

One View of the Current State of Understanding in Basal Ganglia Pathophysiology and What is Needed for the Future

Erwin B. Montgomery Jr.

Department of Neurology,
University of Alabama
at Birmingham,
Birmingham, USA

Deep Brain Stimulation (DBS), arguably, is the most dramatic development in movement disorders since the levodopa for Parkinson's disease. Yet, its mechanisms of action of DBS are unknown. However, DBS related research already has demonstrated that current concepts of basal ganglia pathophysiology are wrong. Specifically, the notion that over-activity of the globus pallidus interna causes parkinsonism, the basis for the most current theories, is no longer tenable. The development of any new theory will be aided by an understanding of how current theories are wrong and why have these flawed theories persist. Many of the problems of current theories are more matters of inference, assumptions, presumptions, and the accepted level of ambiguity than they are of fact. Consequently, it is imperative that these issues be addressed. Just as the inappropriate use of a tool or method is grounds for criticism, methods of reasoning are tools that can be used inappropriately and should be subject to discussion just as misuse of any other tool. Thorough criticism can provide very important lessons though the process could be mistaken as harsh or personal; neither is the case here. At the least, such analyses can point to potential pitfalls that could be avoided in the development of new theories. As will be discussed, theories are important for the development of therapies but perhaps most important, for the acceptance of new therapies, as was the case for the recent resurgence of interest in surgical therapies.

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The Implications of Deep Brain Stimulation

Deep Brain Stimulation (DBS), arguably, is the most dramatic development in the treatment of movement disorders since the use levodopa for Parkinson's disease. When viewed from the more appropriate perspective of symptomatic rather than disease specific treatments, there does not appear to be any movement disorder that could not benefit.¹ The indications are limited only by the co-morbidities that constrain the impact of DBS on quality of life and increase the risk of surgical complications.

DBS is more effective than the best application of medications and for some conditions, the only effective treatment. Further, DBS for movement disorders is the prototype from which DBS is being extended to other neurological and psychiatric disorders. But perhaps what is most remarkable is what is below the surface appearance in the clinical responses. Until DBS, most treatments have focused on affecting dopamine receptors and more rarely on cholinergic receptors. To be sure there has been interest in the N-methyl-D-aspartate receptors but primarily as a means to improve dyskinesias secondary to long-term levodopa and dopaminergic medications.

DBS acts through different means, and that is electrical. Although one could argue that ultimately electrical activity is mediated through chemical neurotransmitter interactions with receptors, this is but a small component and is tantamount to saying that computers require electrons. This is true but only in the philosophical sense of trivially true, which means the statement does not perform any intellectual work such as contributing to a complete understanding. To equate the neurophysiology and pathophysiology of the basal ganglia-thalamic-

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Corresponding author

Erwin B. Montgomery Jr. MD
Department of Neurology,
Sparks Center 350,
University of Alabama at Birmingham,
1720 7th Avenue South,
Birmingham, AL 35294, USA
Tel +1-205-996-2094
Fax +1-205-996-0412
E-mail emontgom@uab.edu

cortical system with the actions of neurotransmitters is to ignore the immense computational power of electrically mediated interactions in the neuronal membrane particularly as they relate to information processing.

DBS and related research provided and continues to provide opportunities to directly test theories of basal ganglia physiology and pathophysiology, an opportunity insufficiently taken advantage of. Already, observations obtained from DBS-related research demonstrate that current theories are wrong to the point where total rejection, rather than continual attempts at modification, is necessary. However, how to develop new hypotheses and theories is not clear. In one sense, a good place to start is where and how the current theories came to be wrong. While this approach would seem reasonable there are numerous obstacles philosophically² and psychologically.³ Never the less, the approach is important to attempt.

The development of any new theory will be aided by an understanding of how current theories are wrong and why have these flawed theories persist. Many of the problems of current theories are more matters of reasoning, those being inference, assumptions, presumptions, and the accepted level of ambiguity, than flaws of fact. Consequently, it is imperative that these issues be addressed as well. Just as the inappropriate use of a tool or method is grounds for criticism, methods of reasoning are tools that can be used inappropriately and should be subject to discussion just as misuse of any other tool. Thorough criticism can provide very important lessons though the process could be mistaken as harsh or personal; neither is the case here. At the least, such analyses can point to potential pitfalls that could be avoided in the development of new theories. As will be discussed, theories are important for the development of therapies but perhaps most important, for the acceptance of new therapies, as was the case for the recent resurgence of interest in surgical therapies.

