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Oscillators and Oscillations in the Basal Ganglia

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Abstract

What is the meaning of an action potential? There must be different answers for neurons that oscillate spontaneously, firing action potentials even in the absence of any synaptic input, and those driven to fire from a resting membrane potential. In spontaneously firing neurons, the occurrence of the next action potential is guaranteed. Only variations in its timing can carry the message. Among cells of this type are all those making up the deeper nuclei of the basal ganglia, including both segments of the globus pallidus, the substantia nigra, and the subthalamic nucleus. These cells receive thousands of excitatory and inhibitory synaptic inputs, but no input is required to maintain the firing of the cells; they fire at approximately the same rate when the synapses are silenced. Instead, synaptic inputs produce brief changes in spike timing and firing rate. The interactions among oscillating cells within and among the basal ganglia nuclei produce a complex resting pattern of activity. Normally, this pattern is highly irregular and decorrelates the network, so that the firing of each cell is statistically independent of the others. This maximizes the potential information that may be transmitted by the basal ganglia to its target structures. In Parkinson's disease, the resting pattern of activity is dominated by a slow oscillation shared by all the neurons. Treatment with deep brain stimulation may gain its therapeutic value by disrupting this shared pathological oscillation, and restoring independent action by each neuron in the network.

Keywords

striatum; globus pallidus; subthalamic nucleus; Parkinson's disease; deep brain stimulation; phase resetting

The disinhibition hypothesis

On page 3 of his beautifully illustrated book on neural dynamics (Izhikevich 2007), there is a cartoon showing Eugene Izhikevich talking to a neuron across an executive's desk. He tells the nerve cell, "neurons do not fire, they get fired!" His point is that neurons don't fire action potentials independently; their firing is triggered by synaptic inputs. This statement reflects a view of neuronal function that dates back to the beginnings of modern Neuroscience, and was clearly summarized by McCulloch in 1965. He said that by firing, each of our neurons asserts a logical proposition – a true or false statement about the activity of our senses, our internal state, or our motor intention. He emphasized that the logical proposition asserted by

a neuron may not always be true. For example, background firing in a sensory neuron might represent a series of erroneous logical assertions. Propositions asserted by large sets of neurons are combined in brain circuits to make higher order propositions asserted by action potentials in the next layer of neurons in the pathway. In this familiar scheme, the job of the neurophysiologist studying neural coding is to identify the proposition asserted by each neuron when it fires.

Although this is the way we usually describe the operation of the nervous system to our students and our colleagues in computer science and engineering, we know it is not always true. Some neurons are autonomous oscillators; they fire even when they get no synaptic input at all. Synapses do not make these cells fire, but only perturb their ongoing spontaneous activity. The propositions asserted by oscillating neurons must not be encoded in whether they fire or not, but rather in when (or perhaps how often) they fire.

In the most upstream part of the basal ganglia circuit (the striatum) we may be encouraged to think of neurons operating in the classical way described by McCulloch (1965). The striatal output neurons may be quiet for long periods of time, and then fire several spikes in succession, for example during execution of learned motor tasks (DeLong 1973 and many others since). The episodes of firing may have specific meanings in the context of the task being performed. However, the neurons receiving synaptic input from the striatal output neurons cannot be viewed in this way. The downstream parts of the basal ganglia (both segments of the globus pallidus and the substantia nigra) consist of neurons that fire continuously at rates of 20–100 spikes/s (DeLong 1972 and many others since), and continue to do so even in the absence of synaptic input.

It is natural to look for some similarity in the activity of globus pallidus and substantia nigra cells and that of the striatal neurons. The striatal output neurons are inhibitory, using GABA as their transmitter, so one might expect that pallidal and nigral neurons would pause, or at least slow down a little, when bursts of spikes are triggered in the striatal neurons. Maybe pallidal and nigral neurons combine the propositions asserted by their striatal afferents using an inverted logic, with pauses that encode the same events that excite responses in striatal neurons. Because the pallidal and nigral cells are also GABAergic and inhibitory, this would lead to the removal of inhibition in their target neurons. Their targets include the cells in the thalamus and superior colliculus that receive most of the synaptic output of the basal ganglia. This is the now-classic and widely accepted “disinhibition hypothesis” of Chevalier and Deniau (1985a & b). The basic features of the disinhibition hypothesis are shown in Figure 1. It has been tested in a variety of ways, and its prediction have been mostly confirmed (e.g Hikosaka and others, 1993; Nambu and others, 2000). In this model, the constant firing of the globus pallidus and substantia nigra neurons does not carry this structure’s message, but rather generates a constant inhibitory background upon which precisely-timed pauses can encode information.

