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Phase-Amplitude Coupling in Parkinson's Disease

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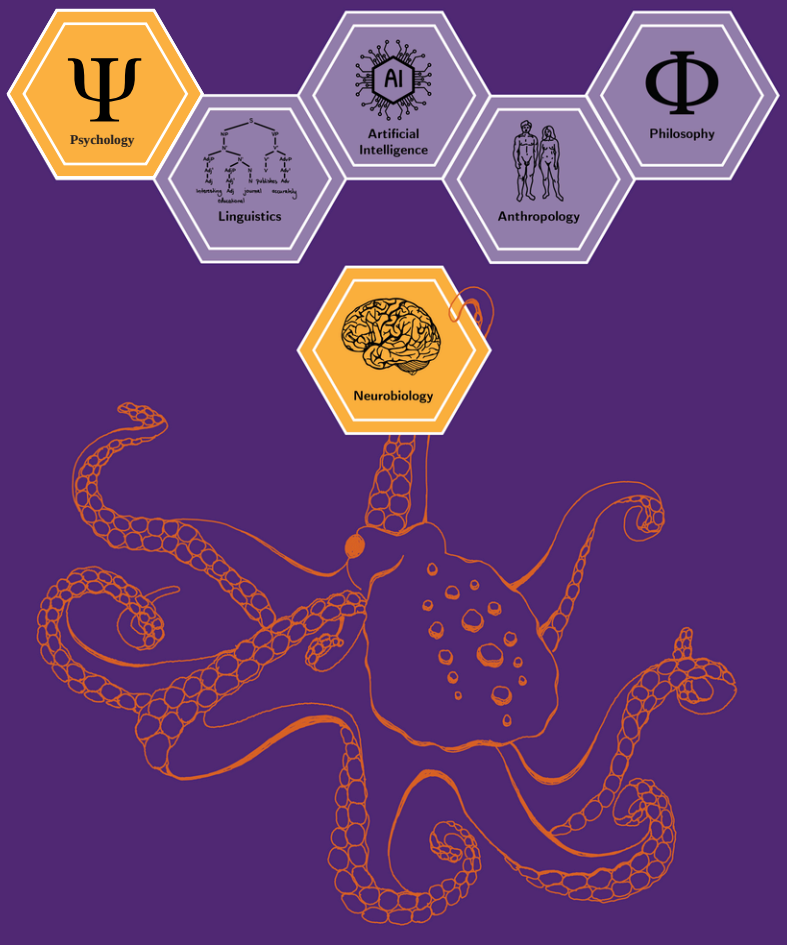

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease in which neurons of the dopaminergic system in the basal ganglia degenerate over time. Physical symptoms include tremor and rigidity, but also cognitive and psychological impairments are seen in patients (Tröster & Garrett, 2017). Research suggests that excessive synchronization of brain activity, in particular the coupling of low-frequency and high-frequency oscillations, is associated with the development of PD (de Hemptinne et al., 2015). Measures of synchronized neural activity could therefore serve as a control signal in the treatment of PD with deep brain stimulation (DBS) (de Hemptinne et al., 2015). However, another study has shown that increased synchronization of brain oscillations also occurs during sleep and might therefore not be sufficient as a biomarker in the early stages of PD (Devergnas et al., 2019). The purpose of this paper is to compare these two different viewpoints regarding the potential of synchronized brain oscillations in PD therapy with DBS.

Keywords of the paper: Parkinson's disease, phase-amplitude coupling, deep brain stimulation

Introduction

With over 8.5 million people diagnosed in 2019, Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (Parkinson's Foundation, 2023; World Health Organization, 2023). Tragically, PD-caused disability and death are also increasing at alarming rates (World Health Organization, 2023). Although pharmacological treatment is quite effective, patients often struggle with a wide range of side effects, like hallucinations, delusions, confusion, and depression (Tröster & Garrett, 2017). Recent research is focusing on the underlying mechanisms of PD, with the objective of developing a more in-depth understanding of the disease, which may lead to alternative possibilities for treatment. One explanation for the disease is the excessive synchronization of brain oscillations in the motor cortex (de Hemptinne et al., 2013). Using measures of synchronized brain activity as a biomarker for PD as well as a control signal for therapeutic deep brain stimulation (DBS) is suggested by de Hemptinne et al. (2015), whereas Devergnas et al. (2019) question the validity of such measures and their implementation in effective DBS therapy as they are not yet fully understood. This paper intends to compare the findings of these two studies in order to better understand the role of synchronized brain oscillations in PD patients.

