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Neurophysiology/Circuitry

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INTRODUCTION

Theories of the role of the basal ganglia within the functional circuitry of the basal ganglia-thalamic-cortical system are entering a state of flux. Current theories, while of heuristic value in explaining many observations, are now inconsistent with an expanding body of knowledge. Most likely, observations supportive of the current theories and their associated circumstances will be found to be special cases of a larger new theory. There is no new general theory yet proposed that is a clear successor. Consequently, there is considerable value in analyzing the epistemic basis of current theories, if for no other reason than avoiding the types of inferences that, in retrospect, are erroneous. Also, such an exercise may help to form a framework by which new theories can develop and be judged. As Charcot said, "we see only what we are ready to see" (1). Typically this statement is made in retrospect to explain why observations and insights are missed or late in being made. A better use would be to prepare prospectively to facilitate new observations and insights. Such preparation must necessarily be theoretical and, to some extent, philosophical because such discussions precede recognition of data.

Understanding the functional circuitry of the basal ganglia-thalamus-cortex in terms of neuronal activities and interrelationships within a large-

scale dynamical system is important now and will become increasingly important in the future. The resurgence of functional stereotactic surgery, both ablative and utilizing deep brain stimulation (DBS), has been fueled by improvement in surgical techniques such as image-based and microelectrode navigation, a realization of the limitations of pharmacological therapy, as well as a justifying rationale based on better understanding of neuronal pathophysiology. Systems physiology and pathophysiology will play an ever-increasing role in developing new electrophysiologically based techniques such as DBS.

Systems physiology and pathophysiology also will play a large role in the further development of neurotransplantation of both fetal dopamine and stem cells. The occurrence of "runaway" dyskinesia in patients who underwent neurotransplantation with fetal cells emphasizes the importance of physiological controls on the implanted cells (2). Considerable research is underway to develop methods to dynamically control transplanted neurons, as well as a greater understanding of the importance of the physiological context or environment. For example, fetal dopamine neurons extracted from the region of the substantia nigra pars compacta (SNpc) have been transplanted into the striatum. However, this is not the normal location for these neurons, and the usual efferents to SNpc that control dopamine neuron function are not located in the striatum.

ANATOMY: THE BASICS FOR CIRCUITRY

This section reviews the basic anatomical interconnections between neurons that make up the basal ganglia-thalamic-cortical circuits. The anatomy is discussed only to a level of detail necessary for conceptual understanding of current models of function and dysfunction and for possible future theories. This section will not cover a fine-grained analysis of interconnections nor the histology (3,4).

Traditional approaches to the anatomy of the basal ganglia have divided it into input and output stages. This approach will be avoided here because such a description implies a sequential and hierarchical organization, which probably is misleading from a physiological perspective. Just as it is hard to say where a circle starts and an arbitrary starting point must be selected, this description will begin with the striatum. The caudate nucleus and putamen (Pt) make up the striatum.

The major sources of input to the striatum come from the cerebral cortex and thalamus. Virtually the entire cortex projects to the striatum in a topographic fashion. Frontal cortex projects to the head of the caudate and anterior putamen while motor and somatosensory cortex project to the postcommissural Pt and temporal cortex projects to the tail of the caudate.

Inputs from the thalamus include projections from the centromedian (CM) and parafasciculus (PF) nuclei of the thalamus. The striatum projects to the globus pallidus external segment (GPe), globus pallidus internal segment (GPi), and substantia nigra pars reticulata (SNr). There appears to be two separate groups of striatal neurons based on projection targets and neurotransmitters. All outputs from the striatum utilize gamma aminobutyric acid (GABA) but differ in the polypeptide cotransmitter. Striatal neurons projecting to the GPe express enkephalin and have predominantly D_2 receptors. Striatal neurons projecting to GPi express substance P and dynorphin and have predominantly D_1 receptors (5).

The GPe has inhibitory GABAergic projections to the subthalamic nucleus (STN) and GPi. The STN has excitatory glutamatergic projections to the GPi and SNr and back to GPe. GPi has GABAergic outputs to the ventrolateral (VL) and ventroanterior (VA) nuclei of the thalamus, which then has extensive projections back to the cerebral cortex. In addition, GPi projects to the pedunculopontine nucleus (PPN) in the brainstem. The PPN has received considerable attention recently. Injections of bicucullin, a GABA antagonist, alleviate symptoms of experimental parkinsonism induced by administration of n-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in nonhuman primates (6). The SNr projects to the superior colliculi and are conceived to be involved in eye movements.

CURRENT CONCEPTS OF PARKINSON'S DISEASE PATHOPHYSIOLOGY

These anatomical/neurochemical circuits have been conceptualized by current theories of physiology and pathophysiology into direct and indirect pathways (7,8). The direct pathway includes the striatum to the GPi to the VL thalamus, finally to motor cortex (MC) and supplementary motor area (SMA). The indirect pathway includes the striatum to GPe to STN to GPi to VL thalamus and then to MC and SMA. SNpc dopamine neurons are excitatory of striatal neurons participating in the indirect pathway and inhibitory of striatal neurons participating in the direct pathway. Consequently, the result of loss of SNpc dopamine neurons can be hypothesized to cause decreased activity in the striatal neurons of the direct pathway. This would result in a reduction of inhibition of GPi neurons, which in turn would result in increased inhibition of the VL thalamus and a reduction of excitation of the MC and SMA, thus providing an explanation for loss and slowing of movements (Fig. 1).

Loss of SNpc dopaminergic drive to striatal neurons of the indirect pathway would result in decreased inhibition of these striatal neurons, which in turn would increase the inhibition of the GPe. Consequent
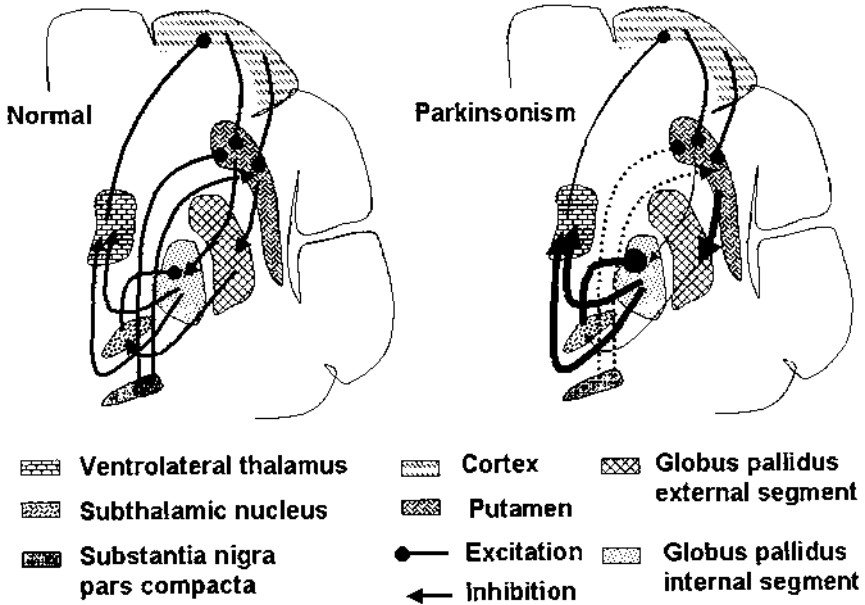
Normal   **Parkinsonism**

