Movement Disorders
Vol. 18, No. 4, 2003, pp. 357–363

Editor-Solicted Review

Oscillatory Nature of Human Basal Ganglia Activity: Relationship to the Pathophysiology of Parkinson's Disease

Peter Brown, MD*

Sobell Department of Neurophysiology and Movement Disorders, Institute of Neurology, Queen Square, London, United Kingdom

Abstract: Alterations of basal ganglia physiology in parkinsonism may consist of two elements, an increase in the firing rate of neurones and a change in the pattern of synchronisation of discharges between neurones. Recent findings suggest the presence of two principal modes of synchronised activity within the human subthalamo-pallidal-thalamo-cortical circuit, at <30 Hz and >60 Hz. These oscillations are dynamically and systematically modulated by task, thereby suggesting a functional role in movement. More importantly, the two frequency modes are inversely affected by movement, consistent with opposing actions, and differentially expressed according to the prevailing level of dopaminergic activity. It is argued that the balance between these modes determines the effects of basal ganglia-thalamocortical projections on the motor areas of the cortex. The lower frequency oscillations facilitate slow idling rhythms in the motor areas of the cortex, whereas synchronisation at high frequency restores dynamic task-related cortical ensemble activity in the gamma band. © 2002 Movement Disorder Society

Key words: oscillations; subthalamic nucleus; globus pallidus; Parkinson's disease; coupling

The basal ganglia play a major role in the regulation of human movement as dramatically manifest in Parkinson's disease (PD), a condition in which dopaminergic denervation of the striatum leads to paucity and slowness of movement. Central to current hypotheses of basal ganglia action is the division of this complex system into two distinct pathways, inversely affected by dopaminergic denervation, and with reciprocal actions on movement.[1–5] Such anatomically constrained theories, however, fail to explain why lesioning or stimulation of the globus pallidus interna (GPi) paradoxically improve dyskinesias, whereas the same interventions in GPi or its thalamic projection sites have no clear deleterious effects on motor function.[6–8] The failure of current anatomical schemata of basal ganglia function to wholly explain the efficacy of functional neurosurgery in PD has focussed attention on the patterning of neuronal discharge in the basal ganglia.[6,9–11] Here, the core assumption is that basal ganglia activity in Parkinson's disease involves abnormal synchronisation and that no activity at the level of pallidal outflow is preferable to a noisy output.[6] In support of the above, studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -treated primates and in patients with Parkinson's disease have found, as well as an increase in firing rate, a tendency toward bursting and abnormal synchronisation in the neurons of the subthalamic nucleus (STN) and GPi.[12–18]

Coming from this perspective the tacit assumption has been that synchronisation is an essentially pathological phenomenon. However, it seems unlikely that the normal functioning basal ganglia would not capitalise on this mechanism, given the superior postsynaptic efficacy of synchronised outputs at subsequent projection targets and nonlinearities in the frequency–current relationship of basal ganglia neurones that might act to further increase the saliency of inputs in particular frequency

*Correspondence to: Peter Brown, MD, Sobell Department of Neurophysiology and Movement Disorders, Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom.
E-mail: p.brown@ion.ucl.ac.uk
Received 28 May 2002; Revised 31 July 2002; Accepted 2 September 2002

bands.[19] Here, I review current knowledge of synchronised oscillations in the basal ganglia, with special emphasis on the findings in patients with PD. The function, deleterious or otherwise, of these oscillations is both unknown and unlikely to be single. Nevertheless, the author will develop the theme that their net effect can be characterised as essentially anti- or prokinetic and speculate how they may contribute to the pathophysiology of parkinsonism. Overall, three major frequency bands of oscillation have been identified in the basal ganglia, <10 Hz, 11 to 30 Hz (beta band), and >60 Hz (high gamma band); each may be coupled to activity in the motor areas of the cerebral cortex (Fig. 1A) and will be considered in turn.

