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3 Functional role of basal ganglia in normal and pathological behaviour

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Abstract

The basal ganglia (BG) appear to exert their major influence on motor functions and their related different behavioral activities. It has been proposed that the BG subserve relatively automatic responses to sensory inputs involving high-level functions like behavioural learning and procedural memory. Moreover, BG play a key role in the processes driving motor performance including emotion, motivation and reward. Severe neurological and neuropsychiatric disorders such as Parkinson's disease (PD), ballism,

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Huntington's chorea, Tourette's syndrome and obsessive-compulsive disorder have been linked to BG dysfunctions. This article emphasizes the role of the BG in appropriate behavioural response to environmental cues suggesting that the inability to execute specific behavioural sequences may be explained by localized deficits as well as by alterations affecting complex cortico-basal ganglia circuits.

Introduction

The basal ganglia (BG) play a key role in mediating several important aspects of behaviour [1]. Lesions of this integrated network of structures provoke severe motor dysfunctions such as those found in Parkinson's disease (PD), Huntington's chorea, ballism and Tourette's syndrome. Moreover, the BG have been involved in a wide range of psychotic disorders often characterized by deficits in high level functions like attention, learning and memory. Interestingly, physiological, pharmacological and morphological data have suggested that cognitive and psychic symptoms of PD could be related to a dysfunction of the circuitries connecting the BG to the frontal lobe and limbic system. In addition, the divergence of projections from the BG-thalamocortical circuit to the thalamic and frontocortical levels, may explain the multiple functional and pathological implications of this open interconnected organization [2] and may be described in its relation to different forms of behaviour.

Basal ganglia and sensory-induced behavioural responses

Recent neurophysiological, clinical and behavioral experiments indicate that noxious somatosensory information is processed in BG, and neurons within the BG modify their activity following both non noxius and noxius stimulation of the skin [3,4]. This sensory information may be used to select the best motor strategy in response to specific environmental demands. Neuron populations able to encode location, intensity and duration of noxious stimuli have been reported to be present in different CNS structures and, recently, also in the BG. These neurons classified as low-threshold-mechanoreceptive (LTM), wide-dynamic-range (WDR) and nociceptive specific (NS) are activated by noxious stimuli but only NS neurons are activated exclusively by this kind of somatosensory stimulation.

Several studies have illustrated the response of nigral neurons (both in substantia nigra pars compacta, SNpc and substanria nigra pars reticulata, SNpr) following noxius stimulation in the rat [5]. Nociceptive neurons may respond with suppression or enhancement of discharge frequency and present receptive fields often including the whole body [5]. The large receptive fields of nociceptive nigral neurons suggest that spatial localization of noxius stimuli

is not performed by substantia nigra units. However, it has been reported that neurons in SNpc respond to increases in electrical stimulation intensity in a graded fashion [5]. This result suggests that nociceptive SNpc neurons can encode stimulus intensity and play a role in the sensory-discriminative dimension of pain [6]. Regarding the caudate-putamen and globus pallidus, it has been reported that, depending on the anaesthesia, between 44 % [4] and 97 % [7] of somatosensory striatal neurons can be classified as nociceptive in the rat. Moreover, nociceptive striatal and pallidal neurons present large receptive fields suggesting a small role also for these neurons in the spatial localization of stimuli. However, since intravenous morphine has been demonstrated to reduce activity of the globus pallidus striatal neurons, a role in the processing of noxious information could be suggested [8].

A large population of striatal nociceptive neurons are also activated by different sensory modalities: auditory, olfactory, somatosensory. This convergence suggests a BG role for coordinated behavioural responses triggered by stimuli significant for the animal.

In human volunteers, painful thermal stimulation of the hand provokes a significant increase in blood flow within the contralateral putamen as measured by positron emission tomography (PET) [9]. A similar increase in caudate and putamen blood flow was observed in subjects with migraine headaches [10]. These findings lead to the hypothesis of the involvement of BG neurons in sensorimotor integration and in the regulation of specific behavioural responses triggered by noxius stimuli. Sensory processing within the BG may influence motor activity by filtering multisensory information directed to motor areas. Thus, nociceptive information would be processed in the BG, then in the thalamus and in the premotor areas.

As to the receptor population involved in pain modulation, striatal dopamine D2/D3 receptors availability has been recently correlated with individual response to pain in humans, suggesting a role for this receptor family in the control of pain [11].

