NeuroImage 220 (2020) 117144

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Neuroimaging and electrophysiology meet invasive neurostimulation for causal interrogations and modulations of brain states

Gabriel Gonzalez-Escamilla [a,1], Muthuraman Muthuraman [a,1], Dumitru Ciolac [a,b,c], Volker A. Coenen [d], Alfons Schnitzler [e], Sergiu Groppa [a,*]

[a] Movement Disorders and Neurostimulation, Biomedical Statistics and Multimodal Signal Processing Unit, Department of Neurology, Focus Program Translational Neuroscience (FTN), Rhine Main Neuroscience Network (rmn2), University Medical Center of the Johannes Gutenberg University Mainz, Germany
[b] Laboratory of Neurobiology and Medical Genetics, State University of Medicine and Pharmacy "Nicolae Testemițanu", Chisinau, Republic of Moldova
[c] Department of Neurology, Institute of Emergency Medicine, Chisinau, Republic of Moldova
[d] Department of Stereotactic and Functional Neurosurgery, University Clinic Freiburg, Germany
[e] Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University, Düsseldorf, Germany

ARTICLE INFO

Keywords:
Deep brain stimulation
Structural MRI
Diffusion MRI
Functional MRI
Brain networks
Microelectrode recording
Local field potentials
Neural oscillations
Beta bursts
Phase-amplitude coupling

ABSTRACT

Deep brain stimulation (DBS) has developed over the last twenty years into a highly effective evidenced-based treatment option for neuropsychiatric disorders. Moreover, it has become a fascinating tool to provide illustrative insights into the functioning of brain networks. New anatomical and pathophysiological models of DBS action have accelerated our understanding of neurological and psychiatric disorders and brain functioning. The description of the brain networks arose through the unique ability to illustrate long-range interactions between interconnected brain regions as derived from state-of-the-art neuroimaging (structural, diffusion, and functional MRI) and the opportunity to record local and large-scale brain activity at millisecond temporal resolution (microelectrode recordings, local field potential, electroencephalography, and magnetoencephalography).

In the first part of this review, we describe how neuroimaging techniques have led to current understanding of DBS effects, by identifying and refining the DBS targets and illustrate the actual view on the relationships between electrode locations and clinical effects. One step further, we discuss how neuroimaging has shifted the view of localized DBS effects to a modulation of specific brain circuits, which has been possible from the combination of electrode location reconstructions with recently introduced network imaging methods. We highlight how these findings relate to clinical effects, thus postulating neuroimaging as a key factor to understand the mechanisms of DBS action on behavior and clinical effects. In the second part, we show how invasive electrophysiology techniques have been efficiently integrated into the DBS set-up to precisely localize the neuroanatomical targets of DBS based on distinct region-specific patterns of neural activity. Next, we show how multi-site electrophysiological recordings have granted a real-time window into the aberrant brain circuits within and beyond DBS targets to quantify and map the dynamic properties of rhythmic oscillations. We also discuss how DBS alters the transient synchrony states of oscillatory networks in temporal and spatial domains during resting, task-based and motion conditions, and how this modulation of brain states ultimately shapes the functional response. Finally, we show how a successful decoding and management of electrophysiological proxies (beta bursts, phase-amplitude coupling) of aberrant brain circuits was translated into adaptive DBS stimulation paradigms for a targeted and state-dependent invasive electrical neuromodulation.

1. Introduction

The treatment options for neuropsychiatric disorders and especially movement disorders have been significantly expanded by the development of deep brain stimulation (DBS). In recent years, there has been a growing body of work contributing to the development of

* Corresponding author. Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstrasse 1, 55131, Mainz, Germany.
E-mail address: segroppa@uni-mainz.de (S. Groppa).
[1] Equal Contribution.

https://doi.org/10.1016/j.neuroimage.2020.117144
Received 3 April 2020; Received in revised form 22 June 2020; Accepted 2 July 2020
Available online 4 July 2020

neurophysiological models on the mechanisms of DBS (Jakobs et al., 2019). DBS allows clinical symptoms to be alleviated by means of stereotactically implanting electrodes into specific targets within deep regions in the brain, which depend on the disease and symptoms being treated, and delivering constant or intermittent electric currents from an implanted battery source.

The acute and long-term effects of DBS may not only be limited to the suppression of cardinal symptoms, but may possibly further positively influence the course of the disease through targeted modulation of the involved circuits. A detailed functional and structural biomarker delimitation, using brain imaging (e.g., MRI) and electrophysiological (e.g., electromyography - EMG, LFP, electroencephalogram - EEG, and magneto encephalogram - MEG) techniques is essential for the selection of brain targets and for improving direct planning of implantation, but also for better understanding DBS mechanisms. Supplementation of imaging data analysis by electrophysiological pre- and intraoperative recordings can synergistically support electrode placement for the surgical procedure, or ease postoperative programming.

The advent of brain imaging on DBS research has shifted the ideas regarding the mechanistic effects of DBS from purely localized effects to the concept of targeted modulation of fiber tracts and wide-spread connected brain regions, with possible chronic neuroplastic effects (Jakobs et al., 2019). The use of functional imaging techniques has allowed the delineation of the targeted network and enabled the visualization of the specific fiber tracts involved. Altogether, the use of brain imaging techniques has resulted in a conceptual paradigm-shift, in which unique effects of focal stimulation of specific brain target regions is no longer considered the main action mechanism, but instead a targeted modulation of the specific network has being hypothesized (Gonzalez-Escamilla et al., 2019; Horn, 2019; Lozano and Lipsman, 2013). This information can also be applied in already implanted patients to enhance DBS effects and advanced programing actions, thereby minimizing side-effect or long-term negative outcomes.

Common brain regions used as targets for movement disorders (Fig. 1) are: the subthalamic nucleus (STN) in Parkinson's disease (PD), the globus pallidus internus (GPi) for dystonia, and the ventral intermediate nucleus of the thalamus (VIM) for essential tremor (ET) (Krack et al., 2019). For other neurologic and psychiatric disorders, the definition of optimal DBS targets is still a matter of investigation. For example, although the centromedian thalamic region and the GPi are most frequently selected for relief of motor tics and comorbid psychiatric symptoms in Gilles de la Tourette syndrome (GTS), due to the complexity of the disease DBS in GTS seems far from being established (Krack et al., 2019). Similarly, for obsessive-compulsive disorders (OCD) no consensus on definite targets has yet been achieved. The presentation of the network profile of DBS target regions further provides extended insights into the mechanisms of action of the therapy postoperatively, while opening up the possibility of defining patient-specific DBS target regions on the basis of connectivity maps obtained preoperatively.

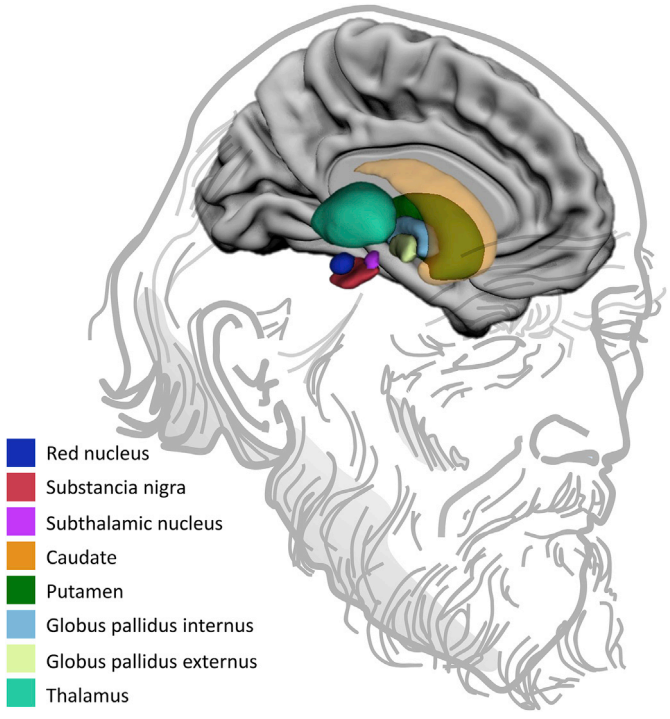

Fig. 1. Common deep grey matter regions used as targets for deep brain stimulation in movement disorders, but also gaining attention as possible targets for neuropsychiatric diseases.

Ultimately, the aim of this review is to present the current state-of-the-art methods to characterize the network modulation by the aid of DBS, neuroimaging and electrophysiology, and to outline the latest research results and perspectives for the further development of the synergistic use of DBS, brain imaging and electrophysiology. Therefore, we discuss how the assessment of structural and functional network properties at local and global brain levels via brain imaging and electrophysiology can be used as a basis for the prediction and optimization of DBS in brain network disorders. Likewise, we show how the subject-specific differences in structure, network connectivity and oscillatory dynamics can personalize the delivery of DBS treatment paradigms on one hand, and increase its effectiveness and reduce potential side effects on the other hand.

2. Deep brain stimulation in the neuroimaging era

2.1. Neuroimaging and DBS in the perioperative period

The inherent aim of DBS is to modulate neural activity by applying extracellular electric fields, which in turn depend on the stimulation parameters (amplitude, pulse width, frequency) and the physiological properties of the brain (Kringelbach et al., 2011). Therefore, accurate allocation/implantation of DBS electrode contacts into the brain is of greatest importance for effective stimulation in patients undergoing surgery.

To help improve targeting accuracy, current stereotaxic implantation of the DBS leads uses a combination of post-mortem atlas-based coordinates and patient's brain structural imaging (usually MRI, providing a good definition of local anatomy) for planning trajectories (Lee et al., 2010), with possible trajectory refinement using neurophysiological microelectrode recordings (MER; see *microelectrode recording for functional STN mapping*) and macrostimulation to functionally map/track the target from awake patients (Lauro et al., 2018; Lee et al., 2018). Then, postoperative structural brain imaging (commonly CT [computed tomography], or MRI at lower magnetic fields, i.e. 1.5T is possible depending on manufacture specifications) is used to verify targeting accuracy by assessing lead contact placement. An alternative to this procedure is the use of interventional real-time MRI, which relies on prospective stereotactic imaging techniques prior to lead implantation, to refine a trajectory that achieves target alignment (Lee and Richardson, 2017; Lee et al., 2018; Ostrem et al., 2016). Due to the incurred cost and risk issues (Burchiel et al., 2013; McClelland, 2011; Zrinzo et al., 2012) and considering that targeting accuracy and DBS outcomes of image-guided operation without MER are comparable to those with MER (Burchiel et al., 2013; Mirzadeh et al., 2014; Starr et al., 2014; Thani et al., 2012), add-on value of MER is now questioned. This may be related to the heterogeneity of MER usage across centers (e.g., use of single or simultaneous MER) (Bjerknes et al., 2018). The use of structural MRI verification of the leads results in outcomes similar to those obtained with MER guidance (Aviles-Olmos et al., 2014; Foltynie et al., 2011), and the use of interventional MRI produces reductions in motor symptoms and medication dosage (Ostrem et al., 2016). Therefore, MRI is

increasingly used as a tool in the study of DBS mechanisms.

Accurate DBS lead implantation is challenged in pure imaging-based approaches due to the brain shift problem (Slotty et al., 2012; van den Munckhof et al., 2010). The brain shift problem comes from an alteration to the intracranial mechanical equilibrium due to the burr hole and opening dura during the lead implantation, which displaces the planned target from the preoperatively determined position and further compromises the alignment between postoperative and preoperative brain scans, the latter being used for surgical planning and targeting. Lead implantation within the functional target with MER-directed adjustments can help address the brain shift problem of the DBS surgery approach, as depicted by decreased distance errors across different clinical reports (Li et al., 2016). A further strategy is to perform the imaging and planning after dura opening (Starr et al., 2014), e.g., during intervention. However, imaging is not possible in all cases or clinics at intervention, and thus, MER have increased relevance for improving lead positioning towards the actual target especially in cases where no interventional CT or MRI is available.

Advanced MRI sequences, when adequately configured, can deliver accurate and direct mapping of the different subcortical structures commonly targeted during neurosurgery (Ewert et al., 2018; Kim et al., 2019; Su et al., 2019). Integrating MRI modalities with brain histology supported the emergence of a detailed 3D deformable atlas of the human basal ganglia (Yelnik et al., 2007), while further developments in MRI technology, such as ultra-high-field imaging, currently allow unprecedented detail of brain structures strikingly emulating histology procedures (Forstmann et al., 2016; Pauli et al., 2018). This may potentially increase the accuracy for the postoperative verification of DBS leads implantation, or even enhance the individualized pre-surgical DBS targeting (Duchin et al., 2018; Patriat et al., 2018). In this view, modern brain imaging has the ability to increase DBS efficacy and reduce adverse effects reported to be associated with suboptimal placement of electrode contacts (Rolston et al., 2016; Wodarg et al., 2012), possibly optimizing a patient's long-term therapeutic outcome.

Preoperatively, structural brain imaging can robustly predict postoperative outcomes across diseases and can, thus, be further implemented for improved selection of those patients who are candidates for DBS intervention (Eross et al., 2020; Gonzalez-Escamilla et al., 2019; Muthuraman et al., 2017). This information can also be used as exclusion criteria for patients who would likely not benefit from DBS therapy (Gonzalez-Escamilla et al., 2019). However, application in clinical settings would be possible only after robust biomarkers of DBS outcomes have been validated. This task is achievable by complementing imaging and electrophysiology measures with DBS recordings, and should go hand in hand with the development of objective and investigator-independent methodologies.

2.2. Causal interrogations of DBS with neuroimaging

Beyond the use of neuroimaging during the perioperative period and intervention, it may further help to better understand DBS mechanisms and detect complications that may accompany the therapy, in other words, it may help explain intended or unexpected effects.

