Akineto-rigid vs. tremor syndromes in Parkinsonism

Adam Zaidel[a,b], David Arkadir[c], Zvi Israel[d] and Hagai Bergman[a,b]

[a]Department of Physiology, [b]The Interdisciplinary Center for Neural Computation, The Hebrew University-Hadassah Medical School, [c]Department of Neurology and [d]Department of Neurosurgery, Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Correspondence to Dr Hagai Bergman, Department of Physiology, The Hebrew University – Hadassah Medical School, P.O. Box 12272, Jerusalem 91120, Israel
Tel: +972 2 6757388; fax: +972 2 6439736;
e-mail: hagaibe@ekmd.huji.ac.il

Current Opinion in Neurology 2009, 22:387–393

Purpose of review

Akinesia, rigidity and low-frequency rest tremor are the three cardinal motor signs of Parkinson's disease and some Parkinson's disease animal models. However, cumulative evidence supports the view that akinesia/rigidity vs. tremor reflect different pathophysiological phenomena in the basal ganglia. Here, we review the recent physiological literature correlating abnormal neural activity in the basal ganglia with Parkinson's disease clinical symptoms.

Recent findings

The subthalamic nucleus of Parkinson's disease patients is characterized by oscillatory activity in the beta-frequency (~15 Hz) range. However, Parkinson's disease tremor is not strictly correlated with the abnormal synchronous oscillations of the basal ganglia. On the other hand, akinesia and rigidity are better correlated with the basal ganglia beta oscillations.

Summary

The abnormal basal ganglia output leads to akinesia and rigidity. Parkinson's disease tremor most likely evolves as a downstream compensatory mechanism.

Keywords

basal ganglia, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, oscillations, Parkinson's disease, synchronization

Curr Opin Neurol 22:387–393

1350-7540

Introduction

In 1817, James Parkinson pointed out two paradoxically related symptoms of the condition known today as Parkinson's disease. These are shaking (tremor) and palsy (poverty and slowness of movements, akinesia/bradykinesia). The third major symptom – rigidity (muscle stiffness) – is clinically associated with the akinetic disorders of the disease. Physiological studies of the basal ganglia in animal models of Parkinsonism and of human patients reveal neuronal oscillations mainly in the beta-frequency range. This review summarizes the correlations between the abnormal beta oscillations and the akinetic–rigid symptoms and suggests that tremor arises due to compensatory phenomena downstream from the basal ganglia.

The basal ganglia network

Cumulative clinical and experimental evidence strongly indicates that the major pathological event leading to the motor symptoms of Parkinson's disease is degeneration of midbrain dopaminergic neurons and their striatal projections. The striatum (composed of caudate, putamen and ventral striatum) is the main input stage of the basal ganglia, receiving input from all cortical areas as well as from many thalamic nuclei [1]. Therefore, a good grasp of the pathophysiology of Parkinson's disease depends first on a comprehensive understanding of the anatomy of the basal ganglia and dopamine networks.

The classical description of the basal ganglia network [2,3] maintains that there are two segregated internal basal ganglia pathways that start in the striatum and converge on the output structures of the basal ganglia (the internal segment of the globus pallidus – GPi and the substantia nigra pars reticulata – SNr). The 'direct pathway' is a direct γ-amino butyric acid (GABA)ergic inhibitory pathway, whereas the 'indirect pathway' is a polysynaptic disinhibitory pathway through the GABA-ergic external segment of the globus pallidus (GPe) and the glutamatergic neurons of the subthalamic nucleus (STN). The striatal projection neurons in the direct pathway express D1 dopamine receptors, whereas those in the indirect pathway express D2 dopamine receptors [4]. Dopamine has differential effects on the two striatopallidal pathways: it facilitates transmission along the direct pathway via the D1 receptors and inhibits transmission along the indirect pathway via the D2 receptors [5,6]. The early biochemical observations are supported by more modern studies using transgenic mice, in which striatal projection (medium spiny neuron, MSN) cells express D1 and D2 receptors. These studies have

uncovered unappreciated differences between D1 and D2 expressing MSNs. Dopamine D1 receptor signaling enhances dendritic excitability, glutamatergic signaling and striatal plasticity in striatonigral MSNs, whereas D2 receptor signaling exerts the opposite effects in striatopallidal MSNs.

