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Fine Temporal Structure of Synchronization of Neural Oscillations in the Basal Ganglia in Parkinson's Disease

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Definition

Hypokinetic motor symptoms of Parkinson's disease are associated with elevated synchronization of neural oscillations in the beta frequency band. This synchronization is intermittent and exhibits specific temporal patterning. The properties of the fine temporal structure of this synchrony may help to understand the mechanisms behind pathological neurophysiology of Parkinson's disease and assist in the development of adaptive brain stimulation techniques to suppress pathological neural activity.

Detailed Description

Neural oscillations and synchrony are believed to be important for various physiological and pathological phenomena in the brain (Buzsáki and Draguhn 2004; Colgin 2011; Fell and Axmacher 2011; Buzsáki and Schomburg 2015; Fries 2015; Harris and Gordon 2015) and have been extensively studied by using approaches and methods of computational neuroscience. Excessively strong or weak synchrony and oscillations of neuronal activities are presumably related to several motor and cognitive disorders (e.g., Schnitzler and Gross 2005; Uhlhaas and Singer 2006; Hammond et al. 2007; Oswal et al. 2013; Pittman-Polletta et al. 2015; Spellman and Gordon 2015), one of the prominent examples being Parkinson's disease.

Synchrony of Neural Oscillations in Parkinson's Disease

Parkinson's disease is a major neurological disorder characterized by degeneration of midbrain dopaminergic neurons resulting in a set of movement-related symptoms as well as other symptoms. The hallmark of Parkinson's disease is overall slowness of movement. This slow, hypokinetic behavior involves bradykinesia, akinesia, and rigidity (slowness of ongoing movement, slowness of movement initiation, and stiffness of joints). The etiology of Parkinson's disease is still a challenging question and perhaps involves different mechanisms outside of the

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basal ganglia. Nevertheless, the midbrain dopamine deficiency and accompanying slowness of movement are associated with excessive synchrony of neural oscillations in the basal ganglia (as well as the cortex, a major input to the basal ganglia) in the beta frequency band, usually defined as 13–30 Hz (Brown 2003; Hammond et al. 2007; Bogacz 2014).

There are different views regarding the origin of the basal ganglia beta oscillations (local, cortical, striatal, or a mixture of all of them), the way how they mediate the movement, and whether they are in a direct causal connection with motor symptoms of Parkinson's disease. However, excessive beta oscillations and synchrony within the basal ganglia and between the basal ganglia and the cortex are observed in Parkinson's disease patients (Marsden et al. 2001; Cassidy et al. 2002; Fogelson et al. 2005; Hirschmann et al. 2011; Litvak et al. 2011; Ahn et al. 2015) and animal models of Parkinson's disease (Sharott et al. 2005; Mallet et al. 2008; Stein and Bar-Gad 2013). The level of synchrony and the power of beta oscillations are changed during movement and movement-related tasks (Cassidy et al. 2002; Levy et al. 2002; Brown 2003; Amirnovin et al. 2004; Kühn et al. 2004; Williams et al. 2005) and are reduced by treatments such as levodopa or deep brain stimulation in subthalamic nucleus (STN) (Silberstein et al. 2005; Stoffers et al. 2008).

Temporal Patterning of Synchronized Activity

The studies (such as discussed above) report elevated yet still moderate synchrony strength at rest. Thus, elevated synchrony in Parkinson's disease is not perfect (at least it does not stay perfect for prolonged intervals of time). This means the synchrony is stronger for some intervals of time and weaker (or nonexistent) for other intervals of time. It exhibits temporal variations changing from potentially very high to very low levels or from synchronized to desynchronized states. Even though it may average into some moderate synchrony strength overall, few long intervals of synchronized activity may be functionally different from many short synchronized episodes. In other words, different temporal patterns of neural synchrony may be related to different symptoms or conditions of the brain.

