

Letters to the Editor

The Current Model of Basal Ganglia Organization: A Clinician's View

Parent and Cicchetti comment that the current model of basal ganglia organization is obsolete, because it has failed to integrate essential anatomic and functional information.¹ Although some neurobiologic data allow a criticism of part of the synthesis contained in this model, evidence based on clinical practice supports it. In the scientific making, models are to provide a synthetic and innovative view on a specific subject and this is clearly the case for the current basal ganglia model. The possibility to disprove a theory (or part of it) supports, rather than weakens, its scientific value.² Furthermore, recent clinical evidence has strongly supported the model despite, or as a result of, its disarming simplicity, whereas fundamental research has progressively collected data which are at odds. Thus, the extreme synthesis provided by the model strengthens its value while providing at the same time matter for criticism.

The most limiting feature of the current basal ganglia model lies in the classification of basal ganglia nuclei as "hyperactive" or "hypoactive." This crude terminology mainly derives from 2-deoxyglucose activation studies.^{3,4} In physiological terms, hyperactivity of basal ganglia nuclei is considered to correspond to a higher than normal overall neuronal activity, a view confirmed by recordings performed in parkinsonian monkeys.^{5,6} Some of the existing criticism clearly points out the need for modeling at a more detailed level (for example, considering the discharge pattern and rate of neural populations, dendritic and synaptic events). Evidence that the simple schema derived from activation studies particularly does not apply to the globus pallidum externum (GPe) does not disprove the model but rather enriches it. Similar evidence is expected for other basal ganglia nuclei and attempts have already been made to detail the complexity of the functional interplay occurring at the neuronal level in "hyperactive" and "hypoactive" nuclei.^{7,8}

Recent critics to the basal ganglia model have not sufficiently acknowledged what still is its most innovative feature: the central role played by the subthalamic nucleus (STN) in basal ganglia organization and functioning. This has been clearly recognized in earlier reviews⁹ before scientific interest concentrated on the globus pallidum internum (GPi) and the pathways directly or indirectly interconnecting it with the neostriatum. The central role played by the STN is now confirmed by clinical evidence. STN inactivation does not simply allow reversal of all parkinsonian features (including rigidity, akinesia, tremor, festination, and off-related freezing),¹⁰⁻¹³ but also compensates for the reduction of antiparkinsonian medication, including levodopa and dopamine agonists. To the contrary, GPi inactivation inhibits the antiparkinsonian efficacy of levodopa, as correctly predicted by the model.¹⁴⁻¹⁶

In a series of seven patients with Parkinson's disease (PD) who were implanted for bilateral STN neurostimulation at the Gemelli Hospital, Unified Parkinson's Disease Rating Scale motor scores in the off-state improved by 42% whereas levo-

dopa equivalent daily doses were reduced by 65% (Table 1). On-state motor condition did not vary, showing that the effect of antiparkinsonian medication did not add up to STN inactivation. The possibility to compensate for a reduction in dopaminergic medication by a functional inactivation of the STN provides substantial support to the role assigned to this nucleus by the current basal ganglia model.

By contrast, critics, based on earlier and more recent experimental data particularly, question the role assigned by the model to the GPi and the GPe. In keeping with this, it has been observed that functional inactivation of the GPi in PD patients has not provided unequivocal results.^{17,18} Notwithstanding, physiological recordings performed in PD patients undergoing basal ganglia surgery have shown that, as predicted by the model, GPi neurons have an increased firing rate which is counteracted by injecting the anti-parkinsonian agent apomorphine.¹⁹ Taken together, clinical data do not indicate that the information provided by the model is wrong, rather that it is incomplete. Clinical evidence requires that the roles assigned to the GPi and to the GPe be expanded and refined.

Although the basal ganglia model adequately explains the elementary pathophysiology of parkinsonian signs and that of choreic disorders,^{20,21} it is inadequate for dystonia or tics. Some patients with primary dystonia benefit from GPi inactivation,²² indicating that a direct interference with basal ganglia outflow pathways is helpful. Response of dystonia to different medications is also poorly predictable, making pathophysiological interpretations based on neurotransmitter function untenable.²³ It appears that the current level of simplification does not provide an adequate interpretation for dystonia, and knowledge on the finer tuning of function at a physiological and pharmacologic level is indeed required.

In summary, current clinical studies provide a direct evalua-

TABLE 1. Bilateral STN stimulation in severe PD patients allows reduction of drug therapy to improve off-state and to reduce maximal differential fluctuation

	Before surgery	Last available visit (on stimulation)	Variation
Worst measured off	67.6 ± 9.9	39.3 ± 12.0	-42%
Best measured on	29.3 ± 9.4	30.5 ± 12.4	5%
Maximal differential fluctuation*	56.7%	21.3%	-34.8%
Total LEDD†	1507.3	521.3	-65.4%

STN, subthalamic nucleus; PD, Parkinson's disease.

* Percent variation of UPDRS-III in best on as compared with worst off.