The disinhibition hypothesis is also the basis of most modern views of basal ganglia pathophysiology, specifically the Albin, Young, and Penny (1989) model and its variants, which continue to be useful today. The extension of the model to pathophysiology has a long history of controversy and much accumulated evidence both pro and con. It is important that

the disinhibition hypothesis was formulated and tested using electrical stimulation of the cortex or basal ganglia structures, not using natural responses, for example during movement. Electrical stimulation has the advantage of producing brief synchronous volleys that generate discrete responses with fixed latencies that can be traced through the circuit. Tracing the progression of responses through the basal ganglia during natural stimulation or movements is less precise. Striatal projection neurons' responses during movements are usually increases in firing, but responses in the pallidum may be increased firing, decreased, or sequences of increases and decreases in firing rates (e.g. Hamada and others 1990). The latencies and durations of responses in all structures are highly variable and hard to compare directly with the results of electrical stimulation (e.g. Mink and Thach 1991).

The subthalamic nucleus as a driving force

In the original disinhibition hypothesis, the origin of the high rate of background firing of pallidal and nigral neurons was not explicitly explained, but was assumed to arise from some excitatory synaptic input. Excitatory inputs to the globus pallidus and substantia nigra are greatly outnumbered by inhibitory ones, but are substantial anyway (see review by Wilson 2013). One prominent source of excitation shared by all of these cells (and known to Deniau and Chevalier) arises from another basal ganglia structure, the subthalamic nucleus. Subthalamic nuclear neurons also fire tonically, although slower than the pallidal and nigral cells (e.g. Wichmann and others 1994). Kitai and Kita (1987) presented the case for the subthalamic neurons as the origin of excitatory input to all the downstream nuclei of the basal ganglia. In addition to explaining the origin of spontaneous activity in these structures, this offered an explanation for some otherwise problematic features of globus pallidus firing. For example, some cells in the globus pallidus pause as expected during movements, but others (especially in the external pallidal segment) show increases in firing rate (e.g. DeLong 1972). These responses are difficult to explain by removal of striatal inhibition, because there are no spiny neurons that respond with decreases in background firing. The subthalamic nucleus receives a strong synaptic excitation from the motor cortex and the details of pallidal responses to synchronous inputs generated by electrical stimulation of the cortex are well explained this way (e.g. Nambu and others 2000; Tachibana and others 2008). The subthalamic input is likely the pathway for bidirectional push-pull control of pallidal firing during movements.

Autonomous oscillations in basal ganglia neurons

There is no doubt that the subthalamic nucleus contributes to transient excitation of pallidal and nigral neurons by synchronous cortical volleys, but it is just as clear that this excitation is not the source of the background activity of pallidal and nigral cells. Globus pallidus cells continue to fire their tonic background activity, even in the total absence of synaptic input. When excitatory and inhibitory synaptic inputs are blocked in vivo by local application of antagonists, (Kita and others 2004), the cells continue to fire at nearly their normal rate. They also fire continuously in slices, even when all their synaptic input is blocked (e.g. Mercer and others 2007). Synaptic inputs, both excitatory and inhibitory, are responsible for the irregularity of firing. When synaptic connections are intact, most cells fire irregularly, but when both excitatory and inhibitory synaptic inputs are blocked, they fire in a rhythmic

clock-like pattern similar to that seen in slices (Kita and others 2004). If synaptic input is not responsible for the high frequency background activity, where does it come from?

