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ROLE OF MONKEY PREFRONTAL, PREMOTOR CORTICES AND BASAL GANGLIA IN GUIDING BEHAVIOR BASED ON SOCIAL INFORMATION

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1. INTRODUCTION

The ability to use contextual cues for the processing of coherent behavioral responses is fundamental for human and non-human primates. Among those cues, information about the social environment is crucial for action planning. This kind of information mostly derives from the understanding of others' actions, together with the knowledge about the agents' identity. In the last years, a large body of evidence described a neural mechanism involved in coding other's actions, the "Mirror Mechanism", that is theorized to play a crucial role in action understanding and present in a particular class of cell called mirror neurons (Di Pellegrino et al., 1992; Gallese et al. 1996; Rizzolatti et al. 1996; Ferrari et al. 2003, Rizzolatti & Sinigaglia, 2010; Rizzolatti & Fogassi, 2014). The mirror neurons (MNs) are cells activated during the execution as well as the observation of motor acts performed by another individual and were originally described in monkey ventral premotor area F5 and in the inferior parietal area PFG (Fogassi et al., 2005; Rizzolatti and Fogassi, 2014; Rozzi et al., 2008). Studies of the last few years provided evidence of the presence of this type of neurons in a more extended network of cortical areas, including the lateral prefrontal cortex (Lanzilotto et al., 2019, 2016; Pani et al., 2014; Rizzolatti et al., 2014; Simone et al., 2017; Tkach et al., 2007). Although, the presence of mirror neurons in the lateral prefrontal cortex is in line with the well-known role of this cortical territory for processing and exploitation of contextual cues as well as social ones for the selection, planning, and guidance of behavioral responses, their exact role remains to be addressed (Tanji & Hoshi, 2008; Yamagata et al. 2012; Yoshida et al. 2011; Simone et al., 2015, 2017; Rozzi & Fogassi, 2017, Bruni et al., 2015).

Neuroanatomical evidence show that specific sectors of the putamen receive projections from premotor, parietal and prefrontal cortical mirror areas (Gerbella et al. 2015), raising the question of the presence of neurons with mirror properties also in this subcortical structure. This possibility is also supported by some electrophysiological and fMRI human studies showed that both execution and observation of hand motor acts activate specific sectors of the basal ganglia (Alegre et al., 2010; Errante and Fogassi, 2020). Based on this evidence two unanswered questions remain: first, whether

the basal ganglia, and in particular the putamen, host mirror neurons and, second, whether and, eventually, to what extent it is involved in the visual and motor processing of self and others' action.

Studies conducted on both human and non-human primates undermined a simplistic view of hierarchical organization of mental functions, leading to the proposal of a more likely functional model in which different cortical and subcortical areas (including basal ganglia) provide specific contributions to different functions, and specific group of areas are organized and integrated in a series of neural networks underlying different cognitive, emotional and behavioral functions. Each mental function, for this model, is thus based on a series of processes that are distributed on a network that involves different cortical and subcortical areas, each cooperating and sending information and inputs to the other, rather than a hierarchical unidirectional flow of information in which higher order areas control lower level areas, which simply execute the commands. Note, however, that this does not mean that each area can play each type of role: within a specific network, each area has a specific role, and contributes to the general network function, and often an area participates to multiple functions being involved in different networks.

Based on this theoretical framework, in the present study we aimed to assess the specific role of the ventrolateral prefrontal and premotor areas containing mirror neurons and of the putamen sector connected to them, during a task in which a monkey had to plan and execute two different actions based on the observations of biological and non-biological cues.

1.1 The Mirror mechanism

Behavior guidance based on the processing of contextual cues relies (like already said above), in a fundamental way, on information extracted from the social environment, in particular from the observation and understanding of others' actions. According to a classical conception of the evolution of social cognition, the reading of others' behavior is mediated by processes of inference and mentalization that presuppose the existence of dedicated modules of the mind. These processes would

part of a mind-reading mechanism called "Theory of Mind" (Premack & Woodruff, 1978; Baron-Cohen et al., 2013; Meunier, 2017). According to this formulation, individuals would be able to read the behavior of others through the ability to attribute mental states such as emotions, desires, intentions etc. However, this view poses several problems because, from a neurobiological point of view, it does not propose any model on the possible neural mechanism operating in mentalization processes. In fact, although several neuroimaging studies indicate the activation of specific areas of the brain in human subjects subjected to inference tasks, they do not give us any information about how mentalization processes operate at the neuronal level. According to another hypothesis, it is possible to recognize an action observed (thus, to exploit this information to guide behavior) because its observation activates, in our brain, the motor representation of that action (see Gallese, 2006). A crucial role in action understanding, thus, would be played by the "Mirror mechanism", defined as the neural mechanism that unifies perception and action, transforming sensory representations of the behavior of others into motor representations of the same behavior in the brain of the observer (Rizzolatti & Sinigaglia, 2010). This mechanism has been firstly discovered in the ventral premotor cortex of the macaque monkey (F5 area) (Rizzolatti et al. 1996; Gallese et al. 1996; Ferrari et al. 2003, Rizzolatti & Fogassi, 2014), particularly in its cortical convexity, and later in the convexity of the inferior parietal lobule (PFG) (Fogassi et al., 2005; Rozzi et al., 2008, Bonini et al., 2010), where populations of mirror neurons (MN), endowed with the property of discharging both when executing an act or observing the same act, have been described. The discovery of mirror neurons occurred during a series of studies aimed at investigating, by recording single neurons, the functional properties of the macaque's ventral motor cortex (area F5), an area involved in the execution of finalized motor acts performed with the hand and mouth. During these experiments, it was observed that a subpopulation of motor neurons, which were activated during the grasp performed by the monkey, were also activated during the observation of the same action performed by an experimenter, as if the monkey itself had grasped it. After excluding that these responses could depend on imperceptible movements performed by the monkey, or on food expectation, it was assumed that their coding

concerned the motor representation of the motor act, regardless of who was performing it. Mirror neurons, therefore, are a class of neurons that is activated both when the monkey performs a finalized motor act, and when it observes another individual or its conspecific performing the same motor act (Gallese et al. 1996; Rizzolatti et al. 1996; Ferrari et al. 2003, Rizzolatti & Fogassi, 2014). Neurons with this property have been observed in several cortical areas (Figure1) capable to encoding visual information concerning others' actions, primarily processed in the superior temporal sulcus (STS, Barraclough et al., 2009; Jellema and Perrett, 2006; Perrett et al., 1989), that are anatomically connected, forming a functionally integrated circuit endowed with the "Mirror mechanism".

These regions include the inferior parietal lobule (Bonini et al., 2010; Fogassi et al., 2005), particularly area AIP (Maeda et al., 2015; Pani et al., 2014; Lanzilotto et al., 2019), the dorsal premotor cortex (Cisek and Kalaska, 2004; Tkach et al., 2007; Papadourakis and Raos, 2017), and the medial frontal cortex (MFC), the pre-supplementary motor (pre-SMA) and anterior cingulate cortex (Mukamel et al., 2010; Yoshida et al., 2011; Livi et al., 2019). The presence of neurons with mirror properties has been documented in the primary motor cortex as well (Dushanova and Donoghue, 2010; Tkach et al., 2007; Vigneswaran et al., 2013), and convergent anatomical (Borra et al., 2011; Gerbella et al., 2013) and functional evidence (Nelissen et al., 2011) suggests that even the ventrolateral prefrontal cortex (VLPF) may host neurons with mirror-like properties (Bonini, 2017; Simone et al., 2017).

