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Assess stimulation-induced dyskinesia and its potential physiological mechanism using phase-amplitude coupling

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Abstract. With the increasing use of deep brain stimulation (DBS) on clinical treatment of Parkinson's diseases, stimulation-induced dyskinesia (SID) becomes more and more common. SID was often detected shortly after DBS treatment on patients. However, the pathogenesis of SID and exact region of SID remains unclear. The aim of this paper is to review the studies of stimulation-induced dyskinesia and try to propose a new method to study and quantify SID, which is phase-amplitude coupling. phase-amplitude coupling (PAC) has been widely used in many other studies of brain-related illness and therapies. It is believed to have a profound relationship with our brain activities. Because of the features of PAC itself, the anatomical regions related to SID after pallidal DBS in Parkinson's disease (PD) patients can be possibly found, and the value of PAC can be served as a biomarker for us to assess the stimulation-induced dyskinesia. However, further researches on patients should be done to verify this method. It is very important to understand how SID is formed and its pathogenesis because it may help us find the appropriate parameters of deep brain stimulation and reduce the damage caused by the implant of electrode.

Keywords: Dyskinesia, Deep brain stimulation, Parkinson's disease, Stimulation-induced Dyskinesia.

1. Introduction

The majority of Parkinson's disease clinical symptoms are connected to motor activities. Deep Brain Stimulation (DBS) has been proved as an effective measure to treat some certain symptoms of Parkinson's disease, especially dyskinesia in recent years. Common surgical procedure of Parkinson related motor symptoms nowadays involve stimulation on two parts of brains, the subthalamic nucleus (STN-DBS) and Globus Pallidus Internus (GPi-DBS) [1]. Both of these ways of DBS is believed to have a suppressive effect on dyskinesia. However, these two major ways of DBS, STN-DBS and GPi-DBS have both been found that they may cause an exact opposite effect worsening or even inducing dyskinesia symptom. We call the dyskinesia triggered by deep brain stimulation as stimulation-induced dyskinesia (SID). In the present study, some patients are detected with a symptom resemble dyskinesia in the preliminary stage (usually no more than one month) after having implantation of electrodes, which we call as stimulation-induced dyskinesia (SID) [2]. Nevertheless, the pathogenesis of SID remains unclear and there is no consensus on which region of STN of GPi may increase the possibility of SID [3]. The passage tries to find the biomarker of SID using phase-amplitude coupling (PAC). Phase amplitude coupling is one of ways of cross frequency coupling (CFC). This coupling

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relationship among the powers of the neural oscillations in higher bandwidth and the phases of neural waves in lower bandwidth has been considered to be a pathophysiological biomarker for Parkinson diseases. The hypothesis is that by computing PAC value in patients with SID using amplitude and phase from the same or different nervous nuclei may reveal whether certain modulation of SID exist and may help decide the parameter of deep brain stimulation.

2. The occurrence of sid

Parkinson-related diseases include various symptoms. In addition to traditional motor symptoms, levodopa-induced dyskinesia (LID) caused by long-term taking L-dopa can also gradually appear with the progress of the disease [4]. Common surgical procedure of LID and Parkinson diseases nowadays involve deep brain stimulation on the subthalamic nucleus (STN-DBS) and Globus Pallidus Internus (GPi-DBS) showing in the figure 1 below. Both STN-DBS and GPi-DBS have been proven effective surgically for Parkinson diseases. They greatly lessen levodopa-induced dyskinesia and several cardinal parkinsonian symptoms. However, current studies find that both STN-DBS and GPi-DBS can may trigger or worsen dyskinesia. Similar adverse effect surgical outcomes also occur in the treatment of Meige Syndrome (MS) using deep brain stimulation on subthalamic nucleus. Some patients are detected with worsening dyskinesia or even new dyskinesia symptoms after having DBS, the occurrence of SID may be related to the stimulus parameters and the position of the stimulus STN in the front, generally 15% of patients who receive deep brain stimulation may encounter stimulation-induced dyskinesia.