There is no current consensus on the action mechanisms of the therapeutic effect of DBS in movement disorders or any other neurological disease (Ashkan et al., 2017; Jakobs et al., 2019). In essence, a neural response is elicited by DBS electric stimulation, resulting in thousands of synaptic events through the dense axonal branching (Herrington et al., 2016). The induced synaptic events may result in excitation or inhibition depending on the specific pathway being reached, spreading across the brain affecting large-scale networks (Horn et al., 2017b; Lozano and Lipsman, 2013). In this sense, previous studies have evidenced that, beyond DBS electrode location, the connectivity patterns of the target region are closely related to the clinical improvement (Horn et al., 2017b). The subsequent network-level modulation is still under further investigation to identify whether afferent and/or efferent axons are stimulated and to elucidate the predicted outcome of DBS.

The two major advances in our understanding of DBS mechanisms brought by modern brain imaging are due to the provided ability to: i) trace specific stimulated pathways or ii) examine functional consequences within brain networks. As an example of the former, volume of tissue activation (VTA) models can be generated around individual electrode contacts with the aid of brain imaging to evaluate the anatomical basis of physiological responses and clinical outcomes (Akram et al., 2017). These VTA models are underlined by mathematical assumptions about the electrical field distribution from the stimulating electrode (amplitude, pulse width, frequency), and thresholds for action potentials in a grid of model axons around the electrode contacts (Butson et al., 2011). After the extent of the electrical field produced by the electrode contacts has been modelled, utilization of brain tractography algorithms, based on diffusion imaging, can help to determine which fibers are being activated (Fig. 2A and B). This information can then be used by clinicians for the correct programming of the electrical pulse in each patient to obtain the best clinical outcome (Fig. 2 C), thereby, preventing the induction of subtle stimulation-induced adverse effects such as dysarthria resulting from excessive current spread (Frankemolle et al., 2010), while achieving equal clinical benefits.

The second progression in DBS due to brain imaging is the allowance of large or multicenter retrospective studies aimed at defining an optimal stimulation location according to disease stage, symptom relief or supposed clinical improvement (Dembek et al., 2017; Gourisankar et al., 2018; Reich et al., 2019), with robust findings as suggested by high out-of-sample prediction accuracy, using an independent dataset (Reich et al., 2019). Noteworthy, the introduction of diffusion imaging has gone beyond connectivity determination from the electrode locations within GM nuclei, recently, it has been also used to assist DBS planning in order to directly target the dentatorubrothalamic tract (DRTT) in ET (Coenen et al., 2011) suggesting an effect in clinical entities with tremor-dominant symptoms (Coenen et al., 2020). Cf. (Calabrese, 2016) for an overview on the topic.

As DBS is becoming increasingly available, finding an optimal stimulation target or "sweet spot" has become essential. The sweet spot is defined as a predominant spatial signature of the electrode locations within the target region that allows the predictability of the clinical efficacy of DBS to be assessed. In this direction, in PD patients a sweet spot within the sensorimotor functional zone of the STN has been found for the optimal clinical outcome after DBS (Bot et al., 2018). This finding on the relationship between the proximity of active DBS contacts to the sweet spot and the clinical outcome has been replicated based on defined coordinates obtained through meta-analyses (Corp et al., 2019; Horn et al., 2019) but also when comparing omnidirectional against directional stimulation and individual VTA modelling (Nguyen et al., 2019). Notably, the spatial overlap between VTA and STN volumes appear equally predictive of clinical improvement (Horn et al., 2019).

A further advance, related to the DBS systems, is the recent introduction of directional leads to provide more control of the stimulation field. Unlike conventional DBS leads, which use cylindrical electrode contacts, directional leads comprise radially segmented contacts (see example electrode contacts in Fig. 2 A). This segmented contacts allow the manipulation of the stimulation field in the plane perpendicular to the lead, or to alternatively be shaped by using a combination of anodes and cathodes in a particular direction (Contarino et al., 2014; Pollo et al., 2014). Thus, directional leads allow the stimulation to be delivered in the direction of the anatomical/functional target region and, possibly, away from aversive-effect locations, at the cost of more complex and potentially more time-consuming DBS setting parametrization by the neurologist. Such lead configurations have impact on the geometry of the modelled VTA and the detection of target-adjacent tracts by diffusion imaging. Directional leads also open the possibility to re-directed stimulation to new sub-targets, which in turn, may foster our understanding of DBS effects on axial and appendicular symptoms and of the physiology of movement, cognition, and mood (Schupbach et al., 2017).

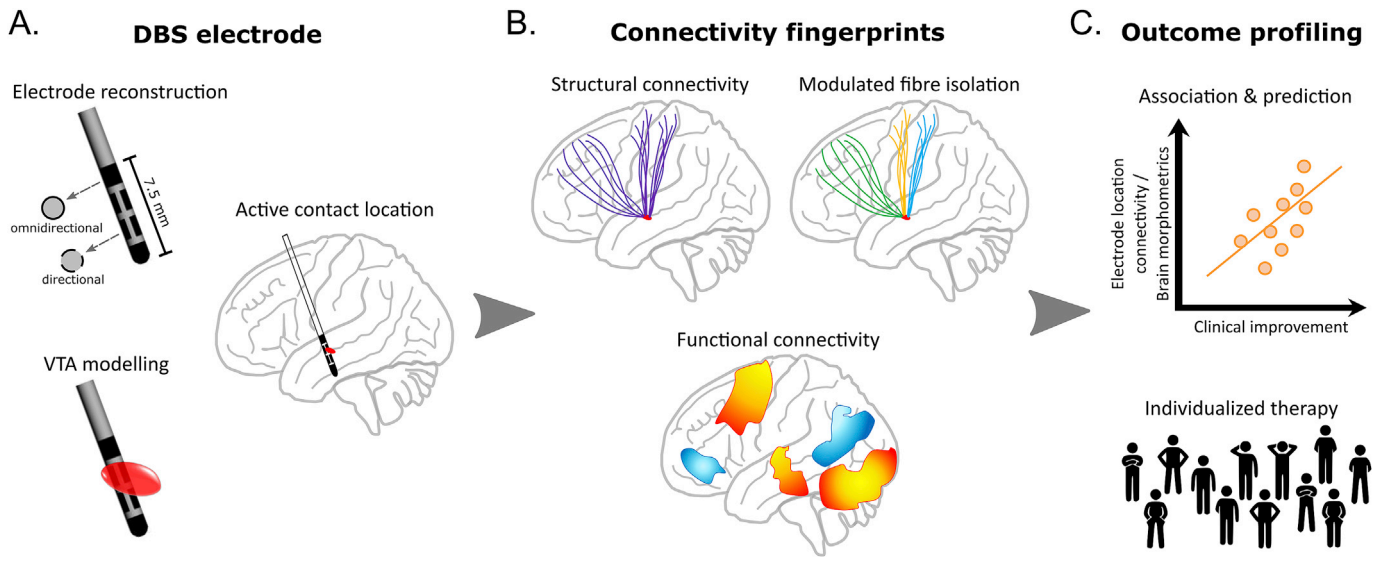

Fig. 2. Overview of the applicability of brain imaging in the study of deep brain stimulation (DBS). (A) The combination of preoperative structural MRI with postoperative CT [computed tomography], or less common postoperative MRI at low magnetic fields, can be used to reconstruct DBS electrode positioning and model individualized volumes of tissue activation (VTA). (B) Once the locations of the active DBS electrode contacts are known or VTAs have been modelled brain imaging can be used to study DBS functional-structural associations. For example, in structural connectivity, diffusion imaging can serve to study modulated fiber pathways and structural MRI serves to study morphometric properties of the connected regions; functional connectivity from fMRI or neurophysiology methods help to elucidate coordinated activity across wide-spread brain regions. Altogether, these brain imaging markers can be used as connectivity and architectural fingerprints of DBS. (C) Patient's connectivity and architectural fingerprints can be used to study the association between location, connectivity and structural integrity with clinical outcomes after DBS, or to create models that predict clinical improvement. The utility of neuroimaging techniques can be translated into clinical practice to deliver individualized DBS therapy.

Noteworthy, VTA models are rough estimations of the spatial extent of activation and quantify the theoretical responses to stimulation assuming tissue homogeneity across individuals. Here, there is a need for novel patient-specific algorithms that are both biophysically realistic and computationally simple.

In other diseases, the relationships between electrode location and clinical improvements are becoming available (Dembek et al., 2017; Gourisankar et al., 2018; Reich et al., 2019). Similarly to the findings in STN-DBS for PD, using VTA overlaps with a probabilistic sweet spot volume could explain more than half of the variance in motor score improvement after GPi-DBS in dystonia patients (Reich et al., 2019). Here, the optimal stimulation point, residing within the ventroposterior GPi and the adjacent subpallidal white matter, was not different for cervical and generalized dystonia (Reich et al., 2019). For essential tremor, an optimal target of tremor suppression could be defined along the inferior border of the VIM and within the adjacent white matter (i.e., the rostral zona incerta) by computing a probabilistic mapping of VTAs (Dembek et al., 2017).

To study the relationship between DBS electrode localization and behavioral responses, patients implanted with DBS electrodes are asked to perform/engage in behavioral/cognitive tasks during DBS stimulation ON and OFF conditions. Using such paradigms, STN-DBS has shown its ability to shift patient's decision-making under conditions of uncertainty (Paliwal et al., 2019; Patel et al., 2018). Here, the efficacy of SNT-DBS in modulating behavior could relate to electrode locations. For example, it is known that during gambling tasks PD patients are more risk-aversive and optimal DBS localization was shown to reduce risk-aversion behavior in PD patients closer to that of the healthy individuals, whereas this was not the case for patients having suboptimal electrode localization (Irmen et al., 2019).

Of notice the correct localization of the DBS active electrode contacts may not be enough to explain the full variance in postoperative outcomes, as in some studies the clinical outcome improvement could be associated to the stimulation volumes, but not the electrode location per se (Reich et al., 2019). This highlights the importance of evaluating the involvement of hyperdirect and indirect cortico-thalamic pathways (Hamani et al., 2017) in modulating reaction times and motor performance.

2.3. DBS electrode connectivity and clinical outcomes

Functionally distinct cortico-subcortical loops, which form elements of the motor, cognitive and affective systems, cross the basal ganglia and thalamus, creating functional sub-regions within these structures. These sub-regions may in turn show distinct electrophysiological fingerprints. As previously mentioned, effective modulation of cognitive function or symptom reduction requires DBS electrodes to be precisely positioned. For example, DBS electrodes placed along the medial border of the STN led to speech deterioration when compared to a more lateral location in PD patients (Tripoliti et al., 2011; Wodarg et al., 2012). A further example is that in PD patients the connectivity profile from DBS electrode locations to primary motor cortex (M1) explains (to a large extent) tremor improvement, while DBS electrode connectivity to supplementary motor area (SMA) explains bradykinesia amelioration and connectivity to both SMA and prefrontal cortex (PFC) explains rigidity modulation (Akram et al., 2017). The location of the active electrode contacts in proximity to the dentate-thalamic tract (DTT) could be associated with tremor improvement (Sweet et al., 2014). The particular association between electrode connectivity to the SMA and PFC with clinical outcomes has been consistently shown in PD patients (Horn et al., 2017b; Koirala et al., 2018; Vanegas-Arroyave et al., 2016) and in animal models (Gradinaru et al., 2009). In contrast, a more ventral-medial STN electrode stimulation in PD patients can decrease beneficial motor outcomes and increase rates of undesirable mood and cognitive adverse events (Castrioto et al., 2014). For GPi-DBS in dystonia, clinical efficacy has been shown for electrode locations anatomically close to the pallidothalamic pathways (Rozanski et al., 2017). In VIM-DBS for treatment of tremor, location of electrodes nearby the DRTT seems crucial to explain clinical improvement (Akram et al., 2018; Calabrese et al., 2015; Groppa et al., 2014). Despite the fact that DRTT modulation may represent the most

accepted concept in DBS for reducing tremor, its ability in further clinical entities with tremor-dominant symptoms is scarce (Coenen et al., 2020; Fiechter et al., 2017) and long-term outcomes are yet to be proven (Coenen et al., 2020). Moreover, involvement of the thalamic SMA/M1 segments appears to further play a role in improving tremor (Akram et al., 2017; Middlebrooks et al., 2018; Pouratian et al., 2011). Clearly, these findings indicate that cortical regions beyond the stimulation site are key factors for the ultimate DBS outcomes (Gonzalez-Escamilla et al., 2019; Muthuraman et al., 2017).

Non-invasive brain circuit tracing, using functional MRI (fMRI), allows the exploration of direct clinical effects of DBS from a different perspective. However, fMRI studies on patients implanted with DBS electrodes are limited because of safety concerns and imaging artefacts (Kahan et al., 2015; Tagliati et al., 2009), therefore, animal models typically are used with these aims. In non-human primates, STN-DBS increases blood oxygenation level-dependent (BOLD) activation in the sensorimotor cortex, SMA, caudate nucleus, pedunculopontine nucleus, cingulate, insular cortex and cerebellum (Min et al., 2014). Similarly, increased BOLD responses in motor, somatosensory, and cingulate cortices to STN- and GPi-DBS are found in rats (Lai et al., 2014). In pigs, DBS targeting on the STN and the entopeduncular nucleus (EN), the non-primate analog of the primate GPi, induces increased BOLD activity in the ipsilateral sensorimotor network, including the premotor, M1, and primary somatosensory cortices, as well as dorsolateral prefrontal and anterior cingulate and insular cortices (Min et al., 2012). The network activations showed differential, target-specific, non-motor network effects (Min et al., 2012).