The Current State of Understanding

The current state of understanding, or theory, regarding the pathophysiology and physiology of the basal ganglia, particularly as it relates to the clinical phenomenology of movement disorders, is in a state of disarray; even if many physicians and scientists do not perceive this. The field is plagued by conceptual confusion, lack of rigor and complacency. Note this statement is not a value judgment of any individual but reflects the current process of gaining scientific understanding in this field. Also this statement does not say that there have not been any advances in scientific facts or technological improvements. Indeed, there have been a remarkable explosion in scientific and technological advances; however, generally they represent incremental increases of a kind within the current state of knowledge. The scientific and technological advances were either serendipitous or merely incremental inter-

polations within the same conceptual framework. The latter is due to the fact that the current conceptual framework generates the hypotheses and at the same time becomes the basis for interpreting the very observations that are meant to be tests of the hypotheses. This circularity leads to validation that is no more than tautology. Most recent theories of basal ganglia physiology and pathophysiology may have internal validity but this does not vouchsafe external validity or validity in the real world. But even granting some internal validity, it is at the expense of any claim to intellectual rigor. Those claims of rigor are given up when there is an arbitrary selectivity in what constitutes valid evidence. In other words, too often, current theories survive only when contravening observations are ignored.

What is addressed in this review is the state of understanding which is different than the state of knowledge. What is meant by state of understanding is the conceptual framework or theory that provides a context for the scientific facts and provides a trajectory to gaining new facts. The current conceptual framework is exhausted. Progress will only be made outside the current conceptual framework that, necessarily, means a rejection of the current framework.

These are bold, and perhaps brash statements but if the author is only partially correct, then the future of scientific understanding of the physiology and pathophysiology that underlie the clinical phenomenology is in doubt and at risk. Even if it is only partially true that future therapeutic advances depend on scientific advances, then physicians must insist on a critical, rigorous, and deep reappraisal of current conceptual approaches. It will be insufficient to merely state that the current theories of basal ganglia physiology and pathophysiology are wrong; it will be necessary to examine how they came to be wrong in the first place. This article cannot hope to be a complete and exhaustive reappraisal but it can provide a survey of the various issues, problems, and possible alternatives.

The Globus Pallidus Interna Rate Theory as the Exemplar

The archetypical theory under analysis is the Globus Pallidus Interna Rate theory that posits over-activity of the globus pallidus interna as causal to hypokinetic disorders such as Parkinson's disease. Similarly, the theory also posits that under-activity of the globus pallidus interna results in hyperkinetic disorders such as ballism and Huntington's disease. In the case of hypokinetic disorders associated with degeneration of dopaminergic neurons of the substantia nigra pars compacta, the loss of dopaminergic inhibition of striatal neurons that project to the globus pallidus externa (called the indirect pathway) is posited to result in increased activity of these striatal neurons. As these particular striatal neurons are inhibitory onto neurons

of the globus pallidus externa, there is a reduction of neuronal activity within the globus pallidus externa. As the globus pallidus externa is thought to be inhibitory onto neurons of the subthalamic nucleus and globus pallidus interna, the reduction in activity of the globus pallidus externa results in increased neuronal activity in the subthalamic nucleus and globus pallidus interna. The increased activity in the subthalamic nucleus increases the activity of the globus pallidus interna as the subthalamic nucleus is thought to be excitatory onto the globus pallidus interna.

Similarly, loss of excitatory dopaminergic input onto the striatal neurons that project to the globus pallidus interna (called the direct pathway) results in decrease in the activity of these striatal neurons causing a loss of these striatal neuronal inhibition onto the globus pallidus interna. The net result is further increase in the activity of globus pallidus interna neuronal activities.

The net result of changes in neuronal activities in both the direct and indirect pathways is increased activity of the globus pallidus, which is theorized to be inhibitory onto neurons of the ventrolateral thalamus. The consequence is reduced activity within the ventrolateral thalamic-motor cortical system that results in decrease activity within the motor cortex and the hypokinetic symptoms of Parkinson's disease.

The Globus Pallidus Interna Rate theory is wrong for a great number of reasons (described elsewhere⁴). They are briefly summarized here in historical order to demonstrate that there has been counter evidence of long standing which raises serious questions about why the Globus Pallidus Interna Rate theory survived and continues to survive to this day. First, evidence is presented that over-activity of the globus pallidus interna is not a necessary condition for parkinsonism as parkinsonism can exist without increased globus pallidus interna neuronal activity.

