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NEURONAL REPRESENTATIONS OF SELF AND OTHER IN THE MONKEY BASAL GANGLIA

RAPPRESENTAZIONI NEURALI DI SÉ E DELL'ALTRO NEI GANGLI DELLA BASE DEL MACACO

Relatore:
Chiar.mo Prof. LUCA BONINI

Correlatore:
Chiar.ma Prof.ssa MONICA MARANESI

Laureando/a:
MATILDE RENI

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Abstract (ENG)

It is widely accepted that the cortical motor system plays a key role not only in motor control, but in a broad range of advanced perceptual, cognitive, and social functions as well. Areas devoted to action planning and execution largely overlap with an extended action observation network (AON) that underlies the processing of others' actions, and recent anatomical data revealed that cortical regions contributing to this network send convergent projection to overlapping territories of the putamen nucleus in the basal ganglia, hinting at a possible involvement of this subcortical structure in the coding of others' observed behavior.

We investigated this issue by recording neuronal activity from 235 single-units in the macaque putamen nucleus during a Mutual Action Task (MAT) in which the animal and an experimenter, facing each other and taking turns based on learned contextual cues, were required to reach and grasp – or to observe the other perform the same action – a multi-affordance object placed in a shared operational space.

Most of the recorded neurons showed task-related activity and were responsive to either action execution (self type), action observation (other type), or both (self-other type), with units of the latter category being the most abundant. During active movement facilitated neurons prevailed, whereas in observation trials we found a balanced number of excited and inhibited units. Amongst self-other type neurons, the majority was facilitated during both action execution and observation (FF type), but we also recorded a sizeable fraction of cells that were suppressed in both conditions (SS type), or that showed opposite discharge patterns depending on which subject was performing the action (FS and SF type).

Our findings constitute one of the first empirical demonstrations of the existence of neurons specifically modulated by others' observed actions in the putamen, supporting the hypothesis of its involvement in the AON and indicating the need to look into its overall modulatory activity on the functioning of the network's cortical nodes.

Abstract (IT)

In letteratura è ampiamente noto il ruolo cruciale che le aree motorie corticali rivestono non soltanto nella pianificazione e nell'esecuzione dei movimenti, ma altresì in un'ampia gamma di funzioni percettive, cognitive e sociali di alto livello. Molte delle regioni implicate nel controllo motorio contribuiscono anche alla circuiteria neurale che sottende l'elaborazione dell'azione dell'altro (AON), e recenti evidenze anatomiche hanno sottolineato l'esistenza di una densa connettività anatomo-funzionale tra i nodi corticali di tale network e il nucleo putamen dei gangli della base, delineando l'ipotesi che anche questa struttura sottocorticale collabori alla decodifica dei comportamenti altrui.

Per esplorare questa possibilità, abbiamo registrato l'attività di 235 neuroni nel putamen del macaco durante un compito di interazione (MAT), in cui era previsto che l'animale e uno sperimentatore, a turno, afferrassero o osservassero l'altro afferrare con diversi possibili tipi di presa un oggetto collocato in uno spazio operativo comune.

La maggior parte dei neuroni registrati era significativamente modulata durante il task e rispondeva all'esecuzione in prima persona (tipologia "self"), all'osservazione dell'azione dell'altro ("other") o, nella maggior parte dei casi, ad entrambe le condizioni ("self-other"). Durante il movimento attivo erano prevalenti i neuroni che mostravano una facilitazione, mentre nell'osservazione facilitati e soppressi erano ugualmente rappresentati. Tra gli appartenenti alla categoria "self-other", i più numerosi erano eccitati sia in esecuzione sia in osservazione ("FF"), ma abbiamo registrato anche neuroni inibiti in entrambe le condizioni ("SS") o modulati in senso opposto a seconda del soggetto agente ("FS" e "SF").

Questi risultati preliminari rappresentano una delle prime prove empiriche dell'esistenza di neuroni specificamente modulati dall'osservazione dell'azione altrui nel putamen, rafforzando l'ipotesi di un suo coinvolgimento nell'AON e mettendo in luce la necessità di indagarne più nel dettaglio l'impatto modulatorio sui nodi corticali del circuito.

1. INTRODUCTION

1.1 The cortical motor system

1.1.1 Brief overview of the anatomy and physiology of the frontal motor cortex

The anatomy and physiology of the cortical motor system is largely based on findings obtained in macaques, which share deep homologies with the corresponding regions of the human frontal cortex. Classically, it was proposed that the agranular frontal cortex – which occupies the caudal sector of the frontal lobe, immediately rostral to the central sulcus – could be distinguished into two distinct cytoarchitectonic regions: Brodmann's areas 6 and 4, functionally corresponding to the primary motor cortex (M1) and the premotor cortex, respectively (Woolsey et al., 1952). It is now clear that this original model was an oversimplification from both the cytoarchitectonic and the functional point of view.

Indeed, macaque's area 6 is composed of a mosaic of regions endowed with very different cytoarchitectonic, histochemical, hodological, and functional properties, thereby playing different functional roles (Matelli et al., 1985; 1991; Rizzolatti et al., 1998). This modern subdivision of the primate frontal cortex highlights the existence of seven distinct motor areas (Figure 1): the mesial areas F6 and F3, the dorsal areas F7 and F2, and the ventral areas F5 and F4. Each of these pairs of areas consists of a rostral and a caudal portion, in turn characterized by stronger links with the prefrontal and parietal regions, respectively (Rizzolatti and Luppino 2001).

Intracortical microstimulation studies have shown that each motor region exhibits different electrophysiological properties and is endowed with an individual somatotopic map (e.g., Wu et al., 2000). Amongst the mesial areas, F3 (corresponding to human SMA proper) is electrically excitable and contains an exhaustive representation of body movements, mainly involving axial and proximal joints, whereas F6 (pre-SMA) requires longer stimulation trains and mostly produces slow, complex forelimb and mouth movements

(Luppino et al., 1991). Concerning dorsal premotor regions, area F2 is sensitive to low-intensity currents and its stimulation produces forelimb and trunk movements (Raos et al., 2003), unlike the scarcely excitable area F7, that has been subject to few functional investigations. Finally, both ventral premotor areas respond to electrical stimulation: F4 encompasses representations of the arm, hand, and face (Gentilucci et al., 1998), and F5 primarily produces hand and mouth movements (Rizzolatti et al., 1988), although both areas have been more recently further subdivided into distinct functional and anatomical sectors (Belmalih et al. 2009; Gerbella et al. 2011; Maranesi et al. 2012; Theys et al. 2012).

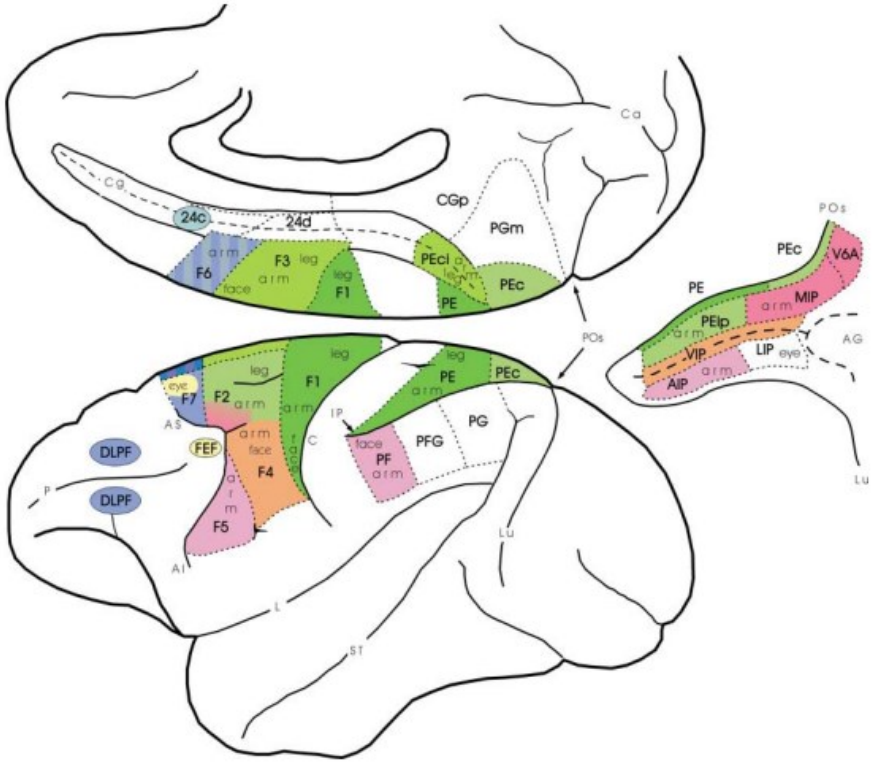

Figure 1. | Mesial and lateral views of the macaque brain showing the cytoarchitectonic parcellation of the frontal motor cortex and the location of other cortical regions cited in the text. Areas buried within the intraparietal sulcus are shown in an unfolded view of the sulcus. Based on the available data, the various body part representations in the motor and parietal cortices are also reported. Single motor areas and their major source of cortical afferents are indicated with the same color: colors in the green range indicate motor cortex that is mostly the target of somatosensory information; colors in the red range indicate either visual or visual and somatosensory information; colors in the blue range indicate predominant prefrontal and/or cingulate afferents. AG, annectant gyrus; Ca, calcarine fissure; CGp, posterior cingulate cortex; DLPF, dorsolateral prefrontal cortex; FEF, frontal eye field; Lu, lunate sulcus; POs, parieto-occipital sulcus. Figure from Luppino and Rizzolatti (2000).

Motor and premotor regions considerably differ in terms of their connectivity pattern as well (e.g., Luppino and Rizzolatti, 2000), which can partly account for the observed variety of evoked motor responses. The first discrepancies are those concerning intrinsic connections, i.e., projections coming from and directed to other motor areas: anterior premotor regions (F6, F7) show no direct connections with F1, but densely communicate with other premotor regions (F2-F5), which in turn project to the primary motor cortex.

Similar differences can be observed in descending projections (Dum and Strick, 1991): F6 and F7 are not directly linked to the spinal cord and can only exert an indirect control over movement through their subcortical relays (e.g., brainstem centres), in contrast to F1-F5, whose efferent projections, though highly different in strength, contribute to the corticospinal tract. Moreover, fibers stemming from premotor areas are almost entirely received by the intermediate sector of the spinal cord and probably contribute to the global control of motor activity, in contrast to those starting from F1, part of which target lamina IX where motor neurons are located, thereby providing a fine-tuned regulation of distal movements.

Extrinsic connections of the motor cortical system mainly consist of fiber pathways linking them with parietal, prefrontal, and cingulate regions. Particularly, frontal areas producing a spinal output (from F1 to F5) are richly connected with specific areas of the parietal lobe, whereas the most anterior areas F6 and F7 largely receive from prefrontal (Bates and Goldman-Rakic, 1993) and cingulate cortices. Such anatomic distinction has critical implication on the functional properties and roles of these different motor regions (Rizzolatti et al., 2014).

1.1.2 Functional properties beyond the coding of executed movements

For a long time, it was commonly thought that the motor cortex exclusively contributed to motor control, acting as a passive executor of command signals provided by higher-level associative areas of the parietal and frontal lobes. Although it is undoubtful that all motor areas play indeed a significant role in motor planning and control, the rostro-caudal gradients in anatomical projections (Nachev et al., 2008; Hanawaka, 2011; Albertini et al., 2020) are paralleled by rostro-caudal functional gradients in the contribution to higher order perceptual and cognitive functions (McFarland and Haber, 2000), with caudal regions more directly involved in the specification of movement execution and rostral areas increasingly involved in the coding of higher order variables.

It is known that parietal and premotor areas have strong, reciprocal, highly specific connections, giving origin to largely segregated circuits (the *frontoparietal networks*), each of which underlies a particular facet of sensorimotor transformation, i.e., the integration of sensory and motor signals for the guidance of motor behavior (Caminiti et al., 2015; Borra et al., 2017). In fact, they underpin the encoding of automatically processed sensory inputs in terms of the potential motor action *afforded* by them, hence contributing to deploy the set of behavioural responses that the environment offers to an animal in a given context (Cisek, 2007; Cisek and Kalaska, 2010).

The posterior parietal cortex (PPC), subdivided by the intraparietal sulcus into a superior (SPL) and inferior parietal lobule (IPL), plays a major role in the analysis of high-order aspects of sensory information. Much alike the motor cortex, the PPC is formed by a mosaic of anatomically and functionally distinct areas, each preferentially projecting to a single motor area. In this respect, of particular interest are the networks involving ventral premotor areas F4 and F5 (Luppino et al., 1999), whose neurons are characterized by some distinctive functional properties.

Many F4 neurons have been found to be bimodal, modulated by both somatosensory and visual stimuli, with visual receptive fields being mostly anchored to the tactile ones (Fogassi et al., 1996). Area F4 is strongly connected with the ventral intraparietal area (VIP), forming a circuit that plays a key role in coding the peripersonal space and converting spatial locations into appropriate motor acts directed towards them (e.g., reaching or avoidance). On the other hand, area F5 contains motor and visuomotor neurons that discharge during active grasping movements, in most cases with marked selectivity for a specific type of grip (Murata et al., 1997; Raos et al., 2006). Some of these visuomotor neurons also respond to the presentation of graspable objects and are referred to as "canonical" F5 neurons (e.g., Jeannerod et al., 1995; Rizzolatti and Fadiga, 1998). Together with the anterior intraparietal area (AIP), F5 forms a pathway that appears to be involved in creating pragmatic representations of observed objects, by matching their intrinsic visual properties with the hand shaping that would be necessary for their successful prehension and subsequent manipulation (Schaffelhofer and Scherberger 2016; Fogassi et al. 2001).

1.1.3 Encoding of others' observed actions

In addition to the canonical visuomotor neurons described above, F5 contains another class of visually responsive cells, the so-called "mirror neurons" (MNs), exhibiting motor responses similar to those of other F5 neuronal categories, but markedly different visual properties. The distinctive feature of MNs is that they respond both during active execution of a certain motor act and when the subject observes (Di Pellegrino et al., 1992; Gallese et al., 1996) – or even listens to (Kohler et al., 2002) – the same action being performed by another individual. Ever since their discovery, these cells have been subject to several investigations and have been proposed to be the neuronal substrate underlying a vast array of complex functions – giving rise to heated debate within the scientific community (e.g.,

Rizzolatti and Sinigaglia, 2010; Cook et al., 2014) –, starting with the presumptive ability to automatically recognize others' actions pairing their visual description with corresponding motor representations belonging to the observer's motor repertoire. Elicitation of internal representations by means of action observation seems to be involved in action imitation and imitative learning as well (e.g., Rizzolatti et al., 2001; Caspers et al., 2010; Mooney, 2014; Heyes and Catmur, 2021).