Synchronization of oscillations is a phenomenon which is not local in time and implies repetitive coordination of dynamics of coupled oscillators. There are multiple ways to define it in mathematical terms (e.g., Pikovsky et al. 2001). It may be impossible to claim that signals or oscillators are synchronized at a particular time instant. However, it is possible to consider the synchronization, for example, measured as a phase-locking strength, over relatively short sliding time windows (especially if one can estimate the statistical significance of the phase-locking measured in this way). Moreover, recent time series analysis developments lead to a way of detecting whether the signals are in synch at each cycle of oscillations, provided there is overall statistically significant level of synchrony (Ahn et al. 2011; Rubchinsky et al. 2014). This approach considers time windows of intermittently synchronized activity to reconstruct the synchronized state from the data. Then, it is possible to check if the oscillations are close to this synchronized state or not at each cycle of oscillations. Statistic of distributions of durations of synchronized and desynchronized episodes reconstructed in this way provides a quantitative description of how synchronous dynamics is patterned in time (Ahn et al. 2011; Rubchinsky et al. 2014).

Temporal Patterns of Neural Synchrony Observed in Parkinsonian Patients

Application of this time series analysis approach to the recordings from the basal ganglia of patients with Parkinson's disease revealed high degree of temporal variability of neural synchrony in the beta frequency band (the references above regarding synchronization and oscillations in Parkinson's disease point to the association of beta-band activity, low dopamine status, and hypokinetic motor symptoms). The analysis of the phase-locking strength over a sliding time window of short length (about 1 s long, that is, about 20 cycles of oscillations) shows substantial variability of synchronization strength, which is going above and below significance level

(Rubchinsky et al. 2012), where the latter was computed via phase-randomized surrogates (Hurtado et al. 2004), Fig. 1.

Each point at the graphs in Fig. 1 is not an "instantaneous" phase-locking strength; rather it represents phase-locking strength over a preceding time window involving tens of oscillatory cycles. It is possible to further improve the temporal resolution (although with some limitations) by adopting a different approach to analysis of the time series. Taking a very long time window, one can find out if there is some (statistically significant) strength of the phase-locking. This essentially provides a description of the synchronized state (the existence of certain preferred phase lag between the signals). Then, at each cycle of oscillations, one can detect if the oscillations are close to this synchronized state (then the signals are synchronized) or not close (then the signals are desynchronized). A way to formalize this approach is described in Ahn et al. (2011) and Rubchinsky et al. (2014). Going from observables to the phase space, this approach looks at whether the system of coupled oscillators is close to a synchronization manifold or not. Then one can measure the statistics of synchronized and desynchronized intervals leading to a description of variation of synchrony on very short time scales.

Analysis of microelectrode recordings from STN and internal globus pallidus (GPi) in parkinsonian patients provided a quantification of this variability (Park et al. 2010; Ratnadurai-Giridharan et al. 2016). The distribution of durations of desynchronized events has a characteristic decaying form and is statistically similar for different locations in the parkinsonian basal ganglia (Fig. 2).

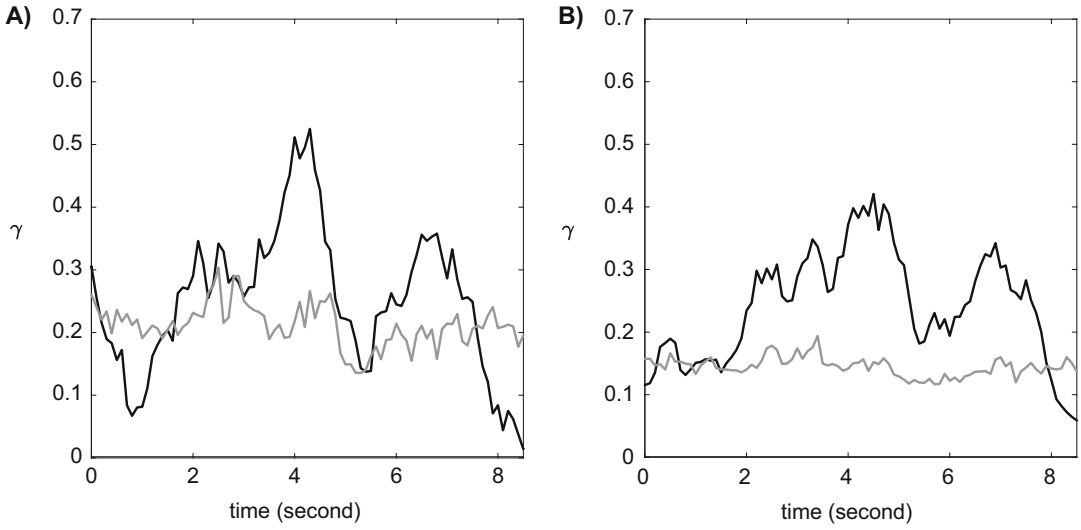
Furthermore, properties of the distributions of the desynchronization durations are correlated with the dopaminergic medication-induced improvements in the motor activity in parkinsonian patients (Ahn et al. 2018), pointing to its potential relevance to parkinsonian motor symptoms. Other studies indicate that transient synchrony states affect the motor performance in parkinsonian patients (Tinkhauser et al. 2020). Thus, the temporal evolution of cortical and basal ganglia synchronization rather than its time-average values may be critical for the parkinsonian neurophysiology (Cagnan et al. 2019).