The ionic currents responsible for spontaneous firing are nearly the same for neurons in the globus pallidus, subthalamic nucleus and substantia nigra. The dominant one is a sodium current (e.g. Surmeier and others 2005). It arises from the same ion channels responsible for the action potential, but begins to be activated at voltages much below the action potential threshold (Do and Bean 2004). Moreover, this component of the sodium current does not undergo rapid inactivation the way sodium current does during the action potential (Do and Bean 2003). Measurement of this persistent sodium current has been performed for globus pallidus neurons (Mercer and others 2007), neurons in the substantia nigra pars reticulata (Atherton and Bevan, 2005) and in the subthalamic nucleus (Bevan and Wilson, 1999). In all cases, the depolarizing sodium current becomes larger than the opposing potassium current when the membrane potential reaches about -65 mV. The result is a gradual membrane depolarization that begins soon after each action potential. Sodium current increases its edge over potassium as the cell depolarizes, so the rate at which the cell depolarizes increases gradually as it approaches threshold. This produces the characteristic scoop-shaped membrane potential trajectory between action potentials (Figure 2). At the action potential threshold, sodium channels regeneratively activate to levels many times greater than achieved between spikes. The channels then inactivate during the action potential. Also during the action potential, a separate set of high-voltage activated potassium channel force rapid repolarization of the cell membrane. Among these are members of the extremely fast Kv3.1/3.2 family of spike repolarization channels, which enable cells to recover quickly from action potentials as required for high frequency firing (e.g. Baranauskas and others 1999).

Another set of potassium currents are triggered by action potentials but are too slow to contribute greatly to spike repolarization. Instead, these channels open during the first 10–50 ms after an action potential is over. They are responsible for the medium-afterhyperpolarization, which delays the takeover of the membrane potential by the persistent sodium current. The most influential of the medium afterhyperpolarization currents is a calcium-dependent potassium current. This current is triggered by calcium entering the cell during the action potential. It decays as calcium diffuses away from the membrane, where the potassium channels are located (Teagarden, and others 2008; Deister and others 2009). In some neurons, especially in the globus pallidus, recovery from the medium afterhyperpolarization is facilitated by another ion channel, a hyperpolarization-activated cation channel (HCN). This channel is turned on by the medium-afterhyperpolarization, and produces a depolarizing current that speeds the transition of the membrane potential into the activation range of the persistent sodium current. Together, the calcium-dependent potassium channel and the HCN channel produce a precisely timed recovery from each action potential that sets the cell reliably on its way to the next one. Blockade of either of these channels in globus pallidus cells causes the cells to fire more irregularly (Chan and others 2004). Complete loss of HCN current can even lead to the cessation of spontaneous firing (Chan and others 2011).

This sequence of ion channel activations ensures that the cell has no resting membrane potential. At rest, it fires rhythmically. The characteristic irregular firing seen in basal ganglia neurons arises because synapses perturb the resting firing pattern.

Synaptic integration in oscillating neurons

Synchronous excitation by electrical stimulation of excitatory afferents can trigger action potentials in any neuron, but normally basal ganglia neurons receive large numbers of relatively weak asynchronous inputs. Synaptic integration of subthreshold synaptic inputs is often viewed as an arithmetic of probabilities. Subthreshold excitatory synapses make a cell more likely to fire an action potential for a brief time, and inhibitory ones make a spike less likely. These probability changes can sum if they arrive within a narrow time window. The temporal window for summation is set by the ion channels responsible for the resting membrane potential. In neurons that have no resting membrane potential, but rather oscillate at rest, synaptic charge placed on the membrane is not dissipated as the membrane potential returns to a resting state. Instead, that charge becomes incorporated into the oscillation. Depolarizing charges increase the activation of the sodium current driving the cell toward the firing point. Hyperpolarizations add to the current opposing and slowing the progression toward firing. Synaptic currents effectively speed up or slow down the intrinsic progression of the cell toward firing. When the synaptic current is over, the resulting gain or loss of progress in the cell's trajectory is retained. There will be a spike in any case; only the timing is changed. We can think of the cell as a clock, steadily progressing toward an inevitable action potential, and synaptic inputs as briefly speeding up or slowing down the clock (Figure 3). The effective time of the clock is usually called phase, and is estimated as the time since the most recent action potential divided by the average interspike interval.