† Levodopa equivalent daily dose (LEDD) was computed for each drug by multiplying the total daily dose by the potency relative to a standard levodopa preparation: levodopa controlled-release preparations = 0.77, bromocriptine = 10, apomorphine = 50, pergolide = 100. The total LEDD is then calculated.

ation in people of the theory of basal ganglia function and allow verification of the model. The currently available model is an excellent basis for collecting new experimental and clinical data aimed at expanding current knowledge in view of a new synthesis to come.

Alberto Albanese, MD
Service de Neurologie
Université de Lausanne
Lausanne
Istituto di Neurologia
Università Cattolica del Sacro Cuore
Rome, Italy

References

1. Parent A, Cicchetti F. The current model of basal ganglia organization under scrutiny. *Mov Disord* 1998;13:199–202.
2. Popper K. *Logik der Forschung*. Vienna: J. Springer, 1934.
3. Crossman AR, Mitchell IJ, Sambrook MA. Regional brain uptake of 2-deoxyglucose in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the macaque monkey. *Neuropharmacology* 1985;24:587–591.
4. Mitchell IJ, Jackson A, Sambrook MA, Crossman AR. Common neural mechanisms in experimental chorea and hemiballismus in the monkey. Evidence from 2-deoxyglucose autoradiography. *Brain Res* 1985;339:346–350.
5. Filion M, Tremblay L, Bédard PJ. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* 1991;547:152–161.
6. Miller WC, DeLong MR. Parkinsonian symptomatology. An anatomical and physiological analysis. *Ann NY Acad Sci* 1989;515:287–302.
7. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia [Review]. *Curr Opin Neurobiol* 1996;6:751–758.
8. Chesselet MF, Delfs JM. Basal ganglia and movement disorders: an update. *Trends Neurosci* 1996;19:417–422.
9. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989;12:366–375.
10. Limousin P, Pollak P, Benazzouz A, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995;345:91–95.
11. Krack P, Pollak P, Limousin P, Benazzouz A, Benabid AL. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. *Lancet* 1997;350:1675.
12. Moro E, Meglio M, Scerrati M, Tonali P, Albanese A. Thalamic and subthalamic stimulation for parkinsonian tremor. *Neurology* 1998. In press.
13. Kumar R, Kim YJ, Sime E, et al. Double-blind evaluation of the effects of subthalamic nucleus (STN) deep brain stimulation (DBS) in advanced Parkinson's disease. *Neurology* 1998;50:A79–80.
14. Krack P, Pollak P, Limousin P, Benabid AL. Levodopa-inhibiting effect of pallidal surgery. *Ann Neurol* 1997;42:129–130.
15. Samuel M, Caputo E, Brooks DJ, et al. A study of pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications. *Brain* 1998;121:59–75.
16. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 1994;117:877–897.
17. Krack P, Pollak P, Limousin P, et al. Opposite motor effects of pallidal stimulation in Parkinson's disease. *Ann Neurol* 1998;43:180–192.
18. Bejjani B, Damier P, Arnulf I, et al. Pallidal stimulation for Parkinson's disease: two targets. *Neurology* 1997;49:1564–1569.
19. Hutchison WD, Levy R, Dostrovsky JO, Lozano AM, Lang AE.

Effects of apomorphine on globus pallidus neurons in parkinsonian patients. *Ann Neurol* 1997;42:767–775.

20. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990;13:281–285.
21. Hallett M. Physiology of basal ganglia disorders: an overview. *Can J Neurol Sci* 1993;20:177–183.
22. Lozano AM, Kumar R, Gross RE, et al. Globus pallidus internus pallidotomy for generalized dystonia. *Mov Disord* 1997;12:865–870.
23. Singer C, Weiner WJ. Primary dystonias: current therapeutic recommendations. *CNS Drugs* 1995;3:186–193.

The Current Model of Basal Ganglia Organization Under Scrutiny

I read with great interest the editorial by Parent and Cicchetti¹ on the shortcomings of the currently popular basal ganglia models.^{2–4} I too have been critical of these models⁵ but now must rise to their defense. Parent and Cicchetti point out several pieces of data (many from Parent's work) that contradict the models. Indeed, Parent and his collaborators have made many important contributions to advancing our knowledge of basal ganglia anatomy in the past two decades. Their points are well made and certainly support the premise that it is time to move beyond those models. However, I strongly disagree with the suggestion to “stay away from basal ganglia models for some time.” As an author of a recent model that includes a “boxes and arrow-type” schematic,^{5,6} I acknowledge some personal sensitivity to the criticism of Parent and Cicchetti. Therefore, I will not discuss our model, but will focus on the models of Albin, Penney, and Young² and Alexander, Crutcher, and DeLong.^{3,4}

The failure of these models to account for all currently available data is not the result of shortcomings of the models, per se. Indeed, the strength of the models lies in the specificity of the hypotheses, the testability of the hypotheses, and the amount of interest they generated. If one measures the value of a model by the amount of scientific research it stimulates, these models have been highly successful. Parent and Cicchetti state “Models in science tend to reassure and appease researchers who do not like to wander alone in the universe of knowledge.”¹ That may be true, but good scientific models contain specific hypotheses. Wandering alone in the universe of knowledge does not necessarily make for good science, but careful hypothesis-driven experimental research does. The models have also been important for treatment of basal ganglia diseases. Together with important empirical data,^{7,8} the models provided the important conceptual foundation responsible for the resurgence of stereotaxic ablation procedures for the treatment of movement disorders. Whereas some results of these surgeries do not support the models, others do.⁹

