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Review

Impairment of brain functions in Parkinson's disease reflected by alterations in neural connectivity in EEG studies: A viewpoint

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HIGHLIGHTS

- EEG studies in PD were reviewed, with the focus on oscillatory activities and DBS.
- Knowledge of EEG patterns in PD enables progress particularly in DBS therapy.
- Progress was reported recently using advanced analytical methods.

ABSTRACT

Clinical symptoms of Parkinson's disease (PD) are accompanied by pathological phenomena detected locally in the basal ganglia (BG) as changes in local field potentials (LFPs) and also in cortical regions by electroencephalography (EEG). The literature published mainly between 2000 and 2017 was reviewed with an emphasis on approaches emerging after 2000, in particular on oscillatory dynamics, connectivity studies, and deep brain stimulation. Eighty-five articles were reviewed. The main observations were a general slowing of background activity, excessive synchronization of beta activity, and disturbed movement-related gamma oscillations in the BG and in the cortico-subcortical and cortico-cortical motor loops, suppressible by dopaminergic medication as well as by high-frequency deep brain stimulation (DBS). Non-motor symptoms are related mainly to changes in the alpha frequency range. EEG parameters can be useful in defining the risk of dementia in PD. Further progress was reported recently using advanced analytical technologies and high-performance computing (graph theory). Detailed knowledge of LFPs in PD enabled progress particularly in DBS therapy, which requires optimizing the clinical effect and minimizing adverse side effects. The neurocognitive networks and their dysfunction in PD and DBS therapy are promising targets for future research.

Contents

Abbreviations: AD, Alzheimer's disease; aDBS, adaptive deep brain stimulation; BCI, brain–computer interface; BP, Bereitschaftspotential; BG, basal ganglia; CNV, contingent negative variation; DBS, deep brain stimulation; DLB, dementia with lewy bodies; EEG, electroencephalography; EP, evoked potentials; ERD/S, event-related de/synchronization; GPi, globus pallidum; HD-EEG, high-density EEG; HDP, hyperdirect pathway; HFOs, high-frequency oscillations; ICD, impulse control disorders; LFPs, local field potentials; MEG, magnetoencephalography; MRI, magnetic resonance imaging; P3, cognitive evoked potential; PFC, prefrontal cortex; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PPN, pedunculopontine nucleus; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; STN, subthalamic nucleus; tCDS, transcranial direct current stimulation; UPDRS, unified Parkinson's disease rating scale.

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1. Introduction

Parkinson's disease (PD) is characterized mainly by motor symptoms of tremor, rigidity, bradykinesia, and postural instability (Aarsland et al., 2011) and is accompanied by several non-motor symptoms. The phenotype of the disease varies among patients. The speed progression is very individual, as is the representation of motor and non-motor symptoms (Eggers et al., 2012). Cognitive impairment and dementia are common in advanced PD. Severe cognitive impairment increases disability and mortality in advanced PD.

Research on brain functions in PD has been focused mainly on metabolic, genetic, imaging, and clinical studies. Much less attention has been paid to electrophysiological studies. Electroencephalography (EEG) and magnetoencephalography (MEG) have several advantages over functional imaging methods, mainly the best time resolution. The fine analysis of the frequency spectrum ranging from very slow (subdelta) to very high frequency oscillations (over 300 Hz) enables precise connectivity studies. The bioelectric activity within the brain tissue may be recorded directly via surgically inserted intracerebral electrodes, even in very small structures like the subthalamic nucleus (STN). The deep brain stimulation (DBS) electrode may be used for recording of the LFPs during the interval between the intracranial implantation and connection to the extracranial current generator.

PD is linked with various electrophysiological signs, from changes of EEG-detected background activity to complex disturbances in functional connectivity on the cortico-subcortical and cortico-cortical levels. The potential for electrophysiological studies in PD has not yet been fully explored. For this reason, we decided to review the recent literature with the aims of identifying the recent electrophysiological findings related to PD, exploring their clinical relevance, and inspiring future research. Detailed knowledge of physiological and pathophysiological phenomena related to PD may help to develop novel approaches in PD treatment, for example in the domains of invasive and non-invasive neuromodulatory treatment.

2. Methods

The recent literature concerning PD-related EEG changes was summarized to provide a viewpoint about the potential of measuring brain bioelectrical activity for clinical use. A large amount of data about EEG in PD has been published; We focused mainly on recent articles concerning oscillatory phenomena and DBS as they may have a clinical impact. The search was performed in the PubMed database. A total of 85 articles, mainly published between 2000 and 2017, were selected and reviewed for this report. Seminal articles published earlier were included only exceptionally.