Recently, anatomical studies have revealed an even more complex map of basal ganglia connectivity. Direct projections from the motor cortex to the STN, termed the 'hyperdirect pathway' [7,8], indicate that similar to the striatum, the STN is a major input stage of the basal ganglia. In addition, striatal neurons projecting to the GPi and SNr have been shown to send collaterals to the GPe [9,10]. Thus, both 'direct' and 'indirect' striatal projection neurons, as well as STN neurons, modulate GPe activity. Moreover, recently described feedback projections from the GPe to the striatum [11,12], as well as the GPe to GPi projection [13–16], strongly suggest that the GPe is a central nucleus in the basal ganglia circuitry rather than simply a relay station in the indirect pathway.

Recent physiological studies have emphasized the role of dopamine in the plastic regulation of the efficacy of corticostriatal transmission [17,18••,19,20], beyond its regulation of striatal excitability [21]. Using brain slices from dopamine D1 and D2 receptor transgenic mice [20], it was demonstrated that dopamine plays complementary roles in D1 vs. D2 MSNs that lead to bidirectional and Hebbian synaptic plasticity. There are other neuromodulators that affect the plasticity and the excitability of striatal neurons. Acetylcholine (ACh) is probably the second major neuromodulator of the striatum [22,23]. Striatal ACh is secreted by the cholinergic interneurons of the striatum (physiologically identified as the tonically active neurons, TANs), and the delicate balance between striatal dopamine and cholinergic activity [24,25•] is an old concept that is still under active research. Additionally, the striatum is innervated by diffuse serotonin, noradrenergic and histamine innervations [26]. Future studies of the different roles of these neuromodulator systems on striatal functioning [27••], as well as their interaction with one another, should lead to a much better understanding of this complex and critical system in normal and pathological control of motor, as well as cognitive and emotional behavior.

Parkinson's disease: clinical symptoms and pathology

Parkinson's disease and Parkinsonism are the most common basal ganglia movement disorder and affect 1–3% of the elderly population [28]. The dopaminergic system is the most seriously affected, and initial successful therapeutic strategies are based on different forms of dopamine replacement therapy.

On the basis of clinical observations of six patients, James Parkinson described two of the most important motor symptoms of Parkinson's disease [29]. The first was shaking – a low (4–7 Hz) frequency tremor at rest (tremor amplitudes decrease during voluntary action, increase during rest and are augmented by mental stress). The second symptom Parkinson described, which was probably contradictory in his mind, was palsy (or akinesia in modern terminology). Akinesia is characterized by poverty of spontaneous movement and slowness (bradykinesia) of voluntary (goal directed) and spontaneous movement. Parkinson also described the postural abnormalities of his patients, one of the other cardinal motor symptoms of Parkinson's disease. However, probably due to the fact that physical examination was not part of the medical routine in his day, Parkinson did not notice the rigidity (increased muscular tonus) of Parkinson's disease patients. Rigidity was only recognized later as one of the major clinical triad of Parkinson's disease. Cognitive and emotional deficits frequently accompany the motor symptoms of Parkinson's disease and its treatment. However, here, we focus on the pathophysiology of the three main motor symptoms of Parkinson's disease: akinesia, rigidity and tremor at rest.

Akinesia/rigidity vs. tremor in Parkinson's disease

Parkinson's disease is not a homogenous disease, neither across patients nor along the natural course of even a single patient. Tremor is usually an episodic phenomenon, as opposed to the unremitting symptoms of akinesia and rigidity, and statistical studies of the motor symptoms of Parkinson's disease indicate the tremor to be independent of the other symptoms [30••]. Although often the presenting symptom of Parkinson's disease, tremor is not present in all human Parkinson's disease patients. Human Parkinson's disease covers a broad spectrum and can present as marked akinesia and rigidity (AR-subtype) or as a predominant resting tremor (T-subtype), usually with akinesia and rigidity. The AR-subtype is also defined as the 'postural instability gait difficulty subtype' (PIGD-subtype). The division of the Parkinson's disease population into these two subgroups probably reflects major pathological differences. T-subtype Parkinson's disease patients have a better prognosis and slower disease progression than AR-subtype patients. Several studies have indicated that the pathology of human T-subtype Parkinson's disease differs from that of the AR-subtype Parkinson's disease, with the retrorubral area more severely affected in the tremor dominant form [31]. Most forms of nonidiopathic Parkinson's disease (e.g. neuroleptic-induced Parkinsonism, progressive supranuclear palsy and multiple system atrophy) display akinesia and rigidity but not rest tremor. Unlike rigidity and akinesia, clinical severity of the Parkinson's disease tremor does not

