Introduction to Basal Ganglia anatomy, physiology and physiopathology

Basal Ganglia (BG) are involved in movements programming and control of movement execution. Dysfunction of BG creates motor disturbances with either an excess of abnormal movements (hyperkinesia) or paucity of movements (akinesia) and a lower execution speed (bradykinesia) or tremor as in Parkinson's disease (PD). BG play also an important role in cognition, emotional functions and non motor behaviors control.

Coronal view of the brain show Basal Ganglia nuclei located deep in the brain close to the thalamus. Those grey matter nuclei contain densely packed non myelinated neuronal bodies. They comprize four main structures, striatum (caudate and putamen), pallidum, composed of Globus Pallidus external (GPe) and Globus Pallidus internal (GPi), Sub Thalamic Nucleus (STN) and Substantia Nigra (SN, composed of pars compacta, SNc and pars reticulata, SNr). Striatum is the largest nucleus. GPe volume is 12 times smaller than striatum. GPi and SNr volumes are 20 times smaller and STN 60 times. These volume reductions is related to an important anatomical convergence from cortex to deeper nuclei. Most BG neurons are synthetizing GABA, an inhibiting neurotransmitter. They are GABAergic. A single nucleus, STN, has an excitatory neurotransmitter, STN uses GLUtamic acid. It is glutamatergic. SNc neurons are DOPAminergic. We will see later the role of this specific neurotransmitter.
The majority of cells in striatum are medium sized spiny neurons. Cortical afferents synapses are localized on distal dendrite spines. Other afferents coming from thalamus and SN make synapses at the dendrite spines base. This explains modulation or inhibition mediated by SN on excitatory influx coming from cortex. Spiny neurons also contain neuropeptides : substance P, dynorphine or enkephaline. These neurons are silent most of the time, however when they receive excitatory signals from a cortical active area, they fire and inhibit their pallidal (GPi) or nigral (SNr) targets. A small number of neurons in striatum are larger, cholinergic and tonically active.
Pallidal and SN neurons morphology is quite different. They have long smooth dendrites, without spines and with only few branches. The majority of synapses are coming from striatal axons, others from STN. They are one hundred time less numerous than striatal neurons.

STN neurons are of intermediate size with smooth dendrites and a few ramifications. STN neurons are GLUtamatergic, with excitatory effect on their pallidal and nigral (SNr) targets.
Using histological labeling and tracing techniques, functional sub territories have been identified inside the striatum, depending on their afferent cortical areas : somatomotor territory and an associative territory. Somatomotor territory is mainly in the putamen and receives bilateral projections from motor cortex of both sides. It is somatotopically organized. Associative territory is mainly localized into Caudate nucleus. It receives homolateral projections from frontal, temporal, parietal and occipital cortex. Ventral striatum is a limbic territory.
A tri dimensional histological and Magnetic Resonance Imaging (MRI) atlas of BG has been developed in our institution. Using registration techniques to identify BG nuclei on a specimen MRI coupled to tri dimensional histological brain slices reconstruction, we obtained a stereotactic deformable atlas giving histological precision to patient MRI. BG nuclei are then very precisely located and the atlas can be used to help targeting in neurosurgical procedures.
BG are connected with motor cortex and thalamus that send them afferent connections and are projecting back efferent outputs toward motor cortex areas, thalamus and midbrain. Striatum is the main entrance gate of afferent messages from cortex to BG while GPi and SNr are BG output nuclei sending efferents to motor cortex via specific relay nuclei of the thalamus.
BG have also a number of complex reciprocal connections. In 1966 Nauta and Mehler described a loop circuit between Thalamus and BG : GPi projects onto Centre Median thalamic nucleus that projects back toward somato motor Putamen. Similarily SNr projects to Para fascicular nucleus of the thalamus that projects to Caudate nucleus.
Then, in the years 1980s Albin, Alexander and Delong studied the anatomy of BG and proposed a functional model of BG. This model not only explains normal operation of movements control system, but it can also explain the abnormal BG operations in hyperkinetic or hypokinetic syndromes. The authors described a network including several parallel circuits including BG and thalamo cortical pathways. Each circuit is independant and has a specific function, motor, associative or limbic. All these circuits comprise cortico-striato-pallido-thalamo-cortical loops connecting specific cortical areas to independant BG territories that in turn project to the same cortical areas through specific thalamic relay nuclei.

The first circuit that has been historically explored, is involved in oculomotor movements called ocular saccades. The circuit origin is in cortical oculomotor area (Brodman's area 8) projecting onto the Caudate Nucleus (CN) and Superior Colliculus (SC). CN is projecting to SNr that sends efferents to SC and back to cortical area 8. SNr neurons tonic discharge inhibits continuously SC neurons. SC neurons can only activate an ocular saccade following oculomotor cortex command if it is not inhibited by SNr. This occurs when oculomotor cortex simultaneously sends an excitatory message to both CN and SC. This was the first described example of a disinhibition, the inhibition of an inhibiting nucleus leading to the activation of a target structure. Motor circuit involves precentral motor cortex (Brodmann's areas 4 and 6) and post central somatosensory cortex projecting to the putamen. In turn putamen projects to efferent structures ventral GPi and SNr. Then, those nuclei send efferents to thalamus Vop (VLa) and Voa (VA) respectively. There are two pathways between striatum and GPi/SNr, a direct monosynaptic striato-GPi/SNr pathway and an indirect striato-STN-GPi/SNr pathway. Direct and indirect pathways have opposite effects on movements. Direct pathway facilitates movements and indirect pathway inhibits movements.

