NEUROPHYSIOLOGICAL BIOMARKERS AT CORTICAL AND BASAL GANGLIA LEVELS IN PARKINSON'S DISEASE

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Abstract
Parkinson's disease (PD) is a complex neurodegenerative disorder, associated with dopaminergic denervation of the basal ganglia (BG), resulting in aberrant activity patterns of surviving neurons. Early electrophysiological recordings in parkinsonian animals at both cortical and BG level helped in investigating cortico-thalamo-BG-cortical circuit dysfunction and developing the models of PD-related changes in neuronal activity (rate, rhythm, or synchronization). In addition, invasive recordings in PD patients during Deep Brain Stimulation (DBS) procedure, apart from verifying a lot of characteristics of the models, contributed to the identification of neurophysiological parameters that could play the role of a biomarker. In the field of DBS neurophysiology, the term biomarker is commonly used to describe a brain activity pattern that provides information, apart from the pathophysiological changes, for a specific clinical condition or a therapeutic effect. Local field potentials (LFPs) represent synchronized presynaptic and postsynaptic activity of large neuronal populations in direct vicinity to the implanted electrode. LFPs from DBS electrodes could give direct insight into electrophysiological dynamics of affected network nodes targeted by DBS. This review will discuss some potential biomarkers that characterize the neurophysiological changes in PD and their possible utility for monitoring and treatment of the corresponding PD symptoms.

Key Words: Parkinson's Disease, biomarkers, cerebral cortex, basal ganglia, neurophysiology, oscillatory activity, phase-amplitude coupling, local field potentials.

ΝΕΥΡΟΦΥΣΙΟΛΟΓΙΚΟΙ ΒΙΟΔΕΙΚΤΕΣ ΑΠΟ ΤΟΝ ΕΓΚΕΦΑΛΙΚΟ ΦΛΟΙΟ ΚΑΙ ΤΑ ΒΑΣΙΚΑ ΓΑΓΓΛΙΑ ΣΤΗΝ ΝΟΣΟ ΤΟΥ ΠΑΡΚΙΝΣΟΝ.

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Περίληψη
Η νόσος του Πάρκινσον (ΝΠ) είναι μια σύνθετη νευροεκφυλιστική διαταραχή, συσχετιζόμενη με τη ντοπαμινεργική απονεύρωση των βασικών γαγγλίων (ΒΓ), που οδηγεί σε ανώμαλα μοτίβα δραστηριότητας των διασωθέντων νευρώνων των ΒΓ. Πρώιμες ηλεκτροφυσιολογικές καταγραφές σε παρκινσονικά ζωικά μοντέλα βοήθησαν στη διερεύνηση της δυσλειτουργίας των κυκλωμάτων φλοιού-θαλάμου-ΒΓ-φλοιού και πρότειναν μοντέλα που περιέγραφαν τις αλλαγές της νευρωνικής δραστηριότητας (συχνότητα, ρυθμός ή συγχρονισμός εκφορτίσεων) που σχετίζονται με την ΝΠ. Επιπλέον, οι επεμβατικές καταγραφές σε ασθενείς με PD κατά τη διάρκεια της διαδικασίας της Εν τω Βάθει Εγκεφαλικής Διέγερσης (DBS), επαλήθευσαν πολλά από τα χαρακτηριστικά των παραπάνω μοντέλων, συμβάλλοντας παράλληλα στην ανάδειξη νευροφυσιολογικών παραμέτρων, που θα μπορούσαν να παίξουν το ρόλο βιοδείκτη. Στη νευροφυσιολογία του DBS, ο όρος βιοδείκτης χρησιμοποιείται συχνά για να περιγράψει ένα πρότυπο εγκεφαλικής δραστηριότητας, που παρέχει πληροφορίες για συγκεκριμένα συμπτώματα ή θεραπευτικά αποτελέσματα. Τα τοπικά δυναμικά πεδίου (LFPs) αντιπροσωπεύουν την συγχρονισμένη προσυναπτική και μετασυναπτική δραστηριότητα μεγάλων πληθυσμών νευρώνων σε άμεση γειτνίαση με τα εμφυτευμένα ηλεκτρόδια. Η καταγραφή των LFPs από τα ηλεκτρόδια θα μπορούσε να προσφέρει άμεση πληροφόρηση για τα ηλεκτροφυσιολογικά δεδομένα των κυκλωμάτων και των πυρήνων – στόχων του DBS. Στην ανασκόπηση αυτή θα γίνει αναφορά σε πιθανούς βιοδείκτες που χαρακτηρίζουν τις εν λόγω νευροφυσιολογικές αλλαγές στην ΝΠ και τη χρησιμότητα τους για την παρακολούθηση και τη θεραπεία των συμπτωμάτων που σχετίζονται με αυτές.

Λέξεις κλειδιά: Νόσος Πάρκινσον; βιοδείκτες; βασικά γάγγλια; εγκεφαλικός φλοιός;νευροφυσιολογία; νευρωνική δραστηριότητα; τοπικά δυναμικά πεδία;

Introduction

Parkinson's disease (PD) is a common and disabling movement disorder owing to dopaminergic denervation in basal ganglia (BG). The core pathology is the degeneration of the dopaminergic neurons in the substantia nigra pars compacta (SNc) that project to the striatum. Striatum is the major gate of the basal ganglia, receiving inputs from thalamus and the cerebral cortex and projecting to the pallidonigral system.[1] Therefore, cortical mode and thalamocortical coupling, being the major carriers of information, could play a major role for basal ganglia function. An early raised question was how the basal ganglia translate cortical inputs under physiological conditions and consequently how is this transformed under abnormal conditions. This 'reading' of cortical activity has been extensively studied in both animals and humans, especially during operations for DBS treatment of PD patients. Physiological studies of simultaneously recorded neurons in basal ganglia, cortex and cerebellum gave us a window for brain dysfunction in PD.

Cortical Dynamics

The recording of neuronal signals directly from the cortical surface of the brain was first reported in rabbits and monkeys by the British physician Richard Caton in 1875[2] and in humans by the German psychiatrist Hans Berger in 1924.[3] Recording of brain potentials by means of electroencephalography and recordings by means of electromyography (mainly during surgical interventions for the treatment of epilepsy) were historically the first organized recordings of the electrical activity of the human cerebral cortex.