correlate with severity of the dopaminergic deficit in the striatum or with clinical progression of the disease. Anticholinergic agents, which were the first drugs available for the symptomatic treatment of Parkinson's disease, tend to have better effects on tremor than on akinetic–rigid symptoms, whereas akinesia and rigidity may show better and earlier response to dopamine replacement therapy. Early stereotaxic surgeries of the thalamus of Parkinson's disease patients further indicated that tremor and rigidity reflect two different entities [32]. The cerebellar-receiving nucleus of the thalamus (e.g. the ventralis-intermedius, Vim) has been considered as the optimal target for stereotaxic procedures for amelioration of Parkinson's disease tremor and other tremors [33,34], whereas another thalamic target (the ventralis-oral-anterior) has been indicated as the optimal target for Parkinson's disease rigidity.

In summary, most clinical human studies indicate that Parkinson's disease akinesia/rigidity and tremor may reflect different, not mutually exclusive, abnormal processes in the central nervous system of Parkinson's disease patients. The role of striatal dopamine depletion and the basal ganglia seem to be much more important in akinesia and rigidity. Parkinson's disease tremor may be modulated by peripheral manipulation and by the activity of other central neuronal systems. It is, therefore, possible that abnormalities of transmitter systems other than dopamine (e.g. cholinergic, serotonergic) or neural circuits other than the basal ganglia (e.g. cerebellum [35]) play a critical additive role in the generation of Parkinson's disease tremor. Below, we will further discuss the evidence from animal models and from electrophysiological studies of both human patients and animal models supporting the distinction between the akineto-rigid vs. the tremor symptoms of Parkinson's disease.

Animal models of Parkinson's disease and dopamine depletion

The clinical studies of Parkinson's disease patients have been enriched by parallel studies of different animal models of this disease. Early animal models of Parkinson's disease were based on lesions of midbrain areas in monkeys [36,37]. These anatomical lesions mainly produced rigidity but only rarely resulted in a spontaneous sustained tremor. Careful analysis of the correlation between the clinical symptoms and the extent of the lesion led to the conclusion that experimental rest tremor is the result of combined damage to the nigro-striatal dopaminergic projections as well as to the cerebellar outflow to the red nucleus and thalamus [38]. Damage to only one of these neuronal systems was not sufficient for reliable generation of experimental tremor.

More modern animal models of Parkinson's disease have shifted from anatomical to chemical lesions. Early chemical – such as, the reserpine and 6-hydroxydopamine (6-OHDA) – animal models of Parkinson's disease were limited (by chemical or anatomical targeting) to dopaminergic damage and mainly reproduced akinesia. Rigidity and tremor are hardly ever reported in studies of 6-OHDA-treated rodents. Modern, molecular biology-inspired rodent models of Parkinson's disease also frequently fail to exhibit the full clinical symptoms of Parkinson's disease. It could be that the rodent brain is less dependent on the integrity of the dopamine system or it is equipped with better compensatory mechanisms for dopamine depletion. We will, therefore, focus below on primate studies.

The more recently introduced primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease [39–41] better mimics the clinical and the pathological picture of Parkinson's disease. Postmortem examination of the brains of MPTP-treated primates reveals that the primary damage is to the dopaminergic system. However, as in human Parkinson's disease, other neuromodulators are also affected [42]. Macaque monkeys treated with MPTP mainly exhibit the akinetic–rigid symptoms of Parkinson's disease. Low-frequency (4–7 Hz) tremor is not readily replicated in MPTP-treated macaque monkeys. But some primate species, notably the vervet (African green) monkey often develop a prominent low-frequency tremor following MPTP injections [43,44].

