Chapter 6
Neural Synchronization in Parkinson's Disease on Different Time Scales

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Abstract Parkinson's disease is marked by an elevated neural synchrony in the cortico-basal ganglia circuits in the beta frequency band. This elevated synchrony has been associated with Parkinsonian hypokinetic symptoms. The application of recently developed synchronization analysis techniques allows us to investigate the temporal dynamics of synchrony on different time scales. The results of this analysis are summarized here, revealing highly variable dynamics of synchronized neural activity on multiple time scales and its association with disease.

Keywords Parkinson's disease · Neural oscillations · Neural synchronization · Desynchronization · Intermittency · Beta-band oscillations

6.1 Beta-Band Oscillations and Synchronization in Parkinson's Disease

Synchronized rhythms of neural activity are widely observed phenomena in the brain and have been studied quite extensively because of their correlations with multiple functions and dysfunctions of neural systems. Neural synchronization plays a crucial role in perception, cognition, and memory, among other processes

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V. Cutsuridis (ed.), *Multiscale Models of Brain Disorders*, Springer Series in Cognitive and Neural Systems 13, https://doi.org/10.1007/978-3-030-18830-6_6

(reviewed in [8, 11, 12]). Abnormalities of neural synchrony (such as excessively strong or excessively weak synchrony) have been related to the symptoms of several neurological and psychiatric disorders (reviewed in [21, 29, 31]).

In particular, abnormalities of neural oscillations and synchrony have been observed in the cortico-basal ganglia circuits in Parkinson's disease. Parkinson's disease is a major neurodegenerative disorder characterized by chronic dopamine deficiency resulting in a set of movement-related as well as other symptoms (see, e.g., [20] and references therein). The loss of dopamine in Parkinson's disease directly affects the basal ganglia, a group of subcortical nuclei which are, among other things, involved in the neural control of movement. The landmark of Parkinson's disease is overall slowness of movement. This hypokinetic behavior involves bradykinesia and akinesia (slowness of ongoing movement/inability to start new movement) and rigidity (stiffness of joints). Another frequent symptom is rest tremor whose biological mechanisms are probably different from those of hypokinesia.

Parkinsonian pathophysiology is marked by increased oscillatory and synchronous activity in the beta frequency band in cortical and basal ganglia circuits. Over the past two decades, many studies have reported on the relationship between excessive oscillations and synchronization in the beta-band and hypokinetic motor deficits in humans with Parkinson's disease and in animal models of this disorder (reviewed in, e.g., [10, 13, 28, 30]).

Even though Parkinsonian brain expresses elevated beta-band synchrony, this synchrony is still relatively mild [22, 30]. It changes in time, and most conventional methods of synchronization estimation miss a complex picture of temporal dynamics of synchrony. However, several techniques for the analysis of the dynamics of synchrony reveal different temporal patterns of synchrony on different time scales (see below). Here we review recent progress in the development of these synchronization analysis techniques and their applications to Parkinsonian neurodynamics.

6.2 Synchronization on Different Time Scales

There are many definitions of synchronization, but the common theme is coordination of the temporal aspects of the oscillations, usually because of the coupling between underlying oscillations. From the observational standpoint, synchronization is inherently non-instantaneous phenomenon, and this is what distinguishes it from a random and non-repetitive coincidence of some oscillatory features of two signals [24]. This leads to the difficulty in estimation of synchrony over short time scales. To make this discussion more specific, let us focus here on phase synchronization.

Phase domain is an appropriate way to analyze weakly synchronized neural signals [14, 17, 18, 24, 32]. As the coupling strength increases from low to moderate values, synchrony may be observed in the phase domain, while the amplitudes of oscillations remain uncorrelated. The phase may provide a more sensitive metric to

explore moderately synchronized neural activity. The phase can be extracted from oscillatory data in different ways including the use of the Hilbert transformation. Let us assume that two phases are extracted from two signals: φ_1 and φ_2. Then one can compute a fairly standard phase-locking (or phase synchrony) index γ:

$$\gamma = \left\| \frac{1}{N} \sum_{j=1}^{N} e^{i\,\theta_j} \right\|^2,$$

where $\theta_j = \varphi_1(t_j) - \varphi_2(t_j)$ is the phase difference, t_j are the times of data points, and N is the number of data points. This phase-locking index varies from 0 (no phase synchrony) to 1 (perfect phase synchrony). This phase-locking index was used to study neural synchronization of widely varying strength, but it naturally provides an average strength of phase synchrony.