1) Since 1979, induction of parkinsonism in non-human primates using dopamine antagonists and electrolytic lesions of the nigro-striatal pathway had not been associated with increased neuronal activity in the globus pallidus interna.⁵

2) In 1979, it was reported that globus pallidus interna neuronal activities initially were increased in non-human primates following induction of parkinsonism using n-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), but the neuronal activities tended towards normal rates following MPTP while the animals were, presumably, still parkinsonian.⁶

3) Since 1986, careful induction of parkinsonism in non-human primates with MPTP did not produce changes in neuronal activities of the striatum, globus pallidus externa or ventrolateral thalamus as predicted by the Globus Pallidus Interna Rate theory.⁷ These observations were extended to the globus pallidus interna and reported in 2009.⁸

4) Since 1989, recordings of neuronal activity in the motor cortex and supplementary motor area demonstrate no changes

in baseline or resting neuronal activities following induction of parkinsonism using MPTP.⁹⁻¹¹

5) Recordings of neuronal activity in the subthalamic nucleus of patients with Parkinson's disease and patients with epilepsy in 2006 demonstrate no change in mean discharge frequencies or in the variability (coefficient of variation) in the discharge rate. Further, the neuronal spike trains of both patients demonstrated the same random Poisson process.¹²

Similarly, there is considerable evidence that over-activity of the globus pallidus interna neurons is not a necessary condition. In other words, it is possible to increase the activity of globus pallidus interna neurons without causing parkinsonism. Evidence is summarized below.

1) DBS of the globus pallidus interna in non-human primates, of the type found therapeutic in humans, drives the output of the globus pallidus interna.¹

2) DBS of the subthalamic nucleus in non-human primates and humans with Parkinson's disease, of the type found therapeutic in humans, drives the output of the globus pallidus interna.²⁻⁴

3) DBS of the globus pallidus interna in humans drives the output of the globus pallidus interna as evidenced by recordings of ventrolateral thalamic neuronal recordings during globus pallidus interna DBS and yet the patient was not made parkinsonian.⁵

4) DBS of the subthalamic nucleus on one side of the brain causes increased neuronal activities in the contralateral subthalamic nucleus and yet, the parkinsonian symptoms ipsilateral to the stimulation in patients are improved and not worsened as would be expected from the Globus Pallidus Interna Rate theory.⁶

5) Preliminary studies of DBS of the globus pallidus interna on one side of the brain causes increased neuronal activities in the contralateral globus pallidus interna and yet, the parkinsonian symptoms ipsilateral to the stimulation in patients are improved and not worsened as would be expected from the Globus Pallidus Interna Rate (Montgomery Jr. EB, Walker HC and Watts RL, 2009 unpublished observations).

Over-activity of the globus pallidus interna is neither necessary nor sufficient for the production of parkinsonism and consequently; thus, it is highly unlikely that over-activity of the globus pallidus interna is causal to hypokinetic syndromes such as Parkinson's disease. Similarly, there is evidence against the notion that under-activity of the globus pallidus interna is causal to hyperkinetic disorders such as Huntington's disease, levodopa-induced dyskinesia or dystonia. The most compelling evidence is the improvement in hyperkinetic disorders by surgical ablation of the globus pallidus interna (pallidotomy).

Yet despite the robust contravening scientific observations, the Globus Pallidus Interna Rate theory still is championed, though in the guise of increased anatomical complexity, with only at most, most indirect and causal nod to dissenting opin-

ions related to the neuronal pathophysiology.^{7,8}

Issue of Scientific and Logical Rigor

It takes only a single counterexample to defeat any induction. To be sure there is evidence demonstrating an association of over-activity of the globus pallidus interna and subthalamic nucleus such as following induction of parkinsonism using MPTP in laboratory animals. However, the fact that careful titration of MPTP produces parkinsonism in non-human primates that does not produce over-activity strongly suggests that those studies demonstrating increased neuronal activity within the globus pallidus interna may have used excessive MPTP which affects not only the dopaminergic neurons.⁹ To be sure, there have been many more articles published demonstrating increased globus pallidus interna activity associated with MPTP-parkinsonism than publications demonstrating no increase in neuronal activity, but scientific (and logical) validity is not a matter of majority vote. There are countless more observations of the sun moving above the earth than there are observations of the earth moving around the sun. In the process of logical or scientific induction, it only takes a single contrary example to disprove the induced principle.

It is important to understand nature of robustness in multiple lines of converging evidence. In an exchange of letters to the editors regarding this issue 2009, Montgomery pointed to microelectrode recordings of subthalamic nucleus neurons in subjects with epilepsy and Parkinson's disease and noted no difference in discharge frequency or variability of discharge rate in direct contradiction to the Globus Pallidus Interna Rate theory.¹⁰ In a counter argument, Obeso and Olanow¹¹ cited the plethora of studies supporting the notion that the globus pallidus interna and subthalamic nucleus is overactive. These included recordings of neuronal activities in the MPTP- and 6-hydroxydopamine (6-OHDA)-parkinsonian laboratory animals. However, the failure of this counter-argument is discussed above. Obeso and Olanow go on to cite changes in cytochrome oxidase and glutamic acid decarboxylase immunostaining and in situ hybridization, 2-deoxyglucose uptake in parkinsonian human and laboratory animals, and ¹⁸C-H₂O positron emission tomography showing hypoactivity of motor cortical areas in patients with Parkinson's disease which was reversed by pallidotomy.