3. Results

3.1. Surface (scalp) EEG/MEG

Several scalp EEG and MEG studies have shown a general slowing of resting state background activity in PD (Neufeld et al., 1988; Soikkeli et al., 1991; Neufeld et al., 1994; Kotini et al., 2005; Sinanovic et al., 2005; Bosboom et al., 2006; Stoffers et al., 2007). Changes were described in de novo PD patients compared to healthy controls, including a widespread increase of power in the theta and low alpha bands, as well as a decrease of beta and gamma power (Stoffers et al., 2007); see Table 1. Levodopa intake modulates scalp EEG activity in PD patients and is associated mainly with power increases in the alpha and beta rhythms in centro-parietal areas (Melgari et al., 2014). The amplitude of movement-related slow potentials (CNV- contingent negative variation and BP- Bereitschaftspotential) is decreased in PD (for review, see Georgiev et al., 2016). Patients with dementia (PDD) have slower background EEG than patients without dementia. An increase of delta activity and a diffuse decrease in alpha power was found in PDD patients compared to PD patients without dementia (Bosboom et al., 2006). Worse cognitive performance was also linked to increases in the central and parietal low alpha activity. This could be a sign of a pathological level of attention, as alpha oscillations have an important role in attentional processes. The higher level of attention might produce increased perseveration (Stoffers et al., 2007). The suppression of alpha activity due to eye opening is reduced in PDD (Soikkeli et al., 1991; Bosboom et al., 2006). The evaluations of cognitive evoked potentials (P3) in PD patients without dementia can serve as predictors of dementia (Tanaka et al., 2000). With increasing dementia in PDD patients, the amplitude and power of P3 potential is decreased, and the P3 latency is increased; see Table 1. Apathy in PD patients is associated with decreased amplitude of novelty P3 potential in a three-stimulus oddball paradigm (Kaufman et al., 2016). Visual reading of EEG should be performed with caution, as the parkinsonian tremor can diffusely influence the scalp signal, mainly in the theta band power through movement artefacts (Timmermann et al., 2003).

3.2. Local field potentials (LFP) in the basal ganglia

Intracranial studies enable direct recordings from the subcortical structures that are not within reach of scalp measurements. The analysis of LFPs has provided accurate knowledge about physiological and pathophysiological phenomena in the BG, mainly in the STN, which is the most frequent DBS target for treatment of motor symptoms in advanced PD. Phase and time locked event-related potentials (evoked potentials) are detected by averaging the EEG signal. Movement-related slow potentials (BP and CNV) as well as cognitive event-related potentials were detected in the STN (Purzner et al., 2007; Baláž et al., 2008). These findings indicate that STN plays an important role not only in self-paced and cued movements but also in cognition. Oscillatory changes in ongoing EEG signals can be evaluated as event-related de/synchronization (ERD/S) of some frequency component. ERD/S are time locked but not phase locked phenomena and are analysed as power changes (squared amplitude values). ERD represents a power decrease, ERS means a power increase (Lopes da Silva, 2006). Oscillations in the beta and gamma frequencies play a major role in motor control in the BG (Brown, 2003; 2006); see Table 2. STN beta activity is desynchronized before self-paced voluntary movement as well as before cued movements and also correlates with the force of motor effort (Williams et al., 2003; Alegre et al., 2005; Androulidakis et al., 2008; Oswal et al., 2012, 2013; Tan et al., 2013). An increase in

Table 1
Surface studies.

	Background activity	EP	Delta	Theta	Alpha	Beta	gamma
PD motor symptoms	General slowing (Neufeld et al. 1988; Soikkeli et al. 1991; Kotini et al. 2005; Sinanovic et al. 2005)	CNV and BP ↓ amplitude (Georgiev et al. 2016)		↑ (Stoffers et al. 2007) tremor ↑ ↑ (Timmermann et al. 2003)	↑(Stoffers et al. 2007)	↓(Stoffers et al. 2007)	↓(Stoffers et al. 2007)
PDD	↑ ↑ general slowing (Bosboom et al. 2006)	P3 ↓ amplitude ↑ latency (Tanaka et al. 2000)	↑ (Bosboom et al. 2006)		↓ (Bosboom et al. 2006)		
Levodopa					↑ CP (Melgari et al. 2014)	↑ CP (Melgari et al. 2014)	

Legend: Summary of the main surface EEG and MEG findings. ↑: Increase, ↓: Decrease. CP: Centroparietal, CNV: Contingent negative variation, BP: Bereitschaftspotential. The summary is based on the comparisons of PD versus healthy controls, PDD versus PD without dementia, and PD on versus off levodopa.