Oscillating cells are not equally sensitive to synapses at all times in the interval between spikes. The sensitivity to stimulation time is represented by the phase resetting curve (Figure 3). The variation in sensitivity depends on the size and direction of oscillating currents active when the synaptic input arrives. During the depth of the spike afterhyperpolarization immediately following an action potential, the current generated by a small synaptic current is overwhelmed by the large afterhyperpolarization current and synapses are relatively ineffective, regardless of whether they are excitatory or inhibitory. Likewise, during the last moments of the interspike interval, when the action potential currents start to ramp up, synaptic currents may have practically no effect. Between these limits, all synapses influence the time of the next action potential, with their relative effectiveness depending on the details of the oscillatory mechanism (e.g. Wilson and others 2014).

Most of the impact of a brief synaptic input is restricted to the interspike interval in which it arrives. This happens because the action potential and spike afterhyperpolarization currents are very large and when they are over, they return the neuron to about the same starting point on each cycle. The action potential erases most of the effects of synaptic inputs that arrived before the spike.

A network of coupled oscillators

The interactions among oscillating neurons give rise to spontaneous patterns of neuronal activity. The background pattern of activity in the subthalamic nucleus, globus pallidus and substantia nigra is mostly not imposed on them by the striatum or cerebral cortex. Instead these nuclei form a network of coupled oscillators that can be expected to spontaneously generate an ongoing pattern of activity (Terman and others 2002). The striatal and cortical inputs to this coupled network should exert their effects by perturbing the autonomous pattern.

The pattern of the autonomous background activity depends greatly on the anatomical arrangements of neurons in the circuits. One critical factor is the divergence of pathways -- how many pallidal neurons are contacted by each subthalamic cell and how many subthalamic neurons are contacted by each pallidal neuron. Another key factor is whether oscillators in each nucleus are connected to one another, as they are in the globus pallidus, subthalamic nucleus and substantia nigra, and the divergence of those connections. Much of this critical information is not known, although some pieces of it are starting to become available (e.g. Baufreton and others 2009). Also, the function interactions between coupled oscillators can be counterintuitive and difficult to predict. In the pallido-subthalamic system there are several different cell types whose oscillations are coupled by synaptic interactions. In the external segment of the globus pallidus, oscillatory pallidal cells are connected to each other by inhibitory synapses. They also inhibit oscillatory cells of the subthalamic nucleus, which project back to the globus pallidus to excite the pallidal cells. Both excitatory subthalamic neurons and inhibitory external pallidal neuron exert a powerful influence on the oscillating output neurons of the internal segment of globus pallidus and the substantia nigra. The dynamics of the circuit are complex because the phase-dependent interactions between oscillators go in both directions. As one oscillator perturbs the other, that change feeds back onto the first one. There is no guarantee that any constant pattern will emerge; the cells could produce changes in each others' firing that never settle down. On the other hand, there are some simple potential outcomes. For example, two connected cells might entrain to each other, and become phase-locked.

A network oscillation will emerge in any large network of cells that entrain in synchrony. That is, any pair of cells will tend to fire together. However, phase locking does not require that cells fire synchronously. Cells might phase-lock out of phase with each other. For example, in antiphase the cells' times of firing are as different as they can possibly be. In the globus pallidus, inhibitory interconnections between the neurons cause the cells to phase lock in antiphase (Figure 4). If a third cell were added to this network it would not be able to lock its firing in antiphase with both of the other two. This influence contributes to the tendency for the local network in the globus pallidus to resist the generation of a network rhythm (Wilson 2013).

Phase locking also does not require that the cells intrinsic oscillations are at the same frequency. If cells excite each other, the faster one may be able to speed the slower one enough for them to become entrained. If they inhibit each other, they may slow each other to a shared compromise rate. If they cannot sustain a stable shared rate, they might still phase