There are at least two issues with the remaining counter argument. First, Obeso and Olanow appeal to the notion of robustness of the multiple types of data, such as the enzymatic, glucose, and blood flow changes, as significant support for the claim of over-activity of the globus pallidus. However, such evidentiary robustness depends on the independence of the various claims.¹² Thus, a multitude of ways to look at the same metabolic changes does not constitute a multitude of independent corroborations. There is essentially only a single claim; that is

there are metabolic changes. Thus, the multiple claims related to metabolic and enzymatic changes do not increase the robustness of the claims in support of the over-activity of the globus pallidus interna.

The second issue is whether enzymatic and metabolic changes trump direct microelectrode recordings regarding the claim of increased neuronal activity of the globus pallidus interna. This does not seem reasonable. There is considerable evidence that inferences drawn from neurometabolic changes are highly problematic and do not necessarily correlate with specific aspects of neuronal electrical activity.¹³ Indeed, recordings of neuronal activities in the basal ganglia of non-human primates made parkinsonian by careful titration of MPTP and 2-deoxyglucose autoradiography demonstrated robust changes in glucose utilization in the same animals that did not have any changes in baseline neuronal activities.¹⁴ This places further doubt on the reasonableness of using neurometabolic inferences to neuronal activities to trump direct recordings of neuronal activities.

There is a human inclination to disregard contrary observations. Perhaps to circumvent the difficulty of allowing neurometabolic and enzymatic changes to trump direct neuronal recordings, Obeso and Olanow wrote "Although we do not question his findings, it should be noted that his is the only report we are aware of indicating that subthalamic nucleus firing rate is as low as 7.5 Hz in PD, and contrasts with multiple reports of greater firing rates (approximately 30 Hz) in the subthalamic nucleus of patients with PD. Indeed, we wonder if the low subthalamic nucleus firing frequencies that Montgomery reported were derived from non-movement-related neurons in the ventral subthalamic nucleus, which typically have a lower firing frequency than those in the dorsolateral motor region." What Obeso and Olanow failed to note was that in the report by Montgomery¹⁵ it was clearly stated that the neurons analyzed demonstrated sensory-motor driving consistent with these neurons being the relevant neurons and further and that the differences likely were related to different methods of neuronal spike detection which was applied to both subjects with Parkinson's disease and epilepsy. Thus, any systematic bias resulting from the different method would apply to both subjects and would not account for the lack of difference.

Another striking example was the early studies on the effects of the neurotoxin, MPTP on neuronal activity in the globus pallidus interna. Filion and colleagues were one of the first to demonstrate that MPTP-parkinsonism in the non-human primate was associated with increased neuronal discharge rate in the globus pallidus interna. It is now known that this is not the case necessarily, and may reflect excessive doses of MPTP. The striking aspect is that Filion and colleagues earlier studied the effects of parkinsonism caused by neuroleptic medications, that is drug-induced parkinsonism, and parkinsonism caused by lesions of the dopaminergic nigro-striatal pathway. They

found no increases in the neuronal discharge frequency in the globus pallidus interna in these parkinsonian non-human primates. The absence of changes in neuronal activity in the globus pallidus interna in these examples of parkinsonism are definitive evidence that the presence of increased activity in the globus pallidus interna is not a necessary condition for parkinsonism.

The question is why did the results of MPTP-parkinsonism trump parkinsonism induced by neuroleptics or lesions of the nigro-striatal pathway. It cannot be because MPTP-parkinsonism in non-human primates had a human analogue whereas the latter did not. Neuroleptic drug-induced parkinsonism in humans is a well established entity. Similarly, there have been case reports of strokes involving the substantia nigra causing parkinsonism in humans. One suspects that the MPTP-induced changes in globus pallidus interna neuronal activity was taken as prototypical while the lack of changes in the case of neuroleptics and structural lesions discounted and subsequently ignored is because the MPTP related changes were consistent with the emerging Globus Pallidus Interna Rate theory. It is human nature to retain a theory with strong intuitive appeal even in the presence of strong contrary evidence.¹⁶

Importance of the State of Understanding (Theory)

The question may arise “why be concerned about theories of physiology and pathophysiology?” Virtually every therapy for Parkinson’s disease, for example, arose before or independent of the Globus Pallidus Interna Rate theory. Even the Dopaminergic/Cholinergic imbalance theories that were predecessors to the Globus Pallidus Interna Rate theory followed from and did not predict pharmacological therapies. Dopaminergic and anti-cholinergic therapies; surgical ablative therapies, such as thalamotomy, pallidotomy, subthalamotomy¹⁷; and DBS¹⁸ were in use before the advent of the Globus Pallidus Interna Rate theory. Subthalamic DBS developed after the Globus Pallidus Interna Rate theory but this was an extension of surgical ablative therapies as evidenced by the early claims that high frequency DBS inhibited the stimulated target, which is now known to be false.³ The possible exception is the notion of reversing the neurotransmitter effects of the subthalamic nucleus onto the globus pallidus interna with an attempt to convert from the normal excitatory neurotransmitter, glutamate, to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).¹⁹ The notion is that over-activity of the subthalamic nucleus would suppress over-activity in the globus pallidus interna.