Table 2
STN local field potentials.

	Off state	On state	Nonmotor
Theta-alpha		↑ dyskinesias, dystonia (Foffani et al. 2005; Barow et al. 2014)	ERS ↑ with attention and ICD (Bočková et al. 2011; Rodriguez-Oroz et al. 2011) ↓ - emotions (Huebl et al. 2014)
Beta	↑↑ Bradykinesia, rigidity (Brown 2003; Kühn et al. 2006; Androulidakis et al. 2007; Giannicola et al. 2013; Chen et al. 2010)	↓ Motor improvement (Brown 2003, Kühn et al. 2006; Androulidakis et al. 2007; Giannicola et al. 2013; Chen et al. 2010) ↑ stop signal (Ray et al. 2012; Wessel et al. 2016)	↓ cognitive complexity ↓ reward (Oswal et al. 2013; Bočková et al. 2017)
Gamma	↓ Bradykinesia, rigidity (Brown 2003; Androulidakis et al. 2007)	↑ Motor improvement (Brown 2003; Androulidakis et al. 2007)	
HFOs	↑ Coupled to low beta (López-Azcárate et al. 2010)	Decoupling, perimovement ↑ (López-Azcárate et al. 2010)	

Legend: Summary of the known functional significance of the oscillations in each frequency band in the STN, during motor off and on states and related to nonmotor functions. ↑: Power increase (ERS), ↓: Power decrease (ERD), ICD: Impulse control disorders

beta power is linked to successful stopping of a motor action (Ray et al., 2012; Wessel et al., 2016). Changes in beta reactivity are also influenced by contextual factors like reward or cognitive complexity (Oswal et al., 2013; Bočková et al., 2017). Beta event-related desynchronization (ERD) was observed during saccadic eye movement; moreover, this beta ERD was increased during antisaccades that required inhibition of reflexive responses (Yugeta et al., 2013) and could therefore reflect the involvement of executive functions. Hypersynchrony in the 13–35 Hz frequency range correlates to clinical motor symptoms in PD and is suppressed by dopaminergic medication and high-frequency DBS, and the degree of suppression is linked with clinical improvement (Brown, 2003; 2006; Kühn et al., 2006; Androulidakis et al., 2007; Giannicola et al., 2010, 2013; Chen et al., 2010); see Table 2.

Increased low-frequency oscillations (5–13 Hz) in PD were detected after dopaminergic medication in the STN as well as in the GPi and are related to chorea and dystonic movements (Silberstein et al., 2003; Priori et al., 2004; Foffani et al., 2005; Marceglia et al., 2007; Barow et al., 2014).

High-frequency oscillations (HFOs) around 300 Hz have also been reported in the STN in PD patients (Foffani et al., 2003; López-Azcárate et al., 2010).

Alterations in LFPs are also related to non-motor functions (attention and decision making), clinical symptoms (depression), and complications in PD (ICD), mainly in lower frequencies (5–13 Hz). Event-related synchronization (ERS) in the low alpha frequency range was detected in the STN as a response to distractor stimuli in a three-stimulus paradigm, reflecting an attentional orienting response (Bočková et al., 2011). An increase in the 5–13 Hz frequency range is related to the conflictual decision-making condition (Fumagalli et al., 2011). A local decrease in alpha power was found for emotionally arousing but not for neutral pictures. This alpha power decrease was reduced for pleasant stimuli and increased for unpleasant stimuli in depressive patients compared with patients without depression (Huebl et al., 2014). This probably reflects the depressive mood disturbances in PD patients with STN-DBS. Increased theta-alpha activity is associated with impulse control disorders (ICD) and pathological gambling in PD (Rodriguez-Oroz et al., 2011; Rosa et al., 2013); see Table 2. Oscillations in one frequency range can be accompanied and influenced by changes in another frequency range. Moreover, it has been shown that the phase of low frequency activity can drive the amplitude of gamma oscillations. These dynamic interactions can be studied as cross-frequency coupling or phase-amplitude coupling and represent both a physiological mechanism and part of the pathophysiology of symptoms in PD. Pathological low-beta and HFOs coupling was observed during the PD off state in the STN, and there was no change during movement performance. In the on state, low-beta activity was suppressed, pathological coupling disappeared, and the HFOs displayed movement-related modulation (López-Azcárate et al., 2010); see Table 2 and Fig. 1.