Neurons with similar properties have been identified in other areas in addition to F5, each receiving from a variety of direct and indirect sources visual information about others' actions (Ferrari et al., 2009) thanks to direct or indirect links with the superior temporal sulcus (Bruni et al., 2018), where the processing of visual signals primarily takes place (Jellema and Perrett, 2006; Barraclough et al., 2009; Orban et al., 2021). Areas belonging to this *extended MN network* (Bonini, 2017; Figure 2) include the inferior parietal areas PFG (Fogassi et al., 2005; Bonini et al., 2010) and AIP (Pani et al., 2014; Lanzilotto et al., 2019), the dorsal premotor (Papadourakis and Raos, 2019) and primary motor cortex (Tkach et al., 2007; Dushanova and Donoghue, 2010), ACC and the pre-SMA in the medial frontal cortex (Yoshida et al., 2011; Livi et al. 2019), possibly even the ventrolateral prefrontal cortex (Nelissen et al., 2011; Simone et al., 2017) and basal ganglia (Bonini, 2017; Caligiore et al., 2013, Alegre et al., 2010).

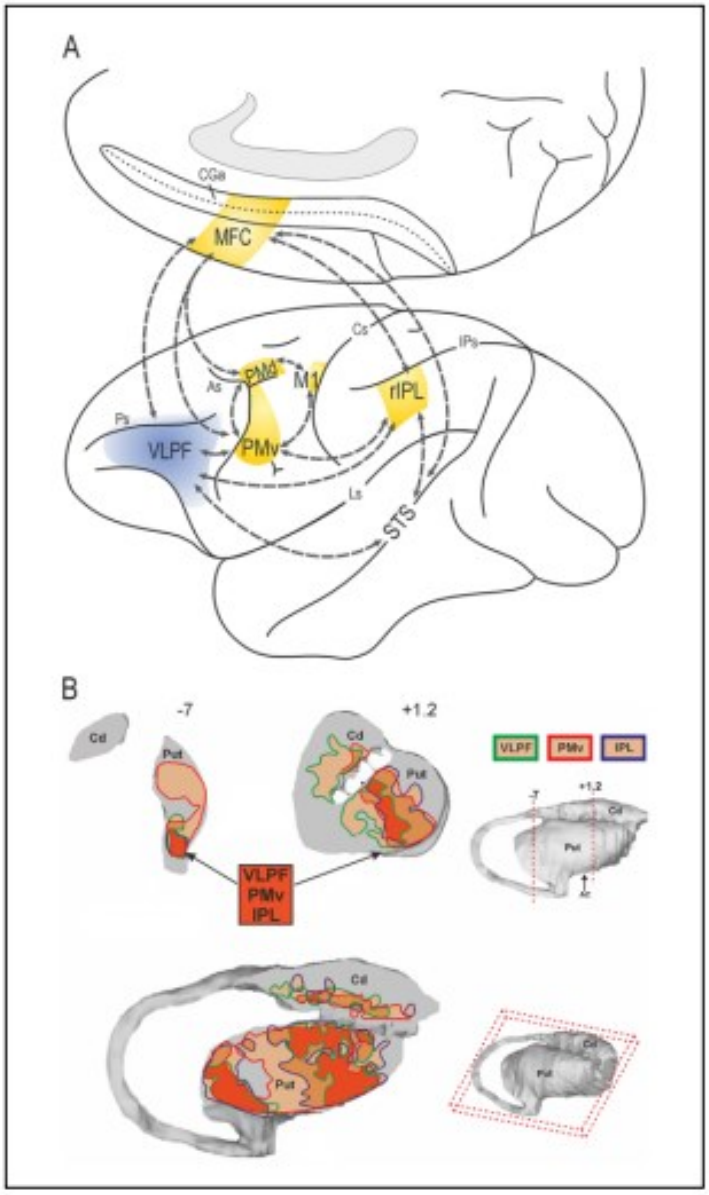

Figure 2. | (A) The extended MN network includes a set of areas in which the presence of single neurons with mirror properties has been directly demonstrated (yellow) as well as other regions (the ventrolateral prefrontal areas 12 and 46) in which the presence of MNs is supported by anatomical evidence but not yet directly demonstrated (blue). The arrows represent the main anatomical connection between these areas. As, arcuate sulcus; Cs, central sulcus; CGa, anterior cingulate gyrus; IPs, intraparietal sulcus; Ls, lateral sulcus; Ps, principal sulcus. M1, hand sector of the primary motor cortex; MFC, medial frontal cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; rIPL, rostral inferior parietal lobule; STS, superior temporal sulcus; VLPF, ventrolateral prefrontal cortex. **(B) Territories of the basal ganglia** (BG) receiving projections from the areas belonging to the cortical MN network, namely, PMv (sector with red borders), IPL (blue borders), or VLPF (green borders). The light and dark orange shadings highlight the BG sectors in which two or even all of these three distinct sources of corticostriatal projections overlap. The coordinates (−7 and +1.2) indicated in the reconstruction on the top right part of the panel show the anteroposterior locations of the two BG slices shown on the left. Put, putamen; Cd, caudate nucleus. Figure from Bonini (2017).

The existence of a similar network involving homologous areas of the human brain is strongly supported by a growing body of evidence – mostly collected by means of indirect techniques (Iacoboni et al., 1999; Buccino et al., 2001; Molenberghs et al., 2012), but one single neuron recording study in epileptic patients also supports the existence of mirror neurons in human brain (Mukamel et al., 2010). Human MNs are not exclusively activated by observation of goal-directed actions, but also respond to intransitive actions, pantomimes, and to the precise sequencing and time course of the movements composing an action, thus showing higher specificity as compared to the monkey's (Rizzolatti and Craighero, 2004).

1.2 The basal ganglia

1.2.1 Structural and functional organization of the basal ganglia

The basal ganglia (BG) complex consists of a group of subcortical nuclei originally known for their involvement in motor control, together with a broader variety of functions, including a role in cognition and emotion. The main constituents are the striatum (composed of the caudate nucleus, putamen, and ventral striatum or nucleus accumbens) and the globus pallidus (GP), located in the depth of the brain hemispheres, whereas related nuclei can be found in the diencephalon (subthalamic nucleus, STN), mesencephalon (substantia nigra, SN), and pons (pedunculopontine nucleus, PPN) (Lanciego et al., 2012).

Among these nuclei, the striatum and STN are input stations, receiving signals from different sources – mostly cortical, nigral, and from the nonspecific thalamus. The external segment of the globus pallidus (GPe) and the substantia nigra pars compacta (SNc) are intrinsic nuclei, which serve as relay sites in the information-processing stream. The internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) act as output nuclei and project outside the BG – mainly to the thalamus, from which the information is forwarded back to the cortex, forming the cortico-basal ganglia-thalamo-

cortical loops (Alexander et al., 1986; Parent and Hazrati, 1995). Some signals are also sent to brainstem's motor centers controlling, for example, eye movement, location, or posture, and reach the thalamus via collaterals, in the form of efference copies (Grillner and Robinson, 2016). These nuclei do not, however, have direct input or output connections with the spinal cord. While most cortical areas provide inputs to the BG, the thalamic feedback is mainly directed to frontal cortical areas, such as prefrontal, premotor and supplementary motor areas (Alexander and Crutcher 1990).

The canonical functional model of the BG depicted them as a "go through" station within the motor loop: cortical inputs were thought to be dispatched to and modulated by these structures, and subsequently sent back to the cortex to facilitate or inhibit motor activity. With respect to how signals coming from different areas are managed, two opposing views have historically been proposed (Nambu, 2011). According to the *parallel processing hypothesis* (Alexander and Crutcher, 1990; Hoover and Strick, 1993), afferent inputs from distinct sources are kept segregated and processed independently in distinct sites of the BG, whereas according to the *information convergence hypothesis* (Chevalier and Deniau, 1990; Percheron and Filion, 1991) different signals are "funneled" and integrated in the same site. A more recent outlook, influenced by the emergence of new empirical data, suggests that both theories are true to a certain extent, i.e., that only cortical influences originating from regions with similar functions tend to converge, unlike those coming from areas that are not functionally related.

Thus, each nucleus of the BG can be further subdivided based on its relationship with relevant cortical projection areas, into discrete regions referring to distinct domains and belonging to parallel, functionally independent circuits, with a supposedly similar basic design. Five major loops were originally identified, designated as *motor*, *oculomotor*, *dorsolateral prefrontal*, *lateral orbitofrontal*, and *limbic*, respectively (Alexander and

DeLong, 1986). Reciprocal connections between the BG and the cortex have been studied using retrograde transneuronal transport of a virus, finding that these subcortical nuclei project to most of the same areas that send efferences to them (Middleton and Strick, 2000).

It has been reported, however, a certain degree of convergence even for focal projections from areas of different domains (Haber, 2010), suggesting the existence of integrative mechanisms through which information can be transferred from one loop to another. The functional organization of the BG can therefore be better described as a set of multiple circuits, characterized by both open- and closed-loop macro-architectures (Kelly and Strick, 2004), where cortical and subcortical projections interact with internal reentry loops, most of which have a putative modulatory role (Figure 3). This organization creates a complex network, ideally designed for the selection and inhibition of behaviors, events, and signals (DeLong and Wichmann, 2009; Lanciego et al., 2012).

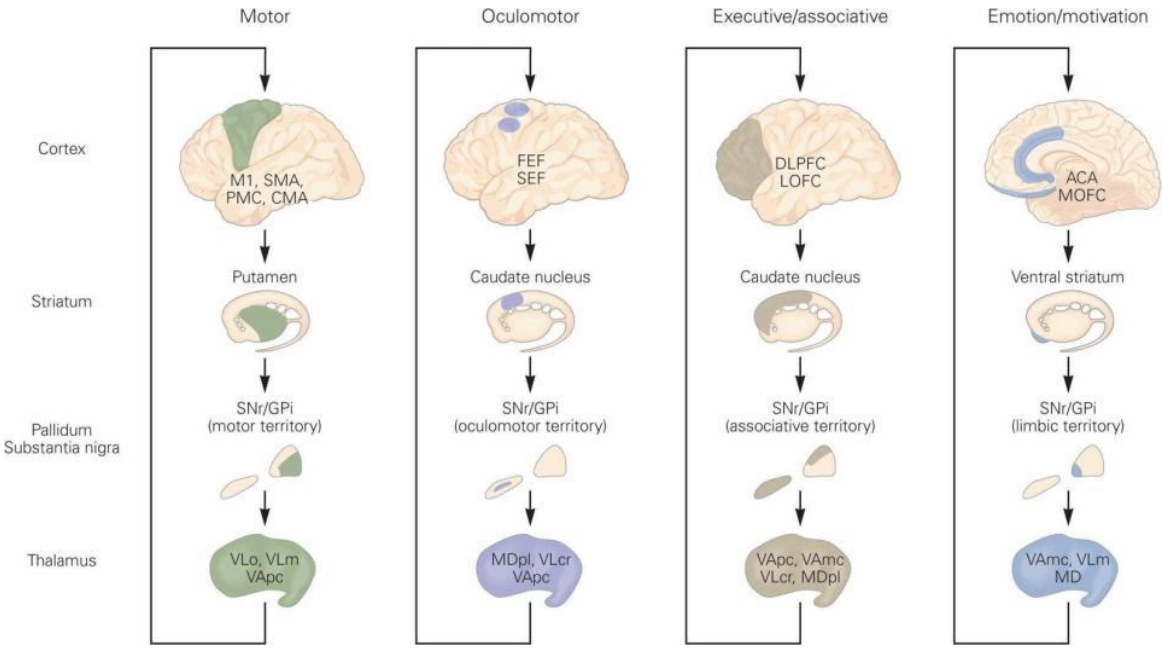

Figure 3. | **Anatomical organization of the circuits connecting the basal ganglia with thalamo-cortical projections**. (ACA, anterior cingulate area; CMA, cingulate motor area; SMA, supplementary motor area; FEF, frontal eye fields; LOFC, lateral orbitofrontal cortex; MOFC, medial orbitofrontal cortex; SEF, supplementary eye fields; DLPFC, dorsolateral prefrontal cortex; PMC, premotor cortex; MDpl, lateral part of the mediodorsal nucleus; GPi, globus pallidus pars interna; M1, primary motor cortex; SNr, substantia nigra pars reticulata; VAmc, magnocellular part of the ventral anterior nucleus; VApc, parvocellular part of the ventral anterior nucleus; VLc, caudal part of the ventrolateral nucleus; VLm, medial part of the ventrolateral nucleus; VLo, oral part of the ventrolateral nucleus). Figure from Kandel (2013).

Cortical excitation can be transferred to the output nuclei through three distinct routes (Figure 4). Unlike the cortex, that relies upon excitatory, glutamatergic projections, the BG contain inhibitory, GABAergic neurons – of the spiny variety in the striatum (MSNs) and of the aspiny type in the output nuclei. Within the direct pathway, MSNs expressing D1 receptors, substance P and dynorphin are directly connected to the GPi/SNr, exerting an inhibitory effect on the tonic activity of these structures, and leading to a pause in their neuronal firing, which is usually associated with occurrence of an action. Since GPi and SNr contain subpopulations of GABAergic neurons characterized by a rather high firing rate at rest, in resting condition the corresponding motor centers are under tonic inhibition, hence their activation requires disinhibition of projection neurons. On the other hand, the indirect pathway depends on striatal neurons expressing D2 receptors and enkephalin, that project polysynaptically to the GPi/SNr through the intrinsic nuclei. The result of these projections is an inhibition of GPe, followed by disinhibition of STN, which finally produces an increased excitation of the output nuclei, and subsequent stopping or halting movement along the thalamo-cortical pathway (Gerfen et al., 1990).

These direct and indirect pathways have opposite functional effects on BG output: the former plays a key role in action facilitation, promoting initiation and execution of body movements through disinhibition of the appropriate motor networks, the indirect pathway is probably engaged in the suppression of competing behavioral patterns. It appears to be a successful arrangement that has remained relatively untouched during evolution, as shown by comparisons between the cyclostome and mammalian BG intrinsic organization, which exhibit consistent similarities (Grillner and Robinson, 2016). Optogenetics studies using mice models (Kravitz et al., 2010; Bateup et al., 2010), based on selective stimulation or inhibition of each pathway, offer an empirical analysis of their distinct contributions,

providing strong support to the notion of a functional equilibrium that would allow effective bidirectional regulation of motor behavior.

In addition to the direct and indirect pathways, there is the hyperdirect pathway, where frontal afferents are received by STN neurons and quickly transmitted to the GPi/SNr, thus bypassing the input nuclei. These direct inputs produce activation of the STN, whose net effect is an activation of the GPi, and therefore inhibition of the motor centers targeted by this pathway, allowing rapid termination of motor acts.

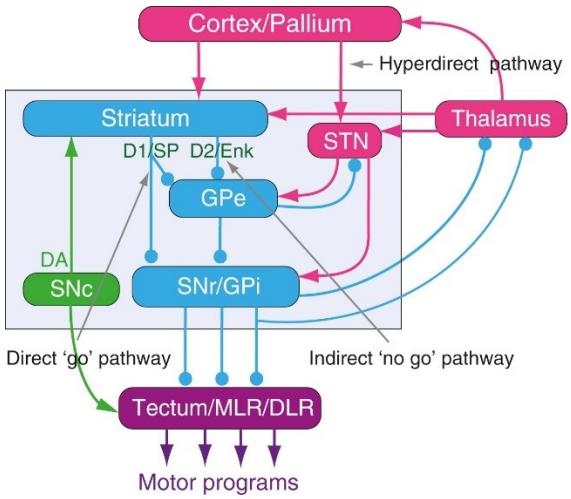

Figure 4. | Schematic representation of the BG main pathways. Excitatory glutamatergic neurons are represented in red and GABAergic structures in blue color. The dopamine input from the SNc to striatum and brainstem centers is represented in green color. Figure from Grillner & Robinson (2016).