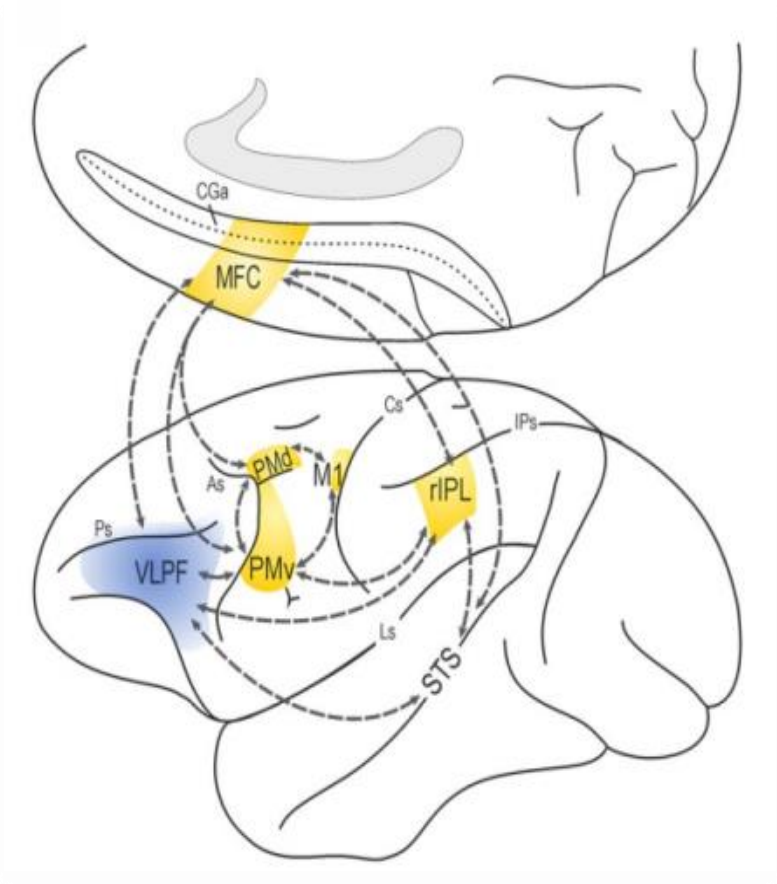

Figure 1. The cortical MN network includes a set of areas in which the presence of single neurons with mirror properties has been directly demonstrated (yellow) as well as other regions (the ventrolateral prefrontal areas 12 and 46) in which the presence of MNs is supported by anatomical evidence but 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. Figure from (Bonini, 2017).

1.2 Properties of F5 mirror neurons

1.2.1 Coding of the actions' goal, action understanding and the concept of motor representation in the cerebral cortex

One of the most important challenges that researchers have faced, following the discovery of the mirror mechanism, has been to shed light on its possible functional role played. After rejecting the possibility that they are only a preparatory class of neurons, it has been proposed that it underlies the recognition and understanding of the meaning of observed motor acts (Gallese et al., 1996; Rizzolatti

et al., 1996, Rizzolatti, & Fogassi, 2014). Planning and executing an action involve having an intention, selecting an appropriate sequence of motor acts, each of which has its own immediate goal, and executing the sequence of movements that constitute each motor act. This view on action structuring implies that different elements (movement, motor act, action) are organized in different hierarchical levels. To achieve the whole action's goal, the individual elements must be linked to each other in a precise temporal structure to generate the "kinetic melody" (Luria, 1973) that characterizes normal behavior. While the primary motor area F1 is fundamental for the execution of the action, the ventral premotor area F5 plays an important role in coding the goal of motor acts and motor intention. Single neuron recordings show that neurons in the monkeys' ventral premotor and posterior parietal cortices (area F5 and PFG) are activated when the monkey performs purposeful actions, such as grasping an object. Specifically, they are activated following the performance and/or observation of motor acts such as grasping, holding, manipulating or ripping. The first studies conducted on F5 mirror neurons (Rizzolatti et al., 1996; Gallese et al., 1996) found that they are activated only when the observed action involves an interaction between effector (hand or mouth) and object. These neurons, however, do not present any discharge during the observation of a mimed action (absence of actual interaction with the object) or following the "mere" presentation of an object (before any interaction has occurred). Furthermore, the discharge is weak when grasping occurs through motor sequences outside the monkey's motor repertoire (e.g. using tools such as pliers). F5 mirror neurons, based on the comparison between visual and motor responses, have been mainly distinguished into strictly congruent and broadly sense (Rizzolatti et al., 1996). In the former we see a high correspondence between the act observed and performed, for example when the animal observes a specific rotation of the experimenter's hand manipulating a piece of food and when it grasps food by performing the same type of rotation. In the latter, however, we can see a congruent but not identical encoding in visual and motor terms, presenting different levels of generalization (Rizzolatti and Sinigaglia, 2006), for example a neuron that is activated when the monkey observes the experimenter grasping an object with a precision grip or with a force grip, while at the motor level it responds only

when the animal grasps the object with a precision grip. Thus, the neuron encodes the general purpose of the action, but the motor response is more specific than the visual response (Rizzolatti et al., 1996). These neurons do not simply code movements involving specific muscle bundles: movement is represented in a more generalized way, and this information is used for other processes that do not necessarily have to be purely motor in nature (Bonini et al. 2010). An example of how F5 neurons code motor acts in terms of goal, rather than specific movements, was provided by a study in which the same goal (taking possession of food) was achieved with completely opposite movements (Umiltà et al., 2008). Monkeys took food using normal pliers (similar to ice pliers) that require closing the hand to take possession of the object, and inverted pliers (similar to escargot pliers) that instead require opening the hand to achieve the same purpose. A population of F5 neurons coded the achievement of the goal (taking possession of the target food) regardless of the specific movement required to achieve it (finger flexion or extension). To understand whether mirror neurons code the purpose of a motor act, it is necessary to test their activation during the observation of an action and, subsequently, whether they also respond to sensory inputs not dependent on the observation of the same motor act. This aspect is crucial for establishing the "generalization" ability of mirror neurons. Thus, if these neurons were involved in the process of understanding the goal of a motor act in a general sense, their activity should reflect the meaning of the observed motor action, not simply its visual characteristics. In this regard, two experiments were conducted: the first investigated whether F5 mirror neurons could recognize the motor act by its sound, while the second investigated whether these neurons where active even if the action execution was not fully visible and, thus, the understanding of the actions' goal was based on memory clues. Kohler and coworkers (2002) studied mirror neurons while the monkey was observing a motor act characterized by a typical sound, such as tearing a sheet of paper or breaking a peanut, and while the same sound was presented without viewing the corresponding motor act. The results show that about 15% of mirror neurons respond to the presentation of motor acts accompanied by the corresponding sounds and also respond to the presentation of the sound alone. The second experiment, conducted by Umiltà and collaborators

(2001), started from the assumption that, if mirror neurons respond to the purpose of the motor act, then they should be activated even when the monkey does not see the action, but has sufficient clues to create a mental representation of what the experimenter is performing. The authors demonstrated how cells that discharge during the observation of a grasp, continue to discharge even when the final part of the action (the moment of interaction between hand and object) is obscured. It seems, therefore, that the meaning of the action is "extracted" regardless of the complete vision of the action, thanks to a prior knowledge of the context, and in particular the memory of the presence of the object. The motor act and its purpose are coded by mirror neurons even if, during execution, the vision of the hand-object interaction is missing: the discharge of these neurons, therefore, reflects the activation of an internal representation of a "potential motor act" that allows to integrate the missing part of the action itself by recognizing its overall meaning. Consequently, the response of mirror neurons during the observation of others' motor acts has been interpreted as a fundamental element in the process of recognition of a specific motor act, in the sequence of movements observed, and differentiation of the type of action observed, recognizing it as part of their motor vocabulary. Based on this evidence, it has been proposed that the F5 area contains a "vocabulary" of motor acts (Rizzolatti et al., 1988) made up of "words" each of which is represented by a population of neurons. Some encode the general purpose of the motor act, others the specific mode of execution, and still others specify the temporal aspects of the act to be performed (Jeannerod et al., 1995).