Tremor usually appears several days after the development of clinical akinesia and rigidity in the MPTP-treated vervet monkeys. This reversed order of presentation of clinical symptoms compared with human reports [45,46] may be due to the fast induction of dopamine depletion and evolution of symptoms in the MPTP model that may not lead to the development of compensatory processes found in the slowly evolving human disease. On the other hand, tremor is a much more overt phenomenon than akinesia and rigidity. Human patients or their family may first become aware of the slow development of Parkinson's disease by the more easily recognizable tremor.

We conclude that, in line with the human clinical studies, the animal models – and especially the primate models – of Parkinson's disease, support the distinction between the akineto-rigid and the tremor symptoms of Parkinson's disease.

Neural oscillations in the dopamine-depleted basal ganglia networks of animal models of Parkinson's disease

Early physiological studies of Parkinsonian MPTP-treated monkeys emphasized changes in the discharge

rate within the GPe, GPi and the STN (decreases rate in GPe and increased discharge rate in STN and GPi) [47–49]. As expected, these changes of pallidal discharge rates were reversed in response to dopamine replacement therapy in both human patients and primates [44,50].

More recently, research attention has been more focused on the potential role of other aspects of neuronal activity such as firing patterns and neuronal synchronization in the pathophysiology of Parkinson's disease. MPTP monkeys show an increase in the fraction of basal ganglia neurons that discharge in oscillatory bursts. These oscillatory bursts have been found in the STN, GPe, GPi and also in the striatum. In most cases, the basal ganglia cells tend to oscillate both at the tremor frequency (alpha or theta range) and at double or even triple the tremor frequency (beta range). Nevertheless, these studies have failed to reveal a significant fraction of neurons whose tremor frequency oscillations are consistently coherent with the simultaneous recorded tremor [43]. Both STN inactivation [51] and dopamine replacement therapy [52] significantly ameliorate the clinical motor symptoms and reduce the GPi 8–20 Hz oscillations (but less so the tremor frequency oscillations), supporting the critical role of beta rather than tremor frequency oscillations in the generation of Parkinson's disease symptoms.

Physiological studies of simultaneously recorded neurons in the basal ganglia of MPTP-treated monkeys demonstrate pair-wise crosscorrelograms with oscillatory peaks [43,53], suggesting that striatal dopamine depletion induces abnormal coupling of basal ganglia loops. In most cases, the maximal power of the synchronous oscillations was found to be at double the tremor frequency. Abnormal pallidal synchronization decreases in response to dopamine replacement therapy [44,52].

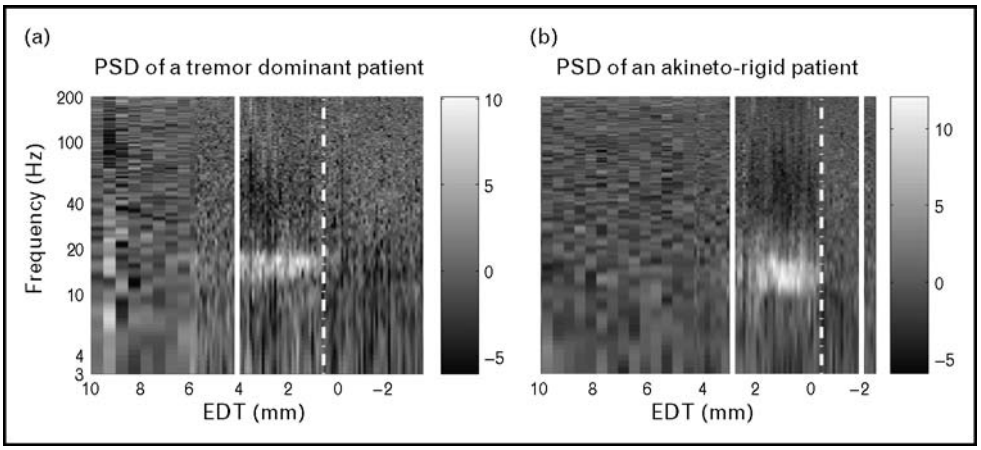
Studies of local field potentials (LFPs) and single unit activity recorded from frontal cortex and the basal ganglia of rats following 6-OHDA lesions of midbrain dopamine neurons revealed significant increases in the power and coherence of beta-frequency oscillatory activity [54••,55]. Administration of the dopamine receptor agonist apomorphine to these dopamine-depleted animals suppressed the beta-frequency oscillations and increased coherent activity at gamma frequencies in the cortex and STN. Thus, the pattern of synchronization between population activity in the STN, GP and cortex in the 6-OHDA-lesioned rodent model of Parkinson's disease is closely parallel to that seen in the MPTP primate model.

