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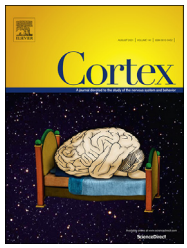

Viewpoint

# A subcortical network for implicit visuo-spatial attention: Implications for Parkinson's Disease

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ABSTRACT

Recent studies in humans and animal models suggest a primary role of the basal ganglia in the extraction of stimulus-value regularities, then exploited to orient attentional shift and build up sensorimotor memories. The tail of the caudate and the posterior putamen both receive early visual input from the superficial layers of the superior colliculus, thus forming a closed-loop. We portend that the functional value of this circuit is to manage the selection of visual stimuli in a rapid and automatic way, once sensory–motor associations are formed and stored in the posterior striatum. In Parkinson's Disease, the nigrostriatal dopamine depletion starts and tends to be more pronounced in the posterior putamen. Thus, at least some aspect of the visuospatial attention deficits observed since the early stages of the disease could be the behavioral consequences of a cognitive system that has lost the ability to translate high-level processing in stable sensorimotor memories.


## 1. Introduction

Our sensory organs are constantly targeted by a multiplicity of stimuli. Given the limited processing capacities of our cognitive system, attentional selection enables us to orient processing resources towards the most relevant stimuli (Chica et al., 2013). In fact, visuospatial selective attention can be defined as the ability to prioritize the processing of behaviorally relevant visual stimuli and to inhibit irrelevant ones (Chica et al., 2013; Fiebelkorn & Kastner, 2020).

Many studies documented the key role of an extended frontoparietal network in visuospatial selective attention, emphasizing how top-down signals of these cortical areas are able to dynamically modulate the neuronal activity in sensory visual cortices (Fiebelkorn & Kastner, 2020). Attentional selection is also influenced by bottom-up activity from subcortical structures such as the SC and Pulv (Fiebelkorn & Kastner, 2020; Krauzlis et al., 2013, 2018; Tamietto et al., 2005), both receiving direct retinal input, and from the amygdala that prioritizes processing of emotional or salient signals from the

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**Abbreviations**

| | |
|---|---|
| Amg | amygdala |
| BG | basal ganglia |
| dlPFC | dorsolateral prefrontal cortex |
| FEF | frontal eye field |
| GPe | globus pallidus externus |
| GPi | globus pallidus internus |
| IPL | inferior parietal lobe |
| OFC | orbitofrontal cortex |
| PD | Parkinson's Disease |
| Pulv | pulvinar |
| SC | superior colliculus |
| SNpc | substantia nigra pars compacta |
| SNpr | substantia nigra pars reticolata |
| SPL | superior parietal lobe |
| STN | subthalamic nucleus |
| VTA | ventral tegmental area |

environment through reentrant projections to sensory cortices (Diano et al., 2017; Nishijo et al., 2018; Pourtois et al., 2013; Tamietto & de Gelder, 2010).

Located deeply in the central regions of the brain, the striatum of the BG widely receives overlapping projections from almost all the cortex (Choi et al., 2017a, 2017b; Jarbo & Verstynen, 2015), forming several parallel closed-loops with the frontoparietal attentional areas, as well as with the Amg (Alexander et al., 1986; Postuma & Dagher, 2006). Through these connections, the BG system integrates and regulates the attention-related top-down signals (van Schouwenburg et al, 2010, 2015). Furthermore, the BG are also highly interconnected with the SC, forming parallel closed-loops similar to those with the cortex (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010). Traditionally, subcortical structures have been assigned a secondary role, although evidence suggests that the mesencephalic-basal closed-loops are both necessary and sufficient to ensure a primordial form of visuospatial selective attention (Krauzlis et al., 2018).

In recent years, research streams converged on two main findings. First, implicit learning can modulate visuospatial selective attention (Todd & Manaligod, 2018). Second, during implicit learning the striatal activity gradually moves from the anterior associative territories to the posterior sensorimotor ones (Hikosaka et al., 2019; Kim & Hikosaka, 2013; Lehéricy et al., 2005). Here, we firstly review the recent literature on the role of the BG in selective attention, reporting the possible existence of a mesencephalic-basal network involved in implicit selective attention; namely, in the selection of visual stimuli based on previous individual experiences. Secondly, we try to explain how this network could explain visuospatial attentional deficits in PD. The core idea is that the BG system is involved in translating the flexible (short-term) value of visual stimuli in stable (long-term) values through the formation, storage and maintenance of sensorimotor memories in the posterior striatum. Once these implicit memories are formed, the mesencephalic-basal closed-loops would be able to manage the selection of visual stimuli in an early, rapid and automatic way, without the need to recruit the frontoparietal attentional areas, which could therefore limit their activity to monitoring functions. Due to dopamine depletion in the posterior striatum (Tang et al., 2010), the BG system of patients with PD would lose the ability to automate the selection of visual stimuli. In other words, at least some aspects of the selective attention deficits of PD could be the behavioral consequences of impaired sensory–motor associations normally acquired through repeated exposure to stimulus-response regularities.

## 2. The basal ganglia architecture

The BG are a group of nuclei, located deeply in the central regions of the brain. Specifically, these nuclei are the caudate and the putamen (that together form the striatum), the STN, the globus pallidus, divided into GPi and GPe, and the substantia nigra of the midbrain, divided into SNpc and SNpr. The striatum is the input structure of the system, whereas the GPi and the SNpr are the output ones. At rest, the GPi and the SNpr inhibit the thalamic activity through tonic release of GABA (Graybiel, 2000). In addition to the projections to the thalamus, the SNpr also sends GABAergic axons to the SC (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010). The striatum receives glutamatergic projections from the frontal, the parietal and the temporal lobes (Choi et al., 2017a, 2017b; Jarbo & Verstynen, 2015), as well as from the SC through the thalamus (Krauzlis et al., 2013; McHaffie et al., 2005; Redgrave, Coizet, et al., 2010). The SNpc is the only dopaminergic structure of the system (Graybiel, 2000).

The BG system is topographically organized. Within the frontal lobe, the more anterior areas mainly project to the anterior striatum, whereas the more posterior ones to the posterior striatum (Verstynen et al., 2012). In register, the motor cortex mainly projects to the dorsolateral striatal regions, whereas the more ventromedial prefrontal areas project to the ventromedial ones (Draganski et al., 2008; Haber, 2003). These gradients of connectivity within the cortico-striatal projections are also present into the parietal lobe, albeit the anterior-posterior gradient is inverted with the more anterior areas projecting to the posterior striatum and vice versa (Yeterian & Pandya, 1993). After being integrated into the striatum, the neuronal signal remains segregated within the projections to the output nuclei (Draganski et al., 2008). In fact, several parallel closed-loops are identifiable (Alexander et al., 1986; Postuma & Dagher, 2006). These have the same intrinsic organization and can be anatomically divided into two main components: the cortico-basal loops and the mesencephalic-basal loops (Fig. 1).