1.2.2 Clinical dysfunctions and functional hypothesis

Investigations of the functional role of the BG have mainly focused on the most common symptoms following their pathological alterations, consisting of impairments in motor and non-motor functions. Normal functioning requires fine tuning of neuronal excitability within each nucleus, which is mediated by the complex organization of the striatum, with dopaminergic transmission playing a major role (Whichmann and Dostrovsky, 2011). In humans, motor deficits depending on BG dysfunctions include a heterogeneous set of clinical manifestations, ranging from hypokinetic to hyperkinetic syndromes. Both extremities of this spectrum can be accounted for by hypothesizing a disruption in

corticostriatal balance, based on changes in the function of MSNs subpopulations (DeLong, 1990; Chesselet and Delfs, 1996).

The best-known example of hypokinetic disorder is the Parkinson's disease (PD), whose main symptoms – including resting tremor, muscle rigidity, slowness of movement or bradykinesia, and postural instability – are thought to be the result of a dopamine (DA) depletion provoked by the degeneration of DA-producing cells in the SNc, which causes the self-stabilizing loops of the BG to fail in their compensatory role. This disturbance leads to increased activity in the indirect pathway and diminished facilitation of direct circuit neurons, giving rise to an amplified GPi/SNr output, which induces excessive inhibition of thalamo-cortical and brainstem motor centers, and reduces the likelihood of movement occurrence (Obeso et al., 2000; 2008). Modulation of this circuitry may constitute an effective therapeutic strategy to improve BG-related motor dysfunctions (e.g., Kravitz et al. 2010): indeed, Kravitz and coworkers showed that the activation of the direct pathway through optogenetic control successfully rescued deficits in a mouse model of PD.

Conversely, hyperkinetic disorders – such as Huntington's disease, levodopa-induced dyskinesia, or hemiballismus – are the result of an excess of movement with uncontrollable and rapid ballistic movements intruding into the normal flow of voluntary activity. These anomalies can be seen as the product of a selective impairment of striatal neurons projecting to the output nuclei, which triggers a surplus of abnormal movement (Albin et al., 1989; Galvan et al., 2012).

Although the BG have classically been implicated primarily in voluntary movement – specifically action selection, followed by inhibition of competing motor mechanisms and movement preparation and execution (Mink, 1996; Gurney et al., 2001) – converging evidence from single-cell recordings, brain imaging studies, and lesion studies (in both animals and humans) have challenged the original view of a contribution limited to motor

control, casting light on the role of BG in a variety of other brain functions as well (Chakravarthy et al., 2010; Stocco et al., 2010). Studies performing muscimol or bicuculline microinjections in different functional territories of the striatum (Worbe et al., 2009; Karachi et al., 2009) suggest that specific lesions of the BG could be involved in the pathophysiology of several neurological and neuropsychological conditions (Bostan et al., 2018; Riva et al., 2018). For instance, perturbation of the striatum can result in impairments of behavioral control (Tremblay et al., 2015) – as observed in Autism Spectrum Disorders (Estes et al., 2011), Attention Deficit/Hyperactivity Disorder (Emond et al., 2009; Durston et al., 2011), Tourette Syndrome (Peterson et al., 2003), and Obsessive-Compulsive Disorder (Milad and Rauch, 2012), but there is also evidence suggesting that dopaminergic hyperactivity in the limbic sector of the BG might mediate the positive symptoms of Schizophrenia (Inta et al., 2010; Simpson et al., 2010).

More complex functions that appear to be implemented by BG activity include procedural memory (Packard and Knowlton, 2002) and working memory (Monchi et al., 2000), habit formation (Yin and Knowlton, 2006), perception (Brown et al., 1997), attention shifting (Ravizza and Ivry, 2001), decision making (Balleine et al., 2007), and various types of implicit learning – such as motor (Hikosaka et al., 2002; Doyon et al., 2009), category (Moustafa and Gluck, 2011), and reward-related (Tanaka et al., 2016).

Caligiore et al. (2013) suggested a role for the BG in the action-observation mechanism as well. Since subcortical areas work in concert with several cortical regions, including those belonging to the MN network, the authors have argued that an analysis of their specific contribution could help to understand the neural basis of some important facets of other's action processing – regarding, for example, the influence of the observer's motor experience, the multiple levels at which an observed action can be represented, and the acquisition of action recognition abilities. Bonini (2017) proposed that the BG could

contribute to the mirror network by providing a mechanism for decoupling MNs activity from the motor input, i.e., preventing us from the automatic enactment of observed actions. Specifically, it is possible that some F1 and PM neurons displaying mirror properties have preferential facilitatory connections with striatal neurons of the indirect pathway and/or with subthalamic neurons of the hyperdirect pathway, thereby reducing the overall thalamocortical facilitation and allowing inhibition of unwanted movements through the decrease – or even suppression – of pyramidal tract neurons (PTNs) during action observation.

Recent studies investigating the BG involvement in action-observation processes in human subjects provided some indirect evidence in support of this hypothesis. Kessler et al. (2006) used whole-head magnetoencephalography (MEG) to investigate the time course of long-range synchronization within cortical networks during an imitation task (of biological vs. non-biological movements): BG activation started earlier in the processing of biological motion (for which selective behavioral advantage was observed), suggesting their possible implication in the selection of suitable motor programs to match the observed stimulus. Alegre et al. (2010) recorded local field potentials (LFPs) from the STN of patients with PD and reported that movement observation was accompanied by changes of the beta oscillatory activity (significant bilateral reduction in STN power and cortico-STN coherence) consistent with those observed during movement execution, although smaller. Ge et al. (2018) had participants observing hand actions (from a first- or third-person perspective) and found comparable fMRI activations not only in key areas of the MN network, but also in several regions of the BG and limbic system, such as the putamen, insula, and hippocampus. Another fMRI study conducted by Fogassi and Errante (2020) described significant shared activation during the execution and observation of object manipulations in several subcortical structures, including bilateral GP and left STN.

Comparative evidence from studies on songbirds (Prather et al., 2008; Mooney, 2014) shows that the avian homologous of the BG (area X) is innervated by a subpopulation of projection neurons located in the telencephalic nucleus HVC, which is known to be essential for normal song perception and learning. Since HVC contains auditory-vocal mirror neurons (Figure 5), these findings further corroborate the hypothesis of a potential role of corticostriatal neurons and putaminal cells in the action-observation circuit.

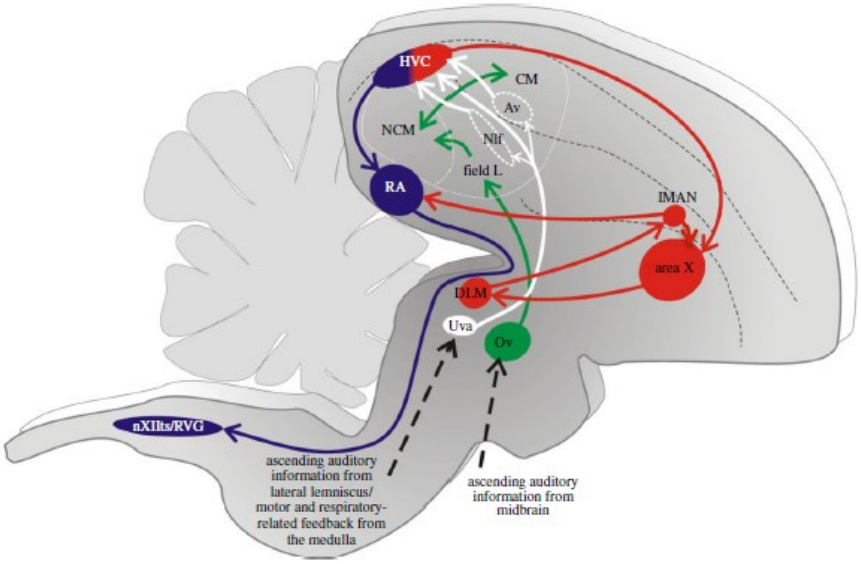

Figure 5. | A schematic representation of the song system emphasizing HVC and its connections. This parasagittal view of the songbird brain shows the song motor pathway (blue) and anterior forebrain pathway (red), the ascending auditory pathways (green) and the auditory inputs to HVC (white). At the microscopic level, HVCX and HVCRA cells are randomly intermingled within HVC. Av, nucleus avalanche; CM, caudal mesopallium; DLM, medial part of the dorsolateral thalamic nucleus; HVC, abbreviation used as proper name; LMAN, lateral magnocellular nucleus of the anterior nidopallium; NCM, caudomedial nidopallium; NIf, nucleus interface; OV, nucleus ovoidalis; RA, robust nucleus of the arcopallium; Uva, nucleus uvaeformis; VRG, ventral respiratory group; nXIIts, tracheosyringeal division of the hypoglossal nucleus. Figure from Mooney (2014).

1.2.3 The putamen nucleus

Among the different nuclei of the BG, the putamen forms, together with the caudate nucleus, the input node of the BG circuit, and its functional properties are still largely unexplored. Using immunoistochemical markers, the striatum has been further subdivided into striosomes – mainly innervated by limbic projections –, and matrix compartments, receiving inputs from motor and sensory cortical areas, together with thalamostriatal projections

(Fujiyama et al., 2011). In addition to the spiny projection neurons previously described, representing about 95% of its neuronal population, the striatum contains various kinds of interneurons with modulative effects, such as tonically active neurons (TANs), and fast-spiking interneurons (FSIs) (Yelnik, 2002; Lanciego et al., 2012).

From a connectional point of view, the putamen receives topographically-organized projections (Nambu et al., 2002) from many sensorimotor areas, such as the primary somatosensory cortex (SI), primary motor cortex (MI), supplementary motor area (SMA), caudal and rostral cingulate motor areas (CMAc/r), and premotor areas (PM). Another possible source of somatosensory inputs is the thalamus, whose contribution to putaminal function has classically been limited to relaying BG output to the cortex: retrograde tracing experiments conducted by McFarland and Haber (2000) showed the presence of projections from the ventral lateral complex (in particular, the VLo, VPLo and VA nuclei) to various sites in the putamen, suggesting that these nuclei might directly modulate striatal activity. Neurons in the centromedian-parafascicular (CM-Pf) nuclear complex have also been proposed to project to the putamen, supplying striatal neurons with information about behaviorally relevant sensory events (Matsumoto et al. 2001).

Putaminal efferents are received by the output nuclei GPi and SNr, whose projections give rise to the major pathways linking the BG with upper motor neurons located in the cortex and in the brainstem. The pathway to the motor cortex is relayed via the VA and VL nuclei of the dorsal thalamus, which in turn project directly to frontal cortical motor areas (Purves and Williams, 2001).

Takada et al. (1998) showed that corticostriatal projections from forelimb representations of MI, SMA and PMv/PMd remained largely segregated and were distributed mainly in the lateral, medial, and dorsomedial sectors of the putamen, in this order (Takada et al., 1998). Anterograde tracing studies, e.g., McFarland et al. (2000), further

investigated the organization of motor afferents in the putamen, pointing out an overlap of MI and SMA terminals in the medio-lateral central zone. A similar convergence exists between projections from the SMA and PM, but not between those from MI and PM. A microstimulation study conducted by Flaherty and Graybiel on squirrel monkeys (1993) suggests that inputs coming from SI also project to the MI territory, and Takada et al. (2001) found the MI-recipient zone to be the target of inputs originating from the CMAc as well.

Somatotopy appears to be preserved throughout the motor loop, so that signals regarding different body parts predominantly target distinct regions of each nucleus. Projections from distinct sensorimotor areas are similarly arranged in the putamen, with a dorsolateral hindlimb region, a ventromedial orofacial sector, and the forelimb zone in between, each extending along virtually the entire rostrocaudal axis (Künzle, 1975). Corticostriatal fibers from proximal and distal regions end in the mediodorsal and ventrolateral part of the putamen, respectively (Tokuno et al., 1999). This organization gives rise to two distinct, although partially overlapping, sets of somatotopic representations: one in the MI-recipient zone and the other in the SMA-recipient zone (Figure 6) – as confirmed by an electrophysiology study conducted by Nambu et al. (2002), who examined orthodromical activation of putamen projection neurons in response to stimulation in the forelimb region of the putative cortical regions.

Similarly, human studies suggest the existence of a topographical organization of corticostriatal connections. Discrete circuits linking the cortex to putaminal posterior (sensorimotor), anterior (associative) and ventral (limbic) compartments have been described (Lehéricy et al., 2004), and a somatotopical organization analogous to that observed in monkeys has been found within the sensorimotor region of the putamen – with the leg lying dorsal, the face in the ventral region, and the arm in between (Delmaire et al., 2005). The presence of a high degree of topographic segregation in the BG, demonstrated

by the presence of a well-defined somatotopic organization in the sensorimotor areas, has gained clinical relevance with the spread of surgical procedures, such as lesioning or deep brain stimulation (DBS), requiring to selectively target restricted subcortical regions in the sensorimotor loop to ameliorate dysfunctions without producing side effects related to interference with non-motor circuits subserving associative or affective processing (Romanelli et al., 2005).

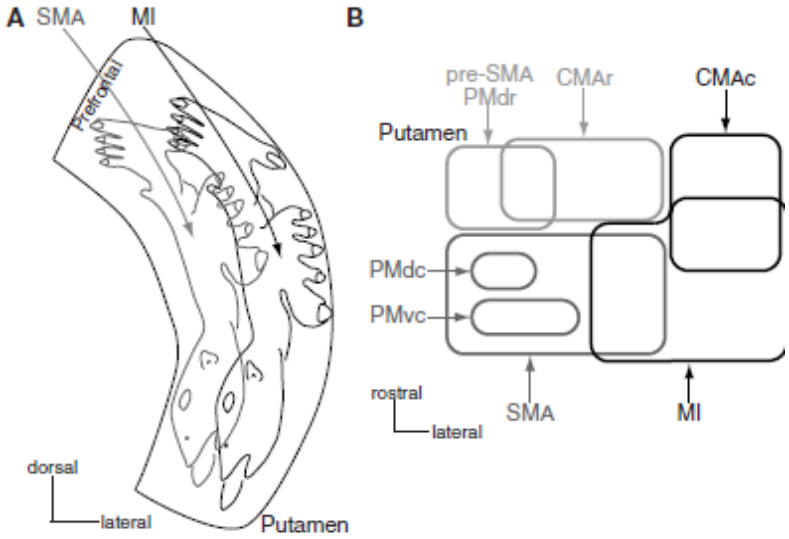

Figure 6. | Somatotopic maps in the putamen. (A) The somatotopy in the SMA region is located dorsomedially to that in the MI region, with projections from the orofacial, forelimb and hindlimb regions elongating along the rostrocaudal axis and converging in the medio-lateral central zone. (B) Schematic representation of cortical motor inputs to the putamen, including those from CMAc and CMAr, PMdc, PMdr, and PMvc. Figure from Nambu (2011).