The early years

There have been several early reports concerning electroencephalography (EEG) in PD. In most of them, EEGs have been diagnosed as abnormal in up to 30-50% of the cases.[4,5,6,7] These early recordings were analogic and their analysis consisted of simple visual qualitive inspection of the signals. Therefore, only rough conclusions could be drawn, concerning obvious signal changes on a restricted time scale. Generally speaking, the most prominent and frequent findings of these early works were an increase in the sum of lower frequencies as well as a slowing of α rate. These findings were non-specific.[8]

In the following years, EEG studies in PD patients noticed that a general disturbance of the EEG, together with some other indicators of brain dysfunction, is related to an increased risk of a progressive dementing process.[9] In 1988, Neufeldt et al. reported a significant association between occipital background slowing and motor disability in non-demented patients.[10] In 1991, Soikkeli et al. suggested that the absolute and relative amplitudes of delta, theta, alpha and beta bands and the peak and mean frequency differed significantly in Parkinson's dementia patients. An interesting finding of the study was the increase of delta activity in Parkinsonian patients without dementia, and the theta activity. The frequencies were slower than in controls.[9]

Digital era

Since the 1990s, the use of digital devices for signal storage and the use of large-scale computational methods for data processing have led to the most profound and most extensive investigation of CNS electrical potentials. Apart from the development of computing power through digital devices, invasive recordings in PD patients, which occurred from the development of invasive treatments for the disease, provided direct information concerning PD neurophysiology. Since the mid-1990s, studies of electrical brain potentials in PD - and movement disorders in general - have been steadily increasing.[11,12,13]

Scalp EEG versus electrocorticography

Scalp EEG is limited by poor source localization and low signal amplitude, which is problematic for studying higher frequencies and is also poisoned by heaps of spurious potentials (movements, etc.).[14] The electrocorticography technique, in contrast, has high signal amplitude, excellent spatial localization, and, in the context of movement disorders surgery, does not require additional brain penetrations or surgical exposure. Furthermore, broadband spectral gamma power in cortical local field potentials is thought to reflect underlying pyramidal cell spiking activity, suggesting that electrocorticography may provide a new technique for assessment of underlying neuronal activation state in human movement disorders.[15] Although widely used in studies of the "normal" physiology of the sensorimotor cortex in humans with epilepsy, electrocorticography had not been applied extensively to the study of the most common movement disorders.[16,17,18,19]

Central oscillations

Neurophysiological recordings were used to highlight the role of central oscillators in tremor in Parkinson's disease. Oscillatory activities have been reported at a variety of frequencies between 4 and 60 Hz.[20] After a series of animal and human studies, especially during Deep Brain Stimulation (DBS) procedures, several discrete forms of oscillatory activity in the basal ganglia have been demonstrated.[21] In addition, electroencephalography (EEG) and magnetoencephalography (MEG) studies have shown oscillatory activity at the tremor frequency throughout the cerebellar-thalamic-cortical circuit.[22,23] These

oscillations play an important role in both normal function and the pathophysiology of movement disorders.[24,25,26] In 2003, Timermann et al. demonstrated tremor-related oscillatory activity within a cerebral network, with abnormal coupling in a cerebello-diencephalic-cortical loop and cortical motor and sensory areas contralateral to the tremor hand. The main frequency of cerebro-cerebellar coupling corresponded to double the tremor frequency.[22] The hypotheses for many of the above studies was that excessive oscillatory synchronization in the basal ganglia–thalamocortical motor network at or near 20 Hz is a clear and distinctive feature and may underlie bradykinesia.[1,27,28] Hammond et al. demonstrated in 2007 that in Parkinsonian patients an abnormally synchronized oscillatory activity occurs at multiple levels of the basal ganglia-cortical loop. Notably, this excessive synchronization correlates with motor deficit, and its suppression by dopaminergic therapies, ablative surgery, or DBS might provide the basic mechanism whereby diverse therapeutic strategies ameliorate motor impairment in PD patients.[1]

Increased cortical beta power

EEG and MEG studies suggest that advanced PD is associated with pathologically increased cortical beta power.[29] This association between beta cortical power and PD has also been demonstrated in animal models of PD with dopamine depletion.[30] However, increased cortical beta power has also been demonstrated in early PD, especially in bilateral primary sensorimotor cortices.[31] In particular, Crowell et al., using corticography during DBS surgery for PD, demonstrated that primary motor cortex broadband spectral power is increased in those patients.[20] This increase extended over a very broad frequency range, from as low as 20 Hz to >200 Hz, always taking into account the specific conditions under which the recordings were made ("off" state, during surgery etc.). Broadband spectral power changes are thought to reflect asynchronous spiking activity in the region underlying the recording electrode.[15] However, we should keep in mind that cortical broadband local field potential (LFP) power also correlates with the blood oxygen level-dependent (BOLD) signal on functional MRI studies.[32] Following this finding, the question raised is whether this is related to the metabolic disorder and not to a real change in neurophysiological pattern.[33]

Cortical desynchronization seems to be a consistent finding and could have different interpretations. Since recordings concern DBS surgeries, we are dealing with patients with advanced disease, and it is not therefore clear if cortical desynchronization reflects a primary abnormality or a compensatory mechanism. DeLong proposed from early 90's that the original 'rate model' of basal ganglia and cortical function in PD posited resting state cortical hypoactivity, driven by excessive inhibitory basal ganglia output.[34] Crowell et al., based on corticocortical recordings, proposed another hypothesis for the increased subthalamic nucleus single unit discharge that is characteristic of the parkinsonian state: subthalamic nucleus hyperactivity may be driven by an overactive cortical area, via the cortico-subthalamic 'hyperdirect' pathway.[20]

Corticography also carries some limitations since its findings depend on the underlying cortical signal generators. How much does brain atrophy affect outcomes in Parkinson's disease? How much are outcomes affected by levodopa administration or the existence or non-existence of tremor? Another disadvantage of corticography studies - not only in Parkinson's disease - is the lack of controls, i.e. healthy controls.

β-synchronization

At this point, it should be noted that in a series of studies with transcranial alternating current there were conflicting results. For example, Timmermann et al. demonstrated worsening of Unified Parkinson's Disease Rating Scale (UPDRS) scores with STN DBS at 10 Hz but not at 20 Hz, compared to no stimulation.[35] Chen et al., studying the increasing slope in a reaction time catch task, demonstrated a reduction with 20 Hz but not with 5 or 10 Hz STN DBS compared to no stimulation.[21] Eusebio et al. reported that finger tapping rate was reduced with STN DBS at 5 Hz and 20 Hz but not at 10 Hz.[36] The above findings suggest that no single pathological frequency may reflect all parkinsonian motor symptoms. It is possible that specific frequency bands are associated with specific motor performance parameters.[37] This led to the concept that measures of brain physiology reflecting β-synchronization could be potential "biomarkers" for the pathophysiology of PD. Such objective measures of PD symptoms would have enormous clinical potential for diagnosing, monitoring, and tailoring patient treatments. In particular, the cortical β-waveform shape may indicate the summation of synchronous inputs (perhaps from the basal ganglia via the thalamus) to cortical pyramidal neurons.[38]

Phase-Amplitude Coupling (PAC)

Another biomarker under investigation in movement disorders is the phase-amplitude coupling (PAC). PAC is the coupling of the phase of slower electrophysiological oscillations with the amplitude of faster oscillations and is thought to facilitate dynamic integration of neural activity in the brain.[39]While conventional signal processing measures, such as β power, have failed to reliably differentiate PD as a function of cortical severity or diagnosis, phase-amplitude coupling (PAC) between β and broadband γ (50–150 Hz) seems more promising.[40,41]Specifically,

phase-amplitude coupling (PAC) over the motor cortex, detected using electrocorticography (ECoG), is increased in PD compared to other groups and decreased with DBS in a clinically relevant manner.[42] Interestingly, after characterizing PAC with ECoG, it was shown that increased PAC can also be detected non-invasively with scalp electroencephalography (EEG).[43] In addition, PAC recorded with scalp EEG could differentiate PD patients on and off medication and differentiate PD patients off medication from healthy controls. Increased beta-gamma PAC in PD was first found with interventional electrocorticography (ECoG) studies,[40,41] and subsequently demonstrated in EEG studies.[44] Increased beta-gamma PAC in the sensorimotor cortex was found in untreated PD patients compared to healthy controls and those taking medication.[43]

Pattern of β-oscillations

The pattern of beta oscillations could be considered as another neurophysiological biomarker. PD patients' brain activity is characterized by beta oscillations with a non-sinusoidal shape. Furthermore, the pattern changes with medication status, as greater sharpness asymmetry and slope asymmetry of regular beta oscillations over sensorimotor cortex, were found in drug-free PD patients as opposed to those on medication. Specifically, β oscillations in areas above sensorimotor cortex in untreated PD patients had greater sharpness and slope asymmetry compared to patients on medication. These findings suggest that new ways of measuring β-synchrony incorporating waveform shape could improve the detection of PD pathophysiology in noninvasive recordings.[44]

Parkinson's Disease: Possible neurophysiological biomarkers at basal ganglia level.