⊞ Ventrolateral thalamus	▨ Cortex
▨ Subthalamic nucleus	▨ Putamen
▨ Substantia nigra pars compacta	●— Excitation
	◄— Inhibition
▨ Globus pallidus external segment	
▨ Globus pallidus internal segment	

FIGURE 1 Schematic representation of the basal ganglia-thalamic-cortical circuits. There are two general pathways, termed the direct and indirect pathways. The direct pathway goes from putamen directly to globus pallidus internal segment, while the indirect pathway goes through, the globus pallidus external segment and subthalamic nucleus before reaching the globus pallidus internal segment. These two pathways also differ in the effect of dopaminergic inputs from the substantia nigra pars compacta. The dopaminergic input is inhibitory of putamen neurons participating in the indirect pathway and excitatory of those putamen neurons participating in the direct pathway. The figure on the left shows the normal circumstance, while the figure on the right shows the consequence of dopamine depletion (represented by the broken arrows) such as occurs in Parkinson's disease. The net result is reduction of inhibition, represented by the thinner arrows, and an increase in excitatory input, represented by the thicker arrow, onto the globus pallidus internal segment with increased inhibition of the ventrolateral thalamus.

decreased activity in GPe would result in reduced inhibition of and increased activity in STN. The increased activity of STN then causes further increased activity in GPi (Fig. 1).

There is considerable empirical evidence in support of this model. However, most of that evidence is indirect. Direct evidence comes from microelectrode recordings in non-human primates before and after the induction of experimental parkinsonism by the administration of MPTP,

which selectively degenerates dopaminergic neurons (9). Some studies have demonstrated the predicted increases in GPi and STN neuronal activities following experimental parkinsonism. Microelectrode recordings in the STN of PD patients also have higher discharge rates than in epilepsy patients undergoing DBS (10). However, STN neurons in PD patients also were more irregular in their firing patterns.

The observations of increased neuronal activity in the STN and GPi and reduced activity in the GPe cannot escape the possibility of being epiphenomenal rather than causally related to the symptoms of PD. These observations could be a special case more related to the severity of dopamine loss than two causal mechanisms. Others have shown no significant changes in baseline neuronal activity of either the striatum, GPe, VL thalamus, or MC following MPTP and animals clearly parkinsonian as evidenced by bradykinesia and changes in regional 2-deoxyglucose utilization typical of parkinsonian nonhuman primates (11). Filion and Tremblay (12) demonstrated that GPi neurons increased activity after MPTP, but the level of neuronal activity returned to baseline within a few weeks. Thus, dopamine depletion to the degree of producing changes in baseline neuronal activity is not a necessary condition for the production of parkinsonism.

Additional evidence offered in support of the current model is the clinical efficacy of pallidotomy. Destruction of the GPi would certainly remove abnormal increased GPi activity and thereby lessen inhibitory inputs onto VL thalamic neurons. However, it is also likely that pallidotomy would eliminate abnormal neuronal firing patterns. Additional supportive evidence of the current models is that dopaminergic replacement reduces neuronal activity in the GPi and STN of human parkinsonian patients.

The current model has been criticized on a number of grounds, primarily anatomical and clinical (13,14). Perhaps the strongest evidence against the current model is the remarkable efficacy of DBS (15). While there remains some controversy regarding the mechanisms of action of DBS, there is increasing evidence in direct microelectrodes in both humans and nonprimates that DBS increases the output of the stimulated structures rather than inhibiting or reducing activity within the stimulated structure. Thus, high-frequency DBS in the STN and GPi drives the output of the GPi at frequencies higher than in PD. Clearly, overactivity of this structure cannot be causally related to the mechanisms of PD.

NEURONAL MECHANISMS OF STN DBS

Preliminary results are reported from microelectrode recordings of GPi neuronal activities during stimulation in the vicinity of the STN in a

nonhuman primate. A DBS lead one-quarter scale relative to the human DBS lead was used to approximate DBS in humans. This type of stimulation is not specific to any single structure, whether it is the STN, axons of cortical projections to the STN, or pallidal-fugal fibers, but it does reflect how DBS leads are used in humans. The anatomical localization of the DBS lead and recording sites within the GPi were histologically confirmed.

DBS stimulation utilized the most ventral contact as the cathode (initial phase) and the most dorsal contact as the anode (initial phase). This reflects the most common active electrode arrangements we use clinically. Stimulation utilized biphasic current balanced stimulation with each phase 90 µs in duration. The current passed was made 80% of the threshold for stimulation to induce a muscle contraction of the contralateral body. This was determined to be 3.9 microcoulombs/cm^2/phase, well below the threshold for tissue injury. Neuronal activity was recorded for 30 seconds before, 30 seconds during, and 30 seconds after stimulation. Three to four trials of each of stimulation were obtained.

Computer software was developed that allowed removal of stimulus-induced artifact such that neuronal activity could be directly studied during stimulation. Previous studies analyzed activity immediately after cessation of stimulation because they were unable to analyze activity during stimulation (16). They inferred that this represented activity during stimulation, which will be shown to be false.

Average neuronal discharge frequencies were determined for prestimulation, during stimulation, and poststimulation for each set of trials associated with each frequency of stimulation. The percent change in the average GPi neuronal discharge frequency during stimulation was compared to the prestimulation period. Cross-correlograms were constructed of GPi neuronal activity referenced to the time of occurrence of the stimulation pulses.

Figure 2 shows a representative recording in GPi. The tracing shows the raw data after stimulus artifact removal. There is greater activity in the GPi segment during stimulation compared to before. Also, the activity following stimulation is less than before stimulation. This is evidence that one cannot infer that the neuronal activity immediately following cessation of stimulation reflects what occurs during stimulation.

One hundred and eleven neurons were recorded before, during, and after stimulation at 130-pulses per second (pps) in the GPi. Sixty-one (55%) neurons increased their discharge frequency associated with stimulation, while 50 (45%) decreased. Cross-correlograms are a method of relating the occurrence of a neuronal discharge to the stimulation pulse (Fig. 3). They are constructed by measuring the time of each neuronal discharge within a
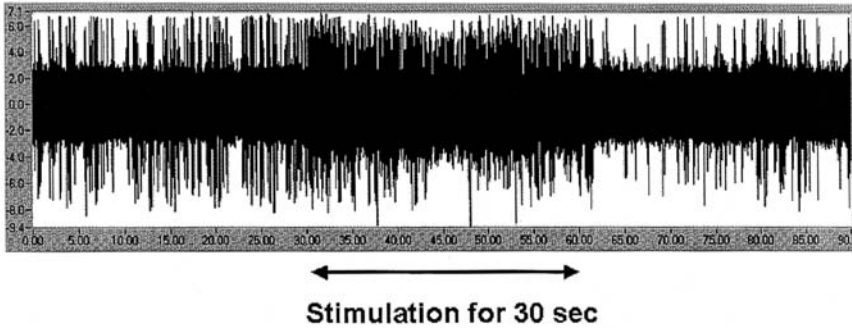
Stimulation for 30 sec

FIGURE 2 Microelectrode recording of the extracellular action potentials of a globus pallidus internal segment neuron in response to DBS in the vicinity of the subthalamic nucleus. There is a 30-second baseline recording followed by 30 seconds of stimulation and then recording for an additional 30 seconds.