As to the functional properties of this subcortical structure, Crutcher and DeLong (1984) found the activity of many putamen neurons to be related to active movements of individual body parts, but also to passive somatosensory stimuli (in most cases, in a highly specific way). They also noticed a greater proportion of cells associated to the proximal than to the distal arm, consistently with the notion of a key involvement of the BG in the control of proximal musculature and posture. Recent recordings of single neuron activity in the caudal putamen even found a subset of neurons with saccade-related activity, suggesting a potential role for this structure in oculomotor control (Phillips and Everling, 2012).

Alexander and DeLong (1985) discovered the existence of *striatal microexcitable zones* (SMZs), i.e., discrete regions of the putamen whose microstimulation elicited the same movement of an individual body part. Evoked motor responses appeared to be consistently contralateral to the intrastriatal stimulation site, sometimes bilateral (only for axial and orofacial movements). Furthermore, in the putamen (as in the GP) the onset of neuronal discharge linked to stimulus-triggered movements followed that of cortical motor areas, hinting at the idea that the BG may receive a corollary discharge, or efference copy, from the cortex. Microstimulation appeared to be much more effective in evoking body movements when applied in the lateral, MI-recipient part of the putamen than in the medial, SMA-recipient one (Nambu et al. 2002).

It is known that putamen neuronal activity is modulated by different features of motor behavior. Neurons in the dorsolateral region are linked to movement onset (Kimura, 1990), while those in the dorsomedial zone respond to pre-movement activity during cued tasks (Gardiner and Nelson, 1992). Alexander and Crutcher (1990) reported that neurons showing instruction-dependent preparatory activity (i.e., task-related changes in firing rate during the post-instruction interval), in addition to being more abundant in the SMA region than in the MI region, were located more rostrally and medially than those responding to movement only. Liles (1983) observed that medial and lateral parts of the putamen responded to distinct aspects of motor task: neurons of the former were sensitive to complex movements, whereas those of the latter primarily fired during movements of agonist muscles.

Putamen neurons activated during voluntary movement may exhibit specificity for target-related variables (reflecting the location of targets in space), kinematics-related variables (direction of movement in space, independently of the associated pattern of muscle activity, cfr, Liles, 1985; Alexander, 1987), or for dynamics-related variables (e.g., most movement-related units respond preferentially to slow, “ramp” movements, rather than to

rapid, “ballistic” ones, cfr, Crutcher and DeLong, 1984). These results suggest a role for the BG in the control of movement direction and in the scaling of movement parameters, such as speed or amplitude, similarly to the SMA, which is the main cortical territory of origin of the corticostriatal projections in the motor loop for movement planning and control.

Kimura (1986; 1990) hypothesized that a subpopulation of putamen neurons, that he names “type IIa cells”, could be involved in movement initiation. Specifically, they would exhibit phasic discharges related to the selection of a previously learned arm or orofacial movement triggered by contextual sensory cues, thus contributing to create a context-specific representation of stimulus-response associations. Ueda and Takada (2003) discovered that a consistent proportion of dorsomedial putamen neurons showed selectivity for preprogrammed combinations of movements and for the direction of the first movement: they proposed that the combination of these properties could play a role in the visuospatial and temporal organization of movements.

Graziano and Gross (1993) found that the macaque putamen contains bimodal neurons responding to both visual and somatosensory stimuli (such as light touch, joint movement, or deep muscle pressure), thus providing a somatotopically arranged map of the visual space surrounding the monkey’s body. The properties of such cells are very similar to those described in cortical areas belonging to the *reaching network* (6, 7b, VIP), so the authors suggested that the putamen may be part of an interconnected circuitry representing peripersonal space in somatotopic coordinates, with a probable role in guiding the animal’s movement and its interactions with objects in its immediate proximity.

A tracer study carried out by Gerbella et al. (2015) to analyze corticostriatal projections provided evidence for a convergence of afferents originating from the macaque hand-related ventrolateral prefrontal (vlPFC), ventral premotor (PMv), and inferior parietal (AIP/PFG) areas, in two distinct putaminal zones – one in the caudal and ventral part, and

the other rostral to the anterior commissure (Figure 7). All the cortical regions of origin of these projections belong to the so-called *lateral grasping network*, which is thought to subserve the control of purposeful hand actions, i.e., their selection and organization, based on information about object properties/identity, contextual information, and behavioral goals and rules (Gerbella et al., 2015). In addition, the fact that these same regions constitute crucial nodes of the cortical MN network for hand actions supports the hypothesis of a possible inclusion of the BG in an extended cortico-subcortical MN network (Bonini, 2017), although no study has directly demonstrated the presence of MNs in these subcortical nuclei so far.

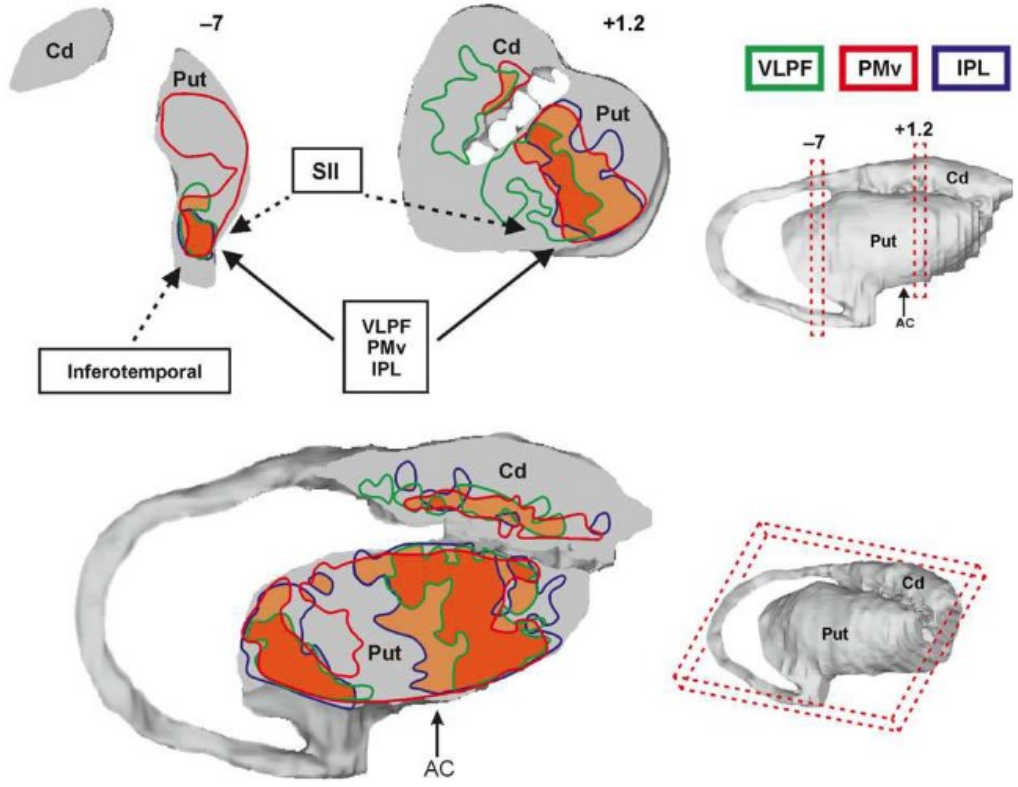

Figure 7. | Composite views of the distribution of the striatal focal projections from VLPF (green lines), PMv (red lines), and IPL (blue lines) hand-related areas obtained by warping the focal projections observed in each individual case to template 1-mm-thick coronal and 2-mm-thick oblique sections. The sections were taken at the levels indicated in the 3D reconstructions of the striatum shown in the right part of the figure. Overlap of the focal projections from 3 and 2 regions is shown in darker and lighter orange, respectively. In the upper part, arrows indicate the sources of projections to the 2 input channels. Dashed arrows indicate possible additional source of projections. Figure from Gerbella et al. (2016).

Much alike what has been proposed for the other BG nuclei, it seems that also the putamen functional role may extend beyond the motor sphere. Specifically, the caudal part is thought to contribute primarily to sensorimotor function, whereas the rostral one probably mediates a variety of non-motor aspects of cognition (Helie and Shawn, 2011). Furthermore, the putamen might be involved not only in the representation of context-specific behaviors, but also in their acquisition, i.e., in the learning of stimulus-response (Horvitz, 2009) and stimulus-category (Cincotta and Seger, 2007) associations, and in the flexible development of new habitual behavior (Yin and Knowlton, 2006). Muranishi et al. (2011) injected muscimol in the monkey putamen, finding that its selective inactivation interfered with the animal's process of action selection based on reward history. Haruno and Kawato (2006) proposed that the putamen substantially contributes to the ability of evaluating actions in terms of sensory contexts and rewards.

The notion of a crucial putaminal contribution to reward-related functions has been corroborated by both monkey and human studies. Cromwell and Schultz (2003) recorded from macaque striatal neurons during a spatial delayed response task and found some cells displaying task-related activity during movement preparation and execution, immediately before and after juice delivery, half of which showed differing response levels dependent on the magnitude of reward to be received. A fMRI study conducted by McClure et al. (2003) reported a correlation between putamen activity and errors in the prediction of reward timing: activation increased after unexpected delivery of juice reward and decreased in response to its unexpected withholding.

This nucleus seems to play a significant role in mnemonic functions as well. Studies conducted on human subjects suggest a contribution for the rostral putamen to working memory maintenance (Voytek and Knight, 2010), with load-dependent activation (Chang et al., 2007), and to the ability to ignore irrelevant information (McNab and Klingberg, 2008).

The left putamen has also been consistently implicated in the encoding of verbal episodic memories (Ystad et al., 2010). Neuroimaging studies based on set-shifting paradigms (Rubia et al., 2006) show an increase of putamen activity in trials requiring a set shift, which may reflect an involvement in the ability to flexibly update strategic responses. Monchi et al. (2006) also reported that the caudoventral part of the putamen is engaged in the execution of non-routine actions based on self-determined novel strategies (as opposed to externally triggered movements), unlike the rostrodorsal one, which is active during preparatory activity and finger movement sequencing.

1.3 Goal of the study

Data from the literature have provided compelling evidence in support of a major involvement of cortical motor areas in a broad range of advanced perceptual, cognitive, and even social functions, suggesting that the motor function should be considered as a large-scale domain, shaped around the concept of potential interactions – with the surrounding environment, objects, and other agents – and provided with blurred boundaries, extending well beyond the mere movement execution. It is also known that the cortical motor system, including high-order premotor regions, has a tight anatomo-functional connectivity with the subcortical complex of the BG, which appears to play a key modulatory role on the activity of such regions. Although the cortico-BG network is clearly required for motor control, as made evident by its clinical dysfunctions, possible contributions of the BG to the control of manual actions and motor-based socio-cognitive and perceptual functions in primates have been poorly investigated.

The present study aims at exploring the functional properties of the putamen by means of single cell recording during a *mutual action task* specifically designed to study neuronal responses during (1) the visual presentation of objects, (2) first-person execution

of grasping actions, and (3) the observation of the same actions performed by another individual.

This approach could shed light on the neuronal mechanisms underlying the involvement of the putamen in the representation of objects' affordances, peripersonal space, and the monitoring of others' behavior – probing the hypothesis that action selection and inhibition is supported by the BG system in individual as well as social contexts.

2. MATERIALS AND METHODS

2.1 Experimental subjects

This study involved two purpose-bred, socially housed, adult male monkeys (*Macaca mulatta*, 9 and 12 kg). Training procedures were carried out by means of operant conditioning with positive reinforcement and step-by-step response shaping methods. Liquid reward (fruit juice or water) was used to reinforce specific behavioural responses matching or resembling the target one, while unwanted behaviours were gradually extinguished by the lack of positive outcomes. At the end of each session, fresh fruit pieces were administered to strengthen collaboration and make of the session an as much as possible positive experience for the animal. Training sessions were conducted on a daily basis, in order to ensure continuity and help the animals to get accustomed to a predictable routine.

The monkeys were initially habituated to enter and sit in a primate chair, that was then transported from the animal enclosure to the laboratory, and to interact and cooperate with the experimenters. Afterwards, they were specifically trained on the main experimental task whose description will be provided in the following section. The task was subdivided into easier steps, each chained to the previous one only after complete acquisition of both of them, until the animal was able to master the whole task.

In preparation for neural acquisitions, the monkeys underwent a surgical procedure for the implantation of a recording chamber, through which recording probes could be inserted during subsequent surgeries. Every surgery was performed in stereotaxic and aseptic conditions, under general anaesthesia induced by intramuscular injection of ketamine (5 mg/kg) and medetomidine hydrochloride (0.05 mg/kg) and maintained with 2% isofluorane vaporized in 100% oxygen. The monkey's vital parameters were constantly controlled with a multiparametric monitor. Hydration of the animal was guaranteed with continuous intravenous infusion of saline solution, and vitamin A gel was used to ensure eye hydration

during anaesthesia. The monkey received analgesics, broad-spectrum antibiotics, and anti-inflammatory medicines both during and after surgical procedures.

All experimental procedures were conducted in agreement with the European (Directive 2010/63/EU) and Italian (D.lgs 26/2014) legislation for the protection of animals used for scientific purposes, received the approval of the Veterinarian Animal Care and Use Committee of the University of Parma (Prot. 52/OPBA/2018), and were authorized by the Italian Ministry of Health (Aut. Min. 802/2018-PR).

2.2 Behavioural paradigm and recordings

The monkeys were progressively trained to perform the *Mutual Action Task* (MAT), whose behavioural paradigm was designed to enable investigation of neuronal properties during action execution and observation, as well as during visual encoding of objects presented in the animal's peripersonal space.

At the beginning of the task, the monkey sat in its primate chair at one end of a table, just in front of the experimenter, who was seated on the opposite side and acted as a partner. They faced a shared operational space containing a multi-affordance device that could be reached and manipulated by both subjects (Figure 8).

Figure 8. | Schematic drawing of setup configuration for the behavioural task (Social Condition).

The object, which was located at a distance of 16 cm from each agent's hand starting point, was 3D-printed in a polylactic acid (PLA) material and was formed by a cylindric body (diameter 5.5 cm, height 6 cm) on top of which a parallelepiped (4.5x1.5x1.5 cm) was inserted. It lent itself to two different types of prehension, since it could be grasped and lifted with either a *precision grip* (PG), by using the thumb and index finger opposed to the central parallelepiped, or a *whole hand prehension* (WH), when the whole hand was wrapped around the main cylinder's body. The kind of grip required in each trial was specified by a visual cue that appeared on a rectangular oled screen (2x1 cm) inserted on the top side of the parallelepiped: an empty square cued the WH, whereas a full white square cued the PG. Both solids composing the object were surrounded by metallic plates, so that each grip resulted in closing of a capacitive circuit that triggered a TTL signal to be recorded and stored together with the other behavioural and task events (Figure 9).