1.3 Properties of PFG mirror neurons

Mirror neurons having functional properties similar to those recorded in F5 have also been identified in the rostral portion of the inferior parietal cortex (PFG area). In the early 1980s, Hyvarinen and collaborators (1981, 1982) observed, in this area, the presence of neurons responding both to sensory stimuli and during the execution of movements, Successively, it was demonstrated that motor neurons in the inferior parietal cortex code for finalized motor acts and that visual and tactile

properties are, almost always, also present at the level of single neurons (Rozzi et al., 2008). In particular, visual neurons in the PFG area respond to the observation of stimuli in the peripersonal field and to the observation of biological movements, including finalized actions (Gallese et al., 2002; Fogassi et al., 2005; Rozzi et al., 2008). Furthermore, an influential experiment on parietal mirror neurons showed that, during the execution of a grasping act, the activity of a subpopulation of them is modulated depending on whether the monkey eats the target food of the movement or puts it in a container. The same type of modulation also occurs when the monkey observes the experimenter performing either action (Fogassi et al., 2005). The differential discharge of mirror neurons could reveal a mechanism by which the monkey can predict the final purpose of the observed action (placing or eating). It has been proposed, therefore, that such activation requires that mirror neurons also receive contextual information independent of the observed movements. These parietal regions, as the premotor cortex (and in particular with the F5 area), have important connections also with specific prefrontal and temporal areas located at the level of the superior temporal sulcus (Pandya & Seltzer, 1982; Rozzi et al., 2006). This network could constitute the nervous circuitry by which the visual description of the observed action is associated with the motor program that the observer uses to actively perform the same action.

1.4 Visual properties of STS neurons

The presence of neurons in the premotor cortex that are activated both during the observation and during the execution of the same motor act raises the question of how visual information related to observed movement can be combined with their motor representation. The origin of visual information could be found in a high-order multisensory area located at the level of the Superior Temporal sulcus (STS), which is connected to F5 by means of PFG (see below), where neurons selectively activated during the observation of biological movements have been observed (Perrett et al. 1989; Allison et al. 2000; Puce & Perrett 2003). It has also been shown that some STS neurons

not only respond to the observation of different purpose-directed hand actions, such as grasping, tearing, and manipulating objects (Perrett, 1989,1990; Jellema et al., 2000), but also appear to be modulated by the shape of the object involved in the action observed. These neurons also show no response when the experimenter's hand is replaced by a tool, such as pliers. STS neurons have been studied in relation to their visual responses, however the presence of any motor responses has never been researched and demonstrated (Keysers & Perrett, 2004). For these reasons, therefore, it is still unclear what role these cells play in understanding observed actions, if we accept the hypothesis that understanding of actions is mediated by the mirror neuron system.

1.5 Neural circuits involved in action observation

Since the 1990s, numerous works have been conducted with the aim of studying the neuronal mechanisms responsible for action observation in non-human primates and the neural circuits involved. After the identification of mirror neurons in the premotor and parietal cortex, functional magnetic resonance imaging (fMRI) studies (Nelissen et al., 2005, 2011) showed that several regions are activated during the observation of grasping actions. Specifically, the monkey was shown several videos depicting finalized actions, conducted by different agents or non-biological effectors, together with their static counterparts: objects and controls obtained from "scrambling" procedures of the above. The results show that action observation activates the ventral premotor cortex, the inferior parietal cortex, a large region of the temporal lobe located at the level of the STS, and a large region of the ventrolateral prefrontal cortex (which will be discussed in more detail below). In the periarcuate region the observation of videos showing decontextualized hands grasping objects (after subtraction of the relative static contrast) activated several cortical areas, such as the premotor areas F5a and F5c and the prefrontal area 45B; the observation of videos showing a full-length subject grasping objects (after subtraction of the relative static contrast), instead, activated only the area F5c (Nelissen et al., 2005). In a subsequent study, conducted by the same team (Nelissen et al., 2011), the activation of

the monkey's superior temporal sulcus and posterior parietal lobe regions during observation of the same videos was examined. The results show that extensive regions of the STS, such as MT/V5 (middle temporal cortex), FST (fundus of the superior temporal area), LST (Lower Superior Temporal Region), LB2 (lower bank of superior temporal sulcus), STPm (superior temporal polysensory area), and some parietal areas such as PFG and AIP (anterior intraparietal area), were activated during the observation of both stimuli described above. In order to understand which of the different activated areas of STS was sending information to the two parietal areas involved in encoding the grasping act, retrograde neural tracers were injected, which allowed tracing the cortico-cortical connections of the injected areas of interest (Rozzi et al., 2006; Borra et al; 2008; Gerbella et al, 2010; Nelissen et al., 2011). These works indicate that areas with a similar activation profile are also anatomically connected to each other, and these connections indicate that the observed action information, encoded by STS, is sent to the ventral premotor cortex (F5) via two distinct circuits. The first one connects the upper bank of STS with the PFG area, which in turn is connected to the premotor area F5c; the second circuit instead connects the ventral part of the lower bank of STS with the premotor areas F5a and F5p through AIP. Although both temporo-parieto-frontal functional circuits transmit visual information regarding the coding of the grasping act, the STPm-PFG-F5c pathway appears to be more sensitive to the presence of the agent in the video, and thus could play a role in contextualizing the action and extracting its underlying intention; instead, the LB2-AIP-F5p/F5a circuit seems to be more focused on the target of the action, and therefore fundamental in understanding the goal of the motor act, not only in terms of how to grasp an object, based on its intrinsic properties, but also in terms of different motor actions performed with the hand. An additional possible circuit responsible for action observation is represented by LB1-LIP-45B (Nelissen et al., 2011), suggesting that information about observed actions can be used for oculomotor control and also involves the ventrolateral prefrontal cortex (Flanagan & Johansson, 2003; Gerbella et al., 2010). Neuroimaging studies in macaques show that a large prefrontal region including areas 45A, 45B, 46v, and 12 is activated during action observation. The area corresponding to area 45A is activated during observation of others' motor acts

(Nelissen et al., 2005). Projections reaching area 45A from the multisensory area STP, which is also activated during the viewing of different biological movements (Oram & Perrett 1994; Barraclough et al., 2005; Jellema & Perrett 2006), suggest that these two areas are part of a network involved in the processing of visual aspects present in the communicative behaviors of the species. Area 45B, on the other hand, is activated following the presentation of images of objects and the observation biological actions performed on them (Nelissen et al., 2005) and the presentation of images of faces (Tsao et al., 2008): this agrees with the connections that this area presents with the TEa (anterior part of the inferior temporal cortex), site of visual processing of three-dimensional objects (Janssen et al., 2000a).

1.5.1 Recent findings about LPFC involvement in action observation

Recent functional (Nelissen 2005; Simone et al., 2015, 2017) and anatomical (Borra et al., 2015; Gerbella et al., 2010, 2013; Saleem et al., 2014) evidence showed that the lateral sector of the prefrontal cortex can be considered as a crucial node of the "Mirror System", with a possible specific role in the organization of socially driven behavior, based on the exploitation of contextual cues such as others' actions (Bonini, 2016, Rozzi & Fogassi, 2017). The details about the anatomical and functional properties of the prefrontal node of the mirror system, specifically the ventral sector of LPFC, will be described in the following sections of this introduction.

