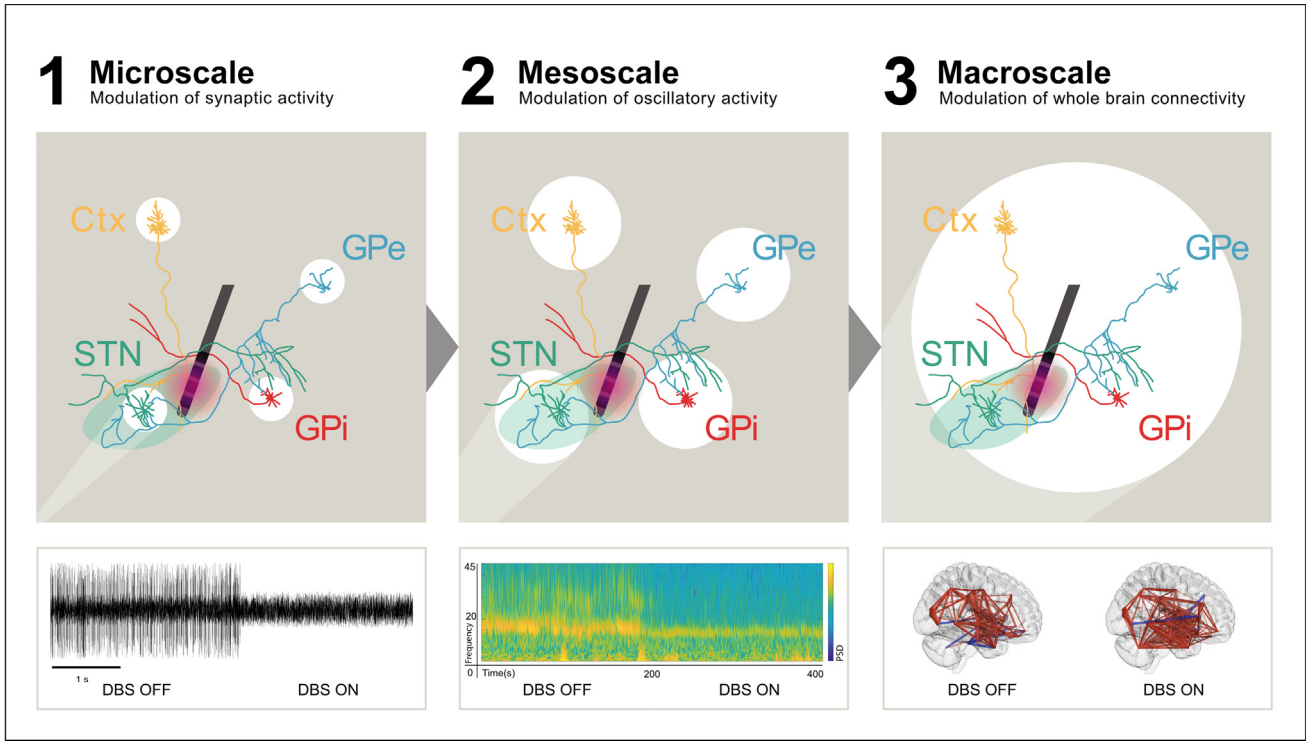

Figure 1. Multimodal neuromodulation research can elucidate multiple layers of neural circuit effects in time and space. At the microscale (left panel), DBS suppresses excessive synchrony in multiunit cell firing patterns of the cortex – basal ganglia circuit (adapted from [152]). In parallel or consecutively neural population synchrony measured as oscillatory local field potential activity is suppressed at the mesoscale (middle panel, adapted from [153]). Modulation of neural population synchrony is accompanied by modulation and rebalancing of whole-brain network communication at the macroscale (right panel; adapted from [87]). We would like to highlight that macroscale changes (e.g., as observable with MRI) may directly result from modulation of microscale effects and their mesoscale consequences. Abbreviations: Ctx, cortex; DBS, deep brain stimulation; GPe, globus pallidus externus; GPi, globus pallidus internus; STN, subthalamic nucleus.