### 2.1. *The three pathways of the basal ganglia*

The neuronal signal is transmitted from the striatum to the output nuclei of BG through the direct and the indirect pathway (Fig. 1). In the direct pathway the striatum sends axons to the GPi and the SNpr, whereas in the indirect pathway the signal, before targeting the GPi and the SNpr, passes first through the GPe and then through the STN (Graybiel, 2000). All neuronal territories of the striatum project

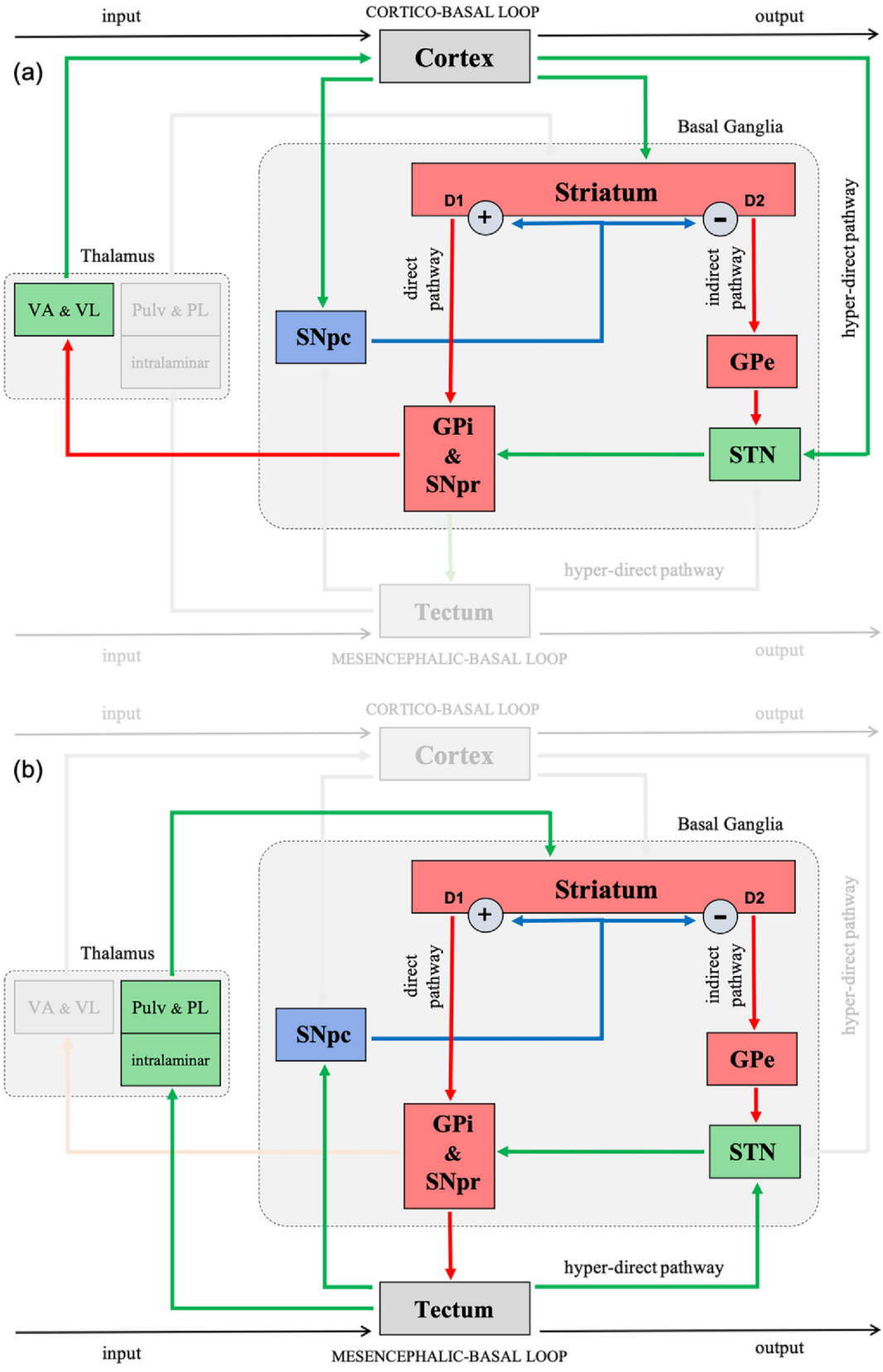


**Fig. 1 – The basal ganglia architecture. The main basal ganglia architectures are anatomically identifiable: the cortico-basal loop (a) and the mesencephalic-basal-loop (b). They have the same intrinsic structure; namely, the basal ganglia system modulates both the tectal and the cortical activity through the direct, the indirect and hyper-direct pathways. In the cortico-basal loop the thalamic nuclei are involved in the transmission of the output signal, whereas they pass on input signal in the mesencephalic-basal loop (McHaffie et al., 2005). The glutamatergic structures and projections are in green; The**

to both the GPi and the GPe, while also receiving axons from the SNpc (Hazrati & Parent, 1992; Hedreen & Delong, 1991; Kim et al., 1976). The projections of the striatum and of the GPe are GABAergic, whereas those of the STN are glutamatergic (Graybiel, 2000). The direct pathway interrupts the tonic inhibition exerted by the GPi and the SNpr over the thalamus and the SC, therefore increasing their excitability (Freeze et al., 2013; Graybiel, 2000; Hikosaka et al., 2006). On the other hand, the indirect pathway stimulates the GPi and the SNpr, reducing the excitability of target brain regions. Hence, the direct pathway concurs to release behavioral responses, whereas the indirect pathway suppresses unnecessary, potentially interfering, movements (Hikosaka et al., 2019).

The direct and the indirect pathway are modulated by two different dopamine receptors, named respectively D1 and D2, which respond differently to the introduction of dopamine into the BG system: the striatal neurons with D1 receptors increase their GABAergic activity on the GPi and on the SNpr, whereas those with D2 receptors decrease their GABAergic activity on the GPe (Graybiel, 2000). Importantly, the two pathways operate in synergy: the optimal level of excitability is thus determined by the balancing between excitatory (direct pathway) and inhibitory activity (indirect pathway) (Calabresi et al., 2014; Oldenburg & Sabatini, 2015).

In addition to these two systems, there is a third pathway, often referred to as hyper-direct pathway (Nambu et al., 2002). In the hyper-direct, the STN receives glutamatergic axons directly from the cortex and from the SC, bypassing the striatum (Nambu et al., 2000; Coizet et al., 2009) (Fig. 1). Based on this anatomical configuration, the putative role of this third pathway is to quickly block neuronal activity initiated by the direct pathway, or to facilitate it through preventive suppression of potentially interfering neuronal activities (Nambu, 2008; Nambu et al., 2002). In line with this account, the neuronal activity in the prefrontal cortex and the STN tends to increase when an inappropriate response must be quickly (and deliberately) inhibited (Aron & Poldrack, 2006; Chen et al., 2020).