defined time period following each stimulation pulse. Thus, the cross-correlogram can be interpreted as the relative probability that the neuron will discharge at a defined time period following delivery of a stimulation pulse. Representative cross-correlograms of GPi neuronal activity indexed to the occurrence of the stimulation pulses are shown Fig. 4, in which several
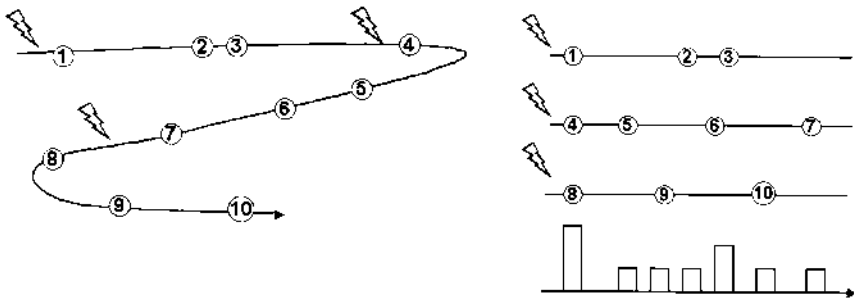

FIGURE 3 Schematic explanation of the cross- correlogram of neuronal activity reference to the stimulation pulses (lightning bolts). The time of each neuronal extracellular action potential are represented by the numbered circle. The figure on the left represents a recording during which three stimuli are delivered. The figure on the right separates the recording into three segments at the time of each stimulus. The times of neuronal discharge relative to the stimuli are then summed across trials to generate a histogram that is the cross-correlogram. The height of each interval in the histogram indicates the relative probability of a spike occurring in a time locked fashion in response to the stimuli.
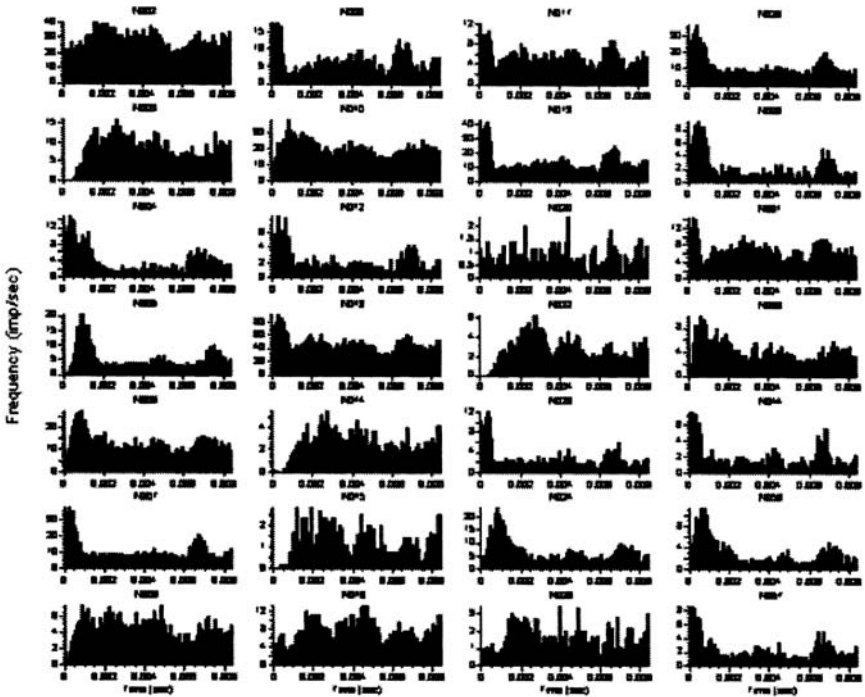
FIGURE 4 Cross-correlogram of activity of globus pallidus internal segment neurons to DBS in the vicinity of the subthalamic nucleus. The activities are reference to a stimulus pulse delivered at 130 pulses per second. The time line for each correlogram is 8 ms and the bin width is 0.1 ms. See text for description.

peaks are seen at different times. An early and narrow peak at approximately 1 msec is most consistent with, although not proof of, antidromic activation of the GPi neuron by stimulation of pallidal-fugal fibers traveling in the lenticular fasciculis and ansa lenticularis near the STN.

Later and border peaks are consistent with mono- and polysynaptic orthodromic activation, perhaps due to stimulation of the STN axons projecting to the GPi. Cross-correlograms of neurons, which, on average, decreased activity with stimulation, also showed activity correlated with stimulation but associated with a reduction of activity. Even neurons that reduced average activity with stimulation had at least a transient increase in neuronal activity with each stimulation pulse. Hasmimoto et al. (17) also demonstrated increased activity in GPi with STN DBS. Anderson (18)

demonstrated reduced activity in VL thalamus consistent with increased GPi output with GPi DBS.

Dostrovsky et al. (19) reported reduced GPi neuronal activity with microelectrode stimulation of the GPi using pairs of microelectrodes to simultaneously stimulate and record. They attributed these findings to increased release of presynaptic inhibitory neurotransmitters onto GPi neurons. However, DBS effects on GPi neuronal cell bodies as would be recorded with microelectrodes may be dissociated from effects on the axon hillocks (initial segments) or first internodes between myelin segments. Thus, stimulation could lead to decreased discharge of the neuronal cell body but increased output due to excited axon hillocks or first internotes as supported by computer modeling of thalamic neurons based on membrane properties, neuronal geometries, and conductance channels (20). STN DBS effects on electromyographic (EMG) activity (21), STN DBS-evoked scalp potentials (22), and clinical efficacy related to chronaxie (23) are consistent with axonal mechanisms.

Preliminary data described here strongly support the notion that DBS drives output. The mechanisms are complex and varied, including antidromic and mono- and polysynaptic orthodromic activation. This is probably related to the many different structures in the region of the STN DBS leads. Consequently, high-frequency therapeutic DBS drives GPi neurons at frequencies higher than in the normal and in the MPTP-parkinsonian nonhuman primate. It is reasonable to conclude that high-frequency DBS also drives human GPi well above the abnormal baseline frequencies associated with PD. Therefore, it cannot be that the pathophysiology of PD is due to overactivity of the GPi, or else high-frequency DBS would make PD symptoms worse instead of better. Rather, these changes in baseline activity most likely represent epiphenomena. The current theory needs restructuring or to be discarded altogether.

ALTERNATIVE HYPOTHESES

The question arises as to what theories will replace the current ones. There are some observations that suggest where to begin. First, pallidotomy and GPi DBS are very effective for levodopa-induced dyskinesia (24), dystonia (25), and hemiballismus (25). In contrast to the overactivity of the GPi in PD, GPi neuronal activity in these other conditions is lower than what is thought normal. However, common to all these conditions is the fact that the pathological neuronal activity is more irregular. Perhaps the therapeutic mechanism of DBS is more related to the irregular activity than changes in average neuronal activity. The question then is how an irregular pattern of activity leads to the symptoms of these disorders.

Information Processing and Misinformation

Information is encoded in the patterns of neuronal activity. Abnormal patterns of activity translate into misinformation. In addition, irregular neuronal activity can have an abnormal effect on downstream information processing through a mechanism of stochastic resonance. This phenomenon is the increase in the signal-to-noise ratio when noise is added. Computer modeling of information transfer and processing demonstrates that stochastic resonance effect is greatest with low-frequency regular and irregular activity (26). The stochastic resonance effect is the least with high-frequency regular activity.