However, behavior and synchrony, which helps to mediate it, usually vary in time, so there is a question of how synchronization varies in time. To address this problem, one may estimate a phase-locking index over time window of certain fixed length. But for confident evaluation of synchrony, one needs to observe it for a relatively long time. One can approach this issue statistically [14], by constructing surrogates to evaluate phase-locking significance. Depending on the time scale used in the analysis, there will be different temporal synchrony patterns [14]. This is not an artifact of the analysis. Depending on which time scale is physiological, synchrony may be significant or not, not only statistically but physiologically.

Decreasing the length of the analysis time window necessarily degrades statistical power. The window size must be long enough for powerful statistics and yet short enough for high temporal resolution. Importantly, this may render short analysis windows impractical. However, if there is an overall synchrony, one can consider how the system gets to a synchronized state and leaves it in time (synchronized state needs to be appropriately defined). This approach was recently developed in [1, 27] and can describe the differences in the temporal structure of synchronization and desynchronization events for the systems with similar overall level of phase-locking. This is important given that the average neural synchrony is frequently not very strong. The underlying network of presumably weakly coupled oscillators spends a substantial fraction of time in the desynchronized state, which justifies the focus on desynchronization episodes.

We will briefly describe one possible realization of this approach by using the first-return map analysis to quantify deviations from the synchronized state, provided that the data exhibit some synchrony on the average. Whenever the phase of one signal crosses zero level from negative to positive values, we record the phase of the other signal, generating a set of consecutive values $\{\phi_i\}$, $i = 1, \ldots, N$. These ϕ_i represent the phase difference between two signals. After determining the most frequent value of ϕ_i, all the phases are shifted accordingly (for different episodes under consideration) so that averaging across different episodes (with potentially different phase shifts) is possible. Thus, this approach is not concerned with the

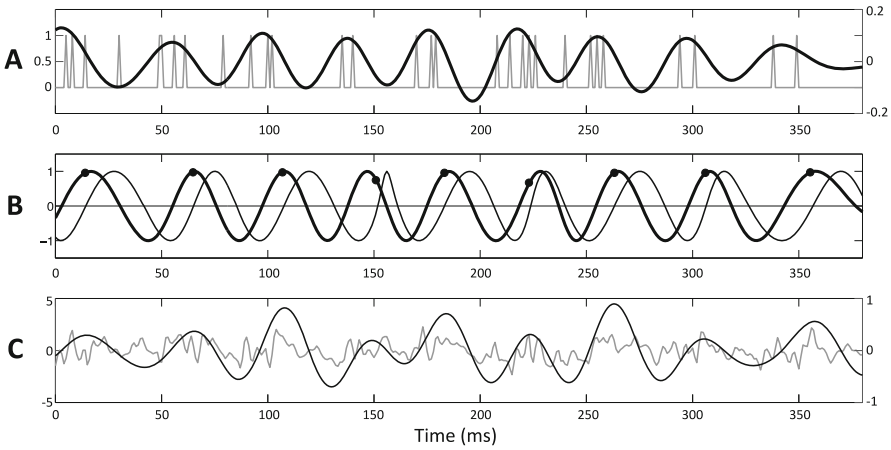

Fig. 6.1 An example of a synchronized episode. (**a**) Raw (thin line) and band-pass (10–30 Hz) filtered spiking signal (thick line). (**c**) Raw local field potential (LFP, grey line) and band-pass filtered signal (black line). (**b**) The sines of the phases of the filtered spiking (thick curve) and the filtered LFP (thin curve) signals. The amplitude information is lost here, but the phase information is preserved. Dots indicate the phases of the filtered spiking signal whenever the phase of filtered LFP signal crosses 0 upward. (Adapted from [22])

value of the phase shift between signals, but rather with the maintenance of the constant phase shift (phase-locking) (see Fig. 6.1).

Dynamics is considered as desynchronized if the phase difference deviates from the preferred phase difference by more than certain amount ($\pi/2$ was used in several studies). The duration of the desynchronized episodes is measured in cycles of the oscillations. Thus, if the phase difference deviates from the preferred phase difference by more than $\pi/2$ once, then the duration of the desynchronized episode is one. If it deviates twice, then the duration is two, etc. This approach distinguishes between many short desynchronizations, few long desynchronizations and the possibilities in between even if they all yield the same average synchrony strength.

