distinct sector of TRN. We have discussed two cortical areas and two thalamic nuclei for each sector, but generally more cortical areas and more thalamic nuclei are involved in any one sector. The important point is that each sector provides a nexus for the interaction of several thalamocortical and corticothalamic circuits, and will prove to be a key site where many cortical areas concerned with one modality can interact. The nature of interactions in this nexus is likely to prove crucial for the cortical and reticular control of relay properties of thalamic cells as these switch from one mode of firing to another, possibly changing as attentional foci shift across cortical areas and within cortical areas. It has recently been shown that the pattern of thalamic reticular connections to the auditory thalamus of the cat resembles that of the somatosensory pathways in this species[44]. However, the cortical connections in the auditory sector of the cat have not yet been defined.

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# Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates


Hagai Bergman, Ariela Feingold, Asaph Nini, Aeyal Raz, Hamutal Slovin, Moshe Abeles and Eilon Vaadia



**There are two views as to the character of basal-ganglia processing – processing by segregated parallel circuits or by information sharing. To distinguish between these views, we studied the simultaneous activity of neurons in the output stage of the basal ganglia with cross-correlation techniques. The firing of neurons in the globus pallidus of normal monkeys is almost always uncorrelated. However, after dopamine depletion and induction of parkinsonism by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), oscillatory activity appeared and the firing of many neurons became correlated. We conclude that the normal dopaminergic system supports segregation of the functional subcircuits of the basal ganglia, and that a breakdown of this independent processing is a hallmark of Parkinson's disease.**



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ALTHOUGH THE CRUCIAL ROLE played by the basal ganglia in the pathogenesis of various movement disorders such as Parkinson's and Huntington's diseases has been known for many years[1,2], the basic mechanisms of information processing by the basal ganglia in health and disease are still under debate. Here, we first highlight the open questions on information processing by the basal ganglia and then summarize our studies of the simultaneous activity of several neurons in the basal ganglia of normal and parkinsonian primates. Finally,



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we develop the hypothesis that segregation of functional subcircuits and independence of activity is a key feature of normal neuronal processing of the basal ganglia.

## Anatomical aspects of information processing in the basal ganglia

Information processing in neuronal systems is bound by the underlying anatomy. The basal ganglia are part of neural circuits that arise from the cortex, pass through areas of the basal ganglia and the thalamus and project back to the frontal cortex (Fig. 1). A comprehensive description of the cellular organization and anatomical connectivity of the basal ganglia has recently been published[3,4]. Each of the structures in the basal ganglia–thalamo–cortical circuitry is composed of many ($10^4$–$10^{10}$) neurons and is characterized by complex spatio–temporal interactions. Therefore, here we will only highlight the most basic aspects of the anatomy of the basal ganglia (Fig. 1). The striatum serves as the recipient of efferents from most cortical areas, and projects via intrinsic pathways to both basal ganglia output nuclei, the internal segment of the globus pallidus (GPi) and to the substantia nigra pars reticulata (SNr). Neurons from GPi and SNr project to the ventral motor and intralaminar nuclei of the thalamus, which, in turn, project back to the frontal cortex and to the striatum, respectively. Dopamine, released from endings of neurons that are located in the substantia nigra pars compacta (SNc), modulates the activity of striatal cells[5] and therefore of the whole circuit.

The neural networks of the basal ganglia are organized as single-layered elements that are connected by sequential feed-forward connections (Fig. 2A). Most neurons in the nuclei of the basal ganglia are projection neurons, with interneurons forming only a small fraction of the total neuronal population. Even the numerous lateral interconnections in the striatum are functionally weak[6,7]. Additionally, unlike the rich bidirectional connections between related cortical areas[8], the main elements of the basal ganglia circuitry have no direct feedback paths. Thus, while there are massive projections from the cortex to the striatum, and from the striatum to the pallidum, most anatomical studies agree that feedback connections along these lines (from the pallidum to striatum, or from striatum to cortex) can be neglected[3,4].

The degree of segregation between the different circuits that pass through the basal ganglia (Fig. 2) is still a matter of debate[9–12]. There are two extreme views: the first holds that neurons in the output stage of the basal ganglia receive many common inputs (information sharing, Fig. 2, left), whereas the second views the basal ganglia as segregated parallel circuits (Fig. 2, right) with minimal interactions between the parallel pathways.

