

Move to the rhythm: oscillations in the subthalamic nucleus–external globus pallidus network

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Recent anatomical, physiological and computer modeling studies have revealed that oscillatory processes at the levels of single neurons and neuronal networks in the subthalamic nucleus (STN) and external globus pallidus (GPe) are associated with the operation of the basal ganglia in health and in Parkinson's disease (PD). Autonomous oscillation of STN and GPe neurons underlies tonic activity and is important for synaptic integration, whereas abnormal low-frequency rhythmic bursting in the STN and GPe is characteristic of PD. These recent findings provide further support for the view that the basal ganglia use both the pattern and the rate of neuronal activity to encode information.

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The basal ganglia are a group of subcortical brain nuclei involved in voluntary movement, association, cognition and emotion [1–6]. Reciprocally connected glutamatergic neurons of the subthalamic nucleus (STN) and GABAergic neurons of the external globus pallidus (GPe) form a key network within the basal ganglia [7–9]. The principal source of afferent input to the basal ganglia, the cerebral cortex, influences the STN–GPe network, directly via monosynaptic projections or indirectly via GABAergic striatal or glutamatergic thalamic neurons. By virtue of their extensive innervation of the GABAergic neurons of the basal ganglia output nuclei, the STN and GPe are in a position to influence powerfully the communication of the basal ganglia with the rest of the brain (Fig. 1).

An important model of basal ganglia dysfunction, commonly used to explain the motor symptoms of Parkinson's disease (PD), implies that the interaction of the STN and GPe is unidirectional and constant over time. It also accounts for the symptoms of PD in terms of changes in the mean rates of activity of basal ganglia nuclei [10–12]. Thus, abnormal over-activity of the GABAergic neurons projecting from the striatum to the GPe reduces the activity of the GPe, which results in disinhibition of the STN and, in turn, drives over-activity of the basal ganglia output nuclei and excessive inhibition of their targets. In contrast to the proposed pathological over-activity of this 'indirect pathway' to the output nuclei, the 'direct pathway' (i.e. the direct projection from the striatum) is proposed to be relatively under-active. Therefore, the reduced inhibition of basal ganglia output nuclei also contributes to their relative over-activity in PD.

Studies of idiopathic and experimental models of PD suggest that changes in the patterns of activity of

STN and GPe neurons could be at least as robust as changes in their mean rates of activity [5,13–27]. Thus, normal information processing in the STN and GPe is characterized by complex spatiotemporal patterns of firing, whereas in PD, STN and GPe neurons display more correlated, synchronous and rhythmic patterns of activity [5,13–37]. The transformation in the pattern of activity in the STN and GPe in PD is mirrored by similar changes in the activity of the basal ganglia output nuclei [5,14–16,21,25,26,38–43]. Pathological, synchronized, oscillatory activity is likely to result in less efficient coding of information by the basal ganglia and could, therefore, contribute to the symptoms of PD. Here we review recent findings concerning the sources of oscillatory activity in the STN and GPe, and their relevance to normal and pathological patterns of activity in the basal ganglia.

Activity patterns in the STN and GPe

During quiet wakefulness, the STN and GPe fire differently, without rhythm and without strong correlation either within or between the nuclei [5,14,25–26,28,37]. During voluntary or passive movement, STN and GPe neurons display intricate spatiotemporal changes in activity, which relate in a complex manner to motor activity [14,28,30,37]. During movement, activity is rarely correlated but it is highly structured, so that there is precise somatotopic specificity [14,28,30,37]. In PD, rhythmic bursting activity at 4–10 Hz and 15–30 Hz is observed in the STN, GPe and other parts of the basal ganglia [5,13–15,17,20–22,25–26]. This activity is often correlated within and between nuclei, although a spectrum of phase relationships exists, even between closely spaced neurons [5,13–15,17,20–22,25–26]. Movement is impaired and the precise somatotopic organization of activity in relation to sensory–motor processing breaks down [5,12–14,18,38]

In addition to these relatively fast rhythms, ultra-slow rhythms (with periods in the range of ~20–100 s) have been described in the activity of STN and GPe neurons of both normal and dopamine-depleted animals [44–46]. The possible functional relevance of these ultra-slow rhythms and their underlying mechanisms have been discussed in the original papers and will not be dealt with further here.

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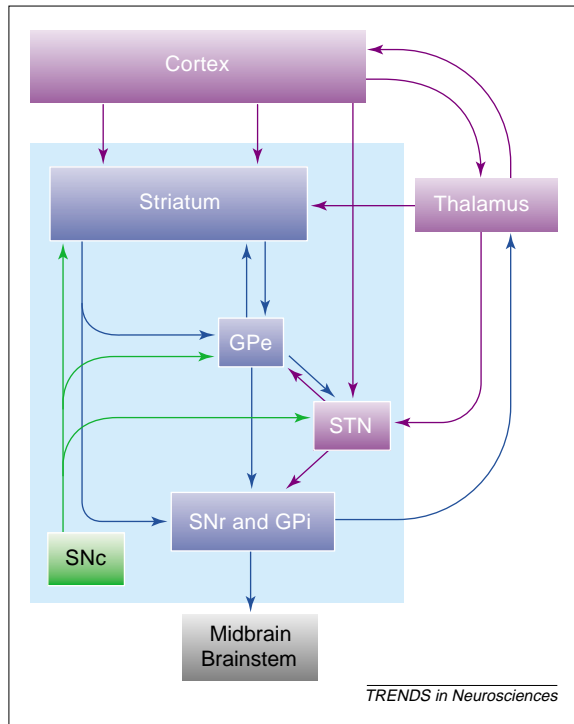