Also, it is worth noting that parkinsonian tremor, while being distinct from hypokinetic symptoms in presentation and in mechanisms, also exhibits specific temporal patterning of synchronization with tremor-related neural activity in the basal ganglia (Hurtado et al. 2005).

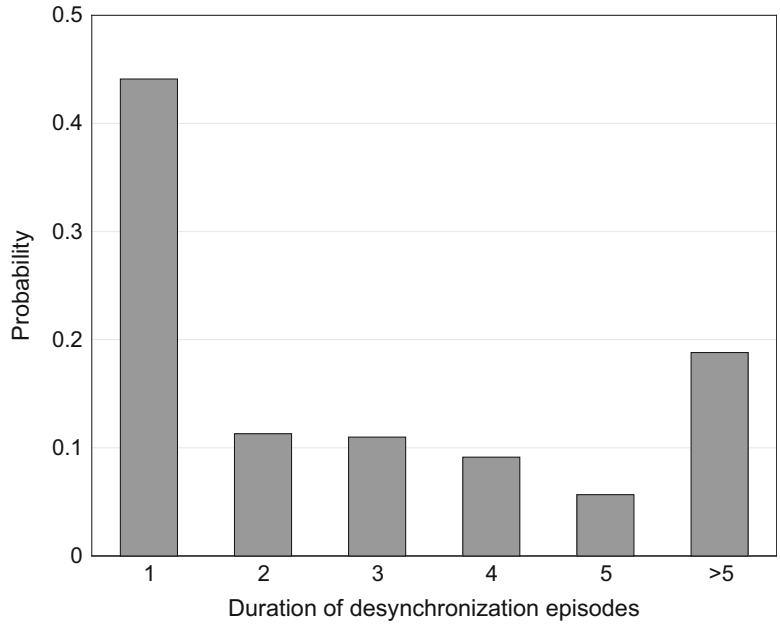
Computational Modeling of the Mechanisms of the Intermittent Synchrony in Parkinsonian Basal Ganglia

There may be several potential factors behind the intermittent synchrony of neural oscillations. For example, the oscillations may go in and out of synchronized state because of noise (synaptic noise, channel noise, noisy inputs, etc.), fluctuations of coupling strength (synaptic plasticity), or insufficient synaptic coupling strength (strong enough to promote some degree of synchrony, but not strong enough to completely stabilize synchronized state). The episodic nature of the oscillations (which may be a generic phenomenon, Jones 2016) may, of course, be a factor too.

