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Clinical Implications of Local Field Potentials for Understanding and Treating Movement Disorders

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Local field potentials · Deep brain stimulation · Parkinson's disease · Essential tremor · Dystonia

Abstract
Background: Deep brain stimulation (DBS) for the treatment of movement disorders has provided researchers with an opportunity to record electrical oscillatory activity from electrodes implanted in deep brain structures. Extracellular activity recorded from a population of neurons, termed local field potentials (LFPs), has shed light on the pathophysiology of movement disorders and holds the potential to lead to refinement in existing treatments. ***Objective:*** This paper reviews the clinical significance of LFPs recorded from macroelectrodes implanted in basal ganglia and thalamic targets for the treatment of Parkinson's disease, essential tremor and dystonia. ***Methods:*** Neural population dynamics and subthreshold events, which are undetectable by single-unit recordings, can be examined with frequency band analysis of LFPs (frequency range: 1–250 Hz). ***Results:*** Of clinical relevance, reliable correlations between motor symptoms and components of the LFP power spectrum suggest that LFPs may serve as a biomarker for movement disorders. In particular, Parkinson's rigidity has been shown to correlate with the power of beta oscillations (13–30 Hz), and essential tremor coheres with oscillations of 8–27 Hz. Furthermore, evidence indicates that the optimal contacts for DBS programming can be predicted from the anatomic location of beta and gamma bands (48–200 Hz). ***Conclusion:*** LFP analysis has implications for improved electrode targeting and the development of a real-time, individualized, 'closed-loop' stimulation system.

Introduction

Over the past decade, deep brain stimulation (DBS) has largely replaced ablative techniques in the surgical treatment of movement disorders such as Parkinson's disease (PD), essential tremor (ET) and dystonia. In addition to providing critical symptomatic relief for patients, DBS provides a unique opportunity to record electrical oscillatory activity from deep brain structures. These oscillations, considered to represent aggregate neuronal discharge from neurons surrounding the electrode [1, 2], are referred to as local field potentials (LFPs).

DBS surgery involves the stereotactic implantation of a macroelectrode into a predetermined target region that

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is selected based on the indication being treated. Target coordinates are derived based on preoperative stereotactic imaging and verified or modified through intraoperative electrophysiological techniques [1]. The most commonly employed electrophysiological techniques include microelectrode recording and/or macrostimulation through the DBS electrode. Microelectrode recording allows the identification of single cells that are characteristic of the target of interest through firing rate, amplitude and activity pattern. For example, through microelectrode recordings, the subthalamic nucleus (STN) is usually identified by high background, increased firing rate and frequency of bursting neurons. The DBS electrode, which typically consists of four platinum-iridium contacts, is subsequently implanted based on the microelectrode findings. Both the microelectrode and DBS electrode are both capable of recording LFPs.

At present, DBS targets for movement disorders include the ventral intermediate nucleus of the thalamus for the treatment of ET, the STN or globus pallidus pars internus (GPi) for PD and the GPi for dystonia. Additionally, the pedunculopontine nucleus (PPN) is currently under investigation for the treatment of postural instability associated with PD [3, 4].

The following review focuses on the clinical significance of LFPs recorded in the context of surgery for movement disorders. Potential clinical applications of these data include the use of LFPs for the following purposes: (1) as a symptom biomarker, (2) to improve surgical targeting during DBS electrode implantation and (3) to inform a 'closed-loop' therapy device.

Functional Characterization of LFPs

LFPs are composite signals divided into a number of frequency bands, as follows: 0–3 Hz (delta), 4–7 Hz (theta), 8–12 Hz (alpha), 13–30 Hz (beta), 31–200 Hz (gamma), and >200 Hz (high frequency; table 1). It should be noted that there is nothing inherently pathological about a given oscillatory frequency range. Rather, the frequency spectrum represents a complex ensemble of neuronal activity – the significance of which depends on its functional and spatial context. This complexity necessitates a thorough evaluation of LFPs for each DBS indication and for each electrode target location.

The instantaneous amplitude and power of the LFP recordings are believed to represent the degree of synchronization between neurons surrounding the electrode tip [5, 6]. A transient increase in power, in response to a specific cue, is often referred to as an event-related synchronization (ERS), while a transient decrease in power is termed event-related desynchronization (ERD) [7]. ERD and ERS are typically calculated by averaging the power across time segments and comparing this average to a reference epoch [8]. ERD and ERS were initially thought to represent activation and inactivation in neuronal circuits, respectively. However, this theory is now disputed. For instance, ERDs detected in the alpha and beta frequency ranges in electroencephalograms were initially thought to represent an activated neural circuit. However, observations in electrocorticography experiments indicated that these cortical ERDs in the alpha and beta bands were associated with an ERS in the gamma-frequency band. Therefore, an ERS can also be activating. Consequently, the interpretation of ERD and ERS phenomena is likely to depend on the tissue of interest and other components of the frequency band [9].

Table 1. LFP frequency-based classification system

Frequency band	Range, Hz
Delta	0–3
Theta	4–7
Alpha	8–12
Beta	13–30
Gamma	31–200
High frequency	>200 Hz

LFP and Parkinson's Disease

Beta Oscillations Positively Correlate with Bradykinesia and Rigidity

In the context of PD, beta-band LFPs have received the most attention. This interest stems from observations in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primate model. The resulting death of dopaminergic neurons in the substantia nigra pars compacta, the hallmark of PD, is characterized by the onset of Parkinson's motor symptoms such as rigidity and bradykinesia in these MPTP-treated monkeys [10–12]. Single-unit recordings from the GPi and the STN in these monkeys have documented an increased firing rate accompanied with synchronous oscillatory bursting activity that is not found in control subjects [13, 14].