Fig. 1. The basal ganglia and their associated structures. A simplified, schematic diagram of the basal ganglia (within the pale blue box) and their associated structures. Glutamatergic connections are in purple, GABAergic connections are in dark blue and dopaminergic connections are in green. Brainstem premotor nuclei and midbrain nuclei, which use a variety of neurotransmitters, are shaded gray. The major afferents to the basal ganglia are from the cortex and thalamus and are directed to both the striatum and the subthalamic nucleus (STN). The striatum influences the basal ganglia output nuclei [substantia nigra *pars reticulata* (SNr) and the internal segment of the globus pallidus (GPi)] directly, or indirectly via connections with the network between the STN and external globus pallidus (GPe). The dopaminergic substantia nigra *pars compacta* (SNc) influences the operation of the basal ganglia via connections with each nucleus. The major targets of the basal ganglia output nuclei are the thalamus and the midbrain and brainstem premotor regions, which influence movement via direct or indirect connections with motor nuclei. Note that the STN–GPe network is the principal site of reciprocally innervated excitatory and inhibitory neurons in the basal ganglia. Through the extensive connections of the STN and GPe with the output nuclei, the network is in a strategic position to have powerful influence on the communication of the basal ganglia with the rest of the brain.

Microcircuitry of the STN–GPe network

Correlated light- and electron-microscopic studies employing the bidirectional transport of neuronal tracers in rats and monkeys revealed that the STN and GPe are made up of repeating neuronal architectures [7,8,47–49]. Thus, functionally related regions of the STN and GPe are reciprocally connected and innervate functionally related regions of the basal ganglia output nuclei. Furthermore, the majority of STN and GPe neurons in rats and monkeys have branched axons that mediate both the reciprocal connections and the innervation of the basal ganglia output nuclei [7,8,50–52]. However, it is still not known whether individual STN and GPe neurons form reciprocally connected pairs of neurons or, if such pairs exist, whether they innervate common basal ganglia output neurons.

One operation of this reciprocal network appears to be the regulation of subthalamic activity by feedback inhibition from the GPe [29,31,32,34–35,53]. However, the existence of reciprocally connected excitatory and inhibitory nuclei implies that the STN–GPe network could also support oscillatory activity and act as a pattern generator. Furthermore, the innervation of common regions of the basal ganglia output nuclei by reciprocally connected regions of the STN and GPe indicates that pattern generation within the STN–GPe network would have a powerful impact on the output of the basal ganglia. Indeed, pathological oscillatory activity in the basal ganglia output nuclei in PD is abolished by disruption of activity in the STN and/or the GPe [5,39,54–56].

Pacemaker activity in single STN and GPe neurons

Neurons of the STN and GPe display spontaneous, rhythmic single-spike activity when they are isolated from synaptic input by severing afferents during the preparation of brain slices and/or by the application of neurotransmitter-receptor antagonists (Fig. 2) [57–61]. The ionic mechanisms underlying this spontaneous activity have been characterized most completely for STN neurons. In these neurons, voltage-gated Na^+ channels that inactivate slowly are the primary source of current during the depolarizing phase of the oscillation [57–58]. The period and precision of the oscillation are controlled, at least in part, by an apamin-sensitive Ca^{2+} -dependent K^+ current [58]. The Ca^{2+} -dependent K^+ current is activated by Ca^{2+} entry through high-voltage-activated Ca^{2+} channels that open briefly during each Na^+ action potential [58]. Hyperpolarization-activated cationic currents and low-threshold Ca^{2+} currents in STN neurons are not activated and remain inactivated, respectively, at the voltages associated with the spontaneous oscillation (~ -45 to -65 mV) [57,58].

Some types of GPe neuron also possess intrinsic properties that underlie rhythmic, autonomous activity and have been demonstrated to fire spontaneously in isolation under certain conditions [59–61]. Taken together, these observations suggest that the resting state of STN and GPe neurons is one of rhythmic activity and that the responses of STN and GPe neurons to synaptic input are determined by the interaction of synaptic currents with the intrinsic oscillatory properties of their membranes. *In vivo*, activities generated by these pacemakers are likely to be sculpted into more complex firing patterns by synaptic inputs and network dynamics. Thus, during wakefulness, the intrinsic properties and interactions of the STN and GPe neurons are likely to generate persistent activity in the absence of extrinsic excitatory input. The influence of inputs from the cortex, thalamus and striatum to the STN–GPe network will be exerted within the context of this intrinsic network activity. Clarifying the