In humans, the recent introduction of normative connectomes derived from large cohorts of participants allows for better definition of the brain network fingerprints of DBS (Fox, 2018). Such studies have evidenced that the connectivity profile of effective VIM-DBS can be successfully estimated (Horn et al., 2017a) and be used to predict clinical

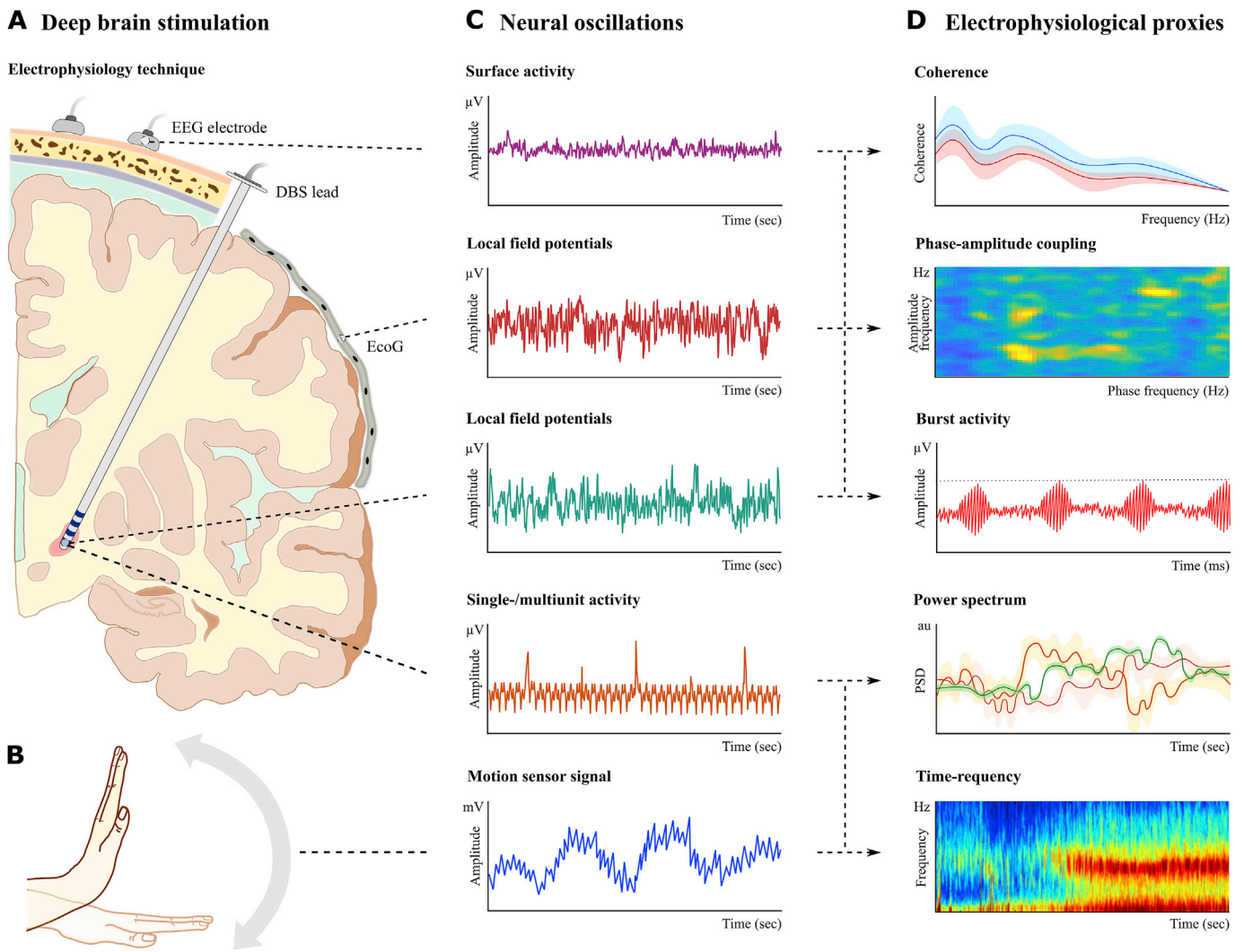

Fig. 3. Integration of electrophysiology techniques in the deep brain stimulation (DBS) setting. (A) Electrophysiological activity from the DBS target, neighboring and distant brain regions is recorded by applying invasive and non-invasive techniques, which serve as tools to detect and measure neural oscillations and map the effects of DBS on local and distributed brain oscillatory networks. (B) Including kinematic parameters from peripheral motion sensors can aid in the characterization of oscillatory networks during gait or limb movement tasks under DBS off/on conditions. (C) Neural oscillations are acquired as local field potentials (LFPs) directly from the implanted electrode in the subcortical structure (here, subthalamic nucleus, STN) and from cortex (subdural electrocorticography strips, EcoG), as single- and multiunit activity (microelectrode recording, MER) or as surface activity (electroencephalography, EEG). (D) The recorded LFP and EEG signals are subjected to computational analysis to extract the functional signatures (electrophysiological proxies) of aberrant circuit activity in time and/or frequency domain (coherence, phase-amplitude coupling, burst activity, power spectral density) and track their dynamical responses to DBS. Electrophysiological proxies (e.g., beta bursts, phase-amplitude coupling) of fluctuating brain states indicative of a specific symptom can be used as feedback signals for closed-loop DBS implantable devices. Single- and multiunit activity (i.e., spike and background characteristics) obtained from MER is mainly used for intraoperative functional mapping of the DBS target (here, STN), and prediction of the optimal electrode implantation site and postoperative outcome.

improvement after DBS (Horn et al., 2017b). These connectivity profiles can be further translated to model or predict the effectiveness of DBS in different clinical populations, which may be of help in cases where these data are not available (Coenen et al., 2020; Elias et al., 2020; Fox, 2018). This concept has been recently applied to OCD where connectivity profiles from normative connectome data showed that a specific tract within the anterior limb of the internal capsule and the nucleus accumbens and projecting to prefrontal cortices was highly predictive of clinical improvement (Baldermann et al., 2019). Results that could be validated using patient-specific connectome data (Baldermann et al., 2019). In the same study, the authors reported that the degree of fiber pathway connectivity between stimulation locations in the nucleus accumbens and medial and lateral prefrontal cortices predicted clinical improvement. Therefore, it is apparent that information about functional and structural brain pathways is crucial to understand the modulatory effects of DBS for beneficial outcomes.

3. Deep brain stimulation and electrophysiology explorations, insights from Parkinson's disease

3.1. Microelectrode recording for functional STN mapping

Besides interventional applications, structural MRI is becoming increasingly common to confirm the correct anatomical placement of the DBS leads (cf. *Neuroimaging and DBS in the perioperative period*), MER is a gold standard approach for this purpose as standalone or also complementary to neuroimaging. MER entails intraoperative recordings with high spatio-temporal resolution of the STN neuronal electrical activity (Fig. 3) and is performed at 0.5–1 mm steps beginning from 10 mm above the planned target to the ventral border of the STN (Camalier et al., 2014; Lozano et al., 2018). In order to optimize the electrophysiological recordings, MER is preferably performed in awake patients under local/-regional anesthesia (Telkes et al., 2016), however, sometimes sedation or general anesthesia is needed, affecting MER (Bos et al., 2019). For a precise electrophysiological mapping of the STN, MER requires either single sequential microelectrode or simultaneous multiple microelectrode insertion (Bjerknes et al., 2018). The latter offers more detailed information on the electrophysiological boundaries of the STN (three--dimensional mapping), and hence, a potentially better intraoperative guidance (Bjerknes et al., 2018; Kocabicak et al., 2015). Importantly, an accurate detection of the STN relies on a proper recognition of the electrophysiological profile of its sensorimotor part, thus, being one of the key factors determining the therapeutic outcome after the surgery. As the electrode enters along its trajectory through the thalamus, zona incerta and substantia nigra (SNr), distinct and region-specific neurophysiological activity patterns are encountered (Seifried et al., 2012; Wong et al., 2009). Therefore, the electrophysiological activity confined to the STN holds a different pattern as from neurons firing beyond its anatomical boundaries (Bour et al., 2010).

During online intraoperative MER, two features of the electrophysiological activity are visually analyzed – spiking activity (firing rate and pattern) and the background activity (Fig. 3) (Camalier et al., 2014). Spikes represent the action potentials of one or more neighboring neurons located in proximity to the electrode, while the background activity arises from the activity of the surrounding neurons. Typically, the amplitude of a spike ranges from 70 to 150 μV and the amplitude of the background activity ranges from 2 to 6 μV. The sensorimotor region of the STN (its dorsolateral part) is identified by a typical neuronal firing pattern – high spiking (high firing rate) and background activity (neuronal "hash") (Bour et al., 2010; Wong et al., 2009). Approaching the lower (ventral) border is marked by the disappearance of this characteristic STN activity pattern (Seifried et al., 2012). Along the longitudinal (dorsoventral) axis of the STN, an electrophysiological gradient is discernible: the dorsal sensorimotor part of the STN is dominated by the presence of bursty or oscillatory activity patterns, whereas the ventral STN predominantly exhibits irregular firing patterns (Seifried et al., 2012). As the microelectrode reaches the SNr, a pattern similar to that of the STN is observed, which consists of high firing rates of single neuronal units with smaller amplitudes and relatively low baseline activity (Camalier et al., 2014).

The analysis of MER can be performed by online real-time implementation of automated techniques based on machine learning algorithms (Karthick et al., 2019; Kostoglou et al., 2016; Wan et al., 2019); this approach can potentially reduce the intraoperative time and subjectivity of the neurophysiological expertise (Telkes et al., 2016). The following parameters are proposed as quantitative measures that can aid in electrophysiological STN mapping derived from online or offline (postoperative) analysis of acquired raw MER data: compound firing rate (number of spikes per second), spike fraction, interspike interval, burst index, absolute amplitude of background activity, power spectral density, root mean square of the signal, etc. (Wan et al., 2019; Wong et al., 2009). An elevation in multi-unit background activity of high frequency (>500 Hz) (Przybyszewski et al., 2016), root mean square of the signal indices (Danish et al., 2008), beta band (13–30 Hz) and gamma band (31–100 Hz) indices (Cagnan et al., 2011) is observed when the electrode is located within the STN borders. The entry into the STN is predicted with high accuracy by an increase in the root mean square of the signal (Cagnan et al., 2011; Telkes et al., 2016). The beta band activity derived from MER indicates an optimal STN location (Michmizos et al., 2014), predicts the optimal track for the proper DBS contact placement within the sensorimotor area (Telkes et al., 2016) and correlates with the postoperative motor improvement (Michmizos et al., 2014).

Parameters of neuronal activity evaluated for MER automation algorithms delineate the STN borders and its adjacent structures with high accuracy and relatively small error rates. A multi-feature approach integrating several properties of the spikes and background activity (Fig. 3) (e.g., increased firing rate, oscillatory activity) can be used for more accurate prediction of the implantation site and depth and, thus, optimize the electrophysiology-assisted intraoperative mapping procedure of the STN (Geng et al., 2018). This approach would allow a more personalized approach for each patient case that accounts for the differences in neurophysiological activity between the subcortical structures and improves the outcome of functional localization.

After the correct target for stimulation is identified and the stimulation parameters (amplitude, frequency, and pulse width) are optimized with intraoperative microelectrodes, these are replaced with the macroelectrode for chronic stimulation. In some centers, electrophysiological explorations even with chronic electrodes are being practiced (Benabid et al., 2009). Stimulation with microelectrodes differs from the macroelectrode stimulation in several ways: microelectrode stimulation provides more localized modulation of the targeted structure, it causes less tissue damage and induces a more pronounced activation of neural tissue (Paffi et al., 2013).

3.2. Beta oscillations as electrophysiological correlates of motor activity

Beta frequency (13–35 Hz) oscillatory activity is a rhythmic representation of neuronal synchronization across the cortico-basal ganglia circuitry that appears as relatively short-lasting phasic bursts under physiological conditions (Fig. 3). The activity of beta oscillations depends upon the level of dopaminergic activity and serves as means to modulate the constancy of the current motor state (Little and Brown, 2014). Much of the insights on the nature and significance of beta oscillations in PD patients were gained from local field potential (LFP) recordings from implanted electrodes (mainly from temporarily externalized electrodes). Bursts of beta activity within LFPs recorded from the STN in PD patients at rest are time-locked to the firing neuronal populations (Little and Brown, 2014), and show a robust stability over months (Neumann et al., 2017) and years after the electrode implantation (Giannicola et al., 2012).

As ascertained by STN LFP studies in PD patients, the exaggerated resting beta synchrony within cortico-basal ganglia loops is tightly linked

to the severity of motor impairment (rigidity, bradykinesia) (Neumann et al., 2016, 2017, 2019; Oswal et al., 2013, 2016; Tinkhauser et al., 2017a). PD patients exhibit beta bursts of longer duration during states off dopaminergic medication compared to the same patients on levodopa treatment and stimulation of the STN (Tinkhauser et al., 2017b, 2018). The role of pathologically elevated beta synchrony was previously suggested by stimulation of the STN in the low beta frequency range that resulted in significant slowing of movements in PD patients (Timmermann and Florin, 2012). Exaggerated beta synchrony is not confined only to the STN but exceeds its anatomical borders and captures the entire cortico-basal ganglia network (Litvak et al., 2011; Tinkhauser et al., 2019), thus disclosing the existence of a beta band network between the STN and motor/premotor cortical regions (Hirschmann et al., 2011; Muthuraman et al., 2018; Oswal et al., 2013). The amplitude of beta oscillations in the STN increases as the beta bursts increase in their duration, consistent with progressively increasing synchronization that compromises the information coding capacity across the motor loops and, hence, the movement performance (Brittain et al., 2014). Beta bursts with shorter duration negatively correlate, while beta bursts with longer duration positively correlate with the motor impairment when PD patients are off stimulation (Tinkhauser et al., 2017b).