1.6 Prefrontal Cortex

1.6.1 Phylogeny and ontogeny of the prefrontal cortex

The development of the nervous system starts in a relatively late phase of the embryogenesis, preceded by the generation of three principal cell layers, namely the endoderm, mesoderm and ectoderm, from which derive the principal structures of the peripheral and central nervous system. The ectoderm gives rise to the neural tube starting from which, in turn, originate three cerebral

vesicles: forebrain, midbrain and hindbrain. The development of the vesicles, thereafter, gives rise to the principal regions of the central nervous system of the adult brain, among which the cerebral cortex is the last to develop fully. The cortex, in adult subjects, is divided in four lobes: occipital, temporal, parietal and frontal, each of which contains several functionally distinct regions that subserve different roles in the processing of information. The frontal lobe is the most anterior portion of the brain, and in humans it's traditionally divided in two portions: - agranular motor frontal cortex, which is in turn subdivided in primary motor cortex (BA 4) and secondary motor areas (BA 6, including pre-motor cortex and both supplementary and pre-supplementary motor areas - SMA and Pre-SMA) - granular prefrontal cortex, which constitutes an extended network linking motor regions with regions that process perceptive stimuli and emotions (Goldman-Rakic, 1995; Passingham, 1995). The phylogenetic development of the prefrontal cortex, and its increase in relative size in human primates' brain compared to non-human primates' brain, can be inferred by studying the latter. The "regio frontalis", which correspond to the PFC (Brodmann, 1909, 1912), occupies 29 percent of the cortex in humans, 17 percent of the cortex in chimpanzees and 11.5 percent of the cortex in macaques. Another comparative study (Semendeferi et al., 2001), focused on the anterior or fronto-polar prefrontal cortex (BA 10), an area involved in complex cognitive functions. The frontal pole can be found in various primates like bonobos, orangutans and gibbons, presenting similar cytoarchitectonic characteristics but varying in its organization between species (specifically the area variations regarding the width of its cortical layers and the space available for connections). The frontal pole of hominoid like the gorilla appears highly specialized, while area 10 in the gibbon occupies only the orbital sector of this region. In humans, area 10 is larger, relative to the rest of the brain, than it is in the other apes and presents more space for connections with higher order association areas. The relative growth in dimension (and connectivity with other regions) of the PFC in humans, compared to the other apes, suggests that this region could represent the neural substrate underlying the various complex cognitive processes that constitute a "patrimony" of our species and that resulted from the phylogenetic differentiation with the other apes (J. Fuster, 2015).

Other than representing the last part of the cortex to develop, both phylogenetically and ontogenetically, the PFC can be defined as the most complex region of the brain. Its complexity is represented by the numerous gyri and sulci that are present in this region, which become more evident and irregular when proceeding through the evolutionary scale of the mammals. The complexity of this region progresses until reaching a grade of differentiation and development such as the one that characterizes the hominoid PFC and especially the human primates, in which this region occupies (as said at the beginning) almost a third of the entire cortex.

Evaluating the ratio between the volume of the frontal lobe and the volume of the entire cortex in various species such as gorillas, bonobos, chimpanzees, orangutans and macaques, it has been demonstrated that the frontal lobe always occupies from 20 to 30 percent of the entire cortex (Table 1). It is obvious, given the data described above, that these regions subserve a fundamental role not only in humans but in other apes too, being in the latter cases strongly developed and occupying a significant part of the entire cortex.

	(Brodmann, 1909)*	(Blinkov & Il'ja, 1968)*	(Semendeferi, et al., 2002)**
Human	36.3	32.8	37.7 (± 0.9)
Chimpanzee	30.5	22.1	35.4 (± 1.9)
Bonobo	NA	NA	34.7 (± 0.6)
Gorilla	NA	ND	35 and 36.9
Orangutan	NA	21.3	37.6 (± 1.1)
Gibbon	21.4	21.2	29.4 (± 9.8)
Macaque	NA	NA	30.6 (± 1.5)
Cebus	22.5	NA	29.6 and 31.5

Table 1: Relative size of the frontal cortex, expressed in percentage of the size of the entire cortex (Semendeferi et al., 2002). *Surface of frontal cortex in percentage of surface of cortex of cerebral hemispheres. **Volume of frontal cortex in percentage of volume of cortex of cerebral hemispheres. NA, not available.

Neuroimaging studies indicated that, in humans, the prefrontal cortex does not develop fully until adolescence (Chugani et al., 1987; Paus et al., 1999; Sowell et al., 1999). These results are in line with experimental evidence indicating that the higher order cognitive functions, which are subserved by the PFC, such as abstract reasoning, are indeed the last to emerge in the developmental processes (J. M. Fuster, 2001). Neurophysiological studies in monkeys and neuroimaging studies in humans have provided a wide view upon the basic activity of PFC, the functions subserved by the various areas found in this region and its numerous connections with other areas throughout the brain. The PFC is composed of various interconnected areas, which, in turn, are connected and communicate virtually with all cortical sensory and motor system and even with subcortical areas (E. K. Miller & Cohen, 2001). Thanks to the strong interconnection with other networks and systems throughout the brain, the PFC is involved in numerous high order cognitive function such as planning and execution of goal-directed behaviors, organization and regulation of emotional behavior, integration of information acquired from the environment, processing in the short-term memory. The heterogeneity of this region entails a variety of processes and outputs, which constitute the so-called "executive functions", that cannot be traced back to specific areas and that allow the individual to adapt its behavior to different social contexts and in a changing environment, full of information to be acquired and used to plan actions directed to specific goals.

1.6.2 Anatomo-functional organization of the macaque prefrontal cortex

The primates' PFC is divided in three regions: lateral, medial and ventral or orbitofrontal. The lateral prefrontal cortex (LPFC) of human primates is characterized by the presence of two sulci originating from the precentral sulcus: the superior frontal sulcus, which separates the superior frontal gyrus from the middle frontal gyrus, and the inferior frontal sulcus, which separates the middle from the inferior frontal gyrus. One of the most useful experimental models available to study the anatomo-functional organization of the primate brain is the macaque, given the similarity of its brain with the human counterpart. The macaque PFC is indeed characterized by the three great subdivisions

described in the human brain (Passingham, 1995; J. Fuster, 1997), but, other than this homology, 33 there are also significant differences: the lateral portion of the prefrontal cortex of macaques is subdivided in two sub-regions (dorsal and ventral) by the principal sulcus. Starting from the first quarter of the 20th century, several authors focused on studying the architectonic structure of the cerebral cortex (including the PFC) of humans and macaques. The different parcellations of the PFC available at the moment are not entirely congruent. The discrepancy between the architectonic "descriptions" of human and macaques PFC is due to the fact that, in experimental investigations of the macaque monkey performed during the last 50 years, the architectonic nomenclature and criteria used to describe the areas found in the prefrontal cortex has been largely based on the map by Walker (Walker, 1940), which was not based on a comparative investigation of the cytoarchitecture of the human and macaque monkey prefrontal cortex. As a result of this, the criteria frequently used for demarcating areas in humans and macaques are not always consistent. The discrepancies existing between different parcellations of the macaque PFC is instead determined mainly by the progressive improvement of histological techniques and the development of new techniques through time. Petrides and Pandya (Petrides & Pandya, 1994,1999,2002a) proposed a parcellation of the PFC (Figure 2), specifically comparing the macaque and human prefrontal cortices, as to resolve the discrepancies existing between the descriptions of this region in the two primates species, due to the problems described above. If we consider the architectonic structure of the PFC in the human and macaque brain, as defined by Petrides and Pandya, it is clear that the two are very similar since the only differences consist in the total area occupied by the whole prefrontal cortex (higher in the human brain) and the presence of few areas that have been localized in the PFC of only one of the two species: area 44, found in the human LPFC but not in the macaque LPFC, area 25, found only in the macaques orbital PFC, and area 45A, found only in both lateral and orbital human prefrontal cortices (while it is localized only in the LPFC of the macaques brain).