The increased oscillatory activity observed in MPTP-treated monkeys was subsequently found in the beta-fre-

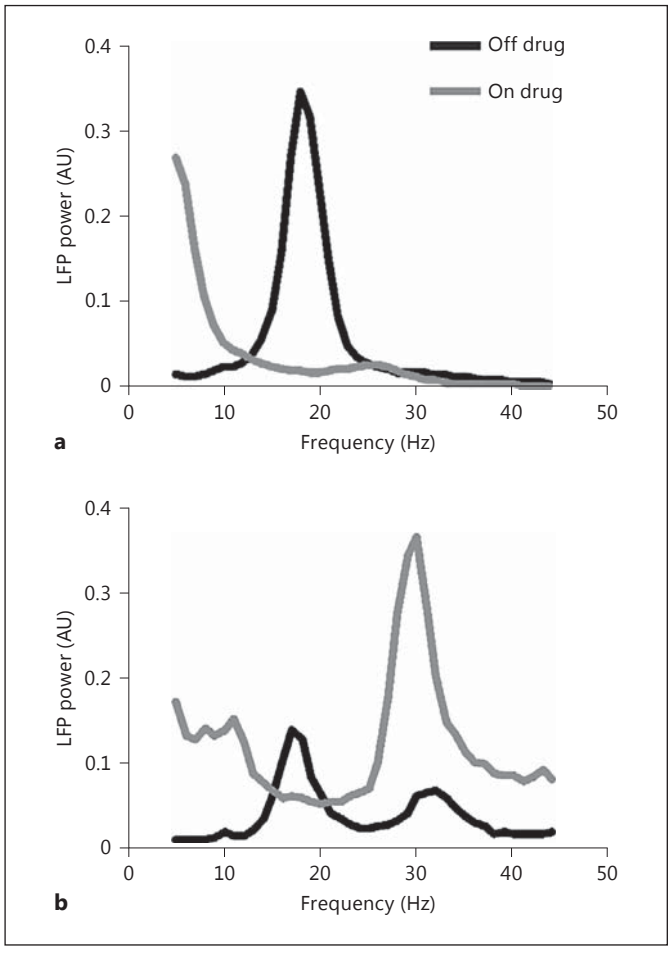

Fig. 1. LFP power spectra recorded from 2 patients with implanted STN electrodes for the treatment of PD. **a** The power of beta-frequency oscillations is severely diminished by dopaminergic medication in this patient. **b** A decrease in low beta oscillations (approx. 17 Hz) is coupled with an increase in high beta oscillations (approx. 30 Hz) in this patient. Taken with permission from Ray et al. [20].

quency band of LFPs recorded from the STN of human PD patients undergoing DBS surgery. Interestingly, the presence of this beta band is abolished by dopamine treatment (fig. 1) [15–19], and the degree of improvement in bradykinesia and rigidity following dopamine therapy has been shown to correlate with the magnitude of beta-band suppression [20–22]. Conversely, Kuhn et al. [23] observed that excessive synchronous beta activity can be induced in patients undergoing GPi-targeted DBS for dystonia by using the dopamine antagonist tetrabenazine. This evidence suggests that highly synchronous beta activity is caused by dopamine depletion. Interestingly, initial studies did not find a correlation between raw beta power and severity of bradykinesia/rigidity in patients withdrawn from dopaminergic medication [20, 22, 24, 25]. However, the absence of LFP power normalization in these studies may reduce the ability to detect a significant correlation between beta oscillations and motor impairment. For example, beta power is known to vary spatially over small distances [26, 27]. Therefore, subtle differences in electrode location relative to target may decrease the correlation between motor impairment and raw beta power. More recent studies employing indirect strategies to normalize synchronous beta activity between subjects have documented a significant correlation between beta oscillations and rigidity and bradykinesia [25, 28, 29]. These normalization strategies include analysis of beta LFP signal complexity and the extent of phase coherence between adjacent macroelectrode contacts.

Similar to the effect of dopamine, STN-targeted DBS causes a suppression in beta-frequency oscillations, and the degree of improvement in rigidity and bradykinesia correlates with the magnitude of beta suppression (measured immediately after stimulus discontinuation) [20]; however, this has not been a universal finding [30]. A limitation of these studies is that the authors were not able to record LFP during stimulation. To address this, Rossi et al. [31] developed a stimulus suppressor capable of recording artifact-free beta-band LFPs while simultaneously stimulating the STN. Using this technique, these authors found that stimulation through the DBS electrode suppressed beta synchronization in patients who were off dopaminergic medication but not while they were on medication. Therefore, while DBS and dopaminergic medication both diminish beta-LFP power, the effect of dopaminergic medication appears to be stronger [32] (fig. 2).

Another line of evidence supporting the hypothesis that beta activity is antikinetic stems from studies correlating beta power with voluntary movement. A beta ERD was observed during movement initiation and ERS during movement termination [16, 33–35]. Moreover, when patients were cued not to move following movement preparation, a significant synchronization was observed in the beta-frequency band [20–22, 36]. These observations support the hypothesis that beta-band activity is antikinetic.