The clinically effective high frequency (130 Hz) DBS of the STN suppresses the beta hypersynchrony both locally (within the STN) and narrowly (in spatially and spectrally distinct STN-cortical networks, including mesial premotor and supplementary motor regions) (Muthuraman et al., 2018; Oswal et al., 2016). Of particular relevance is the local suppression of the low beta band (13–20 Hz), which is associated with motor improvement. On the contrary, the suppression of STN-cortical motor regions coupling across the entire beta band does not associates with the clinical outcome (Oswal et al., 2016). This suppression of beta burst's amplitude is achieved differentially by conventional and adaptive DBS (Meidahl et al., 2017; Tinkhauser et al., 2017a).

Adaptive DBS alters both the distribution and frequency (number of cycles/second) of beta bursts by promoting a shift from long beta bursts to shorter bursts and increasing the occurrence of shorter bursts. Conventional DBS alters neither the frequency of beta bursts nor the distribution of short- and long-lasting bursts; instead, the reduction in global beta activity is achieved by suppression of the amplitudes of all beta bursts (Tinkhauser et al., 2017a). As long-lasting beta bursts, indicative of enhanced synchronization, negatively impact motor performance it is plausible that short-lasting beta bursts appear to be physiologically normal for information processing during executive motor skills. The extent of beta activity suppression by clinically effective high-frequency DBS of the STN correlates with the clinical improvement in motor performance (axial and limb motor function) expressed as a decrease in the Unified Parkinson's Disease Rating Scale (UPDRS) part III score (Little et al., 2013a, 2016; Oswal et al., 2016; Whitmer et al., 2012). At first glance it might appear that short-lasting beta bursts carry only a beneficial effect, however, even short-lasting beta bursts can negatively affect motor performance when they occur in the time window before the movement initiation (discussed below).

As described above, the exaggerated beta activity dominates the resting state cortico-basal ganglia motor loops in PD. But how do the beta bursts behave before and during motor task performance and what are their effects on the accuracy of performed movement? In healthy humans, beta oscillations show a systematic and notable reduction of mean beta power before and during a voluntary movement (Fischer et al., 2016; Torrecillos et al., 2015). In PD patients the beta decrease becomes assymetric between the two primary sensorimotor regions (Meziane et al., 2015). A pattern of sustained suppression of beta power below its level at rest is also recognized in the cortico-basal ganglia networks of PD patients while performing continuous non-isometric movements (Bichsel et al., 2018). Moreover, when PD patients perform a repetitive motor task, despite suppression of beta bursts they are still detectable during the movement, but show a lower amplitude and shorter duration (Lofredi et al., 2019). Beta band activity is modulated differently during voluntary movements of upper and lower limbs with greater involvement of higher (24–31 Hz) beta frequency for lower limbs, equally on contra- and ipsilateral sides (Tinkhauser et al., 2019). Several task-based motor studies demonstrate that the STN beta bursts occurring before and during movement are associated with measurable changes in motor performance (Fischer et al., 2018; Lofredi et al., 2019; Torrecillos et al., 2018). Beta bursts (including short-lasting beta bursts) occurring in the time window immediately prior the movement onset reduce the peak velocity of that movement. This negative effect on the movement is amplified by the amplitude of the burst (Torrecillos et al., 2018). Additionally, movement velocity progressively decreases during continuous movement in PD patients and the beta burst duration (defined as the percentage of time in which the beta band power is above the same band power at rest) predicts the velocity decrement of bradykinetic movement (Lofredi et al., 2019). This slowing of movements is related to the cumulative effect of multiple bursts occurring at short intervals before the movement onset (Tinkhauser et al., 2020). The deleterious effect of the recent multiple bursts on motor performance is enhanced by the engagement of distributed basal ganglia networks (Tinkhauser et al., 2020). Altogether, these data point towards the fact that not only the duration and timing of beta bursts but also their recent history prior to the movement initiation can aggravate the motor impairment in PD, further confirming that the modulation of beta bursts might serve to improve the motor performance.

Thanks to studies investigating LFP activity (Fig. 3) on basal ganglia, beta bursts have emerged as a reliable marker of cortico-basal ganglia circuit hypersynchrony and as neurophysiological correlates of motor impairment that have been incorporated into experimental closed-loop neuromodulatory devices for PD patients.

3.3. *Dynamic time- and space-dependent properties of beta oscillations*

In PD, the level of beta activity in cortico-basal ganglia circuits is dynamic, fluctuating over time with variations in the dopaminergic pool, as a response to salient internal and external cues (Jenkinson and Brown, 2011; Little et al., 2013b). Investigating the dynamic nature of beta synchronization in a time- and space-dependent manner within cortico-subthalamic networks is crucial for both understanding its role and searching for efficient therapeutic ways to suppress this synchrony.

The time course of cortical and basal ganglia synchronization follows that of the cortical beta burst amplitude at the level of neuronal ensembles and single neurons (Cagnan et al., 2019). The onset, peak, and offset of cortical beta bursts relate to neuron-specific ways of spiking, depending on the cortical phase. Temporal evolution of synchronization and oscillations in basal ganglia neuronal populations during cortical beta bursts are underpinned by the precise phase relationships of specific populations of neurons to cortical beta oscillations (Cagnan et al., 2019). Early alignment of cortical and basal ganglia activity provides the preparatory conditions through which beta oscillations are amplified and propagated across the networks (Cagnan et al., 2019). The time course of bilateral cortical synchronization over motor cortex strongly correlates with the time course of spiking unit–LFP synchronization in the STN, whereas, the time course of cortical synchronization over frontal regions correlates weaker with the time course of basal ganglia synchronization (Ahn et al., 2015). Dynamically elevated local synchronization within the STN and phasic coupling across the motor network is expressed in terms of burst overlapping between STN and cortex and between bilateral STN, which increases with the duration of beta bursts (Tinkhauser et al., 2018). Pathologically prolonged beta bursts do not only involve local synchronization within the basal ganglia-thalamocortical circuit but also dynamic long-range synchronization in terms of amplitude correlation and phase synchrony (Tinkhauser et al., 2018).

The properties of beta oscillations show temporal dynamics depending on dopaminergic medication. In PD patients with electrodes implanted in STN, during rest, the percentage of shorter beta bursts is higher during ON levodopa compared to OFF levodopa conditions, while

the percentage of longer bursts follows the opposite response. Similarly, the amplitude and duration of beta bursts are higher before compared to after administration of levodopa (Tinkhauser et al., 2017b). During movements (joystick movements) the frequency and duration of beta bursts are substantially attenuated in the OFF levodopa condition, bringing beta burst characteristics more in line with those seen in the ON levodopa condition (Tinkhauser et al., 2017b). Periods of high amplitude beta activity substantially overlap across the hemispheres during both ON and OFF levodopa conditions, indicating a coherence between left and right STN. A neurofeedback training allows PD patients to volitionally modulate the average beta power and to canalize the temporal dynamics of beta oscillations in STN LFPs in the desired direction with reduced incidence of beta bursts per unit time and reduced average beta burst duration within the STN (He et al., 2019a, 2019b). The neurofeedback paradigms also lead to reduced coherence (synchrony) between the STN and ipsilateral motor cortex that results in improved movement initialization.

Exploring the temporal variations and topographic distribution of beta oscillations is a key feature of current experimental closed-loop DBS approaches in PD (Neumann et al., 2019).

3.4. Phase-amplitude coupling from simultaneous multi-site recordings

Behavioral motor acts are mediated by evolving patterns of neural oscillations through phase, amplitude and phase-amplitude coupling (PAC), which span over distributed subcortical and cortical brain regions and across distinct frequency bands (Combrisson et al., 2017). PAC represents a cross-spectral measure that quantifies the interaction between the oscillations, where the phase of a low frequency oscillation is coupled to the amplitude of a higher frequency one (Fig. 3). By carrying important information about the underlying neural activity, PAC is considered to play a key role in neuronal encoding and information processing (Sanders, 2016). Computational models of synchronized single-cell bursting produce PAC that closely resembles the PAC detected in LFP recordings of PD patients (Sanders, 2016). Further systematic investigation on the nature of PAC in LFPs picked up from STN of PD patients uncovered the mechanisms driving the increased PAC in PD. Within STN, the phase of beta frequency is coupled to the amplitude of high frequency oscillations (HFO, 150–400 Hz) (Meidahl et al., 2019; Shreve et al., 2017; van Wijk et al., 2016), which relates to the firing rate and pattern of single STN neurons (Meidahl et al., 2019); lower HFO frequencies (<270 Hz) are coupled with the phase of low beta frequencies (Shreve et al., 2017). PAC within the STN LFPs is higher during the beta bursts, progressively increasing with the duration of beta bursts (enhanced beta synchronization), suggesting that increased PAC within the STN is driven by spiking activity locked to the hypersynchronous beta oscillatory network (Meidahl et al., 2019). The resting state spectral power in alpha/beta frequency band and PAC are stronger in the STN of the hemisphere contralateral to the clinically more affected side, and tremor attenuates the alpha/beta band oscillations and the power in the resting state beta peak (Shreve et al., 2017).

Exaggerated PAC extends beyond the STN and is recognizable over the M1 cortex. In the LFPs recorded from subdural electrocorticography on M1 cortex, the phase of beta band frequency (13–30 Hz) is excessively coupled to the amplitude of broad band gamma activity (50–200 Hz) (De Hemptinne et al., 2013). However, this aberrant PAC is not confined strictly only to STN or M1 cortex but a cross-regional coupling occurs. The amplitude of HFO (150–400 Hz) in the STN is coupled with the phase of beta oscillations in M1 cortex and is dominant in the high-beta range (~25 Hz), as it is evidenced by simultaneous STN LFP recording and magnetoencephalography (van Wijk et al., 2016). Similarly, aberrant cross-frequency coupling between the phase of the STN beta rhythm and the gamma power (50–200 Hz) in the M1 cortex is observed (De Hemptinne et al., 2013). Excessive coupling within the M1 cortex is likely to represent the cortical manifestation of the excessive synchronization across the motor cortico-basal ganglia circuitry. The latter interferes with the timing of neuronal activity and compromises motor function in PD patients: at rest and during preparation for movement, PAC is associated with akinesia and rigidity, whereas during execution of the movement PAC is associated with bradykinesia (De Hemptinne et al., 2015).

Beta band power and PAC recorded from the STN LFPs in PD patients correlate positively with the severity of motor impairment (Meidahl et al., 2019; van Wijk et al., 2016) and this effect is more pronounced within the low beta range (van Wijk et al., 2016). One of the key questions is how DBS of the STN modulates the PAC and whether this modulation improves the motor performance. Therapeutic DBS reversibly suppresses the exaggerated cortical PAC during rest and during motor task (reaching movement task) by decoupling the high-frequency activity from low-frequency rhythms (De Hemptinne et al., 2013, 2015). During rest and movement DBS does not instantly modulate beta or broadband activity but rather attenuates the interaction between the two frequency bands (De Hemptinne et al., 2015); the suppression effect on PAC lasts for 4–5 min after offset of stimulation (De Hemptinne et al., 2013).

Along with beta bursts, PAC has been suggested as a potential feedback signal for experimental implantable closed-loop DBS devices to further improve its therapeutic efficacy (Gunduz et al., 2015; Meidahl et al., 2019; Neumann et al., 2019). However, data obtained on PAC are commonly received from offline processing of invasive LFP recordings (STN, electrocorticography), while the adaptable DBS pulse delivery platforms would benefit considerably from the real-time analysis of PAC (Alexandre et al., 2018; Lu et al., 2018) from non-invasive electrophysiological techniques, such as scalp EEG (Fig. 3) (Rajagopalan et al., 2019; Swann et al., 2015).

3.5. Oscillatory network effects of DBS on gait kinematic readouts

Gait is an automatic sequence of steady-state stepping movements associated with postural reflexes, limb coordination, body alignment and optimal muscle tone, mediated by integrating sensori-motor inputs at multiple levels within the locomotor gait control network. Gait impairment like freezing of gait (FOG) or postural instability and gait dysfunction (PIGD) is frequently encountered in PD patients and is often refractory to current treatment options. To track the effects of DBS on gait-related oscillatory activity in PD patients, motion studies are conducted by simultaneous recordings of LFPs from the implanted sensing neurostimulator (Neumann et al., 2019; Ramirez-Zamora et al., 2019), peripheral signals from sensors (accelerometer, gyroscope, magnetometer) and kinematic parameters (stride length, stride velocity, stride time, swing time, cadence, stance phase duration) (Fig. 3) (Rizzone et al., 2017).

In PD patients without FOG, both bicycling and walking under OFF stimulation condition led to drops in the relative power of high beta frequency range (20–30 Hz) in bilateral STN (Storzer et al., 2017) but without recognizable attenuation in other frequency bands or under the ON stimulation condition (Hell et al., 2018). Likewise, during gait, the life-time and amplitudes of beta bursts in the high beta band decrease across bilateral STN (Hell et al., 2018). While performing stepping cycles, beta oscillatory activity is modulated relative to each step, alternating between the left and right STN: beta oscillations are suppressed after ipsilateral heel strikes, when the contralateral foot has to be raised, and reappear after contralateral heel strikes, when the contralateral foot rests on the floor (Fischer et al., 2018). Modulation of beta power during stepping resembles the modulation during free walking without concurrent modulations in gamma band (Fischer et al., 2018).