OSCILLATIONS BELOW 10 HZ

Very low frequency (around 1 Hz) oscillations synchronous between neurones in STN and globus pallidus externa (GPe) have been detected in mature rat organotypic cortex–striatum–STN–GPe cultures[20] and in anaesthetised rats.[21] These observations serve to stress the potential for oscillatory interaction in the STN–GPe circuit. Nevertheless, recordings from monkeys and patients undergoing functional neurosurgery suggest that synchronisation within and between the nuclei of the basal ganglia tends to occur at higher frequencies in the alert state. Microelectrode single unit (neurone) studies[5,13,16,18,22–26] demonstrate a tendency for discharge in STN and GPi to occur in three modes, irregular, bursting, and oscillatory.[27] Of these, only the oscillatory mode is accompanied by an established and strong tendency to synchronisation between neurones. Such synchronised discharges predominantly occur at the frequency of parkinsonian rest and action tremor at 3 to 10 Hz and are more prominent in the untreated parkinsonian state. The degree of synchronisation between neurones during non-oscillatory (i.e., an inconstant period of time between grouped discharges) bursting is unclear, and the available evidence is in favour of this mode actually increasing when parkinsonian patients are treated with the dopamine agonist apomorphine.[17,27] Indeed bursting may be particularly prominent during dyskinesias,[27] hemiballismus,[10] and generalised dystonia,[11] suggesting involvement in the pathophysiology of dystonic movements rather than a mechanistic role in bradykinesia itself. Coherence (coupling) between STN and GPi activity, and between these nuclei or their thalamic projection site and cortex has been confirmed in the frequency range of tremor and bursting, emphasising that these discharge modes may have a profound influence on subcortico-cortical networks.[28–30]

STN activity appears to lead that in GPi at tremor frequency,[29] and activity in GPi's thalamic projection site, the ventralis anterior thalami, precedes cortical activity.[28] Thus, the available evidence would be consistent with the net driving of motor cortical areas at tremor frequencies through the GPi–thalamo–cortical pathway (Fig. 1A). However, it must be stressed that the techniques used to date only give a picture of the overall direction of coupling within a frequency band and do not exclude bidirectional coupling in which one direction of information flow dominates. Another question yet to be resolved is the extent to which synchronised oscillations at 3 to 10 Hz within STN and GPi may be found in the parkinsonian state in the absence of tremor. Certainly, there is evidence that human STN and GPi units firing at tremor frequency show only transient periods of locking to peripheral tremor,[31] and there is one report of such oscillations in a patient without clinical tremor.[27] The question is an important one for, if synchronisation in STN and GPi at low frequency were to be confined to patients with tremor, then theories that seek to explain bradykinesia in terms of synchronisation at these frequencies (see later) will not explain the phenomenon in those 25% or so of PD patients without tremor.[32]

OSCILLATIONS AT 11–30 HZ

Although microelectrode studies suggest that synchronisation at frequencies under 30 Hz is unlikely to be a strong phenomenon in the pallidum of healthy, alert monkeys,[15] the monkey pallidum does display a pronounced tendency to synchronisation at frequencies under 30 Hz after treatment with MPTP.[15] Microelectrode studies in patients with PD have also demonstrated synchronisation of single units in STN[18,26] and GPi[27] at 11 to 30 Hz, particularly in tremulous patients. Some of this synchronisation of pallidal activity may be related to the greater influence of striatal tonically active neurones in the parkinsonian state.[33] In addition, synchronous oscillations at 11 to 30 Hz are found in local field potentials (LFPs) between STN and GPi, and these structures and cortex, especially the supplementary motor area (SMA), in parkinsonian patients undergoing functional neurosurgery.[30,34] Such LFP recordings are usually made directly from the stimulating macroelectrode, postoperatively, in the interval between implantation and subsequent connection to a subcutaneous stimulator. The timing of neuronal discharges is closely related to fluctuations in LFPs, which can be used, therefore, as a surrogate marker of synchronisation of neuronal discharge,[35,36] backed up by the demonstration of coupling between oscillations in LFPs and those in single units[37] and