While beta-band LFP activity has received intensive scrutiny in recent years, it is important to keep in mind that the boundaries of the LFP frequency bands are somewhat arbitrary. For instance, there is evidence that low beta activity (12–20 Hz) may derive from a different underlying physiological process than high beta activity

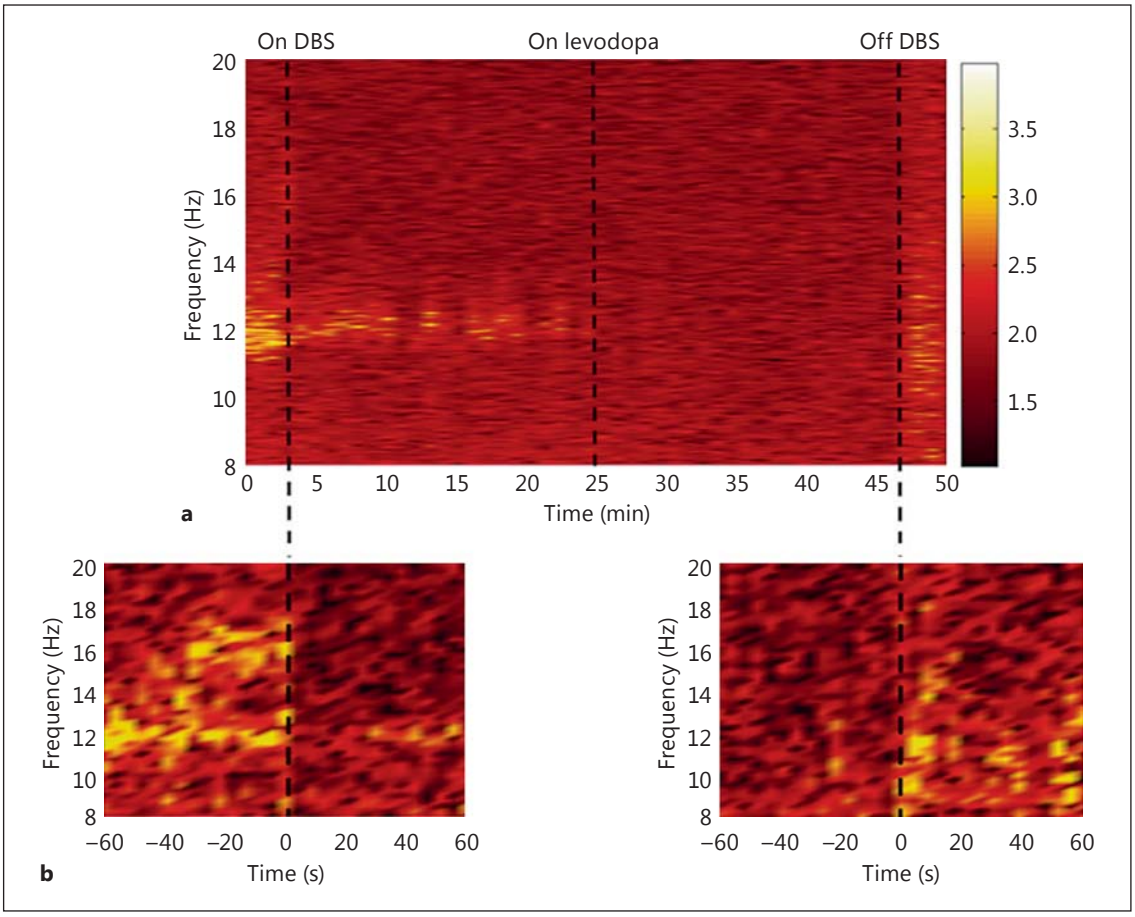

Fig. 2. a Time-frequency plot of beta-frequency LFPs (8–20 Hz) recorded from the STN during DBS initiation, levodopa administration and termination of stimulation in a patient with PD. **b** Enlarged view of the transition from DBS 'off' to DBS 'on' (left panel) and vice versa (right panel). DBS initiation is associated with a reduction in the power of beta oscillations detected from a DBS electrode implanted in the STN. The residual elevated beta oscillations are completely abolished by dopamine administration. DBS cessation is associated with an immediate return of beta oscillations. Taken with permission from Foffani et al. [30].

(20–30 Hz). This is supported by the observation that oscillatory power suppression in response to dopaminergic medication is greater in the low beta frequencies compared to high beta frequencies [29, 37]. However, an understanding of how these different beta subbands relate to the underlying pathophysiology of PD remains enigmatic.

Gamma and High-Frequency Oscillations Are Prokinetic

In contrast to beta-band activity, theta- [38], gamma- [15] and high-frequency band power have been found to increase following dopaminergic treatment [39, 40]. Interestingly, when patients are off levodopa, gamma activity nonetheless increases bilaterally during active movement. In the on state, this increase in gamma-band activity becomes lateralized to the hemisphere contralateral to the active motion [41]. These findings suggest that gamma-band activity may promote normal, voluntary movement. Furthermore, lateralization of the ERS suggests that dopaminergic medication restores this activity to a more normal physiological pattern. Interestingly, high-frequency oscillations (HFO) above 200 Hz have been detected in the STN of patients undergoing DBS for dystonia and ET – both of which are considered hyperkinetic movement disorders [42]. Furthermore, dopaminergic medication may enhance HFO power while shifting the peak frequency [29, 39, 43]. Specifically, an increase in oscillatory power in the frequency range of 300–350 Hz has been observed at the expense of 250-Hz oscillations.