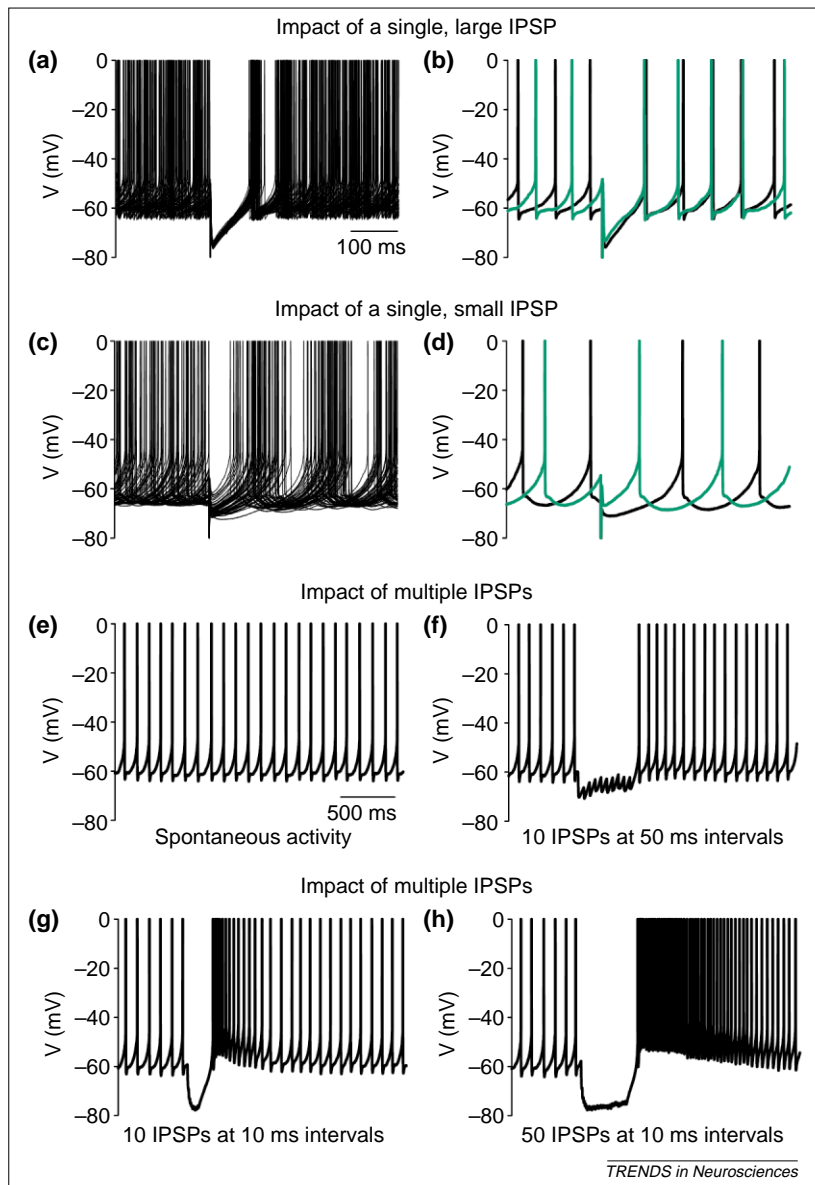


Fig. 2. GABA_A inhibitory postsynaptic potentials (IPSPs) regulate the timing and pattern of action potential generation in subthalamic nucleus (STN) neurons. Recordings were made from STN neurons in brain slices using the perforated-patch technique and GABA_A IPSPs were evoked by electrical stimulation of the internal capsule. (a,b) Single large IPSPs consistently reset the spontaneous oscillatory cycle so that activity following the IPSP occurs within a relatively narrow time window (a, 50 superimposed sweeps; b, two representative sweeps, one in black and one in green). (c,d) The inter-spike intervals associated with relatively small IPSPs are of similar duration regardless of the phase at which IPSPs are evoked (c, fifty superimposed sweeps; d, two representative sweeps, one in black, one in green). The spontaneous activity of STN neurons in the absence of IPSPs (e) can be reduced (f) or augmented (g,h) by multiple IPSPs. When ten IPSPs are evoked within the same 2.5 s sampling period, they can inhibit activity (f) or generate rebound burst activity (g), depending on their degree of summation. Comparison of (g) and (h) reveals that increasing the number of IPSPs in the 2.5 s sampling period increases the rebound burst activity of the STN neuron. Inhibitory synaptic potentials can, therefore, lead to the paradoxical excitation of STN neurons when channels underlying rebound activity are primed by IPSPs. Scale bar in (a) also applies to (b–d); scale bar in (e) also applies to (f–h). For clarity, action potentials have been truncated at 0 mV and the stimulation artifact present in (a–d) has been removed from (e–h). Reproduced, with permission, from Ref. [63].

relationship between intrinsic oscillations of single cells and the rhythmic firing patterns seen in the STN and GPe requires a thorough understanding of the synaptic interactions among neurons in the circuit.

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Response of STN neurons to GPe input

The principal GABAergic input to the STN arises from the GPe and acts at GABA_A receptors. *In vitro* patch recordings of STN neurons, using the perforated configuration to maintain the natural intracellular concentration of Cl⁻ (the principal permeant ion of the GABA_A receptor), have revealed that the equilibrium potential of GABA_A receptor-mediated inhibitory postsynaptic potentials (IPSPs) is approximately -80 mV [62–63]. Thus, GABA_A IPSPs can, in theory, hyperpolarize STN neurons 10–20 mV below the voltages associated with the most negative phase of the spontaneous oscillation. In practice, therefore, single GABA_A IPSPs disrupt and inhibit the spontaneous oscillation that underlies rhythmic single-spike firing in STN neurons (Fig. 2). As the magnitude of the IPSP increases, the effectiveness of the IPSP in prolonging the interspike interval is related more strongly to the phase of the oscillation at which the IPSP occurs. Thus, large IPSPs reset the oscillatory cycle and are likely to lead to synchronization (Fig. 2a,b), whereas small IPSPs produce relatively phase-independent delays in firing and could lead to desynchronization (Fig. 2c,d) [63]. The response of STN neurons to multiple IPSPs is more complex because summated IPSPs can produce sufficient hyperpolarization to prime ion channels that are not operational during spontaneous rhythmic activity (i.e. channels responsible for low-threshold Ca²⁺ current and hyperpolarization-activated cationic current). Indeed, multiple IPSPs can produce sufficient hyperpolarization to activate a rebound depolarization, which generates a single spike, restores rhythmic spiking and/or generates a burst of activity (Fig. 2g,h) [63]. Multiple IPSPs can also reduce and/or prevent action-potential generation (Fig. 2f) [63]. The pattern and rate of inhibitory input are, therefore, crucial in determining whether STN neurons fire in a single-spiking or bursting pattern. The level of polarization of STN neurons is also crucial in determining the response to GPe input, implying that neuromodulators that influence the polarization of STN neurons over long periods (e.g. ACh, serotonin and dopamine) will have a profound effect on the operation of the network [63]. Taken together, these data suggest that inhibitory input from the GPe can contribute to the range of firing patterns expressed by STN neurons *in vivo*. They also confirm that the firing mode of STN neurons is related more intimately to the magnitude and pattern of inhibitory input than to the frequency of input averaged over long periods. Furthermore, these findings illustrate that certain patterns of inhibitory GABAergic input can actually augment, rather than reduce, the activity of STN neurons.