In sum, the BG system modulates the neuronal activity of target brain regions through the direct, indirect and hyper-direct pathway. The striatum attenuates through the direct pathway the inhibitory activity exerted by the GPi and SNpr, or contributes to this inhibition via indirect pathway (Graybiel, 2000). Both these agonistic and antagonistic activities over GPi and SNpr can be quickly modulated through the hyper-direct pathway that mobilizes activity in the STN bypassing the striatum (Nambu et al., 2002) (Fig. 1).

### 2.2. *The functional striatal subdivisions*

Traditionally, the striatum is subdivided in associative, sensorimotor and limbic zones (Nakano et al., 2000; Postuma & Dagher, 2006). This anatomical and functional subdivision is based on the specific areas of origin of the corticostriatal projections and is identifiable in throughout the BG system (Nakano et al., 2000).

The associative striatum (Fig. 2a) occupies the anterior putamen, most of the head of the caudate, and the middle parts of the body and the tail of the caudate. It receives afferents from the cortical associative areas, such as the FEF, the SPL, the IPL, and the dlPFC. The sensorimotor striatum (Fig. 2b) encompasses the dorsolateral and posterior putamen and of the dorsolateral rim of the caudate, and receives axons from the motor and premotor cortex, from the supplementary motor area, and from the somatosensory cortices. Finally, the limbic striatum (Fig. 2c) corresponds to the ventral portions of the putamen and of the caudate, including the nucleus accumbens. These limbic territories receive afferents from brain regions involved in affective processing and reward learning, such as the Amg and the OFC, as well as from temporal areas involved in spatial processing and memory, such as the hippocampus (Nakano et al., 2000; Postuma & Dagher, 2006). Importantly, several studies reported overlapping striatal zones, suggesting that the boundaries between associative, sensorimotor and limbic territories are more blurred than previously thought (Averbeck et al., 2014; Choi et al., 2017a, 2017b; Jarbo & Verstynen, 2015). For example, the dorsomedial portion of the anterior striatum receives converging axons from the dlPFC, the IPL and the OFC (Choi, Tanimura, et al., 2017; Jarbo & Verstynen, 2015).

Similar to the striatum, also the STN presents associative, sensorimotor and limbic zones, defined by virtue of its inputs and outputs. In general, the associative territory is located in the ventromedial part of the STN, the sensorimotor is in the dorsolateral part, and the limbic zone is in the most medial parts (Nakano et al., 2000; Temel et al., 2005).

Summing up, the BG system is involved in cognitive, sensorimotor and affective processing. Within the striatum, the associative territories are mainly located in the most anterior portions, the sensorimotor areas are the most posterior, and the limbic zones are those located more ventrally (Nakano et al., 2000; Postuma & Dagher, 2006).

### 2.3. *The mesencephalic-basal loops*

The mesencephalic-basal architecture includes brain structures phylogenetically ancient, such as the SC. Similar to the cortico-basal circuit, multiple closed-loops can be identified (Fig. 3) (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010).

A first closed-loop originates from the superficial layers of the SC (Fig. 3a) and projects to the Pulv and to the posterior lateral nucleus of the thalamus. The information then reaches the lateral territories of the body and tail of the caudate, and the dorsolateral putamen, providing early visual input to the BG system. A second closed-loop originates from the deep layers of the SC (Fig. 3b) that sends axons to the intralaminar nuclei of the thalamus, which, in turn, project to all territories of the striatum. In both loops, the neuronal information is

**GABAergic structures and projections are in red; The dopaminergic structures and projections are in blue; GPe = globus pallidus externus; GPi = globus pallidus internus; SNpc = substantia nigra pars compacta; SNpr = substantia nigra pars reticulata; STN = subthalamic nucleus; Pulv = pulvinar; PL = posterior-lateral nucleus; VA = ventral-anterior nucleus; VL = ventral-lateral nucleus.**

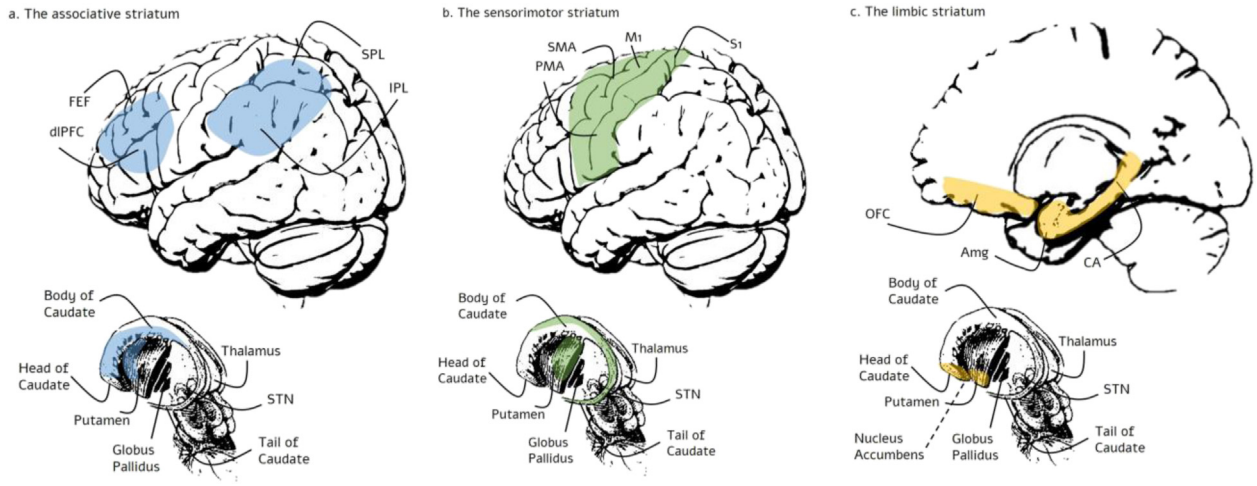


**Fig. 2 – The functional striatal subdivisions. The associative striatum mainly occupies the most anterior territories of the striatum (a), whereas the sensorimotor striatum the most posterior ones (b) and the limbic striatum the most ventral ones (c). Amg = amygdala; CA = hippocampus; dlPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; IPL = inferior parietal lobe; M1 = primary motor cortex; OFC = orbitofrontal cortex; PMA = premotor area; S1 = primary somatosensory cortex; SMA = supplementary motor area; SPL = superior parietal lobe; STN = subthalamic nucleus.**