The BG have also been shown to have a role in sensorimotor association learning [12], for example in complex sequences of behavioural patterns like those involved in feeding behavior: indeed, a large number of neurons in the SNpr of the monkey have been demonstrated to be related to mouth movements or to the detection of sensory stimuli from the intra-or perioral areas during food ingestion. Thus, a role for SNpr in the sensorimotor basis of mouth movement oriented to feeding behaviour has been suggested.

Given the established close link between pain and BG, BG dysfunction is often characterized by pain abnormalities. Parkinson’s disease may present abnormal pain sensation even if the origin of this symptom is unknown. About 40% of patients affected by PD present sensory abnormalities with pain being the most common symptom (10-30 %) [13].

The pain is described as intermittent, difficult to localize, sometimes pulsating, and occasionally bilateral or contralateral to the body side presenting motor deficits, and therefore is not directly related to motor impairments. Recent psychophysical studies have demonstrated that patients affected by PD show clear modifications in somatosensory function. Interestingly, abnormal tactile temporal discrimination thresholds have been observed in patients with neostriatal lesions [14].

Some pieces of research show correlations between neurotransmitter levels and pain in PD: a positive correlation has been observed with dopamine, noradrenaline, acetylcholine and serotonin. In addition, interesting results concern reduced cerebrospinal fluid (CSF) levels of beta-endorphin [15] and Met-enkephalin [16] in PD patients and reduced striatal and pallidal levels of Met-and Leu-enkephalin [17].

Previous studies have demonstrated that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a drug which provokes the degeneration of neurons in SNpc, causes a reduction in striatal dopamine with a long-term hyperalgesia and attenuation of orientation to tactile stimuli in mice [18] and cats [19]. Consequently, it has been hypothesized that MPTP has an effect on BG neurons involved in somatosensory responses and that the motor deficits observed in PD may originate from the inability to encode somatosensory signals [20].

Degeneration of cortical and striatal cholinergic and GABAergic neurons characterizes Huntington's disease. Somatosensory deficits, and among them diffuse pain, have also been described [21] in Huntington's disease-affected patients. Moreover, modifications of pain withdrawal reflexes and phantom limb pain have also been demonstrated after lesion in the caudate nucleus (e.g. stroke, trauma) and putamen. Interestingly, induction of parkinsonism by MPTP treatment causes an oscillatory, syncronous neuronal activity in the globus pallidus of the monkey suggesting that the dopaminergic system supports segregation of the functional subcircuits of the BG leading to the most diffuse functional impairments in PD [22].

In addition, three facts point to the hypothesis that BG are involved in gating processes and in the regulation of sensory information flow to high order cortical areas: first, neuronal degeneration in several diseases is not restricted to BG, i.e., in PD a decrease of dopamine concentration is present in substantia nigra, striatum, cerebral cortex, hypothalamus; second, different neurotransmitter actions are affected within BG; third, cognitive and emotional disorders are often present with pain symptoms. Thus, abnormalities of movement may result from a disturbance of the sensory gating processes performed by BG resulting in abnormal sensory input to motor areas. This hypothesis is supported by the following evidences concerning tests applied to the orofacial region: patients with PD make significantly more errors than

controls in sensorimotor tests (movement of tongue in response to sensory stimulation and targeted head movement in response to perioral sensory information), and there is an increased threshold of perioral two-points discrimination and tongue localization in PD.

Effects of basal ganglia stimulation or lesion on behaviour: Correlations with human diseases

Stimulation at different loci in the BG has been reported to induce contraversive head turning and circling, contralateral limb flexion, arrest of motor behaviour, licking, chewing or swallowing movements, and modification of cortically induced movements. Unilateral pallidal ablation has no motor or behavioural effects. Bilateral pallidal ablation produces a hypoactive animal seldom moving around or changing position, simulating the hypokinesia of PD [23]. Moreover, an impairment of reaction time performance has been observed in rats following depletion of dopamine in the caudate nucleus [24]. Correlation of data from ablation experiments with human disease is possible only with selective ablation of the subthalamic nucleus, which results in ballism, and in the nigral effect of MPTP resulting in many parkinsonian symptoms.