macroscale, subthalamic DBS modulates beta oscillations in distant brain regions, including sensorimotor cortex and supplementary motor areas, when recorded during DBS [14,40,68]. Invasive ECoG recordings further demonstrated increased phase amplitude coupling and altered waveform asymmetry in PD that is suppressed with DBS at rest and during gait [35,40,41]. Beyond local subthalamic or cortical changes, DBS alters large-scale interregional cortico-subthalamic communication with decreased beta-band coherence between the supplementary motor area and STN [14]. While DBS may have multiple parallel effects, we speculate that its synaptic mechanisms can result in a decoupling and reduction of susceptibility of the target nucleus for excessive synchronization from afferent input. More specifically, decoupling of STN neurons from striatal, pallidal and cortical drive may lead to reduced recruitment of action potential bursts that encode beta activity at the microscale [6], which in turn suppresses the emergence of exaggerated beta in the local neural population on the mesoscale and rebalances the global network on the macroscale (Figure 1).

It is important to note that the aforementioned network effects are likely dynamic in nature. The sheer complexity of the many neurophysiological results has previously commonly required a deliberate dimensionality reduction for the sake of easier interpretation by researchers, often through averaging in the temporal domain. This should not be misinterpreted or understood as evidence that the described phenomena are stationary. Changes in beta power in PD can be reflected in a prolongation of transient episodes of beta bursts [9,17,24,69,70], which can be

shortened with adaptive DBS [71]. Adaptive DBS is a new therapeutic avenue that aims to translate peripheral sensor [72] or neurophysiological signals into closed-loop control policies in real time [59]. Pioneering studies in this area have demonstrated that monitoring beta activity can be used to adapt stimulation to concurrent therapeutic demand [48,59,73–75], but in the future more complex combinations of biomarkers may be evaluated as feedback signals [76]. Therefore, the precise temporal dynamics of biomarkers and synchronization phenomena with relation to clinical phenomenology and therapeutic response need to be characterized. Adaptive DBS can inspire new approaches for network-neuromodulation that are further discussed below.

Connectomic approaches to understand neuromodulation

From meso- to macroscale by means of MRI

A main component that is often lacking when studying electrophysiological data is the one of space. Spatial resolution of EEG and magnetoencephalography (MEG) is limited, and the precise location of invasive recordings (MER/LFP) in the brain – albeit being focal – can be uncertain. Some electrophysiological concepts, such as DBS-evoked potentials [77–79] or combined MEG/LFP [36,80,81] experiments have been successfully used to study macroscale networks. However, a key ingredient to interpret resulting data is to reconstruct precise electrode locations. Structural brain imaging data can complement DBS recordings to fill this gap. Combining neurophysiological analysis with MRI can shed light on anatomical locations of electrophysiological recordings (Figure 2A). For instance, biomarker activity – such as the elevated beta synchrony observed in both the STN and internal pallidum (GPi) in patients with PD – has been localized to specific recording sites within these structures using MRI-based electrode reconstructions [43,56,82,83]. When this is done repeatedly and from multiple electrodes across a patient cohort, recording values can be mapped to space in a probabilistic fashion [84]. In STN DBS for PD, a study using MRI-based mapping confirmed that elevated beta synchrony localized to the dorsolateral somatomotor subzone of the STN [82]; a finding promptly reproduced and extended by others [85]. Given the clinical significance of these markers discussed in the preceding text, these localizations could be useful to identify optimal stimulation sites that may guide both DBS targeting and programming. A further study localized movement velocity dependent gamma bursts to a similar region in the STN, hence extending findings observed at rest to localized electrophysiological signatures observed during movement [43]. Finally, aforementioned theta activity in dystonia has been located to a subregion of the GPi in close proximity to the border with the external pallidum (GPe) [56]. In a similar fashion, one can map changes in clinical symptoms or behavior induced by DBS onto the anatomy of the brain (Figure 2B). The prime example of this concept – termed Sweet spot mapping – is to relate motor improvement estimates (% change in Unified Parkinson's Disease Rating Scale III) to DBS electrode locations that were coregistered into standard space across patient cohorts [86]. This can inform statistical models that then estimate the optimal stimulation site. In PD, many groups have convergingly identified the superior edge of the posterolateral STN as the optimal stimulation site [84] – which matches the aforementioned site of maximal expression of beta power synchrony [82].