Neural oscillations in the basal ganglia networks of human Parkinson's disease patients

Several lines of human noninvasive and invasive research support the critical role of the beta oscillations in the generation of Parkinson's disease akinetic–rigid symptoms. Magnetoencephalographic (MEG) studies of T-type Parkinson's disease human patients have revealed strong coherence between activity in the motor and sensory cortices and the cerebellum at double tremor (beta range), rather than at tremor frequency [56]. Dopamine replacement therapy significantly reduced these oscillations [57].

As in animal models of Parkinson's disease, single unit studies of the basal ganglia of human Parkinson's disease

Figure 1 Typical examples of beta oscillatory activity in the subthalamic nucleus of human Parkinson's disease patients with akineto-rigid symptoms, with and without tremor



The power spectral density (PSD) as a function of estimated distance to (center of STN) target (EDT) of (a) a tremor dominant and (b) an akineto-rigid patient. The patients' tremor, rigidity and akinesia/bradykinesia aggregate UPDRS scores off-treatment were (a) 25; 16; 58 and (b) 4; 17; 48 (out of 28; 20; 60), respectively. The gray-scale represents 10 $\log_{10}$(PSD power/average PSD power) per EDT. The white solid vertical lines indicate STN entry and exit; the dot–dash lines indicate the ventral boundary of the beta oscillatory region. STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

patients (performed during electrophysiological mapping of the target area for therapeutic implantation of stimulating electrodes) have reported a high fraction of GPi or STN cells oscillating at the tremor frequency or at its higher harmonics. However, as in the primate, the human studies show that these oscillations are not fully coherent with the simultaneous recorded tremor [58,59] or with the clinical symptoms of the patients (Fig. 1). The sharp contrast between this transient and inconsistent pallidal-tremor synchronization and the high synchronicity found between thalamic Vim neurons and the tremor [60] suggest that pallidal neurons cannot be viewed as the tremor generators.

Synchronization of basal ganglia neuronal activity is also evident in the LFP recorded in the subthalamic region of Parkinson's disease patients by the macroelectrodes used for high-frequency stimulation of these structures [61]. These oscillations occur mainly in the beta range (15–30 Hz) and following treatment with deep brain stimulation (DBS) or levodopa ameliorate or shift to higher frequencies in the gamma range. A recent study revealed that these LFP oscillations are correlated with akineto-rigid clinical symptoms but not with the tremor [62•]. Finally, movement (as measured by tapping rate) has been impaired following stimulation of the STN of human Parkinson's disease patients in the beta-frequency range [63••].

Conclusion

In this review, we have explored the possible relationships between basal ganglia oscillatory activity and Parkinson's disease akineto-rigid vs. tremor symptoms. Cumulative clinical and experimental evidence supports the view that the Parkinson's disease motor symptoms are not generated by identical neuronal mechanisms. Following striatal dopamine depletion, many basal ganglia neurons develop synchronous oscillations at the beta range. However, these oscillations are better correlated with the akineto-rigid symptoms, and the Parkinson's disease tremor is not strictly driven by this oscillatory activity. It seems that the abnormal synchronous oscillations in the basal ganglia provide noisy input to the frontal cortex, hence leading to Parkinson's disease akinesia and rigidity. Tremor is probably generated by neuronal mechanisms struggling to compensate for Parkinson's disease akinesia and rigidity. Future clinical studies of the temporal relationship between akinesia/rigidity and tremor in Parkinson's disease patients, as well as their electrophysiological correlates in human and animal models, will hopefully lead to better understanding of Parkinson's disease mechanisms. This should lead to patient optimized (pharmacological and surgical) therapy, hopefully with better clinical results and less side effects.