We will describe the results of application of these techniques to the studies of Parkinson's disease neurophysiology in the next section.

6.3 Synchronization in Parkinson's Disease on Different Time Scales

The application of the synchronization variations analysis to the subcortical intraoperative recordings from Parkinsonian patients indicates that the phase-locking index γ exhibits substantial variation in time. Figure 6.2 illustrates that the question of

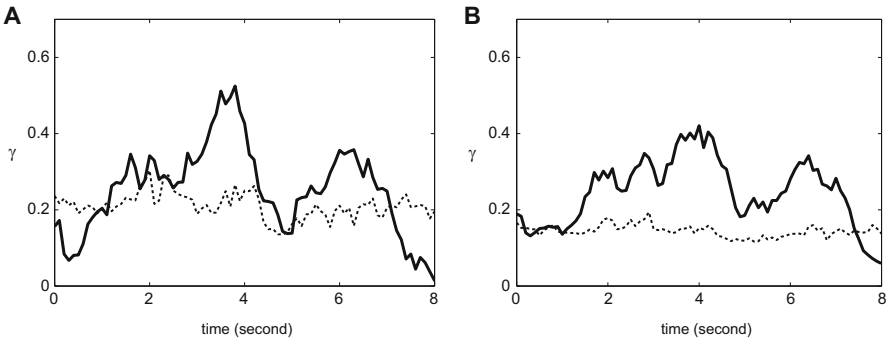

Fig. 6.2 Temporal dynamics of synchronous activity depends on the analysis window length. Black curve is the phase-locking index γ computed over a short time window with duration of 1 s (**a**) and 1.5 s (**b**). Dotted curve is the 95% significance level estimate, obtained from surrogate data. (Adapted from [28])

whether the dynamics is synchronous or not depends on the time scale. The data used here are the spiking activity and LFP in the subthalamic nucleus of patients with advanced Parkinson's disease (subthalamic nucleus LFP is likely to reflect pallidal input to the subthalamic nucleus, so this synchrony may be indicative of pallidal-subthalamic relationship or input-output relationship for subthalamic nucleus, discussed in [22]). The values of γ depend on the analysis window length. This is natural, for long time windows one expects to see less time variability, while for shorter time window, one has a better temporal resolution and more time variability as well as less powerful statistics.

The synchronization between motor cortices in Parkinson's disease follows a similar pattern [7]. The time course of synchrony (as evaluated in this time-dependent manner) in cortical and basal ganglia networks happens to be correlated in a manner specific to pairs of EEG electrodes over motor and prefrontal cortical areas, pointing to potentially global functional interaction between cortex and the basal ganglia in Parkinson's disease, when elevated synchrony in one network may impact synchronous dynamics in another one.

The synchronization index γ considered above does not inform about the fine temporal structure of synchrony because the analysis window length is not very small. A window size of 1 s corresponds to ~20 cycles of beta oscillations. Exploration of synchrony patterns on finer time scales is possible with techniques described in the previous section. This approach revealed the intermittent nature of activity in Parkinsonian brain and specifically the fine temporal structure of beta oscillations: synchronous states are interrupted by frequent, but short desynchronizations (see Fig. 6.3). The signals go out of phase for just one cycle of oscillations more often than for two or a larger number of cycles in the basal ganglia [22, 25].

Beta-band activity in Parkinson's disease is associated with hypokinetic symptoms. Another prominent Parkinsonian symptom is rest tremor. It is confined to other frequency band (3–8 Hz), is expressed independently of beta activity [26], and

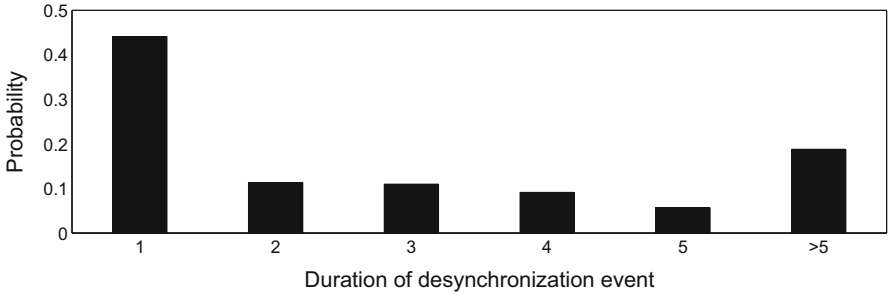

Fig. 6.3 The histogram of desynchronization event durations (measured in cycles of oscillations). For the duration >5, all durations longer than 5 are pooled together. The data are for the window length for the computation of synchronization index γ equal to 1.5 s. (Adapted from [22])

is likely to have separate network mechanism. However, it also expresses temporal patterning of neural (or neuro-muscular) synchrony, which is different on different time scales [15, 16]. High temporal variability of all these pathological neural synchronized dynamics may be related to the fact that these oscillations per se may be normal, but being overexpressed synchrony leads to pathological symptoms (see discussion in [22, 23, 28]).

