[Frontiers in Bioscience 19, 1291-1299, June 1, 2014]

Neuronal oscillations in Parkinson disease

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1. ABSTRACT

Parkinson Disease (PD), characterized by tremor, rigidity, and bradykinesia, is one of the most prevalent neurodegenerative disorders in the world. The pathological hallmark of PD is the loss of dopaminergic cells in the substantia nigra and other brain regions. The pathophysiological mechanisms by which dopaminergic cell loss leads to the motor manifestations of PD are yet to be fully elucidated. A growing body of evidence has revealed abnormal neuronal oscillations within and between multiple brain regions in PD. Unique oscillatory patterns are associated with specific motor abnormalities in PD. Therapies, such as dopaminergic medication and deep brain stimulation that disrupt these abnormal neuronal oscillatory patterns produce symptomatic improvement in PD patients. These findings emphasize the importance of abnormal neuronal oscillations in the pathophysiology of PD, making the disruption of these oscillatory patterns a promising target in the development of effective PD treatments.

2. INTRODUCTION

Coordinated oscillatory activity can occur within and between populations of neurons. These neuronal oscillations are categorized by frequency into multiple bands ranging from low to high, known as the delta (~1-4 Hz), theta (~4-8 Hz), alpha (~8-13 Hz), beta (~13-30 Hz) and gamma (~30-100 Hz) bands, respectively. Abnormalities in neuronal oscillatory patterns have been identified in the pathophysiology of Parkinson disease (PD) (Figure 1) (1-4). The alteration of this pathological oscillatory activity is now increasingly recognized as an important therapeutic determinant relating to the effectiveness of dopamine and deep brain stimulation for the treatment of PD.

PD is a degenerative disease characterized by the loss of dopaminergic neurons within the substantia nigra pars compacta. Neuronal loss also occurs in the ventral tegmental area, the dorsal motor nucleus of the vagus, and other brain regions (5). Each of these neuronal populations

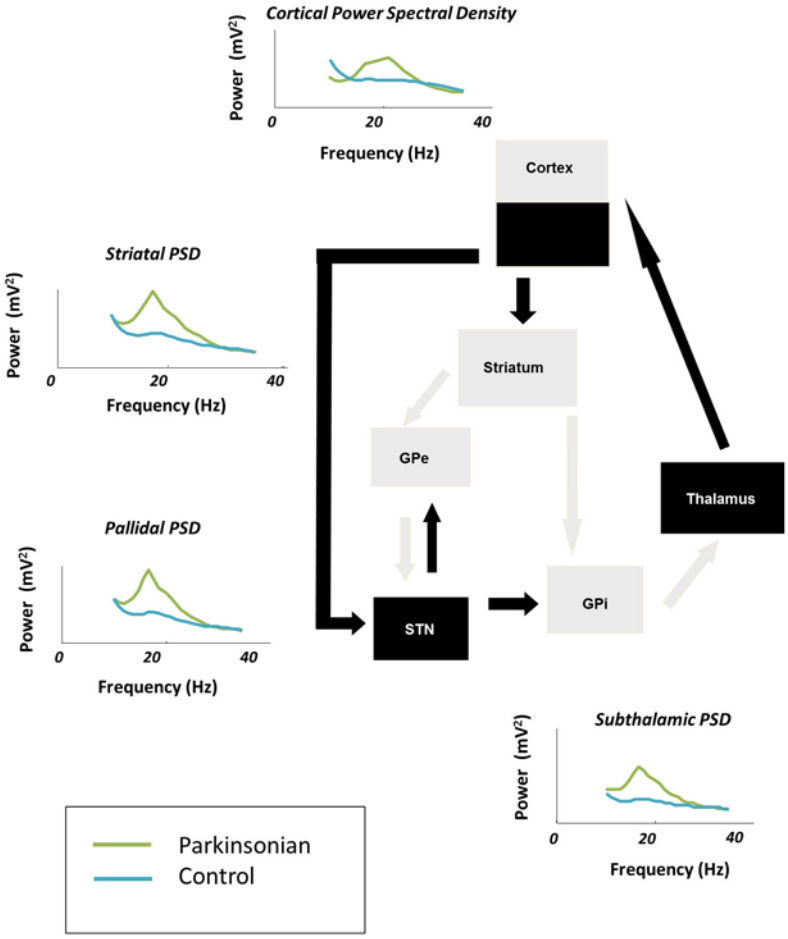

Figure 1. Cortico-basal ganglia-thalamo-cortical connections through which synchrony emerges in PD. Prominent oscillatory activity at beta frequencies is observed at rest in PD patients undergoing DBS surgery and in recordings from animal models of PD. Light gray arrows represent inhibitory projections; black arrows represent excitatory projections. PSD = power spectral density.

has widespread connections throughout the brain. As a result, changes in neuronal oscillations within multiple brain regions are found in PD. The fundamental change seen in the oscillatory activity of these widespread interconnected brain regions is excessive synchrony in multiple frequency bands at multiple anatomic scales (6, 7, 8). The degree of synchrony appears to be dynamic and related to the amount of degeneration, as patients in different stages of the disease from mild to severe show different levels of ensemble couplings (9). Abnormalities in different frequencies are related to specific nuclei and specific symptoms.