lock if their rates are rational multiples of each other. For example, if the faster cell is firing at twice the rate of the other, the slower one may only fire on average 1 cycle to the other cell's 2, but always at the same relative phase. Of course, in the presence of inputs from many cells (of the same and other types), phase locking to any particular periodic input is constantly disrupted. This is what produces the strong dependence of these networks on the details of connectivity. In mean field models, in which cells of a type are treated as effectively a single firing rate, network oscillations readily emerge (e.g. Holgado and others 2010). A cell-level model of the subthalamo-pallidal interaction showed that these structures could produce a wide range of intrinsic activity patterns, depending on the connectivity of neurons in both structures, the strength of their synaptic connections, and the level of extrinsic excitation and inhibition (Terman and others 2002). Among the patterns that emerged from that interaction were some that might be considered anti-patterns. They were very disorganized irregular patterns of activity with no discernible repeating structure in time or in position across the nucleus. These disorganized patterns were not noise.; noise was not added to the model. Instead, they were deterministic, actively generated patterns that produced a different and apparently independent firing pattern in each pallidal and subthalamic neuron. These results from the model are interesting because they match the normal relationship between neurons in the globus pallidus and subthalamic nucleus. Neurons in these nuclei show little or no spike timing correlation, even among neurons located very near each other, and probably share common sets of inputs and having similar sensory and motor responses during movement (see review by Wilson 2013). This decorrelation of activity in the basal ganglia output nuclei maximizes the potential information capacity of the basal ganglia.

Parkinsonism - Oscillations gone wrong

It is strange that the oscillatory nature of pallidal, nigral, and subthalamic neurons might be responsible for the prevention of synchronous network oscillations. In many other brain regions, neuronal oscillations give rise to network patterns of activity, rather than active desynchronization (Buzsaki 2006). In the basal ganglia, synchronized network oscillations do occur, but they are pathological.

Basal ganglia network oscillations are a signature feature of Parkinson's disease and are closely related to the pathophysiology of the disorder (e.g. Brown 2007; Brittain and others 2014). Recordings from human Parkinson's disease patients undergoing surgical treatment for the disease show oscillations in the local field potential, and in single unit activity in the globus pallidus and subthalamic nucleus. Some animal models of the disease show similar oscillations, especially African green monkeys made parkinsonian by treatment with MPTP (e.g. Rivlin-Etzion and others 2010). The dominant frequency of the oscillations is in the beta (13–30 Hz) range. For pallidal cells, this means that neurons are firing on average faster than the pathological oscillation, and individual cells fire more than once on each cycle. The oscillation appears as a rate modulation, or in extreme cases, as rhythmic bursting. In the subthalamic nucleus, where firing rates are closer to the beta frequency, parkinsonism is accompanied by an increased average firing rate and increased tendency of the cells to burst. There the beta oscillation appears as bursting phase-locked to the field potential but not necessarily occurring on every cycle. The field potential in basal ganglia structures is not as

easily interpreted as field potentials in layered structures like the olfactory bulb or hippocampus, but as in those structures it probably reflects the sum of synaptic currents flowing in the vicinity of the recording electrode.

What synapses are responsible for the oscillating synaptic current? This is not a simple question to answer experimentally. The problem is that there are too many candidates for the job of oscillatory driver. In the subthalamic nucleus for example, there are few (perhaps no) local connections among the neurons, so the oscillating synaptic currents must come from afferents. One obvious source is projections from the external segment of the globus pallidus, where we know the neurons' firing is also oscillating. However, the other major input, from the cerebral cortex, also has the parkinsonian oscillation (Goldberg and others 2004). A similar surfeit of sources for the oscillation occurs in the globus pallidus. There the oscillation could be generated by excitatory afferent synapses from the subthalamic nucleus, or inhibitory ones from the striatum or from the other neurons in the globus pallidus. Neurons in the external segment of the globus pallidus inhibit the subthalamic nucleus and also make local inhibitory connections on one another and inhibit neurons of the internal segment and substantia nigra. Thus the external segment of the globus pallidus, like the subthalamic nucleus, could be a driver of oscillation in all the related nuclei. In neuronal circuits that form loops, it is very difficult to determine which neurons are driving the oscillation, and which are being driven.

