Brainstem interactions with the basal ganglia

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Abstract

The basal ganglia are a group of interconnected subcortical nuclei that represent one of the brain’s fundamental processing units. In humans basal ganglia dysfunctions have been associated with numerous debilitating conditions, including Parkinson’s disease. To appreciate fully how complicated systems can malfunction, it may first be necessary to understand how such networks work normally. The present review therefore provides an outline of basal ganglia architecture emphasising their interactions with brainstem structures. The potential functions of the basal ganglia network are then considered together along with resulting insights that may help our understanding of Parkinson’s disease and other basal ganglia-related disorders.

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1. Components

The basal ganglia have two principal input nuclei, the striatum and the subthalamic nucleus, and two principal output nuclei, the substantia nigra pars reticulata and the internal globus pallidus. The external globus pallidus is mainly an intrinsic structure that receives most of its afferents from, and provides efferent connections to, other basal ganglia structures. Finally, dopaminergic neurons in the substantia nigra (pars compacta) and the adjacent ventral tegmental area provide the other basal ganglia nuclei, principally the striatum, with important modulatory signals. The anatomical structures themselves and the intrinsic projections between them, together with their afferent and efferent connections with external structures, are remarkably similar in all vertebrate species [1]. The same is true for the intrinsic cell types and neurotransmitters systems of the basal ganglia. This suggests that throughout the course of vertebrate evolution the functional anatomy of these structures has been very highly conserved [1].

2. Input/output architecture

2.1. Inputs

Input to the striatum from all major sources – the cerebral cortex, limbic structures and the thalamus – are topographically ordered [2] and may comprise a series of independently organised functional channels. Afferent connections to the subthalamic nucleus, at least from the cerebral cortex, are also topographically organised [3]. Pharmacological signals received by basal ganglia input nuclei from the cerebral cortex, limbic structures and the thalamus are mediated by excitatory glutamatergic neurotransmission [4].

2.2. Outputs

Basal ganglia outputs contact regions of the thalamus (the intralaminar and ventromedial nuclei) that project directly back to basal ganglia input nuclei but also back to those cortex regions providing original inputs to the striatum [2,4]. Similarly, basal ganglia outputs to the brainstem target those regions that provide indirect input to the striatum via the thalamic midline and intralaminar nuclei [5]. The basal ganglia exert influence over target structures by a fundamental process of disinhibition [6]. GABAergic neurons in the basal ganglia output nuclei have high tonic firing rates (40–80 Hz). This activity ensures that target regions of the thalamus and brainstem are maintained under a tight and constant inhibitory control. Focused excitatory inputs from external structures to the striatum can impose a focused suppression, (mediated via ‘direct’ GABAergic inhibitory connections), on sub-populations of output nuclei neurones. This focused reduction of inhibitory output activity releases (disinhibits) local regions in the thalamus and brainstem from normal inhibitory control.

2.3. Cortical loops

Manifest topographies associated with input projections, intrinsic connections and outputs of the basal ganglia provided a basis for the influential organisational principle suggested by Alexander and colleagues [2]. Thus, a sub-set of
the connections between the cerebral cortex and basal ganglia can be viewed as a series of parallel projecting, largely segregated cortico–striato–nigro–thalamo–cortical loops or channels (Figure 1A). Within this framework, projections from different functional territories of cerebral cortex (e.g. limbic, associative, sensorimotor) project to exclusive functional territories in the basal ganglia input nuclei, which are then maintained in the internal circuitry. Output signals from functional territories represented in the output nuclei are returned, via appropriate thalamic relays, to the cortical regions providing the original input signals [2].

2.4. Sub-cortical loops
The concept of potentially segregated parallel projecting loops through the basal ganglia has been extended to their connections with sensorimotor and motivational structures in the brainstem, including the superior colliculus, periaqueductal grey, cuneiform, pedunculopontine and parabrachial nuclei [5]. An important difference is that, in the case of cortical loops, the thalamic relay is on the output side of the loop, whereas for the sub-cortical loops the thalamic relay is on the input side (Figure 1B). The anatomical connections identifying individual components of the proposed closed loops between subcortical regions and the basal ganglia have been documented; however, the full extent to which they represent functionally segregated parallel closed-loops remains to be determined. For one midbrain structure, the superior colliculus, anatomical evidence for closed-loop connectivity with the basal ganglia is robust [5].