Origins of correlated, rhythmic activity in the STN–GPe network in PD

There has been considerable debate on the origins of correlated, rhythmic firing in the STN–GPe network

in idiopathic and experimental models of PD. This activity could be an emergent property of the STN–GPe network itself and/or be driven by rhythmic activity in the cortex.

Intrinsic origin of rhythmic activity

Evidence for an intrinsic origin of correlated, rhythmic firing in the STN–GPe network comes from studies of organotypic co-cultures of the STN and

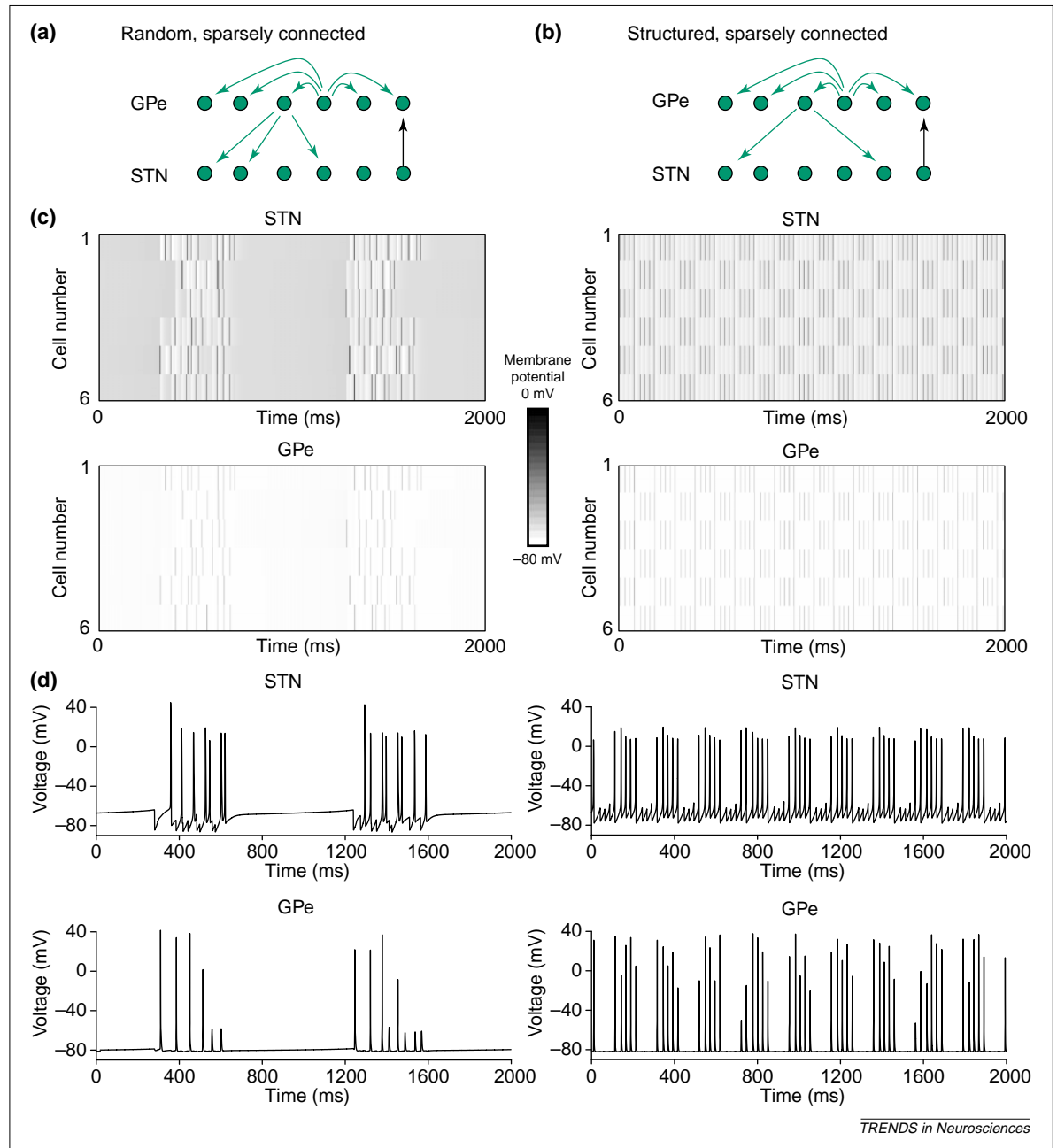


Fig. 3. Activity patterns in the connections between subthalamic nucleus (STN) external globus pallidus (GPe) depend on architecture. The left column displays activity patterns for the random, sparsely connected network shown in (a). Each GPe cell sends inhibitory input to a small proportion of the STN neurons selected at random (straight green arrows). The STN cells also project sparsely (each connecting to only one GPe cell, black arrow), making random connections. For clarity, neurons are sorted in a and b to align STN cells with the GPe cells they innervate, and only connections with respect to a single, representative STN cell are shown. The right column displays activity patterns for the more-structured architecture shown in (b). In this architecture, each STN neuron still connects to only one GPe neuron, and each GPe cell inhibits a small number of STN neurons. The difference is that GPe cells do not project back to the STN randomly. Instead they project to STN cells that are near to, but different from, the one that connects to them (avoiding reciprocal connections). In both architectures, GPe cells inhibit each

other through all-to-all connections. (c) Network activity of the STN (upper two panels) and GPe cells (lower two panels). In each plot, six rows show the voltage traces of six cells over a time period of 2000 ms. Voltage is coded in grayscale, ranging from black at 0 mV to white at -80 mV, as shown centrally. (d) Membrane potential (mV) as a function of time (ms) for representative individual cells during each activity pattern. The randomly connected network exhibits episodic activity, in which cells fire irregularly. Each episode lasts for ~ 300 ms and the silent period between the episodes is ~ 500 ms. The more topographically organized, structured network exhibits clustered rhythms, in which each structure is divided into two subsets of neurons that become highly correlated with each other. The frequency of the bursts is close to 5 Hz. During each burst of activity, cells spike at ~ 40 Hz. The frequency of bursting, the size of clusters and the firing rate within bursts depend on the strength of connections in the network and the intrinsic cellular properties of the neurons.