Albin, Penney, and Young acknowledged the limitations of their model, indeed any model.¹⁰ They wrote “What would be most beneficial at this time would be for the model to break down.” Further, they stated “We look forward to the destruction of this model and its resurrection in a more realistic form.” The model has broken down and by virtue of that breakdown we have the opportunity to develop an improved conceptual framework for understanding the normal physiology and pathophysiology of the basal ganglia. The improved framework will include many key aspects of the existing models which have

been proven correct or have not been tested. It must also account for the facts that are pointed out by Parent and Cicchetti.¹ If the next generation of basal ganglia models stimulates as much research as the last, our progress will be great. However, a moratorium on new models will do little to encourage research or further our conceptual understanding of this rich system.

Jonathan W. Mink, MD, PhD
 Movement Disorders Section
 Department of Neurology
 Washington University School of Medicine
 St. Louis, Missouri, U.S.A.

References

1. Parent A, Cicchetti F. The current model of basal ganglia organization under scrutiny. *Mov Disord* 1988;13:199–202.
2. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989;12:366–375.
3. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 1990;13:266–271.
4. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990;13:281–285.
5. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 1996;50:381–425.
6. Mink JW, Thach WT. Basal ganglia intrinsic circuits and their role in behavior. *Curr Opin Neurobiol* 1993;3:950–957.
7. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 1992;76:53–61.
8. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 1990;249:1436–1438.
9. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. *Curr Opin Neurobiol* 1996;6:751–758.
10. Albin RL, Young AB, Penney JB. The functional anatomy of disorders of the basal ganglia. *Trends Neurosci* 1995;18:63–64.

Reply

We thank Drs. Albanese and Mink for their comments on our recent editorial concerning the current basal ganglia model.¹

Albanese has provided some interesting clinical observations, but we disagree with his idea that it is principally the data derived from basic research that are at odds with the model. We believe that there are as many experimental data that are congruent with the model as there are clinical findings that do not follow the model's predictions. Unfortunately, most of the clinical issues raised in our editorial were not directly addressed in Albanese's letter. We concur with Albanese's remark that the subthalamic nucleus occupies a crucial position in basal ganglia organization, a position that was clearly established following experimental studies undertaken before the elaboration of the model.² We also acknowledge the fact that the subthalamic nucleus is hyperactive in Parkinson's disease

(PD), but we argue against the idea that this hyperactivity is mediated only through the indirect pathway. We are thankful to Albanese for having provided new clinical data from stimulation of the subthalamic nucleus and for having drawn our attention to the fact that the current model does not explain dystonia and tics.

Mink rightly argues that, when measured by the interest it has generated, the current basal ganglia model has been highly successful and that science progresses through careful hypothesis-driven experimental work. However, simple and testable hypotheses are not to be confounded with models, which are complex intellectual constructs designed to predict how different entities will behave under various conditions. When examined in that perspective, we consider that the current model is no longer tenable. We question Mink's inference to the model as a source of a resurgence of stereotaxic surgery for movement disorders. Functional surgery has been around for quite some time and this approach was initiated long before any basal ganglia models had ever been formulated. It was particularly popular in the 1950s and early 1960s, at a time when the beneficial effects of pallidotomy or thalamotomy on PD symptoms were thought to result from the elimination of an excessive *excitatory drive* exerted on premotor thalamocortical neurons by the internal pallidum. Functional surgery fell from its pedestal at the end of the 1960s, not because a new model of basal ganglia was born, but because of the discovery that PD was the result of a lack of striatal dopamine that could be overcome by the systemic administration of L-dopa.^{3,4} Likewise, the recent resurgence of stereotaxic surgery was fueled mostly by the need to alleviate the side effects of L-dopa treatment, principally dyskinesia, a phenomenon that was not at all predicted by the current basal ganglia model.

Albanese and Mink are right in assuming that the formulation of a new basal ganglia model could be an exciting endeavor. However, we believe that major breakthroughs in our understanding of basal ganglia are likely to come from elsewhere, particularly from detailed studies of the physiopathologic mechanisms involved in diseases that specifically target this set of subcortical structures.

André Parent, PhD, FRSC
 Francesca Cicchetti, MSc
 Centre de recherche Université Laval Robert-Giffard
 Beauport, Québec, Canada

References

1. Parent A, Cicchetti F. The current model of basal ganglia under scrutiny. *Mov Disord* 1998;13:199–202.
2. Kitai ST, Kita H. Anatomy and physiology of the subthalamic nucleus: a driving force of the basal ganglia. *Adv Behav Biol* 1987;32:357–373.
3. Birkmayer VW, Hornykiewicz O. Der L-3,4-Dioxyphenylalanin (= DOPA)-Effekt bei der Parkinson-Akinese. *Wien Klin Wochenschr* 1961;73:787–788.
4. Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism—chronic treatment with L-dopa. *N Engl J Med* 1969;280:337–345.