Acknowledgements

This research was supported in part by the 'Fighting against Parkinson' Foundation of the Hebrew University Netherlands Association (HUNA) and the FP7 select and act grants.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 442–443).

1 Haber SN. The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat 2003; 26:317–330.

2 Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989; 12:366–375.

3 DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990; 13:281–285.

4 Gerfen CR, Engber TM, Mahan LC, *et al.* D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 1990; 250:1429–1432.

5 Surmeier DJ, Ding J, Day M, *et al.* D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends Neurosci 2007; 30:228–235.

6 Gertler TS, Chan CS, Surmeier DJ. Dichotomous anatomical properties of adult striatal medium spiny neurons. J Neurosci 2008; 28:10814–10824.

7 Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci Res 2002; 43:111–117.

8 Tachibana Y, Kita H, Chiken S, *et al.* Motor cortical control of internal pallidal activity through glutamatergic and GABAergic inputs in awake monkeys. Eur J Neurosci 2008; 27:238–253.

9 Levesque M, Parent A. The striatofugal fiber system in primates: a reevaluation of its organization based on single-axon tracing studies. Proc Natl Acad Sci U S A 2005; 102:11888–11893.

10 Nadjar A, Brotchie JM, Guigoni C, *et al.* Phenotype of striatofugal medium spiny neurons in parkinsonian and dyskinetic nonhuman primates: a call for a reappraisal of the functional organization of the basal ganglia. J Neurosci 2006; 26:8653–8661.

11 Bolam JP, Hanley JJ, Booth PA, Bevan MD. Synaptic organisation of the basal ganglia. J Anat 2000; 196 (Pt 4):527–542.

12 Kita H, Kita T. Number, origins, and chemical types of rat pallidostriatal projection neurons. J Comp Neurol 2001; 437:438–448.

13 Hazrati LN, Parent A, Mitchell S, Haber SN. Evidence for interconnections between the two segments of the globus pallidus in primates: a PHA-L anterograde tracing study. Brain Res 1990; 533:171–175.

14 Sato F, Lavallee P, Levesque M, Parent A. Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. J Comp Neurol 2000; 417:17–31.

15 Kita H. Neostriatal and globus pallidus stimulation induced inhibitory post-synaptic potentials in entopeduncular neurons in rat brain slice preparations. Neuroscience 2001; 105:871–879.

16 Kita H. Globus pallidus external segment. Prog Brain Res 2007; 160:111–133.

17 Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997; 275:1593–1599.

18 •• Wickens JR. Synaptic plasticity in the basal ganglia. Behav Brain Res 2008;12;199:119–128.
This review summarizes the current thinking of the basal ganglia as a device for reinforcement learning. It focuses on synaptic plasticity in the corticostriatal pathway. Dopamine, via intracellular signaling cascades, plays a crucial role in determining the magnitude and direction of plasticity and in modulating the requirements for induction. Endocannabinoids also play an important role in mediating presynaptic expression of synaptic depression. The review links the molecular and cellular mechanisms of synaptic plasticity to learning operations at the systems level, which are expressed behaviorally as reinforcement-related learning.

19 Arbuthnott GW, Wickens J. Space, time and dopamine. Trends Neurosci 2007; 30:62–69.

20 Shen W, Flajolet M, Greengard P, Surmeier DJ. Dichotomous dopaminergic control of striatal synaptic plasticity. Science 2008; 321:848–851.

21 Day M, Wokosin D, Plotkin JL, *et al.* Differential excitability and modulation of striatal medium spiny neuron dendrites. J Neurosci 2008; 28:11603–11614.

22 Centonze D, Gubellini P, Pisani A, *et al.* Dopamine, acetylcholine and nitric oxide systems interact to induce corticostriatal synaptic plasticity. Rev Neurosci 2003; 14:207–216.