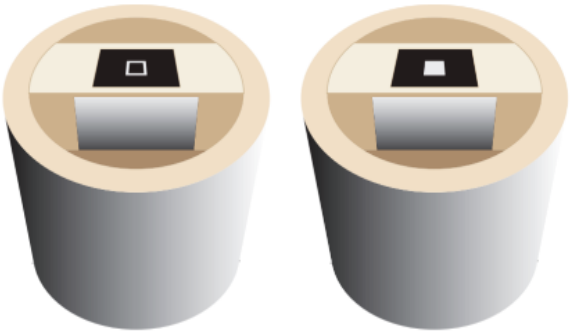

Figure 9. | Object description. On the left, oled showing an empty square (*precision grip* cue). On the right, oled with a full square (*whole hand prehension* cue).

Each agent was trained to selectively respond to a specific auditory cue. A pure high tone (a sine wave of 1200 Hz) instructed the monkey to perform a grasping action (*Go signal*), while the experimenter had to remain still; on the contrary, a pure low tone (a sine wave of 300 Hz) acted as a Go signal for the experimenter, while the monkey had to remain still (*No-Go signal*).

Each trial (Figure 10) started in complete darkness, with both subjects seated still in the starting position, pressing a manipulandum with the right (dominant) hand. After 1 second, either the high or the low sound was presented (*Sound onset*), instructing each subject in an opposite way (Go vs. No-Go): specifically, the high tone instructed the monkey to Go and the experimenter to remain still, and viceversa for the low tone (*Agent Condition*). After 770 ms from sound onset, the oled screen was turned on (*Oled onset*), showing either the empty or the full square – i.e., the visual cue related to the PG or the WH, respectively. Next, 730 ms after Oled onset, an environmental light was turned on making the whole object visible (*Light on*). After further 570 ms, the sound ceased (*Go/No-go signal*) and the subject that received the Go signal had to release the manipulandum to reach the object, grasp it with the specified prehension type within 1 s (*Grip Condition*), and hold it up for at least 500 ms (*Up-keep*) to get the reward.

Whenever the monkey managed to successfully perform every step of the sequence – including remaining still during Go trials of the partner –, liquid reward was automatically administered in a fixed amount, otherwise the trial was aborted. Each experimental trial was considered correct only if both agents succeeded. Possible errors leading to exclusion of the trial from analyses included starting before sound end, failing in discriminating the auditory cue – i.e., leaving the manipulandum during the other's trials, or staying still during one's own –, performing the wrong type of grip, and not holding the object up enough.

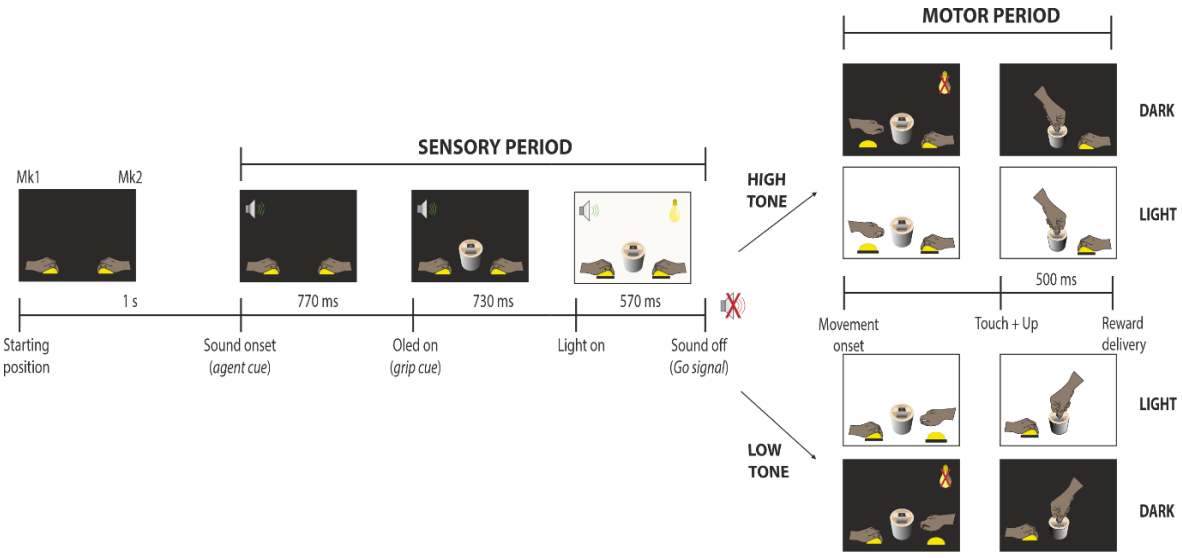

Figure 10. | Temporal sequence of events (Social Condition).

In half of the trials the light remained on until the completion of the task (*Light Condition*), whereas in the remaining half it was turned off as soon as the manipulandum was released, requiring the subject to execute the action in the dark (*Dark Condition*): these conditions (*Visual feedback*) ensure that potential motor responses recorded from putamen neurons could be considered as actually motor, and do not depend on visual feedback from the moving hand. We collected 12 trials for each of the 8 conditions (2 grip types x 2 agents x 2 visual feedback), for a total of 96correct trials per session.

The task was also carried out with an additional condition (*Barrier Condition*) in which the temporal sequence of events remained the same, but all trials were performed with the light on, and a transparent sliding barrier was interposed between one of the subjects and the target object, thus preventing potential interactions and only allowing to observe the partner's action without having to move before the reward was delivered.

Detection of behavioural events was allowed by distinct contact sensitive devices signalling hand-target interaction – object touch (specific for prehension type), object lifting, and positioning of the barriers – with the generation of TTL signals that were fed to a PC equipped with a dedicated LabView-based software. The software was used to monitor the

subjects' performance but also to control digital output signals associated with the control of auditory and visual cues, lighting settings, and reward administration – or withdrawal, in case of errors committed by one or both subjects during the trial. All input and output signals were recorded and stored in parallel with the neural data and synchronized to them, and were subsequently used to align the neural signal for statistical analysis.

2.3 Neural acquisitions

To be able to acquire neural responses, one of the monkeys (Mk1) was implanted with a biocompatible plastic recording chamber (45x50x25 mm; Figure 11) housing on its top a removable lid to protect a batch of parallel grooves (width 2 mm, inter-groove distance 1 mm) that served as slots for up to 8 connectors blocks (Omnetics Connector Corporation). The connectors interfaced the multielectrode contacts with the headstages, in turn linked with the neural acquisition system.

The chamber was cut and shaped on a 3D reconstruction of the animal's cranial theca realized with the 3D Slicer software, starting from 7T magnetic resonance images previously acquired. After complete recovery from the positioning of the chamber, secured to the skull with titanium bone screws and dental cement, briefer surgeries were performed to implant individual, linear multielectrode probes through a small craniotomy performed within the chamber, leaving intact most of the remaining bone. Collagen-based dural regeneration matrix (DuraGen) was placed around the insertion sites to decrease cerebrospinal fluid (CSF) leakage, and liquid dental cement was poured in the recording chamber; it rapidly solidified securing the probes and preventing contamination.

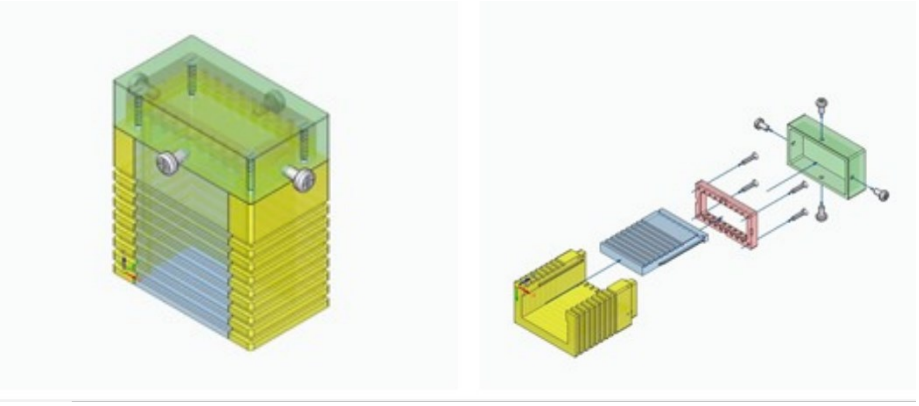

Figure 11. | Design of the recording chamber. On the left, chamber assembly. On the right, chamber exploded view. Yellow: main body. Blue: sliding panel. Pink: constituent with grooves. Green: removable lid.

Neural recordings were performed by means of individual, chronically implanted linear silicon probes (ATLAS Neuroengineering; Figure 12) endowed with 32 Iridium Oxide (IrOx) recording sites arranged along the shaft (Barz et al., 2017) with an intersite distance of 250 μm. Each probe had a total length of 24 mm, it was 30 μm large and 100 μm thick, and electrodes had an average impedance ranging from 0,23 to 0,29 MΩ. All probes were equipped with the pointy tip feature, which significantly reduces any tissue dimpling during probe insertion, thereby facilitating the penetration. The shaft was attached to a highly flexible polyimide-based ribbon cable with a zero-insertion-force (ZIF) connector that could be electrically connected to the recording data logging devices.

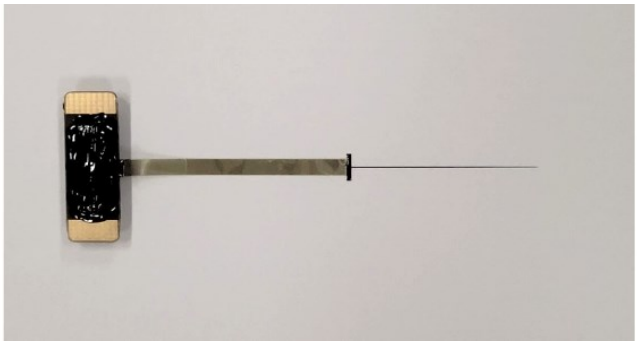

Figure 12. | Linear silicon probe. From the left: connector, ribbon cable, recording shaft.

Five different linear probes were implanted, using a dedicated insertion device, in two different surgeries, performed two months away from each other. The two probes that were implanted first were removed during the second operation.

The sites of insertion were established in terms of stereotaxic coordinates of the region of interest obtained on the basis of the MRI images. Penetration angle was set to 90° (vertical), considering the deviation in the probe trajectory while passing through the tissue because of the pointy tip angle and calculated following in vitro experiments with agarose, a viable simulation of the brain tissue mechanic features because of its poroelasticity properties (Pomfret et al., 2013). These tests allowed the detection of a probe deflection of 0.05-0.12 mm per millimeter (which translates into 1.2-2.9 mm of systematic deviation along 24 mm probe length), always in the opposite direction with respect to the tip's beveling, that was accordingly considered during the surgeries.

Exact location of probes' tips was subsequently assessed through post-mortem examination of the monkey's brain (Fig. 13). At the end of the study, the animal was deeply anesthetized with an overdose of sodium thiopental and perfused through the left cardiac ventricle consecutively with saline (about 2 L in 10 min), 3.5% formaldehyde (5 L in 30 min), and 5% glycerol (3 L in 20 min), all prepared in 0.1 M phosphate buffer, pH 7.4. The brain was then blocked coronally on a stereotaxic apparatus, removed from the skull, and placed in 10% buffered glycerol for 3 days and 20% buffered glycerol for 4 days. Finally, it was cut frozen into coronal sections of 60 μm thickness, two series of which were stained with the Nissl method (0.1% thionin in 0.1 M acetate buffer, pH 3.7).

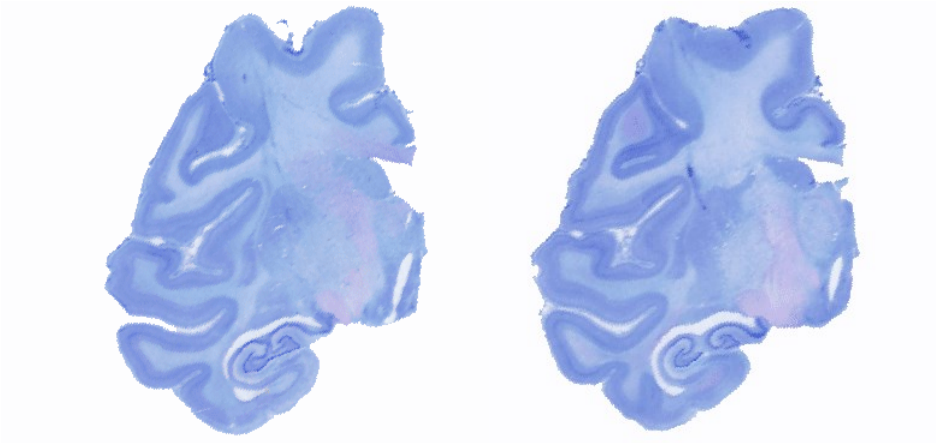

Figure 13. | Nissl-stained coronal sections of the monkey's brain showing probes' tracks in the left putamen nucleus.

Neural signals were recorded using a small, lightweight neural logger (Deuteron Technologies Ltd) that allows the acquisition of neural data from freely-moving animals. In this experiment, although the monkey's movement was limited by the primate chair, the head was unrestrained and all upper body movements were allowed. Specifically, for the first implant (64 channels) a RatLog64 was used (Figure 14), whereas a RatLog128 was employed for the second implant (96 channel). The device is powered by a small external battery (two hours maximum duration) to which it is connected via a short cable, and it is equipped with a magnetic on/off switch to ensure the possibility of prompt response in the event of system crash or malfunctioning during a recording session.

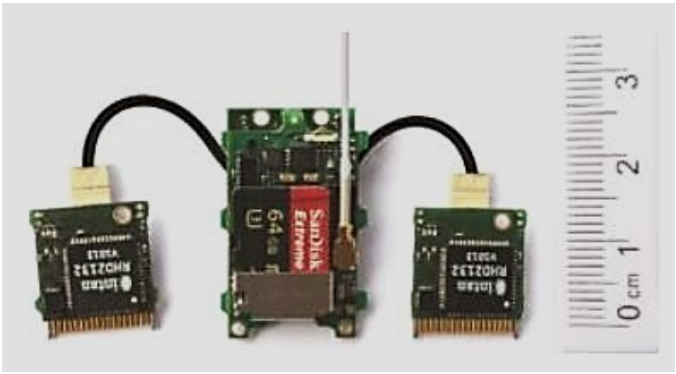

Figure 14. | Deuteron neural logger (RatLog64).

Once the logger device was linked to the electrode arrays, all the components were sealed with a cover on top of the recording chamber. A digital bandpass filter with upper and lower cut-off frequencies set at 2 and 7000 Hz, respectively, and a conversion rate of 32000 Hz on each channel was applied, permitting to sample both local field potentials (LFPs) and single/multi-unit activity. Signals were amplified, digitized, and locally stored in a MicroSD memory card (64 GB) to prevent possible transmission errors. The logger communicated with a computer through a transceiver with 4 BNC connectors for digital inputs and one for digital outputs, which was connected to the host computer via USB.