The computer model used two neurons (X and Y) synapsing on a third neuron (Z) (Fig. 5). The effects of activity in neuron Y, either spontaneous or in response to DBS, on information transfer between neurons X and Z were analyzed. The information was represented by an idealized waveform to which Gaussian noise was added and then converted to neuronal like activity. Neuron Z simply added the inputs from neurons X and Y. The gain
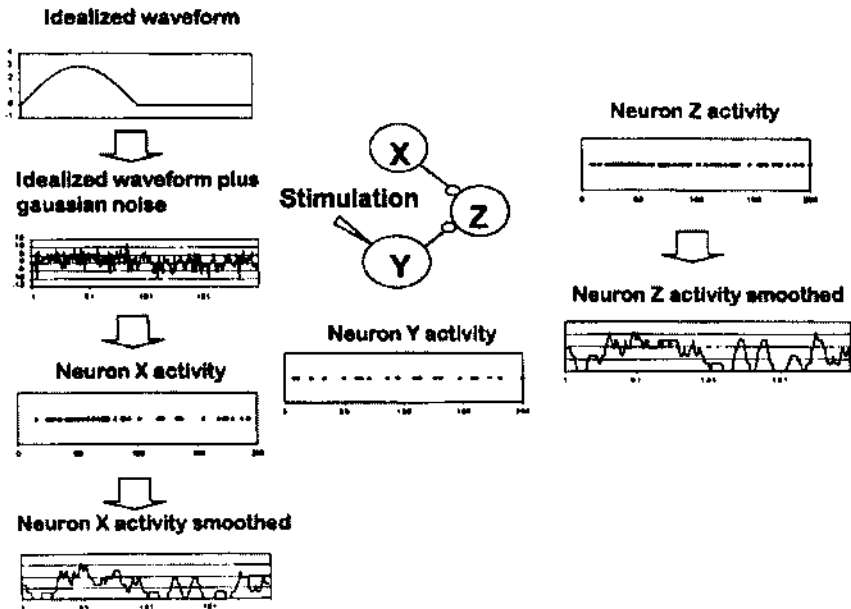

FIGURE 5 Schematic representation of the modeling of information processing: the effects of activity in neuron Y, either spontaneous or in response to DBS, on information transfer from neuron X to neuron Z. See text for description. (From Ref. 26.)

of information between neuron X and Z was determined where a positive difference represents information gain and a negative difference represents information loss. High-frequency irregular activity nearly always results in a loss of signal-to-noise ratio. Low-frequency regular or irregular activity also results in instances of loss of signal-to-noise ratio but occasionally results in abnormal gain. The high frequency and regular activity pattern had the least impact (Fig. 6).

PD results in overall loss of function because of the higher and more irregular GPI activity. The slow and irregular GPI neuronal activity in levodopa-induced dyskinesia, dystonia, and Huntington disease results in
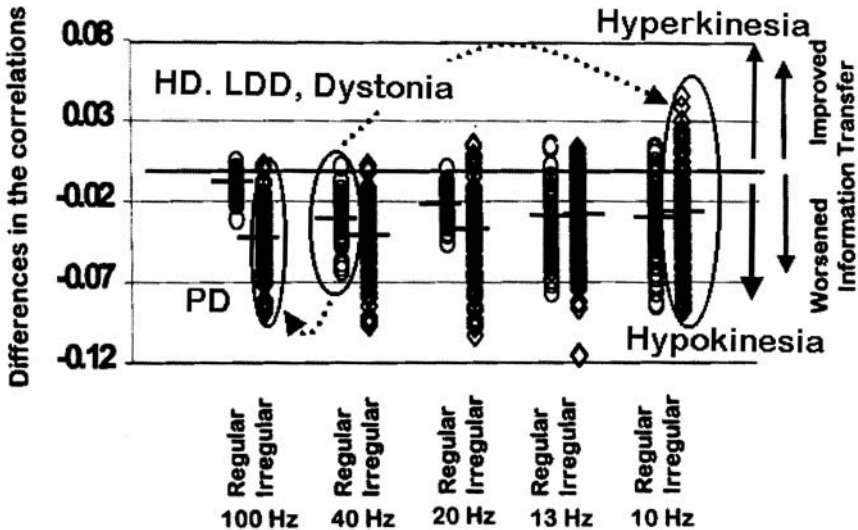

FIGURE 6 Results of computational modeling of the effects of neuron Y on information transfer from neuron X to neuron Z. A difference in correlation below zero represents loss of information, while differences in correlations above zero represent a gain in information. The effects of pathology of the basal ganglia are represented. Normal activity of the globus pallidus internal segment is represented by the circle for 40 Hz regular activity in neuron Y. In Parkinson's disease (PD) there is an increase in neuronal activity that becomes more irregularly represented. In contrast, Huntington's disease (HD), levodopa induced dyskinesia (LDD), and dystonia result in information transfer that loses information as well as instances of abnormal gain of information. The former may account for many of the negative symptoms associated with Huntington's disease, levodopa-induced dyskinesia, and dystonia, while the episodes of abnormal gain of information may account for the hypherkinesias or involuntary movement. (Modified from Ref. 26.)

both a loss of function and episodes of abnormal gain of function that could explain the involuntary movements of these disorders. Driving GPi to high frequency and regular activity minimizes the misinformation and abnormal loss or gain in the signal-to-noise ratio or information content (Fig. 7).

Preliminary studies described above support the hypothesis of more regular activity in GPi with STN DBS. Figure 8 is a schematic explanation of the autocorrelogram, which is similar to a cross-correlogram. The autocorrelogram indicates the relative probability that one neuronal discharge will be associated with another discharge occurring at some defined time earlier or later. Peaks in the autocorrelogram indicate organization in the spike train such as oscillatory or regular behavior. There is better organization of GPi neuronal activities during stimulation at 130 pps as evidenced by peaks in the autocorrelogram during stimulation compared to before stimulation (Fig. 9). This is particularly evident in the autocorrelogram of the population of GPi neurons. Thus, GPi neuronal
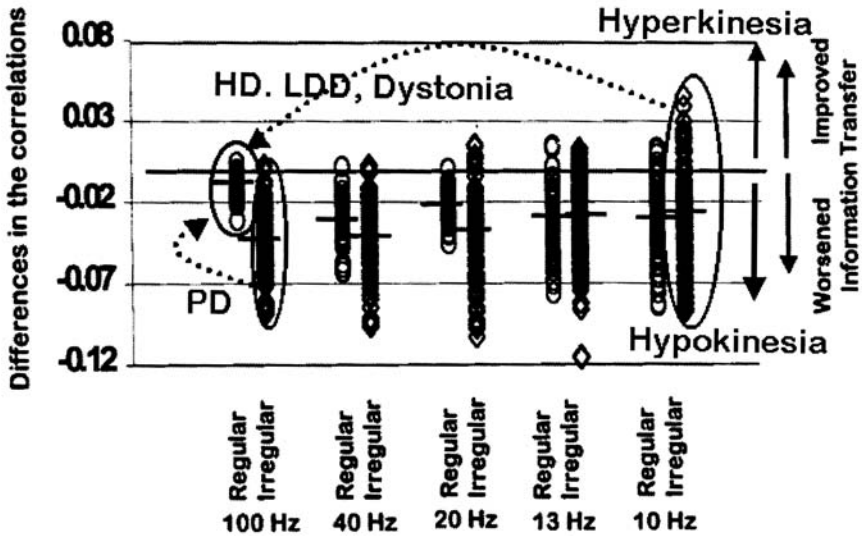