Moreover, the pathophysiological importance of HFO is emphasized by the observation of coupling between beta oscillations and HFO in PD patients. This beta-HFO coupling has been noted to be significantly attenuated following the administration of dopaminergic medication and in patients with less severe PD [29, 43]. Thus, gamma- and high-frequency band activity is generally considered to play an important prokinetic role in the motor symptoms of PD.

Dyskinesia

Dopaminergic medications have proven effective in treating rigidity, bradykinesia and, to a lesser extent, resting tremor associated with PD. However, prolonged usage in the majority of patients leads to the development of dyskinesia [44]. Levodopa-induced dyskinesia has been correlated with LFP power in PD patients implanted with macroelectrodes in the GPi and/or STN. Consistent with the view of beta power as being antikinetic, recordings from GPi have demonstrated that desynchronization events in the beta-frequency range are significantly associated with dyskinetic states [45]. Additionally, high beta frequencies have been shown to synchronize between the GPi and the STN in a patient bilaterally implanted with macroelectrodes [30].

Resting Tremor

In contrast to antikinetic symptoms, most studies have indicated that Parkinson's resting tremor does not correlate with beta-frequency oscillations [20, 46]. However, epochs in which significant rest tremor is present have been associated with greater power in the low gamma-frequency band (35–55 Hz) which, as described above, is generally viewed as being prokinetic [47]. Additionally, oscillations around tremor frequency (4.5–5.5 Hz) and double-tremor frequency (approx. 10 Hz) correlate with tremor-related electromyogram (EMG) activity. These LFP oscillations and their coherence with tremor appear to be spatially localized in clusters within STN and, to a lesser extent, the zona incerta [48]. Interestingly, the location of tremor-EMG coherence clusters within the STN differs between the resting and postural tremors associated with PD [49]. Furthermore, tremor-related activity is more easily identified with LFP recorded from the STN than from the GPi [50].

The coherence between tremor and LFP oscillations at double the frequency of tremor may represent a real physiological correlate, harmonic waveform noise or a combination of both [51]. However, when comparing tremor-related EMG-LFP coherence between tremor dominant and bradykinetic PD subtypes, the differences in coherence in the single tremor frequency range between PD subtypes appeared to be independent of differences in the double-tremor range [49]. This supports the hypothesis that double-tremor frequency LFP is physiologically important.

Postural Instability

While STN- and GPi-directed DBS have been effective in alleviating tremor, rigidity and bradykinesia, they are ineffective in treating the gait abnormalities and postural instability that are frequently present in PD patients. Furthermore, gait and postural symptoms do not respond to dopaminergic therapy, indicating that they are controlled by a neural pathway that is separate from the dopamine-dependent pathway that underlies the tremulous/antikinetic symptoms of PD [52]. Nonhuman primate studies have indicated that the PPN is implicated in the induction and maintenance of locomotion [53]. Building on this work, stimulation of the PPN has also been investigated in the treatment of PD [3, 4].

LFP recordings from DBS macroelectrodes implanted in the PPN have demonstrated that the power of oscillations in the frequency range of 7–11 Hz is enhanced by the administration of dopaminergic medication and during the planning of self-paced movements. Furthermore, levodopa administration was found to induce synchronization between LFPs of 7–11 Hz and simultaneously recorded electroencephalogram activity [54]. A beta-band peak has also been reported in PPN recordings from PD patients in the off state [55, 56]. Relative power in the beta- and sub-beta-frequency bands has been shown to vary spatially and between subjects [56]. In a gait performance paradigm, oscillations of 7–10 Hz recorded in the PPN – in contrast to beta-band oscillations – significantly correlated with improved gait performance [56].

LFP and Essential Tremor

DBS targeted at the ventral intermediate nucleus of the thalamus for the treatment of tremor was the first application of DBS approved by the US Food and Drug Administration, and remains the second most common indication of DBS today [57]. Efforts to correlate LFP with tremor have been complicated by the 'microthalamotomy', or 'microlesion' effect that is often observed during surgery for the treatment of ET [58]. Despite this challenge, oscillations of 8–27 Hz recorded postoperatively from macroelectrodes are significantly coherent with

tremor frequency recorded from surface EMG of the first dorsal interosseous muscles [58, 59].

Additionally, coherence between spatially close (1 mm apart), independent thalamic microelectrodes has been compared between ET patients and patients undergoing DBS for the treatment of tremor of multiple sclerosis or for chronic central pain. ET patients, in contrast to subjects with MS tremor or central pain, exhibited enhanced coherence of 5–15 Hz when the electrodes were located in the ventral intermediate and ventral oral posterior nucleus of the thalamus. In the ventral caudal nucleus, significantly elevated coherence was observed only at 10–15 Hz [59]. Therefore, these analyses demonstrate the following points: (1) LFP recordings provide information about the spatial heterogeneity of the thalamus, which could help with localization during surgery and (2) differences in the spatial synchronization of LFP may be associated with the pathology of ET.