New DBS targets are being examined and introduced in PD. Pedunculopontine nucleus (PPN) has been recently introduced as

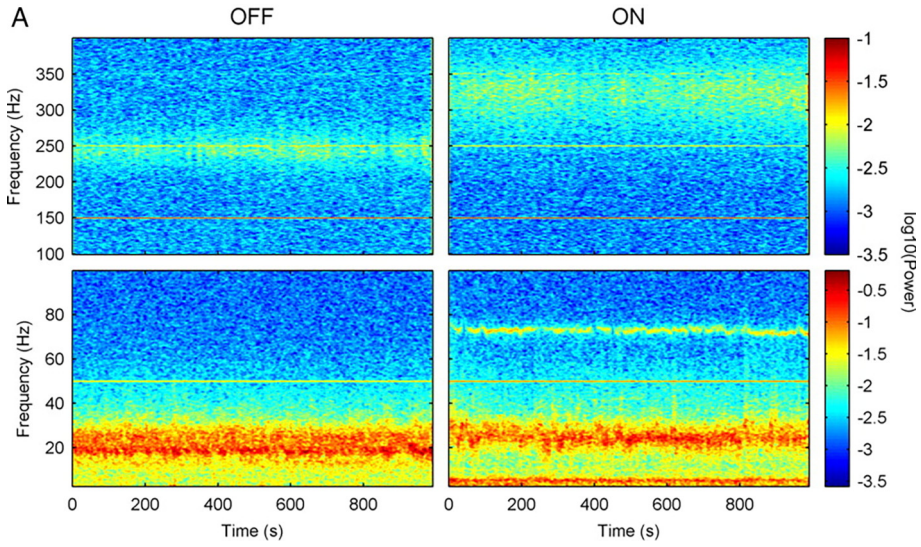

Fig. 1. Time-frequency analysis showing oscillatory dynamics during off and on states in the STN. Pathological beta hypersynchrony linked to the main motor symptoms in the PD off state is reduced while gamma activity (60–80 Hz) is restored during the on state after dopaminergic medication intake. Changes in HFOs are also displayed. Pathological phase-amplitude coupling between low-beta and HFOs was demonstrated. These beta-coupled HFOs show little or no change during voluntary movements, depending on the level of bradykinesia and rigidity. In the on state, the beta hypersynchrony disappears, leading to functional decoupling with clear movement-related modulation in HFOs (used from López-Azcárate et al. 2010, with permission).

Table 3
STN functional connectivity (FC).

Symptoms	STN FC to				Prefrontal cortex
	GPi	Thalamus	Motor cortex (SMA)	Temporo- parietal cortex	
Tremor	3–10 Hz coherence spreading from STN to GPi, from GPi to thalamus and then from thalamus to motor cortex(Volkmann et al., 1996; Brown et al. 2001; Williams et al. 2002)				
Bradykinesia, rigidity	11–30 Hz hypersynchrony (Marsden et al 2001; Williams et al. 2002; Brown 2003)		11–30 Hz hypersynchrony (Marsden et al 2001; Williams et al. 2002; Brown 2003)		
Prokinetic effect/ clinical improvement	synchronous gamma oscillations (over 60 Hz) (Brown et al. 2001; Williams et al. 2002; Cassidy et al. 2002)		synchronous gamma oscillations (over 60 Hz) (Brown et al. 2001; Williams et al. 2002; Cassidy et al. 2002)		
Non-motor functions				7–12 Hz oscillations cognitive functions (Litvak et al. 2010; Litvak et al. 2011; Hirschmann et al. 2011)	4–8 Hz coherence conflict conditions and error monitoring (Zavala et al. 2014, 2016).

Legend: summary of the functional coupling (connectivity) of the STN to the subcortical and cortical structures in relation to motor and nonmotor PD symptoms.

a promising target mainly in patients with severe gait disorders. Direct LFP recordings have detected mainly alpha oscillations that are enhanced after levodopa intake (Androulidakis et al., 2008). Another interesting finding is a different beta band reactivity of PPN LFPs in comparison to STN and GPi. Movement-related beta ERD was observed during the off state and surprisingly premovement beta ERS occurred in the on state. Beta oscillations probably have a prokinetic nature in the area of PPN (Tsang et al., 2010). Somatosensory evoked potentials were recorded from PNN, suggesting probably direct somatosensory connections of the PPN (Yeh et al., 2010; Insola et al., 2014).