Studying DBS effects on a macroscale by means of MRI

Moving on to the macroscale (Figure 2D,E), functional MRI (fMRI) and positron emission tomography can be used to study DBS effects by contrasting scans acquired in DBS ON versus OFF states [87–89]. Here, a robust network termed the Parkinson's Disease Related Pattern (PDRP) has been described, whose activity correlates with symptom severity [88]. The pattern was characterized by relative metabolic increases in the pallidum, thalamus, pontine and cerebellar regions, and sensorimotor cortex, as well as metabolic decreases in the lateral premotor cortex and parieto-occipital association regions. Using fMRI, it has been repeatedly observed that DBS-induced network changes transform the activity and connectivity pattern within these

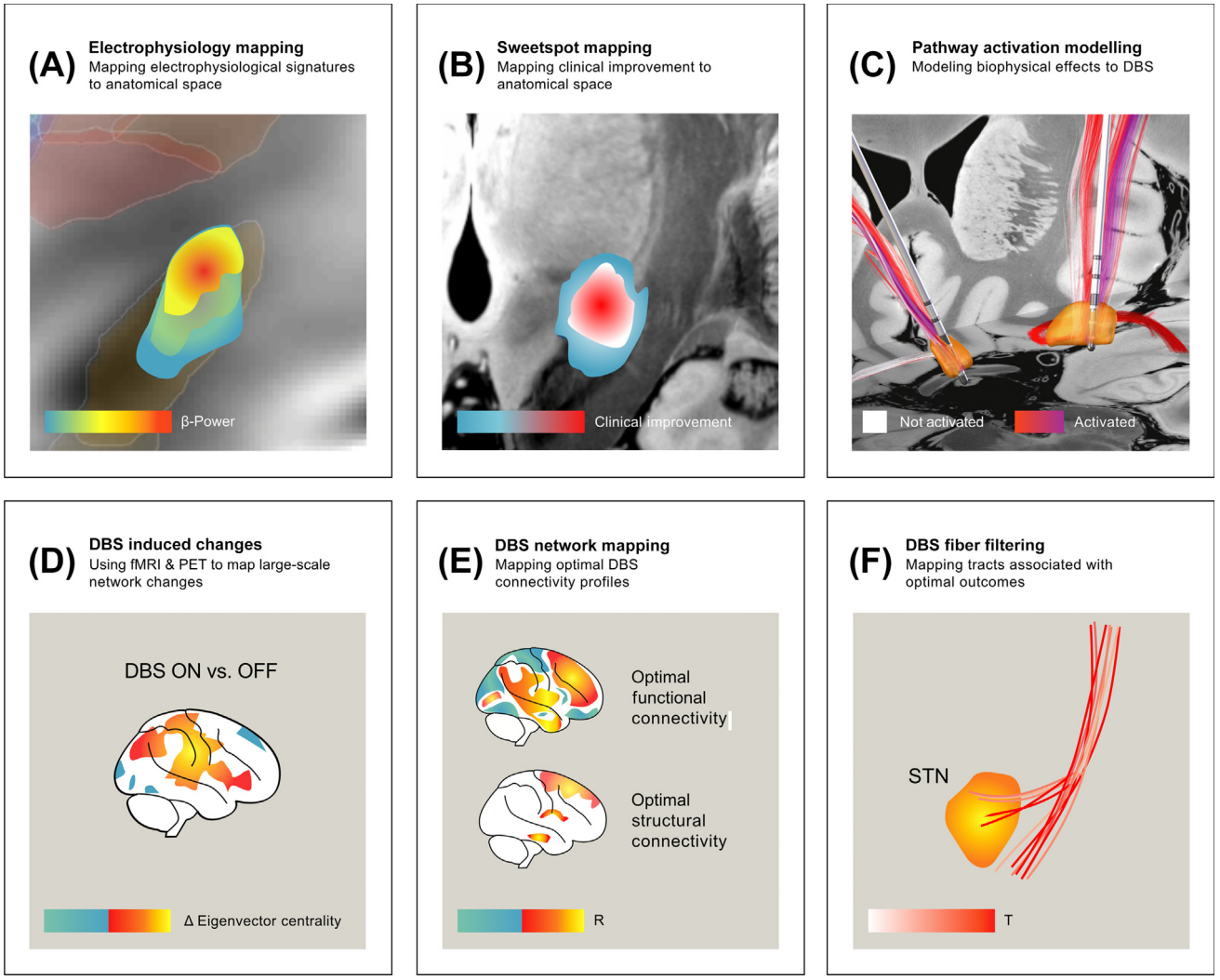

Figure 2. Overview of DBS imaging methods. A combination of DBS electrode localizations, computational modeling and MRI-based neuroimaging methods allows analysis of DBS network effects on mesoscopic (A–C) and macroscopic (D–F) levels. (A) Electrophysiological mapping is used to map biomarkers recorded from DBS electrodes to anatomical space, on a group level. The panel shows that increased beta synchrony is maximally expressed in the dorsolateral motor zone of the STN (adapted from [82]). (B) Sweet spot mapping is used to map clinical improvements or side effects to anatomical space, on a group level. Here, optimal clinical effects were again associated with modulating the dorsolateral sensorimotor STN (adapted from [86]). Pathway activation modeling is used to study the biophysical effects of DBS on surrounding axon cable models (image courtesy of K. Butenko, calculated with OSS-DBS software [154]). (D) Measuring effects of DBS on a whole-brain level by means of functional MRI or positron emission tomography is a powerful method to study whole-brain network effects. Top versus bottom panels show examples of maximal versus minimal modulation of DBS networks by a well- versus misplaced electrode (adapted from [87]). (E) DBS network mapping is used to calculate optimal DBS connectivity profiles on a whole-brain level. After mapping electrode reconstructions, functional and structural connectomes can be used estimate their connectivity profiles (adapted from [93]). (F) DBS fiber filtering is used to associate specific fiber tracts with DBS effects. In the present example, modulating hyperdirect projections to the STN (orange) was associated with optimal clinical improvement in PD (adapted from [86]). Abbreviations: DBS, deep brain stimulation; STN, subthalamic nucleus.

circuits of PD patients towards a healthy state [87,90]. However, after nearly two dozen publications investigating brain function using fMRI under active DBS in PD, more specific conclusions remain elusive [91]. For instance, distant effects of STN DBS on resting state activity during ON/OFF-cycling were often observed in the primary motor cortex, which showed an ipsilateral or bilateral increase or decrease [91]. Reasons for the variable results may be differences in acquisition schemes, with some publications cycling DBS ON versus OFF for seconds and others

contrasting effects across blocks of minutes. Also, differences in phenotypes (tremor dominant vs akinetic-rigid types) could play a role. While mixed results on changes in activity have been reported, more conclusively, changes in connectivity have been investigated by means of fMRI. A robust finding seems to be a stimulation related increase in corticothalamic and corticostriatal coupling, as well as weakening of STN connectivity, when comparing DBS OFF and ON [92].