There is considerable anatomical evidence that supports the first view. The long dendrites of pallidal neurons are completely covered with synapses. Most (80–90%) of these are from the striatum, whereas 5–10% of the synaptic contacts are created by nerve endings from the subthalamic nucleus (STN), and the rest by ending from the thalamic parafascicular nucleus and many other diverse sources. Classically, the wide dendritic arborization of pallidal neurons oriented at right angles to the incoming striatal axons[13,14], and the strong reduction in the number of neurons from the source (striatum) to the globus pallidus (Fig. 2A, left) suggest extensive convergence or funneling at the pallidal level. Funneling of inputs from remote striatal neurons to a focal area in the pallidum was also demonstrated in a recent electrophysiological study[15]. However, this anatomical organization also suggests that the striato–pallidal connection is a divergent system (Fig. 2B, left), with many pallidal neurons receiving synapses from a single striatal axon[16]. Similarly, anterograde tracing studies[11] suggest that the subthalamic projections are uniformly distributed over a vast collection of pallidal neurons, that is, the subthalamo–pallidal connection, also form a divergent system. A high probability of interaction between a single incoming (striatal or subthalamic) axon and pallidal dendrites means that many pallidal cells share the same inputs, indicating that information sharing is the hallmark of pallidal processing (Fig. 2, left).

On the other hand, many recent studies agree that the main circuits that pass through the basal ganglia remain separate under normal conditions (Fig. 2, right). This separation is supported by studies of transneuronal transport of herpes virus that show multiple segregated circuits in the basal ganglia[17] and by anatomical studies that show considerable specificity and

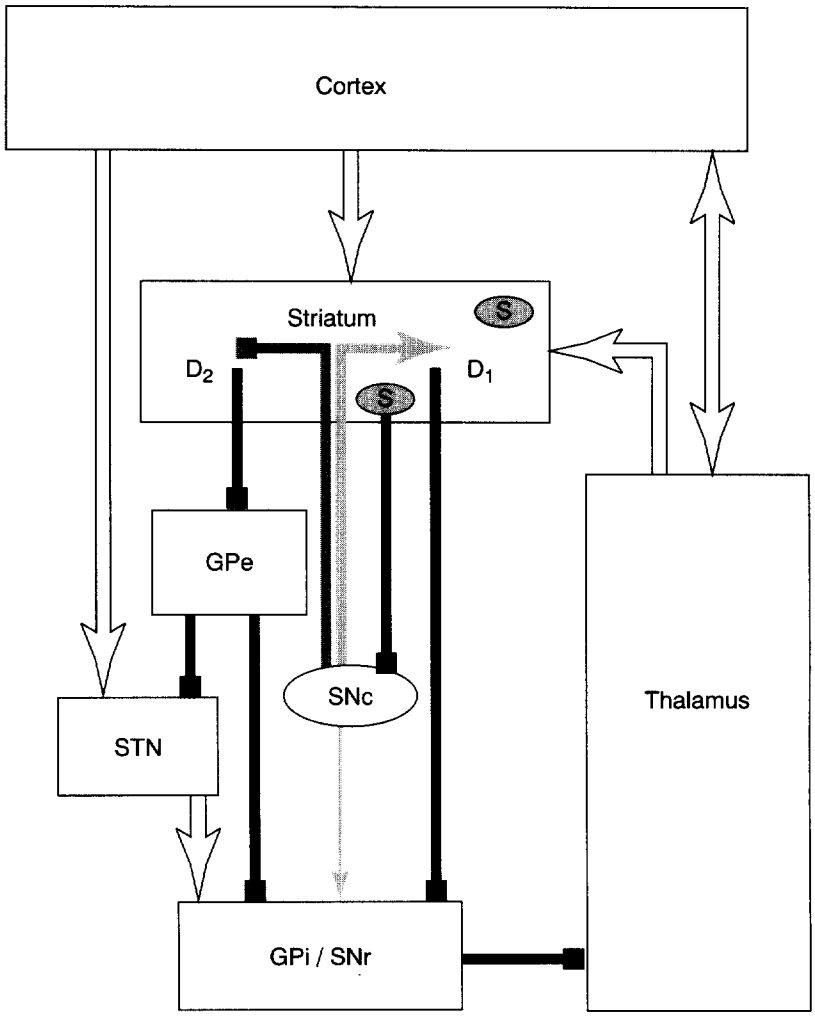


**Fig. 1.** ***The basal ganglia–thalamo–cortical circuits.*** *An outline of the basic circuitry and the transmitters in the basal ganglia. Open lines represent glutamatergic connections, black lines represent GABAergic connections and gray lines represent dopaminergic connections. Lines that end in squares represent probable inhibitory connections (GABA, $D_2$), and lines that end in triangles show probable excitatory connections. Abbreviations: $D_1$, $D_2$, dopaminergic receptors; GPe, external division of the globus pallidus; GPi, internal division of the globus pallidus; S, striatal striosome; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.*