3. ABNORMAL OSCILLATIONS IN SUBCORTICAL NUCLEI AND RELATED CIRCUITS IN PD

3.1. Abnormal oscillations in the subthalamic nucleus, substantia nigra pars reticulata, and globus pallidus

Abnormal synchrony within the basal ganglia is associated with dysfunction of multiple circuits in PD. Coherent oscillatory frequencies result from interconnected neuronal ensembles in the subthalamic nucleus (STN), cortex and striatum. Under normal physiologic conditions, movement preparation is accompanied by an increase in synchrony in the beta frequency range, which disappears during actual movement (2, 7, 9), where gamma-range activity becomes evident (10-12), and recurs again after movement as a 'beta-rebound', lasting for up to hundreds of milliseconds (13). This coordination, however, is disrupted in PD. In PD, neuronal frequencies within the STN are dominated by the alpha and beta range while at rest in the 'off' medication state (11, 12, 14). Increased beta oscillations are often correlated with the clinical state of patients (15), and are modulated by the presence of dopamine (16). In particular, for bradykinesia and rigidity, the predominant oscillatory abnormality is in the beta frequency band (6, 17).

The power of beta local field potentials is highest in the dorsal STN, and decreases ventrally (18-23). Simultaneous recordings from bilateral STN during deep brain stimulation (DBS) surgery for PD show highly coherent beta-frequency oscillations (24). In animal PD models, synchronization at beta frequencies has also been

observed between local field and unit recordings (25). Simultaneous micro-recordings from the STN and substantia nigra pars reticulata (SNr) of PD patients also show interesting correlation in the beta band, with 86% coherence between local field potentials in these two nuclei (18). The typical background firing rate for SNr neurons is a regular firing pattern in the 60-90 Hz range (26). SNr coherence in the beta band suggests the influence of the beta-dominated STN.

Differences in the oscillatory frequency of the bilateral STN have also been found between tremor and non-tremor sides of STN nuclei. On the non-tremor side, STN neurons oscillate in a beta frequency (27). In contrast, dorsal STN neurons on the tremor side oscillate in a characteristic theta frequency corresponding to the patient's resting tremor (28). Multiple studies indicate that tremor-frequency oscillatory cells are common in the STN (15, 26, 29, 30), suggesting that tremor frequency STN neurons may be directly related to the tremor symptoms common in PD.

Evidence also exists for very high frequency oscillations within the STN that are activity and dopamine dependent. In a series of 9 PD patients, local field potential (LFP) recordings through DBS electrodes revealed the presence of oscillations at 300 Hz prevalent at rest with the administration of levodopa which was modulated by voluntary movement (31).

Neuronal oscillatory activity in the globus pallidus (GP) is seen in both the <30 Hz and 60-90 Hz ranges (26, 32). Synchrony between the internal segment of the globus pallidus (GPi) and STN is increased in PD patients in a dopamine-modulated fashion (10). Oscillatory coupling between the STN and GPi in the lower range is increased in PD patients in the absence of dopamine. In contrast, oscillatory coupling between the STN and GPi at approximately 70 Hz is seen only in dopamine-treated patients (32).

3.2. Abnormalities in basal ganglia-cortical connections

Coordinated neuronal activity is required for coordinated movement. For example, coordinated beta-frequency activity is necessary in the normal physiologic state between cortical regions including the motor cortex (33). This cortical rhythmicity is likely modulated at least in part by subcortical inputs, and disruption of these inputs has been linked to the motor symptoms of PD. In a recent study which combined cortical magnetoencephalography (MEG) and STN recordings in the resting state of PD patients, oscillations were identified in the alpha range within the temporoparietal cortex and the beta range within the frontal cortex which were coherent with the STN (34). Interestingly, beta coherence between the STN and prefrontal cortex was modified by administration of dopamine (34). Combined electroencephalography (EEG) and DBS studies further indicate that this coherence between cortical and subcortical structures is bidirectional and dynamic.

Subthalamic-cortical coherence is particularly prevalent at 20 Hz in patients with PD. STN stimulation in PD patients at 20 Hz shows increased amplitude of the cortical response, consistent with resonance within this circuit. This response is dampened by the administration of dopamine (35). STN activity is also coherent with activity in specific areas of the cerebral cortex around 45 Hz, with the cortical activity found to lead the STN by approximately 20 ms (36). In levodopa-treated patients, neuronal oscillatory coherence between the STN, GPi, and the neocortex is seen in the 70-85Hz band, but in this range, the STN phase leads the cortex by approximately 20 ms (11). Coupling between the STN and motor cortex has also been shown over a higher frequency range (50-200 Hz), though the amplitude in this range is modulated by lower-frequency phase-synchronized gamma activity (37). Taken together, these studies indicate a levodopa dependent functional connectivity between the cortex and the basal ganglia which may be altered or disrupted in the low dopamine state of PD.