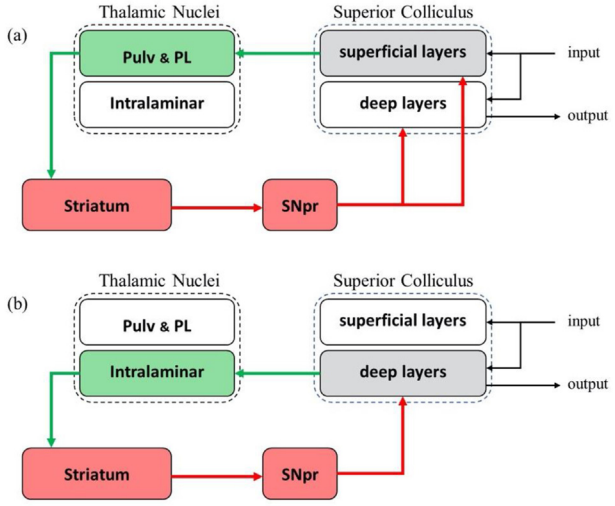


**Fig. 3 – The two main closed-loops of the mesencephalic-basal system. (a) The closed-loop originating from the superficial layers of the superior colliculus. (b) The closed-loop originating from the deep layers of the superior colliculus. The glutamatergic structures and projections are in green; The GABAergic structures and projections are in red; Pulv = pulvinar; PL = posterior lateral nucleus; SNpr = substantia nigra pars reticolata. Modified from: McHaffie et al. (2005).**

retransmitted from the striatum to the SC mainly through the SNpr, thus closing the loop (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010). The SC also sends ascending projections to the SNpc (Comoli et al., 2003; May et al., 2009; McHaffie et al., 2006). Therefore, the SC transmits to the striatum through both dopaminergic and glutamatergic neurons, presumably simultaneously (Redgrave, Coizet, et al., 2010).

Notably, two mesencephalic-basal loops process different types of information: the superficial layers of the SC receive only visual input directly from the retina and are mainly sensory, whereas the deep layers are both premotor and multimodal. In fact, they receive visual, auditory and somatosensory input, as well as signals from the BG and the cerebellum (May, 2006). According to this segregated anatomy, these two loops probably perform distinct functions (McHaffie et al., 2005).

The deep layers of the SC project not only to the striatum, but also to the STN (Coizet et al., 2009; Tokuno et al., 1994). Since the basal ganglia developed earlier than the cerebral cortex during evolution, these tecto-subthalamic projections are probably the phylogenetically ancestors of the cortico-basal hyper-direct pathway (Redgrave, Coizet, et al., 2010). In fact, the STN exhibits an early increase of activity after the onset of an unexpected stimulus (Bočková et al., 2011; Wessel et al., 2016). Likewise, STN activation interrupts behavior, and blocking the STN blunts the interruptive effect of surprise (Fife et al., 2017). Accordingly, the functional significance of the tecto-subthalamic projections, which compose the mesencephalic hyper-direct pathway, is that of quickly stopping ongoing activities when salient and unexpected visual stimuli summon our attention (Redgrave, Coizet, et al., 2010).

In sum, the BG form parallel closed-loops pathways not only with the cortex, but also with the SC. A first closed-loop originates from the superficial layers of the SC and mainly involves the sensorimotor striatum, whereas a second closed-loop originates from the deep layers of the SC and involves the whole striatum (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010).

## 3. The role of the basal ganglia in visuospatial selective attention

Many studies have investigated the role of the cortico-basal loops in visuospatial selective attention, highlighting the

involvement of the BG in (i) suppressing the processing of perceptually salient but task-irrelevant stimuli (Deijen et al., 2006; Lee et al., 2010; McNab & Klingberg, 2008), (ii) supporting shifts of attention (Ravizza & Ivry, 2001; Shulman et al., 2009), (iii) integrating top-down cortical signals in order to optimally regulate the attention-related changes in visual cortex (van Schouwenburg et al, 2010, 2015). It has long been known that the brain structures of the mesencephalic-basal loops are implicated in attentional processes. Nevertheless, the possibility that these closed-loops play a primary role in many aspects of selective attention has been put forth only recently (Krauzlis et al., 2018).

In the past decade, some studies on non-human primates showed that each striatal territory contributes differentially to modulate activity in the SC (Hikosaka et al., 2019). Inactivation of the head of the caudate selectively compromises the ability to select visual stimuli based on the associated flexible (short-term) values, sparing the selection based on stable (long-term) values. On the other hand, inactivation of the tail of the caudate selectively compromises the selection of visual stimuli based on stable (long-term) values, but leaves unaltered the selection based on flexible (short-term) values (Kim & Hikosaka, 2013). In other words, the head of the caudate is crucial when the selection of visual stimuli is based on recent events, whereas the tail of the caudate contributes to selection based on repeated experiences (Hikosaka et al., 2019).

The stable values associated with certain visual stimuli are stored not only in the tail of the caudate, but also in the posterior putamen. Notably, the tail of the caudate, the posterior putamen, the ventral-posterior GPe and the posterior-dorsolateral SNpr seem to be part of a unique subcortical network involved in long-term (but not in short-term) value coding of visual stimuli; namely, in discriminating visual stimuli for shifts of attention based on individual experiences (Anderson et al., 2014; Kim et al., 2017; Kunimatsu et al., 2019; Yamamoto et al., 2013). Visual stimuli previously associated with a large reward trigger inhibition of the posterior-dorsolateral SNpr (direct pathway), thus facilitating eye movements, whereas those previously associated with a small reward trigger inhibition of the ventral-posterior GPe (indirect pathway) with consequential disinhibition of the posterior-dorsolateral SNpr and suppression of eye movements (Amita et al., 2019; Kim et al., 2017; Kunimatsu et al., 2019).

In sum, the striatum modulates the SC through the direct and indirect pathway, enhancing or attenuating its activity (Hikosaka et al., 2006). The head of the caudate is mainly involved in discriminating visual stimuli based on flexible (short-term) values (Kim & Hikosaka, 2013), whereas the tail of the caudate and the posterior putamen are mainly involved in discriminating visual stimuli based on stable (long-term) values, acquired through prolonged and repeated exposure to the same visual stimuli (Anderson et al., 2014; Kim et al., 2017; Kunimatsu et al., 2019; Yamamoto et al., 2013). The head of the caudate is highly interconnected with the dlPFC (Choi, Tanimura, et al., 2017; Jarbo & Verstynen, 2015), which plays a crucial role in regulating deliberate shifts of attention, especially when subjects have to keep in mind specific abstract rules (Johnson et al., 2007; Loose et al., 2006). Conversely, the tail of the caudate and the posterior putamen contain many sensorimotor neurons (Nakano et al., 2000; Postuma & Dagher, 2006). Taken together, these data suggest that one of the primary roles of the BG system in visuospatial selective attention is to extract regularities for the formation of sensorimotor memories (Herman et al., 2020).

### 3.1. *A subcortical network for implicit visuospatial selective attention*

Implicit learning can modulate visuospatial attention (Todd & Manaligod, 2018). With practice subjects tend to become faster in detecting the target stimulus and in suppressing the interfering effect of distractors (Failing et al., 2019; Ferrante et al., 2018; Leber et al., 2016). This general improvement is accompanied by a reduction of the cortical attention-related activity (Mukai et al., 2007), thus suggesting a transition from intentional and attention-dependent to implicit and less resource-dependent modes of processing.