FIGURE 7 Schematic representation of the possible effects of high-frequency DBS. In Parkinson's disease (PD), Huntington's disease (HD), levodopa-induced dyskinesia (LDD), and dystonia, high-frequency DBS drives the activity of the globus pallidus internal segment to high and regular frequencies, thereby minimizing the effects on information processing downstream and mitigating disease symptoms, both positive and negative. (Modified from Ref. 26.)
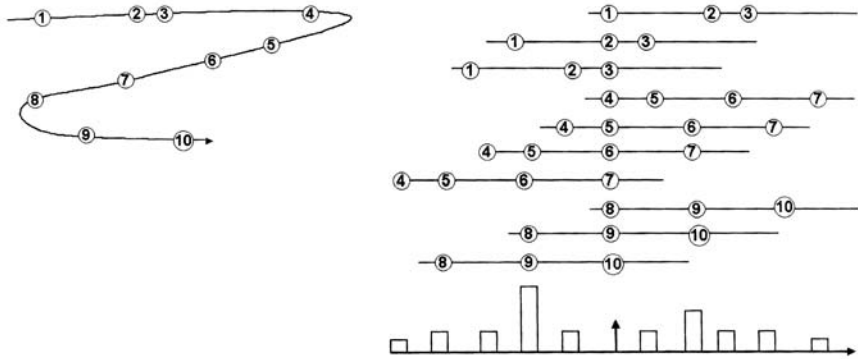
FIGURE 8 Schematic explanation of the autocorrelogram. The figure on the left shows the time course of a recording of neuronal activity. The figure on the right shows the time course broken into segments. Segments are duplicated and organized so that each neuron discharge becomes centered on the upward arrow. The times of neuronal discharge are then collapsed across trials and summed in the resulting histogram. The height of each interval in the histogram indicates the relative probability of a neuronal discharge occurring at a specific time before and after the occurrence of an individual discharge. Peaks in the autocorrelogram indicate organized activity that may be oscillatory.
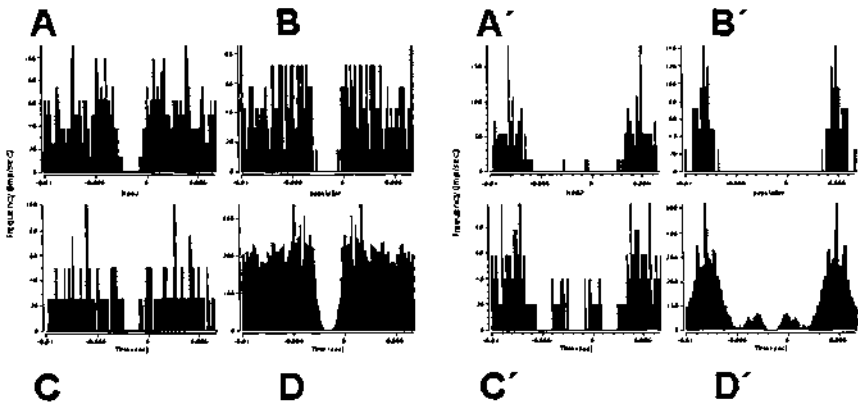

FIGURE 9 Autocorrelograms of three individual neurons (A and A', B and B', and C and C') and the ensemble population of eleven neurons (D and D') recorded at a single site in the globus pallidus internal segment. Autocorrelograms A, B, C, and D were from recording 30 s before DBS in the vicinity of the subthalamic nucleus at a regular 130 pulses per second. Autocorrelograms A', B', C', and D' were from recordings during 30 s of stimulation. The time line for each correlogram is 10 ms and the bin width is 0.1 ms.

activity is more regular during STN DBS, which then removes information content (27).

The hypothesis follows that the abnormal patterns of GPi neuronal activity result in misinformation and that DBS changes misinformation to essentially no information. Ablation eliminates the source of the misinformation. This may explain the similarity of the clinical efficacy of pallidotomy and DBS.

DBS Effects on ''Systems''

The effects of DBS are not limited to the STN or GPi but rather influence multiple components of the basal ganglia-thalamic-cortical circuits or systems. It is possible that the therapeutic mechanisms of DBS are due to these effects and, if so, that concepts of PD pathophysiology need to be extended to these systems.

Preliminary studies in a nonhuman primate, as described above, included analysis of responses of neurons in the MC and Pt (Fig. 10). The responses to STN DBS included very short duration narrow responses, suggesting antidromic activation of neurons in the motor cortex and longer latency and broader peak responses, suggestive of polysynaptic orthodromic activation in both the MC and Pt. It is interesting to note the temporal relationships between the peaks of the increased polysynaptic activity in the Pt and GPi. Increased activity within the Pt was followed by decreased activity in the GPi with a lag time of approximately 1.6 msec, which is consistent with the monosynaptic connections between Pt and GPi (Fig. 10). This is analyzed further in Fig. 11. The top tracing shows the cross-correlogram of 12 Pt neurons that are normalized to the maximum value in each correlogram. The tracings of each cross-correlogram are superimposed. A similar analysis for GPi neurons is shown in the middle tracing of Fig. 11. The bottom tracing shows the average of the individual tracings for the Pt and GPi superimposed. A phase relationship with a lag time of approximately 1.6 msec can be seen. There is a suggestion of a similar relationship between cortical and Pt activity. High-frequency DBS in the vicinity of the STN generates oscillations within the basal ganglia-thalamic-cortical circuits as evidenced by STN DBS evoked potentials found over the scalp and in the contralateral STN (22).

How activation of oscillations within this circuit is causally related to the therapeutic mechanisms of action of high-frequency DBS is unclear. One possibility might be reinforcement of a resonance frequency within the basal ganglia-thalamic-cortical circuit. If one assumes a four-segment circuit reflecting the direct pathway and further assumes a 1.6 ms time lag (seen in the cross-correlograms of Fig. 10 and the modified cross-correlogram of Fig.
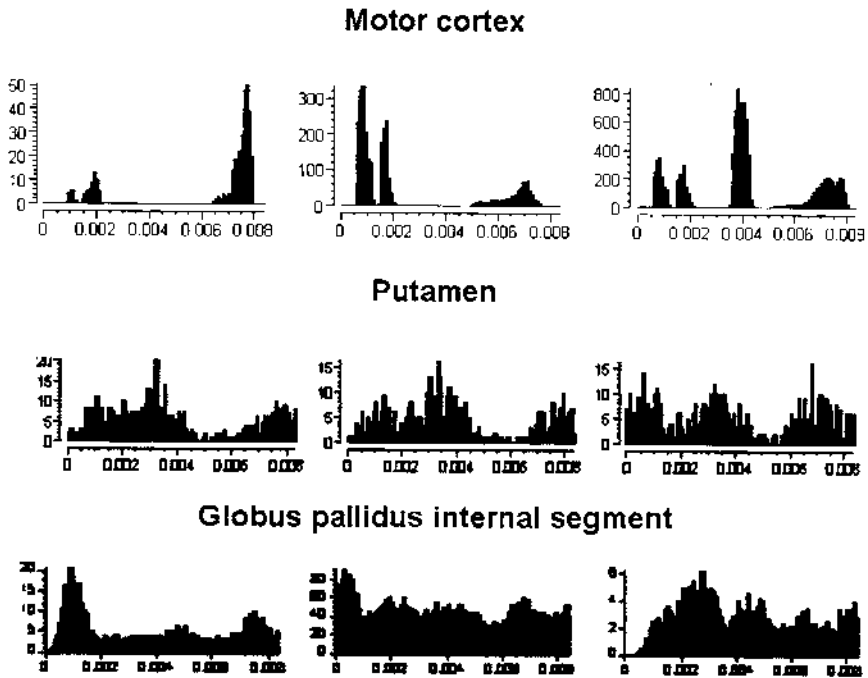
Motor cortex

