Neuronal Oscillations in the Basal Ganglia and Movement Disorders: Evidence from Whole Animal and Human Recordings

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Neuronal oscillations underlie a number of physiological processes, such as respiration, diurnal rhythms of the sleep–wake cycle, and gait. Oscillatory activity can be observed in many different brain regions and can be synchronized across these different regions or nuclei. Oscillatory activity has long been recognized in the electroencephalogram (EEG), in which synchrony between thalamus and cortex can be observed at different frequencies. These oscillations are generally subdivided into types on the basis of their characteristic frequency and location, such as theta (2–7 Hz), alpha (7–13 Hz in visual cortex), beta (11–30 Hz), and gamma (30–80 Hz), and mu (7–12 Hz, sensorimotor). Recent studies in animals and humans have revealed the existence of several types of oscillatory activity in the various nuclei of the basal ganglia and, although still poorly understood, are believed to play an important function in both the normal physiology and pathophysiology of this system. This mini-symposium will describe the findings of recent studies that have examined various aspects of oscillatory activity in the basal ganglia.

In the past decade, there has been an increase in basal ganglia surgery for movement disorders, primarily for Parkinson’s disease, but also dystonia and Huntington’s disease, which has provided a unique opportunity for neurophysiologists such as William Hutchison and Jonathan Dostrovsky to probe these subcortical structures in the clinical setting. Although previous surgeries involved the stereotactic placement of lesions in the brain, the era of neuroablative procedures has given way to “neuroaugmentive procedures” involving chronic indwelling electrodes implanted for deep brain stimulation. Many centers use microelectrodes to map the basal ganglia targets in the internal globus pallidum (GPI) and, more recently, the subthalamic nucleus (STN). During the course of these mapping procedures, it became evident that oscillatory activity could be detected in the firing of individual neurons in these structures, particularly in the patients with tremor (Hutchison et al., 1997, 1998; Levy et al., 2000, 2002a,b), and this was also reflected in the recordings of rhythmic activity in local field potentials from the relatively large contacts of the deep brain stimulation leads (Levy et al., 2002).

Before and concurrent with this clinical work, animal models of Parkinson’s disease, such as the 6-hydroxydopamine (6-OHDA) rat model and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model, have made, and continue to make, a substantial contribution to our knowledge of the underlying neurophysiological changes that give rise to the pathophysiology of the disease (Raz et al., 1996, 2000; Ruskin et al., 1999b, 2003; Goldberg et al., 2004). These changes include increases in firing rate, a tendency to fire in a more irregular pattern, and abnormal oscillatory synchronization.

The canonical model of basal ganglia dysfunction proposes that alterations in neuronal firing rates underlie the spectrum of movement disorders. For the specific example of Parkinson’s disease, there is decreased activity of the inhibitory direct pathway connecting the basal ganglia striatal input to its output in the GPI and increased activity in the so-called indirect pathway via the external globus pallidum (GPe) and STN (Fig. 1). The net effect of this imbalance between the pathways is to elevate the firing rate of inhibitory neurons in GPI that project to important premotor structures, such as the thalamus. Inhibition of premotor centers explains the symptoms of akinesia and bradykinesia but does not as easily explain tremor or rigidity. However, animal and patient studies report only small increases in GPI firing rates in the order of 10–22% in the parkinsonian state (Hutchison et al., 1994; Wichmann et al., 1994, 1999; Levy et al., 2001). Another prediction of the rate model is that hyperkinetic movements, such as dystonia and chorea, are related to low firing rates in GPI output neurons, but recent observations indicate that the GPI activity is similar to that in Parkinson’s disease (Hutchison et al., 2003). Other studies also question the predictions by this model of...
changes in firing rates because many basal ganglia neurons have been shown to have intrinsic pacemaker-like properties that set the rate of firing in the absence of synaptic connectivity (for review, see Bevan et al., 2002).

Effort has now shifted to examining firing patterns and especially synchronous oscillations in the basal ganglia of movement disorder patients to further our understanding of the pathophysiology of abnormal movements (Fig. 1B). One puzzle in the surgical treatment of movement disorders has been why a lesion and electrical stimulation should produce the same therapeutic effect when one obliterates the tissue and the other excites the tissue. The rate model does not reconcile this contradiction, but a model based on network oscillations predicts that either a lesion or deep brain stimulation would disrupt these pathological oscillations, leading to an improvement in symptoms. Pathological oscillatory activity in the alpha frequency (3–7 Hz) develops in the basal ganglia network, especially in the GPi and in the STN, after MPTP treatment in some monkeys and is also present in the GPi and STN of Parkinson’s disease patients with tremor at rest. In addition to tremor-related oscillations, higher-frequency oscillations in the beta range (15–25 Hz) can be observed in the STN and pallidum even in patients without tremor. However, the relationship between pathological oscillatory activity and the Parkinson’s disease symptoms such as bradykinesia and akinesia is unclear.