3.3. Functional connectivity disturbances in Parkinson's disease on the cortico-subcortical level

Integration of activity within various brain areas is necessary for normal brain functioning. Dynamic relationships called coupling between different brain regions can be studied as functional connectivity using several methods. Functional connectivity is defined as a statistical relation between the neural activity of regions of interest. Neurological disorders such as PD are associated with changes in the functional connectivity of oscillatory reactivity (Schnitzler and Gross, 2005).

Coherence evaluation is one of the analytical methods for testing if different brain regions have similar oscillatory activity. It measures the level of association of frequency spectra of two or more areas. Coherence coupling between STN and GPi LFPs and between their thalamic projections and the cortex in the 3–10 Hz oscillation range are related to tremor in untreated parkinsonian states. STN activity precedes that of GPi, and activity in the GPi's thalamic projection precedes cortical activity. This finding is consistent with the net driving of the motor cortex at tremor frequencies through the GPi-thalamo-cortical pathway (Volkmann et al., 1996; Brown et al., 2001; Williams et al., 2002; for review see Brown, 2003); see Table 3. Beta and gamma range oscillations are crucial in motor control in cortico-basal ganglia loops (Brown 2006). Beta band coherence (11–30 Hz) between the STN, GPi, and cortical structures (mainly the supplementary motor area - SMA) has a strong antikinetic character. It is greater in the hypodopaminergic condition and decreased before and during voluntary movement (Marsden et al., 2001; Williams et al., 2002; Brown 2003); see Table 3. Gamma synchrony (over 60 Hz) was

found in the STN, GPi, and SMA after levodopa medication. These oscillations are considered to be prokinetic in nature. A prokinetic effect in PD patients is observed during stimulation of the STN and GPi using frequencies higher than 60 Hz (Brown et al., 2001; Williams et al., 2002; Cassidy et al., 2002; Brown, 2003); see Table 3. Reduction in the cortico-subthalamic gamma activity was observed to be related to response inhibition and was disturbed in patients with impulse-control disorders (ICD) (Alegre et al., 2013).

Two different functional networks with frequency-specific couplings have been described between the STN and cortical structures in PD (Litvak et al., 2010; 2011; Hirschmann et al., 2011); see Table 3. The temporo-parietal areas are coupled to STN at alpha band (7–12 Hz). The motor and premotor regions are coupled to the STN at beta frequencies (13–30 Hz). A recent combined simultaneous surface MEG and intracranial LFP recording study during ongoing DBS showed that clinically effective STN-DBS suppresses local low beta activity in the STN and furthermore that the level of this suppression correlates with improvement of motor symptoms. DBS also suppressed synchronization between the STN and mesial premotor regions, mainly the SMA. Coupling between these structures is predominantly in the high beta band. Beta coupling between the STN and primary (lateral) motor cortex was surprisingly not influenced by DBS. High and low beta band connectivity between the cortex and the STN may reflect coupling via the hyperdirect pathway (HDP) and indirect pathways (Oswal et al., 2016). Beta-band resynchronization was found in the STN in conflict situations (Stroop effect) and stops the motor system until the conflict is resolved. This is considered to be the correlate of the hyperdirect inhibitory activity from the cortex to the STN (Brittain et al., 2012). Subdural cortical (strip) recordings were used to obtain direct signal from the motor cortex corresponding to the HDP during STN-DBS. STN local beta power was decreased dependent on the voltage used during high-frequency DBS. Beta power reduction in the motor cortex was most likely propagated antidromically or orthodromically through cortico-basal ganglionic pathways, which supports the hypothesis that DBS improves the motor clinical symptoms by reducing excessive synchrony in the sensorimotor network (Whitmer et al., 2012). However, this reduction is fixed and depends on the ongoing DBS. This stimulation condition leads to the absence of an ideal balance in network functioning (excessive reduction of beta synchrony and disturbed cross-frequency coupling) and can impair other behaviour performance (Brittain et al., 2014). For example, theta band coherence between the prefrontal cortex and STN is important in conflict conditions and error monitoring. It has been hypothesized that this theta coupling could be disturbed via DBS, leading to impulse control disorders (Zavala et al., 2014, 2016). Moreover, it has been shown that DBS does not supress beta hypersynchrony in all subjects, in contrast to levodopa. The diverse responsiveness to DBS in some patients remains to be clarified. There is no additional effect of DBS when beta oscillations are already suppressed by levodopa (Giannicola et al., 2010). These findings have contributed to the development of 'smart' stimulators that provide spatially targeted stimulation based on real-time readouts of neural signals reflecting the patient's actual clinical state that is displayed in LFPs. In adaptive DBS (aDBS) a brain–computer interface (BCI) system is used to detect and subsequently suppress excessive beta activity that is recorded directly from the STN. This feedback-dependent intermittent stimulation can be more efficient and clinically superior to current standard continuous DBS (Little et al., 2013).

