Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part II
DOI: 10.54254/2753-8818/4/20220695

The Analysis of Parkinson's Disease using Phase-Amplitude Coupling Method

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Abstract. Parkinson's disease (PD) is now the second most prevalent chronic neurological illness worldwide. For motor symptoms of PD, PD is linked to a number of dyskinesia, including rigidity, bradykinesia, postural instability, and tremor at rest. PD dyskinesia is the most common cause of Parkinsonism. Meanwhile, PD dyskinesia may be closely linked to the neural oscillations between neural circuits. PD dyskinesia is associated, in particular, with beta oscillation, which is directly related to the incidence and development of the motor. For the purpose of analysing neural oscillations between neural circuits, phase-amplitude coupling (PAC) can be utilised as a biomarker. As a potential biomarker of beta oscillation, PAC has been widely used in the research of PD. Therefore, this article reviews the latest concepts of dyskinesia, methods of calculating PAC and applications of PAC in Parkinson's disease, aiming to provide a good theoretical basis for finding neural circuits involved in PD dyskinesia to establish better deep brain stimulation therapy.

Keywords: Parkinson's disease, dyskinesia, neural oscillations, phase-amplitude coupling, biomarker

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease that typically affects older people and shares the same position as Alzheimer's disease[1]. The neural nuclei that control the motor system and the neural circuits that connect them are important in the emergence of PD dyskinesia. Neural oscillation is a sort of rhythmic or repeating neuronal activity and may be a representation of the interplay of neural nuclei. In addition, mounting experimental and clinical evidence has demonstrated that phase-amplitude coupling (PAC) can be used to quantitatively describe the relationship between neural oscillations and cast light on the link between neural nuclei[2]. Thereby, the address of this review is fourfold. First, this review presents the fundamental theory of PD and emphasises the pathological alterations connected to PD, in particular. Second, this review addresses two different factors that can cause movement disorders. One is levodopa treatment, and the other is deep brain stimulation (DBS). And then current review elaborates on the four prominent dyskinesia caused by pathological alterations in PD patients and highlights the impact on the motor systems. Third, this review introduces the fundamental theory of neural oscillations and the neural oscillations generated by brain circuits that are likely connected to PD. Fourth, this review focuses on a biomarker called phase-amplitude coupling (PAC), which aids in the detection of brain oscillations linked to PD. Finally, it introduces three common approaches for calculating PAC and reviews several studies on the

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DOI: 10.54254/2753-8818/4/20220695

relationship between PD and PAC calculated by the MI method. To have a comprehensive view of the application of PAC in PD dyskinesia, this article will review PD and dyskinesia, probable neural nuclei linked to PD dyskinesia and functions of PAC as a biomarker and address the potential application value of PAC in other dyskinesia aiming to provide excellent theoretical support to reveal the neural nuclei and neural circuits behind PD dyskinesia.

2. Parkinson's disease and Dyskinesia

2.1. Parkinson's disease

The most prevalent neurodegenerative disease, Parkinson's Disease (PD), which shares the same position as Alzheimer's Disease, primarily affects middle-aged and older persons and has a significant negative impact on families and society. According to growing evidence, the pathological changes in Parkinson's disease (PD) are primarily characterised by the degenerative death of dopaminergic neurons in the substantia nigra pars compacta of the midbrain, which is also accompanied by Lewy body formation, the cytologic biomarker of PD that contains misfolded α-synuclein, and gliosis, which causes a decrease in dopaminergic fibres in the dopamine deficiency causes the indirect pathway to become more active and the direct pathway to become less active, inhibiting cortical motor activation. Finally, the combined result of these pathological changes is dyskinesia. Unfortunately, it is yet unclear what causes pathological alterations. In addition to the biological sex, ageing, genetics, environmental toxins, infections, and oxidative stress have all been shown to be intimately associated with PD. Dyskinesia worsens with time in PD, eventually developing into Parkinsonism. PD is thus the most typical cause of Parkinsonism.

2.2. Dyskinesia in Parkinson's disease

Dyskinesia is a general term for a series of motor dysfunction plaguing Parkinson's patients with non-dyskinesia symptoms, including tremor, bradykinesia, rigidity, and postural instability. The two most common types of dyskinesia in PD patients are levodopa-induced and stimulation-induced dyskinesia[3].