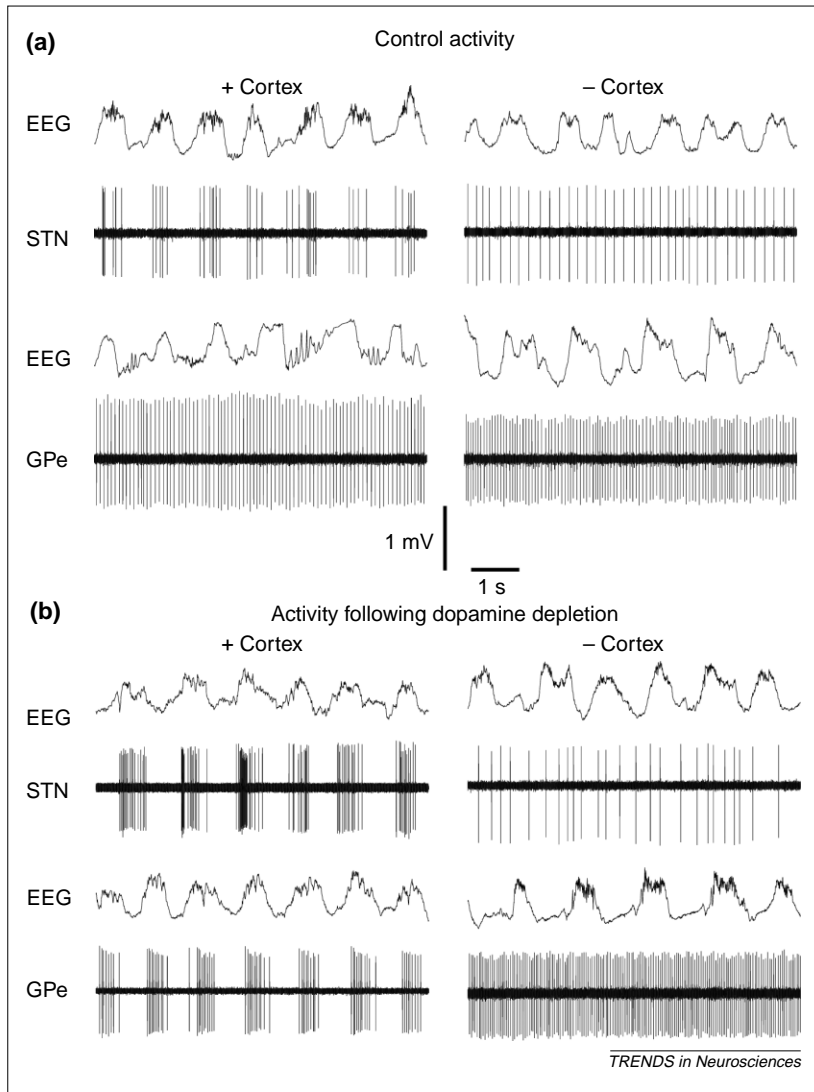


Fig. 4. Low-frequency rhythmic activity in subthalamic nucleus (STN) and external globus pallidus (GPe) neurons *in vivo* is related to coincident cortical activity and is augmented by the depletion of dopamine. Coincident patterns of activity in the cortex, STN and GPe were assessed from simultaneous recordings of frontal cortical electroencephalogram (EEG) and the unit activity of individual STN or GPe neurons in deeply anesthetized rats. (a) Neurons in the STN of anesthetized control rats exhibit low-frequency rhythmic firing (~1 Hz) during periods of slow-wave activity in the ipsilateral cortex (+ Cortex). The rhythmic, burst-like discharges of STN neurons are phase-locked to the cortical slow-wave. By contrast, GPe neurons fire in a rhythmic single-spike manner, irrespective of slow-wave activity in the cortex. Rhythmic bursting activity in the STN is abolished by ablation of the ipsilateral cortex (- Cortex), whereas activity in the GPe is not altered. Note that following ipsilateral cortical ablation, the depth of anesthesia was assessed from the contralateral frontal EEG. (b) Following the chronic depletion of dopamine [unilateral 6-hydroxydopamine (6-OHDA) lesion of midbrain dopaminergic neurons], STN neurons continue to display low-frequency rhythmic activity during ipsilateral cortical slow-wave activity, but the burst-like discharges are more intense (mean rate of firing increases two- to threefold). Neurons in the GPe also develop low-frequency oscillatory activity that is phase-locked to ipsilateral cortical activity. Low-frequency rhythmic activity in STN and GPe neurons of dopamine-depleted rats is also largely abolished by ipsilateral cortical ablation (- Cortex). Taken together, these data suggest that, under some conditions, low-frequency network oscillations depend on rhythmic cortical activity. Scale bars apply to all panels. Reproduced, with permission, from Ref. [23].

GPe. These have demonstrated that the STN-GPe network can support such activity when isolated from two of its major afferents (the cortex and the striatum) [9]. The mechanism underlying this rhythmic activity was proposed to be similar to that described for spindle oscillations in the thalamus [64], which are characterized by the priming of

low-threshold Ca^{2+} currents in excitatory neurons by bursts of GABA-mediated inhibition. Thus, synchronous bursting activity in GPe neurons generates sufficient hyperpolarization in STN neurons for rebound burst activity which, in turn, drives bursting activity in GPe neurons and leads to the perpetuation of the rhythm [9]. Interestingly, the frequency of the rhythm in organotypic co-cultures (0.4–1.2 Hz) [9] is much lower than that observed in conscious patients with idiopathic PD or in awake dopamine-depleted animals. Computer simulations of the STN-GPe network suggest that higher-frequency rhythms can arise from networks that incorporate the more complex patterns of synaptic connectivity that might be present *in vivo*.