One approach to distinguishing driver from driven would be to isolate individual cells or small groups of cells in a parkinsonian animal from specific components of their synaptic input, and determine whether those cells were still components of the oscillating system. For example, would a subthalamic neuron continue to show parkinsonian beta oscillation after it was deprived of its cortical input but had its pallidal input intact? Would a pallidal neuron still have the beta oscillation in the absence of input from the subthalamic nucleus, even if its striatal and local connections were still there? Tests of this kind were performed by Tachibana et al (2011) using single unit recordings in monkeys made parkinsonian using MPTP. Parkinsonian oscillations were measured as instantaneous rate modulations in the firing of the neurons. Most of the experiments did not rely on a complete blockade of oscillations throughout the basal ganglia, which is difficult to achieve and impossible to verify. Drugs were injected into the brain in the vicinity of the recorded neuron and were only required to affect that neuron.

When Tachibana and others injected glutamate antagonists to block cortical input (and other fast excitatory inputs) to a subthalamic neuron its firing rate did not change, and its bursting actually increased. However, the parkinsonian oscillation was clearly decreased, indicating that cortical inputs contribute to the oscillatory input to subthalamic nucleus cells, but they were not required to keep the cells firing at their normal rate. During similar blockade of fast synaptic excitation to neurons of the external globus pallidus, the parkinsonian beta oscillation in that nucleus was mostly blocked. In contrast, application of the GABA receptor antagonist gabazine into the vicinity of recorded neurons in the external pallidal segment (depriving them of striatal and local inhibition) did not alter the beta oscillation of those neurons. Thus the external segment neurons interacting with each other via their inhibitory interactions can be eliminated as a potential generator of the

parkinsonian oscillation. It should also be noted that this result also eliminates oscillatory striatal inhibition as a cause of the parkinsonian oscillation. A similar result was obtained in pallidal internal segment, where local loss of excitatory input blocked the parkinsonian oscillation. Because the synaptic blockade was localized to the vicinity of the recorded neuron, it is likely that this treatment did not alter the oscillation of neurons in the external segment. Local blockade of GABAergic inhibition (mostly from the striatum and external pallidal segment) in the internal segment significantly increased the beta oscillation. These results indicate that the oscillation of internal pallidal segment neurons, like that of external segment, is driven by excitatory inputs to the (probably from the subthalamic nucleus), and not by oscillatory inhibition from striatum or external pallidal segment. A final question is whether inhibitory feedback from the external segment is required to generate the beta oscillation in the subthalamic nucleus or whether the neurons in that nucleus are simply driven by the cortical oscillation. This question was approached in a different way. Instead of blocking GABAergic transmission in the locale of recorded subthalamic nucleus neurons by local microinjection, Tachibana and colleagues (2011) made larger injections of the GABAergic agonist muscimol into the pallidal internal segment in an attempt to silence the entire nucleus, not just to block feedback inhibition to in a local region. These injections strongly reduced the parkinsonian bursting in subthalamic neurons, and also reduced their parkinsonian oscillation. Although it is impossible to verify the completeness of the block of pallidal activity, the positive result suggests that the mechanism of pathological subthalamic and pallidal bursting in parkinsonism relies largely on feedback between the subthalamic nucleus and the external pallidal segment. The parkinsonian oscillation depends both on this mechanism and on oscillations in the cortical (and perhaps other) excitatory inputs to the subthalamic nucleus, which can be expected to reinforce each other.

Although these experiments help to pin down the location of the parkinsonian oscillation generator, they do not provide a mechanism for the oscillation. We know which nuclei are required, but we don't know what has changed in Parkinson's disease. If the basal ganglia can make this beta-frequency oscillation, why don't they normally do it? One possibility is suggested by the normal lack of correlations in basal ganglia neurons. The parkinsonian oscillation is a synchronous network oscillation. Perhaps the mechanism of the oscillation is always present, but its expression is prevented by active decorrelation of neurons in the network. The loss of the decorrelating mechanism might arise from changes in the connectivity or strength of connections between or within nuclei. Changes in connectivity and synaptic strength have been observed in experimental parkinsonism (Fan and others 2012). The decorrelation mechanism may also depend on the presence of autonomous oscillations in the basal ganglia nuclei (Wilson 2013), and the mechanisms responsible for that oscillation are apparently weakened after dopamine depletion (Chan and others 2011).