Finally, an even less mechanistic and more correlational method, termed DBS network mapping, has been used to investigate optimal connectivity profiles of DBS (Figure 2E). Instead of analyzing changes of activity/connectivity that are induced by DBS, this method correlates baseline connectivity profiles with clinical outcomes. By doing so, optimal networks can be identified, which, when modulated, lead to maximal improvements. To do so, both structural connectivity as measured by diffusion-weighted imaging based tractography, as well as functional connectivity as measured by resting-state fMRI have been used. An early report applying this approach in PD showed that structural connectivity between electrodes and supplementary/premotor areas was associated with optimal clinical outcomes [93]. Functional connectivity estimates showed largely overlapping results on positive correlations with supplementary/premotor areas, while anticorrelations between DBS electrodes and primary motor cortices accounted for optimal clinical outcomes, as well [93]. While this study focused on STN-DBS, the same network could be identified in GPi-DBS for PD [94]. The method has since been applied to estimate models of optimal network profiles in essential tremor (ET) [95], obsessive compulsive disorder [96], epilepsy [97], dystonia [98], and Alzheimer's disease [99]. Furthermore, it was used to estimate connectivity profiles associated with side effects [100,101], such as depressive symptoms in STN DBS for PD [101] or ataxia and dysarthria in thalamic ventral intermediate nucleus (VIM) DBS for essential tremor [95]. Finally, the method was used to create and implement predictive models for behavioral effects mediated by DBS (which go beyond clinical apparent symptoms or side effects), such as response inhibition [102], motor learning [103], and stopping ongoing movements [100] in STN DBS for PD. Precise characterization of networks associated with specific symptoms, side effects, or behavioral changes may allow to personalize treatment by specifically stimulating the exact networks associated with the symptoms from which the individual patients suffers the most [104]. DBS network mapping aims at answering, which set of brain regions DBS electrodes should be connected to reach a certain (clinical, behavioral, or unwanted) effect. A related emerging approach has been termed discriminative tractography or DBS fiber filtering (Figure 2F, bottom) [96]. Instead of a voxel-centric view (as in DBS network mapping), this method takes a fiber-centric view and solves mass–univariate statistical models for several predefined tracts. Different evolutions of the method have been introduced since 2019 but essentially, they all aim at identifying tracts that are predominantly modulated by DBS electrodes in top responders (and predominantly not modulated by DBS electrodes in poor responders). By doing so, specific fiber bundles have been identified that – when modulated – were associated with optimal clinical response. A key issue of this concept resides in modeling the activation of tracts properly (before carrying out the actual filtering to relate activations with clinical improvements). Several elaborate concepts have been introduced, with the aim to model fiber activations as realistically as possible [105,106]. By doing so, activations of specific pathways by DBS can be modeled to study the biophysical effects of the treatment on (modeled) micro- and mesoscopic structures. This line of research led to concepts such as retrograde activation of hyperdirect projections [105] or that modulating fibers or passage could mediate treatment effects [7]. The mechanistic role of these fiber tracts remains under debate (Box 1 and see Outstanding questions). In addition, statistical methods that are relatively less sensitive to the actual pathway activation function have been introduced, as well [98,99]. Still, a consensus solution of how exactly to carry out fiber filtering has not yet been reached, and one should be cautious in interpreting the direction (antidromic vs. orthodromic) and modulation (activation vs inhibition) of these robust correlations.