The above findings show that, as the flexible assignment of values to visual stimuli becomes stable, the neuronal activity in the striatum gradually moves from the anterior associative territories (the head of the caudate) to the posterior sensorimotor ones (the tail of the caudate and the posterior putamen) (Hikosaka et al., 2019). In humans, this gradient of progression (from the anterior striatum to the posterior striatum) has been observed during motor sequence learning (Lehéricy et al., 2005), suggesting that it is a general mechanism through which the BG system translates new goal-directed behaviors in habitual (well-learned) responses (Graybiel, 2008; Redgrave, Rodriguez, et al., 2010). In this context, at least some of the attentional phenomena observed after repeated exposure to same visual stimuli may be the consequence of forming stable sensory–motor associations in the posterior striatum (Herman et al., 2020).

In novel and unexpected situations, early visual input from the superficial layers of the SC reaches (through the Pulv) the Amg, thus prioritizing the processing of salient stimuli (Diano et al., 2017; Nishijo et al., 2018; Pourtois et al., 2013; Tamietto et al., 2012), regardless of whether these are emotionally loaded or not (Georgy et al., 2016); Balderston et al., 2011). Simultaneously, visual input also reaches (through the deep layers of the SC) the STN (mesencephalic hyper-direct pathway), which suppresses the ongoing processes (Nambu, 2008; Nambu et al., 2002; Redgrave, Coizet, et al., 2010). Therefore, during novel situations, the deliberate (controlled) selection of visual stimuli is mainly managed by the anterior fronto-striatal network (Hikosaka et al., 2019; Kim & Hikosaka, 2013). After having integrated top-down (goal-directed) signals from the cortex with bottom-up (stimulus-driven) signals from the deep layers of the SC, the head of the caudate (associative striatum) modulates activity in the SC, enhancing the processing of the target stimulus (direct pathway) and attenuating that of salient but task-irrelevant stimuli (indirect pathway) (Hikosaka et al., 2019).

With practice, stable sensory–motor associations are gradually created and stored in the tail of the caudate and in the posterior putamen (sensorimotor striatum) (Anderson et al., 2014; Kim et al., 2017; Kunimatsu et al., 2019; Yamamoto et al., 2013). Once settled, the sensorimotor mesencephalic-basal closed-loops can manage the selection

of visual stimuli in a rapid way (Hikosaka et al., 2019), thus reducing cognitive load.

Importantly, the described mechanism is dynamic and flexible. Top-down (goal-directed) and bottom-up (stimulus-driven) signals can always interrupt the selection of visual stimuli (through the cortical hyper-direct pathway and the mesencephalic one, respectively). In fact, studies in non-human primates have shown that a subpopulation of neurons in the STN exhibits a change in activity when animals have to switch from automatic to controlled eye movement (Isoda & Hikosaka, 2008; Pasquereau & Turner, 2017). Furthermore, the activity of the STN in response to a distractor tends to decrease when this is frequent, but not when it is rare (Bočková et al., 2011).

In sum, with experience, we implicitly learn that in certain situations some stimuli may be relevant whereas others tend not to be, albeit salient from an evolutionary standpoint (Codispoti et al., 2016; Failing et al., 2019; Micucci et al., 2020). This implicitly acquired automatic selection of visual stimuli seems to be managed by the sensorimotor mesencephalic-basal closed-loops (Hikosaka et al., 2019).

### 3.2. *A possible link between emotional stimuli, implicit selective attention and human behavior*

Emotional stimuli are able to automatically capture attention, regardless of whether they are pleasant (i.e., positively valenced) or aversive (i.e., negatively valenced) (Pourtois et al., 2013; Tamietto et al., 2005). Several studies reported that after prolonged and repeated exposure to the same emotional stimuli, the attentional capture prompted by emotional distractors is significatively attenuated. Notably, task-irrelevant emotional stimuli that are presented more frequently tend interfere less than those that infrequent (Codispoti et al., 2016; Micucci et al., 2020).

Recently, Maeda et al. (2018) reported that the Amg facilitates shifts of attention towards task-relevant visual stimuli by processing the emotional context. They found that, in non-human primates, there are neurons within the Amg that are activated differently by the emotional context, based on the specific valence acquired through experience (e.g., dangerous vs. safe contexts). Noteworthy, the ventral portions of both the caudate and the putamen receive overlapping projections from the Amg and prefrontal areas such as the OFC and the dlPFC (Choi, Ding, & Haber, 2017). Thus, these data converge in indicating that the BG system (specifically the associative striatum) integrates cognitive and affective signals from different cortical and subcortical regions in order to implement new (controlled) behavioral responses (Fig. 4a). When these new responses are adaptive, they tend to form stable sensorimotor memories and shift toward more automatic forms of processing (Fig. 4b) (Graybiel, 2008; Herman et al., 2020; Redgrave, Rodriguez, et al., 2010).

An important question is whether the BG play a direct role in emotional processing (e.g., automatic modulation of the innate activity of the Amg) or (only) in the automation of behavioral responses (e.g., inhibition of attentional shifts towards task-irrelevant emotional stimuli) related to specific emotional stimuli. Some data point to the second hypothesis. In fact, albeit the attentional capture triggered by emotional distractors decreases over time, the late neuronal activity closely related to emotional processing remains constant (Codispoti et al., 2016; Micucci et al., 2020). Notably, the Amg receives early visual input from the superficial layers of the SC (Diano et al., 2017; Tamietto & de Gelder, 2010). However, the ventral caudate and the ventral putamen (i.e., the striatal portions that receive axons from the Amg) projects through the SNpr to the deep layers of the SC, but not to the superficial ones (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010). Accordingly, the BG system likely operates to automatize new behavioral responses to specific stimuli based on high-level processing (Graybiel, 2008; Redgrave, Rodriguez, et al., 2010), without modifying the innate emotional processing of these stimuli (Codispoti et al., 2016; Micucci et al., 2020). Regardless of individual experience, early visual signals from the superficial layers of the SC would always trigger activity in the Amg and innate emotional processing. In addition, sensorimotor memories acquired through experience, and stored in the posterior putamen and in the tail of the caudate, are also recruited to contextualize behavioral responses (Fig. 4b). In other words, the cognitive system implicitly learns to ignore emotional stimuli if they are rarely associated to significant consequences in specific context, while maintaining the ability to monitor such stimuli and recognize they can be salient and informative under different circumstances.

## 4. A model of visuospatial attention deficits in the early stages of Parkinson's Disease

The PD is an idiopathic neurological condition associated with neuronal loss in the SNpc, which causes striatal dopamine depletion (Poewe et al., 2017). In addition to the cardinal motor symptoms, visuospatial selective attention deficits are often observed in subjects with PD since the early stages of disease (Deijen et al., 2006; Sharpe, 1990). Notably, they show no deficit in reflexive orienting of attention (Briand et al., 2001), but have difficulty in deliberate shifts of attention, both overt and covert (Briand et al., 1999; Yamaguchi & Kobayashi, 1998). Furthermore, they tend to commit more errors and need more time to respond, compared to healthy subjects, when a salient but task-irrelevant stimulus is presented simultaneously to the target stimulus (Deijen et al., 2006; Tommasi et al., 2015). Similarly, they tend to have difficulties in inhibiting task-irrelevant information when performing visuospatial working memory tasks (Lee et al., 2010), suggesting an impairment in suppressing the processing of distractors.