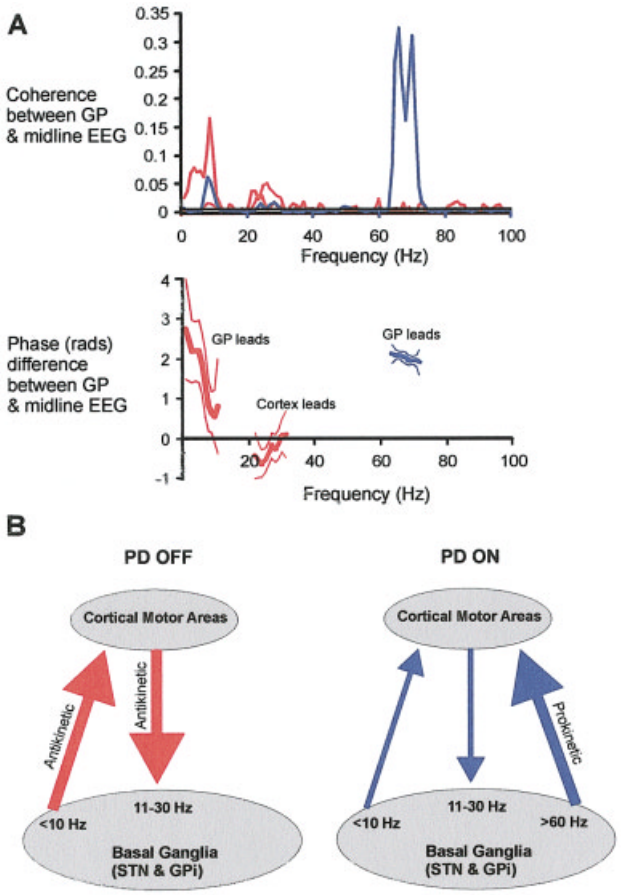

FIG. 1. Oscillatory coupling between globus pallidus (GP) and cortex. **A:** Coupling between GP and electroencephalogram (EEG) in the region of the supplementary motor cortex in a Parkinson's disease (PD) patient off medication (red, GP contacts 12 and 23) and after reinstitution of levodopa (blue, GP contact 23). Note that off medication, coupling (coherence) between GP and cortex is dominated by activity <10 Hz and at 20 to 30 Hz. GP leads and lags cortex at <10 Hz and 20 to 30 Hz, respectively. These couplings are reduced after levodopa, when strong coupling at >60 Hz appears. GP leads cortex in the latter. The thin lines in the spectra are the 95% confidence limits. **B:** Schematic summary of oscillatory basal ganglia–cortical interactions. The arrows show the dominating direction of connectivity in each frequency band. STN, subthalamic nuclei; GPi, GP interna.

postsynaptic effects in terms of coupling between LFPs in distant sites.[29]

LFP oscillation at 11 to 30 Hz and related coherence at the same frequency between STN, GPi, and cerebral cortex is greater in the relative absence of dopamine and reduced before and during voluntary movement.[29,37,38] The bulk of cortical activity coupled with that in STN and GPi in the 11 to 30 Hz band (Fig. 1A) drives these subcortical structures.[30,34] STN activity is also coherent with electromyography (EMG) during voluntary contractions. Here EMG leads STN, perhaps through a combination of peripheral re-afferance and corollary discharge to the STN from cortical neurones projecting to the pyramidal tract.[34]

In summary, the STN and GPi demonstrate a tendency to synchronisation at 11 to 30 Hz, as well as at tremor frequencies. However, the former is likely to be driven from the motor areas of the cortex and may represent some form of corollary discharge. It is most marked in the untreated parkinsonian state. Interestingly, animal models suggest that one effect of dopaminergic denervation is to make the STN more susceptible to rhythmic cortical inputs.[39]

The finding of coupling at 11 to 30 Hz may also prove to be useful in functional neurosurgery. Those STN macroelectrode contact sites that, when recorded from, demonstrate the highest coherence with midline electroencephalogram (EEG) in the beta band closely correspond to those sites that produce the best clinical effect when they are electrically stimulated at high frequencies.[34] Anatomical studies suggest that, although the primary motor cortex projects to the part of the STN that outputs to the GPe, the supplementary motor area projects to that part of the STN that outputs to GPi.[40] Thus, the presence of beta oscillatory activity coherent with midline EEG (likely arising from the supplementary motor area) may be a useful marker that the relevant contacts of the macroelectrode span the part of the STN