Dopamine produced by SN pars compacta (SNc) neurons facilitates movements. Nigro striatal DOPAminergic neurons innervate two sets of striatal neurons. Direct pathway neurons have D1 receptors while indirect pathway neurons have D2 receptors with an opposite response to dopamine. Dopamine mediates an excitation through D1 receptors and an inhibition through D2 receptors. The effect of Dopamine is to reduce the activity of efferent BG nuclei resulting in a disinhibition of thalamo cortical pathway, facilitating movements execution.

GPi microelectrode recordings by Michel Deniau's team at Collège de France (Paris) showed how BG performs a time calibration of movements. They have stimulated motor cortex and recorded a single GPi neuron response. Response is triphasic, with an increase of the cell firing rate, followed by a silence, followed by another increase of the neuron firing. Cortical message is reaching GPi through three possible pathways. The cortico pallidal pathway via STN gives the shortest delay response. The second one is the direct pathway. The longest delay response goes through the indirect pathway via striatum, GPe and STN. First phase could have a role in the selection of movements by inhibition of unwanted movements. The second phase on the contrary could perform a facilitation of programmed movements. BG network could then help in movement selection, spatial calibration (focalization) and time calibration (amplitude) of movements. Unitary recordings on monkey trained to execute

learned movements have shown that BG motor circuit is implied in movement execution as well as voluntary movement preparation.

BG motor network dysfunction gives abnormal movements : for example akinesia in Parkinson's disease or involuntary abnormal movements (hyperkinetic or dyskinetic syndromes). Other non motor BG loops (associative, limbic) dysfunction can be responsible of other pathologies close to psychiatric diseases such as impulsivity, apathia (associative circuit), mood disorders (mania, depression) or Obsessive Compulsive Disorders, OCD (limbic and orbito frontal lateral circuit).

In early 1960's D. Albe-Fessard was able to record and stimulate thalamus Ventral Intermediate (Vim), Ventro Oral Posterior (Vop) and other thalamic nuclei during neurosurgical procedures. She recorded neuronal spike activity synchronized with tremor in Vim of Parkinsonian patients. Acute stimulation of Vim and Vop stopped tremor and coagulation of lower part of Vim also definitively stopped tremor. Nearly thirty years later, A. L. Benabid, P. Pollak et al. cured Parkinson's tremor by implanting electrodes into thalamus Vim nuclei to deliver chronic high frequency stimulation (HFS). This was the beginning of DBS era. Next step was the successful treatment of Levodopa induced dyskinesia by GPi HFS. Monkeys receiving MPTP develop parkinsonism, an animal model of PD. Unilateral coagulation of STN removed parkinsonism without creating hemiballism. STN HFS also cured monkey parkinsonism. In 1993, A.L. Benabid, P. Pollak et al. treated patients with PD by chronic bilateral STN HFS. It must be noticed that STN stimulation removes all signs of PD : tremor, akinesia and rigidity. Philippe Coubes, neurosurgeon in Montpellier, France, was the first to save a dying child with Primary Generalized Dystonia by chronically stimulating her both GPi. Some years later it was discovered by our team in La Pitié-Salpétrière that STN stimulation could also improve dramatically Obsessive Compulsive disorders (OCD) and that stimulation of limbic part of GPi could give significant clinical results in Tourette's Syndrome. Therapeutic effect of DBS is highly dependent on stimulating electrode location with a necessary precision close to one millimeter. Microelectrode stereotactic recording and stimulation in the operating room helps to achieve such precision. Each BG nucleus has its own functional signature that can be recognized according to the recorded pattern of neuronal spike discharge. For example, inside of STN, movement dependent responses and tremor cells can be recorded with some somatotopia. Outside of a nucleus there is no recording of activity. Nucleus limits are then easy to detect and stimulation gives clinical responses such as

disappearance of rigidity or hypokinesia improvement and, over all dyskinesia, that are good predictors of patients symptoms outcome under chronic DBS.

The question of the mechanism of HFS is still debated. In 2000 Dostrowski et al. studied the effect of pallidal stimulation on human GPi cell activity. Each HFS stimulus was followed by a short inhibition of pallidal discharge. In 2004 we investigated the effect of STN HFS on STN activity itself. We found that HFS decreased the spontaneous firing rate of STN neurons. Other teams found the same result in BG output nuclei, GPi and SNr with STN HFS. In 1985 Kita et al. performed studies in order to understand the mechanism of HFS paradoxical inhibition. They demonstrated that STN stimulation was activating two circuits. A monosynaptic excitatory GLUtamatergic STN-GPi pathway and a disynaptic STN-GPe-GPi pathway releasing GABA to Gpi at the last level. At high stimulation frequency, direct monosynaptic pathway EPSP (Excitatory Post Synaptic Potential) is cancelled by disynaptic inhibition (Inhibitory Post Synaptic Potential, IPSP), resulting in a reduction of GPi activity.