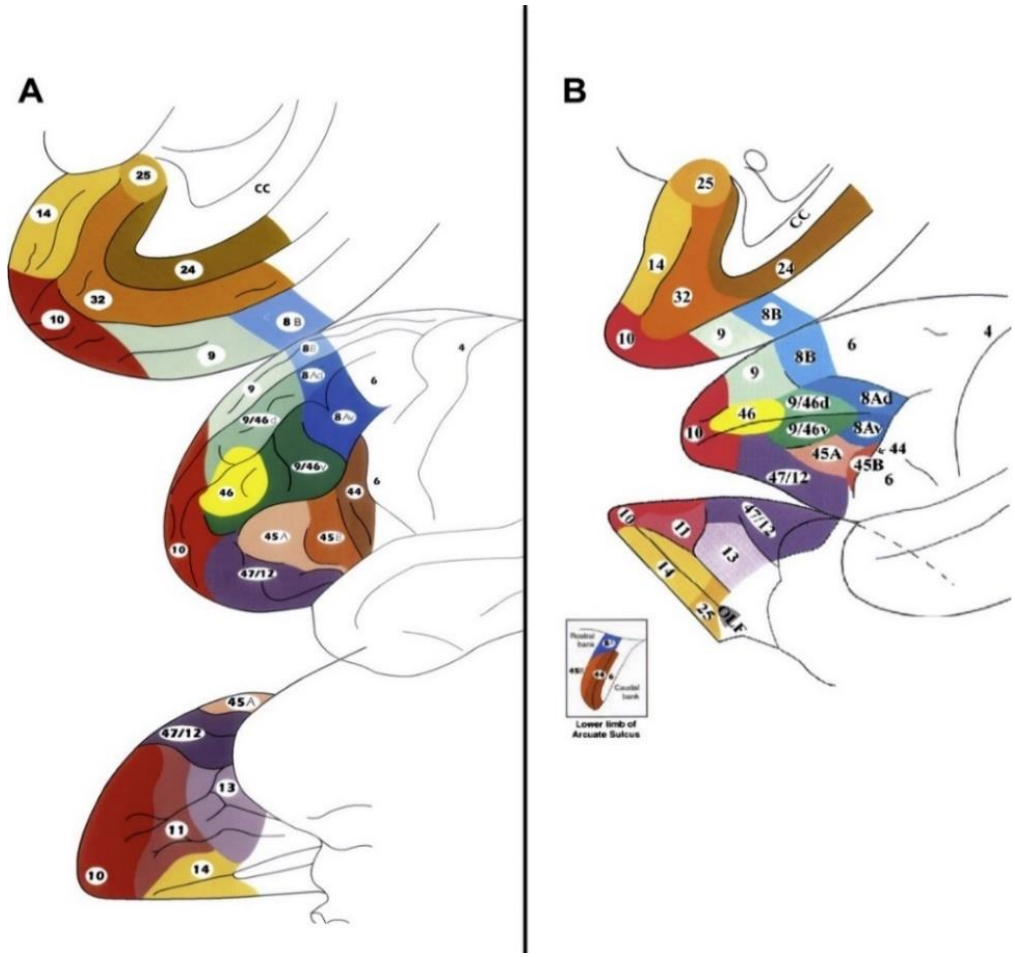

Figure 2: Cytoarchitectonic maps of the PFC in human (a) and macaque (b) brain as parcellated by Petrides and Pandya in 1994 (Petrides & Pandya, 1994).

The prefrontal cortex is extensively connected with various areas, including the parieto-premotor circuits (and therefore, with the mirror neurons contained in these areas). The LPFC represents the region of the prefrontal cortex most connected to motor areas, basal ganglia and cerebellum, and it is through these extensive interconnections that it exerts its control onmotor behaviors (Tanji & Hoshi, 2008) This region is anatomically connected, both directly and indirectly, also to other cortical areas such as the associative temporo-parietal cortices, the limbic cortex and several subcortical structures.

The LPFC can be divided in a dorsal and ventral portion (DLPFC and VLPFC) which are involved in different networks (Figure 4). The mediodorsal network (that includes DLPF) receives inputs from multimodal areas situated in the temporal cortex or auditory areas of the superior temporal gyrus and it is involved in the processing of spatial information. The orbito-ventral network (which includes

VLPF) mostly receives sensory inputs from visual, auditory, somato-sensory, gustatory and olfactory areas, and it is involved in the processing of non-spatial information.

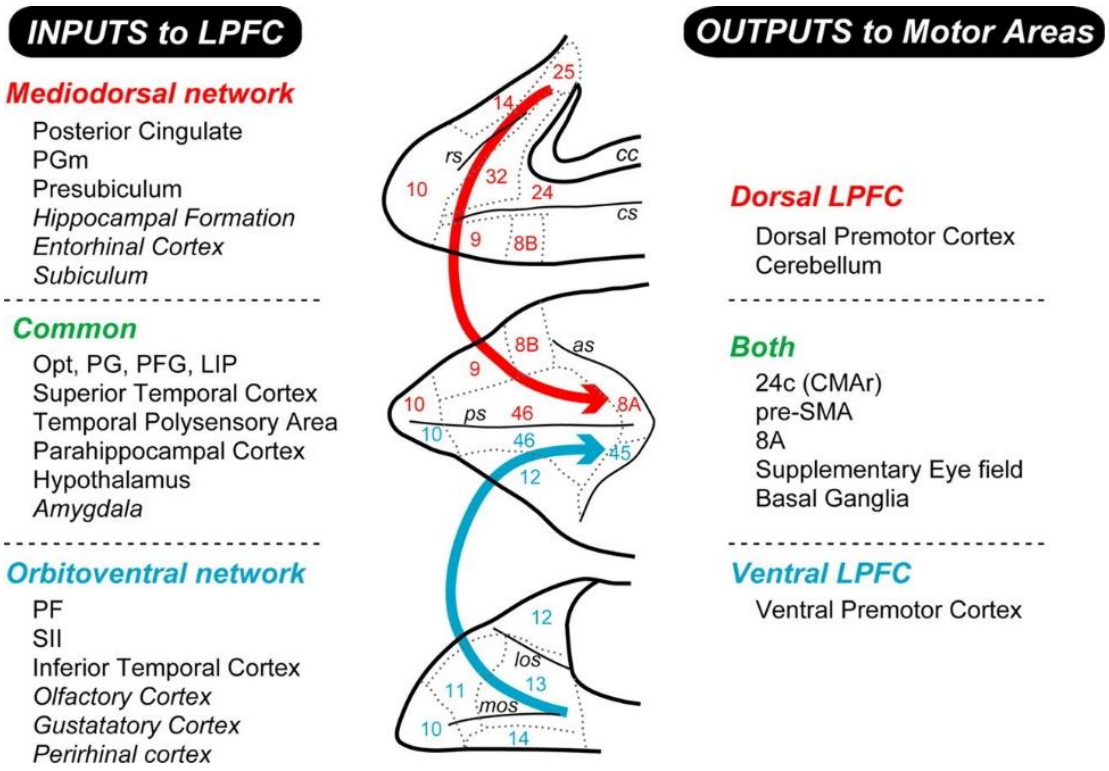

Figure 4: Schematic illustration of the cytoarchitecture of the prefrontal cortex and input-output organization of the lateral prefrontal cortex (LPFC). (Tanji & Hoshi, 2008). Rs, rostral sulcus; cs, cingulate sulcus; cc, corpus callosum; as, arcuate sulcus; ps, principal sulcus; mos, medial orbital sulcus; los, lateral orbital sulcus. PF, PFG, PG, PGm, and Opt are subareas in the parietal cortex (Pandya & Seltzer, 1982). SII, secondary somatosensory area; LIP, lateral intraparietal area; CMAr, rostral cingulated motor area; pre-SMA, pre-supplementary motor area.