3.3. Abnormalities in cortico-cortical connections

In addition to basal ganglia-cortical associations, cortico-cortical relationships in PD are also abnormal. Beta frequency oscillations are normally present in motor cortex (33, 38), though excessive synchronization is present in PD and likely contributes to its motor manifestations. PD patients show increased cortical power in the beta frequency (13–30 Hz) during rest and steady-state muscle contraction when compared to healthy controls who show suppression of this activity during the same movement (39), suggesting the inability of the cortex to release from beta oscillation in PD. Surface EEG studies of Parkinson's patients at rest show coherence in distributed cortical areas in the beta frequency (10-35Hz) which decrease with dopamine administration and STN stimulation, and both of which correlate with reduction in contralateral hemibody UPDRS motor scores (40).

Oscillatory connectivity between the premotor cortex, supplemental motor area, and primary motor cortex is also altered in PD. Relative to control patients, PD patients in the off-medication state show loss of gamma-frequency coupling between the premotor and supplemental motor cortices. Coherence in this frequency range, as well as feedback between the premotor and motor cortices at beta frequency, and associated improvement in motor function, is seen with the administration of dopamine (41). Similarly, task-induced oscillatory coupling between prefrontal and premotor cortices is absent in PD patients performing a motor task in the off-medication state, and present in healthy controls. Task-induced coherence is re-established with the administration of levodopa in the PD subjects (42). Given the preponderance of beta oscillations in cortical circuits implementing top-down control generally, it may be that coordinated beta coupling plays a common role throughout brain circuits, signaling the 'status-quo' or maintaining the current cognitive state and rendering pathologically synchronous circuits less flexible (43).

These pathologic cortico-cortical couplings vary with the severity of disease, as patients in the earliest stages of PD show abnormalities isolated to the alpha band,

whereas disease progression has been positively correlated with progression into other frequencies including the beta range, among others (44). Lower frequency oscillations in the range of tremor frequency (approx. 3-7 Hz) have also been reported in the cortex of the hemisphere contralateral to tremor (45-47). Recently, it was also shown that there is increased amplitude of low frequency oscillations in the primary and secondary motor areas in PD patients off medication which are reduced by the administration of dopamine (48). Together, these findings indicate that abnormal, levodopa-responsive oscillatory patterns exist in cortico-cortical networks in PD.

4. ABNORMAL NEURONAL OSCILLATIONS ASSOCIATED WITH BRADYKINESIA AND RIGIDITY DIFFER FROM TREMOR

Multiple cortical and subcortical domains are involved in the initiation, coordination, and completion of motor tasks. These areas include premotor and supplemental motor cortices, the primary motor cortex, the thalamus and the basal ganglia. Coordinated movement requires complex integration between these areas, the basis of which relies on dynamic neuronal coupling through synchronous discharges. For execution of movements in both the physiologic and pathologic states, these couplings can have both linear, same frequency couplings, as well as nonlinear relationships (49, 50). As reviewed above, many of these areas show abnormal intrinsic and circuit-level oscillatory patterns in PD which exist in multiple frequency bands and are dynamic relative to both dopamine availability and motor activity. These abnormalities contribute significantly to the motor features of bradykinesia, rigidity, and tremor characteristic of PD.

Evidence supports the correlation between pathologic neuronal oscillations, particularly oscillatory activity in the beta frequency range, with the symptoms of bradykinesia and rigidity, (21, 51-54). For example, STN phase coherence in the beta frequency band has been correlated in PD patients with the severity of limb and axial bradykinesia and rigidity (55). It has also been shown that stability within beta frequency LFP in the STN also positively correlates with both bradykinesia and rigidity, indicating that loss of reactivity in the beta frequency might contribute to the motor symptoms of PD (56). These findings align with the observation that desynchronization of beta activity in the STN has been shown to be necessary for movement preparation (57).

Treatment with levodopa, which reduces these clinical symptoms, also decreases these abnormal oscillations. Multiple studies indicate that the administration of dopamine results in a reduction of both persistent STN beta synchrony as well as motor impairment (21, 54, 58-60). The reduction of beta frequency activity in the STN associated with the administration of dopamine correlates with improved UPDRS motor scores (52). Furthermore, the degree of beta synchronization within the STN correlates with the clinical response patients obtain from dopamine (21). The amount of suppression of STN LFP beta activity is predictive of the reduction of motor symptoms (60). While the presented evidence highlights studies of the STN, it must be noted that measured LFPs likely reflect oscillation of the entire cortical-subcortical network, as the basal ganglia are largely coherent with the cortex and this activity likely reflects large-scale circuit abnormalities (32, 36, 61). For example, recent studies of network interactions that have attempted to delineate causal pathways from multi-region local field potential recordings have emphasized the importance of STN afferents from cortex and striatum in beta genesis (62, 63).

Several studies also report induced bradykinesia after stimulating the STN at beta frequencies. Direct stimulation applied to the STN at approximately 20 Hz in PD patients with preserved baseline function caused a significant frequency-selective decrease in finger tapping rate (64). These findings were expanded in a follow-up study which demonstrated slowed finger tapping in multiple low frequency bands ranging from 5 to 20 Hz, again in PD patients that had relatively preserved baseline function (65). In a similar study, bilateral stimulation of the STN in the beta frequency range of 20 Hz induced frequency-specific slowing of the development of grip force (66). Again, these findings were significant only in PD patients who retained the best baseline activity (66).