3. The superior colliculus: an exemplar
The superior colliculus, the mammalian homologue of the optic tectum, is, from a phylogenetic perspective, an ancient structure responsible for the sensorimotor transformations required to direct gaze shifts towards or away from unexpected, biologically salient events [7]. It is sub-divided into the superficial layers, which receive unsensory visual input from the retina (and visual cortex in mammals), and the deep layers, which receive multisensory visual, auditory and somatosensory (tactile and noxious) and non-sensory modulatory inputs from widespread cortical and subcortical regions. Descending outputs from the deep layers make direct contact with hindbrain pre-motor nuclei responsible for directing the animal toward or away from salient cues [7,8]. In addition to its sensorimotor connections, the superior colliculus is one of the principal targets of both major output nuclei of the basal ganglia [4]. Traditionally, these connections are considered to be the principal routes whereby information processing within the basal ganglia influences brainstem motor mechanisms, particularly in the context of oculomotor control [9]. In addition to their descending projections to the pons and the medulla, both the superficial and deep layers of the superior colliculus also have ascending connections which target specifically those regions of the thalamus that provide direct input to the striatum, including the lateral posterior nucleus and the midline/intralaminar nuclear complex [5]. This arrangement suggests that the superior colliculus is an important afferent source of both sensory and motor information, as well as a principal recipient of basal ganglia output. In this particular case, the input–output relationships are best characterised as several possibly independent, but overlapping, closed-looped systems [5].

In addition to this general colliculo–thalamo–basal ganglia–collicular looped architecture, the superior colliculus also provides direct inputs to the other principal input ports of the basal ganglia. Recently it has been shown that the superior colliculus is the main, if not exclusive
source of short-latency visual input to dopamine neurons in the substantia nigra pars compacta and ventral tegmental area [10]. Moreover, just as cortical regions have ‘hyperdirect’ efferent contact with the subthalamic nucleus, so the superior colliculus also has a substantial efferent projection to the subthalamic nucleus through which visual information is relayed at short-latency (Coizet, Graham and Redgrave, unpublished observations). Consequently, it is now appreciated that prior to the evolutionary development of the cerebral cortex, the main components of the basal ganglia were present with appropriate input and output connections at least to one of the brainstem’s principal sensorimotor structures, namely, the superior colliculus. The issue we will now consider is why the colliculus, whose principal function is ‘reflexive’ orienting, should require the services of the basal ganglia. The likely answer is that the looped architecture described above provides a solution to a fundamental computational problem faced by the superior colliculus.

4. The selection problem

A fundamental computational issue arises when multiple distributed parallel-processing sensory, cognitive and affective systems, each with the potential to influence movement, have to share a limited set of motor resources – the final common motor path [11]. Clearly, it is not possible to execute two exclusive acts (approach/run away) using the same set of muscles (the legs) at the same time. Similar difficulties are faced by sensory systems that can simultaneously represent more than one stimulus that can motivate or guide exclusive movements. Because one cannot look at two different things at the same time, it is this version of the selection problem that confronts the superior colliculus. Its multisensory maps can represent multiple stimuli simultaneously, each of which could be used to drive a gaze-shift (Figure 2). One solution to this problem could be local to the superior colliculus. Representations of competing sensory events could be directed to inhibit each other – i.e. with reciprocal inhibitory connections. In this architecture the most active representation would inhibit all the others more than it would be inhibited by them. This connectional organisation is an effective solution to the selection problem, rapidly producing a winner-takes-all [12]. However, this model requires all competing elements to be connected to each other with inhibitory projections. While this may true locally, the required reciprocal inhibitory connections do not extend sufficiently throughout the collicular sensorimotor maps [13]. However, even if the maps were fully connected with reciprocal inhibitory projections, the consequences for survival may not be ideal – the eyes would tend to be attracted to the most physically salient event in the scene. For example, the representation of a brightly coloured but innocuous bird flying overhead would suppress that of a slight slithering movement in the grass denoting the presence of a potentially dangerous snake. Decisions concerning the direction of gaze are probably not best left to a structure largely ignorant of context. It is probably for this reason that the looped architecture linking the superior colliculus and the basal ganglia evolved.