Levodopa medication is one of the most effective treatment options. However, it has serious adverse effects, one of which is Levodopa-Induced Dyskinesias (LIDs). Previous studies have a wide range of aberrant motor symptoms, including orofacial movements, ballism or chorea-like movements of the limbs, as well as dystonic postures, which might be linked to LIDs.

Furthermore, Stimulation-Induced Dyskinesias (SIDs) are observed in a wide range of people and are frequently connected to positive clinical outcomes after surgery. When SIDs are incapacitating, it might be essential to lower the overall L-dopa dosage. However, what needs to be pointed out is that this strategy might not work when dyskinesias are mostly stimulation-induced.

2.2.3. Tremor. One of the cardinal PD dyskinesia, tremor, often manifests at PD start and affects 80% of PD patients. Tremor is a very heterogeneous symptom. Therefore, there are multiple diverse types of tremors in people with PD. The most typical PD tremor is described as happening at rest, being negligible during movement, and typically occurring at a frequency of 4-6 Hz. Therefore, another name for this tremor is "Tremor-at-rest". The distal digits of one upper limb are frequently the first to experience tremor-at-rest, which then spreads to the ipsilateral lower limb, as well as the contralateral upper and lower limbs[4]. The patient gradually develops a tremor-at-rest in their head, jaw, mouth, and tongue. The wide variety of PD tremor symptoms is a reflection of the disease's complex aetiology, and the exact processes that cause PD tremors are not fully known at this time.

2.2.2. Bradykinesia. Bradykinesia, a characteristic symptom of basal ganglia dysfunction in PD, is another prominent manifestation of dyskinesia in PD patients, currently defined as slowness of movement coupled with a sequence effect. Specifically, as the movement continues, the amplitude or speed of movement gradually declines. Although the pathogenesis of bradykinesia is unknown, new research has shown evidence that the basal ganglia-thalamic-cortical pathways that lead to

DOI: 10.54254/2753-8818/4/20220695

bradykinesia may be involved in cognitive slowness. Slowness in motor execution in Parkinson's disease was not due to a general lack of motor preparation, according to abnormal simple reaction times and no changes in choice reaction times, and the role of a prolonged simple reaction time in causing bradykinesia could be explained as a failure in programming a motor response.

2.2.3. Rigidity. Rigidity is defined as muscle activity that considerably increases with muscle stretching but is independent of velocity. After tremors, rigidity is the second most noticeable clinical symptom in PD patients and has individual differences. Typically, PD patients with clinical tremor symptoms have varying degrees of muscle rigidity. Rigidity's underlying pathophysiological mechanisms are yet unknown. However, one potential mechanism is that the excitatory changes in cortical and subcortical pathways are thought to enhance myoshuttle control, leading to increased myoshuttle reactivity and resistance in passive movements5. The brainstem, which is known to play a role in postural motor control, may also degenerate, leading to rigidity. In other words, the neurodegeneration in the brainstem nuclei, especially the locus coeruleus and raphe nuclei, as well as the pontomedullary reticulospinal system, is what causes the early and progressive α-synuclein deposition in PD. Namely, norepinephrine and serotonin can affect the spinal cord motor control system through the descending pathway.

2.2.4. Postural instability. Postural instability (PI), which marks the beginning of moderate to severe phases, has once been identified as a characteristic of late-stage PD. The loss of postural reflexes, specifically the inability to adapt to balance, adopt a flexed posture, and rotate the trunk, causes PI in PD patients. These symptoms are brought on not only by the death of dopaminergic neurons but also by comorbid white matter disease and cholinergic system degeneration. Several lines of evidence suggest that PI can arise for various reasons, including ageing, genetics, diet, white matter and basal ganglia lesions, grey matter atrophy, aberrant proprioception, and biomechanical alterations[6].

3. Neural Oscillation

Based on electroencephalograms, the first research on neural oscillations was conducted. The delta (1~4 Hz), theta (4~8 Hz), alpha (8~13 Hz), beta (13~30 Hz), and gamma (>30 Hz) bands make up the brain rhythm, which is based on electrical activity in the brain.