In contrast to these associations between beta oscillations and the symptoms of bradykinesia and rigidity, correlation with tremor symptoms is less clear (67). While evidence does exist for beta oscillations in PD patients with tremor symptoms (68, 69), multiple studies have identified tremor-coherent cells in the STN oscillating in the tremor frequency (15, 69, 70) as well as frequencies which approximate a double-tremor range (71). Also in contrast to other stereotypical motor symptoms of PD, tremor activity is not reduced when beta LFP is reduced in the STN (52). While DBS treatment reduces clinical tremor symptoms in PD, and has been shown to suppress tremor frequency (72), treatment-induced suppression of beta synchrony shows less correlation with improvement of the resting tremor (9). These findings again implicate the poor correlation between beta oscillation and tremor symptoms (67). Similarly, administration of dopaminergic medication, which improves the symptoms of bradykinesia and rigidity in correlation with changes in beta LFP and single unit oscillations, does not have the same effect on tremor frequencies (21, 73). Furthermore, neurons oscillating in the tremor frequency show a high degree of interneuronal coherence, suggesting the presence of a significant STN tremor network (30). Interestingly, Reck et al. (2009) demonstrated in a series of 8 tremor-dominant PD patients that tremor-related activity in the STN can be synchronized or desynchronized to the electromyography (EMG) depending on the spatial distribution within the STN. These muscle-specific tremor-associated LFPs in the STN were found predominately in the tremor and double-tremor frequencies (72). Finally, coherence between neuronal STN activity and muscular activity measured by EMG appears to instead occur predominantly at the tremor frequency, and only to a lesser extent in the beta frequency range (69).

Also in contrast to the correlations between STN beta oscillations and the symptoms of bradykinesia and rigidity, evidence implicates tremor-frequency thalamic

oscillations, generated by "tremor cells", as contributing to tremor in PD (74). Single unit analysis of ventral thalamic cells in PD patients demonstrate that thalamic cells exhibiting high amplitude signal at tremor frequency were correlated significantly with EMG activity during tremor, suggesting that these cells or at least a subpopulation are involved in the generation of tremor (75). Movement-related cells in the human thalamus can be classified into those which are activated in response to somatosensory stimulation and those which are not (combined cells and voluntary cells, respectively) (76). Many of the combined and voluntary thalamic cells were not only correlated with EMG at the tremor frequency, but also led the EMG during tremor (77). Tremor-locked cells (i.e. those which appeared only with rest tremor and were synchronized with the tremor) have been identified in the centromedian-parafascicular complex (78). A second population of cells has been identified which demonstrate rhythmic spike bursts which oscillate periodically at tremor frequency, though these are not phase-locked with the tremor and are present independent of tremor (78). In PD patients, neurons with tremor activity are concentrated in the ventral intermediate nucleus of the thalamus (VIM), and that tremor-related cells are more prevalent in PD patients compared to patients with other tremor-related disorders (79).

In summary, these findings suggest that the cardinal motor symptoms of PD are associated with abnormal neuronal oscillations. Abnormal oscillations associated with bradykinesia and rigidity differ from tremor in multiple ways. First, bradykinesia and rigidity are correlated with beta frequency oscillations, whereas tremor is associated with tremor-frequency oscillations. Second, the cell populations associated with these symptoms appear to have unique anatomic distributions within the basal ganglia and the thalamus. Finally dopamine-related reductions in beta oscillations have been directly linked with the reduction of bradykinesia and rigidity, but not tremor. These findings suggest that oscillations in multiple frequency ranges in distinct but functionally connected brain regions underlie the various motor features of PD.

5. DISRUPTION OF ABNORMAL OSCILLATIONS RELATES TO THE THERAPEUTIC EFFECTIVENESS OF DBS

Over the past two decades, DBS has emerged as an effective treatment for the motor manifestations of PD (80),(81). Standard DBS targets for PD are the STN and the GPi, with effectiveness reported for both unilateral and bilateral stimulation (82). The effects of DBS on neural tissue are complex and multifactorial (83). As with dopaminergic treatment, DBS can suppress beta band coherence in the STN and GP, correlating with improvements in bradykinesia and rigidity (7). In addition to decreasing beta oscillations, STN DBS can decrease gamma and tremor frequency oscillations in the motor thalamus, leading to symptomatic improvements in resting tremor. Recent findings of a prodromic disruption of synchronized output from motor cortex under STN stimulation suggest that further refinements in our understanding of DBS beta disruption in patients will be forthcoming (84).

6. CONCLUSIONS

The cardinal motor features of PD are associated with abnormal oscillations within and between multiple neuronal populations and their associated networks. Abnormal oscillations associated with bradykinesia and rigidity differ from tremor in multiple ways, including different oscillation frequencies and different initiating neuronal populations. Whereas bradykinesia and rigidity are associated with beta oscillatory patterns in the STN and GP, tremor is associated with tremor frequency oscillatory patterns in the STN and thalamus. These neuronal populations are functionally connected in cortico-basal ganglia-thalamic networks. The therapeutic effectiveness of dopaminergic medication and DBS relates, at least in part, to their ability to disrupt the abnormal oscillatory patterns within these networks. The identification of dysfunctional neuronal oscillations is a significant advance in our understanding PD pathophysiology, and represents an important target in PD therapeutics.