23 Calabresi P, Di FM. ACh/dopamine crosstalk in motor control and reward: a crucial role for alpha 6-containing nicotinic receptors? Neuron 2008; 60:4–7.

24 Morris G, Arkadir D, Nevet A, *et al.* Coincident but distinct messages of midbrain dopamine and striatal tonically active neurons. Neuron 2004; 43:133–143.

25 • Joshua M, Adler A, Mitelman R, *et al.* Midbrain dopaminergic neurons and striatal cholinergic interneurons encode the difference between reward and aversive events at different epochs of probabilistic classical conditioning trials. J Neurosci 2008; 28:11673–11684.
A recent study showing that dopamine encodes more than just a pleasure prediction error and that the concept of a dopamine–ACh balance can be extended to new physiological domains.

26 Parent A, Cote PY, Lavoie B. Chemical anatomy of primate basal ganglia. Prog Neurobiol 1995; 46:131–197.

27 •• Doya K. Modulators of decision making. Nat Neurosci 2008; 11:410–416.
This article aims to sort out factors that affect the process of decision making from the viewpoint of reinforcement learning theory and to bridge between the computational needs and their physiological substrates. The authors suggest that dopamine in the anterior cingulate cortex motivates patients to go for an action despite a large cost. Norepinephrine and the orbitofrontal cortex promote risk taking and exploratory choices. Serotonin in the dorsal striatum and dorsal prefrontal cortex facilitate consideration of longer-delayed rewards.

28 Bennett DA, Beckett LA, Murray AM, *et al.* Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 1996; 334:71–76.

29 Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely and Jones; 1817.

30 •• Stochl J, Boomsma A, Ruzicka E, *et al.* On the structure of motor symptoms of Parkinson's disease. Mov Disord 2008; 23:1307–1312.
This study used robust statistical methods to investigate the structure of Parkinson's disease motor symptoms as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) of 405 patients with Parkinson's disease. The authors show that the Motor Section of the UPDRS incorporates five main latent symptom factors (rigidity, tremor, bradykinesia of the extremities, axial/gait bradykinesia, speech/hypomimia) and two additional factors for laterality, which account for asymmetry of tremor, rigidity and bradykinesia of the extremities. Tremor was found to be an independent symptom factor of Parkinson's disease.

31 Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 1991; 50:743–755.

32 Narabayashi H, Maeda T, Yokochi F. Long-term follow-up study of nucleus ventralis intermedius and ventrolateralis thalamotomy using a microelectrode technique in parkinsonism. Appl Neurophysiol 1987; 50:330–337.

33 Lenz FA, Normand SL, Kwan HC, *et al.* Statistical prediction of the optimal site for thalamotomy in parkinsonian tremor. Mov Disord 1995; 10:318–328.

34 Papavassiliou E, Rau G, Heath S, *et al.* Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. Neurosurgery 2008; 62 (Suppl 2):884–894.

35 Timmermann L, Florin E, Reck C. Pathological cerebral oscillatory activity in Parkinson's disease: a critical review on methods, data and hypotheses. Expert Rev Med Devices 2007; 4:651–661.

36 Poirier LJ. The development of animal models for studies in Parkinson's disease. Contemp Neurol Ser 1971; 8:83–117.

37 Poirier LJ. Experimental and histological study of midbrain dyskinesias. J Neurophysiol 1960; 23:534–551.

38 Marsden CD. Origins of normal and patholgical tremor. In: Findley LJ, Capildeo R, editors. Movement disorders: tremor. New York: Oxford University Press; 1984. pp. 37–84.

39 Burns RS, Chiueh CC, Markey SP, *et al.* A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci U S A 1983; 80:4546–4550.

40 Langston JW, Forno LS, Rebert CS, Irwin I. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrine (MPTP) in the squirrel monkey. Brain Res 1984; 292:390–394.

41 Langston JW, Irwin I, Langston EB. A comparison of the acute and chronic effects of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-induced parkinsonism in humans and the squirrel monkey. Neurology 1984; 34 (Suppl. 1): 268.

42 Pifl C, Schingnitz G, Hornykiewicz O. Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on the regional distribution of brain monoamines in the rhesus monkey. Neuroscience 1991; 44:591–605.