Concerning the PPN area, LFP alpha activity is coupled to similar cortical activity after levodopa before self-paced movement performance. These interactions are probably related to attentional processes that are necessary for correct movement performance (Androulidakis et al., 2008). A direct connection between PPN and STN was confirmed using direct recordings of PPN-evoked potentials during STN stimulation (Neagu et al., 2013).

3.4. Functional connectivity disturbances in Parkinson's disease on the cortical level

Growing interest has been focused on DBS-induced connectivity modifications on the cortical level. DBS-induced changes of PD-related EEG phenomena might be important and are still largely unknown. Here we summarise some studies with heterogeneous and partly contradictory results. Disease stage-specific markers are also documented. New methodological approaches, such as high-density EEG, source reconstruction, and graph theory might be helpful in this field.

In earlier studies, an increased resting-state cortico-cortical functional connectivity in the alpha frequency band was found to be a sign of early PD. A 4–30 Hz range functional connectivity disturbance increases with disease progression (Stoffers et al., 2007, 2008). Interregional functional connectivity between different brain areas is increased in theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz) bands in PD patients without dementia compared to healthy individuals (Bosboom et al., 2009). Cortico-cortical alpha-beta coherence (10–35 Hz) is linked to the severity of clinical symptoms, mainly bradykinesia, and is reduced after both levodopa and DBS (Silberstein et al., 2005).

Cognitive dysfunctions are associated with increased interhemispheric functional connectivity in the alpha range (Stoffers et al., 2008).

Current studies report specific movement-related coupling from the prefrontal cortex (PFC) to the SMA in the gamma band in healthy controls. PD patients in the off state did not express any frequency-specific coupling between these areas and the physiological pattern was reinstated after levodopa (Herz et al., 2013).

EEG connectivity patterns are a promising tool for detecting cognitive impairment risks in PD. In PD patients with dementia (PDD), reduced functional coupling in the delta (0.5–4 Hz), theta, and alpha rhythms was found, and it was most pronounced in the inter-temporal and fronto-temporal functional connections (Bosboom et al., 2009). Slowing in neuronal activity and a reduction in functional connectivity in PDD patients was described in comparison to PD patients without dementia (Ponsen et al., 2012). Compared to PD patients, PDD patients had more delta and theta power in the parieto-occipital and fronto-parietal areas. The PDD patients had less alpha and beta power in the parieto-temporo-occipital and frontal areas. In addition, connectivity in PDD patients between pairs of regions was stronger in the theta band and weaker in the delta, alpha, and beta bands. EEG parameters can be useful in defining the risk of dementia in PD. Both a lower-than-median background rhythm frequency and a higher-than-median EEG power in the theta band are associated with a higher risk of dementia in this population (Klassen et al., 2011). Impulse control disorders (ICDs) in PD are associated with deficient modulation of frontocentral theta activity (Carriere et al., 2016).

A network science called graph theory is a new methodological approach. It enables a macroscopic perspective of brain connections on the regional and whole brain network level and has therefore become a popular tool for distinguishing between health and disease since it can capture whole brain changes. Graph theory characterizes a network and the relationships between its nodes (different brain areas) by measuring the node degree as the number of connections with neighbouring nodes, the node strength by taking node weights into account, the clustering coefficient as a measure of segregation, and the shortest path length as a measure of integration. The clustering coefficient defines how neighbouring nodes are interconnected. The shortest path length is the

length of the shortest path between any two nodes. Longer path lengths suggest a loss of links between functionally distant nodes. To capture nodes with important positions in network topology, there are numerous measures of centrality. A more regular character of the network suggests decreased efficiency in transferring information between distant regions of the brain (for review, see Bullmore and Sporns, 2009). In a recent graph theory study in PD, resting-state brain networks in early stage patients showed decreases in local clustering with preserved path length in the delta range in comparison to controls. A long-term analysis over a four-year period showed progressive impairment in local clustering in multiple frequency bands and also a decrease in path length in the alpha range. The longitudinal network changes were linked to the deterioration of motor and cognitive functions (Olde Dubbelink et al., 2014). According to a recent MEG study using graph analysis, a reversal of the physiological posterior-to-anterior information flow might play an important role in PD-related cognitive impairment (Boon et al., 2017).