DBS of the STN attenuates beta power (Hell et al., 2018) and shortens the pathologically prolonged beta bursts (Anidi et al., 2018; Scholten et al., 2017), thereby, improving the spatial and temporal kinematic measures of gait (Anidi et al., 2018), whereas, normal gait parameters accompanied by shorter bursts are not altered by DBS (Anidi et al., 2018). Stride length and velocity improve in a similar manner during unilateral and bilateral DBS of the STN with a clearer benefit with the stimulation contralateral to the less affected side (Lizarraga et al., 2016). Similarly,

the unilateral stimulation of the 'dominant' STN is almost as efficacious as bilateral STN stimulation in improving gait kinematics (gait speed, stride length) (Rizzone et al., 2017). Distinct effects on spatial and temporal kinematics of gait are achieved by monostimulation of the STN and SNr due to differential network effects of DBS-targeted structures within the locomotor network (Scholten et al., 2017). While stimulation of STN improves both spatial (stride length) and temporal (swing time symmetry) gait parameters, stimulation of the SNr impacts only the latter, likely, by modulating the pedunculopontine nucleus of the mesencephalic locomotor region (Scholten et al., 2017; Weiss et al., 2015). DBS of the STN as well improves the performance of turning kinematics (Lohnes and Earhart, 2012) and postural misalignment (Schlenstedt et al., 2019, 2020); the differences in turning strategies among PD patients (Gavriliuc et al., 2019) should be considered while assessing the effects of DBS on turning kinematics.

Combining the electrophysiological recordings, kinematic, kinetic and other sensor measurements (Fig. 3), might aid the depiction of gait-related oscillatory network responses to DBS and personalize the DBS algorithms according to the phenotype of gait impairment.

4. Future perspectives

Despite the capability of DBS to modulate neural activity, in order to further validate its clinical efficacy and safety, larger controlled trials are required in relation to an advanced model of surrounding anatomy and connectivity. To this end, modern imaging has opened new opportunities for the improvement of stereotactic and functional neurosurgery in movement and neuropsychiatric disorders.

A further step for the efficacy of DBS is related to surgery settings, which critically depend on the preoperative selection of suitable candidates, the stimulation volume of a defined target, and the appropriate individualized positioning within target brain regions. This has been advanced thanks to the consistently evidenced relationship between DBS efficacy and the correct positioning of the electrodes, also improved by optimal parameter setting selection to target particular fiber pathways and modulate the appropriate brain circuits. But there is still work to be done.

Neuroimaging and neuroelectrophysiological studies have evidenced that chronic high-frequency stimulation by DBS induces a number of neuroplastic changes, including acute plasticity/reorganization of the brain that can propagate along anatomical projections on the long-term, however, the exact underlying mechanisms of action of DBS remain still elusive. Moreover, some effects of DBS are not yet fully understood. For example: i) the mechanisms that make patients irresponsive to DBS, ii) the reduced or absent responsivity of certain symptoms to DBS (e.g. freezing of gait in PD or speech and swallowing abnormalities that are less responsive than other dystonic symptoms), or iii) the present adverse effects. For instance, in some disorders DBS has almost immediate effects (particularly PD), whereas DBS in other diseases (e.g., dystonia) usually takes weeks to months to achieve clinically significant improvement. Moreover, DBS also presents certain paradoxical or adverse effects, including movement disorders induced by DBS, such as cases of dystonia in PD or cases of Parkinsonism in dystonia. Clarification on these topics may facilitate application of DBS to further medical conditions.

Because of the low number of existing cases, there is still uncertainty about indicating DBS for medical conditions other than PD, dystonia and ET. In particular, questions remain about the ideal target and it is still unclear whether there is an advantage to simultaneously stimulating different targets. On the patient selection side, appropriate candidates for DBS may be characterized by their most debilitating symptoms specific to the clinical syndrome. Further clinical considerations may include that the main symptoms cannot be handled by other therapies and that the target brain region for DBS does not endure structural pathology on MRI. Therefore, differential indications and efficacy need to be explored on the basis of neuroimaging.

The optimal DBS is still challenging, because excessive current can spread into close neighboring fiber pathways causing unwanted side effects. However, neuroimaging is opening new opportunities to advance the understanding of DBS mechanisms and enhance therapeutic outcomes. The complementary application of these data and newer MRI techniques should aim at fulfilling the need to deliver individualized DBS and may help to counteract unwanted effects and overcome current limits in predicting the response profiles.

Existing evidence from combined DBS-electrophysiology studies in movement disorders suggests that abnormal oscillatory activity within cortico-basal ganglia networks may be both causally and quantitatively incriminated in generating motor impairment (Bočková and Rektor, 2019; Guridi and Alegre, 2017; Neumann et al., 2019). These studies demonstrate how the electrical properties of local neural structures and interconnected networks obtained by the aid of DBS advance our knowledge of the underlying dynamic processes and lead to clinically effective therapeutic interventions. However, extensive work remains to be carried out in order to explore, optimize and implement the wide range of DBS stimulation parameters and algorithms to modulate the transient brain states based on functional characterization of oscillatory networks.

Despite the evident value of precise electrophysiology-assisted mapping of DBS targets, it should be noted that neither technique can fully substitute the intraoperative macroelectrode stimulation and clinical testing by an experienced neurologist. This is important for two reasons: first, identification of the neuroanatomical target is of utmost importance for rendering optimal motor benefit of stimulation, and, second, optimal positioning of the DBS lead is also critical to prevent unwanted side effects after DBS (Allert et al., 2018). As employment of MRI-guided localization of DBS targets is gaining traction and overtaking neurophysiological mapping, one possibility to boost the latter is the application of a network mapping approach, rather than mapping of a single structure that will translate into improved clinical outcomes of DBS (Ramirez-Zamora et al., 2019). This idea comes from proof-of-principle studies specifically focusing on dynamic oscillatory activity demonstrating that separate networks have distinct therapeutic responses to differential DBS stimulation (Guridi and Alegre, 2017; Neumann et al., 2019). Another scenario is the implementation of closed-loop DBS platforms with cortical sensors (e.g., electrocorticography) (Fig. 3) that will require intraoperative functional connectivity mapping of the target network for an optimal placement of stimulating and sensing electrodes (Neumann et al., 2019; Parastarfeizabadi and Kouzani, 2017; Ramirez-Zamora et al., 2019).

Mapping the oscillatory network effects elicited by DBS with subsequent inferring of electrophysiological signatures of abnormal circuit signals, as biomarkers, is garnering significant attention. These electrophysiological markers are particularly relevant in identifying the dynamic patterns of the entire networks involved and driving forward our understanding on the interaction between the DBS action and the response of the targeted malfunctioned circuits at multiple levels (Krack et al., 2019). Recognizing these patterns depending on the dynamic states of the brain can further inform on the nature of cortico-basal ganglia network disruptions, their fluctuations over time and under influence of chronic DBS delivery (Bočková and Rektor, 2019; McMackin et al., 2019; Neumann et al., 2019). However, employing a single, unidimensional electrophysiological marker might be only partly useful and strategies to integrate several neurophysiological features into multidimensional markers (Fig. 3) in real-time to control disabling symptoms are evolving (McMackin et al., 2019). The efforts in identifying the electrophysiological markers should be directed to the delivery of stimulation algorithms that are optimized to interfere with pathological circuits in a disease-and phenotype-specific manner (Krack et al., 2019). However, plenty of open questions remain to be addressed in future empirical and modelling studies.

Regarding the highlighted need for large controlled trials to validate new approaches for DBS, it is noteworthy that there is still high variability in DBS outcome across patients. Even when we do not know yet

the mechanisms of this, this variability is likely related to a considerable variability in lead placement (Horn et al., 2017b; Menchon et al., 2019; Pauls et al., 2017; Zittel et al., 2020). Cf. *Causal interrogations of DBS with neuroimaging* for an extended discussion on the DBS electrode locations and clinical outcomes.

DBS represents one of the major scientific and clinical breakthroughs in the era of high-precision and translational neuroscience. The field of DBS is constantly expanding with the development of new targeting techniques, imaging modalities, electrode, and pulse generator algorithms and stimulation paradigms that shape the contemporary scientific landscape and clinical environment (Bari et al., 2018; Krack et al., 2019; Lozano et al., 2019). These achievements in conjunction with advanced analytical tools and high-performance computational modeling for circuit-specific decoding embedded in neuromodulatory devices will facilitate the integration of DBS, neuroimaging, and electrophysiology for individualized network interrogation and targeted brain network modulation.

CRediT authorship contribution statement

Gabriel Gonzalez-Escamilla: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Muthuraman Muthuraman:** Conceptualization, Writing - original draft. **Dumitru Ciolac:** Writing - review & editing, Visualization. **Volker A. Coenen:** Writing - review & editing. **Alfons Schnitzler:** Writing - review & editing. **Sergiu Groppa:** Conceptualization, Writing - review & editing.

References

Ahn, S., Zauber, S.E., Worth, R.M., Witt, T., Rubchinsky, L.L., 2015. Interaction of synchronized dynamics in cortex and basal ganglia in Parkinson's disease. Eur. J. Neurosci. 42, 2164–2171.

Akram, H., Dayal, V., Mahlknecht, P., Georgiev, D., Hyam, J., Foltynie, T., Limousin, P., De Vita, E., Jahanshahi, M., Ashburner, J., Behrens, T., Hariz, M., Zrinzo, L., 2018. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. Neuroimage Clin. 18, 130–142.

Akram, H., Sotiropoulos, S.N., Jbabdi, S., Georgiev, D., Mahlknecht, P., Hyam, J., Foltynie, T., Limousin, P., De Vita, E., Jahanshahi, M., Hariz, M., Ashburner, J., Behrens, T., Zrinzo, L., 2017. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. Neuroimage 158, 332–345.

Alexandre, M., Luan, S., Mari, Z., Anderson, W.S., Salimpour, Y., Constandinou, T.G., Grand, L., 2018. Embedded phase-amplitude coupling based closed-loop platform for Parkinson's disease. In: 2018 IEEE Biomedical Circuits and Systems Conference (BioCAS). IEEE, pp. 1–4.

Allert, N., Cheeran, B., Deuschl, G., Barbe, M.T., Csoti, I., Ebke, M., Glaser, M., Kang, J.-S., Kelm, S., Krack, P., 2018. Postoperative rehabilitation after deep brain stimulation surgery for movement disorders. Clin. Neurophysiol. 129, 592–601.

Anidi, C., O'Day, J.J., Anderson, R.W., Afzal, M.F., Syrkin-Nikolau, J., Velisar, A., Bronte-Stewart, H.M., 2018. Neuromodulation targets pathological not physiological beta bursts during gait in Parkinson's disease. Neurobiol. Dis. 120, 107–117.

Ashkan, K., Rogers, P., Bergman, H., Ughratdar, I., 2017. Insights into the mechanisms of deep brain stimulation. Nat. Rev. Neurol. 13, 548–554.

Aviles-Olmos, I., Kefalopoulou, Z., Tripoliti, E., Candelario, J., Akram, H., Martinez-Torres, I., Jahanshahi, M., Foltynie, T., Hariz, M., Zrinzo, L., Limousin, P., 2014. Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. J. Neurol. Neurosurg. Psychiatry 85, 1419–1425.

Baldermann, J.C., Melzer, C., Zapf, A., Kohl, S., Timmermann, L., Tittgemeyer, M., Huys, D., Visser-Vandewalle, V., Kuhn, A.A., Horn, A., Kuhn, J., 2019. Connectivity profile predictive of effective deep brain stimulation in obsessive-compulsive disorder. Biol. Psychiatr. 85, 735–743.

Bari, A.A., Thum, J., Babayan, D., Lozano, A.M., 2018. Current and expected advances in deep brain stimulation for movement disorders. In: Current Concepts in Movement Disorder Management. Karger Publishers, pp. 222–229.

Benabid, A.L., Chabardes, S., Mitrofanis, J., Pollak, P., 2009. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol. 8, 67–81.

Bichsel, O., Gassert, R., Stieglitz, L., Uhl, M., Baumann-Vogel, H., Waldvogel, D., Baumann, C.R., Imbach, L.L., 2018. Functionally separated networks for self-paced and externally-cued motor execution in Parkinson's disease: evidence from deep brain recordings in humans. Neuroimage 177, 20–29.

Bjerknes, S., Toft, M., Konglund, A.E., Pham, U., Waage, T.R., Pedersen, L., Skjelland, M., Haraldsen, I., Andersson, S., Dietrichs, E., Skogseid, I.M., 2018. Multiple microelectrode recordings in STN-DBS surgery for Parkinson's disease: a randomized study. Mov. Disord. Clin. Pract. 5, 296–305.

Bočková, M., Rektor, I., 2019. Impairment of brain functions in Parkinson's disease reflected by alterations in neural connectivity in EEG studies: a viewpoint. Clin. Neurophysiol. 130, 239–247.

Bos, M.J., Sanchez, A.M.A., Smeets, A.Y., Bancone, R., Ackermans, L., Absalom, A.R., Buhre, W.F., Roberts, M.J., Janssen, M.L., 2019. Effect of anesthesia on microelectrode recordings during deep brain stimulation surgery in Tourette syndrome patients. Stereotact. Funct. Neurosurg. 97, 225–231.

Bot, M., Schuurman, P.R., Odekerken, V.J.J., Verhagen, R., Contarino, F.M., De Bie, R.M.A., van den Munckhof, P., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry 89, 493–498.

Bour, L.J., Contarino, M.F., Foncke, E.M., de Bie, R.M., van den Munckhof, P., Speelman, J.D., Schuurman, P.R., 2010. Long-term experience with intraoperative microrecording during DBS neurosurgery in STN and GPi. Acta Neurochir. 152, 2069–2077.

Brittain, J.S., Sharott, A., Brown, P., 2014. The highs and lows of beta activity in cortico-basal ganglia loops. Eur. J. Neurosci. 39, 1951–1959.

Burchiel, K.J., McCartney, S., Lee, A., Raslan, A.M., 2013. Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording Clinical article. J. Neurosurg. 119, 301–306.