7. REFERENCES

1. Uhlhaas, P. J. and W. Singer: Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology. *Neuron*, 52(1), 155-168 (2006)

2. Schnitzler, A. and J. Gross: Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci*, 6(4), 285-96 (2005)

3. Uhlhaas, P. J. and W. Singer: Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. *Neuron*, 75(6), 963-80 (2012)

4. Hauck, M., J. Lorenz and A. K. Engel: Role of synchronized oscillatory brain activity for human pain perception. *Rev Neurosci*, 19(6), 441-50 (2008)

5. Braak, H., K. Del Tredici, U. Rub, R. A. de Vos, E. N. Jansen Steur and E. Braak: Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*, 24(2), 197-211 (2003)

6. Stein, E. and I. Bar-Gad: Beta oscillations in the cortico-basal ganglia loop during parkinsonism. *Exp Neurol*, 245(0), 52-59 (2013)

7. Hammond, C., H. Bergman and P. Brown: Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci*, 30(7), 357-64 (2007)

8. Bronte-Stewart, H., C. Barberini, M. M. Koop, B. C. Hill, J. M. Henderson and B. Wingeier: The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. *Exp Neurol*, 215(1), 20-8 (2009)

9. Berendse, H. W. and C. J. Stam: Stage-dependent patterns of disturbed neural synchrony in Parkinson's disease. *Parkinsonism Relat Disord*, 13 Suppl 3, S440-5 (2007)

10. Brown, P., A. Oliviero, P. Mazzone, A. Insola, P. Tonali and V. Di Lazzaro: Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci*, 21(3), 1033-8 (2001)

11. Williams, D., M. Tijssen, G. Van Bruggen, A. Bosch, A. Insola, V. Di Lazzaro, P. Mazzone, A. Oliviero, A. Quartarone, H. Speelman and P. Brown: Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain*, 125(Pt 7), 1558-69 (2002)

12. Priori, A., G. Foffani, A. Pesenti, F. Tamma, A. M. Bianchi, M. Pellegrini, M. Locatelli, K. A. Moxon and R. M. Villani: Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol*, 189(2), 369-79 (2004)

13. Jurkiewicz, M., W. Gaetz, A. Bostan and D. Cheyne: Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. *Neuroimage*, 32(3), 1281-1289 (2006)

14. Alegre, M., F. Alonso-Frech, M. C. Rodríguez-Oroz, J. Guridi, I. Zamarbide, M. Valencia, M. Manrique, J. A. Obeso and J. Artieda: Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. *Eur J Neurosci*, 22(9), 2315-2324 (2005)

15. Levy, R., W. D. Hutchison, A. M. Lozano and J. O. Dostrovsky: High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J Neurosci*, 20(20), 7766-75 (2000)

16. Levy, R., P. Ashby, W. D. Hutchison, A. E. Lang, A. M. Lozano and J. O. Dostrovsky: Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain*, 125(Pt 6), 1196-209 (2002)

17. Gatev, P., O. Darbin and T. Wichmann: Oscillations in the basal ganglia under normal conditions and in movement disorders. *Mov Disord*, 21(10), 1566-77 (2006)

18. Alavi, M., J. O. Dostrovsky, M. Hodaie, A. M. Lozano and W. D. Hutchison: Spatial extent of beta oscillatory activity in and between the subthalamic nucleus and substantia nigra pars reticulata of Parkinson's disease patients. *Exp Neurol*, 245(0), 60-71 (2013)

19. Kuhn, A. A., T. Trottenberg, A. Kivi, A. Kupsch, G. H. Schneider and P. Brown: The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. *Exp Neurol*, 194(1), 212-20 (2005)

20. Moran, A., H. Bergman, Z. Israel and I. Bar-Gad: Subthalamic nucleus functional organization revealed by parkinsonian neuronal oscillations and synchrony. *Brain*, 131(Pt 12), 3395-409 (2008)

21. Weinberger, M., N. Mahant, W. D. Hutchison, A. M. Lozano, E. Moro, M. Hodaie, A. E. Lang and J. O. Dostrovsky: Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. *J Neurophysiol*, 96(6), 3248-56 (2006)

22. Trottenberg, T., A. Kupsch, G. H. Schneider, P. Brown and A. A. Kuhn: Frequency-dependent distribution of local field potential activity within the subthalamic nucleus in Parkinson's disease. *Exp Neurol*, 205(1), 287-91 (2007)

23. Zaidel, A., A. Spivak, B. Grieb, H. Bergman and Z. Israel: Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. *Brain*, 133(Pt 7), 2007-21 (2010)

24. de Solages, C., B. C. Hill, M. M. Koop, J. M. Henderson and H. Bronte-Stewart: Bilateral symmetry and coherence of subthalamic nuclei beta band activity in Parkinson's disease. *Exp Neurol*, 221(1), 260-6 (2010)