In Huntington's chorea a loss of striatal neurons has been observed provoking a disinhibition of the external pallidal segment, inhibition of subthalamic nucleus, decreased excitation of the internal pallidal segment and SNpc and reduced inhibition of the thalamus. Accordingly, Huntington's chorea is characterized by involuntary movements.

A role of BG has also been suggested in the generation of voluntary saccades; the reported oculomotor abnormalities in Huntington and Parkinson's diseases seems to confirm such a hypothesis [25].

Recent advances in knowledge of BG functional anatomy and physiology, and new information on dopamine modulation of striatal circuits have provided the basis for a BG dysfunction hypothesis in Tourette's syndrome (TS). It is generally accepted that there is a complex genetic basis and that the pathophysiology most likely involves the BG and frontocortical circuits [26]. This disease with onset in childhood is a neurobehavioral disorder characterized by multiple chronic motor and vocal tics. Tics are involuntary, repetitive muscle contractions that produce stereotyped movements. In TS, tics may occur many times daily, nearly every day for a period of more than one year. Recent advances in the knowledge of TS arise from neuroimaging studies, from post-mortem anatomical evidences and from behavioural studies in rodents and non-human primates. Due to the worsening of tics during later childhood and early adolescence in the male, a role for gonadal hormonal influence in the pathophysiology of TS has been suggested [27].

The first association of TS with a gene has been recently reported by Abelson et al. [28]. They identified a child with an inversion on chromosome 13 evidencing that the gene encoding Slit and Trk-like (SLITRK1), a member of a family implicated in neurite outgrowth, was close to one of the breakpoints. SLITRK1 is expressed in the developing and postnatal brain, and the implications of a molecule regulating neuronal development leads to interesting explanations of TS pathogenesis. As to the pharmacology of TS and the often associated (approximately 50% of affected individuals) obsessive-compulsive behaviours, a suppression of tics has been obtained by dopamine antagonists and serotonin-reuptake inhibitors. The regions where dopaminergic and serotoninergic neurons interact are the striatum, the substantia nigra and the prefrontal cortex. Clinical, pharmacological and anatomical evidences confirm that TS is a BG disorder specifically dependant on the dysfunction of striatal mechanisms. In particular, recent preliminary reports of surgical treatment of TS have shown that high-frequency deep-brain stimulation of the centromedian-parafascicular (CM-PF) thalamic complex or of the internal pallidal segment improves tics and obsessive-compulsive behaviours [29]. CM-PF complex is reciprocally connected with the BG, sends large projections to the striatum and receives inputs from the internal pallidal segment. Magnetic resonance imaging (MRI) and PET have shown: i) smaller lenticular volumes; ii) smaller caudate volumes in childhood predicting the severity of tics in early adulthood. By means of single-photon-emission computed tomography (SPECT) an increase of markers for striatal dopaminergic terminals and an increase of striatal dopamine transporter (DAT) density have been shown. All these data contribute to strengthening the argument for the involvement of BG in the pathophysiology of TS and obsessive-compulsive behaviours [30].

Basal ganglia and behavioural learning

Recently, it has been demonstrated that following tetanic stimulation of corticostriatal fibres both long-term depression (LTD) and long term potentiation (LTP) of excitatory transmission in the striatum can be induced. These different forms of striatal synaptic plasticity depend on the subtype of ionotropic glutamate receptor activated during the tetanus. This evidence leads to the hypothesis that the BG play an important role in the formation and storage of memory. In particular, the striatum seems to be involved in the generation and maintenance of motor skills. Moreover, alterations in striatal synaptic plasticity and the loss of striatal projection neurons, disrupting the striatal control on BG output nuclei, could explain motor as well as learning deficits in PD and Huntington’s chorea patients [31]. However, a different picture suggesting the involvement of the external segment of globus pallidus, with its widespread projections, and of the subthalamic nucleus with its

multiple inputs, may account for BG circuitry implication [32]. The advent of methods for identifying striatal interneurons in stained tissue slices and in physiological experiments together with clarification of their individual role in striatal function, have been useful to understand how the BG process information and how the dysfunction of BG circuitry can explain the origin of human movement disorders [33].

Single unit recording studies in awake monkeys support the view that the BG participate in movement control and are activated during the performance of learned limb or eye movements [34]. Two basic mechanisms of BG function in behavioural learning have been suggested: first, the behavioural context-dependent activity of striatal neurons is acquired through behavioural learning with the nigrostriatal dopamine system playing a crucial role; second, striatal inputs from the limbic system and from the nigrostriatal dopamine system, which are related to reinforcement or incentive, may be essential to the involvement of BG in behavioural learning. Therefore, the expression of learned striatal activity could contribute to the initiation of learned motor behaviour [35].