Deep brain stimulation - Fighting fire with fire

One of the most effective treatments for Parkinson's disease is deep brain stimulation – high frequency periodic stimulation of the subthalamic nucleus or globus pallidus (either segment). This treatment was originally thought to work by paradoxical inactivation of the subthalamic nucleus neurons, but it is now clear that axons of those cells (and other axons in the vicinity) are directly driven by the stimulus (McIntyre and others 2004). At least part of

the therapeutic mechanism of deep brain stimulation is apparently the disruption of synchronous bursting and pathological oscillations in the basal ganglia output neurons. Not all symptoms of Parkinson's disease originate in the basal ganglia, and some symptoms may be relieved because of direct stimulation of cortical axons near the subthalamic nucleus but unrelated to the basal ganglia (Johnston and others 2012). However, some of the positive effects of deep brain stimulation are apparently due to disrupting the pathological beta oscillation. One hint is the fact that stimulation is effective in both the subthalamic nucleus and the globus pallidus. The axonal pathways present in both of these structures are likely to be important targets of therapeutic stimulation. Among the axons present in both the subthalamic nucleus and globus pallidus are the axons of subthalamic and external pallidal neurons.

How might deep brain stimulation disrupt the pathological oscillations in Parkinson's disease? Deep brain stimulation is rife with paradox. It is itself an oscillation imposed on the brain by the periodic nature of the stimulation; non-periodic stimulation at the same mean frequency is not effective (Dorval and others 2010). It is also frequency-dependent. It is not surprising that stimulation in the beta frequency range is not helpful, and may in fact make parkinsonian symptoms worse (Chen and others 2007). It is not fully explained why the ideal frequency is so high, 5–6 times the beta range, and about 50% higher than the sustained firing rate seen in the basal ganglia output neurons. One possibility is raised by the periodicity of the deep brain stimulus itself, and its interaction with the intrinsic oscillation of basal ganglia neurons. Unlike neurons with a resting membrane potential, oscillating neurons driven by periodic stimuli need not be entrained by their inputs, but can exhibit a wide range of responses. Among them is a highly irregular pattern, in which each individual neuron goes its own way, and synchrony in the population is lost (Wilson and others 2011). This pattern arises when oscillating cells are driven by a periodic input that is between 1 and 2 times their native frequency of oscillation. One intriguing possibility is that deep brain stimulation triggers the generation of a highly irregular and decorrelated pattern in the oscillatory subthalamo-pallidal network. While not the natural resting activity pattern of the network, it may be similar in that it prevents resting correlations among neurons, partly restoring the information capacity of the basal ganglia signal to the rest of the brain (Wilson and others, 2011).

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Figure 1.
The Disinhibition Hypothesis, schematically showing some the relevant synaptic circuits and their characteristic responses to cortical stimulation (at arrow).

Figure 2. mechanism of oscillation of basal ganglia neurons. A. The membrane potential trajectory of a subthalamic neuron firing rhythmically in a slice in the absence of synaptic inputs. B. Ionic currents responsible for the intrinsic resting oscillation of the cell membrane.

Figure 3.

synaptic influence on spike timing. A. Membrane potential of a subthalamic nucleus neuron perturbed by an evoked synaptic excitation at time t_{stim} following an action potential. As a result, of the synaptic input the progression of the cell toward firing is advanced, and the cell fires earlier by amount ΔISI . Both t_{stim} and ΔISI can be converted to phase units by dividing by the average interspike interval (ISI). The inset illustrates the cell's progression to firing on the circle, in phase units, where firing occurs at phase 0. The stimulus causes a shift in cell phase which is retained and appears as an early action potential. B. The phase shifts caused by many synaptic inputs delivered at various phases. The phase shift for the stimulus (scaled by stimulus size) is used to generate a phase resetting curve, illustrating the phase-dependency of the synaptic effect (Wilson and others 2014).

Figure 4.

Antiphase firing of pair of globus pallidus cells connected by artificial inhibitory synapses. The traces show a paired recording from globus pallidus cells connected reciprocally using the dynamic clamp technique. Each time one cell fires, the dynamic clamp circuit creates an artificial inhibitory synaptic conductance and IPSP in the other. Also note spontaneous IPSPs in one of the cells (at arrowheads), probably arising from a natural synaptic inhibition from another (unseen) globus pallidus neuron firing at about the same rate.