2.4 Spike sorting and data analysis

All formal signal analyses were performed offline with a fully automated sorting software, Mountainsort (Chung et al., 2017), setting -3.0 standard deviations of the signal-to-noise ratio of each channel as a threshold for detecting units. The main criterion used to distinguish between single- (SUA) from multi-unit activity (MUA) was the noise overlap, which represents the fraction of points overlapping with the noise cluster, i.e., estimates the fraction of ‘‘noise events’’ (above-threshold events not associated with well-isolated clusters) in a waveform cluster. In most of the recording sessions, the noise overlap distribution is bimodal, with putative single units associated with values below 0.1 and putative multi-units with values above 0.3. Thus, we considered as well-isolated single units only those with noise overlap values lower than 0.1 (i.e., a very low false-positive rate). We excluded from analyses all possible artifacts (i.e., units with very noisy waveforms), but not units having a very low firing rate/number of spikes, since our goal was to provide an as much as possible unbiased and inclusive overview of the neuronal behavior of an area whose functional properties are mostly unknown yet, rather than investigating the responses of a specific functional category of neurons.

To avoid oversampling, units that were consistently found in the same channel among different recording sessions were only considered once for further analyses, except when they displayed a significantly different activity pattern – in terms of spike shape, ISI, and response properties.

We first computed the baseline firing rate for each individual neuron, corresponding to an interval of 500 ms preceding cue-sound presentation (Sound On). We then computed the net normalized activity of each unit: its baseline activity in a given condition was subtracted from the firing rate of each bin, and the resulting net activity vector was soft-normalized dividing each data point by the absolute maximum across all conditions + 5 spk/s; this latter constant factor was used to reduce the more the overall net normalized activity of a neuron the lower its raw firing rate.

Since the task was conceived in order to enable separate assessment of sensory and motor responses – both related to the planning and execution of the monkey's own action and to the observation of the experimenter's – for all analyses neuronal activity was aligned to a specific task-related or behavioral event and only evaluated within a precise time interval around it. The selected period for the sensory epoch included the 2.1 s preceding the Go signal (sound off), whereas the one used to assess motor responses started with movement onset (release of the manipulandum) and ended after 1.5 s.

Net normalized activity thus obtained ranged theoretically between -1 and 1 and was used to produce heatmaps showing individual neurons' firing rate in a comparable form during task-unfolding periods. Neurons were classified as either facilitated or suppressed depending on the sign of the average modulation shown during the selected time interval. To test whether the neurons' facilitated or suppressed response was statistically significant, we compared the baseline activity with each bin of the entire epoch of interest applying a one-tailed sliding t test (window = 200 ms, step = 20 ms, $p < 0.05$, uncorrected) to the

selected interval around the events (see above). We considered as significantly modulated all the neurons with at least five consecutive significant bins, whereas neurons that did not meet this criterion were classified as non-significantly modulated. The statistical criterion here adopted is much more permissive than conventional epoch-based approaches, which – especially given the considerable number of epochs of our task – would have strongly biased the results and would have been too restrictive for the purpose of our investigation.

We also investigated the possible presence of neurons specifically modulated by the subject performing the action, i.e., units that responded differently to first-person execution vs. observation trials. To test this hypothesis, we applied the same procedure used to determine whether the recorded units were significantly modulated during movement period, but we merged the trials with the two grip conditions, distinguishing only between agent conditions (24 trials per condition).

All analyses concerning the monkey's execution trials were performed considering the Dark Condition only, while those of the Light Condition were used as a control. Conversely, neuronal responses during the monkey's observation trials were analyzed only in trials belonging to the Light Condition – in which the monkey was able to visually witness the experimenter's action – and those of the Dark Condition were used as control.

3. RESULTS

3.1 Neuronal properties

The final dataset included 235 single units recorded from the putamen nucleus during the Mutual Action Task, collected over 20 recording sessions and fulfilling all established criteria for single and independent neuron identification.

We found that 214 neurons (91%) showed task-related activity (see Methods) during the sensory period (2.1 s from Go/No-Go cue to Go/No-Go signal) and 203 neurons (86.4%) resulted to be modulated during the motor period (1 s following movement onset). Units were classified as modulated if their activity was either significantly facilitated or suppressed (regardless of the sign of such modulation) in any of the four considered conditions (2 grips x 2 agents) during the selected time intervals.

As summarized in Figure 15, most units (n = 196; 83%) were responsive during both intervals, whereas a smaller fraction of cells only displayed sensory-related activity (n = 18; 8%), motor-related activity (n = 7; 3%), or no significant modulation at all (n = 14; 6%).

Examples of task-related single-units discharging during the two considered time frames are shown in Figure 16.

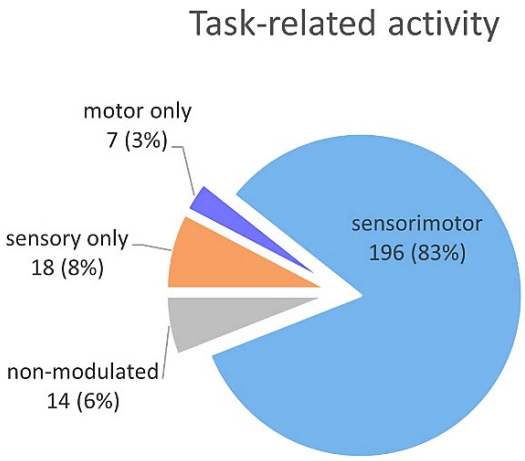

Figure 15. | Percentage of task-related units responding during the sensory period (orange section), the motor period (dark blue section), or both (light blue section).

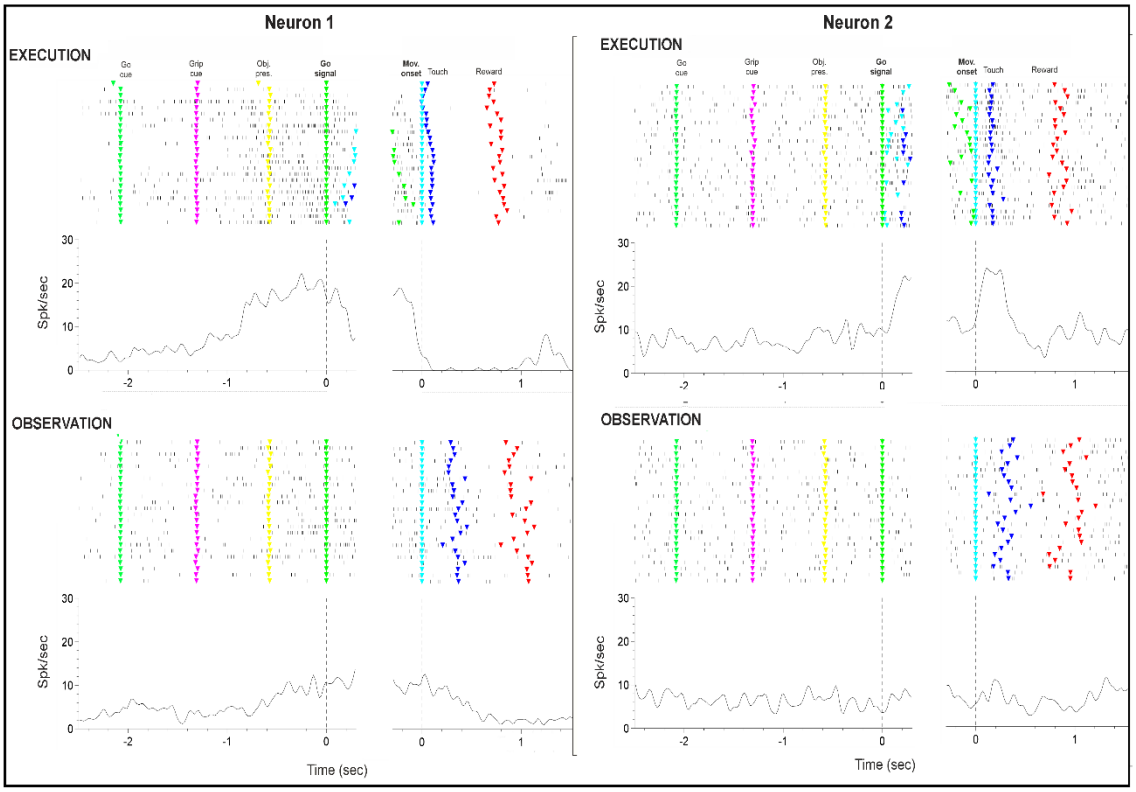

Figure 16. | Example of modulated neurons recorded in the monkey's putamen during the Mutual Action Task. In the first portion of each panel (before the gap), neuronal activity (rasters and histograms) is aligned (vertical dashed lines) to the Go signal (from -2.5 s to +0.3 s), whereas in the second one (after the gap) it is aligned to movement onset (from -0.3 s to +1.5 s). The upper part of each panel refers to activity during the monkey's Go trials, while in the lower part are represented the experimenter's Go trials (No-Go trials for the monkey). Triangular markers correspond to sound onset and sound end (green markers), oled onset (violet markers), light onset (yellow onset), movement onset (light blue markers), touch (blue markers), and reward delivery (red markers). On the left (Neuron 1) is shown the discharge pattern of a unit significantly facilitated during the sensory interval. On the right (Neuron 2), the activity of a neuron specifically responding to the monkey's grasping action.

3.1.1 Responses during the sensory epoch

In Figures 17-18, histograms on the right of each panel report the percentage of neurons that were significantly facilitated (red bars), suppressed (blue bars), or non-modulated (grey bars), during at least five consecutive 200 ms bins (slit forward in steps of 20 ms) of the sensory period (2.1 s from Go cue to Go signal), separately for the four conditions. The mean firing rate and standard error of each class of neurons (facilitated and suppressed) during the

whole task unfolding period is shown by red and blue lines, respectively, while the black one represents the average activity of all recorded cells, superimposed to the heatmap of individual units' normalized activity. The time interval on which analyses were performed for the sensory epoch was identical in Light and Dark trials (that started to differ at movement onset only), so we assumed not to find any significant differences in neural activity as well. We therefore considered only the Dark condition, in order to have the same number of trials (n = 12) used for the motor epoch.

In execution trials (Fig. 17) where the monkey was required to perform a precision grip, 46 neurons (19.5%) were classified as facilitated, 89 (37.9%) as suppressed, and 100 (42.6%) as non-modulated. When it had to grasp the object with a whole hand prehension, the fractions were not too different: facilitated units were 43 (18.3%), the suppressed ones 89 (37.9%), and the non-responsive ones 103 (43.8%).

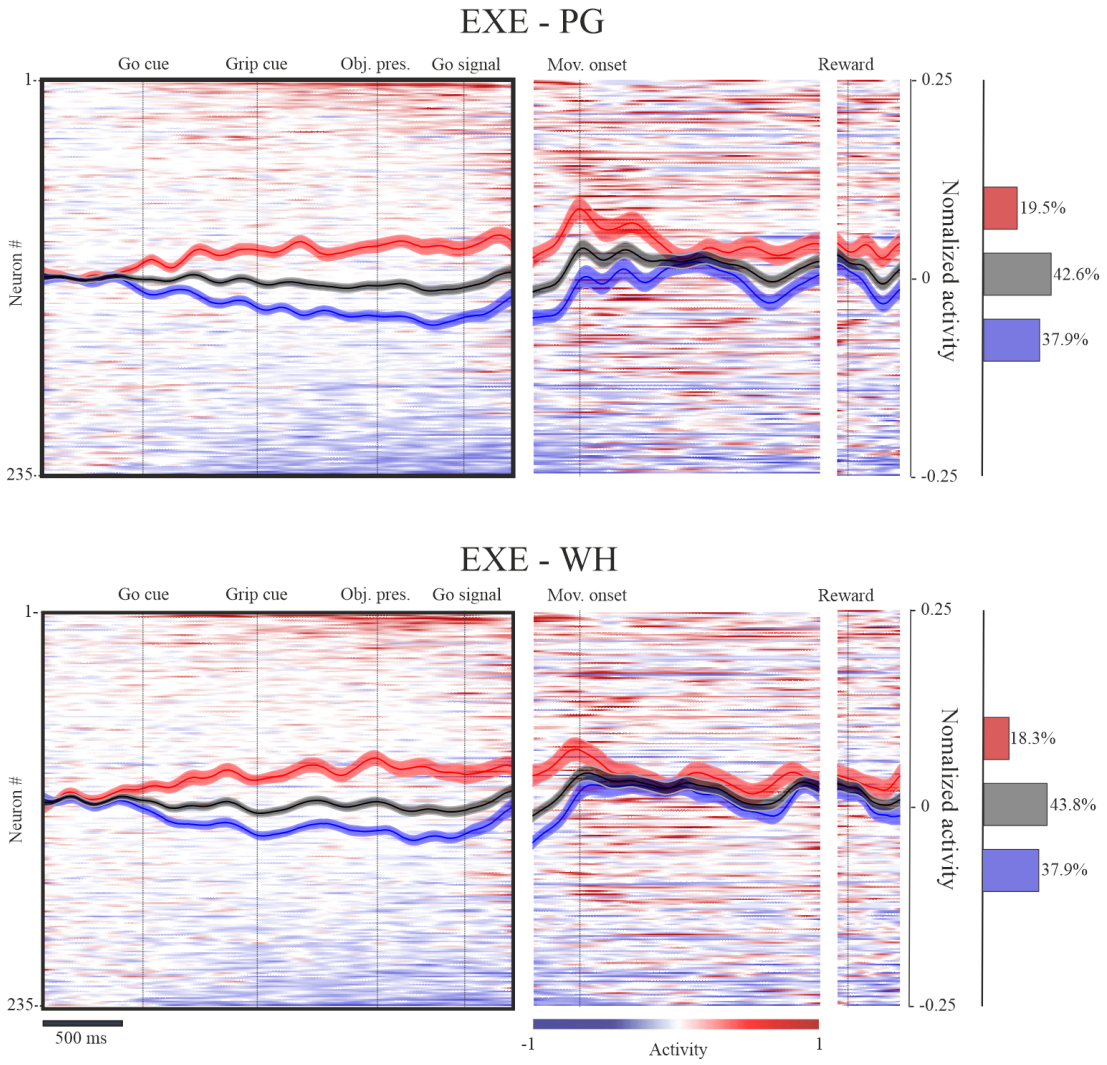

Figure 17. | Functional fingerprint of putaminal neurons during the sensory interval (Dark Condition). The two panels show the heatmaps of all recorded neurons during the MAT in the PG-Execution (above) and WH-Execution (below) conditions. Each line represents one cell (its average neuronal activity over the task unfolding period in the 12 trials of the selected condition) and cells are ordered (from top to bottom) based on the magnitude of their activity with respect to baseline (red, facilitated; blue, suppressed) in the interval of 2.1 s before the Go signal, independently for the two conditions. Each cell's baseline activity was calculated in a period of 500 ms preceding the Go cue. Black lines represent the averaged response of each population as a whole. The histograms on the right indicate the percentage of facilitated (red), suppressed (blue), and nonsignificant (grey) neurons. Dashed vertical lines represent significant sensory events with fixed timing – sound onset (Go cue), oled onset (grip cue), and light onset (object presentation) – and the main reference events to which neuronal activity was aligned – sound off (Go signal) and release of the manipulandum (movement onset).