In the middle column of figure 4, the middle panel shows the cytoarchitectonic boundaries of the LPFC (Walker, 1940). The top and bottom panels show the cytoarchitectonic boundaries of the medial and orbital prefrontal cortices, respectively (Carmichael & Price, 1994). The medial cortex (top panel) is shown upside down. In the orbital cortex (bottom panel), the midline is along the bottom. Rostral is to the left in all views. The red and blue arrows indicate the mediodorsal and orbito-ventral trend, respectively, of cytoarchitectonic differentiation, according to Barbas and Pandya (Barbas & Pandya, 1989). The red-colored areas in the medial prefrontal cortex and the dorsal LPFC

belong to the mediodorsal network and the blue-colored areas in the orbital prefrontal cortex and the ventral LPFC belong to the orbito-ventral network. In the left column, trends of inputs to these networks are summarized. Inputs are classified into three categories: areas preferentially projecting to the mediodorsal network (top), areas preferentially projecting to the orbito-ventral network (bottom), and areas commonly projecting to both networks (middle). Areas chiefly projecting to the orbital or medial prefrontal cortex, but less to the LPFC, are italicized. In the right column, trends of outputs from the lateral prefrontal cortex to major motor areas are summarized: areas to which the dorsal LPFC preferentially projects (top), areas to which the 39 ventral LPFC preferentially projects (bottom), and areas to which both parts of the LPFC project (middle). The LPFC is directly or indirectly connected with widespread structures in the brain through the mediodorsal and orbito-ventral networks. Additionally, the two networks are also extensively interconnected, and this organization allows the lateral prefrontal cortex to integrate multiple sets of information on a large scale, playing a fundamental role in collecting, integrating, sorting and modulating the diverse sets of "data" processed in other parts of the brain (Tanji & Hoshi, 2008; Preuss & Goldman-Rakic, 1989; Pandya & Yeterian, 1991; Petrides & Pandya, 2002). The LPFC is interconnected with premotor areas, the basal ganglia, and the cerebellum. Through these connections, the LPFC can control broad aspects of finalized motor behavior. Moreover, the LPFC modulates the flow of information in other areas of the central nervous system, in conforming to behavioral requirements, serving as a center for the control and sorting of information flowing through cortical and subcortical structures (Tanji & Hoshi, 2008).

1.6.3 Functions of the prefrontal cortex

Thanks to its extended interconnection with other cortical and subcortical areas, the prefrontal cortex has access to a diverse set of data regarding both the internal state of the subject and the external world, being therefore fundamentally involved in a broad spectrum of emotional and cognitive processes such as planning and temporal organization of actions (process in which the integration of

multisensory information plays a fundamental role), selection of appropriate behavioral responses in relation to the social context (included in the broader category of the executive functions), inhibitory control, emotion regulation and expression, attention, working memory (Barbas et al., 2003; Tanji & Hoshi, 2008; Gray et al., 2002). This broad spectrum of functions will be further exposed in the next paragraphs.

Sensory functions

Several studies demonstrated the presence of neurons in the monkey PFC that code visual (L. M. Romanski, 2007), acoustic (Sugihara et al., 2006; Genevieve&Petrides, 2007; Belmalih et al., 2009) and somatic (L. M. Romanski, 2007) stimuli. One of the regions most involved with the 41 processing of sensory stimuli is the ventrolateral prefrontal cortex, in that neural cells showing a strong response to visual stimuli have been found specifically in the pre-arcuate regions (including area 8/FEF) and in the lateral surface of the prefrontal convexity (Sugihara et al., 2006). Some neurons show a response to complex stimuli such as faces (O'Scalaidhe et al., 1997) or to the presentation of food in both visual and gustatory modalities (Thorpe et al., 1983a). The ventrolateral prefrontal cortex seems to be designated to the coding of others identity. Neurophysiological studies have in fact evidenced the presence of neurons in this region coding faces that are either static (O'Scalaidhe et al., 1997; O'Scalaidhe et al., 1999) or associated to congruent vocalizations (Sugihara et al., 2006; L. Romanski & Diehl, 2011). The latter response described is related to multisensory neurons specifically coding complex audiovisual communication stimuli, which activity is thus related to the presentation of a conspecific vocalization matched to the corresponding facial gesture (L. M. Romanski, 2007; L.Romanski& Diehl, 2011; Sugihara et al., 2006). In addition, other authors have found PFC neurons both during the presentation of visual and auditory stimuli and during the execution of motor tasks (Nelson& Bignall, 1973; Schechter & Murphy, 1975; Benevento et al., 1977; Ito, 1982). The evidence here described clearly the fundamental involvement of the prefrontal cortex, specifically LPFC (which receives multiples inputs from sensory areas and multimodal association areas), in the

integration and processing of multisensory inputs aimed to efficiently plan and execute behavioral responses appropriate to the context in which one operates and to the information available in it. This aspect will be further discussed later in this introduction.

Executive functions

The term "executive functions" refers to the processes that allow to set behavioral goals, plan, execute and monitor the output of a sequence of responses aimed to reach those goals and, if necessary, to modify ones behavioral responses in order to adapt it to a new situation and new conditions. This broad category included numerous coordinated "sub-processes" aimed principally at selecting actions appropriate to the context (and aimed to reach a specific goal). Neuropsychological data (among other evidences derived electrophysiological studies) allowed to localize executive functions in the prefrontal cortex, in that a lesion in this region determines the so called "*disesecutive syndromes*" which are characterized by significant deficits in elaborating a behavioral strategy in new or unusual situations.

Working memory

The term "working memory" refers to a system that allows us to acquire, memorize and manipulate information that are fundamental for the complex cognitive processes necessary to the control of behavior (Collette & Van der Linden, 2002). Although there is still no clear evidence about the specific localization of the central components of the working memory, it is possible to assume that a great part of the neural substrate that subserves this system is localized in the lateral prefrontal cortex. This assumption is based on electrophysiological studies performed on monkeys which provided evidence regarding the presence of neurons in the LPFC that are activated during the latency period that follows the presentation of visual (J. M. Fuster & Alexander, 1971; Funahashi et al., 1989; Di Pellegrino & Wise, 1993b; E. K. Miller et al., 1996) or acoustic (Bodner et al., 1996) cues

indicating the goal to achieve or the action to perform. On this matter, it seems that the dorsal LPFC is less likely to be involved on information storing and retention, being more likely more involved on the processing of information aimed at the correct execution of the task. Thus, it seems that the ability to store the information for a brief period of time is not essential for the functional role of the LPFC. The contribute of this region to the working memory system is most likely related to the processes involved in the control of behavior that operate at an abstract level with respect to the elaboration of single sensory inputs. Attentional modulation and control, interpretation and use of the instruction stored in the memory, selection of appropriate response, generation (through a series of trials) of a response model to guide behavior and interferences modulation are the working memory aspects in which LPFC seems fundamentally involved (Tanji & Hoshi, 2008).

Attention for action

The involvement of LPFC in the processes related to attentional modulation and control has long been known (Di Pellegrino & Wise, 1993a; Boussaoud & Wise, 1993; Wise et al., 1997). The prefrontal cortex plays an essential role in orienting attention in order to efficiently code relevant information for the current behavior, thus filtering irrelevant signals (Desimone,1996; E.K.Miller etal.,1996;Lumer et al.,1998; E. K. Miller & Cohen, 2001). These results are congruent with a top-down "model" in which the attentive processes, controlled by the frontal cortex, modulate the activity of posterior areas in order to promote the flow of information relevant for the goal directed action to perform (Pessoa&Desimone, 2003; B. 45 T. Miller & D'Esposito, 2005), blocking those that are irrelevant. The role of LPFC in maintaining the attention "fixed" on an object, rather than maintaining the object in memory, has been reported in fMRI studies in human subjects (Rowe & Passingham, 2001; Lau et al., 2004); However, it is difficult to pinpoint the different components of this cognitive process in specific anatomical areas (Nagahama et al., 2001).