Future outlook: translational opportunities for network neuromodulation

We aim to highlight the clinical utility and translational opportunities resulting from research outlined in this Review (Figure 3, Key figure). We follow the inverse order from macro- to microscale, as neuroimaging- and connectomics-related methods can provide advances in therapeutic planning and implantation even before DBS electrode implantation, while meso- and microscale findings may only be applied after electrode placement. However, we have arranged these opportunities in chronological order in Figure 3 to guide the reader in accordance with steps aligned to the timepoint of DBS implantation from pre- to postoperative.

Macroscale: image-guided DBS advances: connectomic DBS and computational DBS parameter prediction

The most imminent innovation in image guided DBS is the automated parameter optimization for postoperative programming based on the reconstruction of DBS leads with relation to predefined sweet spots. A recent study has demonstrated the noninferiority of this approach for STN DBS in PD [107], which may significantly shorten programming time of DBS parameters in the clinic. The extension of this approach to brain networks implicated in brain stimulation therapy at the macroscale has translational potential for both, improved preoperative targeting and postoperative stimulation parameter adaptation [104]. Currently, neurosurgeons delineate DBS targets based on stereotactic coordinates in combination with direct anatomical visualization using MRI before and during the implantation procedure [84]. This allows neither considering functional territories within target areas, nor does it reflect the network nature of the disease. Considering whole-brain connectomic fingerprints of optimal DBS outcome may be used to adjust preoperative DBS targeting and postoperative programming to the individual patient. Specifically, subregions of DBS targets with optimal connectional fingerprints to other brain areas that had been associated with optimal outcomes could be leveraged [12]. This could be done in a symptom-specific fashion; for instance, by predominantly targeting tremor-related networks in patients with tremor-dominant PD [108]. Beyond general clinical response, early studies have described additional network fingerprints of DBS side effects, that could serve as 'veto' connections that could be avoided through preoperative targeting or postoperative programming [12]. Finally, somatotopic network targets could further improve therapeutic specificity, for instance by modulating connections to hand regions of primary motor cortex and cerebellum in patients with predominant hand tremor [95,104] or considering pallidal topography/connectivity profiles with respect to body distribution in patients with dystonia [98]. Thus, for the next generation of connectomic DBS, understanding the macroscale DBS effects may allow the definition of symptom-specific network targets [104,109]. Preoperative target refinement could be based on the patient's individual disease profile; for example, for PD, including presence and severity of tremor, bradykinesia, and freezing of gait and nonmotor symptoms, such as apathy and depression [104]. In the future, refined imaging sequences may indicate neurodegenerative processes underlying specific symptoms directly. Here, neuromelanin imaging is currently an important research field for PD and may promise novel insight into DBS targeting in the future [110]. After electrode implantation, neuroimaging and whole brain connectomics can further aid the identification of optimal stimulation parameters in space [111]. DBS electrodes nowadays commonly have eight different stimulation contacts, allowing directional adjustment of stimulation current. The identification of treatment specific target networks in combination with novel advances in pathway activation modeling [105] may significantly accelerate the process of DBS parameter optimization. Beyond predefined network fingerprints, also the response to DBS can be characterized with neuroimaging and it was recently shown in a proof-of-concept study, that fMRI network metrics during DBS can help predict optimal contact selection [104]. In a similar vein, quantification of network specific inter-regional coupling between subcortical LFPs from DBS targets and cortex (e.g., using MEG or ECoG) may help identify optimal