Striatal dopamine is found to be involved both in motor activation and reward-mediated learning. In these functions dopamine appears to mediate synaptic enhancement in the corticostriatal pathway, even if electrophysiological data report that dopamine inhibits corticostriatal transmission. Different dopaminergic receptor populations may explain different effects [36]. Evidences obtained from electrophysiological studies suggest that dopamine D1 receptors may be involved in synaptic reinforcement occurring in reward-mediated learning, whereas the D2 ones may have an inhibitory role on cholinergic terminals mediating inhibition of dopamine striatal neurons [37].

Recent data obtained by single unit recording and brain imaging suggest that striatal reward signals originate in the orbitofrontal cortex and basolateral amygdala, regions that largely project to the striatum. An abnormal processing of sensorimotor and incentive motivational-related glutamate input signals to the striatum could account for impairments in motor activity and incentive motivational processes that follow from nigrostriatal dopaminergic neuronal loss [38]. An interesting, different hypothesis has been proposed by Houk and Wise [39]: in their model, motor outputs are determined by the input-output processing of distributed neural modules involving corticocortical connections of the frontal cortex. They proposed that learning in frontal networks is guided by subcortical inputs, those coming from BG being among the most important. Houk and Wise suggested that BG and cerebellar inputs would alter synaptic weight in the frontal cortical network promoting a cortical output consistent with a particular input-output function [40]. Thus, sensorimotor processes which drive behavioural learning might depend on corticocortical relationships with the BG and cerebellum gradually training the frontal cortex [39].

Basal ganglia and behavioral pattern selection

The complexity of intrinsic interactions, with feedback loops between and within the different nuclei, suggests that the BG could be implicated in the problem of action selection [41]. Action selection can be defined as the mechanism by which conflicts are resolved between sensorimotor systems seeking access to the final common motor path [42,43]. Previous data have shown that dopamine in the BG is involved in the ability to arbitrarily switch motor programs, i.e. to switch from one motor program to another without the help of external stimuli [44,45]. Recently, the BG have been suggested to represent a biological solution to the problem of selection. To test this hypothesis a high level computational model of intrinsic BG circuitry and its interactions with thalamocortical connections has been proposed [42]. A small mobile robot has been used to evaluate an embedded BG model. Results of the experiments demonstrated: i) the computational model of BG switches effectively between competing channels depending on the salience of the input; ii) the performance is enhanced if simulated thalamocortical circuitry is included; iii) the robot model shows appropriate switching between different actions and is able to produce a correct behavioural sequence [42].

An interesting hypothesis about the BG's contribution to information processing in cortical networks and about the interactions between cortex and BG during learning and behaviour has been proposed by Djurfeldt et al. [46]. They suggested that the BG control cortical activity by pushing a local cortical network into a new attractor state, thereby selecting certain attractors over others. A modular learning system capable of acquiring behaviour with sequential structure could account for this activity [46].

Basal ganglia and human behaviour: Results from high resolution techniques of analysis

In spite of much study on the functional role of the BG in animals few data exist on their role in humans. To shed light on this matter a functional magnetic resonance imaging (fMRI) approach has been used by Scholz et al. [47]. Unilateral movements produced bilateral activation in the striatum even when motor cortex activation was unilateral. Moreover, bilateral performance of the tasks led to consistently smaller BG activation than unilateral one, suggesting less inhibition of contralateral movements during bilateral tasks. In addition, a striking dominance pattern in BG motor activation was observed, i.e. the left BG were more active than the right for right handers, regardless of the hand used. This lateralization appears much stronger than that previously reported for the motor cortex. Therefore, by means of fMRI, a left hemispheric dominance and an inhibition of contralateral movements can be observed following activation of the Cortico-Basal Ganglia motor loop [47].

Final remarks

In conclusion, the BG appear to be a group of structures more developed in mammals than in other species having undergone major elaboration processes during evolutionary transitions [48]. These elaborations might have been the origin of specific neural mechanisms crucially implicated in the execution of movements or more complex behavioural sequences characterizing the abilities of primates.

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