Putamen

Globus pallidus internal segment

FIGURE 10 Representative cross-correlogram of activity of globus pallidus internal segment, motor cortex, and putamen neurons to DBS in the vicinity of the subthalamic nucleus. The activities are reference to a stimulus pulse delivered at 130 pulses per second. The time line for each correlogram is 8 ms and the bin width is 0.1 ms. See text for description.

11) between activities within the circuits, then information could circulate the circuit in approximately 6.4 ms. This would correspond to a frequency of 156 Hz. Information could traverse the indirect pathway, made up of five segments, with a frequency of 125 Hz. These frequencies are in the range of those found therapeutic for DBS. Stimulation at the resonance frequency could reinforce normal information processing within the basal ganglia-thalamic-cortical circuit and, therefore, improve motor function.

"Systems" and "Theoretical" Approach

The critical question now becomes: What will be the basis for a future model of basal ganglia physiology and pathophysiology? The current model is a model of anatomy and neurochemistry rather than physiology. Most of the
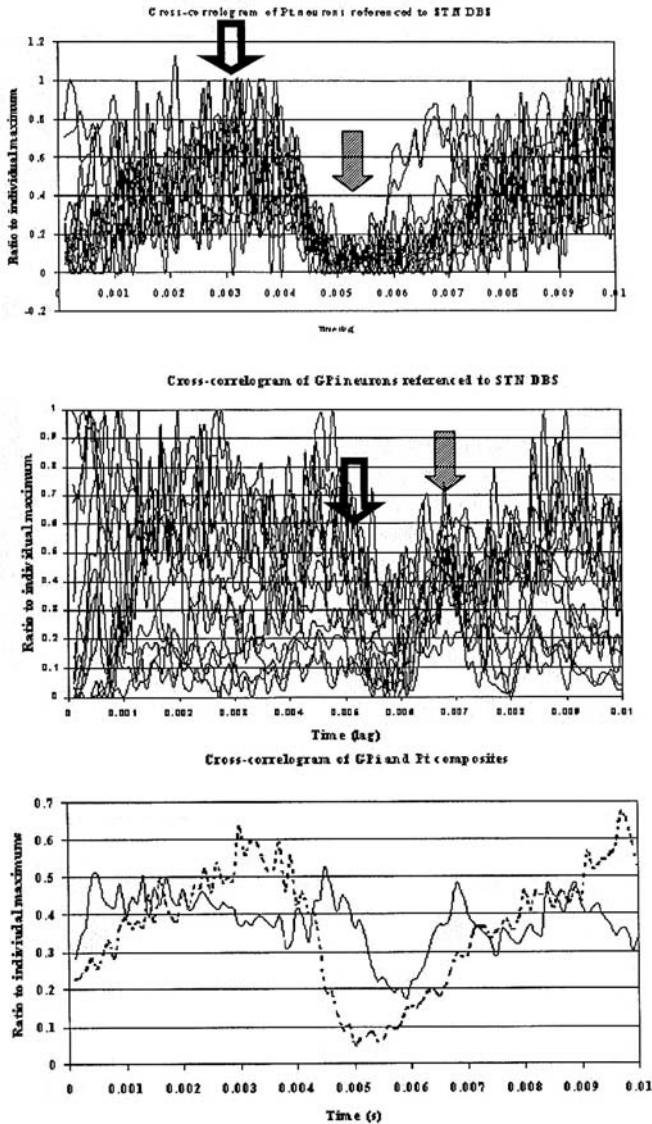
FIGURE 11 Normalized tracings from the cross- correlograms of Pt and GPi neurons. The upper tracings are from Pt neurons and the middle tracings from GPi neurons. The bottom tracing shows the average of the individual tracings, solid line for Pt and broken line for GPi. The peak of neuronal activity in Pt is followed by a reduction in GPi activity (open arrows), while a reduction in Pt activity is followed by an increase in GPi activity (gray-filled arrows).

physiological assertions are inferences from the anatomy and neurochemistry. As will be discussed, these inferences do not explain the temporal dynamics of complex systems.

The current model uses single neurons substituted for whole structures. This is referred to as the "macro-neuronal" approach. For example, single neurons represent the cortex, Pt, of the indirect pathway, Pt of the direct pathway, GPe, GPi, STN, SNpc, SNr and VL thalamus. These "macro-neurons" are linked by inhibitory or excitatory neurotransmitters. The dynamics of this model are one-dimensional "push-pull" interactions (Fig. 1). The predicted findings of this model have been supported for changes in baseline, steady-state, or resting activity of the different basal ganglia structures. However, these changes may be epiphenomenal as described above.

The temporal dynamics of the circuits relative to the behaviors they are thought to mediate is critically important. For example, Fig. 12 shows the time course of neuronal activity in the motor cortex associated with a
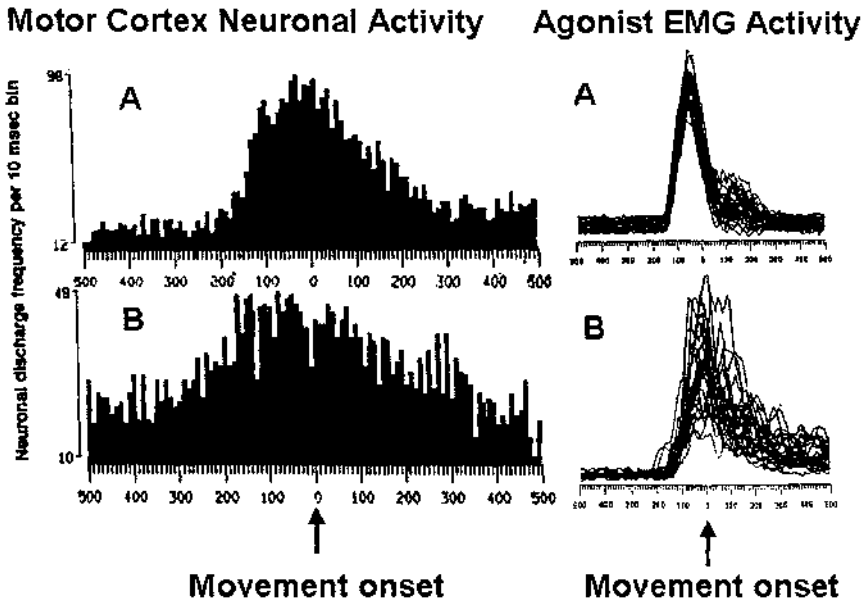

FIGURE 12 Time course of motor cortex neuronal activity and wrist flexor electromyographic (EMG) activity associated with a wrist flexion task in a nonhuman primate before (A) and after (B) induction of parkinsonism using *n*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Recordings are made from 500 ms before to 500 ms after movement onset over multiple trials. (From Ref. 28.)

wrist flexion task (28). Changes in neuronal activity in the normal condition begin approximately 200 ms before movement onset and reach a new baseline or steady state approximately 300 ms after movement onset. Information can traverse the basal ganglia-thalamic-motor cortex within 6.4–8 ms. It is possible for information to have traversed the circuits 63–78 times during the course of a 500-ms-long behavior. Thus, the sequential nature of the one-dimensional "push-pull" dynamics of the current model cannot begin to account for such a complex reentrant system. Rather, the function or dysfunction associated with disorders of the basal ganglia must be reconceptualized into a distributed and parallel system of re-entrant oscillating circuits. The basic units of function and therefore the subject of analyses are no longer the individual structures of the cortex, basal ganglia, and thalamus but rather the basal ganglia-thalamic-cortical circuit as a whole.