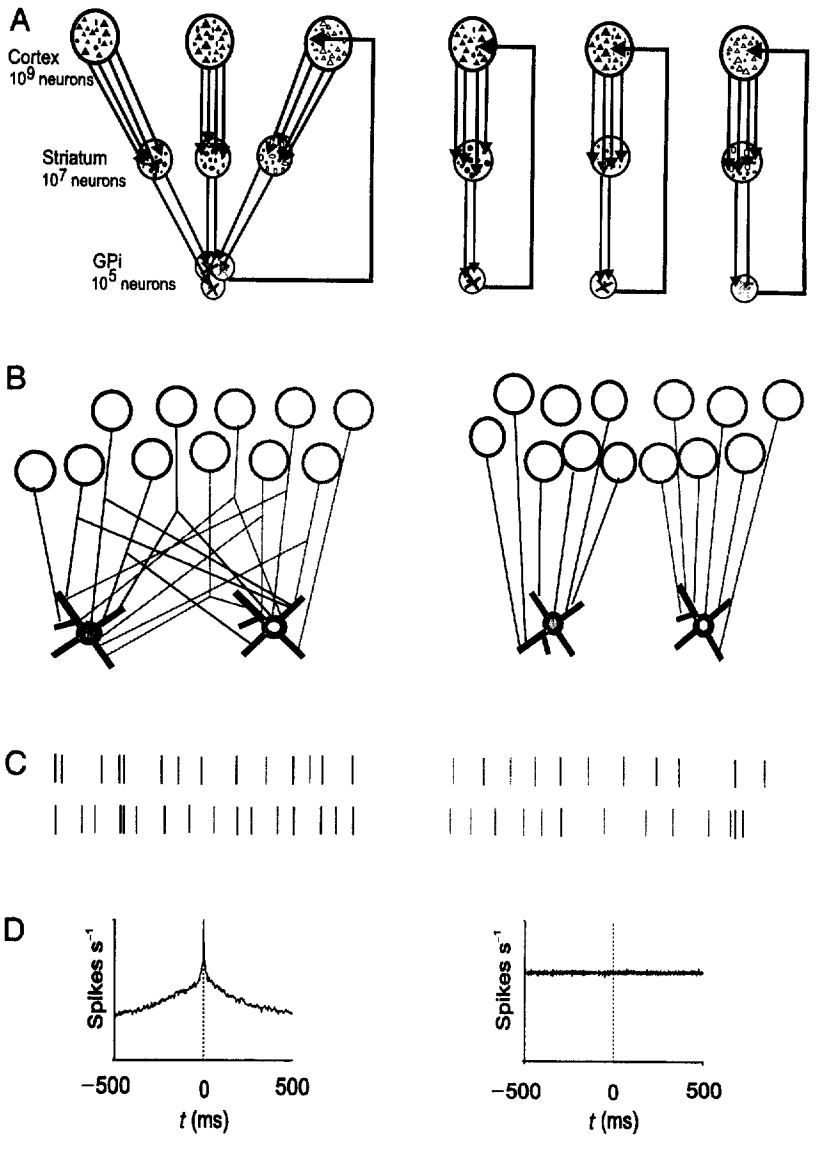


**Fig. 2.** ***Conflicting views of information processing in the basal ganglia: information sharing (left) vs segregated parallel processing (right).*** **(A)** *Schematic diagram of the main axis (cortex→striatum→GPi) of the basal ganglia according to the two views. Approximate numbers of neurons in each of the three structures in the monkey brain are listed at left.* **(B)** *Zooming into the striatum→GPi or STN→GPi connections according to the two models.* **(C)** *Schematic representation of action potential (spike) trains of two pallidal units. According to the model of information sharing (left), the two cells integrate the same information from many input sources, and therefore there are many cases of coincident action potentials (black spikes). According to the segregated parallel model (right), there is no overlap in the incoming information to the two cells, and therefore there are no more coincidences in action potential than chance level.* **(D)** *Predicted cross-correlograms of two simultaneously recorded cells in the globus pallidus. A correlogram with double-sided peak (left) reflects the loose coincidences of the firing of the two neurons, whereas the flat correlogram (right) reflects the independent firing of these neurons. Abbreviations: GPi, internal division of the globus pallidus; STN, subthalamic nucleus.*

topographic organization in the inputs to pallidal neurons[18–21]. Electrophysiological stimulation studies also showed segregation of pallidal neurons that receive inputs from different cortical fields[22]. Finally, single-unit studies that show the absence of pallidal units with clear relation to both arm and leg movements[23] suggest that the segregation might even apply to specific body parts.

## Functional connectivity can be evaluated by cross-correlation methods

The study of cross-correlograms of the discharge activity of pairs of neurons that are recorded simultaneously[24,25] can reveal whether these neurons receive common inputs and whether they directly affect each other's activity. Common inputs lead to many coincident action potentials (Fig. 2C, left), resulting in a double-sided peak in the cross-correlation function (Fig. 2D, left). Flat cross-correlograms, on the other hand, indicate an absence of direct and indirect interactions between the neurons (Fig. 2C,D, right). The two above-mentioned views of neural processing in the basal ganglia therefore give rise to opposite predictions about the mutual activity of pallidal neurons. The information-sharing view holds that neurons in the output stage of the basal ganglia that belong to the same subcircuit share common inputs and their activity would thus be expected to show some correlation. In contrast, the segregated parallel processing view predicts uncorrelated activity of pallidal cells.