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Key figure

Next-generation neuromodulation approaches benefit from neuroscientific insight across scales

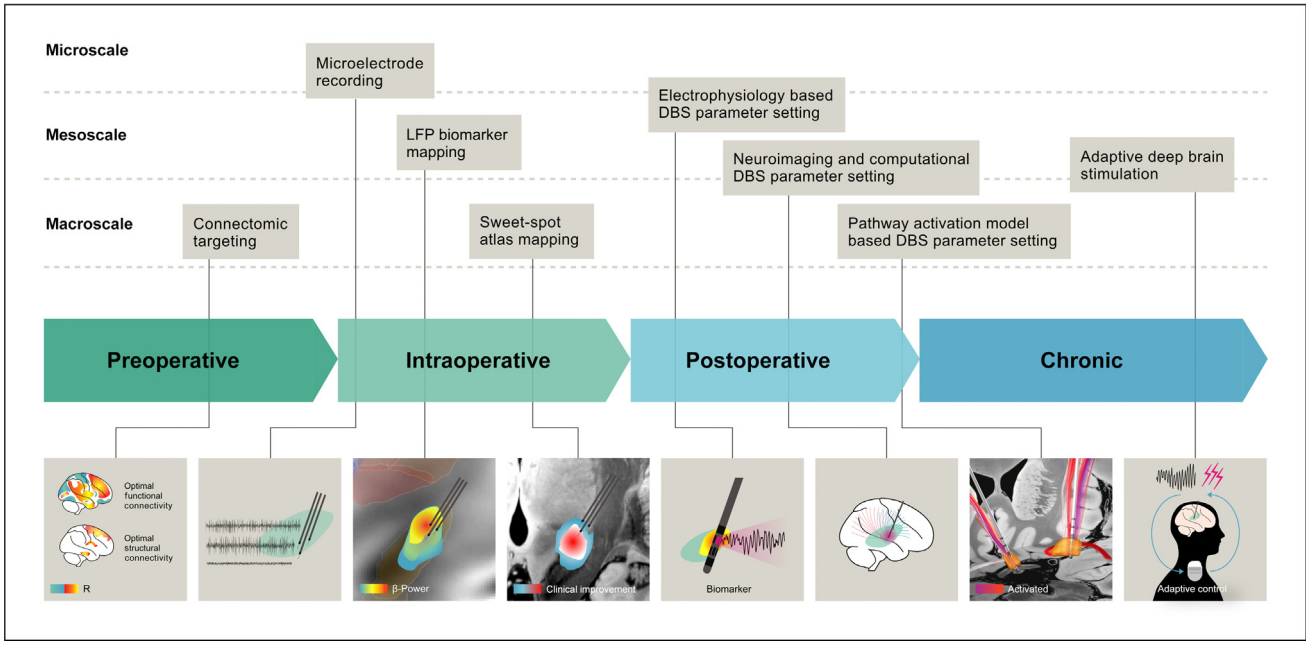

Figure 3. Preoperatively, high-resolution MRI can aid connectomic targeting (adapted from [87]). During the electrode implantation, neural cell-firing, LFP oscillations and neuroimaging atlas based visualizations can guide the implant trajectory (adapted from [82,86,152]). After electrode implantation, both neurophysiology and neuroimaging can be used to optimize stimulation parameters, based on local biomarkers in LFP signatures, whole-brain connectivity profiles and pathway activation models. Electrophysiological features can be utilized for precise temporal stimulation adjustment with chronic adaptive DBS. Abbreviations: DBS, deep brain stimulation; LFP, local field potential.

stimulation contacts intra- or postoperatively (e.g., by quantifying coherence in the beta frequency range in PD patients). Similarly, DBS-induced evoked potentials may help to identify optimal stimulation contacts [78,112,113]. Thus, the definition of DBS induced network effects at the macroscale, can support preoperative neurosurgical targeting and postoperative DBS parameter optimization.