Parkinson's Disease

This section provides a brief overview of Parkinson's disease. PD is a progressive neurodegenerative disorder that is associated with the loss of dopaminergic neurons in some parts of the basal ganglia, in particular, the substantia nigra and the striatum (Chiken & Nambu, 2015). When symptoms appear, 70 – 80% of these cells have already degenerated (Tröster & Garrett, 2017). In the development of the disease, cell loss also occurs in other parts of the brain, such as the locus coeruleus, dorsal raphe nuclei, nucleus basalis of Meynert, and dorsal vagal nucleus, additionally affecting other neurotransmitter systems (Tröster & Garrett, 2017). This excessive loss of neurons causes both motor and non-motor disruptions such as "akinesia, tremor, rigidity, postural instability, cognitive impairments and depression" (Chiken & Nambu, 2015, p. 314). PD is mostly seen in people over 50 years, and a higher prevalence occurs among males than females (Tröster & Garrett, 2017). It is estimated that the worldwide prevalence will increase to 8.7 – 9.3 million by 2030 (Tröster & Garrett, 2017). The UK Parkinson's Disease Society Brain Bank criteria define PD in terms of the presence of bradykinesia and at least one other symptom (rigidity, tremor, or postural instability) without any other pathological causes such as stroke, head injury, or the use of neurotoxins or dopamine-depleting drugs (Tröster & Garrett, 2017). Bradykinesia is defined as slowness of general physical actions,

having difficulty initiating movements as well as a reduction of automatic movements (e.g. blinking) and a reduction in facial expressions (Parkinson's Foundation, n.d.). Symptoms of PD are treated both pharmacologically using levodopa, which enhances dopamine levels, and through neurosurgical means, for instance, with deep brain stimulation (Tröster & Garrett, 2017). Phase-amplitude coupling of neural oscillations, which will be explained in the next section, is proposed to be used in deep brain stimulation therapy (de Hemptinne et al., 2015).

Synchronization of Neural Activity

This section discusses the role of cross-frequency coupling, particularly phase-amplitude coupling, in motor coordination in healthy populations and PD patients. In a healthy brain, the rhythmic changes in the membrane potential of neurons results in brain oscillations at different frequency bands (Malkki, 2015; Salimpour & Anderson, 2019). Cross-frequency coupling refers to the synchronization of different oscillations (Salimpour & Anderson, 2019). One form of cross-frequency coupling is phase-amplitude coupling, which describes the coupling of the phase of low-frequency beta oscillations and the amplitude of broadband gamma activity (de Hemptinne et al., 2015; Salimpour & Anderson, 2019). This coupling has been shown to help coordination and communication within and across different brain regions (de Hemptinne et al., 2015; Malkki, 2015). In the motor cortex, phase-amplitude coupling is crucial for the inhibition of movement; however, a reduction in phase-amplitude coupling is needed for the preparation and execution of movement (de Hemptinne et al., 2015). In PD patients, the synchronization of beta and gamma oscillations in the primary motor cortex is abnormally high and is considered to be associated with bradykinesia and rigidity (de Hemptinne et al., 2015; Kühn et al., 2008). This exaggerated coupling might be caused by the lack of dopamine neurons in the striatum that can no longer weaken beta oscillations from the cortex (de Hemptinne et al., 2013).

Phase-Amplitude Coupling in Parkinson's Disease and Its Use in Deep Brain Stimulation Therapy

Having discussed the role of phase-amplitude coupling in motor coordination and its potential implications for motor symptoms in PD, this section discusses the two studies mentioned above regarding their findings on phase-amplitude coupling in PD. DBS is a neurosurgical treatment for PD whereby the thalamus, globus pallidus, or subthalamic nucleus are stimulated with high-frequency electrical impulses via implanted electrodes (Tröster & Garrett, 2017).

In a study by de Hemptinne et al. (2015), electrocorticography (ECoG) signals from the motor cortex of 23 PD patients were recorded before, during, and after DBS of the subthalamic nucleus. While the phase of the beta oscillations (12-30 Hz) and the amplitude of the gamma rhythm (50-200 Hz) were strongly synchronized before and after stimulation, researchers found a significant decrease of phase-amplitude coupling in the motor cortex during stimulation while the patient was immobile. Although rigidity was significantly correlated with phase-amplitude coupling before and after DBS, there was no significant relation between phase-amplitude coupling reduction and improvement in rigidity during DBS. The same results were observed while 12 of the participants executed an arm movement task. Additionally, the movement duration was reduced with DBS, indicating improved mobility. Given the reduction of exaggerated phase-amplitude coupling during stimulation and the improved mobility, the authors conclude that excessive phase-amplitude coupling is an important biomarker for PD. Furthermore, they suggest that cortical phase-amplitude coupling measures could be included in an adaptive DBS therapy as a control signal that determines how subcortical structures

are stimulated. The development of these "smart" DBS systems allows for a dynamical adjustment of stimulation based on real-time feedback.