We have used such correlation methods to study the degree of segregation between subcircuits that pass through the basal ganglia and to test whether this segregation is modified under parkinsonian conditions. Multiple-electrode recordings (Fig. 3A and Fig. 4A, inset) were made from the basal ganglia of monkeys performing a visual–spatial GO/NO-GO task[26,27]. Whenever possible, spike sorting was used to discriminate

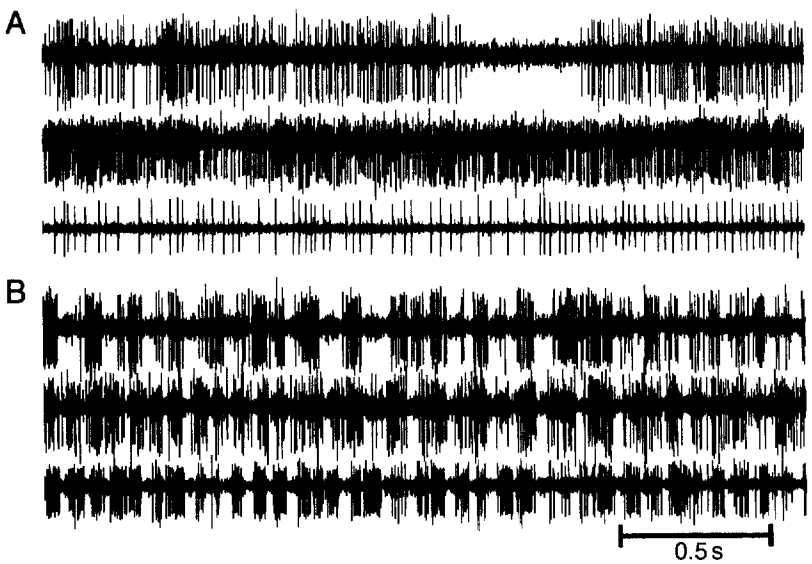


**Fig. 3.** ***Multiple-electrode recordings in the globus pallidus of*** **(A)** ***normal and*** **(B)** ***parkinsonian monkeys.*** **(A)** *An example of 2.5 s of the simultaneous output of three electrodes that were positioned in the globus pallidus of a normal behaving monkey. The upper trace shows the 'high-frequency discharge with pauses' firing patterns typical of GPe cells, whereas the two lower traces are of high-frequency discharge units in the GPi.* **(B)** *An example of the simultaneous recording of three electrodes in the globus pallidus of an MPTP-treated (parkinsonian) monkey. Time scale as in* (A). *Intermittent episodes of synchronous, periodic bursting are seen in about one-third of the recorded pallidal neurons of the MPTP-treated monkeys, but never in the normal monkey. Abbreviations: GPe, external division of the globus pallidus; GPi, internal division of the globus pallidus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.*

between two neighboring units whose electrical activities were recorded by a single electrode[25].

### Firing of pallidal neurons is uncorrelated in the normal monkey

Cross-correlation studies in the pallidum of normal monkeys reveal that pallidal neurons fire independently[26]. Almost none of the cross-correlograms of pallidal cells of normal, awake, nonbehaving[28] and behaving monkeys[26] had significant double-sided peaks (Fig. 4A). Even when two neurons showed covariation of their discharge in response to behavioral events, the normalized spike-to-spike correlations (calculated by subtracting the expected rate covariation[25]) were also flat. The independence of pairs of neurons in the pallidum was not a function of the distance between them. Uncorrelated spiking activity was found between neighboring neurons (recorded by the same electrode, estimated distance less than 200 μm) as well as between remote (distances up to 5 mm) neurons. In contrast, in most other brain areas studied, correlated firing was shown by a significant fraction (20–50%) of neuronal pairs[25,26,29]. Furthermore, we have recently demonstrated[27] an even higher degree of correlation of discharge among striatal tonically active neurons (TANs), which are probably the cholinergic interneurons of the striatum[30]. The exceptional lack of pallidal synchronization suggests that direct lateral interactions between pallidal neurons are ineffective, and that the spike trains of most pallidal neurons are not driven by common inputs.