Butson, C.R., Cooper, S.E., Henderson, J.M., Wolgamuth, B., McIntyre, C.C., 2011. Probabilistic analysis of activation volumes generated during deep brain stimulation. Neuroimage 54, 2096–2104.

Cagnan, H., Dolan, K., He, X., Contarino, M.F., Schuurman, R., van den Munckhof, P., Wadman, W.J., Bour, L., Martens, H.C., 2011. Automatic subthalamic nucleus detection from microelectrode recordings based on noise level and neuronal activity. J. Neural. Eng. 8, 046006.

Cagnan, H., Mallet, N., Moll, C.K., Gulberti, A., Holt, A.B., Westphal, M., Gerloff, C., Engel, A.K., Hamel, W., Magill, P.J., 2019. Temporal evolution of beta bursts in the parkinsonian cortical and basal ganglia network. Proc. Natl. Acad. Sci. Unit. States Am. 116, 16095–16104.

Calabrese, E., 2016. Diffusion tractography in deep brain stimulation surgery: a review. Front. Neuroanat. 10, 45.

Calabrese, E., Hickey, P., Hulette, C., Zhang, J., Parente, B., Lad, S.P., Johnson, G.A., 2015. Postmortem diffusion MRI of the human brainstem and thalamus for deep brain stimulator electrode localization. Hum. Brain Mapp. 36, 3167–3178.

Camalier, C.R., Konrad, P.E., Kao, C., Remple, M., Davis, T., Hedera, P., Phibbs, F., Molinari, A., Neimat, J., Gill, C., 2014. Methods for surgical targeting of the STN in early-stage Parkinson's disease. Front. Neurol. 5, 25.

Castrioto, A., Lhommee, E., Moro, E., Krack, P., 2014. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol. 13, 287–305.

Coenen, V.A., Madler, B., Schiffbauer, H., Urbach, H., Allert, N., 2011. Individual fiber anatomy of the subthalamic region revealed with diffusion tensor imaging: a concept to identify the deep brain stimulation target for tremor suppression. Neurosurgery 68, 1069–1075 discussion 1075-1066.

Coenen, V.A., Schlaepfer, T.E., Sajonz, B., Dobrossy, M., Kaller, C.P., Urbach, H., Reisert, M., 2020. Tractographic description of major subcortical projection pathways passing the anterior limb of the internal capsule. Corticopetal organization of networks relevant for psychiatric disorders. Neuroimage Clin. 25, 102165.

Combrisson, E., Perrone-Bertolotti, M., Soto, J.L., Alamian, G., Kahane, P., Lachaux, J.-P., Guillot, A., Jerbi, K., 2017. From intentions to actions: neural oscillations encode motor processes through phase, amplitude and phase-amplitude coupling. Neuroimage 147, 473–487.

Contarino, M.F., Bour, L.J., Verhagen, R., Lourens, M.A., de Bie, R.M., van den Munckhof, P., Schuurman, P.R., 2014. Directional steering: a novel approach to deep brain stimulation. Neurology 83, 1163–1169.

Corp, D.T., Joutsa, J., Darby, R.R., Delnooz, C.C.S., van de Warrenburg, B.P.C., Cooke, D., Prudente, C.N., Ren, J., Reich, M.M., Batla, A., Bhatia, K.P., Jinnah, H.A., Liu, H., Fox, M.D., 2019. Network localization of cervical dystonia based on causal brain lesions. Brain 142, 1660–1674.

Danish, S.F., Baltuch, G.H., Jaggi, J.L., Wong, S., 2008. Determination of subthalamic nucleus location by quantitative analysis of despiked background neural activity from microelectrode recordings obtained during deep brain stimulation surgery. J. Clin. Neurophysiol. 25, 98–103.

De Hemptinne, C., Ryapolova-Webb, E.S., Air, E.L., Garcia, P.A., Miller, K.J., Ojemann, J.G., Ostrem, J.L., Galifianakis, N.B., Starr, P.A., 2013. Exaggerated phase–amplitude coupling in the primary motor cortex in Parkinson disease. Proc. Natl. Acad. Sci. Unit. States Am. 110, 4780–4785.

De Hemptinne, C., Swann, N.C., Ostrem, J.L., Ryapolova-Webb, E.S., San Luciano, M., Galifianakis, N.B., Starr, P.A., 2015. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. Nat. Neurosci. 18, 779.

Dembek, T.A., Barbe, M.T., Astrom, M., Hoevels, M., Visser-Vandewalle, V., Fink, G.R., Timmermann, L., 2017. Probabilistic mapping of deep brain stimulation effects in essential tremor. Neuroimage Clin. 13, 164–173.

Duchin, Y., Shamir, R.R., Patriat, R., Kim, J., Vitek, J.L., Sapiro, G., Harel, N., 2018. Patient-specific anatomical model for deep brain stimulation based on 7 Tesla MRI. PLoS One 13, e0201469.

Elias, G.J.B., Giacobbe, P., Boutet, A., Germann, J., Beyn, M.E., Gramer, R.M., Pancholi, A., Joel, S.E., Lozano, A.M., 2020. Probing the circuitry of panic with deep brain stimulation: connectomic analysis and review of the literature. Brain Stimul. 13, 10–14.

Eross, L., Riley, J., Levy, E.I., Vakharia, K., 2020. Neuroimaging of deep brain stimulation. Neurol. Clin. 38, 201–214.

Ewert, S., Plettig, P., Li, N., Chakravarty, M.M., Collins, D.L., Herrington, T.M., Kuhn, A.A., Horn, A., 2018. Toward defining deep brain stimulation targets in MNI

space: a subcortical atlas based on multimodal MRI, histology and structural connectivity. Neuroimage 170, 271–282.
Fiechter, M., Nowacki, A., Oertel, M.F., Fichtner, J., Debove, I., Lachenmayer, M.L., Wiest, R., Bassetti, C.L., Raabe, A., Kaelin-Lang, A., Schupbach, M.W., Pollo, C., 2017. Deep brain stimulation for tremor: is there a common structure? Stereotact. Funct. Neurosurg. 95, 243–250.
Fischer, P., Chen, C.C., Chang, Y.-J., Yeh, C.-H., Pogosyan, A., Herz, D.M., Cheeran, B., Green, A.L., Aziz, T.Z., Hyam, J., 2018. Alternating modulation of subthalamic nucleus beta oscillations during stepping. J. Neurosci. 38, 5111–5121.
Fischer, P., Tan, H., Pogosyan, A., Brown, P., 2016. High post-movement parietal low-beta power during rhythmic tapping facilitates performance in a stop task. Eur. J. Neurosci. 44, 2202–2213.
Foltynie, T., Zrinzo, L., Martinez-Torres, I., Tripoliti, E., Petersen, E., Holl, E., Aviles-Olmos, I., Jahanshahi, M., Hariz, M., Limousin, P., 2011. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. J. Neurol. Neurosurg. Psychiatry 82, 358–363.
Forstmann, B.U., de Hollander, G., van Maanen, L., Alkemade, A., Keuken, M.C., 2016. Towards a mechanistic understanding of the human subcortex. Nat. Rev. Neurosci. 18, 57–65.
Fox, M.D., 2018. Mapping symptoms to brain networks with the human connectome. N. Engl. J. Med. 379, 2237–2245.
Frankemolle, A.M.M., Wu, J., Noecker, A.M., Voelcker-Rehage, C., Ho, J.C., Vitek, J.L., McIntyre, C.C., Alberts, J.L., 2010. Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. Brain 133, 746–761.
Gavriliuc, O., Paschen, S., Andrusca, A., Berg, D., Schlenstedt, C., Deuschl, G., 2019. Spin turns in advanced Parkinson's disease: a new clinical gait sign? Park. Relat. Disord. 69, 19–22.
Geng, X., Xu, X., Horn, A., Li, N., Ling, Z., Brown, P., Wang, S., 2018. Intra-operative characterisation of subthalamic oscillations in Parkinson's disease. Clin. Neurophysiol. 129, 1001–1010.
Giannicola, G., Rosa, M., Servello, D., Menghetti, C., Carrabba, G., Pacchetti, C., Zangaglia, R., Cogiamanian, F., Scelzo, E., Marceglia, S., 2012. Subthalamic local field potentials after seven-year deep brain stimulation in Parkinson's disease. Exp. Neurol. 237, 312–317.
Gonzalez-Escamilla, G., Muthuraman, M., Reich, M.M., Koirala, N., Riedel, C., Glaser, M., Lange, F., Deuschl, G., Volkmann, J., Groppa, S., 2019. Cortical network fingerprints predict deep brain stimulation outcome in dystonia. Mov. Disord. 34.
Gourisankar, A., Eisenstein, S.A., Trapp, N.T., Koller, J.M., Campbell, M.C., Ushe, M., Perlmutter, J.S., Hershey, T., Black, K.J., 2018. Mapping movement, mood, motivation and mentation in the subthalamic nucleus. Roy. Soc. Open Sci. 5, 171177.
Gradinaru, V., Mogri, M., Thompson, K.R., Henderson, J.M., Deisseroth, K., 2009. Optical deconstruction of parkinsonian neural circuitry. Science 324, 354–359.
Groppa, S., Herzog, J., Falk, D., Riedel, C., Deuschl, G., Volkmann, J., 2014. Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. Brain 137, 109–121.
Gunduz, A., Morita, H., Rossi, P.J., Allen, W.L., Alterman, R.L., Bronte-Stewart, H., Butson, C.R., Charles, D., Deckers, S., De Hemptinne, C., 2015. Proceedings of the second annual deep brain stimulation think tank: what's in the pipeline. Int. J. Neurosci. 125, 475–485.
Guridi, J., Alegre, M., 2017. Oscillatory activity in the basal ganglia and deep brain stimulation. Mov. Disord. 32, 64–69.
Hamani, C., Florence, G., Heinsen, H., Plantinga, B.R., Temel, Y., Uludag, K., Alho, E., Teixeira, M.J., Amaro, E., Fonoff, E.T., 2017. Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. eNeuro 4.
He, S., Mostofi, A., Pereira, E., Syed, E., Torrecillos, F., Tinkhauser, G., Fischer, P., Pogsyan, A., Ashkan, K., Hasegawa, H., 2019a. Neurofeedback linked suppression of subthalamic beta oscillations speeds up movement initialisation in Parkinsonian patients. bioRxiv 687582.
He, S., Syed, E., Torrecillos, F., Tinkhauser, G., Fischer, P., Pogosyan, A., Pereira, E., Ashkan, K., Hasegawa, H., Brown, P., 2019b. Beta oscillation-targeted neurofeedback training based on subthalamic LFPs in Parkinsonian patients. In: 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER). IEEE, pp. 81–84.
Hell, F., Plate, A., Mehrkens, J.H., Bötzel, K., 2018. Subthalamic oscillatory activity and connectivity during gait in Parkinson's disease. Neuroimage Clin. 19, 396–405.
Herrington, T.M., Cheng, J.J., Eskandar, E.N., 2016. Mechanisms of deep brain stimulation. J. Neurophysiol. 115, 19–38.
Hirschmann, J., Ozkurt, T.E., Butz, M., Homburger, M., Elben, S., Hartmann, C.J., Vesper, J., Wojtecki, L., Schnitzler, A., 2011. Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. Neuroimage 55, 1159–1168.
Horn, A., 2019. The impact of modern-day neuroimaging on the field of deep brain stimulation. Curr. Opin. Neurol. 32, 511–520.
Horn, A., Kuhn, A.A., Merkl, A., Shih, L., Alterman, R., Fox, M., 2017a. Probabilistic conversion of neurosurgical DBS electrode coordinates into MNI space. Neuroimage 150, 395–404.
Horn, A., Li, N., Dembek, T.A., Kappel, A., Boulay, C., Ewert, S., Tietze, A., Husch, A., Perera, T., Neumann, W.J., Reisert, M., Si, H., Oostenveld, R., Rorden, C., Yeh, F.C., Fang, Q., Herrington, T.M., Vorwerk, J., Kuhn, A.A., 2019. Lead-DBS v2: towards a comprehensive pipeline for deep brain stimulation imaging. Neuroimage 184, 293–316.
Horn, A., Reich, M., Vorwerk, J., Li, N., Wenzel, G., Fang, Q., Schmitz-Hubsch, T., Nickl, R., Kupsch, A., Volkmann, J., Kuhn, A.A., Fox, M.D., 2017b. Connectivity Predicts deep brain stimulation outcome in Parkinson disease. Ann. Neurol. 82, 67–78.
Irmen, F., Horn, A., Meder, D., Neumann, W.J., Plettig, P., Schneider, G.H., Siebner, H.R., Kuhn, A.A., 2019. Sensorimotor subthalamic stimulation restores risk-reward trade-off in Parkinson's disease. Mov. Disord. 34, 366–376.
Jakobs, M., Fomenko, A., Lozano, A.M., Kiening, K.L., 2019. Cellular, molecular, and clinical mechanisms of action of deep brain stimulation-a systematic review on established indications and outlook on future developments. EMBO Mol. Med. 11.
Jenkinson, N., Brown, P., 2011. New insights into the relationship between dopamine, beta oscillations and motor function. Trends Neurosci. 34, 611–618.
Kahan, J., Papadaki, A., White, M., Mancini, L., Yousry, T., Zrinzo, L., Limousin, P., Hariz, M., Foltynie, T., Thornton, J., 2015. The safety of using body-transmit MRI in patients with implanted deep brain stimulation devices. PLoS One 10, e0129077.
Karthick, P., Wan, K.R., Yuvaraj, R., See, A.A., King, N.K.K., Dauwels, J., 2019. Detection of subthalamic nucleus using time-frequency features of microelectrode recordings and random forest classifier. In: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE, pp. 4164–4167.
Kim, J., Duchin, Y., Shamir, R.R., Patriat, R., Vitek, J., Harel, N., Sapiro, G., 2019. Automatic localization of the subthalamic nucleus on patient-specific clinical MRI by incorporating 7 T MRI and machine learning: application in deep brain stimulation. Hum. Brain Mapp. 40, 679–698.
Kocabicak, E., Alptekin, O., Ackermans, L., Kubben, P., Kuijf, M., Kurt, E., Essselink, R., Temel, Y., 2015. Is there still need for microelectrode recording now the subthalamic nucleus can be well visualized with high field and ultrahigh MR imaging? Front. Integr. Neurosci. 9, 46.
Koirala, N., Fleischer, V., Glaser, M., Zeuner, K.E., Deuschl, G., Volkmann, J., Muthuraman, M., Groppa, S., 2018. Frontal lobe connectivity and network community characteristics are associated with the outcome of subthalamic nucleus deep brain stimulation in patients with Parkinson's disease. Brain Topogr. 31, 311–321.
Kostoglou, K., Michmizos, K.P., Stathis, P., Sakas, D., Nikita, K.S., Mitsis, G.D., 2016. Classification and prediction of clinical improvement in deep brain stimulation from intraoperative microelectrode recordings. IEEE (Inst. Electr. Electron. Eng.) Trans. Biomed. Eng. 64, 1123–1130.
Krack, P., Volkmann, J., Tinkhauser, G., Deuschl, G., 2019. Deep brain stimulation in movement disorders: from experimental surgery to evidence-based therapy. Mov. Disord. 34 (12), 1795–1810.
Kringelbach, M.L., Green, A.L., Aziz, T.Z., 2011. Balancing the brain: resting state networks and deep brain stimulation. Front. Integr. Neurosci. 5, 8.
Lai, H.Y., Younce, J.R., Albaugh, D.L., Kao, Y.C.J., Shih, Y.Y.I., 2014. Functional MRI reveals frequency-dependent responses during deep brain stimulation at the subthalamic nucleus or internal globus pallidus. Neuroimage 84, 11–18.
Lauro, P.M., Lee, S., Ahn, M., Barborica, A., Asaad, W.F., 2018. DBStar: an open-source tool kit for imaging analysis with patient-customized deep brain stimulation platforms. Stereotact. Funct. Neurosurg. 96, 13–21.
Lee, J.Y., Kim, J.W., Lee, J.-Y., Lim, Y.H., Kim, C., Kim, D.G., Jeon, B.S., Paek, S.H., 2010. Is MRI a reliable tool to locate the electrode after deep brain stimulation surgery? Comparison study of CT and MRI for the localization of electrodes after DBS. Acta Neurochir. 152, 2029–2036.
Lee, P.S., Richardson, R.M., 2017. Interventional MRI-guided deep brain stimulation lead implantation. Neurosurg. Clin. N. Am. 28, 535–544.
Lee, P.S., Weiner, G.M., Corson, D., Kappel, J., Chang, Y.F., Suski, V.R., Berman, S.B., Homayoun, H., Van Laar, A.D., Crammond, D.J., Richardson, R.M., 2018. Outcomes of interventional-MRI versus microelectrode recording-guided subthalamic deep brain stimulation. Front. Neurol. 9, 241.
Li, Z., Zhang, J.G., Ye, Y., Li, X., 2016. Review on factors affecting targeting accuracy of deep brain stimulation electrode implantation between 2001 and 2015. Stereotact. Funct. Neurosurg. 94, 351–362.
Little, S., Beudel, M., Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M., Neal, S., Cheeran, B., Cagnan, H., Gratwicke, J., 2016. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 87, 717–721.
Little, S., Brown, P., 2014. The functional role of beta oscillations in Parkinson's disease. Park. Relat. Disord. 20, S44–S48.
Little, S., Pogosyan, A., Neal, S., Zavala, B., Zrinzo, L., Hariz, M., Foltynie, T., Limousin, P., Ashkan, K., FitzGerald, J., 2013a. Adaptive deep brain stimulation in advanced Parkinson disease. Ann. Neurol. 74, 449–457.
Little, S., Tan, H., Anzak, A., Pogosyan, A., Kühn, A., Brown, P., 2013b. Bilateral functional connectivity of the basal ganglia in patients with Parkinson's disease and its modulation by dopaminergic treatment. PloS One 8.
Litvak, V., Jha, A., Eusebio, A., Oostenveld, R., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M.I., Friston, K., Brown, P., 2011. Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. Brain 134, 359–374.
Lizarraga, K.J., Jagid, J.R., Luca, C.C., 2016. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation on gait kinematics in Parkinson's disease: a randomized, blinded study. J. Neurol. 263, 1652–1656.
Lofredi, R., Tan, H., Neumann, W.-J., Yeh, C.-H., Schneider, G.-H., Kühn, A.A., Brown, P., 2019. Beta bursts during continuous movements accompany the velocity decrement in Parkinson's disease patients. Neurobiol. Dis. 127, 462–471.
Lohnes, C.A., Earhart, G.M., 2012. Effect of subthalamic deep brain stimulation on turning kinematics and related saccadic eye movements in Parkinson disease. Exp. Neurol. 236, 389–394.
Lozano, A.M., Lipsman, N., 2013. Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron 77, 406–424.
Lozano, A.M., Lipsman, N., Bergman, H., Brown, P., Chabardes, S., Chang, J.W., Matthews, K., McIntyre, C.C., Schlaepfer, T.E., Schulder, M., 2019. Deep brain stimulation: current challenges and future directions. Nat. Rev. Neurol. 15, 148–160.