Simulations of conductance-based models of subthalamo-pallidal network of the basal ganglia suggested that the moderately elevated (due to the lack of the dopamine) synaptic strength of some dopamine-modulated synapses may lead to the synchronized dynamics with temporal patterns similar to those in the experiments (Park et al. 2011). Computational modeling of the parkinsonian basal ganglia is a complex field of research with multiple and sometimes contradictory models (Rubin 2017), of which these numerical studies are not an exception. However, they compared not only the average synchrony strength but also the rates of transitions between synchronized and desynchronized states, thus comparing the structure of the phase space of the experimental system and that of the model. Further modeling indicates that dopaminergic degeneration-induced changes in the cellular properties of the basal ganglia cells may work cooperatively with this phenomenon (Park and Rubchinsky 2012) and the beta-band activity coming from the cortex may further facilitate



Fine Temporal Structure of Synchronization of Neural Oscillations in the Basal Ganglia in Parkinson's Disease, Fig. 1 Dynamics of synchronous activity in the basal ganglia in a parkinsonian patient. Black line is the phase-locking strength computed over a time window of 1 s (**a**) and 1.5 s (**b**). The gray line is the 95% significance level computed with phase-randomized surrogate data. (See the details of the analysis in Rubchinsky et al. 2012)



Fine Temporal Structure of Synchronization of Neural Oscillations in the Basal Ganglia in Parkinson's Disease, Fig. 2 Distribution of the durations of desynchronizations between spiking units and LFPs from the subthalamic nucleus of PD patients at the beta frequency band. Duration is measured in the number of cycles of oscillations. (See the details of the analysis in Rubchinsky et al. 2012)

synchronized beta oscillations locally generated in the subthalamo-pallidal circuits (Ahn et al. 2016).

An interesting observation of these modeling studies (Park et al. 2011) was that the dynamics with the realistically patterned synchronized oscillations is located (in the space of parameters) on the border of the synchronized and desynchronized dynamics. Therefore, the highly variable evolution of neural synchrony in the basal ganglia in Parkinson's disease may be indicative of the propensity of these brain circuits to

express the transient episodes of synchronized beta-band activity, which is a physiological phenomenon in the healthy state (Engel and Fries 2010). The pathological low-dopamine state would present itself in the network, which is more strongly connected than the healthy one and exhibits ongoing intermittent synchrony instead of the functional ability to generate brief episodic synchronous dynamics only when needed (Park et al. 2011; Rubchinsky et al. 2012).

Intermittent Oscillations and Synchrony in Parkinson's Disease and Adaptive Deep Brain Stimulation

One of the techniques to treat the symptoms of Parkinson's disease is deep brain stimulation (DBS). DBS delivers electrical stimulation to subcortical brain areas via implanted electrodes. In the case of Parkinson's disease, the targets include STN and GPi (Wichmann and DeLong 2006; Kringelbach et al. 2007). The conventional DBS delivers relatively high-intensity current, and experimental evidence suggests that it may work by suppressing oscillations and/or synchronization of neural activity in the beta band (e.g., Wingeier et al. 2006; Kühn et al. 2008). This naturally brings the issue of using stimulation only when oscillations or synchrony is relatively strong, that is, using stimulation adaptively as a control tool (see, for example, Schiff 2012). Some approaches of adaptive DBS have been tested clinically, yielding promising results (e.g., Little et al. 2016). Understanding the nature of the intermittently synchronized oscillatory neural activity in the parkinsonian basal ganglia and its relation to parkinsonian motor symptoms may facilitate the model-based development of more efficient adaptive DBS strategies.

Cross-References

- ▶ Basal Ganglia: Beta Oscillations
- ▶ Basal Ganglia: Overview
- ▶ Computational Model-Based Development of Novel Stimulation Algorithms
- ▶ Computational Models of Deep Brain Stimulation (DBS)
- ▶ Deep Brain Stimulation (Models, Theory, Techniques): Overview
- ▶ Globus Pallidus Cellular Models
- ▶ Local Field Potential and Deep Brain Stimulation (DBS)
- ▶ Local Field Potential and Movement Disorders
- ▶ Parkinson's Disease: Deep Brain Stimulation
- ▶ Phase-Locking Methods
- ▶ Subthalamic Nucleus Cellular Models
- ▶ Subthalamopallidal Loop and Oscillations

References

Ahn S, Park C, Rubchinsky LL (2011) Detecting the temporal structure of intermittent phase locking. Phys Rev E 84(1–2):016201

Ahn S, Zauber SE, Worth RM, Witt T, Rubchinsky LL (2015) Interaction of synchronized dynamics in cortical and basal ganglia networks in Parkinson's disease. Eur J Neurosci 42(5):2164–2171