At first glance, the uncorrelated pallidal activity seems to contradict the anatomical evidence for funneling in the circuitry of the basal ganglia. However, the striato–pallidal funneling projection does not exclude parallel, independent processing[10,15]. Funneling or convergence can be limited to the neurons within one functional subcircuit, and does not necessarily lead to information sharing between neurons in the output stage. Indeed, anatomical studies[3,31] have shown that close pallidal sites can receive inputs from very different striatal areas. Moreover, a recent quantitative study[32] has shown that a striatal axon provides 240 synapses in the pallidum and makes ten contacts with one pallidal neuron on average. Considering the total number of striatal and pallidal neurons (~$10^7$ and ~$10^5$, respectively), the number of striatal synapses on a single pallidal neuron (~$10^4$), and assuming a random distribution of striatal synapses on pallidal neurons, we can calculate the probability that two pallidal neurons receive common inputs from the striatum. This rough estimate gives a probability of 10% for finding two pallidal neurons with ten common synapses (that is, emitted by a single striatal neuron). Even those neurons with ten common synapses still have ~$10^4$ striatal synapses of different origins, suggesting that

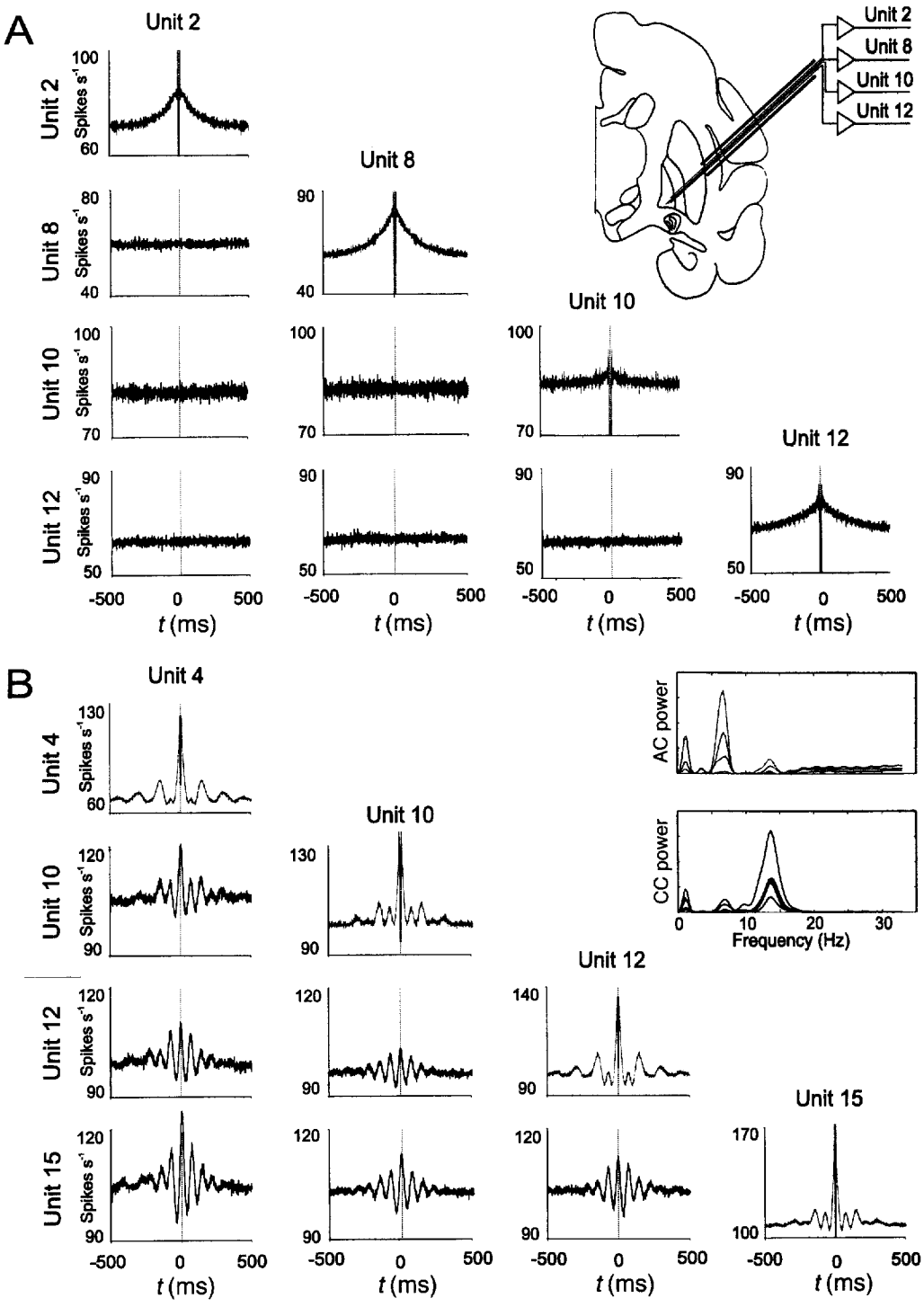


**Fig. 4.** ***Correlation matrices of simultaneously recorded units in the pallidum of normal and parkinsonian monkeys.*** *Correlation matrices in the globus pallidus of* **(A)** *normal vervet monkey and* **(B)** *MPTP-treated tremulous vervet monkey. Multiple-electrode recordings were made during the performance of a GO/NO-GO spatial delayed task. The ID of the trigger units appears in the upper row, and of the reference units in the left column. Each matrix displays all possible correlation pairs, with autocorrelograms (in gray) on the main diagonal. The correlograms were calculated with 1 ms bin. The right insets show* (A) *schematic illustrations of the recording location and electrode setup, and* (B) *the superimposed power spectra of the auto-correlograms (upper) and cross-correlograms (lower) of the units shown in the matrix. Abbreviations: MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.*