The principal goal of Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) or internal globus pallidus (GPi) is the improvement of major clinical motor symptoms of Parkinson's disease (PD) such as tremor, bradykinesia and rigidity, along with improvement of motor response complications.[45,46] However, the success of DBS depends fundamentally in placing the DBS electrodes with high precision into the sensorimotor region of the STN corresponding to the dorsolateral posterior part of the nucleus, or the GPi corresponding to its posteroventral part.[47] To achieve a high precision implantation in this region, intraoperative microelectrode recordings (MER) of the neuronal electrical activity from targeted structures are widely used. The main principle underlying this procedure is that in hypo-dopaminergic (parkinsonian) state increased firing rates and discharge patterns of neurons both in the STN and the GPi are so characteristic that constitute the hallmark of the nuclei.[48,49]

The increased firing rates of STN and GPi are in concordance with the so-called "rate" or "classical" model of basal ganglia (BG). The classical model of basal ganglia function has critically helped understanding of how dopamine contributes to motor output and how loss of midbrain dopamine neurons leads to circuit-level changes underlying the motor symptoms of PD.[50,51] Its basic assumption, generating several (but not all) testable predictions regarding changes in firing rate throughout the basal ganglia in Parkinson's disease, is that information is encoded in the firing rate of individual neurons.[52,53] Moreover, evidence linking changes in basal ganglia neurophysiology with PD motor deficits, including both observational and interventional evidence obtained from PD patients, as well as parkinsonian nonhuman primate and rodent models, also revealed changes in firing patterns and synchrony.

Indeed, additional neurophysiological characteristic findings in BG in parkinsonian state, are the emergence of burst discharges, greater synchrony of firing between neighboring neurons, oscillatory activity patterns, and excessive coupling of oscillatory activities at different frequencies, which are in concordance with what is called "pattern" model.[1,54] Such oscillatory activity could be generated internally within the basal ganglia but also, and perhaps more likely, as part of a larger network involving the cortex and thalamus. All these alterations of neuronal activities in parkinsonism prevent the normal separation of the firing of individual neurons in the basal ganglia, limiting the space available for information coding through spatial selectivity and/or temporal patterning and thus impairing motor processing.[1] Consequently, the pattern model provides an attractive view of adaptive and maladaptive plasticity processes involved in PD.

Local Field Potentials (LFPs)

The resulting neuronal synchrony is also implied by the finding of increased amplitudes of local field potentials (LFPs) in the beta-band range of frequencies (10–30 Hz) in the basal ganglia and cortex.[55,56] LFPs are summations of extracellular electrophysiologic activity of a population of neurons occupying a small area, being recorded using intracerebral electrodes.

Further on, recording LFPs through macroelectrodes implanted in the STN or GPi for DBS in Parkinsonian patients has brought to light the following associations: (a) The 11–30 Hz (beta band) peak characterizes the "off" parkinsonian state and a 4–6

Hz peak appears in patients with tremor. (b) In the "On" pharmacological state there is a predominant 60–80 Hz gamma band peak, while beta rhythm is drastically attenuated. (c) In patients with levodopa-induced dyskinesias there is predominant 4–10 Hz activity. These findings indicate that the degree of neuronal synchronization and discharge pattern in PD change drastically within the BG in direct relation with the degree of dopaminergic deficit or replacement.[57,58,59] The same holds true for the antiparkinsonian effect of DBS. Recordings from STN during electrical stimulation at frequency of 130 Hz have revealed a tapering of beta band during "Stim ON" phase.[60,61]

Moreover, several other recording data suggest that: (a) Patterns of LFPs of GPi are different in Parkinson's disease from dystonia.[62] (b) The detection of dorsolateral posterior STN LFPs activity is considered as the electrophysiological "sweet spot" for effective clinical outcome.[63] These neurophysiological characteristics contribute to the definition of the optimal DBS implantation trajectory, as well as to the optimum adjustment of stimulation parameters.[64,65,66] (c) LFP recordings may also prove useful toward quantification of motor subtypes of Parkinson's disease[67] and severity of rigidity and bradykinesia in PD.[68]

Recent studies have further used various recordings using MER with the advent of sophisticated analysis and modeling for localizing dorsal–ventral border of STN[69] and predicting therapeutic volume of tissue activation.[70]

Phase-Amplitude Coupling (PAC)

As already mentioned earlier, changes in coupling between the phase of low-frequency and the amplitude of high-frequency oscillations [phase-amplitude coupling (PAC)] have also been proposed as biomarkers of PD. More recent studies hypothesize that PAC could be a robust biomarker of PD.[40,71] PD patients exhibited a reduction of PAC measured in the STN after levodopa administration[72]. The studies by de Hemptinne et al. showed that PD patients were more likely to exhibit significant measurements of PAC in the primary motor cortex (M1) compared to epilepsy and dystonia controls, and that cortical PAC was reduced during therapeutic STN DBS.[40,41] A study using LFPs from microelectrode recordings in the nonhuman primate MPTP PD model demonstrated that PAC in the pallidum progressively increased in concordance with parkinsonism severity.[71]

High Frequency Oscillations (HFOs)

Other researchers have suggested that changes in the high-frequency side of the spectrum (200-400 Hz) may also be associated with PD. For example, it was showed that levodopa administration elicited an increase in power at 320 Hz in the STN of PD patients implanted with DBS leads and demonstrated that the power between 200 and 300 Hz in the internal segment of the globus pallidus (GPi) of PD patients was movement dependent.[73,74] Both groups of investigators hypothesized that these high-frequency oscillations (HFOs) are required for normal information processing and motor control. On contrary, recent findings from GPi recordings provide evidence that exaggerated, movement-modulated HFOs in the GPi are pathophysiological features of PD. These findings suggest that the functional role(s) of HFOs may differ between the STN and GPi and motivate additional investigations regarding their relationship to motor control in normal and diseased states. The same group stress the possibility of the utility of HFOs in the development of electrophysiological-based adaptive DBS approaches, for example with HFOs in the GPi being a potential functional marker of motor state.[75]

Towards biomarkers for closed-loop (adaptive) DBS

Therefore, identifying neurophysiological biomarkers that correlate with motor symptoms or disease severity will be supportive in understanding the pathophysiology of PD and developing more effective treatments. As a matter of fact, there is particular interest in incorporating such biomarkers into devices that could deliver closed-loop deep brain stimulation (DBS) tailored to the clinical state of individual patients.[76,77] Biomarkers derived from LFPs seem attractive for closed-loop-sensing DBS because they can be recorded continuously from brain structures via permanently implanted electrodes.[78,79]

Along with its definition as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention,[80] a biomarker should also fulfil three criteria of clinical usefulness. An ideal biomarker should be:

1. Indicative (Is the neurophysiological biomarker sufficiently linked to the severity of fluctuating symptoms?)
2. Individual (Is the neurophysiological biomarker detectable in every patient and patient-specific if needed?)
3. Implementable (Is the neurophysiological biomarker (technically) capable of automatically titrating stimulation?).[81]

Hence, current adaptive applications such as sensing-enabled DBS devices, would likely need to be improved addressing all three of the criteria, providing an optimum performance to the patients, through valid closed-loop algorithms, that can automatically detect relevant biomarkers for titrating stimulation with minimum clinical intervention.