Mesoscale: adaptive DBS and resynchronization for network disorders

The direct clinical utility of local field potential recordings from DBS target regions has been demonstrated for intraoperative target optimization [114–116], postoperative DBS parameter optimization [117], and real-time DBS adaptation [73]. During DBS electrode implantation, LFPs can be recorded and pathological synchronization, such as exaggerated beta activity in PD, can be monitored. Given the known overlap of beta activity and optimal DBS target in the STN, beta activity has direct utility for (i) intraoperative identification of optimal implant trajectories and (ii) definition of effective stimulation contacts for postoperative stimulation parameter optimization. It remains unclear whether beta activity has a causal role in PD pathophysiology, but the correlational relationship of beta suppression and PD symptom alleviation is a robust finding [19]. Therefore, recent advances for individualized neuromodulation therapy have used beta

band activity as a biomarker and feedback signal for adaptive stimulation [59,118]. Here, DBS parameters are adapted to beta band activity changes. Under laboratory conditions, adaptive DBS has proven effective with fewer side effects such as dysarthria [119] and dyskinesia [120], and reduced total stimulation energy delivered compared to conventional therapy [121]. Current efforts use novel devices that record and stimulate simultaneously allowing to track local STN beta activity during activities of daily living and with respect to diurnal and circadian cycles [48,122–124]. The clinical utility of these recordings still need to be proven in larger patient cohorts, which is currently ongoing in clinical trials [125] (https://clinicaltrials.gov/ct2/show/NCT04547712) with new implantable devices capable of chronic sensing of oscillatory activity and adaptive DBS. A limiting factor may be the fact that beta is not found in all relevant recordings. A recent study on 106 patients confirmed that peaks were present in the vast majority of recordings (>90%) but exceptions exist and have been discussed, although controversies remain [83]. Variation is not entirely understood yet but may partially be due to high contact impedances in specific electrode models, misplaced electrodes and sensitivity of LFPs to noise, movement, and other sources of artifacts [83,126]. Some recordings exhibit a lower alpha (8–12 Hz) frequency peak instead of beta (13–35 Hz), which still falls into the range of activity correlated with PD motor symptoms [17]. Nevertheless, whether beta or alpha activity that is related to motor signs of PD can be captured reliably across patients will have to be validated for each device separately. Ultimately, the general principle of LFP-based adaptive DBS is promising and may also be transferable to nonmotor symptoms (as shown for impulse control disorder biomarkers in PD) [127] and other movement disorders [128], especially with episodic worsening of symptoms such as Tourette's syndrome [129]. Beyond oscillatory activity, DBS may be improved through the localization of evoked resonant neural activity (ERNA); a DBS-induced single pulse response in the local field surrounding the stimulation electrode [130–133]. ERNA may have complementary value for DBS implantation planning, as it is known to be present even during general anesthesia and overlaps spatially with sources of highest beta activity and thus target region [132]. ERNA could also be useful for postoperative programming, for contact selection and amplitude definition [134]. For adaptive DBS, ERNA and beta dissociate during sleep, where ERNA may remain stable while beta activity changes with sleep stages. This could help refine adaptive DBS control algorithms. In the future, local field potential and ECoG recordings may be combined with machine-learning based brain signal decoding [76]. This may allow the real-time translation of brain network activity into patient tailored and symptom-specific therapeutic adjustments with potentially unprecedented spatiotemporal precision [10,42,76].

Beyond adaptive DBS, the specific pattern of stimulation has been hypothesized to enable control of mesoscale synchronization phenomena. Here, coordinated pulses based on mathematical models have been proposed to systematically desynchronize the neural population [135]. Computational evolution may be used to refine temporally specific stimulation patterns that optimize energy delivery, suppression of pathological synchronization, and improvement of symptom alleviation [136]. Together, neural synchronization measures at the mesoscale, recorded as invasive brain signals can elevate the therapeutic potential by advancing DBS targeting and individualized parameter optimization at an unprecedented temporal and spatial precision.