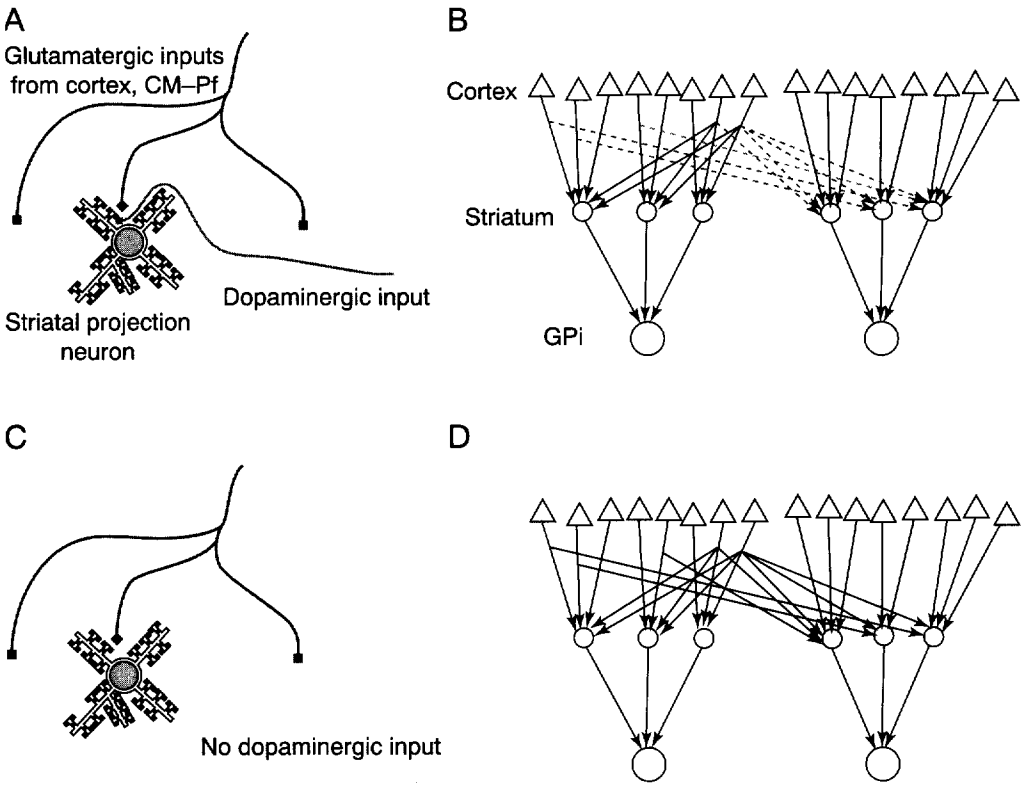


**Fig. 5.** ***Dopamine modulation of functional connectivity in the basal ganglia – a working hypothesis.*** *We hypothesize that the main action of dopamine is to regulate the coupling level between the different subcircuits of the basal ganglia. In the normal state* **(A)**, *dopamine endings on striatal spines can veto divergent glutamatergic inputs to the striatum, thereby reducing the efficacy of cross-connections between channels.* **(B)** *Diagrammatic model of the resulting segregated channels in the normal state. Gray broken arrows represent cross-channel connections with reduced efficacy. Following dopamine depletion* **(C)** *this segregation of afferent channels is lost, resulting in synchronized activation of pallidal cells* **(D)**. *Abbreviations: CM–Pf, centromedian–parafascicular nuclei; GPi, internal division of the globus pallidus.*

pallidal neurons do not share many common inputs from the striatum, despite the strong anatomical convergence from the striatum to the pallidum. The other possible source of common input to the pallidal cells is the STN (Fig. 1). However, it is much harder to inject circumscribed areas or single cells in the STN than in the striatum, and no quantitative descriptions of the branching properties of a single subthalamic axon, or of other pallidal afferents, in the pallidum are yet available.

Be the anatomical connectivity what it may, anatomical connections can give only the 'maximal aperture of the system'[10], whereas the present physiological results suggest that in the normal state, pallidal neurons act independently. Independent activity of neurons maximizes the information content carried by their activity. Our working hypothesis is that neural activity in the basal ganglia reflects certain key elements of information extracted from the more complex information contained in the activity of cortical neurons. Such reduction of information content might be achieved in a way similar to methods of 'dimensional reduction' (for example, principal-components analysis) commonly used by engineers for representing a large set of signals by a smaller set of independent (uncorrelated) vectors. The reduced cortical representations are then sent to the neural networks of the frontal cortex (Fig. 1).