LFP and Dystonia

Dystonia is a movement disorder characterized by sustained cocontraction of opposing muscles and is associated with significant disability and pain [60]. Symptoms can be generalized or anatomically confined and are caused by genetic mutation, CNS injury or other disease states [61]. Due to the high prevalence of medication-refractory cases, the FDA approved DBS for the treatment of segmental and generalized dystonia under a humanitarian device exemption status in 2003. While this approval allows for the targeting of either the STN or the GPi, the GPi is the target of choice for DBS in dystonia [62].

The frequency spectrum of LFPs recorded from microelectrodes implanted in the GPi for the treatment of dystonia has been documented in several studies [63, 64]. These studies have consistently reported relatively high power in the 3- to 12-Hz frequency range compared to other frequency bands. In contrast to recordings from GPe, LFPs recorded from GPi have been shown to synchronize with simultaneously recorded spike activity [63]. Additionally, LFP activity in the frequency ranges of 4–10, 11–30 and 65–85 Hz significantly correlates with the sternocleidomastoid muscle EMG signal in patients with cervical dystonia [65]. Similarly, in patients with myoclonus dystonia, LFP oscillations of 3–15 Hz are coherent with surface EMG activity associated with affected muscle groups [64, 66]. This coherence was found to be stronger during the preparation and execution of a wrist extension task [64]. Interestingly, the response to voluntary movement across the LFP spectrum recorded from the GPi in dystonia patients is similar to the response observed in the LFP recordings from the STN in PD patients. During a wrist movement task, a significant ERD is observed at low beta frequencies (approx. 10–24 Hz), while a significant ERS is observed at gamma frequencies (approx. 64–68 Hz) [67].

Patients with cervical dystonia are capable of alleviating dystonic symptoms by touching their chin with the hand that is contralateral to the dystonic head motion [68]. Interestingly, the use of this sensory trick in patients with implanted DBS devices leads to a significant, bilateral desynchronization in the 6- to 8-Hz frequency range [69]. Furthermore, performing a task similar to the sensory trick (but ineffective in improving dystonic symptoms) leads to a bilateral synchronization in the 4- to 6-Hz frequency range. This finding supports the notion that low-frequency oscillations are implicated in the pathophysiology of dystonia.

The power across the LFP frequency spectrum has been compared between patients with dystonia and PD implanted with GPi DBS electrodes. Notably, whereas elevated relative power of the beta spectrum has been found in PD, beta power was diminished in dystonia. Furthermore, relative power in the 4- to 10-Hz frequency band is higher in dystonia compared to that reported in PD patients in both the 'on' and 'off' medication state [18].

Furthermore, Weinberger et al. [70] compared GPi LFP recordings from dystonia and PD patients. These investigators similarly found higher LFP power in a lower (8–20 Hz) frequency band compared to PD patients (11–30 Hz). Additionally, they noted less coherence between single-unit activity and LFP oscillations in dystonia compared to PD patients. Therefore, the synchronization between neurons firing at beta frequencies appears to be a more prominent feature of PD than dystonia.

Current and Prospective Clinical Applications of LFP Recording

Target Localization

One challenge in DBS surgery remains the ability to precisely place the electrode contacts within the structure of interest – which is often 2–6 mm in maximal diameter and situated many centimeters from the cortical entry site. Interpatient anatomical variation and insufficient image resolution make it necessary for surgeons to perform neurophysiological recordings with microelec-

trodes. However, with microelectrodes, the clinician must rely on single neuron activity parameters to interpret the location of the electrode in the brain. These parameters are susceptible to technical (e.g. impedance) and physiological (e.g. cerebrospinal fluid and blood) fluctuations. The subjective nature of interpreting microelectrode signals can lead to variability in correlating single-unit activity with brain region localization. In contrast, because LFP signals reflect an aggregate of electrical activity from an area of neural tissue, they are more resistant to physiological fluctuations. In addition, since LFPs are less variable across conditions, analytic tools that have been developed to correlate LFP activity with electrode depth could be more readily compared across practitioners and institutions and permit standardization of data analysis and interpretation [71]. Specifically, analysis of LFP beta oscillations have been used to delimit the boundaries of the STN [72–74]. In particular, oscillatory beta power is significantly higher within the STN compared to regions rostral and caudal to the STN [27, 75, 76].

While it is clear that beta activity is enhanced upon entering this region, the STN is a functionally heterogeneous nucleus with a sensorimotor territory situated dorsolaterally and a limbic/associative territory situated ventromedially. Indeed, stimulation of the dorsolateral STN results in optimal symptomatic improvement with minimal stimulation-related side effects compared to ventromedial stimulation [77]. LFP power in the beta-frequency band has been shown to correlate with topographical subregions of the STN and with single-unit activity simultaneously recorded from the STN [6]. Additionally, in a study evaluating the coherence between tremor-related EMG and LFP, the spatial distribution of 'coherence clusters' significantly correlated with the position of the contact that was subsequently selected for chronic stimulation [48]. This EMG activity was coherent with LFP in tremor and double-tremor frequency ranges. Collectively, this evidence suggests that oscillatory activity recorded from the basal ganglia can help inform DBS electrode targeting. Using LFP signals from multiple microelectrodes has the advantage of standardizing the interpretation of STN subdivisional boundaries. LFPs will not replace the need to use multiple electrodes, given the spatial area that the microelectrode is intended to resolve from imaging variability and error. However, real-time analysis of LFP signals may be more instructive and objective for the placement of the DBS implant and ultimately might serve as the better adjunct to intraoperative MRI placement of DBS electrodes.