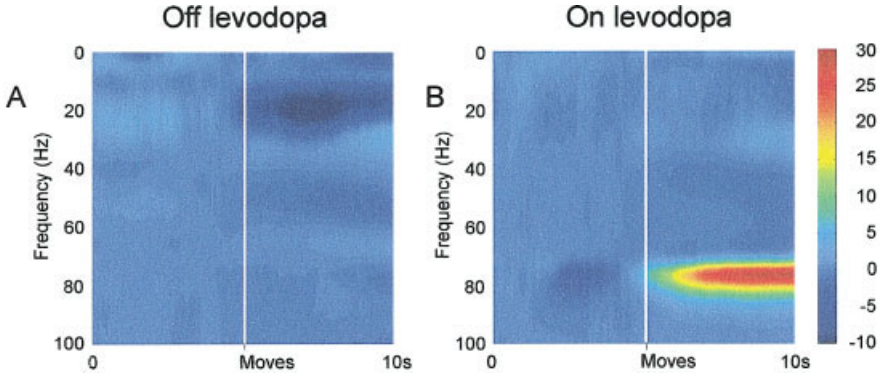

FIG. 2. Coherence changes between STN and GPi during self-paced movements of a hand-held joy-stick performed off and on levodopa in a parkinsonian patient with macroelectrodes implanted in both structures. Coherence change has been averaged (n = 24) around movement onset (vertical line). Movements lasted 300 to 500 msec and were repeated every 12 to 25 seconds. Off treatment, there is a decrease in coupling at around 20 Hz that begins just before movement. After levodopa administration, there is an increase in coupling at >60 Hz that begins just before movement. Reproduced by permission of Oxford University Press.[38]

projecting to GPi and are likely to give a good clinical result upon stimulation at high frequency.

OSCILLATIONS GREATER THAN 60 HZ

The synchronisation of single units in STN or GPi at high frequencies has not been demonstrated in microelectrode studies to date. However, synchronous high-frequency oscillations have been found in LFPs between STN and GPi, and these structures and cortex, especially SMA, but only after PD patients have been treated with levodopa,[29,30,38] as illustrated in Figure 1A. The difference between intraoperative microelectrode single unit and postoperative macroelectrode LFP studies probably lies in the greater sensitivity of the latter[34,41] and the difficulty in recording patients fully *on* and therefore possibly dyskinetic, during surgery.

The coherence between STN, GPi, and cortex tends to occur at around 60 to 80 Hz, although coherence at double this frequency may also occur.[29] This high-frequency coherence is increased before and during voluntary movement.[38] Thus, elements within the pallidum and STN form a dynamic functional network that, in the presence of a normal dopaminergic drive, resonates at frequencies in the high gamma band. The bulk of STN and GPi activity coupled with cortical activity in this band leads cortex.[30] The likely path based on anatomical considerations is by means of GPi/substantia nigra pars reticulata and thalamus.[42]

The origin of the synchronisation in the high gamma band found in parkinsonian patients after restoration of dopaminergic activity is unclear. It is interesting to note that synchronisation of EEG at similar frequencies recently has been identified in subdural recordings from motor areas in epileptic patients without obvious abnormalities of movement[43] and from the scalp in healthy subjects.[44,45] Like the coherence between the cortical and subthalamic activity, this synchronisation is maximal during or slightly before self-paced movements. It is possible, therefore, that the oscillatory interactions in the high gamma band have physiological correlates in the healthy human. This idea receives support from the recent demonstration of similar oscillations in the LFP of the STN of the rat.[46]

CONSEQUENCES OF ABNORMAL, SUBCORTICALLY DRIVEN, CORTICAL RHYTHMICITY IN PARKINSON'S DISEASE

Of the basal ganglia oscillations coupled with activities in motor cortical areas, there are two that may be considered essentially antikinetic. The first is greatest in the absence of adequate dopaminergic stimulation and occurs at tremor frequencies (3–10 Hz). Stimulation of the pallidum and entopeduncular nucleus (homologue of the medial pallidum) in cats at similar frequencies leads to large-scale synchronisation of the EEG at alpha frequencies in cortical motor areas and to gradual slowing and eventual cessation of spontaneous movements.[47–50] Comparable effects have been provisionally reported after low-frequency stimulation in the region of the human STN,[51,52] consistent with an essentially antikinetic effect of basal ganglia oscillatory synchronisation at 3 to 10 Hz.

Could this abnormal, low-frequency, synchronous oscillatory activity in GPi and its input STN act, by means of the thalamus, to hold the motor cortex in a low-frequency antikinetic state in Parkinson's disease?[7] Neurons in the specific and nonspecific thalamic nuclei tend to oscillate at gamma frequencies upon depolarisation,[53] and GPi overactivity and low-frequency bursting in Parkinson's disease might diminish these fast oscillations and their action on the cortex. This could be brought about by GABA-induced hyperpolarisation of thalamocortical neurones and deinactivation of low-threshold calcium channels, triggering short bursts of very high-frequency action potentials synchronised by and phase-locked to pallidal discharges, in much the same way as phasic GABAergic inputs from nucleus reticularis thalami may drive sleep spindles.[54] The result would be a pervasive synchronisation of cortical activity at frequencies of 3 to 10 Hz.