However, the pathogenesis of SID remains unclear. Stimulation-induced dyskinesia have a lot to do with the placement of electrode used during the surgical process of DBS and is strongly related to the contact between electrode and STN. But it still doesn't have a consistent view on which region of STN may increase the possibility of SID (some suggest that placing electrode in the dorsolateral region of the STN may lead to dyskinesia, while some suggest the dorsoventral region of the STN. Some think the placing electrode in the upper part of STN may increase the possibility of SID, some think in the inferior part).

Furthermore, few is known about the mechanism behind SID. One study indicated that the activation of the electrode's contacts in the patients' ventral part of the dorsolateral motor area of the STN may have led to SID. In the experiments, the researches use mice with intermittent Parkinson diseases as the subjects, trying to find the the pathology behind SID. The result suggested that the stimulation on spiny neuron terminals can have a adverse effect on some certain neurons like substantia nigra reticulata (SNr), which lead to the dyskinesia symptom resemble LID [5]. This study provides a possible explanation of how electrode planted in the STN may lead to this stimulation-induced dyskinesia. But there is still no clear quantification of how this SNr matter could influence our motor functions. Further investigations need to be done with larger dataset to find this correlation relationship. And to corroborate this conclusion, more detailed mechanistic studies are required. Identification of anatomical areas linked to stimulation-induced dyskinesia and elucidation of the physiological pathophysiology of SID may offer helpful data for the forecasting of therapeutic result and the tuning of DBS on STN or GPi parameters. As shown in figure 1.

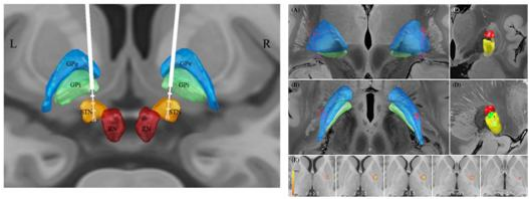


Figure 1. DBS on STN and Gpi: The left picture shows the position of STN and Gpi, the right picture shows Anatomic regions related to SID (in red) identified by VTA(volume of tissue activated) analysis.

DOI: 10.54254/2753-8818/4/20220694

3. Cross frequency coupling and phase-amplitude coupling

3.1. The theory of cross frequency coupling

The PAC we discussed above is a way of Cross Frequency Coupling.

Neurophysiological signals always show strong oscillation [7]. To be noted, a number of theoretical theories and laboratory results has shown the significance of interactions between activities occurring at various frequencies, especially in processing and transmissing information. However, to find the exact relationship between different frequency bandwidth require methods different from the traditional way of processing information such as wavelet convolution or STFT, which always focus on the independent oscillatory activity and therefore very hard to show the relationship between different frequency bands and even across different neural nucleus, as shown in the figure2 [8].

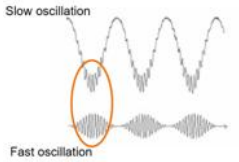


Figure 2. Cross Frequency Coupling usually find coupling relationship between slow and fast oscillation of neural wave.

The coupling between theta and gamma in the hippocampus of rodents is one of the most well-studied examples of cross-frequency coupling (CFC). Recent years, many CFC phenomenon have been detected in different species, part of brains, and different neural activities, but how CFC works in the brain remains unclear and their neuronal substrates are unclear too. The current hypothesis is that CFC in different brain regions can have different functions, and couplings between these oscillations also have a certain relationship with different neural activities.

Cross-frequency coupling (CFC) analyses are specifically created to detect the relationship or an synchronization level between different frequency band. A lot of researches have come to realize the occurrence of this phenomenon. For example, scientists have found that both human and animals can be found with this coupling phenomenon of different frequency segments, and especially the theta-gamma coupling can assist the integration of several networks in various places over longer time scales and the temporary coordination of local networks on short time periods.

Besides, CFC is also related to various task-related processes, including perception cognitive control, memory and emotional processing. Cross frequency coupling has also been linked to spontaneous activity while sleeping and resting. In general, cross frequency coupling is widely considered to be the potential mechanism of how information is temporally organized and communicated during neural activities across frequency bands [9].