5. An alternative solution

An alternative solution to the selection problem, which was also devised independently for artificial control systems [12], is to have competing functional systems/representations separately submit phasic excitatory ‘bids’ (or inputs) to a central selection mechanism, which in turn exerts tonic inhibitory control over all competitors via individual return inhibitory links (the outputs) (Figure 2). Based on the relative salience of the input bids, the central selector, through a process of selective disinhibition [12], withdraws inhibition from the ‘winning’ competitor, thereby allowing it sole access to relevant components of the motor plant. This selection mechanism relies on a largely segregated looped architecture comprising phasic excitatory inputs to, and tonic inhibitory outputs from, a central selection mechanism. It is on this basis that the basal ganglia were proposed as a mechanism to arbitrate between distributed,
parallel processing functional systems within the brain [11]. Uniquely, this proposed functionality has been supported by the use of biologically constrained models of basal ganglia architecture, both in simulation and in the control of action selection in a mobile robot (for relevant references see [14]). In the context of orienting gaze shifts, subcortical loops linking the basal ganglia with the superior colliculus may therefore serve to interrupt ongoing behaviour and allow the guidance of oculomotor and related motor plant to be switched to biologically salient events [5]. The advantage of this arrangement is that the multiple and diverse inputs to the basal ganglia representing relevant aspects of context and reinforcement history could be used to modulate such decisions of where to look [10].

6. General implications

If the above analysis is correct, it is possible that the function performed by the basal ganglia for the superior colliculus could provide insight into the functional role of the connections the basal ganglia has with other structures of the brain including cerebral cortex. First, it should be noted that the internal micro-architecture of each basal ganglia structure is retained across the representations of different functional territories (limbic/affective, associative, sensorimotor) [4]. Thus, signals from a pre-cortical visual system (the superior colliculus) are processed by more-or-less the same arrangement of cell types and microcircuits in the basal ganglia nuclei that process the highly sophisticated inputs from the pre-frontal cortex. Insofar as function is an emergent property of connectivity, the presence of common architectures suggests that similar computational processes are being applied to inputs from drastically different functional origins. On this basis, whatever function(s) is performed by the basal ganglia, it is likely to be very general. It this context, is noteworthy that goal-directed behaviour can be conceived as a three-tier hierarchy with selections required at each level: (a) selections of overall goal; (b) selections of actions to achieve a selected goal; and (c) selections of movements to achieve a selected action [11]. It is possible that the same microcircuitry shared by the different functional territories of the basal ganglia could, in principle, select between competing goals, actions and movements. ‘Selection’ may, therefore, represent a function of sufficient generality to be consistent with the presence of canonical networks throughout the basal ganglia nuclei.

If the basal ganglia are acting as a general purpose selection mechanism [11], it should be possible to interpret many of the human basal ganglia-related disorders in terms of selection malfunctions. For example, the akinesia of Parkinson’s disease would be interpreted as a failure to disinhibit tonic inhibitory output signals on any of the sensorimotor channels. Similarly, bradykinesia could result from partial or incomplete disinhibition of selected channels. Aspects of schizophrenia, attention deficit disorder and Tourette’s syndrome may reflect different forms of failure to maintain inhibitory output activity in non-selected channels. This activity could interfere with the output of selected targets (motor/verbal tics) and/or make the selection system vulnerable to interruption from distracting stimuli (schizophrenia, attention deficit disorder). The opposite situation would be where the selection of one functional channel is abnormally dominant, thereby making it difficult for competing events to interrupt or cause a behavioural or attentional switch. Such circumstances could underlie addictive compulsions or obsessive compulsive disorder.

Finally, in its most general form, the current proposal of cortical and pre-cortical control systems interacting with a central selection mechanism (Figure 1) has implications far beyond the redirection of gaze (Figure 2). Sensory and motivational processing is represented at both cortical and brainstem levels. Cortically based representations are likely to rely on sophisticated perceptual and cognitive processing, while those in pre-cortical structures may reflect more the immediate sensory environment. Do the appropriate looped architectures through the basal ganglia mean that cortical and pre-cortical sensory and motivational systems can compete directly (Figure 1)? If so, those occasions where pre-cortical systems dominate could explain how knowingly irrational actions are sometimes chosen and momentary lapses of control claimed [15]. Possible examples would include the addictions: addicts can often articulate many intellectual (cortical?) reasons why they should abstain from drug use, yet at certain times, especially when faced with sensory stimuli associated with prior drug taking, feel uncontrollable (sub-cortical?) urges to indulge. Other examples would include most of the phobias, anxiety/panic attacks, post-traumatic stress disorders, psychopathy, and in more normal circumstances, situations involving sex and violence. It is interesting that common treatment advice for these conditions is to avoid environments where immediate sensory stimuli promote loss of control. Advice from our proposed model of selection by the basal ganglia would be similar: adopt strategies that boost the salience of inputs from cortical systems predicting the consequences of actions, while at the same time reducing the salience/frequency of inputs from the lower (possibly pre-cortical) sensory and motivational systems.

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Conflict of Interest statement

None declared.
References