The effect of DBS on cortical connectivity was also studied. Movement-related power decreases in the upper alpha and beta ranges were more facilitated with stimulation 'on' than with stimulation 'off' in many areas: the bilateral sensorimotor, premotor, SMA, parietal and prefrontal cortex. During the 'on' state, interhemispheric cortico-cortical coherence in the beta band was significantly reduced between the bilateral sensorimotor areas. The clinical effect on motor symptoms could be predicted from this cortical decoupling (Weiss et al., 2015).

4. Discussion, viewpoint and perspectives:

Electrophysiological phenomena related to motor dysfunctions in PD, mainly bradykinesia, tremor, and dyskinesias, have been widely studied and precisely described. Beta hypersynchrony in motor circuits is currently the most important finding enabling therapeutic progress: the development of adaptive neurostimulators (Little et al., 2013). However, these stimulators reflect beta oscillations only; changes in other frequency bands are not considered. It has been reported that non-motor symptoms in PD are associated with oscillatory activity in all frequency ranges – theta (impulse control disorders), alpha (depression), beta (cognitive impairment), and gamma (cognitive inflexibility). Moreover, there are dynamic relationships between lower and higher frequency ranges like phase-amplitude coupling with physiological and pathological significance. Pathological low-beta/HFO coupling is described in relation to PD motor symptoms. In general, phase-amplitude coupling is known to play an important role in cognitive functioning in large-scale brain networks. However, there is a lack of information about such interactions linked to non-motor symptoms in PD. Frequency-specific interregional couplings related to different actions and conditions is rather complex and remain to be fully elucidated by further research. For example, while pathologically increased power in the low beta range was observed in the STN, interregional pathological coupling between the STN and motor cortex occurs in the upper beta band. In the cognitive STN/temporo-parietal network, the connectivity in the alpha range plays a major role; for a review, see Oswal et al. (2013).

Current DBS with constant settings suppresses beta hypersynchrony and improves movement-related gamma reactivity resulting in improvements of bradykinesia and rigidity. Beta suppression may result in behavioural disturbance, for example in situations requiring the stop signal where rapid synchronization is necessary. The optimal level of beta ERD/S is not fully constant; it is task dependent. Moreover, the fine cross-frequency and phase-amplitude coupling relationships on local, subcortico-cortical, or cortico-cortical levels can be modified by DBS, resulting in diminished flexibility during cognitive and complex motor cognitive performance. To focus exclusively on beta suppression is helpful, but closed-loop neurostimulation based on the analysis of broader frequency bands and possibly also more flexible interfaces could increase effectivity and decrease the adverse effects of DBS.

These DBS related phenomena have yet to be fully clarified as the cognitive impairment and non-motor neuropsychiatric side effects of DBS therapy are poorly understood. Detailed knowledge of cross-frequency interactions in large-scale networks under different conditions could be helpful for further progress in aDBS in making the brain-computer interface more flexible. New potential structural targets and parameter settings could be defined.

The individual oscillatory reactivity related to DBS represents another interesting issue. It has been shown that there is variability in oscillatory reactivity to DBS even in such well-known responses as beta hypersynchrony reduction, which was absent in some patients (Giannicola et al., 2010). Frequency peaks in the STN vary among subjects. Different frequency reactivity in motor and cognitive tasks could underlie diverse effects of DBS and the occurrence of neuropsychiatric side effects. In some predisposed patients, DBS could influence both the beta band and the alpha range, resulting in cognitive dysfunctions. Biomarkers for identifying these subjects remain to be elucidated. Short-term DBS at individualized gamma frequencies did not differ from commonly used high-frequency stimulation in a clinical evaluation using UPDRS. Surprisingly, beta peak DBS did not lead to worsening of the clinical state (Tsang et al., 2012). Individualized stimulation frequencies should be also tested in long-term studies.

Closed-loop cortical stimulation of the motor cortex via epidurally implanted electrodes is another possible development direction in neuromodulatory therapy in PD. This line of research may help to provide next generation of neurostimulators using computational models of brain activity (Beuter et al., 2014). Mapping PD-related electrophysiological phenomena on the cortical level might also help to introduce non-invasive cortical stimulation techniques (rTMS, tCDS, etc.) into clinical practice.

High-density EEG (HD-EEG) and HD-EEG combined with direct local field recordings can reveal large-scale cortical and cortico-subcortical networks involved in PD pathophysiology, including non-motor circuits and the influence of DBS treatment. Advanced analytical technologies and high-performance computing methods, such as source reconstruction analysis and graph theory could help to define biomarkers indicating various disturbances in PD. Modelling of a system network is often a simplification, but it makes it possible to describe global organization and interactions between brain areas and helps to capture processes happening in the whole brain. For this reason, the network analysis approach could provide additional information to the local field and interregional coupling studies.