## The physiological basis of the motor symptoms of Parkinson's disease

Parkinson's disease is a very common disorder that affects the elderly and its symptoms are related to abnormal functioning of the basal ganglia[33,34]. Besides problems with initiation and execution of movement (akinesia/bradykinesia), abnormal postural reflexes and muscular rigidity, a low-frequency tremor at rest is seen in many patients. These symptoms can be reproduced in primates treated with the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) dopaminergic neurotoxin. The biochemical, anatomical and clinical changes that are produced by systemic treatment of primates with MPTP resemble those found in humans with Parkinson's disease. The introduction of this reliable animal model has considerably advanced the experimental study of parkinsonism[35].

After MPTP treatment, dopaminergic cells in the midbrain degenerate, depriving the striatum of dopamine[36]. This leads to a prominent increase in neuronal discharge rate[37–39] and sensitivity[40–42] in the internal pallidum. Since the GPi–thalamic projections are inhibitory (Fig. 1), increased GPi discharge leads to inhibition of the thalamo–cortical networks[33,35]. This might also be caused by increased GABA release of neurons in the external segment of the globus pallidus[34]. In any case, it is likely that these changes in activity play a role in the pathogenesis of parkinsonism because inactivation of the STN or GPi improves most parkinsonian motor symptoms[43,44].

The development of parkinsonian akinesia and rigidity is more easily explained by the increase in inhibitory output of the basal ganglia than is the pathogenesis of the tremor. This is because tremor is an oscillatory phenomenon that seems to be unrelated to tonic changes in firing rate. Indeed, many previous models of parkinsonian tremor have placed the origin of the rhythmic neural activity outside the basal ganglia, for example, in thalamo–cortical circuits[45], or offered a thalamic filter mechanism[46] that translates the high-frequency oscillations found in the pallidum of dopamine-depleted rhesus monkeys[37,38,47] into low-frequency clinical tremor. For tremor to originate in the basal ganglia, neurons in these structures would have to discharge in low-frequency periodic bursts. Moreover, there would need to be a substantial coupling between the discharge of these neurons in order to permit the expression of tremor, in contrast to the independent activity in the pallidum of a healthy monkey.

## Synchronous oscillations of basal ganglia neurons after MPTP treatment

Oscillatory activity has been described in several single-unit studies of the thalamus[48,49] and basal ganglia[50] of human parkinsonian patients. Periodic oscillatory activity of both low (4–7 Hz) and high (10–16 Hz) frequency was detected in the STN, GP and striatal TANs of MPTP-treated monkeys[27,28,37,38]. The low-frequency

oscillations were often correlated with the arm tremor. Our cross-correlation analysis of simultaneously recorded pallidal cells in MPTP-treated monkeys revealed that the spiking activities of many of these neurons are synchronized (Figs 3B and 4B). The neuronal oscillations in the pallidum are more in phase in the tremulous MPTP-treated vervet monkey than in the nontremulous parkinsonian rhesus monkey.

Although the MPTP-treated monkeys were not engaged in a behavioral task (owing to their parkinsonian akinesia), the differences in pallidal synchronization are probably associated more with the development of the parkinsonian state than with unavoidable changes in arousal level. Independent activity of pallidal neurons in the normal monkey was detected in all behavioral conditions tested, including behavioral epochs that demand minimal attention (like intertrial intervals or pre-cue periods in the NO-GO mode), and periods when the monkey did not perform the behavioral task. Moreover, oscillatory activity of single units was very seldom encountered in previous studies of the normal globus pallidus even during periods of sleep[51]. Since the appearance of the synchronized activity is highly (but not fully) correlated with the appearance of single-cell oscillations, both are probably due to the MPTP-induced dopamine depletion and the development of the parkinsonian state.

## Concluding remarks

The independent firing of neurons in the output stage of the basal ganglia suggests that normal functioning of the basal ganglia is characterized by uncorrelated activity of their functional subcircuits (Fig. 5A, B). It is further postulated that dynamic reorganization of these functional subcircuits represents part of the neural substrate of innate motor learning[52,53]. After the development of parkinsonian symptoms, the networks of the basal ganglia lose their ability to keep the activity of pallidal neurons independent, and the previously inhibited cross-connections between 'parallel' subcircuits become more active (Fig. 5C,D). Electron-microscopic studies suggest that most dopaminergic synapses in the striatum target the head or neck of a dendritic spine (Fig. 5A), always with a second, probably cortical, synapse located on the same spine head[54,55]. Thus, dopamine can modulate the cross-connections between different cortico–striatal modules and facilitate independent action of striato–pallidal modules in the normal state.