In addition to the alpha and beta range oscillations, slower oscillations in basal ganglia activity have been recorded by Judith Walters in the 6-OHDA rat model. Their relationship to normal motor control or Parkinson’s disease pathophysiology is less readily understood. Connectivity modeling based on the STN–GPe network indicates that slow oscillations may also arise as a property of neuronal networks (Terman et al., 2002). Two types of slow oscillation have been studied. Slow oscillations at 0.3–2 Hz are often observed in basal ganglia recordings of both local field potential and single-unit activity in anesthetized rat preparations. Ultraslow, multiscale oscillations (2–60 sec and longer) are frequently seen in basal ganglia recordings from awake immobilized and partially restrained rats. Alterations in dopamine receptor stimulation induce dramatic changes in the properties of these oscillations and the relationships between single-unit activity and local field potentials (Hu et al., 2003, 2004). The slow oscillations appear to be more prominent in the firing pattern of basal ganglia neurons of dopamine-depleted rats and are correlated with the local field potentials recorded in cortex and basal ganglia. In contrast, the ultraslow oscillations appear to be enhanced by increases in dopaminergic stimulation, with a greater degree of correlation both within and between various basal ganglia nuclei [GP and substantia nigra pars reticulata (SNr)] on these multiscale timescales (Ruskin et al., 1999a,b, 2003). Lesioning the STN was not found to alter the genesis or transmission of these ultraslow oscillations but did affect dopamine agonist-induced modulation of mean firing rate, oscillatory period, and phase relationship between GP and SNr. These data further support a role for dopamine in modulating coherent oscillatory activity in the basal ganglia and for the STN in shaping the effects of dopamine receptor stimulation on basal ganglia output.

The general view from the movement disorders literature is that basal ganglia oscillations are pathological, but Richard Courtemanche has studied a possible normal physiological function for such oscillations in basal ganglia networks in relation to cortical control of movement (Courtemanche et al., 2003). In the study to be discussed, simultaneous recordings were made with up to eight microelectrodes placed in different parts of the striatum of normal monkeys at rest. Oscillatory activity of the local field potentials in the beta band was observed and was synchronized across many or all of these electrodes, indicating a global synchronization in the striatum. This oscillatory activity was different from simultaneously recorded cortical frontal eye field local field potentials. Single-unit recordings from these same electrodes showed that some cells tended to fire at a specific phase value of the local field potential. Monkeys were also trained to make saccadic eye movements to visual targets, and, as the monkeys performed saccades, the beta-band oscillations decreased across all electrodes. Local field potential synchronization across sites also showed a task-related decrease, yet only for sites that were neuronally engaged in the task, as evidenced by local mul-

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**Figure 1.** A, Schematic figure of the rate model of Parkinson’s disease. The major nuclei of the basal ganglia, the predominant connections, and the neurotransmitters involved are depicted. Information flow is implied by the arrows. In this model, changes in neuronal activity attributable to loss of striatal dopamine are indicated by thick (increased) and thin (decreased) arrows. In Parkinson’s disease, activity in the direct pathway from striatum to GPi/SNr is decreased and that in the indirect pathway via GPe and STN is increased, leading to increased firing rates in the output. This inhibits premotor centers, such as thalamus, that facilitate corticospinal motor output. B, Schematic figure of the oscillation model of Parkinson’s disease. In the absence of dopamine in the striatum, pathological oscillations arise or are enhanced in the basal ganglia, which rhythmically drive other regions or nuclei (depicted by arrows). Frequencies under 10 Hz (i.e., rest tremor frequency at 3–7 Hz) arise in the basal ganglia and spread to the cortex leading to an antikinetic effect. The STN is driven by oscillations in the cortex in the beta band (11–30 Hz) that can also be considered antikinetic. Oscillations in the gamma band (>70 Hz) that facilitate movement (prokinetic) are suppressed or absent in Parkinson’s disease (thin blue arrow). Thal, Motor thalamus; glu, glutamatergic (excitatory) pathway; GABA, inhibitory pathway.
activity. If so, the local field potential oscillations could serve the 
train more neurons to give rise to pathological oscillatory spike 
in-phase with the oscillations. In pathological conditions, such as 
as the monkeys rested, showed that some striatal neurons fired 
simultaneously recorded local field potential oscillations, made 
chrony were maintained. Comparisons of spike timing and the 
motor fixation before saccades were made, high levels of syn-
chrony were maintained. Comparisons of spike timing and the 
increased with daily injections of MPTP but occurred later than the 
onset of bradykinesia. These two facts taken together [(1) the 
inter-individual variability and (2) the lack of correlation be-
tween the occurrence of motor impairment and the significant 
increase of synchronized oscillations] argue against a direct re-
tention between the pathological oscillatory activity and parkin-
sionian bradykinesia. However, it raises the question of the rela-
tionship between these 4–9 Hz and 11–14 Hz oscillations and parkin-
sionian tremor because tremor onset can occur simulta-
neously or even can precede bradykinesia in parkinsonian pa-