The second basal ganglia activity that may be essentially antikinetic in nature is that at 11 to 30 Hz. Although the directionality of net coupling between STN/GPi and cortex at 11 to 30 Hz is against a direct basal ganglia effect on cortex, it is possible that this input may act to suppress prokinetic high gamma oscillations in the basal ganglia. Thus, task- and drug-induced changes in these two bands are usually reciprocal,[38] as illustrated in Figure 2. Such an antikinetic effect would be consistent with the observation that stimulation of the feline pallidum and entopeduncular nucleus at around 30 Hz leads to freezing of movement.[47–50]

In contrast, basal ganglia activity synchronized at >60 Hz may be considered prokinetic in nature. Thus, it is found in PD after treatment with levodopa, when bradykinesia is ameliorated and is increased before voluntary movements.[38] A prokinetic effect is further suggested by the antiparkinsonian effects of stimulation of STN or GPi at frequencies >60 Hz.[55–57] Nevertheless, the oscillations occurring after the reinstitution of dopaminergic stimulation are unlikely to be directly related to the execution of voluntary movement as they occur at rest as well as during motor activity. Instead they could be related to attentional processes operating in the executive domain, acting through the thalamus to favor cortico–

cortical interactions in the gamma band.[7,58] Specifically, it has been argued that the latter interactions provide a mechanism for favoring and, therefore, selecting and binding together those distributed cortical activities necessary for the prompt and successful execution of a movement,[7,59] although a role for synchronisation at high frequency in higher order aspects of motor control remains speculative.[60,61] In support of this attentional hypothesis is the disappearance of the >60 Hz activity in STN with drowsiness.[29] The observation that the >60 Hz activity is reduced during tonic voluntary contraction[29] but increased during movement[38] also argues for a close relationship with cortical motor gamma activities that, as expressed in the cortical drive to motoneurones, show parallel changes.[62,63]

The above speculation regarding the prokinetic effects of basal ganglia activity in the high gamma range is borne out by the results of some old studies in cats. Stimulation of the pallidum and entopeduncular nucleus (equivalent to GPe and GPi, respectively, in the primate) at such high frequencies causes desynchronisation of EEG over motor cortical areas,[47,49] a phenomenon associated with increased cortico–cortical interactions in the gamma band.[64] More importantly, the same high-frequency stimulation is able to reverse the bradykinetic effects of low-frequency stimulation of the basal ganglia.[48]

So, how may these different patterns of synchronization affect movement? First, the synchronisation at low frequency off antiparkinsonian medication will involve pyramidal neurons through its effects on cortex, with consequent driving of muscle at low frequencies, manifest as parkinsonian rest and action tremor. This in turn leads to a suboptimal unfused pattern of muscle activation, thereby slowing the onset of voluntary actions and decreasing contraction strengths.[63] Second, the trapping of cortical activity in synchronous oscillations of low-frequency through low-frequency driving and the possible suppression of the >60 Hz mode by the 11 to 30 Hz cortical input to the basal ganglia prevents cortico–cortical interaction in the gamma band thereby contributing to bradykinesia.[7,59] In this case, one would predict an association between bradykinesia and the failure to shift cortical activity to higher frequencies in motor areas both with and without major projections to the spinal cord. This mechanism should be particularly evident in complex movements, which are especially difficult in Parkinson's disease and has been confirmed in parkinsonian subjects performing manual tracking or combined and sequential motor tasks on and off levodopa.[65,66]

On the other hand, basal ganglia oscillations at >60 Hz may be prokinetic by virtue of their facilitation of motor cortical interaction in the gamma band. This will include pyramidal neurons so that high-frequency cortical drive to muscles is restored, reversing any bradykinesia and weakness due to unfused contraction. A recent magnetoencephalography study has provided strong support for the hypothesis that the basal ganglia, operating in the presence of adequate dopaminergic stimulation, act to release motor cortical activity from idling frequencies and encourage corticomotor oscillations in the beta and gamma range.[67] However, the degeneration of dopaminergic neurons in PD includes both the substantia nigra pars compacta and ventral tegmental area, leading to secondary dopamine depletion in both the striatum and motor areas of the cerebral cortex.[68] Thus, the demonstration that STN stimulation has a similar effect on corticomuscular activity as levodopa has been important in confirming that dopaminergic effects on cortical rhythmicity are mediated through pathways involving the striatum and thereby STN.[69]