The argument is advanced that the development of the Globus Pallidus Interna Rate theory was largely responsible for the resurgence of interest in pallidotomy and subsequently, DBS, in the early 1990’s.¹⁸ Alternative explanations, such as

advanced imaging and surgical techniques are insufficient. Indeed, some of the leaders in DBS surgery employed ventriculograms for localization in the same manner as done decades earlier. Also, it was not as though there were sudden failures of other therapies such as pharmacological approaches. The long term complications and problematic responses to levodopa were apparent from the first large scale clinical use and for those reasons, controversies over the role of levodopa as initial therapy in Parkinson’s disease broke out as soon as there were viable alternatives, the first being bromocriptine.

The development of the Globus Pallidus Interna Rate theory provided a cogent rationale for, initially, pallidotomy, and subsequently DBS as reflected in a commentary by Goetz et al.²⁰ Thus, in a practical sense, theories are important. The Globus Pallidus Interna Rate theory provided intellectual cover for resurgence in surgical therapies. These therapies doubtlessly improved the quality of life for tens of thousands of patients so the resurgence of surgical therapies was “right” but for the “wrong reason”.

The question is whether the Globus Pallidus Interna Rate theory has “outlived” its usefulness and now represents an impediment. What clearly are hypotheses in the Globus Pallidus Interna Rate theory have taken on the epistemic status of fact (termed quasi-fact) and have become arbitrators of grants and publications effectively blocking consideration of alternative hypotheses. Admittedly this claim is based on the author’s personal experience and informal discussions with colleagues. The necessary evidence seldom is made readily available. Still, the validity of the claim is reasonable to raise.

Conceptual Confusion

Perhaps contrary to popular belief, the Globus Pallidus Interna Rate theory is not a theory of physiology or pathophysiology. Rather, the theory is an anatomical and neurochemical theory that has been extrapolated into a theory of physiology.²¹ The approach is to substitute a single macro-neuron for the anatomical structures within the basal ganglia-thalamic-cortical system; in the case of the striatum, there are two macro-neurons, one each for the direct and indirect pathways. The theory then asks, based on their neurotransmitters, how would these neurons interact? The result is a one-dimensional push-pull dynamics that were described above. The consequences and failures of this macro-neuron one-dimensional push-pull theory have been reviewed elsewhere.^{9,21,22} The greatest problem of the Globus Pallidus Interna Rate theory is the complete lack of appreciation for dynamics, which is change in neuronal activities and states over time. Merely piecewise increments in the complexity of the anatomy from that inherent in the Globus Pallidus Interna Rate theory is not likely to meet much greater success. Rather, increases in complexity to the point of qualitative, rather than just quantitative, changes in

the dynamics will be necessary, such as those of Complex Systems theory involving chaotic and non-linear interactions.^{23,24}

A central and critical feature in the Globus Pallidus Interna Rate theory is the effects of putative inhibitory neurotransmitters. Indeed, the one-dimensional push-pull dynamics rest on the notion of reciprocal activities in structures connected by pathways mediated by GABA. The changes in the in the efferent structure (the source of the GABAergic neurotransmission) is reciprocal to the activities in the afferent (where the effects of GABA take place). However, the reality is not so simple. Recordings of ventrolateral thalamic neuronal activities during high frequency DBS of the globus pallidus interna demonstrate an inhibition approximately 3 ms after the stimulation pulse lasting approximately 3 ms and consistent with inhibition of ventrolateral thalamic neurons by the output of the globus pallidus interna. However, the inhibition of the ventrolateral thalamic neurons was followed by rebound post-inhibitory rebound excitation.⁵ For the many ventrolateral thalamic neurons, the rebound excitation was sufficient to result in a net excitation following activation of globus pallidus interna output. Similarly, post-inhibitory rebound excitation has been demonstrated in the rodent endopeduncular nucleus (the rodent analog of the globus pallidus interna)²⁵ and subthalamic nucleus.²⁶ Thus, the Globus Pallidus Interna Rate theory fails, as it cannot account for the effects of post-inhibitory rebound excitation.