25. Mallet, N., A. Pogosyan, A. Sharott, J. Csicsvari, J. Bolam, P. Brown and P. Magill: Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. *Neurosci*, 28(18), 4795-4806 (2008)

26. Hutchison, W. D., R. J. Allan, H. Opitz, R. Levy, J. O. Dostrovsky, A. E. Lang and A. M. Lozano: Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. *Ann Neurol*, 44(4), 622-628 (1998)

27. Contarino, M. F., L. J. Bour, M. Bot, P. van den Munckhof, J. D. Speelman, P. R. Schuurman and R. M. de Bie: Tremor-specific neuronal oscillation pattern in dorsal subthalamic nucleus of parkinsonian patients. *Brain Stim*, 5(3), 305-14 (2012)

28. Contarino, M. F., L. J. Bour, M. Bot, P. van den Munckhof, J. D. Speelman, P. R. Schuurman and R. M. de Bie: Tremor-specific neuronal oscillation pattern in dorsal subthalamic nucleus of parkinsonian patients. *Brain Stim*, 5(3), 305-314 (2012)

29. Magariños-Ascone, C. M., R. Figueiras-Mendez, C. Riva-Meana and A. Córdoba-Fernández: Subthalamic neuron activity related to tremor and movement in Parkinson's disease. *Eur J Neurosci*, 12(7), 2597-2607 (2000)

30. Amtage, F., K. Henschel, B. Schelter, J. Vesper, J. Timmer, C. H. Lucking and B. Hellwig: High functional connectivity of tremor related subthalamic neurons in Parkinson's disease. *Clin Neurophysiol*, 120(9), 1755-61 (2009)

31. Foffani, G., A. Priori, M. Egidi, P. Rampini, F. Tamma, E. Caputo, K. A. Moxon, S. Cerutti and S. Barbieri: 300□Hz subthalamic oscillations in Parkinson's disease. *Brain*, 126(10), 2153-2163 (2003)

32. Brown, P., A. Oliviero, P. Mazzone, A. Insola, P. Tonali and V. Di Lazzaro: Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci*, 21(3), 1033-1038 (2001)

33. Brown, P.: Cortical drives to human muscle: the piper and related rhythms. *Prog Neurobiol*, 60(1), 97-108 (2000)

34. Litvak, V., A. Jha, A. Eusebio, R. Oostenveld, T. Foltynie, P. Limousin, L. Zrinzo, M. I. Hariz, K. Friston and P. Brown: Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain*, 134(2), 359-374 (2011)

35. Eusebio, A., A. Pogosyan, S. Wang, B. Averbeck, L. D. Gaynor, S. Cantiniaux, T. Witjas, P. Limousin, J. P. Azulay and P. Brown: Resonance in subthalamo-cortical circuits in Parkinson's disease. *Brain*, 132(Pt 8), 2139-50 (2009)

36. Marsden, J. F., P. Limousin-Dowsey, P. Ashby, P. Pollak and P. Brown: Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson's disease. *Brain*, 124(2), 378-388 (2001)

37. Shimamoto, S. A., E. S. Ryapolova-Webb, J. L. Ostrem, N. B. Galifianakis, K. J. Miller and P. A. Starr: Subthalamic nucleus neurons are synchronized to primary motor cortex local field potentials in Parkinson's disease. *J Neurosci*, 33(17), 7220-33 (2013)

38. Miller, K. J., E. C. Leuthardt, G. Schalk, R. P. N. Rao, N. R. Anderson, D. W. Moran, J. W. Miller and J. G. Ojemann: Spectral Changes in Cortical Surface Potentials during Motor Movement. *J Neurosci*, 27(9), 2424-2432 (2007)

39. Pollok, B., V. Krause, W. Martsch, C. Wach, A. Schnitzler and M. Südmeyer: Motor-cortical oscillations in early stages of Parkinson's disease. *J Physiol*, 590(13), 3203-3212 (2012)

40. Silberstein, P., A. Pogosyan, A. A. Kühn, G. Hotton, S. Tisch, A. Kupsch, P. Dowsey-Limousin, M. I. Hariz and P. Brown: Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. *Brain*, 128(6), 1277-1291 (2005)

41. Herz, D. M., E. Florin, M. S. Christensen, C. Reck, M. T. Barbe, M. K. Tscheuschler, M. Tittgemeyer, H. R. Siebner and L. Timmermann: Dopamine replacement modulates oscillatory coupling between premotor and motor cortical areas in Parkinson's disease. *Cereb Cortex* (2013)

42. Herz, D. M., H. R. Siebner, O. J. Hulme, E. Florin, M. S. Christensen and L. Timmermann: Levodopa reinstates connectivity from prefrontal to premotor cortex during externally paced movement in Parkinson's disease. *Neuroimage* (2013)

43. Engel, A. and P. Fries: Beta-band oscillations--signalling the status quo? *Curr Op Neurobiol*, 20(2), 156-165 (2010)

44. Stoffers, D., J. L. Bosboom, J. B. Deijen, E. Wolters, C. J. Stam and H. W. Berendse: Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: an MEG study. *Neuroimage*, 41(2), 212-22 (2008)