Most methods aim to find the relationship between oscillations in a relatively lower frequency band and a relatively higher frequency band. Many different coupling shave been tested, including amplitude-amplitude coupling (AAC), phase-frequency amplitude (PFC) and also phase-amplitude coupling (PAC). Although from the definition of CFC, the coupling between different frequency bands, among all these methods, PAC has been given the most focus. Many experiments and theories also show its potential. The neural oscillation is recorded and different frequency band are retrieved from the filtered signals, and typically the magnitude of the higher frequency oscillation wave is extracted while the phases of the lower frequency oscillation is retrieved from the neural waves we get, as shown in the figure3 below [10].

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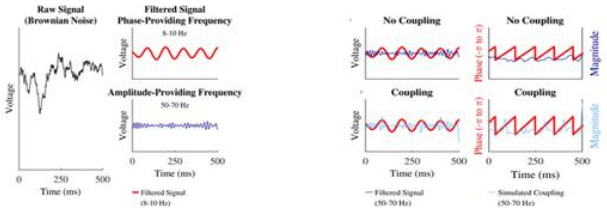


Figure 3. The process of phase-amplitude coupling.

3.2. PAC computing method

The increasing phenomenon of PAC in different researches have brought various methods for estimating PAC. No one specific estimation has yet emerged itself as perfect or ideal. However, four methods among all the other methods have been most commonly used, below is the brief introduction of these 4 methods.

(i). Mean Vector Length (MVL). In the MVL computation method, phase and amplitude are retrieved respectively from the low and high frequency filtered analytic signal, in MVL. The magnitude and phase of each data are quite directly used. The amount of PAC is represented by the length of the MVL by adding together all the vectors (each data point) and constructing a mean vector [12]. According to the theory, the sum of the vectors would be very close to null if without coupling relationship. The following formula is used to determine the MVL

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

Here, n denotes the amount of data points, at represents the power at certain time t and ϕ t symbols the phase of lower accordingly. Due to its role as the mean vector's length, this value cannot go negative based on the hypothesis that the minimum of MVL is zero when there is no coupling at all.

(ii). Modulation Index: To have the MI value, the first attempt is to make phases from 180◦ to 180◦ included into a certain number of bins. The tradition is to use 18 bins of 20◦ each [13]. The results would be different according to different choose of bins , as it explains below. The following formula is the first step of MI, calculating and normalizing the mean amplitude in each phase bin.

$$p(j) = \frac{\overline{a}}{(\sum_{k=1}^{N} \overline{a_k})} \tag{2}$$

a equals the average amplitude in a single bin, k denotes the bin's index, and N is the predetermined amount of bins. Then Shannon entropy is calculated:

$$H(p) = -\sum_{j=1}^{N} p(j) log p(j) \tag{3}$$

Since Phase-amplitude coupling's distribution can be seen as the deviation from the equidistribution;. KL distance can be used as an index to compute the disparity of these two distributions by the following formula.

$$KL(U, X) = \log N - H(p) \tag{4}$$

The ultimate calculation method of MI can be obtained by combining the formulas mentioned above.

$$MI = \left| \frac{KL(U, X)}{\log N} \right| \tag{5}$$

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(iii). GLM-CFC uses a scatter plot to depict extracted phase and amplitude. If PAC phenomenon is present, amplitude values would be specifically high at certain phase values [14]. GLM-CFC expects to use a mathematical function to present the non-linear relationship between amplitude and phase, as it perfect meet the characteristic of phase-amplitude relationship, which exhibit a highly non-linear relationship in many researches.

(iv). Phase-Locking-Value. To calculate PLV, the amplitude sequence is through Hilbert transformation, and the phase is retrieved from another filtered signal which does not go thorough Hilbert Transformation [15]. As a result, two phase points will be obtained from both time series accordingly.

$$PLV = \frac{1}{n}\sum_{t=1}^{n} e^{i}[\phi_{lt} - \phi_{ut}] \tag{6}$$

like any other methods above, n represents the length of the time sequence. For ϕlt and ϕut, the former one equals the phase angle of the lower frequency band and the latter one is the phase angle of the higher frequency band amplitude time series through Hilbert Transformation.