Regarding the techniques for capturing neural oscillations, EEG signals can represent neural oscillations in the motor cortex, and local field potentials (LFPs) can reflect neural oscillations in the downstream cortical nuclei. The relationship between the frequency bands of various frequencies and spatiotemporal resolution indicates that these bands correspond to different neural populations. Numerous studies have investigated neural oscillations in the brain at multiple levels and found that neural oscillations play a vital role in neural information processing. Therefore, the presence of neural oscillations during the onset of symptoms may reveal the neural circuits that generate these processes and thus reveal the physiological and pathophysiological mechanisms of symptoms[7]. The Summary of neural oscillation is shown in table 1.

DOI: 10.54254/2753-8818/4/20220695

Table 1. Summary of Neural Oscillation.

	Frequency (Hz)	Detection(s)	Meaning(s)	Function(s)
Delta	1~4	Frontal & cingulate cortex	Cognitive correlation of event-related activity	Interference suppression & attention enhancement
Theta	4~8	hippocampus & frontal cortex	Communication with hippocampus	Memory processes & spatial positioning
Alpha	8~13	occipitoparietal brain regions	Inverse correlation with cognitive performance	Modulated in sensory stimulation, spatial navigation task, memory & attentional processes
Beta	13~30	unknown	Activation, nervousness, stress, etc.	Motor & cognitive tasks requiring sensorimotor interaction
Gamma	>30	almost all brain structural	Cortical activation	Attentive processing of information, active maintenance of memory contents and conscious perception

3.1. Beta oscillations

Beta oscillation generally refers to the EEG signal with a frequency in the range of 13-30Hz. According to the distribution of beta oscillations, beta oscillations can be divided into two types: the first type is called Rolandic beta oscillations, and the other category is called frontal beta oscillations. Under physiological conditions, Beta oscillations have characteristic changes during voluntary movements. Firstly, Beta oscillation is the maximum in the preparation process of the motor; Secondly, Beta oscillations will be weakened when the motor onset; Thirdly, it remains in a low state during the motor; Finally, when the motor ends, Beta oscillations show a post-movement Beta rebound (PMBR)[8]. The enhancement of Beta oscillations in motor preparation may be closely linked to the inactivation of the indirect pathway and sensorimotor cortical excitation. However, there is still no unified theoretical explanation. The attenuation of Beta oscillations during motor is considered a physiological mechanism conducive to motor changes. The PMBR at the end of the motor is known as the motor cortex restoring its original state and preparing for the following motor. Several lines of evidence have suggested a potential hallmark of basal ganglia beta oscillations enhancement in PD and PD dyskinesia, such as akinesia and rigidity during wakefulness. The possible explanation for the abnormal enhancement of beta oscillations is that the direct pathway is inhibited while the indirect pathway is activated in PD patients. As for the relationship between Beta oscillation and dyskinesia, abnormally enhanced Beta oscillation acts on the thalamic-cortical neural circuit, which weakens the motion-related information transmitted between the circuits and decreases the accuracy, thus causing dyskinesia. Several explanations exist for the Beta oscillation enhancement associated with rigidity in PD patients. Some believe that Beta oscillations from pyramidal tract neurons recruit more motor neurons to produce rigidity, while others believe that Beta oscillations from the cortex cause motor neurons to have high-intensity firing sequences and trigger rigidity.

3.2. Other oscillations

Delta oscillations are mainly observed in the frontal and cingulate cortex, linked to interference suppression and attention enhancement. Theta oscillations often occur in the hippocampal and

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entorhinal cortex related to memory and spatial positioning. Alpha oscillations were most active in the occipitoparietal cortex during spatial navigation, memory, and attentional processing. Gamma oscillation is active in almost all brain structures and functional states, especially related to the functional state of the hippocampus, mainly pertaining to cortical activation, information processing, memory retention and consciousness.

4. Applications of phase-amplitude coupling in PD

In general, PAC represents how much the phase of low-frequency oscillations modulates the amplitude of high-frequency oscillations. It is crucially functional in the processing of brain information and cognition. The occurrence and transmission of numerous neurological disorders, including epilepsy, schizophrenia, Parkinson's disease, and Alzheimer's disease, have also been explained in terms of alterations in PAC under various pathological situations. In recent years, a number of approaches for calculating PAC have been suggested. However, there is still potential for improvement in terms of resilience and accuracy for a number of widely used classical PAC measures, including phase-locked value, mean vector length modulation index, KL modulation index, and general linear model modulation index.