Preparatory set and regulation of cross-temporal contingencies

The idea that the general function of the LPFC is the temporal organization of behavior is a traditional concept (Jacobsen, 1935; Pribram & Tubbs, 1967; Milner & Petrides, 1984) that has been re-emphasized by authors such as Fuster (J. M. Fuster, 1997). The preparatory set is a prospective cognitive function that specifies the occurrence of a forthcoming action with a proper timing and order; it regulates the temporal relations between the occurrence of different events and action, that is, it regulates the cross temporal contingencies (J. M. Fuster & Alexander, 1971; Fukushima, 2003). Considering the results of a study carried out by Fukushima, the representations of temporal contingencies may be updated in agreement with the instructions used to reach a specific goal (Fukushima, 2003). Genovesio and collaborators (2006) observed that two distinct group of PFC neurons coded preceding or future goals. It has been demonstrated that the interaction between PFC and the inferior temporal cortex plays a crucial role in associating a visual stimulus with an action during a visuomotor task (Bussey et al., 2002) and in strategy implementation in which the subject could maximize the gain in terms of reward by following a planned way to make a choice of objects (Gaffan et al., 2002). These results indicate that PFC has a central role in defining the temporal relations that occur between actions or, in general, between relevant events, in accordance with the current behavioral context (Tanji & Hoshi, 2008).

Behavioral vs motor planning

The fact that a substantial part of the prefrontal cortex neurons are involved in preparing a movement has received significant support from studies that examined the neural activity of LPFC (Boch & Goldberg, 1989; Requin et al.,1990; Sakagami & Niki,1994; Iba&Sawaguchi, 2003). Until recently, the results of several studies led to the consolidation of the idea that neurons in the LPFC play a considerable role in preparing or planning an intended movement. White e Wise (White & Wise, 1999) demonstrated that the movement related activity of LPFC neurons, as well as the activity related to the presentation of instructional cue signals or to the delay periods, were significantly

modulated by the rule guiding the experimental paradigm. Thus, it is possible that behavioral factors not directly relevant for the specification of motor variables constituting the planned movement (such as the motor parameters) are the principal elements processed by the PFC, which may not be involved in the specification of "characteristics" of the movements. In a series of studies aimed to solve this issue, monkeys were trained to move a cursor on a video monitor by operating two manipolandums with either hand (Mushiake et al., 2006). The instruction given indicated the final position to be occupied by the cursor; the results of these studies indicate that for a great part of the neurons recorded in PFC, the activity during the period of movement preparation reflected the movement of the cursor (or its localization) on the screen, but not the movement to execute (for example which hand was used or the direction of the movement). The neurons recorded primarily represented the movement of an object that would result from the finalized movement of the limb, rather than the limb movement parse. These results suggest the possibility that the planning of motor behavior in the PFC is generally executed in terms of an end result, which occurs as a consequence of an action, rather than in terms of motor parameters and selection of movements.

Reward expectancy and reward-based control of behavior

Other than the orbito-frontal cortex, which represents the primary and most studied reward coding region (Rolls, 2000; Thorpe et al., 1983b), it has been observed that there are neurons in LPFC whose activity is modulated by the reinforcers (Niki & Watanabe, 1979; Rosenkilde et al., 1981; Ono et al., 1984). Watanabe (1996) found that the activity of LPFC neurons during a delay period reflected not only reward expectancy but also the reward type. Both the orbito-ventral and dorsolateral portion of the PFC present neurons encoding reward quantity, while neurons modulated by reward expectancy and reward quality seem to be localized only in the dorsolateral portion (Tremblay & Schultz, 1999; Hollerman et al., 2000). Furthermore, it has been described that neuronal activity in the LPFC could also reflect the discrepancy between the expectancy of a specific reward and the reward obtained (Leon & Shadlen, 1999). These results appear to be congruent with the hypothesis that the orbito-

frontal cortex codes primarily the reward per se, while LPFC uses reward related information to control behavior Kobayashi and collaborators (Kobayashi et al., 2002) conducted further studies in which they verified that the information processing in the LPFC differs depending on whether the expected reward following the execution of a behavior is positive or negative.

Response inhibition

Dias and coll. observed that lesions of LPFC in monkeys caused the loss on inhibitory control in attentional selection, while lesions of the orbitofrontal cortex caused the loss in inhibitory control of affective processing (Dias, et al., 1996). In human subjects, LPFC lesions are associated with deficit in performing the Wisconsin Card Sort Test (WCST). A following fMRI study highlighted that the area, localized in VLPFC, active during the process of set shifting (thus during the WCST) coincided with the area active during a No-Go response (Konishi et al., 1999), suggesting that VLPFC could be involved in the inhibition of different targets (the go response in the latter tasks and the cognitive set during WCST). These findings indicate the presence of multiple inhibitory mechanisms in the LPFC.

1.7 Ventrolateral prefrontal cortex

1.7.1 VLPFC and action execution

The activity of VLPFC neurons has been analyzed during a Go-No Go task in which the monkeys were required to observe or execute grasping actions in different conditions (Simone et al., 2015). At the beginning of each trial (excluding the blocked motor and naturalistic conditions), a cue was turned on, indicating the monkey which condition to perform: a red LED instructed the monkey to fixate the object during the whole task, a green LED instructed the monkey to reach and grasp the presented object. Subsequently, while the LED was still on, the object was presented to the monkey. The LED was then turned off, indicating the monkey to either execute a grasp or maintain fixation. The grasping actions were executed in different conditions: the object to be grasped could be either illuminated

(motor condition), thus allowing the execution of a visually guided action, or not (dark motor condition), in which case the action was executed without visual control. In the blocked motor condition, the object was not presented during each trial, but only at the beginning of each block of trials. In this case, the monkey after the green LED was turned off, had to grasp the object under mnemonic guidance. Two naturalistic condition, grasping in light and in dark, were added to better evaluate the properties of the neurons studied in the motor conditions. In the grasping in light condition, the experimenter presented a piece of food to the monkey, who freely reached for and grasped it. In the grasping in dark condition, the monkey was prevented from seeing the scene, and the food was introduced near the monkey in a fixed position, so that it could know the position of the food to be grasped. The authors found that a sector of the VLPF cortex hosts neurons that are active during the execution of goal-directed reaching-grasping actions. These movement-related neurons were typically activated both with and without visual control of hand-object interaction, when the object had to be grasped under mnemonic guidance and in a naturalistic context in the absence of learned rules. Some of them were active during object presentation, generally discharging more strongly when the object had to be grasped rather than simply observed. Finally, although some movement-related neurons showed a preference for a grip type, none of them showed selectivity during object presentation. This study demonstrated that movement-related neurons are activated during grasping in different behavioral situations (grasping under visual control, grasping in darkness, memory-guided grasping, and simple grasping of food), indicating that VLPF neuronal activity is not necessarily dependent on the learned relationship between instruction and motor output. Many of these neurons displayed a response during task epochs preceding movement execution, in line with several studies showing that the VLPF cortex employs information about the visual context to generate goals by forming associations between cues and goals (White & Wise, 1999; Asaad et al., 2000; E. K. Miller, 2000; Wallis et al., 2001). A high percentage of movement related neurons responded during set (250 ms before the offset of the cue) and/or go (from the offset to the release of the hand) epochs, in agreement with studies describing the role of the 56 VLPF cortex in movement