More recent research by Devergnas et al. (2019) questions these conclusions. Devergnas et al. (2019) investigated the relationship between the degree of parkinsonian symptoms and the level of phase-amplitude coupling between low (4-10 Hz) and high-frequency oscillations (50-150 Hz). In contrast to de Hemptinne et al. (2015), the authors recorded ECoG signals from the primary motor cortex and the supplementary motor area of three rhesus monkeys that were rendered parkinsonian using the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Phase-amplitude coupling was measured at baseline and during three stages of parkinsonism, both during wakefulness and sleep. The difference in the recorded low-frequency oscillations between the monkeys (4-10 Hz) and PD patients (12-30 Hz) is due to the fact that pathologic brain oscillations target lower frequencies in monkeys than in humans (Devergnas et al., 2019). It is also important to notice the difference between PD and parkinsonism. Parkinsonism differs from PD in that it is not a distinct disease but a combination of motor symptoms that is seen in different conditions (Tröster & Garrett, 2017). Similar to the results of de Hemptinne et al. (2015), Devergnas et al. (2019) observed increased phase-amplitude coupling between low- and high-frequency oscillations in monkeys in the parkinsonian state compared with their baseline state. Also, increased phase-amplitude coupling was positively correlated with motor deficits in a late stage of parkinsonism, mirroring the results of de Hemptinne et al. (2015) before and after DBS. However, the correlation between phase-amplitude coupling and parkinsonism was only significant when the animals were fully parkinsonian but not in the early stages of parkinsonism. Motor disturbances, which were already present in early stages of parkinsonism, might thus not necessarily be linked to excessive phase-amplitude coupling (Devergnas et al., 2019). Devergnas et al. (2019), therefore, object that phase-amplitude coupling could be used as a biomarker for early parkinsonism and argue that it is not a sufficient condition for the development of the disease. It is important to note, however, that the animal study only examined phase-amplitude coupling levels at rest while the study with PD patients also analyzed phase-amplitude coupling during a movement task. Different states of mobility could affect whether significant phase-amplitude coupling changes are detected in the early phases of parkinsonism (Devergnas et al., 2019). A further difference between the studies is that, unlike the study by de Hemptinne et al. (2015), the study by Devergnas et al. (2019) did not use DBS to normalize phase-amplitude coupling levels but treated the parkinsonian monkeys with levodopa. This treatment resulted in an increase in motor abilities and a decrease in phase-amplitude coupling showing that both treatments are effective in regulating the strength of phase-amplitude coupling (Devergnas et al., 2019). Beyond the study of de Hemptinne et al. (2015), Devergnas et al. (2019) found patterns of excessive phase-amplitude coupling not only in the primary motor cortex but also in the supplementary motor area although they have different functions in voluntary movement. Similar to earlier research by de Hemptinne et al. (2013), they suggest that both cortical regions are affected due to a lack of dopamine in subcortical structures. Moreover, Devergnas et al. (2019) examined cortical phase-amplitude coupling levels during sleep and found an increase in phase-amplitude coupling compared to wakefulness in the non-parkinsonian state. Furthermore, they did not find the same pattern of higher phase-amplitude coupling with an increase of parkinsonism during sleep, as the difference in phase-amplitude coupling between baseline and the three stages of parkinsonism was not significant. These results point out that using phase-amplitude coupling measures as a control signal for adaptive DBS devices, as suggested by de Hemptinne et al. (2015), might be problematic in early stages of the disease and during sleep. Based on their findings, the authors raise concern that increased phase-amplitude coupling might not be exclusively a pathologic phenomenon associated with parkinsonism but might be caused by specific physiologic states (Devergnas et al., 2019). Thus, they strongly suggest that further research is needed to fully understand the influence of the state of wakefulness on phase-amplitude coupling

before including it in a control loop for therapeutic DBS.

Conclusion

Excessive coupling between the phase of low-frequency oscillations and the amplitude of high-frequency activity in the motor cortex has been shown to be associated with motor signs of parkinsonism in both studies. Although the methodology of the two presented studies differs in terms of participants (PD patients vs. monkeys with induced parkinsonism), both suggest that phase-amplitude coupling is abnormally increased in advanced parkinsonism. The different findings during a motor task and during sleep, point toward the fact that the mechanisms and causes for increased phase-amplitude coupling are not fully understood. Using phase-amplitude coupling measures in adaptive DBS devices as a control sign could thus be premature at this point. The comparative analysis showed that further research on the influence of different states (wakefulness vs. sleep; rest vs. movement) on increased phase-amplitude coupling levels in PD patients is necessary. Bearing in mind that PD is one of the most common degenerative diseases and both pharmacological and neurosurgical treatment approaches only target symptoms of the disease, investigating the underlying mechanism of changes in phase-amplitude coupling could be critical progress in understanding and treating PD.

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