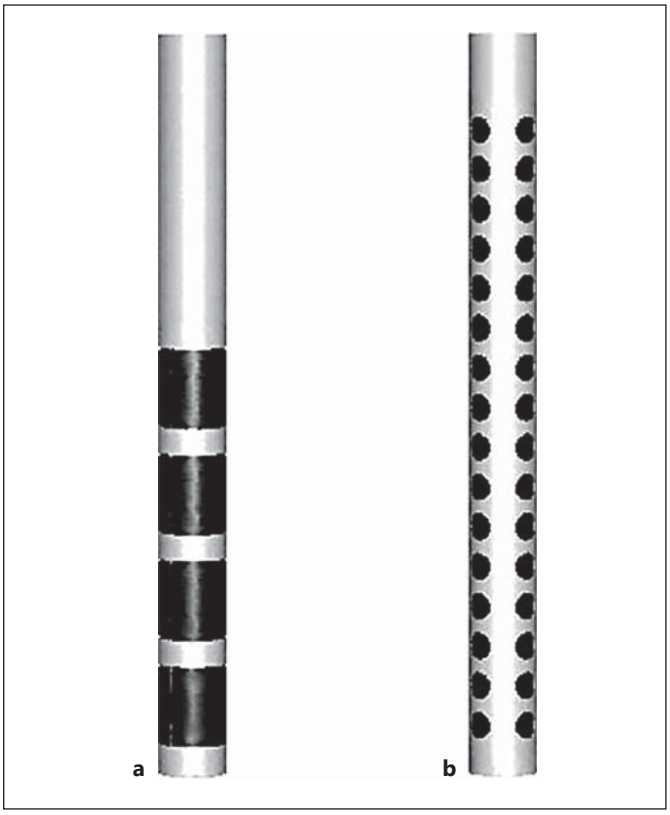

Fig. 3. a Contemporary DBS macroelectrode with 4 cylindrical contacts. **b** Novel high spatial resolution electrode with 64 contacts. Taken with permission from Zaidel et al. [74].

Programming Guidance

The programming of DBS devices is currently achieved via a lengthy algorithmic process in which each of the four contacts is tested individually while increasing the voltage or current. The clinician makes note of benefits and side effects – both objective and through patient self-report – and ultimately selects the optimal settings for chronic stimulation. While this process is uncomfortable for patients (who must be off medication during the process) and laborious for both clinicians and patients alike, it remains feasible due to relatively small combinations of programming parameters. However, the next generation of DBS macroelectrodes is likely to present increased complexity for programming. For instance, Martens et al. [78] have developed a 64-contact macroelectrode that could allow for the 'steering' of current away from structures such as the internal capsule – the stimulation of which would result in side effects (fig. 3). Such guided stimulation is achieved by using multiple, smaller electrodes arrayed around the circumference of a solid sup-