In the monkey's observation trials, (Fig. 18), when the instructed action was a precision grip, 42 neurons (17.9%) were facilitated, 73 (31%) were suppressed and 120 (51.1%) were not significantly modulated. When the experimenter was required to perform a whole hand prehension instead, 47 neurons (20%) were classified as facilitated, 74 (31.5%) as suppressed, and 114 (48.5%) as non-responsive. Compared to the monkey's Go condition, more units overall were classified as non-modulated and the proportion of the inhibited ones slightly decreased.

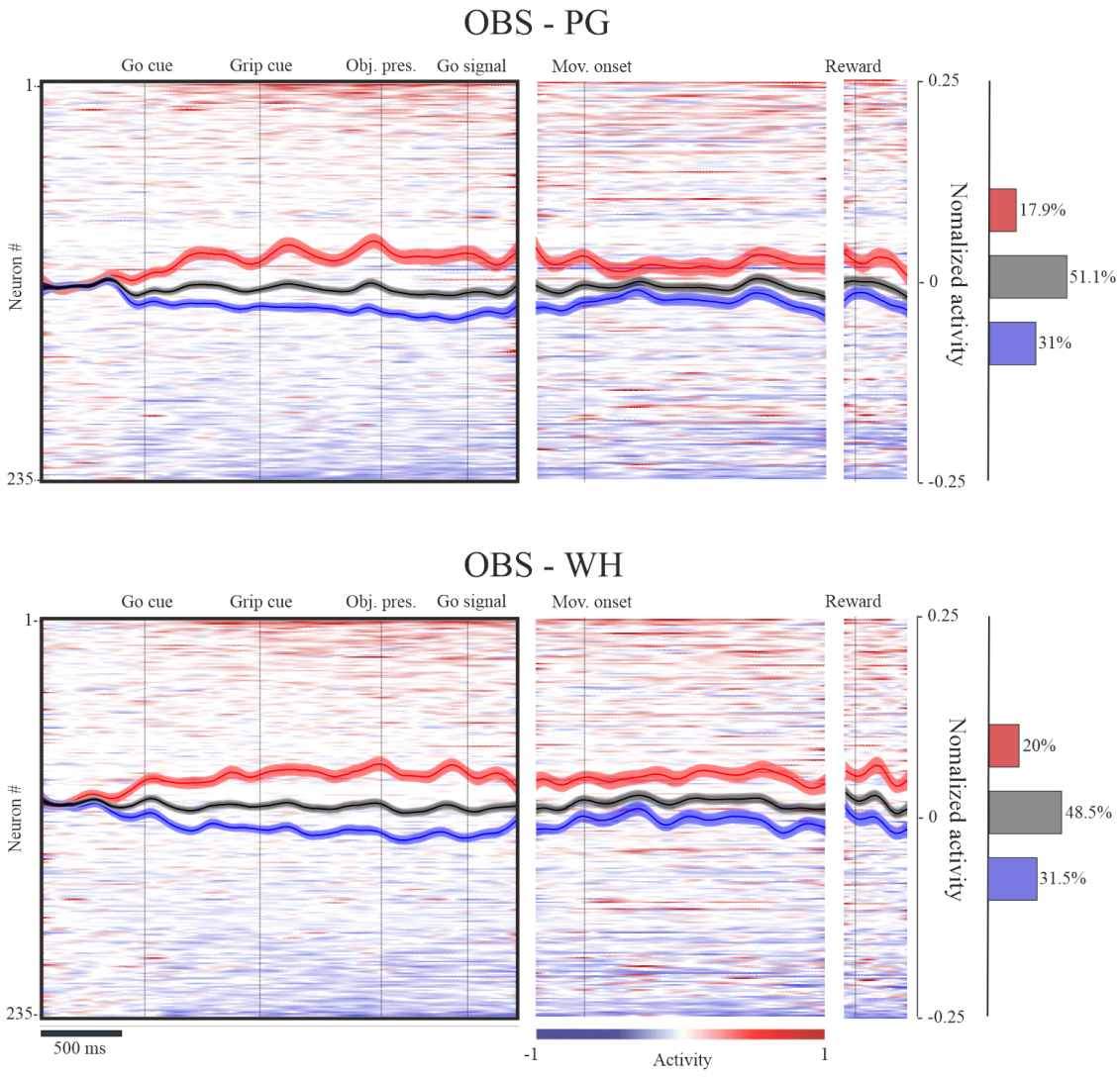

Figure 18. | Functional fingerprint of putaminal neurons during the sensory interval (Dark Condition). The two panels show the heatmaps of all recorded neurons during the MAT in the PG-Observation (above) and WH-Observation (below) conditions. All other conventions as in Fig. 17.

3.1.2 Activity patterns during movement period

Modulation of neural activity during the 1 s epoch included in the motor interval (starting with movement onset) was analyzed as well and it is summarized in Figures 19-20.

During the monkey's execution (Fig. 19) of precision grip, we found that 96 neurons (40.8%) were significantly facilitated, 62 (26.4%) were suppressed, and 77 (32.8%) were non-modulated. During whole hand prehension trials, 84 neurons (35.7%) were classified as facilitated, 67 (28.5%) as suppressed, and 84 (35.7%) as non-responsive.

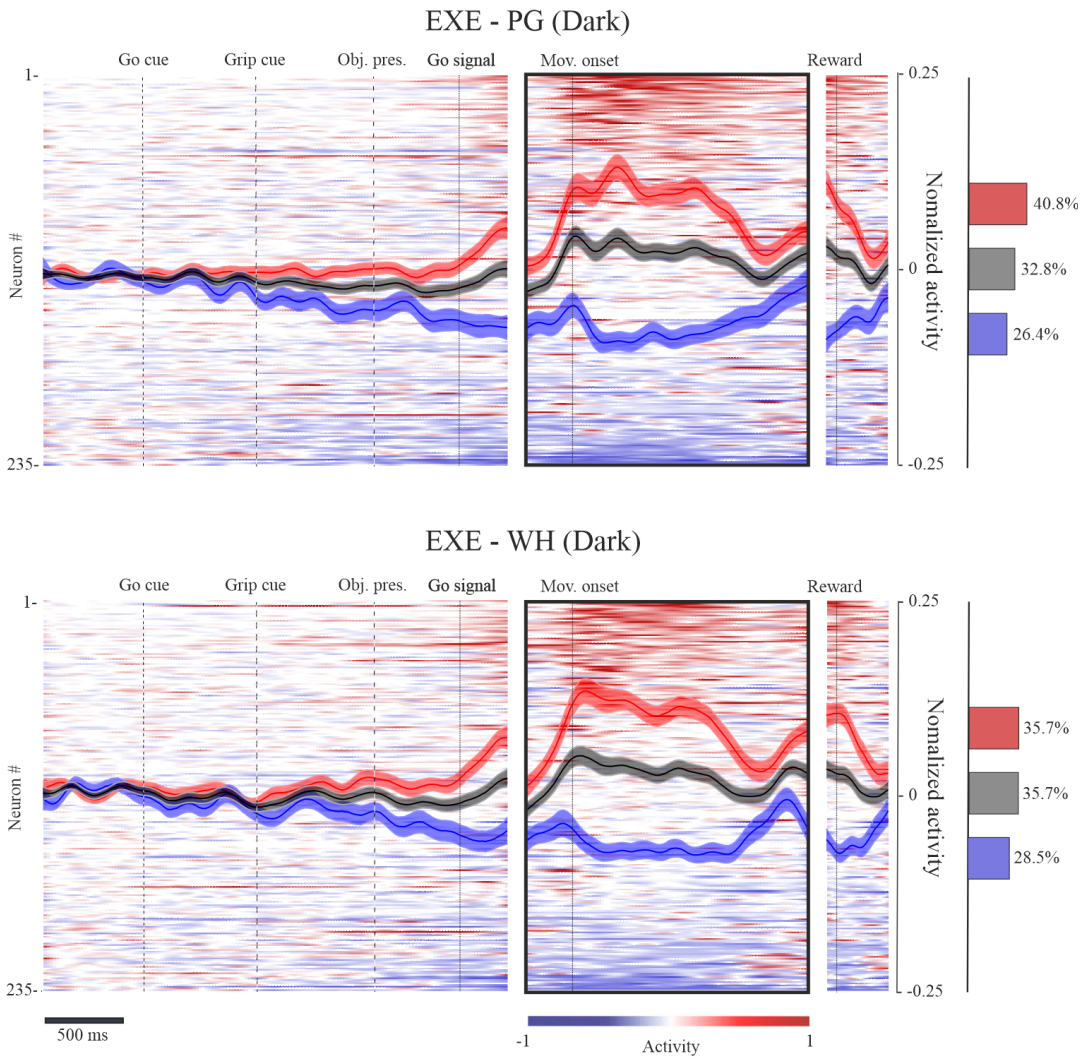

Figure 19. | Functional fingerprint of putaminal neurons during action execution (Dark Condition). The two panels show the heatmaps of all recorded neurons during the movement period of the Mutual Action Task in the PG-Execution (above) and WH-Execution (below) conditions. Neuronal activity was calculated in the interval of 1.5 s after movement onset. All other conventions as in Fig. 17.

During observation (Fig. 20) of the experimenter's precision grips, 50 neurons (21.3%) were facilitated, 60 (25.5%) suppressed and 125 (53.2%) not significantly modulated. When the monkey observed a whole hand prehension, we found 54 (23%) facilitated neurons, 58 (24.7%) suppressed ones, and 123 (52.3%) non modulated ones.

Compared to the sensory responses previously described, a considerably higher percentage of units (about twice as many) showed excitatory behavior during the monkey's movement (but not during the experimenter's action, when the proportion of facilitated units was overall lower).

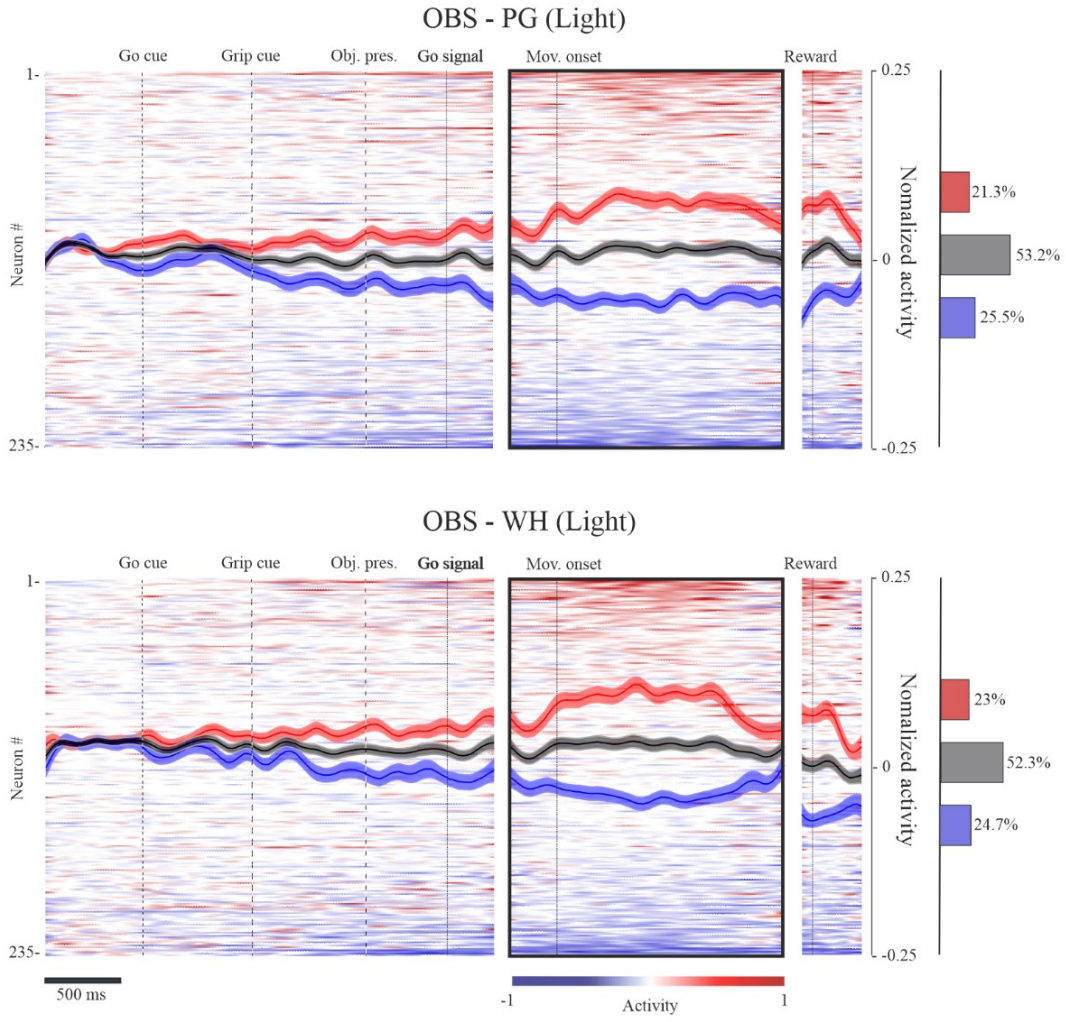

Figure 20. | Functional fingerprint of putaminal neurons during action observation (Light Condition). The two panels show the heatmaps of all recorded neurons during the movement period of the Mutual Action Task in the PG-Observation (above) and WH-Observation (below) conditions. All other conventions as in Fig. 19.

3.1.3 Modulation for self and others' action

After assessing neuronal responses separately for the four conditions described above, we further analyzed changes in neural activity within the motor interval by excluding the grip type variable and only focusing on which subject was required to grasp the object. We therefore calculated whether each unit was significantly modulated during movement period in trials requiring action execution vs observation regardless of the type of grip.

After merging trials involving the two different types of grip, we found that in execution trials 94 neurons (40%) were facilitated, 68 (29%) were suppressed, and 73 (31%) did not significantly differ from the unit's baseline. During observation, 68 neurons (28.9%) showed an increase in their firing rate, 69 (29.4%) discharged less, and 98 (41.7%) did not change their activity.

Neurons whose activity changed during execution trials only were classified as *self type* (n = 46; 19.6%), those that were exclusively modulated during observation trials were defined as *other type* (n = 21; 9%), whereas those that responded in both conditions were referred to as *self-other type* and turned out to be the majority (n = 116; 49.4%). A smaller fraction of units (n = 52; 22%) did not show any action-related modulation. Some examples of agent-specific modulation can be observed in Figure 21.