Neurophysiological biomarkers to optimize DBS in Parkinson's disease

Implantation of DBS electrodes provides the unique opportunity to record in vivo deep brain activity. Local field potentials (LFPs) represent synchronized presynaptic and postsynaptic activity of large neuronal populations in direct vicinity to the target area. LFPs from DBS electrodes could give direct insight into electrophysiological dynamics of affected network nodes targeted by DBS, enabling therefore a systematic phenotyping of oscillatory patterns in patients undergoing DBS surgery.

In the field of DBS neurophysiology, the term biomarker is commonly used to describe a brain activity pattern that provides information on specific symptoms or therapeutic effects. An ideal biomarker should have a direct correlation to clinical symptoms, tracking disease state constantly and dynamically, with minimal sampling error. In the case of neurophysiological biomarkers, desirable characteristics include signal stability over time and across multiple conditions, as well as differentiation from ongoing spontaneous activity. Fulfillment of the aforementioned criteria is very important when we are dealing with adaptive DBS (aDBS), since adaptive control systems require a reliable and informative feedback signal to support appropriate therapeutic adaptations.[82]

LFPs in the beta band frequency (13-35 Hz)

LFP recordings from the STN or GPi consistently demonstrate excessively synchronized activity in the beta band frequency (13-35 Hz) in patients with PD during "off" periods or after withdrawal of dopaminergic medications. Beta power was first found by Peter Brown in 2001 to be abnormally high in the STN of untreated PD patients. Beta power decreases during movement preparation and execution, showing a significant rebound after movement termination. One should keep in mind that beta activity is not specific to PD or even pathological per se. Excessive beta activity in PD most likely reflects a pathological alteration of physiological synchronization involved in dynamic brain state transitions.[83]

Beta band and aDBS

Beta band is the most studied neurophysiological biomarker in the design of aDBS. Beta activity is considered to be the most suitable feedback sign for aDBS due to its clinical relevance and consistency. Beta activity correlates with the presence of contralateral rigidity and bradykinesia. Moreover, dopaminergic and DBS induced suppression of beta activity correlates with the improvement of motor impairment. Clinical implementation of sensing-enabled pulse generators provides the opportunity of safe, long-term recording of beta activity. Interestingly, the significant correlation between beta power and disease severity does not diminish over time. Since beta activity is measurable and consistently correlates with contralateral akinetic-rigid symptoms and their response to DBS therapy, it is currently regarded as a reliable neurophysiological biomarker to optimize DBS in patients with PD.[84]

Low beta (13-20 Hz) and high beta (21-35 Hz) bands

Beta activity is divided into two separate frequency components with rather distinct functions: low beta (13-20 Hz) and high beta (21-35 Hz). Low beta activity is more dominant within the STN and is generally considered as a pathological oscillation. Low beta activity is more sensitive to the beneficial effects of levodopa. Moreover, the power of low beta activity correlates with disease severity. In contrast to the low beta band, which plays a local (intraregional) role, high beta is related to long-distance (interregional) coupling. It has been suggested that high beta activity is a unique spectral signature of the hyperdirect pathway.[85]

Phase-amplitude coupling (PAC)

Phase-amplitude coupling (PAC) between STN high beta activity and cortical high-frequency oscillations (HFOs) is regarded as prokinetic and physiological. Higher high beta-cortical HFO coupling is in principle associated with significantly better motor performance. Hence, phase-amplitude coupling (PAC) between STN and motor cortex is regarded as a promising electrophysiological biomarker for aDBS.[86]

Beta bursts and aDBS

Physiological beta activity consists of some short-lived phasic bursts. Larger and longer duration bursts usually indicate pathological beta activity. In PD, the presence of abnormal beta bursts is significantly correlated with the degree of motor impairment and the severity of akinetic-rigid symptoms.[87,88] Diminishment of beta bursts amplitude and duration during movement, along with the levodopa and DBS effect on STN beta bursts distribution from long to short duration, make beta bursts a promising biomarker for aDBS. Having set a threshold to quantify and define beta bursts, aDBS could selectively trim larger and longer bursts, leading to a restoration of physiological STN beta activity, as well as a prevention of overtreatment that will cause dyskinesias.

Beta band and post-operative programming

Beta activity can also serve as a feedback signal to predict the optimal stimulation contacts. The contact pair with maximal STN beta power is very likely to provide the best symptom control and has the widest therapeutic window. If a particular contact pair has stronger beta activity, these two contacts are

more likely to be close to the pathological source. Accordingly, a lower amount of current is required to reach clinical improvement.[89]

Low frequency (LF) range: theta (4-7 Hz) and alpha (8-12 Hz) bands

Theta (4-7 Hz) and alpha (8-12 Hz) are usually discussed together, collectively referred to as the low frequency (LF) band. LF activity, recorded both from STN and GPi, showed a great increase after levodopa intake or DBS stimulation, in association with PD motor symptoms alleviation. LF has been also correlated to peak-dose as well as biphasic dyskinesias.[90] Therefore, it has been suggested that LF could be considered as biomarker for aDBS.

LF/beta power ratio

In particular, LF/beta power ratio has been introduced as a reliable feedback signal for triggering closed-loop DBS. In the "off" state, STN power is low in LF and high in beta band, triggering the stimulation to turn on. On the contrary, in the "on" – as well as in the "overtreatment" – state, STN power is in a way transferred from beta to the LF band, increasing the LF/beta ratio and consequently turning the stimulation off. It has been suggested that application of LF/beta ratio as a biomarker could also help reducing stimulation-related side effects.[58]

LF vs. beta power

Compared with beta power alone, STN LF activity may have two advantages as a supplementary feedback signal. First, beta activity is mainly located in the dorsolateral STN, while LF is usually more widespread, with its peak tracked in the ventromedial STN. In view of the fact that the stimulating electrode is constantly adjusted to achieve optimal efficacy, while simultaneous stimulating and recording cannot be performed in the same contact, it is obviously meaningful to be able to record feedback signals from both the dorsal and ventral STN. Second, beta activity is more correlated with rigidity and bradykinesia compared to rest tremor.[91] LF band, ranging from 4 to 12 Hz, normally includes tremor frequency band (4-8 Hz). Therefore, LF could potentially serve as a supplementary electrophysiological biomarker in tremor dominant patients. However, since LF band enhancement has been associated with rest tremor as well as levodopa-induced dyskinesias (LIDs), a lack of precise distinction between these two states could lead to undesirable side effects when applying DBS. Machine learning algorithms and multifeatured engineering have been proved helpful for the quick and accurate detection of rest tremor.[92,93]

Tremor frequency (4-8 Hz)

