Keynote Lecture IV
The Basal Ganglia in Health and Disease

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Paul Bolam received his first degree (1975) and PhD (1979) in pharmacology from the University of London. He then moved to the Department of Pharmacology in Oxford as a Departmental Demonstrator and in 1983 he was awarded an MRC Senior Research Fellowship. In 1985 he joined the MRC Anatomical Neuropharmacology Unit as a Senior Scientist.

Since completing his PhD his main research interest has been the neurobiology of the basal ganglia. He has made many significant contributions to the anatomical and synaptic organisation of the basal ganglia and more recently the physiological organisation, in both normal conditions and in models of Parkinson's disease.

In 1997 he was awarded the title of Professor of Anatomical Neuropharmacology by University of Oxford. He has recently completed a term as President of the International Basal Ganglia Society.

The basal ganglia are a group of sub-cortical nuclei involved in a variety of processes including motor, cognitive and mnemonic functions. One of their major roles is to integrate sensorimotor, associative and limbic information in the production of context-dependent behaviours. These roles are exemplified by the clinical manifestations of neurological disorders of the basal ganglia such as Parkinson's disease and Huntington's disease. Advances in many fields, including pharmacology, anatomy, physiology and pathophysiology provided converging data that led to a unifying hypothesis concerning the functional organisation of the basal ganglia in health and disease, the 'direct/indirect pathway'model (Albin et al., 1989; DeLong, 1990). This model has led to renewed interest in, and the development of, surgical interventions in the treatment of Parkinson's disease.

The major input to the basal ganglia is derived from the cortex. Virtually the whole of the cortical mantle projects in a topographical manner onto the striatum, this cortical information is 'processed' within the striatum and passed via the so-called *direct* and *indirect* pathways to the output nuclei of the basal ganglia, the internal segment of the globus pallidus and the substantia nigra pars reticulata. The basal ganglia influence movement by the projections of these output nuclei to the thalamus and thence back to the cortex, or to sub-cortical 'pre-motor' regions. Under resting conditions the basal ganglia tonically inhibit neurons in these target nuclei. Activity in the *direct* pathway leads to a disinhibition of neurons in the target nuclei and is associated with movement whereas increased activity in the indirect pathway leads to a greater inhibition and is associated with the attenuation of movement. An imbalance of activity in favour of the indirect pathway has been proposed to underlie the movement disorders of Parkinson's disease and hence the aim of surgical intervention is to restore the balance in the two pathways by reducing activity in the indirect pathway.

Despite the clear success of the surgical interventions in the treatment of Parkinson's disease, the apparent rational basis on which these interventions are based, and the clear synaptic organisation of the basal ganglia that can account for the physiology and pathophysiology (Smith et al., 1998), there is a great deal of data suggesting that the organisation is much more complex than indicated by the model. Some of the data leading to this conclusion include the following observations: i) *direct* and *indirect* pathways converge at the single cell level in the output nuclei of the basal ganglia (Bevan et al., 1994); ii) spiny neurons of the *direct* pathway do not only project to the output nuclei of the basal ganglia but also send axon collaterals to the external segment of

the globus pallidus (GPe) (Kawaguchi et al., 1990; Parent et al., 1995; Wu et al., 2000); iii) neurons of the GPe do not simply relay striatal information to the subthalamic nucleus but rather, they are in a position to influence the activity of neurons in every region of the basal ganglia (Bolam et al., 2000); iv) the cortical input to the subthalamic nucleus is critical in setting activity in the indirect pathway (Magill et al., 2000); v) dopaminergic innervation of the basal ganglia is far more widespread than previously thought (see for instance Cragg et al., 2004).

In this lecture the anatomical, neurochemical and physiological organisation underlying the direct/indirect pathway model of the basal ganglia will be described. How the model accounts for the pathophysiological changes in Parkinson's disease and led to the new surgical interventions in the treatment of Parkinson's disease will then be described. Finally, some of the new data that leads us to have to reconsider the functional organisation of the basal ganglia will be discussed.

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