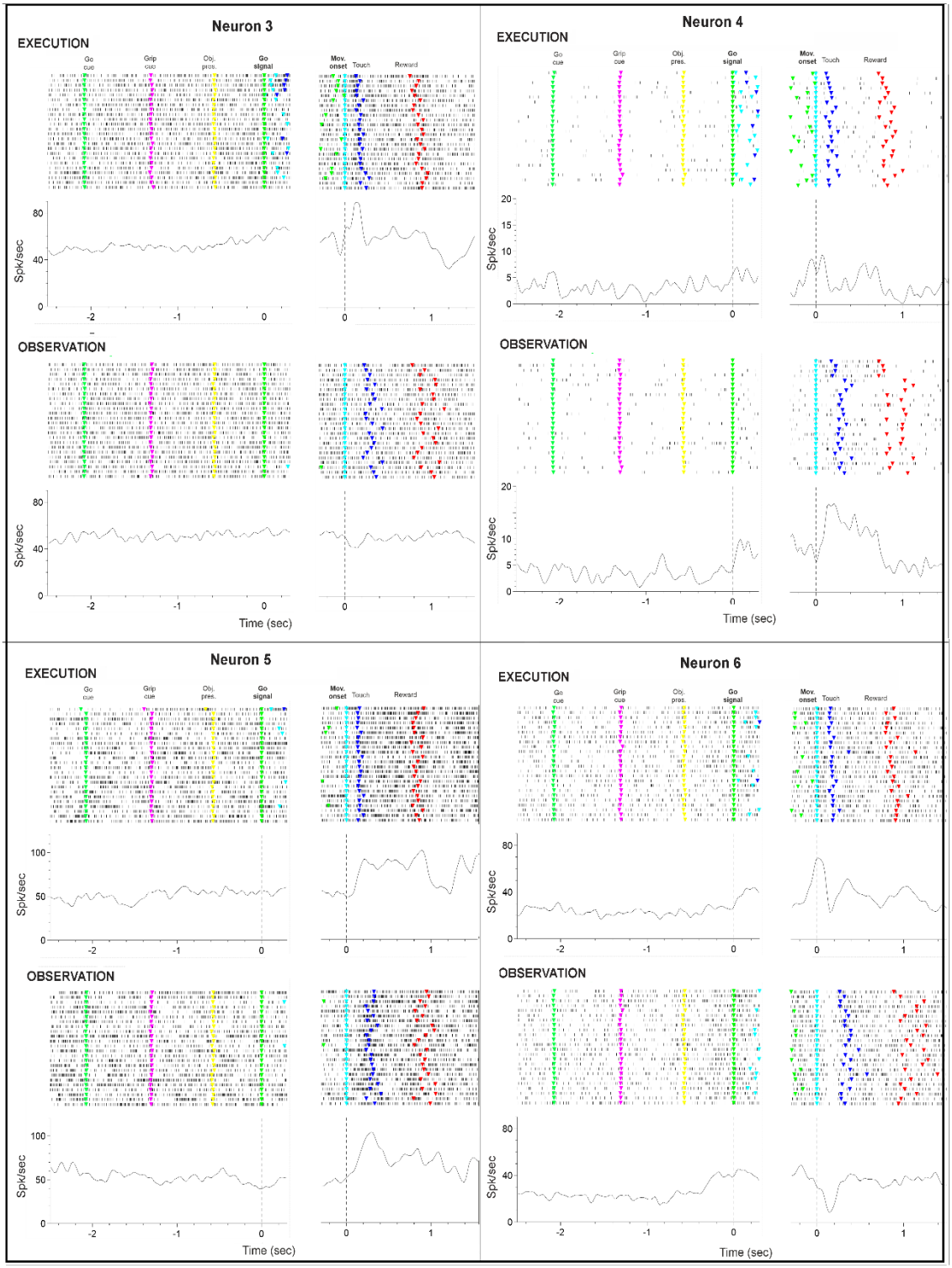

Figure 21. | Examples of neurons responding to self and other's action. Upper left (Neuron 3): activity of a unit that during the motor interval only responded to the monkey's Go trials but not to observation of the experimenter's action ("self type F"). Upper right (Neuron 4), a unit discharging more during observation trials ("other type F"). Bottom left (Neuron 5): activity of a neuron that resulted facilitated during both execution and observation ("self-other type FF"). Bottom right (Neuron 6): a neuron showing the opposite firing pattern, i.e., discharging significantly more during execution and less during observation ("self-other type FS"). All other conventions as in Fig. 16.

Amongst those units that showed a significant change in their firing rate both during first-person execution and observation of grasping actions performed by the experimenter, we further investigated the sign of such modulation, to assess consistency of neuronal responses in the two examined conditions.

We found that 47 neurons out of a total of 116 (40.5%) were facilitated in both cases (facilitated-facilitated, *FF*), 34 (29.3%) were always suppressed (suppressed-suppressed, *SS*), 22 (19%) were significantly excited during active movement but inhibited during action observation (facilitated-suppressed, *FS*), and 13 (11.2%) showed the opposite discharge pattern, i.e., were inhibited during execution and excited in observation trials (suppressed-facilitated, *SF*). The proportion of neurons belonging to each of these functional classes is reported in Figure 22.

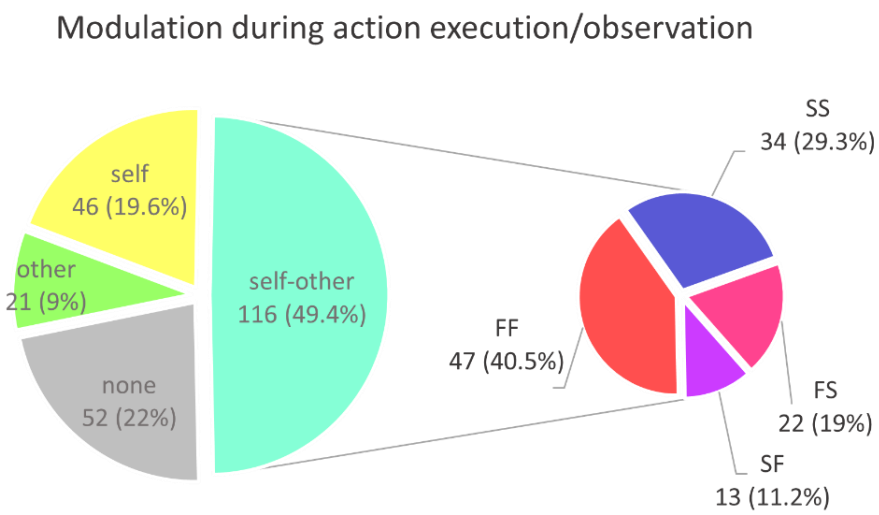

Figure 22 | Distribution of neuronal responses during the motor interval only considering the two agent conditions, regardless of grip type. On the left**,** a pie chart reporting the fraction of neurons that during the motor period responded to first-person movement only (yellow section), to action observation only (green section), or to both execution and observation trials (light blue section), and the fraction of neurons that showed no significant modulation neither in the monkey's Go trials nor the experimenter's ones (grey section). The nested pie chart on the right illustrates a further subdivision of self-other type neurons, based on the sign of their average modulation in the two conditions (EXE/OBS): units belonging to the "FF" category (+/+) are represented in red, those of the "SS" class (-/-) are shown in blue, "FS" neurons (+/-) correspond to the fuchsia section, and "SF" neurons (-/+) to the violet one.

4. DISCUSSION

A growing body of evidence support a major role of areas belonging to the cortical motor system in action planning and execution, as well as in a broad range of advanced perceptual, cognitive, and even social functions. In particular, it is widely accepted the notion that regions devoted to motor control largely overlap with those that contribute to an extended action observation network (AON) underlying others' action processing (see Kilner and Lemon, 2013). Recent anatomical data demonstrated the existence of a tight anatomo-functional connectivity between most of the acknowledged cortical nodes of the AON and specific territories of the putamen nucleus in the basal ganglia (e.g., Gerbella et al., 2015), hinting at a possible contribution of this subcortical structure to motor-based socio-cognitive and perceptual functions, such as the coding of others' actions (Bonini, 2017). However, the functional properties of putamen's neurons remained, so far, poorly known.

Thus, we recorded single neuron activity from the macaque putamen nucleus during a Mutual Action Task, in which the animal and an experimenter, facing each other and taking turns based on learned contextual cues, were required to reach and grasp – or to observe the other subject's executing the same action – a multi-affordance object placed in a shared operational space. The task was conceived to allow the investigation of the mechanisms underlying action selection, inhibition, and observation within a social context.

4.1 Processing of behaviorally relevant contextual information

Most of the recorded units showed some modulation during the task-unfolding period, most often during both the sensory epoch and the action execution/observation one, in at least one of the four considered conditions (2 agents x 2 objects). We found that the fraction of units significantly inhibited during the sensory cue period was higher than that of the facilitated

units, both in the monkey's and experimenter's execution trials, even though in this latter condition a smaller amount of units was classified as task-responsive. Clearly, a fraction of the neurons modulating their firing rate throughout the sensory epoch may be represented by false-positive occurrences due to the length of the selected interval (about twice the time of the action execution/observation phase) and to the fact that it included several behaviorally relevant events, such as Go/No-Go cue, grip cue, object presentation, and Go/no-Go signal. Further investigation will be necessary to better scrutinize which stimulus (or stimuli) specifically modulated single neuron activity, as – for example – the auditory instruction cue only weakly modulates the discharge of neurons recorded from cortical areas that are source of anatomical projections to the putamen (Bonini et al., 2014; Bruni et al., 2015; Lanzilotto et al., 2016; Livi et al., 2019; Lanzilotto et al., 2020), whereas visual stimuli are much more effective. A reasonable expectation is that visual stimuli exert the most powerful and reliable source of modulation of putaminal neurons as well, in line with a few previous studies employing different behavioural paradigms (Romero et al., 2008; Vicente et al., 2012).

The activation of putaminal neurons during the initial, instructive phases of the task would be consistent with the extensively recognized implication of the BG in the process of action selection (e.g., of the type of grip that has to be performed) and inhibition (required in the experimenter's Go trials). Previous data support the idea that striatal neurons may receive behaviorally relevant sensory information about the current context (Matsumoto et al., 2001; Gerbella et al., 2015), generating instruction-dependent preparatory activity that ultimately impact on the selection and generation of the cortical action plan (e.g., Alexander & DeLong, 1990).

4.2 Representation of self and other's actions

Consistently with the notion of a key role of the putamen in the control of purposeful hand actions directed to objects that are included in the animal's peripersonal space (Gerbella et al., 2015), the great majority of single units recorded in the present work turned out to be significantly modulated during the movement unfolding period as well.

Most neurons were active during either the monkey's own movement ("self type"), the observation of the experimenter's action ("other type"), or both these conditions ("self-other type"); only a smaller fraction did not show any action-related modulation. Interestingly, the largest class was represented by self-other neurons, that embraced nearly half of the total amount of the recorded units. Unlike what we observed for the sensory epoch, during first-person action execution neurons exhibiting facilitated activity prevailed over suppressed ones, whereas in observation trials facilitated and suppressed units were balanced, and a smaller fraction of unit were found to be modulated.

In a recent work by Ferroni et al. (2021), single-neuron activity was acquired from three of the crucial nodes of the AON (premotor areas F6 and F5, and AIP) that are known to have reciprocal connections with the BG. Since the task used by the authors was broadly similar to the one employed in the present study and we applied the same approach to neural data analysis, our findings can be directly compared with those in the cortical areas that are source of anatomical projection to the putamen (Gerbella et al., 2015; Borra et al., 2021), casting light on the possible differences and similarities in the cortical and BG properties.

In line with what we could assess in the putamen, where most of the recorded units showed facilitated activity in execution trials, in AIP and F5 more than half of the neurons were facilitated during active movement of the monkey, differently from what was found in F6, where suppressed neurons prevailed. In action observation trials, similarly to what we observed for putaminal neurons, the overall modulation was smaller compared to action

execution ones in all investigated areas; moreover, the number of excited and inhibited units was balanced, as in the putamen, both in AIP and in F5 (where the facilitated ones were only slightly more numerous), unlike in F6, in which a prevalence of cells with reduced firing rate was found.

To validate the specificity of the responses to other's observed actions additional testing would undoubtedly be necessary – for instance, we did not acquire EMG activity during the task, leaving the possibility that the observed modulation was actually a byproduct of the monkey's covert movement. Nonetheless, this possibility appears to be unlikely as we recorded simultaneously from multiple neurons, some of which (self-type) showed clear preparatory and motor-related discharge, but they remained silent during the same action observation trials during which other- and self-and-other type neurons became active, thus suggesting the genuinely visual nature of these responses. Other visual stimuli, such as non-biological motion, may have to be tested to evaluate the selectivity of the visual responses, although it is known that it may be very low even in the cortical areas that are source of projection to the putamen, such as the dorsal and mesial premotor cortices (Albertini et al. 2021). Another aspect that will have to be investigated is the possible congruence in the visual and motor selectivity for the target object in self-other type neurons, which represent a debated topic for cortical "mirror" neurons as well (Papadourakis and Raos, 2019).

It would be interesting to further explore both the firing properties of task-responsive units in the putamen (especially with respect to their spike waveforms), and the temporal dynamics of the observed modulation, to compare these additional data with what has already been described for cortical areas (Ferroni et al., 2021) and gain supplementary knowledge about how and when self and other's actions may be represented in the BG.

4.3 Regulation of motor resonance

Another notable result of the present work is that, amongst those neurons that resulted modulated during both action execution and observation, we did not find exclusively cells with "classical" mirror-like properties (i.e., showing a brisk increase in firing rate during both conditions; FF), although they were the more numerous, but also a sizeable fraction of units that were consistently suppressed (SS), and others that displayed opposite changes in activity in the two considered conditions (FS and SF).

Kraskov et al. (2009) demonstrated the existence of mirror-like activity in F5 pyramidal tract neurons (PTNs) and were the first to describe the presence of suppressed MN activity. Significant modulation during observation of precision grips performed by the experimenter was noticed in about half of the tested units (a proportion that is also in line with our findings), among which a substantial fraction responded with a pattern of discharge suppression during action observation. Examples of mirror-like neurons exhibiting diminished activity during action observation have been described in M1 as well (Vigneswaran et al., 2013; Kraskov et al., 2014).

The authors hypothesized that, while facilitated ventral premotor output is believed to underlie the "motor resonance" phenomenon (e.g., Rizzolatti et al., 2001), this inhibitory mirror-like PTNs activity might be one of the mechanisms involved in producing the disfacilitation of motoneurons that subserves the suppression of unwanted self-movement during observation of other's actions. They also proposed that this inhibitory modulation could be directly transmitted to other regions of the motor network, including its subcortical components, such as the BG, whose crucial role in action inhibition is widely acknowledged. It is likely that cortical and subcortical mechanisms operate together to decouple cortical motor representations from the motor output, preventing the observer from automatically re-enacting the witnessed action (Bonini, 2017). To provide causal evidence and a deeper

understanding of these possible mechanisms, direct chemical perturbation of putaminal neurons activity with agonist/antagonist of specific dopamine receptors (D1 or D2) is a viable and necessary step to be made in future studies.

4.4 Conclusions

Despite preliminary, our findings constitute one of the first empirical demonstrations of the existence of neurons specifically modulated by others' observed actions in the putamen. This result strengthens the hypothesis – which seems to be supported by the results of previous human studies as well (Kessler et al., 2006; Alegre et al. 2010) – of an involvement of this subcortical nucleus in the AON and points out the need to examine in depth its overall modulatory activity on the functioning of the AON cortical nodes and to look into its possible functional role.

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