43 Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000; 20:8559–8571.

44 Heimer G, Bar-Gad I, Goldberg JA, Bergman H. Dopamine replacement therapy reverses abnormal synchronization of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of parkinsonism. J Neurosci 2002; 22:7850–7855.

45 Rajput AH. Clinical features of tremor in extrapyramidal syndromes. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Marcel Dekker, Inc.; 1995. pp. 275–291.

46 Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord 2002; 17 (Suppl 3):S28–S40.

47 Miller WC, DeLong MR. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: Carpenter MB, Jayaraman A, editors. The basal ganglia II. New York: Plenum Press; 1987. pp. 415–427.

48 Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991; 547:142–151.

49 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.

50 Filion M, Tremblay L, Bedard PJ. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991; 547:152–161.

51 Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. III: changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J Neurophysiol 1994; 72:521–530.

52 Heimer G, Rivlin-Etzion M, Bar-Gad I, *et al.* Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of Parkinsonism. J Neurosci 2006; 26:8101–8114.

53 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.

54 •• Mallet N, Pogosyan A, Marton LF, *et al.* Parkinsonian beta oscillations in the external globus pallidus and their relationship with subthalamic nucleus activity. J Neurosci 2008; 28:14245–14258.
Using a rat model of Parkinson's disease, the authors demonstrate that oscillatory activity in the rodent GP (homologue of the primate GPe) neuronal networks becomes excessively and selectively synchronized at beta frequencies. Importantly, they identify two main types of GP neurons according to their distinct and inversely related firing rates and patterns. The authors conclude that the precisely timed discharges of GP and STN neurons are due to the recurrent excitation and inhibition in the STN–GP network and lateral inhibition between GP neurons. The exaggerated STN–GP beta oscillations propagate throughout the entire basal ganglia in Parkinson's disease.

55 Mallet N, Pogosyan A, Sharott A, *et al.* Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. J Neurosci 2008; 28:4795–4806.

56 Timmermann L, Gross J, Dirks M, *et al.* The cerebral oscillatory network of parkinsonian resting tremor. Brain 2003; 126:199–212.

57 Pollok B, Makhloufi H, Butz M, *et al.* Levodopa affects functional brain networks in parkinsonian resting tremor. Mov Disord 2009; 24:91–98.

58 Lemstra AW, Verhagen ML, Lee JI, *et al.* Tremor-frequency (3–6 Hz) activity in the sensorimotor arm representation of the internal segment of the globus pallidus in patients with Parkinson's disease. Neurosci Lett 1999; 267:129–132.

59 Hurtado JM, Rubchinsky LL, Sigvardt KA, *et al.* Temporal evolution of oscillations and synchrony in GPi/muscle pairs in Parkinson's disease. J Neurophysiol 2005; 93:1569–1584.

60 Lenz FA, Kwan HC, Martin RL, *et al.* Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain 1994; 117:531–543.

61 Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 2007; 30:357–364.

62 Kuhn AA, Tsui A, Aziz T, *et al.* Pathological synchronisation in the subthalamic
• nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009; 215:380–387.
The authors collected and analyzed LFP and clinical data in 30 patients with Parkinson's disease. They found significant correlations between levodopa-induced LFP power suppression and rigidity. The correlations were found only when power suppression profiles were realigned to the frequency of peak synchronization. These data suggest that levodopa-induced clinical improvements scale with the degree of suppression of oscillatory power in the STN LFP and that this is true irrespective of the frequency at which synchronization occurs across a broad band from 8 to 35 Hz.

63 Eusebio A, Chen CC, Lu CS, *et al.* Effects of low-frequency stimulation of the
•• subthalamic nucleus on movement in Parkinson's disease. Exp Neurol 2008; 209:125–130.

To address the causal relationships between beta oscillations and Parkinson's disease symptoms, the authors stimulated the STN of 18 Parkinson's disease patients bilaterally at 5, 10 and 20 Hz, and the effects of the low-frequency DBS on a finger tapping task were compared to performance without DBS. Tapping rate decreased and variability of tapping increased at 5 and 20 Hz stimulation.