Ahn S, Zauber SE, Worth RM, Rubchinsky LL (2016) Synchronized beta-band oscillations in a model of the globus pallidus – subthalamic nucleus network under external input. Front Comput Neurosci 10:134

Ahn S, Zauber SE, Worth RM, Witt T, Rubchinsky LL (2018) Neural synchronization: average strength vs temporal patterning. Clin Neurophysiol 129:842–844

Amirnovin R, Williams ZM, Cosgrove GR, Eskandar EN (2004) Visually guided movements suppress subthalamic oscillations in Parkinson's disease patients. J Neurosci 24:11302–11306

Bogacz R (2014) Basal Ganglia: beta oscillations. In: Jaeger D, Jung R (eds) Encyclopedia of computational neuroscience. Springer, New York

Brown P (2003) Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 18:357–363

Buzsáki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926–1929

Buzsáki G, Schomburg EW (2015) What does gamma coherence tell us about inter-regional neural communication? Nat Neurosci 18:484–489

Cagnan H, Mallet N, Moll CKE, Gulberti A, Holt AB, Westphal M, Gerloff C, Engel AK, Hamel W, Magill PJ, Brown P, Sharott A (2019) Temporal evolution of beta bursts in the parkinsonian cortical and basal ganglia network. Proc Natl Acad Sci U S A 116(32):16095–16104

Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Di Lazzaro V, Brown P (2002) Movement-related changes in synchronization in the human basal ganglia. Brain 125:1235–1246

Colgin LL (2011) Oscillations and hippocampal-prefrontal synchrony. Curr Opin Neurobiol 21:467–474

Engel AK, Fries P (2010) Beta-band oscillations – signaling the status quo? Curr Opin Neurobiol 20:156–165

Fell J, Axmacher N (2011) The role of phase synchronization in memory processes. Nat Rev Neurosci 12(2):105–118

Fogelson N, Kühn AA, Silberstein P, Limousin PD, Hariz M, Trottenberg T, Kupsch A, Brown P (2005) Frequency dependent effects of subthalamic nucleus stimulation in Parkinson's disease. Neurosci Lett 382:5–9

Fries P (2015) Rhythms for cognition: communication through coherence. Neuron 88(1):220–235

Hammond C, Bergmann H, Brown P (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 30(7):357–364

Harris AZ, Gordon JA (2015) Long-range neural synchrony in behavior. Annu Rev Neurosci 38:171–194

Hirschmann J, Özkurt TE, Butz M, Homburger M, Elben S, Hartmann CJ, Vesper J, Wojtecki L, Schnitzler A (2011) Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. NeuroImage 55:1159–1168

Hurtado JM, Rubchinsky LL, Sigvardt KA (2004) Statistical method for detection of phase-locking episodes in neural oscillations. J Neurophysiol 91(4):1883–1898

Hurtado JM, Rubchinsky LL, Sigvardt KA, Wheelock VL, Pappas CTE (2005) Temporal evolution of oscillations and synchrony in GPi/muscle pairs in Parkinson's disease. J Neurophysiol 93(3):1569–1584

Jones SR (2016) When brain rhythms aren't 'rhythmic': implication for their mechanisms and meaning. Curr Opin Neurobiol 40:72–80

Kringelbach ML, Jenkinson N, Owen SL, Aziz TZ (2007) Translational principles of deep brain stimulation. Nat Rev Neurosci 8(8):623–635

Kühn AA, Williams D, Kupsch A, Limousin P, Hariz M, Schneider GH, Yarrow K, Brown P (2004) Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. Brain 127:735–746

Kühn AA, Kempf F, Brücke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A, Schneider GH, Hariz MI, Vandenberghe W, Nuttin B, Brown P (2008) High-frequency stimulation of the subthalamic nucleus suppresses oscillatory β activity in patients with Parkinson's disease in parallel with improvement in motor performance. J Neurosci 28(24):6165–6173

Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO (2002) Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 125:1196–1209

Little S, Beudel M, Zrinzo L, Foltynie T, Limousin P, Hariz M, Neal S, Cheeran B, Cagnan H, Gratwicke J, Aziz TZ, Pogosyan A, Brown P (2016) Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. J Neurol Neurosurg Psychiatry 87(7):717–721

Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P (2011) Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. Brain 134:359–374

Mallet N, Pogosyan A, Sharott A, Csicsvari J, Bolam JP, Brown P, Magill PJ (2008) Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. J Neurosci 28:4795–4806

Marsden JF, Limousin-Dowsey P, Ashby P, Pollak P, Brown P (2001) Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson's disease. Brain 124:378–388

Oswal A, Brown P, Litvak V (2013) Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol 26(6):662–670

Park C, Rubchinsky LL (2012) Potential mechanisms for imperfect synchronization in parkinsonian basal ganglia. PLoS One 7(12):e51530

Park C, Worth RM, Rubchinsky LL (2010) Fine temporal structure of beta oscillations synchronization in subthalamic nucleus in Parkinson's disease. J Neurophysiol 103(5):2707–2716

Park C, Worth RM, Rubchinsky LL (2011) Neural dynamics in parkinsonian brain: the boundary between synchronized and nonsynchronized dynamics. Phys Rev E 83:042901

Pikovsky A, Rosenblum M, Kurths J (2001) Synchronization: a universal concept in nonlinear sciences. Cambridge University Press, Cambridge, UK

Pittman-Polletta BR, Kocsis B, Vijayan S, Whittington MA, Kopell NJ (2015) Brain rhythms connect impaired inhibition to altered cognition in schizophrenia. Biol Psychiatry 77:1020–1030

Ratnadurai-Giridharan S, Zauber SE, Worth RM, Witt T, Ahn S, Rubchinsky LL (2016) Temporal patterning of neural synchrony in the basal ganglia in Parkinson's disease. Clin Neurophysiol 127(2):1743–1745

Rubchinsky LL, Park C, Worth RM (2012) Intermittent neural synchronization in Parkinson's disease. Nonlinear Dyn 68(3):329–346

Rubchinsky LL, Ahn S, Park C (2014) Dynamics of desynchronized episodes in intermittent synchronization. Front Phys 2:38

Rubin JE (2017) Computational models of basal ganglia dysfunction: the dynamics is in the details. Curr Opin Neurobiol 46:127–135

Schiff SJ (2012) Neural control engineering. MIT Press, Cambridge, MA

Schnitzler A, Gross J (2005) Normal and pathological oscillatory communication in the brain. Nat Rev Neurosci 6(4):285–296

Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P (2005) Dopamine depletion increases the power and coherence of beta oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. Eur J Neurosci 21:1413–1422

Silberstein P, Pogosyan A, Kühn AA, Hotton G, Tisch S, Kupsch A, Dowsey-Limousin P, Hariz MI, Brown P (2005) Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. Brain 128:1277–1291

Spellman TJ, Gordon JA (2015) Synchrony in schizophrenia: a window into circuit-level pathophysiology. Curr Opin Neurobiol 30:17–23

Stein E, Bar-Gad I (2013) Beta oscillations in the cortico-basal ganglia loop during parkinsonism. Exp Neurol 245:52–59

Stoffers D, Bosboom JL, Deijen JB, Wolters EC, Stam CJ, Berendse HW (2008) Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: an MEG study. NeuroImage 41(2):212–222

Tinkhauser G, Torrecillos F, Pogosyan A, Mostofi A, Bange M, Fischer P, Tan H, Hasegawa H, Glaser M, Muthuraman M, Groppa S, Ashkan K, Pereira EA, Brown P (2020) The cumulative effect of transient synchrony states on motor performance in Parkinson's disease. J Neurosci 40:1571–1580

Uhlhaas PJ, Singer W (2006) Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 52:155–168

Wichmann T, DeLong MR (2006) Deep brain stimulation for neurologic and neuropsychiatric disorders. Neuron 52(1):197–204

Williams D, Kühn A, Kupsch A, Tijssen M, van Bruggen G, Speelman H, Hotton G, Loukas C, Brown P (2005) The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. Eur J Neurosci 21:249–258

Wingeier B, Tcheng T, Koop MM (2006) Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. Exp Neurol 197(1):244–251