Recent modeling studies incorporating the known biophysical properties of STN and GPe neurons with a variety of network architectures have been useful in examining the principles that underlie activity patterns in the STN-GPe network [65]. Although many important anatomical questions remain, recent studies have established that the connections between the STN and GPe are roughly topographical and reciprocal, and that individual axons of both structures make sparse and distributed arborizations, in which average connectivity is low [7,8,50–52]. Computer simulations using a range of structural arrangements within the limits of the known anatomy suggest that the STN-GPe network is capable of generating patterned and persistent activity of a variety of types. Randomly connected STN-GPe networks are capable of generating the slow, rhythmic firing seen in organotypic co-cultures but are incapable of generating 4–10 Hz or 15–30 Hz rhythmic activity, as seen in idiopathic and experimental models of PD. In simulations of more realistic, topographically organized but sparsely connected networks, the STN and GPe exhibited clusters of neurons whose activity was correlated and rhythmic in the frequency range associated with PD. As predicted from experimental studies, rebound bursts in STN neurons, which follow barrages of IPSPs arising from the GPe, were crucial to the rhythm. Small changes in the strength of synaptic connections between STN and GPe neurons and among GPe neurons could produce qualitative changes in firing pattern. For example, rhythmic activity at 4–6 Hz occurred continuously when synaptic inputs from the STN to the GPe were strong but occurred in discrete episodes when the strength of this connection was diminished. The nature of the network activity pattern also depended crucially upon inhibitory input to the GPe from the striatum. Irregular, uncorrelated activity arose in the network when connections between GPe neurons were strong and striatal inhibition was weak. Local GPe collateral projections opposed clustered rhythms because they diminished bursting activity in GPe neurons and reduced the coherence of activity in the reciprocal pathways between the STN and GPe (Fig. 3). Striatal

inhibition in the model enhanced 4–6 Hz rhythms by suppressing asynchronous activity among GPe neurons, often with no effect on mean rate. The model suggests that the over-activity of the striatal pathway to GPe neurons in PD could alter activity patterns in the STN–GPe network directly via postsynaptic action [31,60], and indirectly through the release of peptide co-transmitters that target presynaptic receptors on the local axon collaterals of GPe neurons [66,67]. Activation of these presynaptic peptide receptors reduces the magnitude of the IPSP arising from GPe intranuclear collateral projections [66,67], which allows clustered low-frequency activity of the STN–GPe network to develop more easily (Fig. 3) [65].

Extrinsic origins of rhythmic activity

Recent studies indicate that the cortex can pattern rhythmic activity in the STN and GPe [23,33]. In anesthetized-control and dopamine-depleted animals, STN neurons exhibited low-frequency rhythmic firing, which was correlated tightly with slow-wave activity (~1 Hz) generated by cortical networks (Fig. 4) [23,33]. Obliteration of slow-wave activity, by ipsilateral cortical ablation or activation, largely abolished low-frequency rhythmic activity [23,33]. The principal effects of dopamine depletion are that GPe neurons begin to express low-frequency oscillatory activity and the STN exhibits more intense oscillatory activity (Fig. 4) [23]. Because the amplitude and period of cortical slow-wave activity are unchanged by dopamine depletion, these data suggest that, in the dopamine-depleted state, the STN and GPe are more sensitive to the cortical rhythm [23].

In both the absence and presence of dopamine in idiopathic PD, rhythmic activity in the cerebral cortex and the basal ganglia are intimately related. Following withdrawal of treatment with the dopamine precursor L-DOPA (3,4-dihydroxy phenyl L-alanine), the cortex, STN and GPe of PD patients displayed relatively strong rhythmic activity in the tremor frequency range (4–10 Hz) and in the alpha (8–13 Hz) and beta ranges (14–30 Hz) [15,20–22,68–71]. When dopamine-receptor agonists

were administered, rhythmic activity below 30 Hz diminished and higher frequency rhythms in the gamma range (30–70 Hz) were expressed in both cortex and basal ganglia [15,22,68]. On the basis of findings in anesthetized animals, some of us have suggested that low-frequency oscillations in the basal ganglia in PD might be abnormal representations of rhythms that are generated within the cortex during quiet wakefulness [23]. Another hypothesis that has been proposed recently is that the dopamine-depleted basal ganglia, through their connections with the thalamocortical, midbrain and brainstem circuits, resonate and amplify the idling rhythms generated by the cortex and, somehow, suppress emergence of higher-frequency rhythms [15,22,68]. Given that, in the sensory–motor cortex, rhythmic activity in the gamma range is associated with the onset of movement [72] and can occur during particular types of movement [73], it follows that the suppression of this high-frequency activity could partly underlie the disruption of movement seen in PD.

Finally, it should be noted that other sources of afferent projections to the basal ganglia, such as the thalamus, also generate oscillatory activity [64] and could, in theory, underlie pattern activity in the STN and GPe. The impact of other potential pattern generators on the STN and GPe remains to be studied.

Conclusions

Rhythmic activity is an important feature of the normal and abnormal operation of the basal ganglia. At the single-cell level, STN and GPe neurons possess intrinsic membrane properties that drive autonomous activity and set the context in which synaptic input is integrated. At the level of the STN and GPe, rhythmic activity might be driven by both intrinsic and external pattern generators. Major challenges that lie ahead are to understand how dopamine modulates the relative contribution of these oscillatory mechanisms to information processing, and to generate models of basal ganglia function and dysfunction that incorporate the dynamic nature of oscillatory processes.