IMPLICATIONS FOR FUNCTIONAL NEUROSURGERY

To what extent can the different patterns of rhythmic activity in the basal ganglia help explain the paradoxical results of functional neurosurgery for Parkinson's disease? Hitherto, the efficacy of this treatment has been difficult to explain in terms of the known physiology of the basal ganglia. There are two surgical techniques, lesioning of GPi or STN and stimulation of the same sites at high frequency through implanted macroelectrodes.[55–57,70] Focal lesions of GPi should destroy the major output of the basal ganglia to the motor cortex and abolish their contributions to normal voluntary movement. Lesions would be expected, therefore, to impair motor performance, but the reverse is seen in Parkinson's disease. On the other hand, the similarity between the effects of stimulation at frequencies in excess of 60 Hz and focal lesioning might suggest that the former works through the induction of a virtual lesion by depolarisation block or some other blocking mechanism.[56] However, human GPi neurones discharge at frequencies of approximately 85 to 140 Hz in Parkinson's disease, suggesting that neural elements are more likely to be driven than blocked by high-frequency stimulation.[16,17,25]

These paradoxical observations could be reconciled if we are correct in hypothesising that the low- and high-frequency modes of the subthalamic–pallidal circuit impair and promote motor function, respectively. In this case, the low-frequency activity (<30 Hz) could be blocked with beneficial effect by either exogenous dopaminergic stimulation or the focal destruction of GPi or STN. At the same time, therapeutic stimulation of either nucleus at high frequency might artificially drive a pro-

kinetic circuit that normally requires dopaminergic stimulation to resonate in its optimal mode. Resonance could be achieved through artificially driving the system at its base frequency of 60 to 80 Hz or multiples thereof. Deep brain stimulation seems to be effective at frequencies >60 Hz,[56] but careful studies are required to confirm whether or not there are some high frequencies that are preferentially effective in overcoming parkinsonism, particularly bradykinesia.

CONCLUSION

The realization that basal ganglia activity may be synchronised in multiple frequency bands, each with different functional significance, provides further insight into the pathophysiology of PD and may resolve some of the paradoxes raised by functional surgery. Figure 1B is a simplistic schematic summary of oscillatory basal ganglia–cortical interactions in PD as proposed in this review. Nevertheless, a full mechanistic understanding of how oscillations contribute to movement and its derangement is some way off.