6.4 Modeling Patterns of Neural Synchrony

Complex interactions within and between nuclei may be responsible for intermittently synchronized beta rhythms in Parkinson's disease. Experiments suggest that two nuclei, subthalamic nucleus and external globus pallidus, may form a key substrate for the synchronous rhythms in the Parkinsonian basal ganglia. Different models of subthalamo-pallidal circuits of basal ganglia were used to study how properties of neurons interact with network properties to generate synchronized rhythms (e.g., [19]). A potential problem with this approach is that getting moderate synchrony in coupled oscillators is easy, so matching frequency and average synchrony strength may not be constraining enough.

Matching the temporal patterning of synchrony, especially on the very short time scales, may be an effective tool to match the modeling and experimental data. While there may be many different characteristics of dynamics to match between model and experiment, for the phenomena where synchrony is important, matching synchronous patterns allows to match the phase space of model and real systems. Since basal ganglia synchronous dynamics is very intermittent, matching synchrony patterns in the model and experiment ensures some similarity between large areas of the phase space of the model and real systems. Thus, the mechanisms of synchronized oscillatory activity considered in the model may be able to produce the experimentally observed dynamics (see discussion in [9, 22]).

We have used the matching of synchrony patterns as a tool to find parameter values for the models of the cortical and basal ganglia networks, which would generate realistic synchronous beta-band oscillations. This approach suggested that Parkinsonian state of basal ganglia networks at rest is on the border of synchronized and non-synchronized activity [23]. This new approach showed how Parkinsonian synchronized beta oscillations may be promoted by the simultaneous action of both cortical (or some other) and subthalamo-pallidal network mechanisms [6]. It also showed that some proposed types of deep brain stimulation in Parkinson's disease may be potentially either effective [25] or ineffective [9] in pathological synchrony suppression. The latter is an interesting observation because it emphasizes that effectiveness of suppression of pathological synchrony may depend on how this synchrony is patterned in time.

6.5 Conclusions

Synchronization is inherently non-instantaneous phenomenon, and its temporal dynamics depend on the time scale used for the analysis. Even the question of whether there is a statistically significant synchrony or not depends on the time scale under consideration [14]. Many neural synchrony phenomena and behaviors that they mediate are short-lived and non-stationary. Thus, the temporal aspects of neural synchrony are likely to be important.

In particular, this is the case for the pathological neural synchrony in Parkinson's disease. As we described here, the basal ganglia express specific temporal patterns of the synchronous beta-band activity [22, 28], which are likely to be dopamine-dependent [23]. Parkinsonian tremor expresses different synchrony patterns on different temporal scales [15]. Temporal variations of the beta-band synchrony in Parkinson's disease are also observed in cortico-basal ganglia interactions, and temporal variability of synchronous patterns in cortical and basal ganglia circuits is related [6, 7]. And we also would like to note that not only temporal but spatial aspects are relevant to Parkinsonian physiology too [33].

The temporal patterning of synchrony phenomena are not confined to Parkinson's disease. Alterations of synchrony patterns on short time scales have been observed in addicted brain [4] and even in the coordination of brainstem-regulated respiratory rhythm and cardiac rhythm in with disease vs. healthy states [5].

Frequently observed patterning of neural synchrony on the very short time scales (the interruption of synchronous dynamics by potentially numerous but predominantly very short desynchronizations) may be a generic property of neural circuits in the brain even in the healthy state [2, 4]. It may be grounded in the very basic properties of the excitability of neural membranes [3]. However, the quantitative differences between patterning of neural synchrony may be related to relatively mild but behaviorally significant changes in the underlying network.

Acknowledgments This paper was supported by the ICTSI/Indiana University Health–IU School of Medicine Strategic Research Initiative, the National Science Foundation Grant DMS 1813819, and National Science Foundation Grant HRD 1700199.

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