Lozano, C.S., Ranjan, M., Boutet, A., Xu, D.S., Kucharczyk, W., Fasano, A., Lozano, A.M., 2018. Imaging alone versus microelectrode recording–guided targeting of the STN in patients with Parkinson's disease. J. Neurosurg. 130, 1847–1852.
Lu, D.C.-C., Boulay, C., Chan, A.D., Sachs, A.J., 2018. Realtime phase-amplitude coupling analysis of micro electrode recorded brain signals. PloS One 13.
McClelland 3rd, S., 2011. A cost analysis of intraoperative microelectrode recording during subthalamic stimulation for Parkinson's disease. Mov. Disord. 26, 1422–1427.
McMackin, R., Muthuraman, M., Groppa, S., Babiloni, C., Taylor, J.-P., Kiernan, M.C., Nasseroleslami, B., Hardiman, O., 2019. Measuring network disruption in neurodegenerative diseases: new approaches using signal analysis. J. Neurol. Neurosurg. Psychiatr. 90, 1011–1020.
Meidahl, A.C., Moll, C.K., van Wijk, B.C., Gulberti, A., Tinkhauser, G., Westphal, M., Engel, A.K., Hamel, W., Brown, P., Sharott, A., 2019. Synchronised spiking activity underlies phase amplitude coupling in the subthalamic nucleus of Parkinson's disease patients. Neurobiol. Dis. 127, 101–113.
Meidahl, A.C., Tinkhauser, G., Herz, D.M., Cagnan, H., Debarros, J., Brown, P., 2017. Adaptive deep brain stimulation for movement disorders: the long road to clinical therapy. Mov. Disord. 32, 810–819.
Menchon, J.M., Real, E., Alonso, P., Aparicio, M.A., Segalas, C., Plans, G., Luyten, L., Brunfaut, E., Matthijs, L., Raymakers, S., Bervoets, C., Higueras, A., Katati, M., Guerrero, J., Hurtado, M., Prieto, M., Stieglitz, L.H., Loffelholz, G., Walther, S., Pollo, C., Zurowski, B., Tronnier, V., Kordon, A., Gambini, O., Ranieri, R., Franzini, A., Messina, G., Radu-Djurfeldt, D., Schechtmann, G., Chen, L.L., Eitan, R., Israel, Z., Bergman, H., Brelje, T., Brionne, T.C., Conseil, A., Gielen, F., Schuepbach, M., Nuttin, B., Gabriels, L., 2019. A prospective international multi-center study on safety and efficacy of deep brain stimulation for resistant obsessive-compulsive disorder. Mol. Psychiatr. In press.
Meziane, H.B., Moisello, C., Perfetti, B., Kvint, S., Isaias, I.U., Quartarone, A., Di Rocco, A., Ghilardi, M.F., 2015. Movement preparation and bilateral modulation of beta activity in aging and Parkinson's disease. PLoS One 10, e0114817.
Michmizos, K.P., Frangou, P., Stathis, P., Sakas, D., Nikita, K.S., 2014. Beta-band frequency peaks inside the subthalamic nucleus as a biomarker for motor improvement after deep brain stimulation in Parkinson's disease. IEEE J. Biomed. Health Inf. 19, 174–180.
Middlebrooks, E.H., Tuna, I.S., Almeida, L., Grewal, S.S., Wong, J., Heckman, M.G., Lesser, E.R., Bredel, M., Foote, K.D., Okun, M.S., Holanda, V.M., 2018. Structural connectivity-based segmentation of the thalamus and prediction of tremor improvement following thalamic deep brain stimulation of the ventral intermediate nucleus. Neuroimage Clin. 20, 1266–1273.
Min, H.K., Hwang, S.C., Marsh, M.P., Kim, I., Knight, E., Striemer, B., Felmlee, J.P., Welker, K.M., Blaha, C.D., Chang, S.Y., Bennet, K.E., Lee, K.H., 2012. Deep brain stimulation induces BOLD activation in motor and non-motor networks: an fMRI comparison study of STN and EN/GPi DBS in large animals. Neuroimage 63, 1408–1420.
Min, H.K., Ross, E.K., Lee, K.H., Dennis, K., Han, S.R., Jeong, J.H., Marsh, M.P., Striemer, B., Felmlee, J.P., Lujan, J.L., Goerss, S., Duffy, P.S., Blaha, C.D., Chang, S.Y., Bennet, K.E., 2014. Subthalamic nucleus deep brain stimulation induces motor network BOLD activation: use of a high precision MRI guided stereotactic system for nonhuman primates. Brain Stimul. 7, 603–607.
Mirzadeh, Z., Chapple, K., Lambert, M., Dhall, R., Ponce, F.A., 2014. Validation of CT-MRI fusion for intraoperative assessment of stereotactic accuracy in DBS surgery. Mov. Disord. 29, 1788–1795.
Muthuraman, M., Deuschl, G., Koirala, N., Riedel, C., Volkmann, J., Groppa, S., 2017. Effects of DBS in parkinsonian patients depend on the structural integrity of frontal cortex. Sci. Rep. 7, 43571.
Muthuraman, M., Koirala, N., Ciolac, D., Pintea, B., Glaser, M., Groppa, S., Tamás, G., Groppa, S., 2018. Deep brain stimulation and L-DOPA therapy: concepts of action and clinical applications in Parkinson's disease. Front. Neurol. 9.
Neumann, W.-J., Staub-Bartelt, F., Horn, A., Schanda, J., Schneider, G.-H., Brown, P., Kühn, A.A., 2017. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. Clin. Neurophysiol. 128, 2286–2291.
Neumann, W.-J., Turner, R.S., Blankertz, B., Mitchell, T., Kühn, A.A., Richardson, R.M., 2019. Toward electrophysiology-based intelligent adaptive deep brain stimulation for movement disorders. Neurotherapeutics 16, 105–118.
Neumann, W.J., Degen, K., Schneider, G.H., Brücke, C., Huebl, J., Brown, P., Kühn, A.A., 2016. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. Mov. Disord. 31, 1748–1751.
Nguyen, T.A.K., Nowacki, A., Debove, I., Petermann, K., Tinkhauser, G., Wiest, R., Schupbach, M., Krack, P., Pollo, C., 2019. Directional stimulation of subthalamic nucleus sweet spot predicts clinical efficacy: proof of concept. Brain Stimul. 12, 1127–1134.
Ostrem, J.L., Ziman, N., Galifianakis, N.B., Starr, P.A., San Luciano, M., Katz, M., Racine, C.A., Martin, A.J., Markun, L.C., Larson, P.S., 2016. Clinical outcomes using ClearPoint interventional MRI for deep brain stimulation lead placement in Parkinson's disease. J. Neurosurg. 124, 908–916.
Oswal, A., Beudel, M., Zrinzo, L., Limousin, P., Hariz, M., Foltynie, T., Litvak, V., Brown, P., 2016. Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. Brain 139, 1482–1496.
Oswal, A., Brown, P., Litvak, V., 2013. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr. Opin. Neurol. 26, 662–670.
Paffi, A., Apollonio, F., Puxeddu, M., Parazzini, M., d'Inzeo, G., Ravazzani, P., Liberti, M., 2013. A numerical study to compare stimulations by intraoperative microelectrodes and chronic macroelectrodes in the DBS technique. BioMed Res. Int. 2013, 262739.
Paliwal, S., Mosley, P.E., Breakspear, M., Coyne, T., Silburn, P., Aponte, E., Mathys, C., Stephan, K.E., 2019. Subjective estimates of uncertainty during gambling and impulsivity after subthalamic deep brain stimulation for Parkinson's disease. Sci. Rep. 9.
Parastarfeizabadi, M., Kouzani, A.Z., 2017. Advances in closed-loop deep brain stimulation devices. J. NeuroEng. Rehabil. 14, 79.
Patel, S.R., Herrington, T.M., Sheth, S.A., Mian, M., Bick, S.K., Yang, J.C., Flaherty, A.W., Frank, M.J., Widge, A.S., Dougherty, D., Eskandar, E.N., 2018. Intermittent subthalamic nucleus deep brain stimulation induces risk-aversive behavior in human subjects. eLife 7.
Patriat, R., Cooper, S.E., Duchin, Y., Niederer, J., Lenglet, C., Aman, J., Park, M.C., Vitek, J.L., Harel, N., 2018. Individualized tractography-based parcellation of the globus pallidus pars interna using 7T MRI in movement disorder patients prior to DBS surgery. Neuroimage 178, 198–209.
Pauli, W.M., Nili, A.N., Tyszka, J.M., 2018. A high-resolution probabilistic in vivo atlas of human subcortical brain nuclei. Sci. Data 5, 180063.
Pauls, K.A.M., Krauss, J.K., Kampfer, C.E., Kuhn, A.A., Schrader, C., Sudmeyer, M., Allert, N., Benecke, R., Blahak, C., Boller, J.K., Fink, G.R., Fogel, W., Liebig, T., El Majdoub, F., Mahlknecht, P., Kessler, J., Mueller, J., Voges, J., Wittstock, M., Wolters, A., Maarouf, M., Moro, E., Volkmann, J., Bhatia, K.P., Timmermann, L., 2017. Causes of failure of pallidal deep brain stimulation in cases with pre-operative diagnosis of isolated dystonia. Park. Relat. Disord. 43, 38–48.
Pollo, C., Kaelin-Lang, A., Oertel, M.F., Stieglitz, L., Taub, E., Fuhr, P., Lozano, A.M., Raabe, A., Schupbach, M., 2014. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain 137, 2015–2026.
Pouratian, N., Zheng, Z., Bari, A.A., Behnke, E., Elias, W.J., DeSalles, A.A., 2011. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation. J. Neurosurg. 115, 995–1004.
Przybyszewski, A., Ravin, P., Pilitsis, J., Szymanski, A., Barborica, A., Novak, P., 2016. Multi-parametric analysis assists in STN localization in Parkinson's patients. J. Neurol. Sci. 366, 37–43.
Rajagopalan, S.S., Miller, A.M., de Hemptinne, C., San Luciano, M., Ostrem, J.L., Starr, P.A., 2019. Washout of chronic therapeutic deep brain stimulation increases cortical phase-amplitude coupling. Park. Relat. Disord. 66, 269–271.
Ramirez-Zamora, A., Giordano, J.J., Boyden, E.S., Gunduz, A., Starr, P.A., Sheth, S.A., McIntyre, C.C., Fox, M.D., Vitek, J.L., Vedam-Mai, V., 2019. Proceedings of the sixth deep brain stimulation think tank modulation of brain networks and application of advanced neuroimaging, neurophysiology, and optogenetics. Front. Neurosci. 13, 936.
Reich, M.M., Horn, A., Lange, F., Roothans, J., Paschen, S., Runge, J., Wodarg, F., Pozzi, N.G., Witt, K., Nickl, R.C., Soussand, L., Ewert, S., Maltese, V., Wittstock, M., Schneider, G.H., Coenen, V., Mahlknecht, P., Poewe, W., Eisner, W., Helmers, A.K., Matthies, C., Sturm, V., Isaias, I.U., Krauss, J.K., Kuhn, A.A., Deuschl, G., Volkmann, J., 2019. Probabilistic mapping of the antidystonic effect of pallidal neurostimulation: a multicentre imaging study. Brain 142, 1386–1398.
Rizzone, M.G., Ferrarin, M., Lanotte, M.M., Lopiano, L., Carpinella, I., 2017. The dominant-subthalamic nucleus phenomenon in bilateral deep brain stimulation for Parkinson's disease: evidence from a gait analysis study. Front. Neurol. 8, 575.
Rolston, J.D., Englot, D.J., Starr, P.A., Larson, P.S., 2016. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: analysis of multiple databases. Park. Relat. Disord. 33, 72–77.
Rozanski, V.E., da Silva, N.M., Ahmadi, S.A., Mehrkens, J., da Silva Cunha, J., Houde, J.C., Vollmar, C., Botzel, K., Descoteaux, M., 2017. The role of the pallidothalamic fibre tracts in deep brain stimulation for dystonia: a diffusion MRI tractography study. Hum. Brain Mapp. 38, 1224–1232.
Sanders, T.H., 2016. Phase-amplitude coupling, an indication of bursting in parkinsonism, is masked by periodic pulses. J. Neurophysiol. 115, 1587–1595.
Schlenstedt, C., Boße, K., Gavriliuc, O., Wolke, R., Granert, O., Deuschl, G., Margraf, N.G., 2020. Quantitative assessment of posture in healthy controls and patients with Parkinson's disease. Park. Relat. Disord. In press.
Schlenstedt, C., Gavriliuc, O., Boße, K., Wolke, R., Granert, O., Deuschl, G., Margraf, N.G., 2019. The effect of medication and deep brain stimulation on posture in Parkinson's disease. Front. Neurol. 10, 1254.
Scholten, M., Klemt, J., Heilbronn, M., Plewnia, C., Bloem, B.R., Bunjes, F., Krüger, R., Gharabaghi, A., Weiss, D., 2017. Effects of subthalamic and nigral stimulation on gait Kinematics in Parkinson's Disease. Front. Neurol. 8, 543.
Schupbach, W.M.M., Chabardes, S., Matthies, C., Pollo, C., Steigerwald, F., Timmermann, L., Visser Vandewalle, V., Volkmann, J., Schuurman, P.R., 2017. Directional leads for deep brain stimulation: opportunities and challenges. Mov. Disord. 32, 1371–1375.
Seifried, C., Weise, L., Hartmann, R., Gasser, T., Baudrexel, S., Szelényi, A., van de Loo, S., Steinmetz, H., Seifert, V., Roeper, J., 2012. Intraoperative microelectrode recording for the delineation of subthalamic nucleus topography in Parkinson's disease. Brain Stimul. 5, 378–387.
Shreve, L.A., Velisar, A., Malekmohammadi, M., Koop, M.M., Trager, M., Quinn, E.J., Hill, B.C., Blumenfeld, Z., Kilbane, C., Mantovani, A., 2017. Subthalamic oscillations and phase amplitude coupling are greater in the more affected hemisphere in Parkinson's disease. Clin. Neurophysiol. 128, 128–137.
Slotty, P.J., Kamp, M.A., Wille, C., Kinfe, T.M., Steiger, H.J., Vesper, J., 2012. The impact of brain shift in deep brain stimulation surgery: observation and obviation. Acta Neurochir. (Wien) 154, 2063–2068 discussion 2068.
Starr, P.A., Markun, L.C., Larson, P.S., Volz, M.M., Martin, A.J., Ostrem, J.L., 2014. Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. J. Neurosurg. Pediatr. 14, 400–408.