Oscillations within the tremor frequency (TF) band (4-8 Hz) are detected in the STN of tremor dominant PD patients. On the other hand, there is no correlation between beta power and rest tremor, likely implying that different pathophysiological mechanisms are involved in tremor generation and akinetic-rigid symptoms. In fact, in tremor dominant PD patients, beta power was found to significantly decrease along with tremor frequency enhancement. It has been hypothesized that rest tremor reduces STN beta power while simultaneously increasing TF. Hence, it has been suggested that a combination of TF and beta power could provide adequate information in the case of aDBS, releasing stimulation whenever STN power increases in the band of TF while decreasing in the beta band. However, it should be noted that TF oscillations normally occur shortly after tremor onset. This short latency period has been reported to vary between 150ms and several seconds. Therefore, the length of the aforementioned latency period should be taken under consideration when using TF as feedback signal for aDBS.[92]

Gamma band (35-200 Hz)

Gamma band activity is generally regarded as prokinetic, acting as a compensatory mechanism for the akinetic role played by beta activity. A positive correlation between movement velocity and an increase in the STN narrow gamma band activity (40-90 Hz) has been established. The synchronization of gamma power during movement occurs in bursts, with gamma burst rates significantly increasing in parallel with fast movements.[94] Movement-related gamma band augmentation is not restricted to the STN, being also present in the cortex. In contrast to beta activity response, levodopa administration leads to gamma power enhancement. Moreover, peak-dose dyskinesias are associated with gamma band overactivity. Nonetheless, studies have shown that low gamma activity (35-45 Hz) is associated with rest tremor severity. A possible explanation to this contradictory finding could be that tremor amplitude increases during stress when STN gamma oscillations become stronger.

High Frequency Oscillations (>200 Hz)

Similar to gamma band activity, high frequency oscillations (HFOs) are considered to be prokinetic. HFO power increases at movement onset, as well as after levodopa administration. Given the prokinetic nature of HFO, it has been postulated that high-frequency STN-DBS improves PD motor symptoms by evoking STN neural activities that are quite similar to HFOs.[95]

Slow HFOs (200-300Hz) and Fast HFOs (300-400Hz) – sHFO/fHFO ratio

HFOs are divided into two subgroups: slow (200-300 Hz) and fast (300-400 Hz) HFOs. These two subgroups have distinct functional roles with clinical relevance in the case of aDBS. Slow HFO (sHFO)

power is more pronounced in the "off" state and undergoes a significant decrease following levodopa administration. On the contrary, fast (fHFO) activity is remarkably enhanced after levodopa intake, resulting in a substantial power increase in the overall HFO band. Moreover, fHFO power is inversely correlated to akinesia. Power transition from sHFO to fHFO is regarded as an electrophysiological signal of shifting from the hypo-dopaminergic to the hyper-dopaminergic state.[96] In particular, power sHFO/fHFO ratio is significantly associated with akinesia/rigidity UPDRS-III scores. Additionally, power sHFO/fHFO is found to be significantly different between tremor and non-tremor states. As previously mentioned, tremor at rest does not reliably correlate with beta band activity. However, a frequency shift from sHFO toward fHFO may be a reliable biomarker of PD tremor. Furthermore, since HFOs are prone to change on a short timescale, a combination of TF, beta power and HFO could be valuable in detecting tremor in aDBS, allowing a much faster triggering of stimulation compared to beta activity.[97]

Conclusion

Deep brain stimulation (DBS) is nowadays considered as an effective neurosurgical treatment for Parkinson's disease (PD). Implanted electrodes provide the unique opportunity to record subcortical electrophysiological activity in vivo. Local field potentials (LFPs) is the term coined to describe the recorded discharges from a cluster of neurons surrounding the implanted electrode. Compared to cortical neural signals such as electroencephalography (EEG), electrocorticography (ECoG), and magnetoencephalography (MEG), LFPs can provide direct insight into basal ganglia function. In Parkinson's disease (PD), local field potentials (LFPs) that are abnormally synchronized in the beta frequency band (13-35 Hz) correlate with the severity of akinetic-rigid symptoms and their response to pharmacological and DBS therapy. Improvement of akinetic-rigid symptoms is associated with DBS suppression of abnormally synchronized LFPs in the low beta frequency band (13-20 Hz) and facilitation of high frequency gamma band (35-250 Hz).

DBS treatment could be optimized by adapting stimulation settings to the presence or absence of PD symptoms through closed-loop control. This critically relies on the use of biomarkers extracted from neurophysiological signals. This form of DBS is called "adaptive" (aDBS) or "closed-loop" DBS, and is currently available as clinical care in some countries. aDBS potentially reduces side-effects due to over-stimulation, saves battery power consumption, and holds promise for implementing symptom-specific stimulation settings. The success of aDBS applications critically depends on the quality and predictive value of the used biomarkers. Ideal biomarkers for adaptive DBS (aDBS) are indicative of symptom severity, detectable in every patient, and technically suitable for implementation. In the last decades, much effort has been put into the detection of local field potential (LFP) biomarkers and in their use in clinical practice. Out of the LFP signal features that have been linked to PD symptom severity so far, the most frequently reported associations are between UPDRS-III (motor) scores of rigidity and bradykinesia and measures of contralateral STN beta (13-35 Hz) oscillations. To date, most aDBS applications have used beta bursts with a minimum duration and amplitude as biomarker for triggering stimulation, with performance comparable but not superior to continuous DBS. It appears, though, that beta power alone is not sufficient to explain the full spectrum of Parkinsonian symptoms. The role of other frequency bands and the interaction between them needs to be further explored. Several strategies are being developed to overcome the limitations of current LFP biomarkers for aDBS. One promising avenue is the simultaneous use of multiple signal features to monitor different symptoms in parallel. In theory, monitoring of the tremor frequency range could be combined with the monitoring of beta and gamma oscillations to control stimulation. In this way, the amplitude of beta oscillations might act as a trigger for switching on or off the stimulation, while the stimulation amplitude can be controlled based on gamma band power.

Choosing the right biomarker(s) for aDBS can be challenging. With further development of hardware and neurophysiological understanding, it might be that additional biomarkers can be identified that are closer to true neurobiological causes. The ideal adaptive DBS system should be able to differentiate and individualize specific characteristics of the measured neurophysiological signals in real time, to then automatically deliver therapeutic electrical pulses of specific parameters for a specific amount of time. Neurophysiological biomarkers have great potential to optimize DBS and move the field toward adaptive DBS modalities.[81]

Review highlights

- Parkinson's disease dopaminergic denervation in BG results in aberrant activity patterns of surviving neurons both at cortical and BG levels due to cortico-thalamo-BG-cortical circuit dysfunction.
- Neurophysiological studies at cortical level in PD have revealed that both β-synchronization and Phase-Amplitude Coupling (PAC) are potential biomarkers.
- DBS intraoperative recordings from BG have detected oscillatory activity patterns at different frequencies that characterize different parkinsonian clinical states ("on" or "off").
- The resulting neuronal synchrony is also implied by the finding of increased amplitudes of local field potentials (LFPs) in the beta-band range of frequencies (10–30 Hz) at off (akinetic-rigid) state.
- Brain abnormal activity pattern configuration could provide valuable biomarkers that characterize not only a pathophysiological substrate, but also a corresponded specific clinical condition or a therapeutic effect.
- DBS treatment could be optimized by adapting stimulation settings according to LFPs recordings from the permanent electrode, combined with the presence or absence of PD symptoms, through closed-loop control.