Parkinsonian state marker was described recently as an increased phase-amplitude coupling between the beta and gamma frequencies over the sensorimotor cortex using scalp EEG (Swann et al., 2015). This finding has the potential to help in differential diagnoses. Studies using novel computational electrophysiological methodologies should be more focused on cognitive and behavioural symptoms in PD itself and in DBS-related disturbances. It has been shown that EEG abnormalities can discriminate between dementia with Lewy bodies (DLB), Alzheimer's disease (AD), and PDD in the early stages of dementia (Bonanni et al., 2008). Quantitative EEG was recently introduced in the guidelines as a supportive biomarker for diagnosing DLB (Ferreira et al., 2016). As EEG is an easily accessible method, its use as a predictor of cognitive decline and possibly other types of non-motor dysfunction in PD might help to individualize the decision of whether DBS or another therapy for advanced PD (intestinal levodopa, apomorphine pumps) is indicated. Longitudinal EEG studies in DBS patients

could reveal biomarkers related to the adverse effects of DBS and in consequence could help to identify subjects at increased risk.

Concerning data acquisition during the DBS ON state, the possibility of synchronizing the clock with the DBS stimulator would be very beneficial. It could make it possible to sample the DBS artefacts (contained in the data during the DBS ON state) very precisely in the same phase in each repetition. In combination with a very high sampling frequency and proper artefact suppression techniques (Erez et al., 2010), it could reduce artefact residues to a minimum and enable the analysis of data in frequencies higher than high gamma (Özkurt et al., 2011). The combination of EEG with other brain mapping methods has been largely unexplored. For example, it was demonstrated recently that combined EEG and MRI indices could assist in the differential diagnosis of AD and DLB (Colloby et al., 2016).

It is evident that the potential of the electrophysiological recording techniques is large and many questions still remain.

5. Conclusions:

The main EEG correlates of PD are:

1. General slowing of scalp EEG-detected resting state background activity (increase in theta and low alpha power, loss of beta and gamma power); this is further increased in PDD.
2. In the BG, an excessive synchronization of 13–35 Hz activity is associated with motor impairment. It is suppressed by dopaminergic medication as well as by high-frequency stimulation of the STN. Non-motor symptoms are related mainly to changes in the alpha frequency range.
3. A characteristic sign in dopamine-depleted motor circuitries in PD is an abnormal cortico-subcortical coupling at beta frequencies (13–30 Hz). Coherence at 11 to 30 Hz between the STN, GPi, and SMA has a strong antikinetic nature. Synchronous oscillations in frequencies over 60 Hz within these structures have been found after levodopa intake and are considered to be prokinetic.
4. Cortico-cortical beta band coupling is related to the severity of parkinsonism, mainly bradykinesia, and is reduced with both levodopa and STN stimulation. STN-DBS facilitates movement-related beta desynchronization. Moreover, movement-induced gamma band coupling from the PFC to the SMA is absent in PD and reinstated after levodopa. Tremor and ICDs are associated with increased coupling in the theta band, cognitive disturbances are associated with increased interhemispheric functional connectivity in the alpha band. The clinical improvement after STN-DBS can be predicted by interhemispheric cortico-cortical decoupling in the beta band.
5. EEG parameters can be useful in defining the risk of dementia in PD. Both a lower-than-median background rhythm frequency and a higher-than-median EEG power in the theta band are associated with a higher risk of dementia in this population. Changes in P3 response and increased functional connectivity in the alpha band are described in relation to PDD.
6. Improved knowledge of cortical large-scale networks involved in PD dysfunctions and DBS therapy could help to individualize the choice of therapy in advanced PD and introduce new neurostimulation techniques. Graph theory has potential to be helpful in evaluating the dynamic consequences in large cortical networks.
7. Future research focused on DBS-related electrophysiological correlates of neuropsychiatric and cognitive side effects could be helpful for clinical practice in defining some biomarkers of DBS-related cognitive decline. Individual frequency reactivity among patients could be one of the clues.
8. Functional coupling in the cognitive networks between the STN and temporo-parietal associative areas is mediated via the alpha band. Alpha reactivity plays a major role in cognitive and non-motor dysfunctions in PD. Beta coupling related to motor activity is also modulated by cognitive factors. These interactions are probably influenced by STN-DBS in some subjects, resulting in neuropsychiatric and cognitive side effects. This remains to be elucidated in future research studies.

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Conflict of Interest

There is no conflict of interest.

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