A recent study by Joshua Goldberg set out to examine the relationship between neuronal synchronization and local field 
entials in the basal ganglia of MPTP primates (Goldberg et al., 
4). Because cortical local field potentials are a reflection of 
synchronous neuronal activity that gives rise to the waveforms of 
EEG, it is likely that the local field potentials recorded in the 
basal ganglia reflect synchronous spiking activity in these nuclei. 
Enhanced neuronal synchrony is an established correlate of par-
kinsonism (Raz et al., 1996, 2000; Hurtado et al., 1999; Levy et al., 
2000, 2002; Goldberg et al., 2002). Using the correlation-based 
method of partial spectra analysis, this study demonstrated that the 
abnormal oscillatory (~10 Hz) correlations between pairs of 
urons in the basal ganglia in the MPTP condition could be 
statistically accounted for to a large extent by the coupling of each 
uron to the local field potentials. One interpretation of this 
finding is that, in the parkinsonian condition, the basal ganglia 
and cortex become more closely entrained by global brain dy-
namics, which are reflected in the widespread local field 
entials.

One hypothesis put forth by Peter Brown is that the oscilla-
tions in the beta band are enhanced to such an extent in Parkin-
sion’s disease and that voluntary movements are not generated 
because the motor command for initiation cannot override the 
enhanced oscillatory state (Fig. 1B). The desynchronization in 
beta band required to initiate movement cannot “break through” 
the elevated threshold, leading to the poverty of movement char-
acteristic of the disorder. In this model, both dopaminergic med-
ication and STN stimulation are hypothesized to decrease the 
pathological oscillations and facilitate movement in parkinson-
ian patients by decreasing the beta band and enhancing the 
gamma band. Several studies from Dr. Brown’s group have sup-
ported this theory (Brown, 2003). In one recent study, Parkin-
sion’s disease patients made voluntary movements on a go/no-go 
task while local field potential recordings were made from the 
contacts in STN (Kuhn et al., 2004). Beta band activity decreased 
just before movement onset on the “go” tasks in which move-
ments were executed, and the onset of the desynchronization 
correlated with reaction time latencies on the task. In the no-go 
task, there was only a transient decrease in beta power, which 
rebounded. These results draw a closer link between the genera-
tion of voluntary movement and the beta-band desynchroniza-
tion in STN.

Following on from this hypothesis, electrical stimulation at 20 
Hz should produce an enhancement of beta synchronization in 
the basal ganglia, which should exacerbate Parkinson’s disease 
symptoms (“antikinetic”), and stimulation in the 60–80 Hz 
range should enhance movements (“prokinetic”). Indeed, recent 
work from Brown’s group indicates that STN stimulation at 20 
Hz increases GPi synchrony (Brown et al., 2004). Whether this 
increased synchrony is associated with an anti-kinetic effect was 
not directly determined, because assessment of motor behavior 
in these patients would have resulted in desynchronization at 
beta-band frequencies and confounded the measurement of syn-
chrony. Stimulation of the STN at higher frequencies (>70 Hz) 
had the opposite effect on GPi, that is, it suppressed the sponta-
neous ongoing local field potential oscillations in the 11–30 Hz 
range. High-frequency STN stimulation is well known to pro-
duce relief of Parkinson’s disease motor symptoms. Because 
much of this evidence is correlative and circumstantial, addi-
tional studies in patients and experimental models of Parkinson’s 
disease are warranted (Brown et al., 2004).

In summary, it is becoming increasingly clear that the basal 
ganglia sustain certain cortically derived oscillations, as detected 
in the recordings from individual neurons and local field poten-
tials. The functional significance of oscillations in this range of 
frequencies remains to be elucidated and will shed light on the 
pathophysiology of movement disorders and solve some of the 
puzzles of therapeutic surgical intervention.

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