45. Volkmann, J., M. Joliot, A. Mogilner, A. A. Ioannides, F. Lado, E. Fazzini, U. Ribary and R. Llinas: Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. *Neurol*, 46(5), 1359-70 (1996)

46. Hellwig, B., S. Haussler, M. Lauk, B. Guschlbauer, B. Koster, R. Kristeva-Feige, J. Timmer and C. H. Lucking: Tremor-correlated cortical activity detected by electroencephalography. *Clin Neurophysiol*, 111(5), 806-9 (2000)

47. Raethjen, J., R. B. Govindan, M. Muthuraman, F. Kopper, J. Volkmann and G. Deuschl: Cortical correlates of the basic and first harmonic frequency of Parkinsonian tremor. *Clin Neurophysiol*, 120(10), 1866-1872 (2009)

48. Kwak, Y., S. Peltier, N. Bohnen, M. Müller, P. Dayalu and R. D. Seidler: L-DOPA changes spontaneous low-frequency BOLD signal oscillations in Parkinson's disease: a resting state fMRI study. *Front Sys Neurosci,* 6 (2012)

49. Chen, C. C., J. M. Kilner, K. J. Friston, S. J. Kiebel, R. K. Jolly and N. S. Ward: Nonlinear coupling in the human motor system. J Neurosci, 30(25), 8393-9 (2010)

50. Hanson, T. L., A. M. Fuller, M. A. Lebedev, D. A. Turner and M. A. L. Nicolelis: Subcortical neuronal ensembles: an analysis of motor task association, tremor, oscillations, and synchrony in human patients. *J Neurosci*, 32(25), 8620-8632 (2012)

51. Brown, P.: Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov Disord*, 18(4), 357-63 (2003)

52. Kuhn, A. A., A. Kupsch, G. H. Schneider and P. Brown: Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur J Neurosci*, 23(7), 1956-60 (2006)

53. Kuhn, A. A., D. Williams, A. Kupsch, P. Limousin, M. Hariz, G. H. Schneider, K. Yarrow and P. Brown: Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain*, 127(Pt 4), 735-46 (2004)

54. Kühn, A. A., A. Tsui, T. Aziz, N. Ray, C. Brücke, A. Kupsch, G.-H. Schneider and P. Brown: Pathological

synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Exp Neurol*, 215(2), 380-387 (2009)

55. Pogosyan, A., F. Yoshida, C. C. Chen, I. Martinez-Torres, T. Foltynie, P. Limousin, L. Zrinzo, M. I. Hariz and P. Brown: Parkinsonian impairment correlates with spatially extensive subthalamic oscillatory synchronization. *Neurosci*, 171(1), 245-257 (2010)

56. Little, S., A. Pogosyan, A. A. Kuhn and P. Brown: beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. *Exp Neurol*, 236(2), 383-8 (2012)

57. Kühn, A. A., D. Williams, A. Kupsch, P. Limousin, M. Hariz, G. H. Schneider, K. Yarrow and P. Brown: Event□related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain*, 127(4), 735-746 (2004)

58. Weinberger, M., W. D. Hutchison and J. O. Dostrovsky: Pathological subthalamic nucleus oscillations in PD: can they be the cause of bradykinesia and akinesia? *Exp Neurol*, 219(1), 58-61 (2009)

59. Kühn, A. A., A. Kupsch, G.-H. Schneider and P. Brown: Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur J Neurosci*, 23(7), 1956-1960 (2006)

60. Kuhn, A. A., F. Kempf, C. Brucke, L. Gaynor Doyle, I. Martinez-Torres, A. Pogosyan, T. Trottenberg, A. Kupsch, G. H. Schneider, M. I. Hariz, W. Vandenberghe, B. Nuttin and P. Brown: High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J Neurosci*, 28(24), 6165-73 (2008)

61. Cassidy, M., P. Mazzone, A. Oliviero, A. Insola, P. Tonali, V. Di Lazzaro and P. Brown: Movement-related changes in synchronization in the human basal ganglia. *Brain*, 125(Pt 6), 1235-46 (2002)

62. Moran, R. J., N. Mallet, V. Litvak, R. J. Dolan, P. J. Magill, K. J. Friston and P. Brown: Alterations in brain connectivity underlying beta oscillations in Parkinsonism. *PLoS Computational Biol*, 7(8), e1002124 (2011)

63. Marreiros, A. C., H. Cagnan, R. J. Moran, K. J. Friston and P. Brown: Basal ganglia–cortical interactions in Parkinsonian patients. *Neuroimage*, 66, 301-310 (2013)

64. Chen, C. C., V. Litvak, T. Gilbertson, A. Kühn, C. S. Lu, S. T. Lee, C. H. Tsai, S. Tisch, P. Limousin, M. Hariz and P. Brown: Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. *Exp Neurol*, 205(1), 214-221 (2007)

65. Eusebio, A., C. C. Chen, C. S. Lu, S. T. Lee, C. H. Tsai, P. Limousin, M. Hariz and P. Brown: Effects of low-frequency stimulation of the subthalamic nucleus on movement in Parkinson's disease. *Exp Neurol*, 209(1), 125-130 (2008)