The conceptual confusion is equating the direct effects of inhibitory neurotransmitter effects on post-synaptic membrane potentials with a larger scale physiology of the neuronal response. There is nothing about GABA that consideration about it would necessarily lead to the notion of post-inhibitory rebound excitation. Consequently, extrapolation from GABA, in terms of its chemical nature, does not lead, necessarily, to the physiological consequences, and indeed, in the Globus Pallidus Interna Rate theory, it leads to the wrong conclusion. The importance of post-inhibitory rebound excitation is well appreciated in the invertebrate nervous system²⁷ and has lessons for any future theory of basal ganglia physiology and pathophysiology. Unfortunately, there is a long history of equating neurochemistry with physiology.²⁸

The conceptual confusion relative to arbitrarily assigning priority to observations gleaned from MPTP-*induce* parkinsonism over those from other forms of parkinsonism parallels another conceptual confusion regarding the nosology of parkinsonism and Parkinson's disease. There are a number of different levels or approaches to the definition of parkinsonism: these include syndromic or phenotypic, that is based on symptoms and signs; pathological; genetic; and neurochemical. Contrary to the aspirations of scientific reductionism, these approaches do not and cannot achieve a single consilience such that any conceptualization becomes universal or not context dependent. In other words, there are many forms of parkinson-

ism depending on the circumstances and the questions to be answered. Conflation of these different notions will skew and limit understanding.

The prototypical example of the neurochemical approach is to equate parkinsonism with dopamine deficiency. Therapeutic replenishment of dopamine would seem to follow naturally. Dopamine responsiveness then seems to be a logical criterion for parkinsonism though it has to be admitted that such logic is circular. The problem is that, not infrequently, patients, who have all the symptoms and signs of parkinsonism in a manner identical to those with dopamine responsive parkinsonism, do not respond to dopamine replacement. Often this is attributed to atypical parkinsonism associated with a unique pathology; however, autopsy control studies demonstrate patients with pathological idiopathic Parkinson's disease that do not respond to dopamine replenishment therapy.²⁹

The problematic nature of conflating the syndromic and neurochemical criteria is seen in the discovery of patients with "symptoms without evidence of dopamine deficiency" (referred to as SWEDDs). Retrospective re-consideration has led some to claim that these patients have a form of dystonia and therefore should not be confused with Parkinson's disease. This smacks of "post hoc ergo propter hoc" illogic. The patients with SWEDDs were first identified during the course of clinical trials of medications for idiopathic Parkinson's disease and were diagnosed by some of the most capable movement disorders neurologists. Thus, the reasonable conclusion is that the syndromic (or phenotypic) definition of Parkinson's disease does not stand in a one-to-one correspondence with the neurochemical definition, that being dopamine depletion. Nor is the relation of phenotypic and neurochemical definitions stand as in the form "if and only if" logic; that is one has phenotypic criterion if and only if one has a dopamine deficiency.

The fact of the matter is that parkinsonism can be associated with many different pathologies including those that do not necessitate dopamine deficiency. Lesions of the globus pallidus externa,³⁰ striatum,³¹ and supplementary motor area³² have been associated with parkinsonism. Similarly, effective treatments include direct electrical stimulation of the subthalamic nucleus, globus pallidus interna, ventrolateral thalamus, motor cortex and striatum and do not presuppose dopamine replenishment. The significance of these observations is that there must be numerous mechanisms that produce the symptoms, signs and disabilities of parkinsonism or perhaps, a set of variations along the same theme, the latter notion favored by Occam's razor. What is striking is that these different mechanisms or variations do not appear to be considered in current theories and why these alternative mechanisms or variations have not been subject to investigation and exploitation for new therapies. Perhaps the old adage "When the only tool you have is a hammer you tend to see every problem as

a nail” (Abraham Maslow). When all one has is an anatomical/neurochemical theory with dopamine as its center point, then everything seems to revolve around dopamine.

Conceptual Complacency

The first publications of the Globus Pallidus Interna Rate theory were in 1989.³³ To be sure, there have been numerous published criticisms but these have been more technical such as at the level of anatomical and neurochemical complexity and not at the conceptual level.³⁴⁻³⁶ Indeed, some of the leading critics of the Globus Pallidus Interna Rate theory also have been its most consistent advocates⁸; thus, evidence of the continued appeal of the underlying conceptual structure of the Globus Pallidus Interna Rate theory. Indeed, it is the continued invidious acceptance of the conceptual structure of the Globus Pallidus Interna Rate theory that allows the theory to continue despite the mounting contrary specific observations. Indeed, a leading advocate pointed out would should have been a fatal flaw many years ago, that being that pallidotomy improved dyskinesia when, according to the Globus Pallidus Interna Rate theory, the opposite should have been the case.

There are numerous corollaries and presuppositions that could have provided tests of the Globus Pallidus Interna Rate theory that appear to have escaped notice. This could only be if such corollaries or presuppositions were taken or assumed to be true or self-evident and consequently of little need for testing. But how can any theory of basal ganglia physiology and pathophysiology be considered complete unless a full and direct causality extends from degeneration of dopamine neurons in the substantia nigra pars compacta to the activities of the motor units that drive the phenotypic expression. The motor unit is the set of muscle fibers innervated by individual lower motor neurons in the spinal cord and brainstem.