In general, a dysfunction of the top-down control mechanisms of attention is considered the basis of these abnormalities in selective attention (Deijen et al., 2006; Tommasi et al., 2015). In line with this interpretation, metabolic reductions in the frontoparietal areas closely related to dopamine depletion in the anterior caudate are not rare in PD (Holtbernd et al., 2015; Niethammer et al., 2013). However, these metabolic changes only occur in more advanced stages of the disease, approximately four years after diagnosis (Tang et al., 2010), whereas visuospatial selective attention

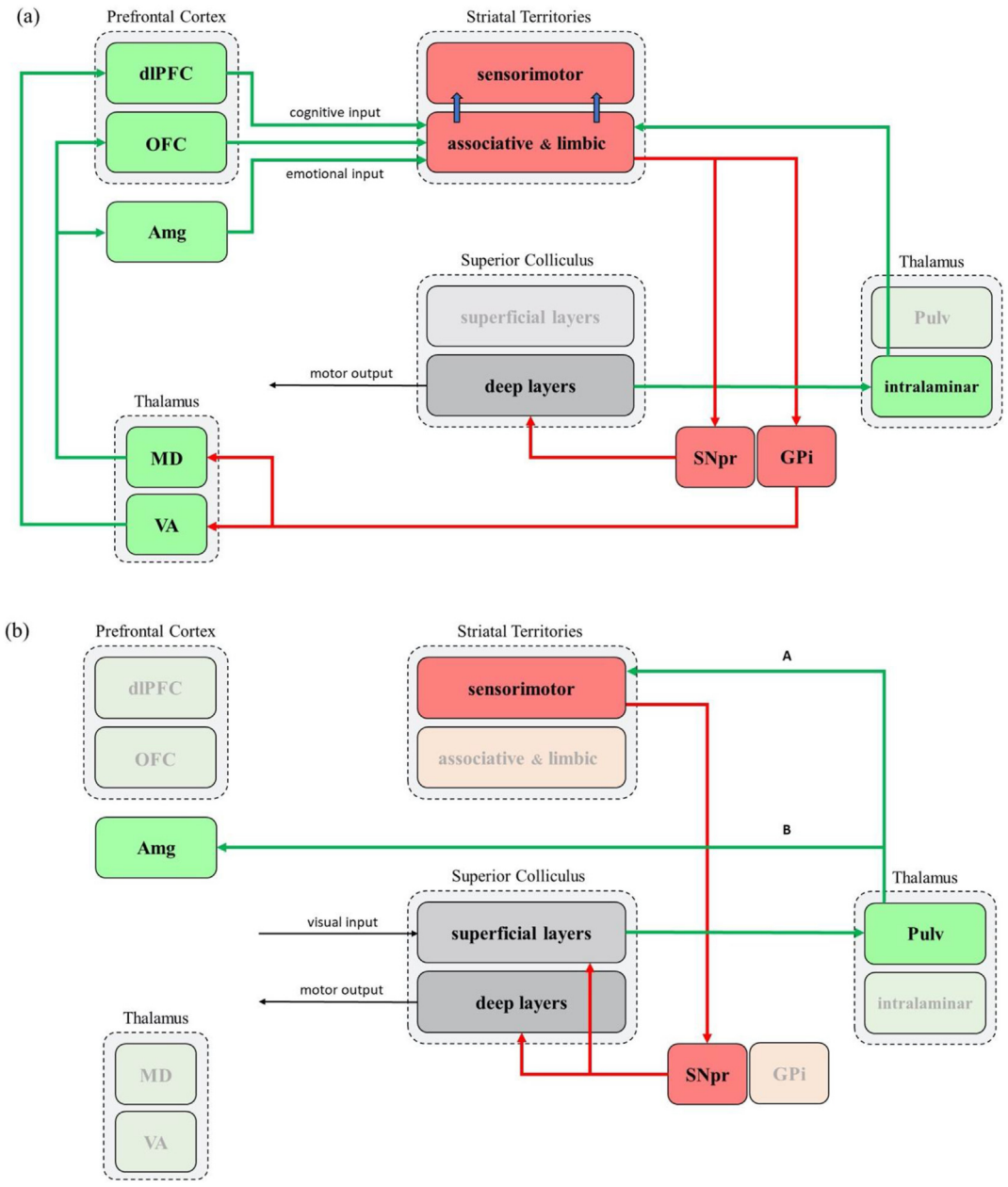


**Fig. 4 – Automation of the responses to salient stimuli. (a) Top-down signals from the prefrontal cortex or the amygdala can modulate the activity of the superior colliculus recruiting the associative and limbic striatum. With practice, implicit memories of these high level-processing are formed and stored in the sensorimotor striatum (blue arrows). (b) Once the new responses are automated, the amygdala can still be activated by early visual input from the superior colliculus: the superficial layers simultaneously send visual signals (through the pulvinar) to the sensorimotor striatum (A), recruiting the responses acquired with experience, and to the amygdala (B). The glutamatergic structures and projections are in green; The GABAergic structures and projections are in red; dlPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; Amg = amygdala; GPi = globus pallidus internus; SNpr = substantia nigra pars reticolata; Pulv = pulvinar; MD = medio-dorsal nucleus of the thalamus; VA = ventral-anterior nucleus of the thalamus.**

deficits are observable since the early stages of PD (Deijen et al., 2006; Sharpe, 1990), thus leaving room to other possible explanations.

In PD, nigrostriatal dopaminergic loss starts and tends to be more pronounced in the posterior putamen (Jokinen et al., 2009; Tang et al., 2010). As reported above, stable sensory–motor associations acquired through experience are stored in the posterior striatum (Anderson et al., 2014; Kim et al., 2017; Kunimatsu et al., 2019; Yamamoto et al., 2013). Accordingly, we portend that at least some aspects of the selective attention deficits of PD observed since early stages of the disease could be interpreted as a loss of the ability to translate high-level controlled processing into implicit sensorimotor memories (Fig. 5).

### 4.1. *Automation of the top-down control mechanisms of attention*

Our model assumes that, as sensorimotor memories are formed and stored in the posterior striatum, the demand for high attentional resources should gradually decrease. Accordingly, a progressive reduction of the attention-related frontoparietal activity should be observed in healthy subjects, but not in subjects with PD. Some data are in line with this assumption. On the one hand, in healthy subjects the FEF-SPL activity gradually decreases with corresponding performance improvements during prolonged and repeated visual attentional tasks (Mukai et al., 2007). On the other hand, greater task-related prefrontal-caudate activity has been reported since the early stages of PD (Trujillo et al., 2015). Interestingly, using high-sensitivity 3D [$^{18}$F]fluorodopa-PET, Kaasinen et al. (2001) observed an increased fluorodopa uptake in the dlPFC (as well as lower fluorodopa uptake in the putamen) of a group of unmedicated subjects with early PD, suggesting a possible compensative neuronal mechanism of the early stages of the disease.