Useful points to clinical practice

- Up to date, beta activity has shown the more consistent characteristics for an electrophysiological biomarker: it scales with hypokinetic motor symptoms (rigidity and bradykinesia).
- Certain types of permanent electrodes currently used for DBS in BG are able to monitor beta band activity (sensing) and provide the most effective configuration of stimulation parameters, optimizing the current delivery for best clinical results.
- Moreover, the so called "adaptive" (aDBS) or "closed-loop" DBS, is currently available as clinical care in some countries.

REFERENCES

[1] Hammond, C., Bergman, H., Brown, P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci. 2007;30(7):357–364.
[2] Caton R. The electric currents of the brain. British Medical Journal. 1875, Aug 28: 278
[3] Jung R, Berger W. Fiftieth anniversary of Hans Berger's publication of the electroencephalogram. His first records in 1924-1931. Arch Psychiatr Nervenkr. 1979: 227: 279-300.
[4] England AC, Schwab RS, Peterson E. The electroencephalogram in Parkinson's syndrome. Electroencephalogr Clin Neurophysiol. 1959 Nov;11(4): 723-731
[5] Ganglberger JA. The EEG in parkinsonism and its alteration by stereotaxically produced lesions in pallidum. Electroencephalogr Clin Neurophysiol. 1961; 13:82.
[6] Sirakov AA, Mezan IS. EEG findings in parkinsonism. Electroencephalogr Clin Neurophysiol. 1963 Apr; 15(2): 321-322.
[7] Yeager CL, Alberts WW, Delattre LD. Effect of stereotaxic surgery upon electroencephalographic status of Parkinsonian patients. Neurology. 1966; 16:904-910.
[8] Soikkeli R, Partanen J, Soininen H, Pääkkönen A, Riekkinen P Sr. Slowing of EEG in Parkinson's disease. Electroencephalogr Clin Neurophysiol. 1991 Sep;79(3):159-65.
[9] Portin R, Rinne UK. Predictive factors for cognitive deterioration and dementia in Parkinson's disease. Adv Neurol. 1987; 45:413-416.
[10] Neufeld MY, Inzelberg R, Korczyn AD. EEG in demented and non-demented parkinsonian patients. Acta Neurol Scand. 1988 Jul;78(1):1-5.
[11] Hirato M, Ishihara J, Horikoshi S, Shibazaki T, Ohye C. Parkinsonian rigidity, dopa-induced dyskinesia and chorea-dynamic studies on the basal ganglia-thalamocortical motor circuit using PET scan and depth microrecording. Acta Neurochir Suppl. 1995; 64:5-8.
[12] Rottach KG, Riley DE, DiScenna AO, Zivotofsky AZ, Leigh RJ. Dynamic properties of horizontal and vertical eye movements in parkinsonian syndromes. Ann Neurol. 1996 Mar;39(3):368-77.
[13] Lörincz A. Static and dynamic state feedback control model of basal ganglia-thalamocortical loops. Int J Neural Syst. 1997 Jun;8(3):339-57.
[14] Pfurtscheller G, Cooper R. Frequency dependence of the transmission of the EEG from cortex to scalp. Electroencephalogr Clin Neurophysiol. 1975 Jan;38(1):93-96.
[15] Manning JR, Jacobs J, Fried I, Kahana MJ. Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. J Neurosci. 2009 Oct28;29(43):13613-20.
[16] Toro C, Deuschl G, Hallett M. Movement-related electroencephalographic desynchronization in patients with hand cramps: evidence for motor cortical involvement in focal dystonia. Ann Neurol. 2000 Apr;47(4):456-461.
[17] Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchroniza-

tion. Brain. 1998 Dec:121 (Pt 12): 2271-2299.
[18] Miller KJ, Leuthardt EC, Schalk G, Rao RP, Anderson NR, Moran DW, Miller JW, Ojemann JG. Spectral changes in cortical surface potentials during motor movement. J Neurosci. 2007 Feb 28;27(9):2424-2432.
[19] Pfurtscheller G. Induced oscillations in the alpha band: functional meaning. Epilepsia. 2003;44 Suppl 12:2-8.
[20] Crowell AL, Ryapolova-Webb ES, Ostrem JL, Galifianakis NB, Shimamoto S, Lim DA, Starr PA. Oscillations in sensorimotor cortex in movement disorders: an electrocorticography study. Brain. 2012 Feb;135(Pt 2):615–630.
[21] Chen CC, Lin WY, Chan HL, Hsu YT, Tu PH, Lee ST, Chiou SM, Tsai CH, Lu CS, Brown P. Stimulation of the subthalamic region at 20 Hz slows the development of grip force in Parkinson's disease. Exp. Neurol. 2011 Sep:231(1):91-96.
[22] Timmermann L, Gross J, Dirks M, Volkmann J, Freund HJ, Schnitzler A. The cerebral oscillatory network of parkinsonian resting tremor. Brain. 2003 Jan;126(Pt 1):199-212.
[23] Muthuraman M, Raethjen J, Koirala N, Anwar AR, Mideksa KG, Elble R, Groppa S, Deuschl G. Cerebello-cortical network fingerprints differ between essential, Parkinson's and mimicked tremors. Brain. 2018 Jun 1;141(6):1770-1781.
[24] Hutchison WD, Lozano AM, Tasker RR, Lang AE, Dostrovsky JO. Identification and characterisation of neurons with tremor-frequency activity in human globus pallidus. Exp Brain Res. 1997 Mar;113(3):557-563.
[25] Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J Neurosci. 2000 Oct 15; 20:7766-7775.
[26] Hutchison WD, Dostrovsky JO, Walters JR, Courtemanche R, Boraud T, Goldberg J, Brown P. Neuronal oscillations in the basal ganglia and movement disorders: evidence from whole animal and human recordings. J Neurosci. 2004 Oct 20; 24(42): 9240–9243.
[27] Engel AK, Fries P. Beta-band oscillations: signalling the status quo? Curr Opin Neurobiol. 2010 Apr;20(2):156-165.
[28] Eusebio A, Pogosyan A, Wang S, Averbeck B, Gaynor LD, Cantiniaux S, Witjas T, Limousin P, Azulay JP, Brown P. Resonance in subthalamocortical circuits in Parkinson's disease. Brain. 2009 Aug;132(Pt 8):2139-2150.
[29] Berendse HW, Stam CJ. Stage-dependent patterns of disturbed neural synchrony in Parkinson's disease. Parkinsonism Relat Disord. 2007;13 Suppl 3: S440-445.
[30] Mallet N, Pogosyan A, Sharott A, Csicsvari J, Bolam JP, Brown P, Magill PJ. Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. J Neurosci. 2008 Apr 30;28(18):4795-4806.
[31] Pollok B, Krause V, Martsch W, Wach C, Schnitzler A, Südmeyer M. Motor-cortical oscillations in early stages of Parkinson's disease. J Physiol. 2012 Jul 1;590(13):3203-3212.
[32] Scheeringa R, Fries P, Petersson KM, Oostenveld R, Grothe I, Norris DG, Hagoort P, Bastiaansen MC. Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. Neuron. 2011 Feb 10;69(3):572-583.
[33] Tang CC, Eidelberg D. Abnormal metabolic brain networks in Parkinson's disease from blackboard to bedside. Prog Brain Res. 2010; 184:161-176.
[34] Delong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch. Neurol. 2007 Jan;64(1):20-24.
[35] Timmermann L, Wojtecki L, Gross J, Lehrke R, Voges J, Maarouf M, Treuer H, Sturm V, Schnitzler A. Ten-Hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. Mov Disord. 2004 Nov;19(11):1328-1333.
[36] Eusebio A, Chen CC, Lu CS, Lee ST, Tsai CH, Limousin P, Hariz M, Brown P. Effects of low-frequency stimulation of the subthalamic nucleus on movement in Parkinson's disease. Exp Neurol. 2008 Jan;209(1):125-130.
[37] Timmermann L, Florin E. 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. 2012 Jan;233(1):123-125.
[38] Sherman MA, Lee S, Law R, Haegens S, Thorn CA, Hämäläinen MS, Moore CI, Jones SR. Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice. Proc Natl Acad Sci USA. 2016 Aug 16;113(33): E4885-4894.
[39] Mariscal MG, Levin AR, Gabard-Durnam LJ, Xie W, Tager-Flusberg H, Nelson CA. EEG Phase-Amplitude Coupling strength and phase preference: Association with age over the first three years after birth. eNeuro. 2021 Jun 24;8(3).
[40] de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, Galifianakis NB, Starr PA. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci USA, 2013 Mar 19;110(12):4780-4785.
[41] de Hemptinne C, Swann NC, Ostrem JL,

Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. Nat Neurosci. 2015 May;18(5):779-786.

[42] Malekmohammadi M, AuYong N, Ricks-Oddie J, Bordeleon Y, Pouratian N. Pallidal deep brain stimulation modulates excessive cortical high β phase amplitude coupling in Parkinson disease. Brain Stimul. 2018 May-Jun;11(3):607-617.

[43] Swann NC, de Hemptinne C, Aron AR, Ostrem JL, Knight RT, Starr PA. Elevated synchrony in Parkinson disease detected with electroencephalography. Ann Neurol. 2015 Nov;78(5):742-750.

[44] Jackson N, Cole SR, Voytek B, Swann CW. Characteristics of waveform shape in Parkinson's disease detected with scalp electroencephalography. eNeuro. 2019 Jun 5; 6(3).

[45] Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of Deep Brain Stimulation. JAMA Neurol. 2013 Feb;70(2):163–171.

[46] Deuschl G, Antonini A, Costa J, Śmiśowska K, Berg D, Corvol JC, Fabbrini G, Ferreira J, Foltynie T, Mir P, Schrag A, Seppi K, Taba P, Ruzicka E, Selikhova M, Henschke N, Villanueva G, Moro E. European Academy of Neurology/ Movement Disorder Society-European Section guideline on the treatment of Parkinson's disease: I. Invasive Therapies. Mov Disord. 2022 Jul; 37:1360–1374.

[47] Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. J Neurol Neurosurg Psychiatry. 2009 Jun; 80:659–666.

[48] Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophys. 1994 Aug;72(2):507-520.

[49] Wichmann T, Dostrovsky JO. Pathological basal ganglia activity in movement disorders. Neuroscience. 2011 Dec 15; 198:232-244.

[50] Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989 Oct;12(10):366-375.

[51] DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990 Jul;13(7):281-285.

[52] Bergman, H, Wichmann T, DeLong, MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 1990 Sep 21;249(4975):1436–1438.

[53] Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. 1991 Apr 26;547(1):142–151.

[54] Wichmann T. Changing views of the pathophysiology of Parkinsonism. Mov Disord. 2019 Aug;34(8):1130-1143.

[55] Connolly AT, Muralidharan A, Hendrix C, Johnson L, Gupta R, Stanslaski S, Denison T, Baker KB, Vitek JL, Johnson MD. Local field potential recordings in a non-human primate model of Parkinsons disease using the Activa PC + S neurostimulator. J Neural Eng. 2015 Dec;12(6):066012.

[56] Goldberg JA, Rokni U, Boraud T, Vaadia E, Bergman H. Spike synchronization in the cortex/basal-ganglia networks of Parkinsonian primates reflects global dynamics of the local field potentials. J Neurosci. 2004 Jun 30;24(26):6003-6010.

[57] Lempka SF, McIntyre CC. Theoretical analysis of the local field potential in deep brain stimulation applications. PLoS One. 2013;8(3): e59839.

[58] Giannicola G, Rosa M, Servello D, Menghetti C, Carraba G, Pacchetti C, Zangaglia R, Cogiamanian F, Scelzo E, Marceglia S, Rossi L, Priori A. Subthalamic local field potentials after seven-year deep brain stimulation in Parkinson's disease. Exp Neurol. 2012 Oct;237(2):312-317.

[59] Weinberger M, Mahant N, Hutchison WD, Lozano AM, Moro E, Hodaie M, Lang AE, Dostrovsky JO. Beta Oscillatory Activity in the Subthalamic Nucleus and its relation to dopaminergic response in Parkinson's Disease. J Neurophysiol. 2006 Dec; 96(6):3248-3256.

[60] Brown P, Williams D. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol. 2005 Nov;116(11):2510-2519.

[61] Kühn AA, Kempf F, Brücke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A, Schneider GH, Hariz MI, Vandenberghe W, Nuttin B, Brown P. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory β activity in patients with Parkinson's Disease in parallel with improvement in motor performance. J Neurosci. 2008 Jun 11;28(24):6165– 6173.

[62] Silberstein P, Kühn AA, Kupsch A, Trottenberg T, Krauss JK, Wöhrle JC, Mazzone P, Insola A, Di Lazzaro V, Oliviero A, Aziz T, Brown P. Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain. 2003 Dec; 126(Pt 12):2597-2608.

[63] Horn A, Neumann WJ, Degen K, Schneider GH, Kühn AA. Toward an electrophysiological "sweet spot" for deep brain stimulation in the subthalamic nucleus. Hum. Brain Mapp. 2017 Jul;38(7):3377–3390.