Evidence in support of a parallel and distributed system within the time frame of behavior is seen in recordings of MC and Pt neuronal activity during the course of a wrist flexion and extension task (29). Utilizing a method that relates changes in neuronal activity to behavioral events (30), it was possible to determine which behavioral event was best related to the change in neuronal activities. Thus, neurons in MC and Pt were identified that were preferentially related to the appearance of the go signal or movement onset. Neurons responding to the go signal typically became active before those related to movement onset (Fig. 13). However, go signal–related neurons in the Pt became active at nearly the same time as those in the MC. Similarly movement onset–related Pt neurons became active at the same time as movement onset–related neurons in MC.

EPISTEMOLOGY OF CURRENT MODELS OF PHYSIOLOGY AND PATHOPHYSIOLOGY

Scientists and philosophers repeatedly warn that attention to how something is known often is as important as what is known. Numerous aphorisms have been coined for such warnings, such as "we see what we are prepared to see" or "when all you have is a hammer, everything becomes a nail." Unfortunately, epistemic discussions in neurophysiology are rare. What follows is such a discussion of our current conceptual approaches to systems neurophysiology that may help to understand why specific questions have been asked rather than others and the origins of the assumptions that underlie those questions. This effort will be very important in creating the new theories of basal ganglia physiology and pathophysiology.
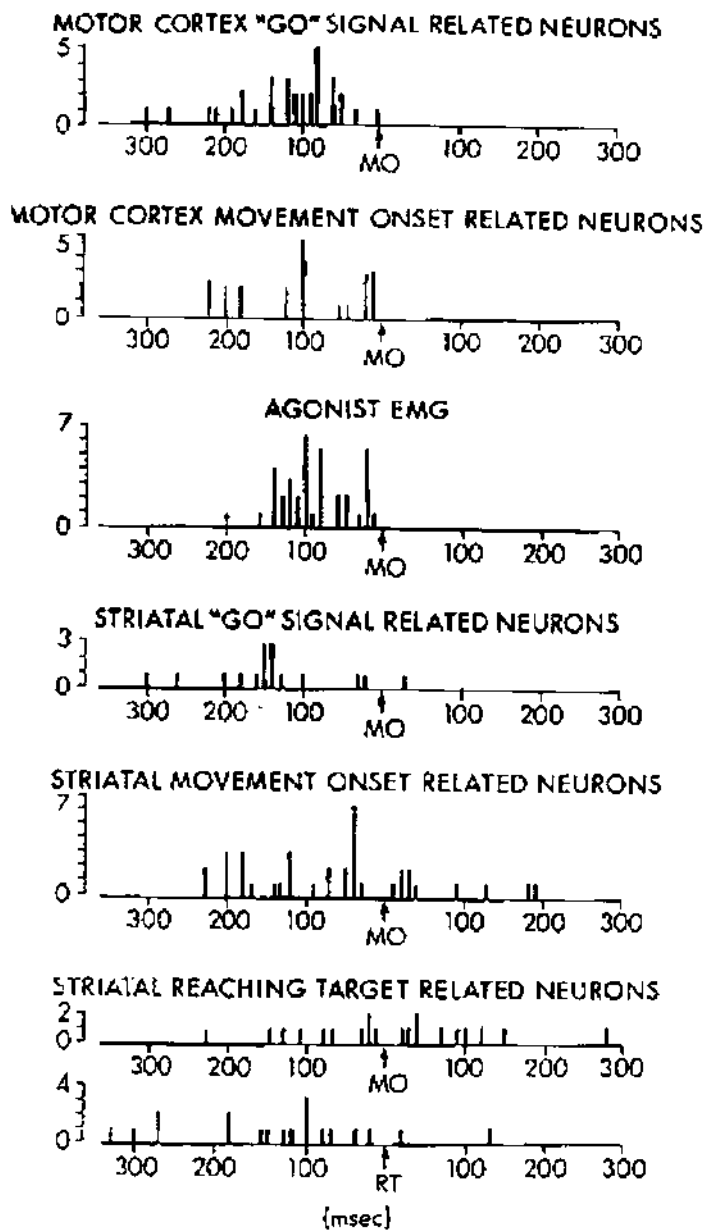
FIGURE 13 The time of onset of neuronal activity of go-signal– and movement onset–related neurons in motor cortex and putamen demonstrating nearly virtually simultaneous onset of activity change. (From Ref. 29.)

Reasoning by Anatomy

The proposition is offered that in conceptual approaches to systems neurophysiology are the results of anatomical studies to the greatest degree followed by clinical observations of disease states. The actual incremental increases in our understanding offered by direct recordings of neuronal activities during the course of behavior have contributed relatively little in comparison. Indeed, there have been circumstances where recordings of neuronal activity would appear contradictory to the inferences drawn from the anatomy (11,26). These contradictory findings have received scant attention.

This is not to discount the importance of anatomical understanding or research. In fact, anatomical data provide a critical reality check because any theory of systems neurophysiology cannot contradict validated anatomical fact. However, the anatomy can only provide information in the widest sense in that its limits are only the maximum possibilities and the physiological realities are likely to be only a subset of the anatomical possibilities (31). Further, as the complexities of anatomical organization and interconnections increase, it will become increasingly difficult to predict function from the structure. This is particularly true if, as is likely, the interactions are highly nonlinear. Any new model would require as its basis the same anatomical facts that underlie the current anatomical model. However, as will be seen, there may be emergent properties of the new dynamical models that are not intuitive from the current anatomical model and, therefore, represent such a quantitative change as to be qualitatively different.

Hierarchical Processing

The macro-neuron approach leads to structures that are then linked with a very specific directional aspect, for example, the cortex projects to Pt, which in turn projects to GPi, which projects to the VL thalamus. Consequently, the presumption has been that information is processed within the cortex, which is relayed to Pt for processing. When completed, the information is then relayed to GPi and so on. This has led to attempts to identify specific functions unique to each structure and to demonstrate timing differences of changes in neuronal activities associated with behavior. For example, experiments attempted to demonstrate that the GPi or Pt nucleus became active before the MC. The results of these experiments were either inconclusive or failed to demonstrate the anticipated timing differences (8,32–34).