Treatment with MPTP results in both increased synchronization and the appearance of oscillatory activity in the pallidum. Previous studies of intrinsic neuronal oscillators have failed to detect correlated activity, even when the neurons had very similar (±1%) oscillation frequencies[56]. The emergence of synchronized neuronal oscillations and tremor in the dopamine-depleted parkinsonian animal therefore appears not only to be due to changes in the intrinsic properties of the neurons, but also to reflect major changes at the network level of the circuitry of the basal ganglia.

An unsolved problem in basal ganglia and Parkinson's disease research is how stereotaxic procedures such as lesions[43,44] or high-frequency stimulation[57] of various targets in the basal ganglia and thalamic regions improve most symptoms of parkinsonism without impairing voluntary movements[58]. The finding of profound synchronization in the basal ganglia of MPTP-treated monkeys suggests that such elevated synchronization also exists in human parkinsonian patients. We therefore hypothesize that surgical therapies of parkinsonism act by desynchronizing the abnormal basal ganglia–thalamo–cortical network activity. If so, might these findings open new avenues of research into the treatment of Parkinson's disease?

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# Amphibians provide new insights into taste-bud development

R. Glenn Northcutt and Linda A. Barlow

**Until recently, the predominant model of taste-bud development was one of neural induction: ingrowing sensory fibers were thought to induce taste-bud differentiation late in embryonic development. Recent experimental studies, however, show that the development of taste buds is independent of their innervation. In amphibian embryos, the ability to generate taste buds is an intrinsic feature of the oropharyngeal epithelium long before the region becomes innervated. These studies indicate that patterning of the oropharyngeal epithelium occurs during gastrulation, and suggest that taste buds or their progenitors play the dominant role in the development of their own innervation.**

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MUCH OF THE PNS of vertebrates arises from neurogenic placodes and the neural crest, embryonic tissues (Fig. 1) that are hallmarks of vertebrate development and underlie vertebrate origins[1–3]. The role of the neural crest is well documented in the genesis of the sensory ganglia of cranial and spinal nerves, and in the genesis and patterning of such diverse structures as the neurocranium, pharyngeal skeleton, teeth and other epidermal derivatives, including feathers and hair[4–6].

The role of neurogenic placodes, localized patches of tall columnar cells, in the development of the PNS is not as widely appreciated. These placodes form within the head ectoderm of all vertebrate embryos (Fig. 1). The most rostral of these placodes, the olfactory placode, invaginates to form the receptors and nerves of the olfactory complex (olfactory and vomeronasal organs and nerves), as well as the closely associated ganglion cells of the nervus terminalis[7,8]. More caudally situated profundal or trigeminal placodes, or both, contribute neurons to the compound sensory ganglion of the trigeminal nerve[3,9], whose fibers innervate much of the skin of the head. The remaining neurogenic placodes can be divided into a dorsolateral series and a ventrolateral (epibranchial) series, adjacent to the developing hindbrain and pharyngeal pouches, respectively (Fig. 1). The dorsolateral series consists of an octaval (otic) placode that invaginates to form the sensory maculae of the inner ear and the sensory ganglion of the eighth nerve[10], and, in fish and many amphibians, an additional six placodes that give rise to the electroreceptive and mechanoreceptive organs of the lateral-line system and the cranial nerves that innervate these receptors[11–16].

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Epibranchial placodes were initially implicated in the development of the gustatory system, primarily on the basis that they were extremely well developed in embryonic catfishes[17], which develop extensive fields of taste buds that cover their entire body surface. This correlation was subsequently reinforced by the experimental observation that the epibranchial placodes contribute neurons to the sensory ganglia of the facial, glossopharyngeal and vagal nerves[9]; these are the only nerves that innervate taste buds in vertebrates. In spite of this correlation, there is still no experimental evidence of whether the neurons that innervate taste buds arise from the neural crest or epibranchial placodes, or both.

Unfortunately, there are few experimental studies on the development of the gustatory system of vertebrates: manipulation of avian and mammalian embryos is quite difficult at later embryonic stages, and it is precisely during this late phase that taste buds develop. Culture of embryonic tissues of amniotes is also limited to short periods of time, which has further precluded the study of taste-bud development[18,19]. However, amphibian embryos offer an alternative developmental model that avoids many of these difficulties. These embryos are resilient to surgical manipulation at any stage of embryogenesis, and embryonic tissues develop normally in culture for up to several weeks. Embryos of the Mexican axolotl, *Ambystoma mexicanum*, are particularly useful because the embryonic cells of the wild type contain cytoplasmic melanin granules that provide a robust, endogenous marker with which to track the fate of the cells when they are transplanted into albino hosts. A number of recent experimental studies using embryonic axolotls[20–22] have provided new insights into the embryonic origin of taste buds



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