4.1. Phase-amplitude coupling

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4.1.1. Phase-Locking Value (PLV). For the calculation of PLV, the main principle is to extract the phase and amplitude from the analytical signal after high and low-frequency filtering. The phase is then retrieved from the "second" parse signal after the amplitude time series undergoes another Hilbert transform. The phase angle difference of each data point was obtained by subtracting the phase angle value of the phase time series from the phase angle value of the Hilbert transform amplitude time series. The calculation formula of PAC is as follows:

$$\mathbf{PLV} = \left| \frac{\sum_{t=1}^{n} e^{i(\theta_{lt} - \theta_{ut})}}{n} \right| \tag{1}$$

Where n means the overall number of data points, t represents a single data point, θ_{lt} represents the phase angle of the lower frequency band, and θ_{ut} represents the phase angle of the Hilbert transformed upper-frequency band amplitude time series.

4.1.2. Mean Vector Length (MVL). When calculating MVL, the phase is extracted from the low-frequency filtered analytical signal, and the amplitude is extracted from the high-frequency filtered analytical signal. The degree of coupling is measured using the phase Angle of the adjoint analytic signal and the magnitude of each complex number. The magnitude of the phase-amplitude coupling strength is determined by the length of the average vector with the specified phase and length. The orientation shows the average phase at the position of maximum amplitude.

$$MVL = \left| \frac{\sum_{t=1}^{n} a_t e^{i\theta_t}}{n} \right| \tag{2}$$

Similarly, where n is the total number of data points, while t is a data point. a_t is the amplitude of data point t, and θ_t is the phase Angle of data point t.

DOI: 10.54254/2753-8818/4/20220695

4.1.3. Modulation Index (MI). In contrast to the first two ways, MI is currently the most popular calculating method to reflect the value of PAC. The analytical signal, amplitude, and phase Angle are based on identical parameters for MI. All potential phases between -180° and 180° are first binned into an arbitrary number of bins before the MI is calculated[9].

$$p(j) = \frac{\bar{a}}{\sum_{k=1}^{N} \bar{a}_k} \tag{3}$$

Where N is the total number of bins, k is the running index for the bins, $\bar{a}$ is the average amplitude of one bin, and p is a vector of N values. These calculations provide the information needed to create the phase-amplitude plot, which graphically displays the real phase-amplitude coupling.

$$H(p) = -\sum_{j=1}^{N} p(j)\, log\, p\,(j) \tag{4}$$

Where N is the total number of bins and p is the vector of normalised mean amplitudes per phase bin.

$$KL(U,X) = log\, N - H(p) \tag{5}$$

Where U is the uniform distribution, X is the data distribution, N is the total number of bins, H(p) is the Shannon entropy determined by formula 4, and N is the total number of bins. Logarithmically, the uniform distribution is depicted (N). Finally, MI is calculated by the following formula.

$$MI = \frac{KL(U,X)}{log\, N} \tag{6}$$

4.2. Abnormal enhancement in PAC is a biomarker of PD

Previous studies have shown that the phase-amplitude coupling (PAC) between beta oscillation phase and gamma oscillation amplitude, as well as beta burst characteristics, can be used as electrophysiological biomarkers of PD. Nevertheless, the neural circuit mechanisms of abnormal enhancement in PAC in PD and their relationship with dyskinesia are still not fully understood.

As mentioned above, PD may develop due to the multiple neurocognitive impairments brought on by ageing, including metabolic, neurotransmission, hormonal, and immunological dysregulation, as well as inflammation. In a study based on apparently healthy elderly subjects and young adults without PD, it was statistically significant to demonstrate that the abnormal enhancement of PAC after excluding spectral power changes and the non-sinusoidal shape of beta oscillation interferences was statistically significant using MI calculations. Additionally, while beta bursts incidence rose among apparently elderly subjects, the proportion of longer beta bursts also tended to increase. Furthermore, research has shown only a weak correlation between beta bursts and aberrant enhancement in PAC, suggesting that the beta bursts and aberrant enhancement in PAC may reflect distinct physiological pathways[8]. The aforementioned research offers a solid theoretical foundation for the selection of biomarkers in elderly people to assess the likelihood of developing PD.