In one way, the Globus Pallidus Interna Rate theory obviates the necessity of a direct causal link all the way to the motor units by claiming that the basal ganglia, and particularly, the globus pallidus interna, do not generate the specific programs determining motor unit behavior; this is done elsewhere (such formulation is the essence of a theory of physiology derivative of the Globus Pallidus Interna Rate theory called the Action Selection/Focused Attention theory). Rather the role of the basal ganglia is to select which, presumably, pre-defined motor program is to be executed much like the role of a librarian in selecting books off the shelf. However, what is the evidence that motor programs exist as discrete ontological entities like books on a shelf? The answer is virtually no evidence. Yet, it would seem that this would be an important presupposition of the Globus Pallidus Interna Rate theory to validate.

An alternative is that over-activity of the globus pallidus interna merely dampens activity within the ventrolateral thalam-

ic-motor cortical circuit and thus, motor programs lack sufficient “energy” to sufficiently drive movement and bradykinesia and akinesia result. However, there are contrary observations. First, patient’s bradykinesia depends on the conditions, for example, patients can move as fast to large targets as normal subjects can move to smaller targets.³⁷ Also, there is the phenomenon of hastening where subjects are asked to tap in synchrony with a metronome of increasing frequency.³⁸ Normal subjects are able to precisely follow the increasing frequency whereas patients with Parkinson’s disease fall behind the metronome, then “jump ahead” by tapping more frequently, then again fail behind. Further, the notion of insufficient activation would not explain the observation of co-contraction of antagonist muscles potentially interfering with the actions of the agonists thereby disrupting movement.³⁹ Clearly, parkinsonism is not merely a issue of insufficient activation of motor units.

Recent studies of motor unit recruitment suggest a very direct role in constructing the program for the orchestration of motor units necessary for normal movement. Small motor units, defined by the number of muscle fibers innervated by the lower motor neuron, are recruited first at low force requirements. As the force requirements increase, progressively larger motor units are recruited. Parkinson’s disease alters the normal recruitment and in some cases reverses the order such that large motor units are recruited before smaller units resulting in abnormal increase in generated force (Montgomery, Haung, Walker and Watts, unpublished observations, 2010). Thus, the role of the basal ganglia-thalamic-cortical system is much more complex than merely selecting pre-defined movements or “energizing” muscle activations. There is nothing in the Globus Pallidus Interna Rate theory that could explain the effects of Parkinson’s disease on the order of motor unit recruitment.

Summary

Conceptual understandings, embodied by theories, are important and drive science and innovation, or they can hinder. A notion of scientific progress as incremental and progressive refinement of conserved knowledge is unlikely to be true. More often, new scientific hypotheses are born in opposition to current theories. They seem incremental only because the subject matter is the same. However, success in scientific advancement will best be served when the scientific community nurtures the “loyal opposition”. This will happen only when it is seen as necessary and for that the highest levels of rigor and the active avoidance of complacency are critical. It is past time for efforts to explore and test radical alternatives to the Globus Pallidus Interna Rate theory; radical because the basic presuppositions, assumptions, conceptual antecedents underlying the Globus Pallidus Interna Rate theory need to be thorou-

ghly exposed and critiqued so that successor theories do not share the same fate.