Microscale: long-term perspective: cell-type specific stimulation, optogenetics, and synaptic plasticity

The intraoperative delineation of DBS target borders based on microelectrode recordings has been a standard routine since the early descriptions of this therapy [137]. Identifying neural single- and multiunit cell firing patterns of distinct subcortical target areas allows the neurophysiological verification of correct electrode placement. Additionally, this procedure allows to perform test stimulation in the operation room, to objectify immediate stimulation related clinical effects. In

case of unsatisfactory results, the trajectory can be reconsidered, and alternative or additional trajectories can be evaluated. More recently, it was also shown that quantification of action potential suppression from single- and multiunit responses to DBS can define therapeutic thresholds for stimulation energy (amplitude and pulse width) required for clinical symptom alleviation [67]. First technological solutions for single-unit recordings in the real world are now emerging and have been tested in epilepsy patients. A translation to movement disorders may soon become viable [138]. While microelectrode recordings are an established technique for DBS surgery, the number of recorded units and spatial relationship of recording sites is highly constrained. Novel recording electrodes, including neuropixel probes, pioneered in animal research for the discovery of neural dynamics are now tested for use in human patients [139,140]. These electrodes provide ~1000 contacts along a linear shank. For DBS and neuromodulation applications, such electrodes could provide further insight into circuit pathophysiology and could accelerate biomarker characterization. However, at this time, the chronic use of these electrodes for therapeutic applications is still far away, mainly due to the fragile nature of the electrode and lack of regulatory approval for human applications. Beyond an expected increase in the number of neurons that are recordable, the field of neurotechnology may be able to extend the target specificity of stimulation approaches. In the future, the identification of cell-type-specific stimulation response characteristics may enable microscale targeting of neuromodulation in humans. A recent landmark proof of concept study in rodents has proven the feasibility to reproduce cell-type-specific optogenetic manipulation effects with specific electrical stimulation patterns [141]. Specifically, with the help of optogenetic methods, brief bursts of electrical stimulation were tailored to excite one set of pallidal neurons, while inhibiting another, with long-lasting therapeutic benefits in a mouse model of PD. Finally, chemical sensing of neurochemicals, for example, to monitor dopamine in PD, may soon become available, as first nonhuman primate studies have showcased its scientific value [142].

Outstanding questions

Are biomarkers causally linked to symptom generation?

What is the interaction between oscillatory biomarkers and clinical and healthy state changes during activities of daily living?

Can we use machine learning to account for symptoms and healthy behaviour and indicate the necessity for treatment adaptation in real time?

What is the functional role of connectomic networks associated with improvement through neuromodulation?

What are the precise synaptic effects of DBS?

Can we modulate neural plasticity with invasive brain stimulation?

Concluding remarks

DBS for movement disorders has helped to establish the characterization of movement disorders as network disorders based on identifying neuroscientific principles of pathological synchronization in motor circuits. DBS has allowed us to identify therapeutic mechanisms of neuromodulation. In the future, the underlying principles and mechanisms can be integrated and defined from micro- to macroscale by combining results from preclinical research, invasive neurophysiology, neuroimaging, and computational modeling. The insights may have direct translational potential for advancing neurotechnological treatments; for example, through refined connectomic targeting, intraoperative neurophysiological trajectory validation, biomarker-based automated parameter setting, and chronic adaptive closed-loop neuromodulation. Future research will have to further refine the precise interplay of candidate mechanisms from synapse to circuit (see Outstanding questions). Nevertheless, we are convinced that many of the described aspects so far can already be identified and extended in other brain disorders, towards an individualized precision medicine approach to invasive neuromodulation.

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Declaration of interests

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests. W.J.N. received speaker's honoraria unrelated to this manuscript from Medtronic, a manufacturer of deep brain

stimulation devices, and is a consultant for InBrain, a company developing invasive neuromodulation therapies. A.H. received speaker's honoraria unrelated to this manuscript from Medtronic, a manufacturer of deep brain stimulation devices. A.A.K. is on the advisory board of Boston Scientific and Medtronic, and has received honoraria unrelated to this manuscript from Boston Scientific, Medtronic, Abbott, Zambon, Stadapharm, Teva and Ipsen, companies manufacturing deep brain stimulation or pharmaceutical therapies.

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