REFERENCES

1. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–376.
2. Alexander GE, Crutcher ME. Functional architecture of the basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990;13:266–271.
3. Delong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281–285.
4. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996;6:751–758.
5. Bergman H, Feingold A, Nini A, et al. Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. Trends Neurosci 1998;21:32–38.
6. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 1994; 117:877–878.
7. Brown P, Marsden CD. What do the basal ganglia do? Lancet 1998;351:1801–1804.
8. Bar-Gad I, Bergman H. Stepping out of the box: information processing in the neural networks of the basal ganglia. Curr Opin Neurobiol 2001;11:689–695.
9. Obeso JA, Rodriguez MC, DeLong MR. Basal ganglia pathophysiology; a critical review. Adv Neurol 1997;74:3–18.
10. Suarez JI, et al. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. Ann Neurol 1997;42:807–811.
11. Vitek JL, et al. Neural activity in the basal ganglia in patients with generalised dystonia and hemiballismus. Ann Neurol 1999;46:22–35.
12. Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991;547:142–151.
13. Bergman H, Wichmann T, Karmon B, Delong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 1994;72:507–520.
14. Sterio D, Beric A, Dogali M, Fazzini E, Alfaro G, Devinsky O. Neurophysiological properties of pallidal neurons in Parkinson's disease. Ann Neurol 1994;35:586–591.
15. Nini A, Feingold A, Slovin H, Bergman H. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophysiol 1995;74:1800–1805.
16. Hutchison WD, Lozano AM, Tasker AE, Dostrovsky JO. Identification and characterization of neurons with tremor-frequency activity in human globus pallidus. Exp Brain Res 1997;113:557–563.
17. Merello M, Balej J, Delfino M, Cammarota A, Betti O, Leiguarda R. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. Mov Disord 1999;14:45–49.
18. Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J Neurosci 2000;20:7766–7775.
19. Bevan MD, Wilson CJ. Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. J Neurosci 1999;19:7617–7628.
20. Plenz D, Kital ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. Nature 1999; 400:677–682.
21. Magill PJ, Bolam JP, Bevan MD. Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. J Neurosci 2000;20:820–833.
22. Taha JM, Favre J, Baumann TK, Burchiel KJ. Tremor control after pallidotomy in patients with Parkinson's disease: correlation with microrecording findings. J Neurosurg 1997;86:642–647.
23. Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group: tremor related activity in functionally identified cells. Brain 1994;117:531–543.
24. Lenz FA, Tasker RR, Kwan HC, Schnider S, Kwong R, Murayama Y, et al. 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 1988;8:754–764.
25. Magnin M, Morel A, Jeanmond D. Single unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience 2000;96:549–564.
26. Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. Synchronised neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci 2002;22:2855–2861.
27. Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM. Effects of apomorphine on subthalamic nucleus and globus pallidus internus in patients with Parkinson's disease. J Neurophysiol 2001;86:249–260.
28. Volkmann J, Joliot M, Mogilner A, Ioannides AA, Lado F, Fazzini E, Ribary U, Llinas R. Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. Neurology 1996;46:1359–1370.
29. Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosci 2001;21: 1033–1038.
30. Williams D, Tijssen M, van Bruggen G, Bosch A, Insola A, Di Lazzaro V, Mazzone P, Oliviero A, Quartarone A, Speelman H, Brown P. Dopamine dependent changes in the functional connectivity between basal ganglia and cerebral cortex in the human. Brain 2002;125:1558–1569.
31. Hurtado JM, Gray CM, Tama LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. Proc Natl Acad Sci U S A 1999;96:1674–1679.
32. Elble R, Koller W. Tremor. Baltimore: John Hopkins University Press; 1990.
33. Raz A, Frechter-Mazar V, Feingold A, Abeles M, Vaadia E, Bergman H. Activity of pallidal and striatal tonically active neurons is correlated in MPTP-treated monkeys but not in normal monkeys. J Neurosci 2001;21:RC128.
34. Marsden JF, Limousin-Dowsey P, Ashby P, Pollak P, Brown P. Subthalamic nucleus, sensorimotor cortex and muscle interrelationships on Parkinson's disease. Brain 2001;124:378–388.