Conflict of Interest

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REFERENCES

- Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. *J Neurophysiol* 2003;89:1150-1160.
- Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci* 2003;23:1916-1923.
- Montgomery EB Jr, Gale JT. Mechanisms of action of deep brain stimulation (DBS). *Neurosci Biobehav Rev* 2008;32:388-407.
- Reese R, Leblois A, Steugerwald F, Deuschl G, Meissner W, Volkman J. Mechanisms of subthalamic high frequency stimulation-A single case study in a parkinsonian patient. Program No. 326.4. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online, 2009.
- Montgomery EB Jr. Effects of GPi stimulation on human thalamic neuronal activity. *Clin Neurophysiol* 2006;117:2691-2702.
- Walker HC, Huang H, Guthrie SL, Guthrie BL, Watts RL Jr. MEB. Subthalamic neuronal activity is altered by contralateral subthalamic deep brain stimulation in Parkinson disease. *Movement Disorders Society International Congress*, 2008.
- Obeso JA, Marin C, Rodriguez-Oroz C, Blesa J, Benitez-Temiño B, Mena-Segovia J, et al. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. *Ann Neurol* 2008;64 Suppl 2:S30-S46.
- Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. *Nat Rev Neurosci* 2010;11:760-772.
- Montgomery EB Jr. Basal ganglia physiology and pathophysiology: a reappraisal. *Parkinsonism Relat Disord* 2007;13:455-465.
- Montgomery EB Jr. Basal ganglia pathophysiology in Parkinson's disease. *Ann Neurol* 2009;65:618.
- Obeso JA, Olanow CW. Basal ganglia pathophysiology in Parkinson's disease reply to Montgomery. *Ann Neurol* 2009;65:618-619.
- Shapin S. *Never Pure: Historical Studies of Science as if It Was Produced by People with Bodies, Situated in Time, Space, Culture, and Society, and Struggling for Credibility and Authority*. Baltimore: The Johns Hopkins University Press, 2010.
- Logothetis NK. The ins and outs of fMRI signals. *Nat Neurosci* 2007;10:1230-1232.
- Montgomery EB Jr, Buchholz SR, Delitto A, Collins RC. *Alterations in Basal Ganglia Physiology Following MPTP in Monkeys*. New York: Academic Press, 1986.
- Montgomery EB Jr. Subthalamic nucleus neuronal activity in Parkinson's disease and epilepsy subjects. *Parkinsonism Relat Disord* 2008;14:120-125.
- Johnson-Laird PN. *How We Reason*. New York: Oxford University Press, 2006.
- Fager CA. Evaluation of thalamic and subthalamic surgical lesions in the alleviation of Parkinson's disease. *J Neurosurg* 1968;28:145-149.
- Hariz MI, Blomstedt P, Zrinzo L. Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg Focus* 2010;29:E1.
- During MJ, Kaplitt MG, Stern MB, Eidelberg D. Subthalamic GAD gene transfer in Parkinson disease patients who are candidates for deep brain stimulation. *Hum Gene Ther* 2001;12:1589-1591.
- Goetz CG, De Long MR, Penn RD, Bakay RA. Neurosurgical horizons in Parkinson's disease. *Neurology* 1993;43:1-7.
- Montgomery EB Jr. Dynamically Coupled, High-Frequency Reentrant, Non-linear Oscillators Embedded in Scale-Free Basal Ganglia-Thalamic-Cortical Networks Mediating Function and Deep Brain Stimulation Effects. *Nonlinear Studies* 2004;11:385-421.
- Montgomery EB Jr. Theorizing about the role of the basal ganglia in speech and language: the epidemic of miss-reasoning and an alternative. *Communicative Disorders Review* 2008;2:1-15.
- Strogatz SH. *Nonlinear Dynamics and Chaos*. Cambridge, Massachusetts: Perseus Publishing, 1994.
- Strogatz SH. Exploring complex networks. *Nature* 2001;410:268-276.
- Nakanishi H, Kita H, Kitai ST. Intracellular study of rat entopeduncular nucleus neurons in an in vitro slice preparation: electrical membrane properties. *Brain Res* 1990;527:81-88.
- Bevan MD, Magill PJ, Hallworth NE, Bolam JP, Wilson CJ. Regulation of the timing and pattern of action potential generation in rat subthalamic neurons in vitro by GABA-A IPSPs. *J Neurophysiol* 2002;87:1348-1362.
- Marder E, Bucher D. Central pattern generators and the control of rhythmic movements. *Curr Biol* 2001;11:R986-R996.
- Valenstein ES. *The War of the Soups and Sparks: The Discovery of Neurotransmitters and the Dispute over How Nerves Communicate*. New York: Columbia University Press, 2005.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181-184.
- Klawans HS, Stein RW, Tanner CM, Goetz CG. A pure parkinsonian syndrome following acute carbon monoxide intoxication. *Arch Neurol* 1982;39:302-304.
- Goto SM, Matsumoto S, Ushio Y, Hirano A. Subregional loss of putaminal efferents to the basal ganglia output nuclei may cause parkinsonism in striatonigral degeneration. *Neurology* 1996;47:1032-1036.
- Dick JP, Benecke R, Rothwell JC, Bay BL, Marsden CD. Simple and complex movements in a patient with infraction of the right supplementary motor area. *Mov Disord* 1986;1:255-266.
- Albin RL, Young AB, Penny JB. The functions anatomy of basal ganglia disorders. *Trends Neurosci* 1989;12:366-375.
- Parent A, Cicchetti F. The current model of basal ganglia organization under scrutiny. *Mov Disord* 1998;13:199-202.
- Parent A, Sato F, Wu Y, Gauthier J, Lévesque M, Parent M. Organization of the basal ganglia: the importance of axonal collateralization. *Trends Neurosci* 2000;23:S20-S27.
- Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, et al. The physiology of the basal ganglia in Parkinson's disease. *Trends Neurosci* 2000;23 Suppl:S8-S19.
- Montgomery EB Jr, Nuessen J. The movement speed/accuracy operator in Parkinson's disease. *Neurology* 1990;40:269-272.
- Freeman JS, Cody FW, Schady W. The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1993;56:1078-1084.
- Montgomery EB Jr, Nuessen J, Gorman DS. Reaction time and movement velocity abnormalities in Parkinson's disease under different conditions. *Neurology* 1991;41:1476-1481.