The anatomically derived hierarchical conceptual approach fails to distinguish anatomical proximity form physiological proximity. The presumption is that neurons in close proximity to each other (such as being within the same nuclei or restricted region of cortex) interact to carry out specific physiological functions. However, it is quite possible, indeed probable in the case of the basal ganglia, that neurons in different and separate structures are more directly linked physiologically than adjacent neurons in the same structure. For example, the majority of neuronal recording studies of simultaneously recorded putamen neurons in close proximity are not cross-correlated, demonstrating very little if any physiological interactions. Yet, there is a very precise and robust physiological interaction between cortex and Pt neurons. Physiologically, it may make better sense to consider neurons tightly linked in the cortical-basal ganglia-thalamic circuit as being the more fundamental physiological working unit, rather than any of the separate nuclei or cortical structures.

The degree of independence between these circuits has been discussed at length (35–37). Evidence for separate basal ganglia-thalamic-cortical loops comes from anatomical studies. Studies using viruses to trace anatomical projections across synapses suggest that there is little or no anatomical overlap between those circuits serving cognitive, limbic, or motor functions (36). However, these studies were not done at the levels of resolution of neuronal populations related to individual extremities or muscles. Recent functional magnetic resonance imaging (fMRI) studies have suggested overlap in areas of the Pt representing the face, fingers, and toes (38). Electrophysiological studies can estimate the degree that electrical activities in individual neurons are coupled using cross-correlation techniques. Little evidence of coupling is found for pallidal neurons, although more couplings have been found for tonically acting striatal neurons, which are probably cholinergic interneurons (35).

An alternative to the anatomically based hierarchical conceptual approach posits that physiological function, such as responding to a go signal, initiating a movement, or completing a movement, is represented in separate basal ganglia-thalamic-cortical circuits. Processing within the circuit is virtually simultaneous within the components of the circuit. There is a hierarchical structure, but it is in physiological terms not anatomical. Thus, during behaviors such as making a movement to a target in response to a go signal, the basal ganglia-thalamic-cortical circuit related to responding to the go signal is hierarchical to the basal ganglia-thalamic-cortical circuit that is associated with movement initiation. This, in turn, is hierarchical to the circuit whose activity changes are preferentially related to reaching the target. This hierarchical organization of function is paralleled by differences in the timing of activity changes in these circuits.

The macro-neuron approach also leads to the inference that physiological functions are specific to the nucleus or subdivision of the nucleus or to a specific region of the cortex. Evidence against the hierarchical arrangement suggested by the macro-neuron model lies in the fact that diseases affecting different structures may produce very similar if not indistinguishable symptoms. For example, lesions of the GPi, SNpc, and the SMA (39–43) all produce parkinsonian akinesia and bradykinesia. As described above, Huntington's disease patients have prolonged reaction times and slowed movement (44). Consequently, physiological function is not likely separately represented in specific and unique structures, otherwise lesions of each specific and unique nucleus would result in specific and distinct dysfunction.

THE NEED FOR MATHEMATICALTHEORETICAL NEUROPHYSIOLOGY

The relative lack of knowledge and understanding in systems physiology and pathophysiology is not for want of talent or effort. More likely it is related to the incredible difficulties encountered and the type of explanation required. The complexities of any interacting system increase enormously as the number of agents and mechanisms of interaction increases. Systems physiology of necessity requires study of large numbers of agents and interactions. One approach to managing complexity is to use statistical descriptions of empirical descriptions gleaned from populations and to use correlations as surrogate markers for causal interactions. However, this is not the level that will provide mechanistic insights that will power development of future research.

Given the daunting challenge, what will it take to reach a full understanding of how complex interconnected neurons organize and interact to create the human experience? Note that the aim is an understanding and not knowledge as in a complete specification of every element. Indeed, it is likely that such a complete specification at the most fundamental level will be so improbable as to be impossible. The question then arises whether there is a level of understanding that has sufficient resolution as to be useful. There are at least two responses. The first is the concept of emergent properties. The second is the use of metaphors of sufficient complexity and realism and whose validation will be in the ability of the metaphors to generate succeeding generations of biologically testable hypotheses.

Emergent properties are reflected in regularities of observed or macroscopic behavior that are not readily apparent from microscopic observation of its constituent agents. For example, it is not possible to

observe the activity of individual neurons in the brain and precisely predict any behavior. However, the notion of emergent properties is not hostile to reductionism. Ultimately, behavior must be the result of activities of individual neurons. But knowledge at the level of the individual neuron is not a necessary, or perhaps even possible, requirement for understanding of behavior as evidenced by the remarkable successes of cognitive neuroscience. For the systems neurophysiologist, the issue becomes whether there are emergent properties at tractable levels of analysis that can be useful.

What alternatives exist to metaphorical knowledge to provide understanding? No alternatives loom on the horizon. Consequently, how can metaphors be made to be useful as surrogate knowledge of brain function? There are two critical pitfalls using metaphors. These are the fallacy of induction and the related logical error of confirming the consequence. The fallacy of induction translates that just because one metaphor may explain a biological phenomena, it is not possible to exclude the possibility that an alternative exists. The only options then are to insist that the biological phenomena be of sufficient richness as to make it hard for a large number of possible alternatives to exist and that an appropriate level of analysis (i.e., emergent properties) is used to determine whether alternatives are truly different.

The second derivative problem is the penchant of experimenters to fall victim to the logical error of confirming the antecedent. This error is of the form (1) if ''a'' then ''b''; (2) ''b'' is true; therefore (3) ''a'' is true. In relevant terms, an error backpropagation neural network model can solve a biological problem, such as distinguishing phonemes in speech, biological systems can distinguish phonemes, therefore, biological systems use backpropagation and the search is on to find backpropagation in individual neurons. These logical errors do not necessarily mean that backpropagation could or would not be demonstrable, but if they are, it is not from logical deduction. These difficulties are probably largely responsible for the hostility that biologists have for model-based explanations. However, at an emergent level there is validity to a backpropagation notion because organisms do learn from their mistakes.

Clearly, the systems neurophysiologist will have to operate at the level of metaphor if there is any chance of formulating an interesting and useful biological testable hypothesis that will drive future empirical research. The issue is what has driven the development of metaphors to date, and what the survival value of continuing that line of development is. The use of metaphors can be liberating or confining. It will be argued that the current basis for metaphor development in the area of basal ganglia physiology and pathophysiology has been anatomical and therefore static. The anatomically

based metaphor has resulted in simplistic expectations that, unfortunately, have been found to be epiphenomenonally true and has created false local minimas in the ignorance of basal ganglia physiology and pathophysiology. So pervasive and seductive has the anatomical metaphor been that it has defied physiological common sense—hence, the false local minimas.

There may be an inclination to avoid constructing any models in the hope that sufficient empirical data could be obtained to provide a sufficient intuitive or self-evident explanation. However, the odds of this are extremely small. Clearly, models of vastly increased complexity, one day possibly approaching the degree of complexity inherent in biological systems, are necessary. Validating such complex models requires developing experimental, analytical, and conceptual methods to understand biological activity of a corresponding degree of complexity. Rapid advances in computer technology and multiple microelectrode arrays will provide vast amounts of empirical data. But there is the danger that the magnitude of the empirical data will overwhelm the ability to make sense of the data. Therefore, conceptual methods of data reduction, particularly nonlinear methods such as chaos and fractal analyses, will become increasingly important. Models will have to be constructed to act as metaphors by which to understand the empirical data. While this approach risks circularity, there seems little alternative.

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