66. Chen, C. C., W. Y. Lin, H. L. Chan, Y. T. Hsu, P. H. Tu, S. T. Lee, S. M. Chiou, C. H. Tsai, C. S. Lu and P. Brown: Stimulation of the subthalamic region at 20 Hz slows the development of grip force in Parkinson's disease. *Exp Neurol*, 231(1), 91-96 (2011)

67. Rivlin-Etzion, M., O. Marmor, G. Heimer, A. Raz, A. Nini and H. Bergman: Basal ganglia oscillations and pathophysiology of movement disorders. *Curr Op Neurobiol*, 16(6), 629-637 (2006)

68. Levy, R., W. D. Hutchison, A. M. Lozano and J. O. Dostrovsky: High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J Neurosci*, 20(20), 7766-7775 (2000)

69. Amtage, F., K. Henschel, B. Schelter, J. Vesper, J. Timmer, C. H. Lücking and B. Hellwig: Tremor-correlated neuronal activity in the subthalamic nucleus of Parkinsonian patients. *Neurosci Lett*, 442(3), 195-199 (2008)

70. Liu, X., H. L. Ford-Dunn, G. N. Hayward, D. Nandi, R. C. Miall, T. Z. Aziz and J. F. Stein: The oscillatory activity in the Parkinsonian subthalamic nucleus investigated using the macro-electrodes for deep brain stimulation. *Clin Neurophysiol*, 113(11), 1667-72 (2002)

71. Reck, C., E. Florin, L. Wojtecki, H. Krause, S. Groiss, J. Voges, M. Maarouf, V. Sturm, A. Schnitzler and L. Timmermann: Characterisation of tremor-associated local field potentials in the subthalamic nucleus in Parkinson's disease. *Eur J Neurosci*, 29(3), 599-612 (2009)

72. Reck, C., E. Florin, L. Wojtecki, H. Krause, S. Groiss, J. Voges, M. Maarouf, V. Sturm, A. Schnitzler and L. Timmermann: Characterisation of tremor-associated local field potentials in the subthalamic nucleus in Parkinson's disease. *Eur J Neurosci*, 29(3), 599-612 (2009)

73. Ray, N. J., N. Jenkinson, S. Wang, P. Holland, J. S. Brittain, C. Joint, J. F. Stein and T. Aziz: Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Exp Neurol*, 213(1), 108-113 (2008)

74. Guiot, G., J. Hardy and D. Albe-Fessard: (Precise delimitation of the subcortical structures and identification of thalamic nuclei in man by stereotactic electrophysiology). *Neurochirurgia (Stuttg)*, 5, 1-18 (1962)

75. Lenz, F. A., R. R. Tasker, H. C. Kwan, S. Schnider, R. Kwong, Y. Murayama, J. O. Dostrovsky and J. T. Murphy: Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3-6 Hz component of parkinsonian tremor. *J Neurosci*, 8(3), 754-64 (1988)

76. Lenz, F. A., H. C. Kwan, J. O. Dostrovsky, R. R. Tasker, J. T. Murphy and Y. E. Lenz: Single unit analysis of the human ventral thalamic nuclear group. Activity correlated with movement. *Brain*, 113 (Pt 6), 1795-821 (1990)

77. Lenz, F. A., H. C. Kwan, R. L. Martin, R. R. Tasker, J. O. Dostrovsky and Y. E. Lenz: Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. *Brain*, 117 (Pt 3), 531-43 (1994)

78. Magnin, M., A. Morel and D. Jeanmonod: Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. *Neurosci*, 96(3), 549-64 (2000)

79. Brodkey, J. A., R. R. Tasker, C. Hamani, M. P. McAndrews, J. O. Dostrovsky and A. M. Lozano: Tremor cells in the human thalamus: differences among neurological disorders. *J Neurosurg*, 101(1), 43-7 (2004)

80. Limousin, P., P. Pollak, A. Benazzouz, D. Hoffmann, J. F. Le Bas, E. Broussolle, J. E. Perret and A. L. Benabid: Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet*, 345(8942), 91-5 (1995)

81. Castrioto, A., A. M. Lozano, Y. Y. Poon, A. E. Lang, M. Fallis and E. Moro: Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol*, 68(12), 1550-6 (2011)

82. Fasano, A., A. Daniele and A. Albanese: Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurol*, 11(5), 429-42 (2012)

83. Laxton, A. W., Dostrovsky, J.O., Lozano, A.M.: Stimulation physiology in functional neurosurgery. In: Textbook of Stereotactic and Functional Neurosurgery, 2nd Edition. Ed A. M. Lozano, Gildenberg, P.L., Tasker, R.R. Springer, Berlin/Heidelberg (2009)

84. Li, Q., Y. Ke, D. C. Chan, Z. M. Qian, K. K. Yung, H. Ko and W. H. Yung: Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor cortex. *Neuron*, 76(5), 1030-1041 (2012)

Key Words: Neuron, Oscillation, Brain stimulation, Bradykinesi, Parkinson's disease, Review

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