[64] Karamintziou SD, Tsirogiannis GL, Stathis PG, Tagaris GA, Boviatsis EJ, Sakas DE, Nikita KS. Supporting clinical decision making during deep brain stimulation surgery by means of a stochastic dynamical model. J Neural Eng. 2014 Oct;11(5):056019.
[65] Michmizos KP, Frangou P, Stathis P, Sakas D, Nikita KS. 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 Inform. 2015 Jan; 19(1):174-180.
[66] Kostoglou K, Michmizos KP, Stathis P, Sakas D, Nikita KS, Mitsis GD. Classification and Prediction of Clinical Improvement in Deep Brain Stimulation from Intraoperative Microelectrode Recordings. IEEE Trans Biomed Eng. 2017 May;64(5):1123-1130.
[67] Telkes I, Viswanathan A, Jimenez-Shahed J, Abosch A, Ozturk M, Gupte A, Jankovic J, Ince NF. Local field potentials of subthalamic nucleus contain electrophysiological footprints of motor subtypes of Parkinson's disease. Proc Natl Acad Sci USA. 2018 Sep 4; 115(36):E8567–E8576.
[68] Camalier CR, Konrad PE, Gill CE, Kao C, Remple MR, Nasr HM, Davis TL, Hedera P, Phibbs FT, Molinari AL, Neimat JS, Charles D. Methods for surgical targeting of the STN in early-stage Parkinson's disease. 2014 Front Neurol. 2014 Mar 19;5(25):1-6.
[69] Valsky D, Marmor-Levin O, Deffains M, Eitan R, Blackwell KT, Bergman H, Israel Z. Stop! Border Ahead: Automatic detection of subthalamic exit during deep brain stimulation surgery. Mov Disord. 2017 Jan;32(1):70–79.
[70] Lu CW, Malaga, KA, Chou KL, Chestek CA, Patil PG. High density microelectrode recording predicts span of therapeutic tissue activation volumes in subthalamic deep brain stimulation for Parkinson disease. Brain Stimul. 2020 Mar-Apr;13(2):412–419.
[71] Connolly AT, Jensen AL, Bello EM, Netoff TI, Baker KB, Johnson MD, Vitek JL. Modulations in oscillatory frequency and coupling in globus pallidus with increasing parkinsonian severity. J Neurosci. 2015 Apr 15;35(15): 6231–6240.
[72] López-Azcárate J, Tainta M, Rodríguez-Oroz MC, Valencia M, González R, Guridi J, Iriarte J, Obeso JA, Artieda J, Alegre M. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. J Neurosci. 2010 May 12;30(19):6667–6677.
[73] Foffani G, Priori A, Egidi M, Rampini P, Tamma F, Caputo E, Moxon KA, Cerutti S, Barbieri S. 300-Hz subthalamic oscillations in Parkinson's disease. Brain. 2003 Oct; 126(Pt 10): 2153–2163.
[74] Tsiokos C, Hu X, Pouratian N. 200–300Hz movement modulated oscillations in the internal globus pallidus of patients with Parkinson's Disease. Neurobiol Dis. 2013 Jun; 54:464–474.
[75] Johnson LA, Aman JE, Yu Y, Sanabria DE, Wang J, Hill M, Dharnipragada R, Patriat R, Fiecas M, Li L, Schrock LE, Cooper SE, Johnson MD, Park MC, Harel M, Vitek JL. High-Frequency Oscillations in the Pallidum: A Pathophysiological Biomarker in Parkinson's Disease? Mov Disord. 2021 Jun;36(6):1332–1341.
[76] Johnson LA, Nebeck SD, Muralidharan A, Johnson MD, Baker KB, Vitek JL. Closed-loop deep brain stimulation effects on Parkinsonian motor symptoms in a non-human primate - is beta enough? Brain Stimulat. 2016 Nov-Dec;9(6):892–896.
[77] Karamintziou SD, Custódio AL, Piallat B, Polosan M, Chabardès S, Stathis PG, Tagaris GA, Sakas DE, Polychronaki GE, Tsirogiannis GL, David O, Nikita KS. Algorithmic design of a noise-resistant and efficient closed-loop deep brain stimulation system: A computational approach. PLoS One. 2017 Feb 21;12(2): e0171458.
[78] Little S, Brown P. What brain signals are suitable for feedback control of deep brain stimulation in Parkinson's disease? Ann N Y Acad Sci. 2012 Aug;1265: 9–24.
[79] Abosch A, Lanctin D, Onaran I, Eberly L, Spaniol M, Ince NF. Long-term recordings of local field potentials from implanted deep brain stimulation electrodes. Neurosurgery. 2012 Oct;71(4):804-814.
[80] FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. 2016. Silver Spring (MD): Food and Drug Administration (US).
[81] van Wijk BCM, de Bie RMA, Beudel M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. J Neurol. 2023 Feb;270(2):1162-1177.
[82] Hoang KB, Turner DA. The emerging role of biomarkers in adaptive modulation of clinical brain stimulation. Neurosurgery. 2019 Sep 1;85(3): E430-E439.
[83] Yin Z, Zhu G, Zhao B, Bai Y, Jiang Y, Neumann WJ, Kühn AA, Zhang J. Local field potentials in Parkinson's disease: A frequency-based review. Neurobiol Dis. 2021 Jul; 155:105372.
[84] Sirica D, Hewitt AL, Tarolli AG, Weber MT, Zimmerman C, Santiago A, Wensel A, Mink JW, Lizárraga KJ. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2012 Aug;11(4):315-328.

[85] Neumann WJ, Degen K, Schneider GH, Brücke C, Huebl J, Brown P, Kühn AA. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. Mov Disord. 2016 Nov;31(11):1748-1751.
[86] Ozturk M, Abosch A, Francis D, Wu J, Jimenez-Shahed J, Ince NF. Distinct subthalamic coupling in the ON state describes motor performance in Parkinson's disease. Mov Disord. 2020 Jan;35(1):91-100.
[87] Tinkhauser G, Pogosyan A, Tan H, Herz DM, Kühn AA, Brown P. Beta burst dynamics in Parkinson's disease OFF and ON dopaminergic medication. Brain. 2017 Nov 1; 140(11):2968-2981.
[88] Tinkhauser G, Pogosyan A, Little S, Beudel M, Herz DM, Tan H, Brown P. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. Brain. 2017 Apr 1;140(4):1053-1067.
[89] Tinkhauser G, Pogosyan A, Debove I, Nowacki A, Shah SA, Seidel K, Tan H, Brittain JS, Pettermann K, di Biase L, Oertel M, Pollo C, Brown P, Schuepbach M. Directional field potentials: A tool to optimize deep brain stimulation. Mov Disord. 2018 Jan;33(1):159-164.
[90] Alonso-Frech F, Zamarbide I, Alegre M, Rodriguez-Oroz M, Guridi J, Manrique M, Valencia M, Artieda J, Obeso JA. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. Brain. 2006 Jul;129(Pt 7):1748-1757.
[91] Eusebio A, Thevathasan W, Doyle Gaynor L, Pogosyan A, Bye E, Foltynie T, Zrinzo L, Ashkan K, Aziz TZ, Brown P. Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. J Neurol Neurosurg Psychiatry. 2011 May; 82(5):569-573.
[92] Hirschmann J, Abbasi O, Storzer L, Butz M, Hartmann CJ, Wojtecki L, Schnitzler A. Longitudinal recordings reveal transient increase of alpha/low-beta power in the subthalamic nucleus associated with the onset of Parkinsonian rest tremor. Front Neurol. 2019 Mar 7; 10:145.
[93] Yao L, Brown P, Shoaran M. Improved detection of Parkinsonian rest tremor with feature engineering and Kalman filtering. Clin Neurophysiol. 2020 Jan;131(1):274-284.
[94] Lofredi R, Neumann WJ, Bock A, Horn A, Huebl J, Siegert S, Schneider GH, Krauss JK, Kühn AA. Dopamine-dependent scaling of subthalamic gamma bursts with movement velocity in patients with Parkinson's disease. Elife. 2018 Feb 1;7: e31895.
[95] Van Wijk BC, Beudel M, Jha A, Oswal A, Foltynie T, Hariz MI, Limousin P, Zrinzo L, Aziz TZ, Green AL, Brown P, Litvak V. Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. Clin Neurophysiol. 2016 Apr; 127(4):2010-2019.
[96] Özkurt TE, Butz M, Homburger M, Elben S, Vesper J, Wojtecki L, Schnitzler A. High frequency oscillations in the subthalamic nucleus: a neurophysiological marker of the motor state in Parkinson's disease. Exp Neurol. 2011 Jun;229(2):324-331.
[97] Little S, Beudel M, Zrinzo L, Foltynie T, Limousin P, Hariz M, Neal S, Cheeran B, Cagnan H, Gratwicke J, Aziz TZ, Pogosyan A, Brown P. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2016 Jul;87(7):717-721.