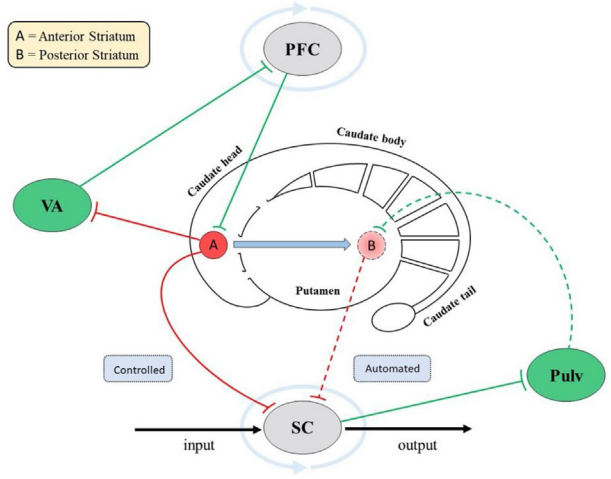


**Fig. 5 – Selective attention deficits in Parkinson's Disease as a lack of sensorimotor memories. While the flexible values of visual stimuli become stable, the striatal activity gradually moves from the anterior associative territories to the posterior sensorimotor ones (blue arrow). Once sensory–motor associations are formed and stored in the posterior striatum, the mesencephalic-basal loop is able to manage the selection of visual stimuli in an automatic, autonomous and rapid way, without having to recruit the expensive activity of cortical regions such as the dorsolateral prefrontal cortex. The dopamine depletion of PD mainly affects the closed-loops involving the posterior putamen (dashed lines). All the other closed-loops are potentially spared, at least in the early stages of the disease. Thus, the selective attention deficits of PD could be the behavioral consequence of a basal ganglia system that has lost the ability to create stable sensorimotor memories, namely, the ability to translate new controlled behaviors in rapid automated responses. The glutamatergic structures and projections are in green; The GABAergic structures and projections are in red; SC = superior colliculus; PFC = prefrontal cortex; Pulv = pulvinar; VA = ventral-anterior nucleus of the thalamus.**

### 4.2. *Attentional capture paradigms*

Tommasi et al. (2015) and Deijen et al. (2006) investigated visuospatial selective attention in PD using an attentional capture task, and reported that patients with PD take longer to provide the correct response and make more mistakes than normal subjects when a perceptually salient distractor is presented simultaneously to the target. Although a dysfunction of the top-down control mechanisms of attention may be a plausible interpretation of these data, it should be noted that the differences found could also be the behavioral consequences of a deficit in the formation, retrieval or maintenance of sensorimotor memories. In fact, the attentional capture tasks often require participants to repeatedly respond to the same visual stimuli. In healthy subjects, after prolonged and repeated exposure to the same visual stimuli, the perceptually salient but (frequently) task-irrelevant stimuli trigger a weaker distracting effect (Failing et al., 2019). Importantly, this phenomenon also occurs with emotional distractors (Codispoti et al., 2016; Micucci et al., 2020), thus suggesting an amodal cognitive mechanism.

In sum, normal subjects automatize distractor suppression with practice, making fewer mistakes and becoming faster to respond. Failure to keep this learning mechanism into account in Tommasi et al. (2015) and Deijen et al. (2006) studies could have masked the inability of subjects with PD to automatize the top-down control mechanisms of attention. In line with our assumption, Hadj-Bouziane et al. (2013) tested a group of subjects with early onset PD (and in advance stages of disease) with a visuomotor associative learning task. Compared to healthy subjects, patients showed difficulties in both the earliest phases of learning, when goal-directed responses are dominant, and in the late stages, when responses start to become well-learned. However, only the late phase deficit correlated to the PD severity and dopamine depletion in the posterior putamen.

### 4.3. *Posner paradigms with central cues (endogenous version)*

In general, subjects with PD show performances similar to that of healthy subjects in Posner paradigms with peripheral cues. However, abnormalities emerge when asked to perform Posner paradigms with central cues. Notably, the 'benefit' amounts (i.e., the effect of valid cueing) are comparable to those of healthy subjects, but the 'cost' amounts (i.e., the effect of invalid cueing) are reduced, if not absent (Grande et al., 2006; Mari et al., 1997; Pollux & Robertson, 2001). Our model can provide an explanation for this finding. During the first phases of the Posner-like procedures, subjects implicitly learn that the central cue (typically an arrow) indicates the position of the target in most (valid trials) but not in all of the occurrences (invalid trials) (Posner, 1980). Healthy subjects are able to implicitly learn to suppress shifts of attention toward the portions of the visual field that are frequently task-irrelevant (Ferrante et al., 2018; Leber et al., 2016). Accordingly, the

reduction in the effect of invalid cueing observed in subjects with PD may be the consequence of the lack of formation of stable sensory–motor associations (e.g., arrow pointing to the right – automatic suppression of shifts of attention towards the left). On the other hand, the normal benefits of valid cueing may instead depend on higher level knowledge, not affected by PD; that is, we consciously know that an arrow pointing to the right indicates that we must pay attention to the right.

### 4.4. *Does nigrostriatal dopamine depletion affect the selection of emotionally salient stimuli?*

The ability to recognize facial expressions of emotions is often impaired since the early stages of PD (Argaud et al., 2018). Further, similar to what is observed in subjects with Amg damage, this deficit is accompanied by a significant reduction in autonomic responses (Kawamura & Kobayakawa, 2009), thus suggesting that dopamine depletion may also have repercussions in Amg functions. In line with this assumption, Tessitore et al. (2002) reported that Amg activity of a sample of patients with PD in off-state medication was absent during a paradigm that involved perceptual processing of fearful stimuli. Moreover, dopamine repletion therapy (i.e., levodopa) partially restored the Amg response, indicating a crucial involvement of the dopaminergic system. However, not all data are convergent. In fact, the attentional capture triggered by negative emotional stimuli is present in PD (Camalier et al., 2018). In addition, Delaveau et al. (2009) measured Amg activity in a sample of subjects with PD and in sample of healthy subjects during a facial emotion recognition task. The participants received either levodopa or placebo. In both samples, Amg activity was reduced only after levodopa administration.