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References

- Alexander, G.E. *et al.* (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Prog. Brain Res.* 85, 119–146
- Graybiel, A.M. (1998) The basal ganglia and chunking of action repertoires. *Neurobiol. Learn. Mem.* 70, 119–136
- Hikosaka, O. *et al.* (2000) Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol. Rev.* 80, 953–978
- Hollerman, J.R. *et al.* (2000) Involvement of basal ganglia and orbitofrontal cortex in goal-directed behavior. *Prog. Brain Res.* 126, 193–215
- Wichmann, T. and DeLong, M.R. (1996) Functional and pathophysiological models of the basal ganglia. *Curr. Opin. Neurobiol.* 6, 751–758
- Wise, S.P. *et al.* (1996) The frontal cortex-basal ganglia system in primates. *Crit. Rev. Neurobiol.* 10, 317–356
- Smith, Y. *et al.* (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* 86, 353–387
- Parent, A. *et al.* (2000) Organization of the basal ganglia: the importance of axonal collateralization. *Trends Neurosci.* 23, S20–S27
- Plenz, D. and Kitai, S.T. (1999) A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* 400, 677–682
- Albin, R.L. *et al.* (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci.* 12, 366–375
- Crossman, A.R. (1989) Neural mechanisms in disorders of movement. *Comp. Biochem. Physiol.* A93, 141–149
- DeLong, M.R. (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 13, 281–285
- Bergman, H. *et al.* (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.* 72, 507–520
- Bergman, H. *et al.* (1998) Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. *Trends Neurosci.* 21, 32–38
- Brown, P. *et al.* (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's Disease. *J. Neurosci.* 21, 1033–1038
- Chesselet, M.F. and Delfs, J.M. (1996) Basal ganglia and movement disorders. *Trends Neurosci.* 19, 417–422
- Filion, M. (1979) Effects of interruption of the nigrostriatal pathway and of dopaminergic agents on the spontaneous activity of globus pallidus neurons in the awake monkey. *Brain Res.* 178, 425–441
- Filion, M. *et al.* (1988) Abnormal influences of passive limb movement on the activity of globus