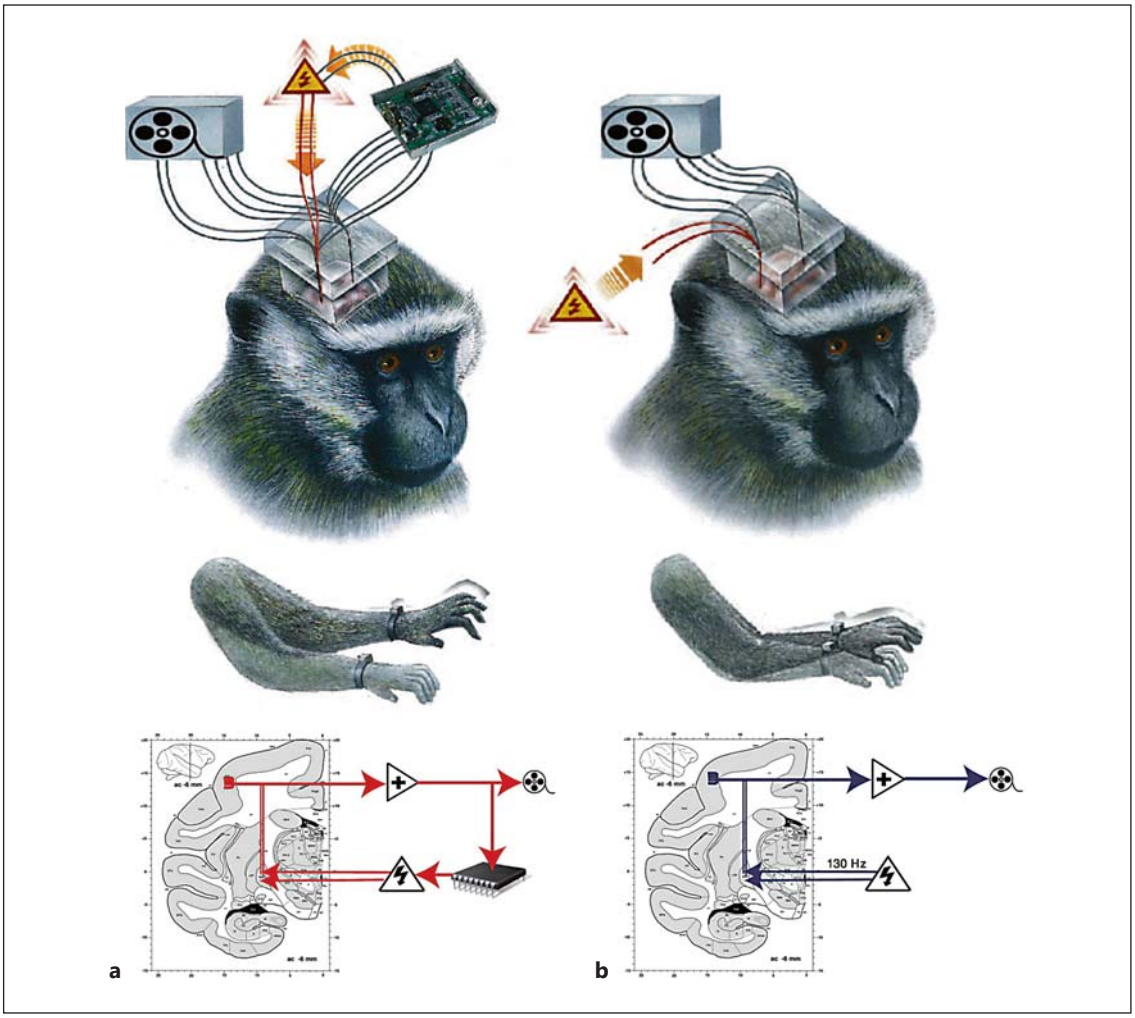

Fig. 4. a Schematic depiction of the African green monkey closed-loop stimulation paradigm in Rosin et al. [89]. Single-unit recordings were detected from 6 electrodes (2 GPi, 4 M1) by a data acquisition system and digital signal-processing chip. Detection of a neuronal spike triggered a short-train stimulus. **b** Schematic depiction of an open-loop stimulation paradigm in an African green monkey.

port instead of the cylindrical contacts used on contemporary electrodes. Although the presence of 64 contacts would render current programming methods impractical, novel analytic methods based on LFPs have been developed to assess spatial reach and efficacy of DBS stimulation [79]. The use of LFPs in improving DBS clinical outcomes has largely been explored in the setting of DBS implantation into STN for the treatment of PD [30, 35, 80, 81]. Recent work in STN LFP analysis suggests that programming could be improved through analysis of macroelectrode-recorded LFPs and modeling of stimulation parameters [79, 82, 83]. One direct clinical application relates to the chronic hypersynchrony evidenced in the basal ganglia of Parkinson's patients: better clinical outcomes correlate with the degree of beta hypersynchrony. Analysis of LFPs through the macroelectrode could be used to set optimal clinical stimulation parameters. Interestingly, those contacts associated with optimal stimulation efficacy significantly correlate with contacts exhibiting maximal beta and gamma power [26, 27, 84]. Moreover, chronic stimulation through contacts which are further from the apparent source of beta activity is associated with a poorer response to stimulation [26]. Thus, LFPs recorded from implanted DBS electrodes might prove useful in improving and automating the programming process. One specific advantage of a DBS electrode