This apparent inconsistency between findings can be resolved by taking into account other neuronal networks. The OFC is highly interconnected with the striatum (especially the ventral portions) (Alexander et al., 1986; Draganski et al., 2008; Postuma & Dagher, 2006) and receives dopaminergic projections from the VTA (Coenen et al., 2018). Its involvement in emotion recognition is well documented in the literature (Adolphs, 2002). Further, it is also crucially involved in emotion regulation: the increase in the activity of the OFC correlates with a decrease in the activity of the Amg (Banks et al., 2007). In PD, deep brain stimulation of the STN can be used as an alternative to levodopa therapy. Some studies reported that the therapeutic stimulation of the STN (through deep brain stimulation) causes specific deficits in the recognition of negative emotions expressed in faces (Biseul et al., 2005; Dujardin et al., 2004). This anomaly occurs only in on-stimulation and is accompanied by abnormalities in the OFC metabolism (Le Jeune et al., 2008). Taking into account all these data, it is therefore possible that reduced Amg activity observed in off-state medication and partially restored by levodopa (Tessitore et al., 2002), was caused by abnormalities in the neuronal activity of the OFC, due in turn to dopamine depletion in the VTA. In fact, in their PD sample there were patients with history of depression. In such cases, the literature indicates that the dopaminergic loss involves not only the SNpc but also the VTA (Sugama & Kakinuma, 2016; Tang et al., 2020; Wei et al., 2018). Thus, dysfunctions of the Amg, when present in PD patients, do not seem depend on damages that involve the nigrostriatal tract (Argaud et al., 2018).

In sum, the nigrostriatal dopamine depletion of PD does not appear to affect the ability to automatically select salient emotional stimuli. Rather, it is more parsimonious to advocate for a deficit in the top-down modulation of innate responses to emotional signals.

## 5. Interim conclusions and open questions

The attentional processes emerge and are managed by a diffuse neuronal network involving both cortical and subcortical regions (Fiebelkorn & Kastner, 2020). An important issue that is currently unsolved is how cortical and subcortical networks interact, determining the complexity of selective attention (Krauzlis et al., 2018). One possible solution is to assume that the prefrontal-caudate loops are fundamental when the selection of visual stimuli depend on abstract rules, namely, when the value of these stimuli is still flexible (Kim & Hikosaka, 2013; Mukai et al., 2007). Since the (deliberate) controlled selection of visual stimuli often requires high level of attentional resources, the human cognitive system seems to have developed the ability to automatize the prefrontal-caudate activity (Graybiel, 2008; Mukai et al., 2007; Redgrave, Rodriguez, et al., 2010), through the formation of stable sensory–motor associations mainly stored in the posterior striatum (Anderson et al., 2014; Kim et al., 2017; Kunimatsu et al., 2019; Yamamoto et al., 2013). Of note, the BG system is crucially involved in both visuospatial selective attention and implicit learning (Herman et al., 2020). Once stable sensorimotor memories are formed and stored in the posterior striatum, the mesencephalic-basal loops could manage the selection of visual stimuli in an early, rapid and automatic way. Activated by early visual inputs from the superficial layers of the SC, the tail of the caudate and the posterior putamen would automatically (and autonomously) modulate activity in the SC, favoring the shift of attention towards frequently relevant visual stimuli (direct pathway) and suppressing shift of attention towards frequently irrelevant visual stimuli (indirect pathway) (Amita et al., 2019; Kim et al., 2017; Kunimatsu et al., 2019).

Our hypothesis is built on several converging findings. First, within the mesencephalic-basal architecture, two main closed-loops are identifiable, one originating from the deep layers of the SC and projecting to all the striatum, and one originating from the superficial layers of the SC and projecting to the sensorimotor striatum (McHaffie et al., 2005; Redgrave, Coizet, et al., 2010). Second, the head of the caudate (associative striatum) is crucially involved in the selection of visual stimuli based on flexible (short-term) values, whereas the tail of the caudate and the posterior putamen (sensorimotor striatum) in the selection based on stable (long-term) values acquired through experience (Hikosaka et al., 2019; Kim & Hikosaka, 2013). Third, during implicit learning the striatal activity gradually moves from the associative territories to the sensorimotor ones (Hikosaka et al., 2019; Lehéricy et al., 2005). Fourth, during prolonged and repeated visuospatial attentional tasks, subjects gradually become faster in detecting the target stimulus and in suppressing distractors (Failing et al.,

2019; Ferrante et al., 2018; Leber et al., 2016), and this improvement correlates with a gradual reduction of the attention-related frontoparietal activity (Mukai et al., 2007), suggesting an automation of the high-level (controlled) processes.

Within this perspective, at least some of the visuospatial selective attention deficits often observed in PD since the early stages of the disease (e.g., the greater susceptibility to perceptually salient but task-irrelevant visual stimuli) could be interpreted as a loss of ability to create, maintain and retrieve stable (long-term) sensorimotor memories. If so, their selective attention deficits would not be attributable to a dysfunction of the top-down control mechanisms of attention, but rather to an impossibility of put these deliberate processes under automatic control. Thus, taking into account the learning curve occurring over time is probably crucial when testing selective attention in subjects with PD.

A few concluding remarks are limitations are worth mentioning. First, in this review we have focused on the visual domain. However, it is possible that the neuronal mechanisms described are also valid for other sensory channels, such as the auditory one. In fact, the deep layers of the SC respond to both visual and auditory stimuli (May, 2006). Furthermore, anomalies in attentional capture were observed not only with visual stimuli, but also with auditory stimuli in PD (Heldmann et al., 2019). To this end, an open question is whether other subcortical structures involved in sensory processing (e.g., the inferior colliculus) send axons to the sensorimotor striatum, similar to the superficial layers of the SC for visual input. Second, we only took into account the domain of selective attention. However, our model could also be tested in other cognitive domains, such as the decision making or the executive functions. These domains are often impaired in PD (Brand et al., 2004; Cipresso et al., 2014; McKinlay et al., 2010; Mimura et al., 2006). Third, the model described may be predictive of selective attention deficits observed in other neurological disorders that directly involve BG, such as Huntington's Disease. Fourth, we have focused on the nigrostriatal dopaminergic system, leaving the possible role of other systems in the background. Nevertheless, data suggest that during visual perceptual learning the formation of sensorimotor memories is mediated by other dopaminergic structures, including the VTA (i.e., the mesolimbic system) (Arsenault & Vanduffel, 2019). Notably, the reward signals alone seem to be sufficient (Kim et al., 2015). Accordingly, the neuronal mechanisms underlying the formation of implicit sensorimotor memories could result partially spared in PD. In any case, the nigrostriatal loss would still compromise the normal functioning of the mesencephalic-basal system, making the retrieval or the maintenance of these implicit memories defective. Finally, in line with the idea that abnormalities within the SC may occur before the dopaminergic degeneration (Hawkes et al., 2007), a hypersensitivity to visual stimulation, that is not affected by levodopa therapy, has been recently found in the SC of a group of subjects with PD and in the early stages of the disease (Moro et al., 2020). This aberrant sensory processing (not related to dopamine depletion) could concur with the inability to automatize high-level processing (strongly related to dopamine depletion) in causing the abnormal susceptibility to distractors. This, in turn, could lead to a greater (basic) excitability of the STN (mesencephalic hyper-directed pathway) and of the Amg. The (later) inability to automate the inhibition of salient but task-irrelevant stimuli would exacerbate the (initial) hypersensitivity to visual stimuli of the SC. In fact, several factors concur in determining the complexity of the symptomatology of PD, albeit the nigrostriatal dopaminergic degeneration is the main one (Poewe et al., 2017).

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Alessia Celeghin: Conceptualization, Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision.

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## Declaration of competing interest

None.

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