Storzer, L., Butz, M., Hirschmann, J., Abbasi, O., Gratkowski, M., Saupe, D., Vesper, J., Dalal, S.S., Schnitzler, A., 2017. Bicycling suppresses abnormal beta synchrony in the Parkinsonian basal ganglia. Ann. Neurol. 82, 592–601.

Su, J.H., Thomas, F.T., Kasoff, W.S., Tourdias, T., Choi, E.Y., Rutt, B.K., Saranathan, M., 2019. Thalamus Optimized Multi Atlas Segmentation (THOMAS): fast, fully automated segmentation of thalamic nuclei from structural MRI. Neuroimage 194, 272–282.

Swann, N.C., de Hemptinne, C., Aron, A.R., Ostrem, J.L., Knight, R.T., Starr, P.A., 2015. Elevated synchrony in Parkinson disease detected with electroencephalography. Ann. Neurol. 78, 742–750.

Sweet, J.A., Walter, B.L., Gunalan, K., Chaturvedi, A., McIntyre, C.C., Miller, J.P., 2014. Fiber tractography of the axonal pathways linking the basal ganglia and cerebellum in Parkinson disease: implications for targeting in deep brain stimulation. J. Neurosurg. 120, 988–996.

Tagliati, M., Jankovic, J., Pagan, F., Susatia, F., Isaias, I.U., Okun, M.S., National Parkinson Foundation, D.B.S.W.G., 2009. Safety of MRI in patients with implanted deep brain stimulation devices. Neuroimage 47 (Suppl. 2), T53–T57.

Telkes, I., Jimenez-Shahed, J., Viswanathan, A., Abosch, A., Ince, N.F., 2016. Prediction of STN-DBS electrode implantation track in Parkinson's disease by using local field potentials. Front. Neurosci. 10, 198.

Thani, N.B., Bala, A., Lind, C.R.P., 2012. Accuracy of magnetic resonance imaging-directed frame-based stereotaxis. Neurosurgery 70.

Timmermann, L., Florin, E., 2012. Parkinson's disease and pathological oscillatory activity: is the beta band the bad guy?—new lessons learned from low-frequency deep brain stimulation. Exp. Neurol. 233, 123–125.

Tinkhauser, G., Pogosyan, A., Little, S., Beudel, M., Herz, D.M., Tan, H., Brown, P., 2017a. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. Brain 140, 1053–1067.

Tinkhauser, G., Pogosyan, A., Tan, H., Herz, D.M., Kühn, A.A., Brown, P., 2017b. Beta burst dynamics in Parkinson's disease OFF and ON dopaminergic medication. Brain 140, 2968–2981.

Tinkhauser, G., Shah, S.A., Fischer, P., Peterman, K., Debove, I., Nygyuen, K., Nowacki, A., Torrecillos, F., Khawaldeh, S., Tan, H., 2019. Electrophysiological differences between upper and lower limb movements in the human subthalamic nucleus. Clin. Neurophysiol. 130, 727–738.

Tinkhauser, G., Torrecillos, F., Duclos, Y., Tan, H., Pogosyan, A., Fischer, P., Carron, R., Welter, M.-L., Karachi, C., Vandenberghe, W., 2018. Beta burst coupling across the motor circuit in Parkinson's disease. Neurobiol. Dis. 117, 217–225.

Tinkhauser, G., Torrecillos, F., Pogosyan, A., Mostofi, A., Bange, M., Fischer, P., Tan, H., Hasegawa, H., Glaser, M., Muthuraman, M., Groppa, S., Ashkan, K., Pereira, E.A., Brown, P., 2020. The cumulative effect of transient synchrony states on motor performance in Parkinson's disease. J. Neurosci. 40 (1), 1571–1580.

Torrecillos, F., Alayrangues, J., Kilavik, B.E., Malfait, N., 2015. Distinct modulations in sensorimotor postmovement and foreperiod β-band activities related to error salience processing and sensorimotor adaptation. J. Neurosci. 35, 12753–12765.

Torrecillos, F., Tinkhauser, G., Fischer, P., Green, A.L., Aziz, T.Z., Foltynie, T., Limousin, P., Zrinzo, L., Ashkan, K., Brown, P., 2018. Modulation of beta bursts in the subthalamic nucleus predicts motor performance. J. Neurosci. 38, 8905–8917.

Tripoliti, E., Zrinzo, L., Martinez-Torres, I., Frost, E., Pinto, S., Foltynie, T., Holl, E., Petersen, E., Roughton, M., Hariz, M.I., Limousin, P., 2011. Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. Neurology 76, 80–86.

van den Munckhof, P., Contarino, M.F., Bour, L.J., Speelman, J.D., de Bie, R.M., Schuurman, P.R., 2010. Postoperative curving and upward displacement of deep brain stimulation electrodes caused by brain shift. Neurosurgery 67, 49–53 discussion 53-44.

van Wijk, B.C., Beudel, M., Jha, A., Oswal, A., Foltynie, T., Hariz, M.I., Limousin, P., Zrinzo, L., Aziz, T.Z., Green, A.L., 2016. Subthalamic nucleus phase–amplitude coupling correlates with motor impairment in Parkinson's disease. Clin. Neurophysiol. 127, 2010–2019.

Vanegas-Arroyave, N., Lauro, P.M., Huang, L., Hallett, M., Horovitz, S.G., Zaghloul, K.A., Lungu, C., 2016. Tractography patterns of subthalamic nucleus deep brain stimulation. Brain 139, 1200–1210.

Wan, K.R., Maszczyk, T., See, A.A.Q., Dauwels, J., King, N.K.K., 2019. A review on microelectrode recording selection of features for machine learning in deep brain stimulation surgery for Parkinson's disease. Clin. Neurophysiol. 130, 145–154.

Weiss, P.H., Herzog, J., Pötter-Nerger, M., Falk, D., Herzog, H., Deuschl, G., Volkmann, J., Fink, G.R., 2015. Subthalamic nucleus stimulation improves parkinsonian gait via brainstem locomotor centers. Mov. Disord. 30, 1121–1125.

Whitmer, D., De Solages, C., Hill, B.C., Yu, H., Henderson, J.M., Bronte-Stewart, H., 2012. High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. Front. Hum. Neurosci. 6, 155.

Wodarg, F., Herzog, J., Reese, R., Falk, D., Pinsker, M.O., Steigerwald, F., Jansen, O., Deuschl, G., Mehdorn, H.M., Volkmann, J., 2012. Stimulation site within the MRI-defined STN predicts postoperative motor outcome. Mov. Disord. 27, 874–879.

Wong, S., Baltuch, G., Jaggi, J., Danish, S., 2009. Functional localization and visualization of the subthalamic nucleus from microelectrode recordings acquired during DBS surgery with unsupervised machine learning. J. Neural. Eng. 6, 026006.

Yelnik, J., Bardinet, E., Dormont, D., Malandain, G., Ourselin, S., Tande, D., Karachi, C., Ayache, N., Cornu, P., Agid, Y., 2007. A three-dimensional, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data. Neuroimage 34, 618–638.

Zittel, S., Hidding, U., Trumpfheller, M., Baltzer, V.L., Gulberti, A., Schaper, M., Biermann, M., Buhmann, C., Engel, A.K., Gerloff, C., Westphal, M., Stadler, J., Koppen, J.A., Potter-Nerger, M., Moll, C.K.E., Hamel, W., 2020. Pallidal lead placement in dystonia: leads of non-responders are contained within an anatomical range defined by responders. J. Neurol. 267, 1663–1671.

Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M.I., 2012. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J. Neurosurg. 116, 84–94.