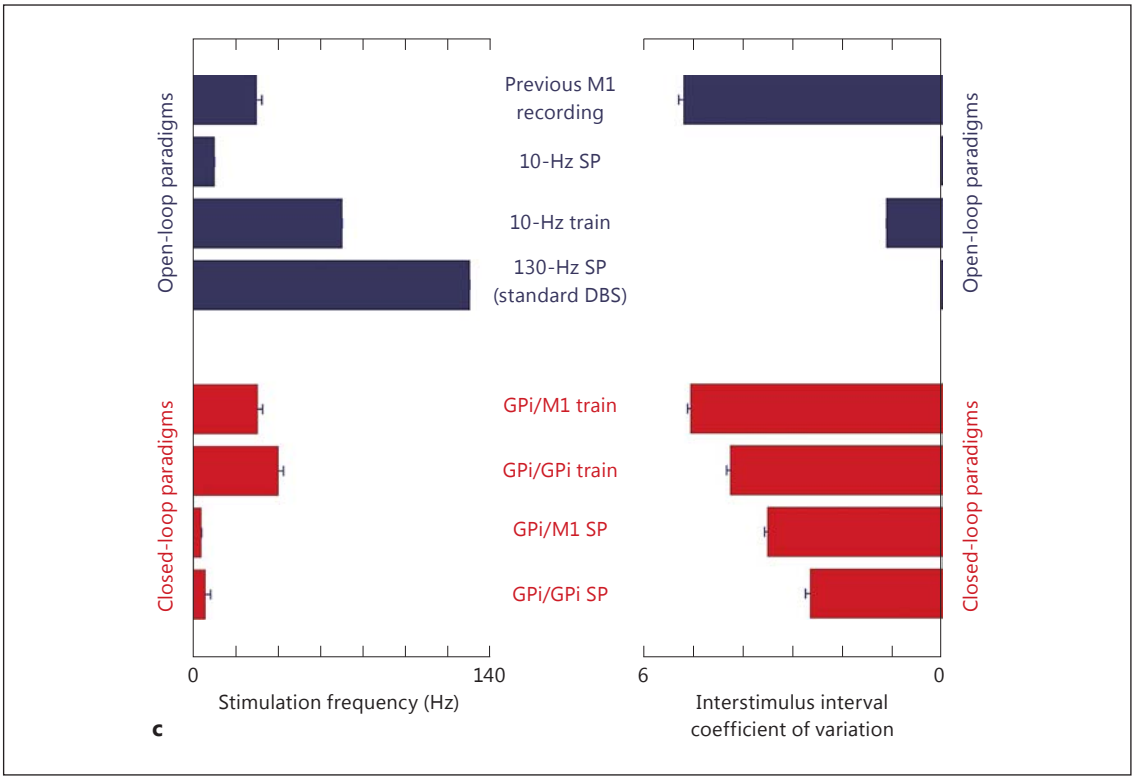

Fig. 4. c The stimulation frequency and coefficient of variation of the interstimulus intervals for the various stimulation paradigms. SP = Stimulation paradigm. Taken with permission from Levy et al. [80].

design that has denser, smaller diameter contacts would be the selective distribution of electrical activity patterns ('steering current'). Furthermore, activity patterns could be based on LFP information, which may reduce the overall stimulation output, thus increasing battery life.

Closed-Loop Therapies

Another challenge in treating movement disorders with DBS is the inability of existing devices to do the following: (1) monitor patient symptoms and (2) adjust stimulation parameters accordingly. The stimulation parameters (voltage, current, pulse width, polarity of stimulation and contact selection) can only be modified by programming personnel using an external computer wand placed over the patient's implanted pulse generator. This process requires patients to visit a clinic staffed with personnel who have expertise in programming implanted DBS devices, thereby inconveniencing patients and burdening these clinics with repeated appointments. Furthermore, without a sensing component to the existing DBS devices, there is no feedback mechanism to allow the device to be turned off during sleep, when Parkinson's symptoms disappear, or to be ramped up when symptoms increase between medication doses. Therefore, there is much interest in developing a closed-loop therapy in which a relevant neural marker, such as LFP oscillations, provides feedback that directs the modulation of stimulation parameters in real time [85–88].

Rosin et al. [89] investigated the feasibility of such a closed-loop stimulating device in an MPTP primate model of PD. Single-unit recordings from the primary motor cortex (M1) and the GPi were used to direct the stimulation of the GPi. Specifically, the detection of a spike in either the GPi or the M1 triggered a short-train stimulus (7 pulses at 130 Hz, 80-ms latency). This form of closed-loop stimulation proved superior to continuous, GPi-targeted stimulation in suppressing pallidal spike and oscillatory activity. Furthermore, closed-loop stimulation was associated with a greater reduction in akinesia compared to continuous stimulation (fig. 4).

Currently, the battery life of nonrechargeable DBS generators is approximately 3–5 years, depending on the stimulation parameters used. Generator replacement surgery involves an invasive 15- to 20-min procedure per-

formed under monitored anesthesia care. Replacement surgeries are associated with a small but significant risk of infection and damage to the existing device. Thus, strategies to increase the battery life of DBS devices are important, considering the number of battery replacement surgeries required over the lifetime of, for instance, a 40-year-old patient with ET. If a closed-loop device was capable of identifying when a patient was asleep, stimulation could be turned off during this period, thus increasing the battery life of the device. In fact, beta-band LFP power has been reported to be significantly lower during stages 2 and 4 of sleep compared to when patients are awake [90]. It is not practical to require PD patients to self-regulate their implantable pulse generator power for sleeping and waking, as a significant number of patients with PD often experience neurogenic bladder dysfunction, which is associated with a greater frequency of micturition [91]. Intentional tremor, a primary sequela of PD, would make turning the implantable pulse generator back on (for bladder evacuation or upon waking) difficult if not impossible. Additionally, different motor symptoms may be determined to have unique LFP profiles, which could be ameliorated with a specific combination of stimulation parameters or by switching active contacts. For instance, differences in stimulation efficacy for bradykinesia have been observed to depend on the site of stimulation within the STN. Switching off electrodes placed in the lateral STN resulted in a rapid return of bradykinesia; however, a more medial placement resulted in a slower return of bradykinesia [92]. Such stimulation device improvements could increase the time between battery changes.

Another consideration for developing a closed-loop DBS device is the integrity of the electrode-brain interface. Postmortem histopathological studies have found the DBS electrode in the brain to be encapsulated by a thin, GFAP-positive capsule years after initial implantation [93, 94]. Moreover, a recent study showed that in patients with PD, the LFP power in the beta-frequency band was significantly lower 3–7 years after the initial DBS implant compared to power recorded at the time of DBS surgery [95]. In contrast, the magnitude of the movement-related desynchronization in the beta band was preserved and detectable over time [95]. Therefore, despite the decrease in beta power over time, the ERD preservation supports the feasibility of using beta-band activity to inform a closed-loop device.

Summary

LFPs recorded from implanted DBS electrodes in human subjects have provided researchers and clinicians with a novel method for understanding, and potentially refining treatments for movement disorders. Correlating aspects of the LFP frequency spectrum with clinical symptoms has provided new insights into the pathophysiology of these disorders, and mounting evidence suggests that LFPs will be useful in improving current therapies in this arena. In particular, LFP oscillations have proven to be useful in localizing DBS surgical targets. LFPs may ultimately be able to inform a closed-loop DBS device that is responsive to individual patient symptoms in real time.

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