Dyskinesia is one of the critical factors that increase the rate of falls in PD patients. In order to avoid the impact of dyskinesia on the daily life of PD patients, it is necessary to select appropriate biomarkers to predict the risk of patients with dyskinesia and provide preventive treatment measures. Currently, mounting studies have shown that PAC can be used as a biomarker for dyskinesia in PD.

In a recent study on the occurrence and treatment of freezing of gait (FOG) symptoms in PD, the research recorded and analysed the neuronal firing characteristics in the subthalamic nucleus (STN) and motor cortex of 16 PD patients with FOG, quantified the FOG index in real-time by an optical motion capture system and calculated PAC by MI method. It was found that the onset of freezing was associated with an abnormal increase in PAC in the beta-gamma band of the primary motor cortex. In addition, Deep Brain Stimulation treatment in STN (STN-DBS) can significantly reduce abnormal coupling and improve FOG symptoms[10]. Meanwhile, the study has suggested that additional dual-tasking walking tests showed that cognitive and motor functions competed for information-processing resources in the motor cortex during walking. STN-DBS treatment can improve the upper limit of

DOI: 10.54254/2753-8818/4/20220695

motor cortex information processing ability. Therefore, based on the above results, a "bandwidth model" was proposed, which for the first time, integrated the effects of motor impairment, cognitive task, and electrical stimulation on dyskinesia in the same model. More importantly, these results imply that increased PAC in the primary motor cortex is associated with an increased risk of FOG in PD patients. Namely, the potential biomarker for FOG is increased PAC. Besides, this model provides necessary data support and a theoretical basis for optimising closed-loop DBS therapy and developing a walking brain-computer interface system.

Similarly, In the treatment of PD, DBS in the globus pallidus internus (GPi) is just as effective as STN-DBS. There is a therapeutic reduction in excessive cortical beta-gamma PAC, according to studies of STN-DBS. It is still unclear whether the effects of GPi-DBS. On this account, a study was conducted aiming to examine the effect of GPi-DBS, and PAC was estimated using the MI method[11]. This elegant study indicated that GPi-DBS, similar to STN-DBS, can reduce beta-gamma PAC in the motor cortex, suggesting that PAC is a generalisable symptom biomarker in PD, independent of the therapeutic target.

Studies of neurodynamics, such as neural oscillations, may reveal the neural circuits involved in physiological and pathophysiological processes and thus suggest plausible explanations for symptoms or diseases. In one study of low-intensity transcranial ultrasound modulation of PD, PD model mice were utilised to stimulate the brain. The power spectrum and the intensity of the phase-amplitude coupling were examined in the local field potentials (LFPs) in the motor cortex of PD mice. The results showed that low-intensity ultrasonic stimulation significantly reduced the beta (13–30 Hz) band's power spectrum intensity in the LFPs, as well as the strength of the PAC between beta and high-gamma (55–100 Hz) and ripple (100-200 Hz)[12]. Therefore, this study has shown that in mice with PD, low-intensity transcranial ultrasonic therapy might considerably lower the brain electrical activity associated with PD.

5. Conclusion

In the past two hundred years, PD and PD dyskinesia research has seen continued interest and advancement. Dyskinesia is still an undesired side effect of LID and SID in PD. It rarely surprises the public anymore that neural circuits and neural oscillations between neural nuclei regulating the motor system play a vital role in dyskinesia. However, unfortunately, the neural circuits controlling various motor disorders have not been uniformly concluded yet. Meanwhile, recent research has demonstrated that abnormally enhanced PAC can serve as a biomarker for PD dyskinesia. This article reviewed PD and PD dyskinesia, likely neural nuclei connected to PD dyskinesia, and the functions of PAC as a biomarker in order to have a comprehensive understanding of the application of PAC in PD dyskinesia. It also addressed the potential application value of PAC in other dyskinesia in an effort to offer excellent theoretical support to reveal the neural nuclei and neural circuits underlying PD dyskinesia. Moreover, there are several studies of levodopa-induced dyskinesia that use PAC as a biomarker of dyskinesia. Understanding the characteristics of dyskinesia and abnormally enhanced PAC should help design better deep brain stimulation protocols for preventing and treating PD dyskinesia. Thus, studies in this direction may be given priority in future studies.

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