35. Creutzfeldt OD, Watanabe S, Lux HD. Relations between EEG phenomena and potentials of single cortical cells. I. Evoked responses after thalamic and epicortical stimulation. Electroencephalogr Clin Neurophysiol 1966;20:1–18.
36. Frost JD. EEG-intracellular potential relationships in isolated cerebral cortex. Electroencephalogr Clin Neurophysiol 1968;24: 434–443.
37. Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002;125: 1196–1209.
38. Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Di Lazzaro V, Brown P. Movement-related changes in synchronisation in the human basal ganglia. Brain 2002;125:1235–1246.
39. Magill PJ, Bolam JP, Bevan MD. Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. Neuroscience 2001;106:313–330.
40. Joel D, Weiner I. The connections of the primate subthalamic nucleus: indirect pathways and the open -interconnected scheme of basal ganglia-thalamocortical circuitry. Brain Res Rev 1997;23: 62–78.
41. Christakos NC. On the detection and Measurement of synchrony in neural populations by coherence analysis. J Neurophysiol 1997; 78:3453–3459.
42. Parent A, Hazrati L-N. Functional anatomy of the basal ganglia. II. The place of the subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Rev 1995;20:128–154.
43. Crone NE, Migloiretti DL, Gordon B, Lesser RP. Functional mapping of human sensorimotor cortex with electroencephalographic analysis. II. Event related synchronisation in the gamma band. Brain 1998;121:2301–2315.
44. Shibata T, Shimoyama I, Ito T, Abla D, Iwasa H, Koseki K, Yamanouchi N, Sato T, Nakajima Y. Event-related dynamics of the gamma-band oscillation in the human brain: information processing during a GO/NOGO hand movement task. Neurosci Res 1999;33:215–222.
45. Cassidy MJ, Penny WD. Bayesian nonstationary autoregressive models for biomedical signal analysis. IEEE Trans Biomed Eng 2002;49:1142–1152.
46. Brown P, Kupsch A, Magill PJ, Sharott A, Harnack D, Meissner M. Oscillatory local field potentials recorded from the subthalamic nucleus of the alert rat. Exp Neurol 2002;177:581–585.
47. Buchwald NA, Heuser G, Wyers EJ, Lauprecht CW. The "caudate-spindle." III. Inhibition by high frequency stimulation of subcortical structures. Electroencephalogr Clin Neurophysiol 1961;13: 525–530.
48. Buchwald NA, Wyers EJ, Lauprecht CW Heuser G,. The "caudate-spindle." IV. A behavioural index of caudate-induced inhibition. Electroencephalogr Clin Neurophysiol 1961;13:531–537.
49. Dieckmann G. Cortical synchronised and desynchronised responses evoked by stimulation of the putamen in cats. J Neurol Sci 1968;7:385–310.
50. Hassler R, Dieckmann G. Arrest reaction, delayed inhibition and unusual gaze behaviour resulting from stimulation of the putamen in awake unrestrained cats. Brain Res 1967;5:504–508.
51. Demeret S, Bejjani B-P, Arnulf I, Damier P, Gervais D, Houeto JL, Pridoux B, Agid Y. Low frequency subthalamic stimulation worsens parkinsonian symptoms. Neurology 1999;52(Suppl. 2):A406.
52. Jimenez F, Velasco F, Velasco M, Brito F, Morel C, Marquez I, Perez ML. Subthalamic prelemniscal radiation stimulation for the treatment of Parkinson's disease: electrophysiological characterization of the area. Arch Med Res 2000;31:270–281.
53. Steriade M, Curró Dossi R, Paré D, Oakson G. Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. Proc Natl Acad Sci U S A 1991;88:4396–4400.
54. Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science 1993;262: 679–685.
55. Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 1994;35:1126–1130.
56. Limousin P, Pollak P, Benazzouz A, et al. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91–95.
57. Starr PA, Vitek J, Bakay RAE. Ablative surgery and deep brain stimulation for Parkinson's disease. Neurosurgery 1998;43:989–1015.
58. Hassler R. Brain mechanisms of intention and attention with introductory remarks on other volitional processes. Prog Brain Res 1980;54:585–614.
59. Brown P. The Piper rhythm and related activities in man. Prog Neurobiol 1999;60:97–108.
60. Farmer SF. Rhythmicity, synchronisation and binding in human and primate motor systems. J Physiol 1998;509:3–14.
61. Hari R, Salenius S. Rhythmical corticomotor communication. Neuroreport 1999;10:R1–R10.
62. Brown P. Muscle sounds in Parkinson's disease. Lancet 1997;349: 533–535.
63. Brown P, Corcos D, Rothwell JC. Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease? Brain 1998; 120:401–408.
64. Munk MH, Roelfsema PR, Konig P, Engel AK, Singer W. Role of reticular activation in the modulation of intracortical synchronization. Science 1996;272:271–274.
65. Brown P, Marsden CD. Bradykinesia and impairment of EEG desynchronisation in Parkinson's disease. Mov Disord 1999;14: 423–429.
66. Wang HC, Lees AJ, Brown P. Impairment of EEG desynchronization before and during movement and its relationship to bradykinesia in Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;66:442–446.
67. Salenius S, Avikainen S, Kaakkola S, Hari R, Brown P. Defective cortical drive to muscle in Parkinson's disease and its improvement with levodopa. Brain 2002;125:491–500.
68. Gaspar P, Duyckaerts C, Alvarez C, Javoy-Agid F, Berger B. Alterations of dopaminergic and noradrenergic innervations in motor cortex in Parkinson's disease. Ann Neurol 1991;30:365–374.
69. Marsden J, Limousin-Dowsey P, Fraix V, Pollak P, Odin P, Brown P. Intermuscular coherence in Parkinson's disease: effects of subthalamic nucleus stimulation. Neuroreport 2001;12:1113–1117.
70. Gill SS, Heywood P. Bilateral dorsolateral subthalamotomy for advanced Parkinson's disease. Lancet 1997;350:1224.