- pallidus neurons in parkinsonian monkeys. *Brain Res.* 444, 165–176
- 19 Hollerman, J.R. and Grace, A.A. (1992) Subthalamic nucleus cell firing in the 6-OHDA-treated rat: basal activity and response to haloperidol. *Brain Res.* 590, 291–299
 - 20 Levy, R. *et al.* (2000) High-frequency synchronization of neuronal activity in the subthalamic nucleus of Parkinsonian patients with limb tremor. *J. Neurosci.* 20, 7766–7775
 - 21 Levy, R. *et al.* (2002) Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. *J. Neurosci.* 22, 2855–2861
 - 22 Levy, R. *et al.* (2002) Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain* 125, 1196–1209
 - 23 Magill, P.J. *et al.* (2001) Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. *Neuroscience* 106, 313–330
 - 24 Ni, Z. *et al.* (2000) Changes in the firing pattern of globus pallidus neurons after the degeneration of nigrostriatal pathway are mediated by the subthalamic nucleus in the rat. *Eur. J. Neurosci.* 12, 4338–4344
 - 25 Nini, A. *et al.* (1995) 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.* 74, 1800–1805
 - 26 Raz, A. *et al.* (2000) 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.* 20, 8559–8571
 - 27 Vila, M. *et al.* (2000) Evolution of changes in neuronal activity in the subthalamic nucleus of rats with unilateral lesions of the substantia nigra assessed by metabolic and electrophysiological measurements. *Eur. J. Neurosci.* 12, 337–344
 - 28 DeLong, M.R. *et al.* (1985) Primate globus pallidus and subthalamic nucleus: functional organization. *J. Neurophysiol.* 53, 530–543
 - 29 Fujimoto, K. and Kita, H. (1993) Response characteristics of subthalamic neurons to the stimulation of the sensorimotor cortex in the rat. *Brain Res.* 609, 185–192
 - 30 Jaeger, D. *et al.* (1995) Neuronal activity in the striatum and pallidum of primates related to the execution of externally cued reaching movements. *Brain Res.* 694, 111–127
 - 31 Kita, H. (1992) Responses of globus pallidus neurons to cortical stimulation: intracellular study in the rat. *Brain Res.* 589, 84–90
 - 32 Kitai, S.T. and Deniau, J.M. (1981) Cortical inputs to the subthalamus: intracellular analysis. *Brain Res.* 214, 411–415
 - 33 Magill, P.J. *et al.* (2000) Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. *J. Neurosci.* 20, 820–833
 - 34 Maurice, N. *et al.* (1998) Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the corticosubthalamic circuits. *J. Neurosci.* 18, 9539–9546
 - 35 Ryan, L.J. and Clark, K.B. (1991) The role of the subthalamic nucleus in the response of globus pallidus neurons to stimulation of the prelimbic and agranular frontal cortices in rats. *Exp. Brain Res.* 86, 641–651
 - 36 Urbain, N. *et al.* (2000) Unrelated course of subthalamic nucleus and globus pallidus neuronal activities across vigilance states in the rat. *Eur. J. Neurosci.* 12, 3361–3374
 - 37 Wichmann, T. *et al.* (1994) The primate subthalamic nucleus. I. Functional properties in intact animals. *J. Neurophysiol.* 72, 494–506
 - 38 Boraud, T. *et al.* (2000) Ratio of inhibited-to-activated pallidal neurons decreases dramatically during passive limb movement in the MPTP-treated monkey. *J. Neurophysiol.* 83, 1760–1763
 - 39 Boraud, P. *et al.* (1995) Reduction of apomorphine-induced rotational behaviour by subthalamic lesion in 6-OHDA lesioned rats is associated with a normalization of firing rate and discharge pattern of *pars reticulata* neurons. *Exp. Brain Res.* 105, 48–58
 - 40 Murer, M.G. *et al.* (1997) Substantia nigra *pars reticulata* single unit activity in normal and 6-OHDA-lesioned rats: effects of intrastriatal apomorphine and subthalamic lesions. *Synapse* 27, 278–293
 - 41 Wichmann, T. *et al.* (1994) 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.* 72, 521–530
 - 42 Wichmann, T. *et al.* (1999) Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra *pars reticulata* in primates. *Exp. Brain Res.* 125, 397–409
 - 43 Hurtado, J.M. *et al.* (1999) Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. *Proc. Natl. Acad. Sci. U. S. A.* 96, 1674–1679
 - 44 Allers, K.A. *et al.* (2002) Multisecond periodicities in basal ganglia firing correlate with theta bursts in transcortical and hippocampal EEG. *J. Neurophysiol.* 87, 1118–1122
 - 45 Ruskin, D.N. *et al.* (1999) Multisecond oscillations in firing rate in the basal ganglia: robust modulation by dopamine receptor activation and anesthesia. *J. Neurophysiol.* 81, 2046–2055
 - 46 Wichmann, T. *et al.* (2002) Slow oscillatory discharge in the primate basal ganglia. *J. Neurophysiol.* 87, 1145–1148
 - 47 Bevan, M.D. *et al.* (1994) Convergent synaptic input from the neostriatum and the subthalamus onto identified nigrothalamic neurons in the rat. *Eur. J. Neurosci.* 6, 320–334
 - 48 Shink, E. *et al.* (1996) The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey. *Neuroscience* 73, 335–357
 - 49 Smith, Y. *et al.* (1994) Synaptic innervation of neurones in the internal pallidal segment by the subthalamic nucleus and the external pallidum in monkeys. *J. Comp. Neurol.* 343, 297–318
 - 50 Bevan, M.D. *et al.* (1998) Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. *J. Neurosci.* 18, 9438–9452
 - 51 Kita, H. and Kitai, S.T. (1994) The morphology of globus pallidus projection neurons in the rat: an intracellular staining study. *Brain Res.* 636, 308–319
 - 52 Sato, F. *et al.* (2000) Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. *J. Comp. Neurol.* 417, 17–31
 - 53 Ryan, L.J. and Clark, K.B. (1992) Alteration of neuronal responses in the subthalamic nucleus following globus pallidus and neostriatal lesions in rats. *Brain Res. Bull.* 29, 319–327
 - 54 Bergman, H. *et al.* (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 249, 1436–1438
 - 55 Krack, P. *et al.* (1998) Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. *Mov. Disord.* 13, 907–914
 - 56 Limousin, P. *et al.* (1995) Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 345, 91–95
 - 57 Beurrier, C. *et al.* (2000) Slowly inactivating sodium current (INaP) underlies single-spike activity in rat subthalamic neurons. *J. Neurophysiol.* 83, 1951–1957
 - 58 Bevan, M.D. and Wilson, C.J. (1999) Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. *J. Neurosci.* 19, 7617–7628
 - 59 Cooper, A.J. and Stanford, I.M. (2000) Electrophysiological and morphological characteristics of three subtypes of rat globus pallidus neuron *in vitro*. *J. Physiol.* 527, 291–304
 - 60 Nakanishi, H. *et al.* (1985) Neostriatal evoked inhibition and effects of dopamine on globus pallidus neurons in rat slice preparations. *Brain Res.* 358, 282–286
 - 61 Nambu, A. and Llinas, R. (1994) Electrophysiology of globus pallidus neurons *in vitro*. *J. Neurophysiol.* 72, 1127–1139
 - 62 Bevan, M.D. *et al.* (2000) Equilibrium potential of GABA-A current and implications for rebound burst firing in rat subthalamic neurons *in vitro*. *J. Neurophysiol.* 83, 3169–3172
 - 63 Bevan, M.D. *et al.* (2002) Regulation of the timing and pattern of action potential generation in rat subthalamic neurons *in vitro* by GABA-A IPSPs. *J. Neurophysiol.* 87, 1348–1362
 - 64 McCormick, D.A. and Bal, T. (1997) Sleep and arousal: thalamocortical mechanisms. *Annu. Rev. Neurosci.* 20, 185–215
 - 65 Terman, D. *et al.* (2002) Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *J. Neurosci.* 22, 2963–2976
 - 66 Ogura, M. and Kita, H. (2000) Dynorphin exerts both postsynaptic and presynaptic effects in the globus pallidus of the rat. *J. Neurophysiol.* 83, 3366–3376
 - 67 Stanford, I.M. and Cooper, A.J. (1999) Presynaptic mu and delta opioid receptor modulation of GABA-A IPSCs in the rat globus pallidus *in vitro*. *J. Neurosci.* 19, 4796–4803
 - 68 Brown, P. and Marsden, C.D. (1999) Bradykinesia and impairment of EEG desynchronization in Parkinson's disease. *Mov. Disord.* 14, 423–429
 - 69 Hellwig, B. *et al.* (2000) Tremor-correlated cortical activity detected by electroencephalography. *Clin. Neurophysiol.* 111, 806–809
 - 70 Volkman, J. *et al.* (1996) Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. *Neurology* 46, 1359–1370
 - 71 Brown, P. and Marsden, C.D. (1999) What do the basal ganglia do? *Lancet* 351, 1801–1804
 - 72 Donoghue, J.P. *et al.* (1998) Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. *J. Neurophysiol.* 79, 159–173
 - 73 Aoki, F. *et al.* (2001) Changes in power and coherence of brain activity in human sensorimotor cortex during performance of visuomotor tasks. *Biosystems* 63, 89–99