4. PAC's application and possibility in assessing

4.1. PAC's application

By synchronizing the time of neuronal activity in brain networks, PAC has been widely considered as to be the potential mechanism for communication between and across different brain areas. The reduction of PAC in motor cortex is seen as a critical step in movement execution.

PAC has also been widely used in assessing many different treatments of different diseases related to brain. Deep brain stimulation therapy for treating Parkinson's disease has been shown to diminish cortical phase-amplitude coupling, supporting the hypothesis that PAC can be seen as a marker of states of Parkinson patients. Focusing on phase-amplitude coupling could lead to the improvement of DBS therapy and the innovation of the adaptive DBS devices. An EEG analysis of epileptic patients showed that during epileptic seizures, the PAC index of rhythm and different low-frequency rhythms were significantly enhanced, and the MI (a way of computing PAC) characteristics of epileptic EEG signals could accurately distinguish between ictal and interictal data [16].

Recent analyses of CFC in intra-cortical signals during speech perception reveal certain causality among different oscillations in different regions. A research used an ingenious method to quantify this relationship between different frequency bands and found that, surprisingly, certain coupling relationship exist during the resting state between the magnitude of gamma wave and the phase slower alpha wave. The coupling between different regions may also provide us some useful information to find the pathological basis of the disease [17].

4.2. Advantages and disadvantages of different PAC methods.

According to the paper, different PAC methods applies for different situation, MVL works best at long epoch data with high sampling rates and low signal-to noise ratio, as it is more susceptible to the change of modulation amplitude and duration than any other methods. By contrast, if the signal is strongly influence by noise, MI method is strongly recommended, because it has the lowest possibility to be impacted by the various factors in the whole process compared with other methods.

The PLV does not distinguish itself out when compared to the other measures. There have no researches giving a positive review on PLV, partly because its potential problem that it directly uses the phase information from the signal's amplitude sequence [18].

The advantages and disadvantages of MI and MVL are actually complementing, so it would be advisably to calculate both. "There is no perfect single analysis technique to evaluate this cross-frequency coupling (CFC)." claimed Kramer and Eden. So even in the most ideal situation, the recommendation is to use at least two methods at the same time to ensure the result can be less effected by the confounding variables in the experiment.

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4.3. PAC's possibility in SID

Phase-amplitude coupling has been widely used in many signal processing researches on EEG signals and is also believed to be a quantitative index for DBS's effect for Parkinson patients. As a result, its very natural to use PAC method to assess the status of SID, which is basically caused by the implantation of electrode in deep brain stimulation therapy. Using phase-amplitude coupling to see patients with SID and detect their change in the PAC values during dyskinesia or after DBS surgery, using both MVL method and MI method to complement each other so as achieve an ideal result. At meantime, we can compute PAC value using amplitude and phase from different nervous nuclei to see whether certain modulation exist between different nuclei, which may unveil the pathophysiological mechanism of SID.

5. Conclusion

DBS is now often used as an effective measure to treat Parkinson related diseases. STN-DBS and GPi-DBS have been proved to be very effective on the treatment of dyskinesia, while at the same time some patients who receive DBS treatment may experience stimulation-induced dyskinesia. PAC has quite a lot advantages over other ways of CFC and has been used widely in assessing the status of brain activity and also as a biomarker of some certain brain diseases. Using PAC to find the biomarker of SID by comparing patients with/without stimulation-induced dyskinesia, may give us a much more profound sight into the pathological basis of the SID and help us adjust the implant of electrodes of DBS. However, in the passage, parameters of the deep brain stimulation is not mentioned a lot. Still a lot of experiments are needed to figure out the optimal parameters of the DBS in order to lower the possibility of patients' getting SID.

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