planning (Quintana & Fuster, 1992; Funahashi et al., 1993; Averbeck et al., 2002; Shima et al., 2007; Yamagata et al., 2012). Among those, many show prolonged differential activity starting from object presentation. This discharge is not affected by the different contextual conditions (Motor condition in light and darkness; Blocked Motor condition), as shown by the population analyses, and could thus represent a type of preparation related to object "*graspability*" or the maintenance of action goal representation. This supports the idea that the VLPF cortex could play a role in action planning and execution, extending this role to the case of natural actions. It has been proposed that neurons found in this study play a role in a wider network subserving grasping action, given the connections of the VLPFC sector analyzed in this study with parietal and premotor areas involved in higher hand motor control (Petrides & Pandya, 1999; Borra et al., 2011; Yeterian et al., 2012; Gerbella et al., 2013). From a functional point of view, the neurons described in this study show similarities but also differences with parieto-premotor neurons. In the sector of the VLPF cortex from which movement-related neurons were recorded, there are many fewer grip-selective neurons than in premotor area F5 and the anterior intraparietal (AIP) area. Furthermore, the response to object presentation of prefrontal grip-selective neurons is not object-specific, and thus lacks the basic prerequisite for establishing congruence between visual and motor preference that is typical of canonical neurons of F5 and object-type neurons of AIP (Murata et al., 1997; Murata et al., 2000; Raos et al., 2006). In addition, most VLPFC movement-related neurons are not affected by the absence of visual control during action execution. This evidence supports the idea that VLPF movement-related neurons, unlike parietal and premotor grasping neurons, are not involved in coding visuomotor transformations or in the visual control of hand-object interactions, but, rather, appear to encode the action goal and, partly, the way to achieve it (Simone et al., 2015).

1.7.2 VLPFC and action observation

Several studies have described the presence of neurons in the VLPF cortex of macaques responding to the observation of actions performed by others (Nelissen et al., 2005; Falcone et al.,

2016; Sliwa & Freiwald, 2017; Simone et al, 2017), suggesting that this region could be part of a broader network activated during action observation, being specifically involved in "social information processing", that is the processing of cues provided by others behavior during interaction, fundamental for selecting and executing an appropriate response. Simone and collaborators (2017) investigated VLPFC neurons response to biological movements and object motion using a paradigm in which the monkeys were required to observe six different types of videos depicting different scenes with varying agents and perspectives: A monkey grasping a piece of food seen from a first (Monkey Grasping I, MGI) or third (Monkey Grasping III, MGIII) person perspective, a human actor (seen from a lateral view) grasping (Human Grasping, HG), or mimicking to grasp (Human Mimicking, HM) or extending his forelimb in front of himself (Biological movement, BM), and the motion of an object (Object Motion, OM). The experiment also included a modified version of the task in which the first or the second phase of the videos showing goal directed or mimicked actions could be partially obscured, allowing to compare the neuron response recorded during the observation of the masked action was with that obtained during the observation of the non-masked stimuli. The results of this study showed the presence of VLPF there are neurons responding to observation of biological movements performed with the forelimb, a majority of which showed a stimulus-specific activity, responding best or exclusively to one of the presented stimuli (HS). Most of these selective neurons presented their strongest discharge during observation of goal-directed actions: the most effective were those performed by a conspecific, while a lower number of neurons responded to human goal-directed actions. Most tested neurons (2/3) did not change their activity when the action was obscured, suggesting that visual information was not the crucial aspect of their coding. As suggested by Umiltà and collaborators (2001), the permanence of the response during the obscured phase could be interpreted as the generation of an internal motor representation that includes the action outcome. This response thus suggests that neurons in this area code high order representation of the observed action rather than a simple visual description of it. Furthermore, several VLPF cortex neurons tested in this study discharge also before movement onset. This behavior could indicate that these neurons

are able to "predict" the type of action the agent is going to perform and its outcome. In this way, based on the context, the monkey could try to interpret other's actions even before their beginning and use it for planning its behavior. In conclusion, the VLPF cortex seems to play a fundamental role in the planning, organization and selection of behavioral output based on cues provided by the social environment, that are processed at a higher order level compared to the parieto-premotor areas. Furthermore, besides having a role in the processing of abstract information finalized to accomplish a specific task, this region seems to use contextual cues to plan and guide behavior responses also in natural situations. In fact, some authors have found neurons encoding both self and another agents past and future goal during human- monkey interactions (Falcone et al., 2016) or specifically responding to the observation of an interaction between conspecifics (Sliwa & Freiwald, 2017), indicating that the VLPF cortex of macaques is involved in monitoring others choices, evaluating their past goals and predicting their future goals in relation to self-past and future goals, in order to generate an appropriate response to others actions or intentions during the interaction in the natural environment.

1.8 The basal ganglia

According to recent anatomical data (Gerbella et al., 2015) most of the above-mentioned areas forming the cortical MN network (i.e., area AIP/PFG, PMv, and VLPF) convergently project to specific regions of the putamen, a nucleus of the basal ganglia (BG) with well-established motor properties (Figure 5). Although the presence of MNs in the BG has not been proved yet, these anatomical data and some previous functional evidence in humans (Alegre et al., 2010; Kessler et al., 2006) strongly suggest that the BG should be included in an extended cortico-subcortical MN network (see Caligiore et al., 2013), and they should be implicated in MNs' functioning (Bonini, 2017).

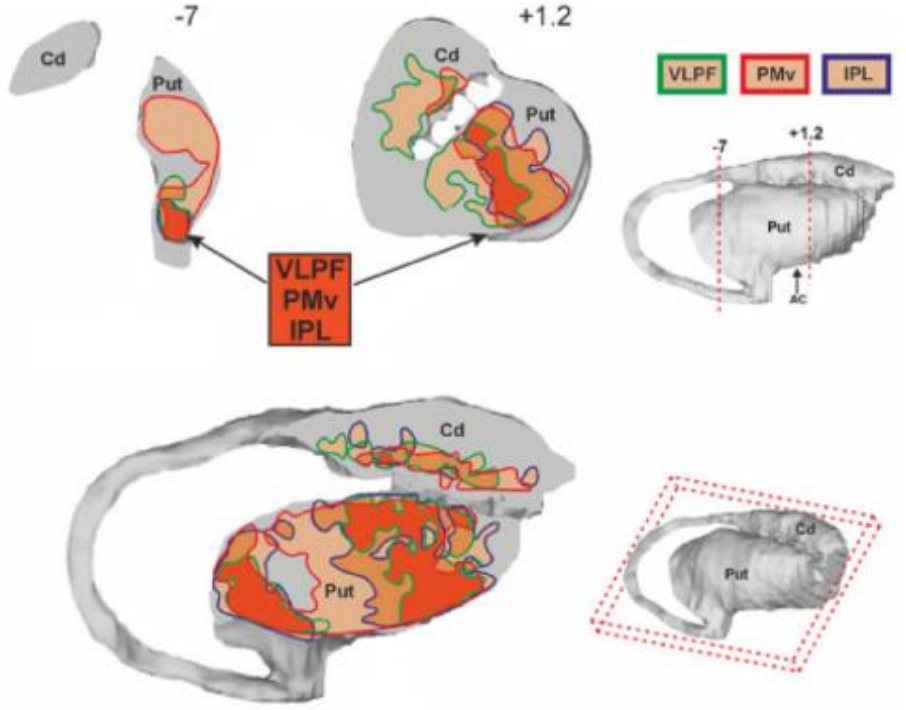

Figure 5. Territories of the BG receiving projections from the areas belonging to the cortical MN network, namely, PMv (sector with red borders), IPL (blue borders), or VLPF (green borders). The light and dark orange shadings highlight the BG sectors in which two or even all of these three distinct sources 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 (Gerbella et al., 2016).

The BG and related nuclei (Figure 6) consist of a variety of subcortical cell groups whose involvement is primarily in motor control, as well as in motor learning, executive functions and emotions (Grillner and Robertson, 2016). The BG nuclei are embedded deep in the brain hemispheres (striatum or caudate-putamen and globus pallidus), whereas related nuclei are structures located in the diencephalon (subthalamic nucleus), mesencephalon (substantia nigra), and pons (pedunculopontine nucleus) (Lanciego et al., 2012). They can be commonly categorized as input nuclei, output nuclei, and intrinsic nuclei.

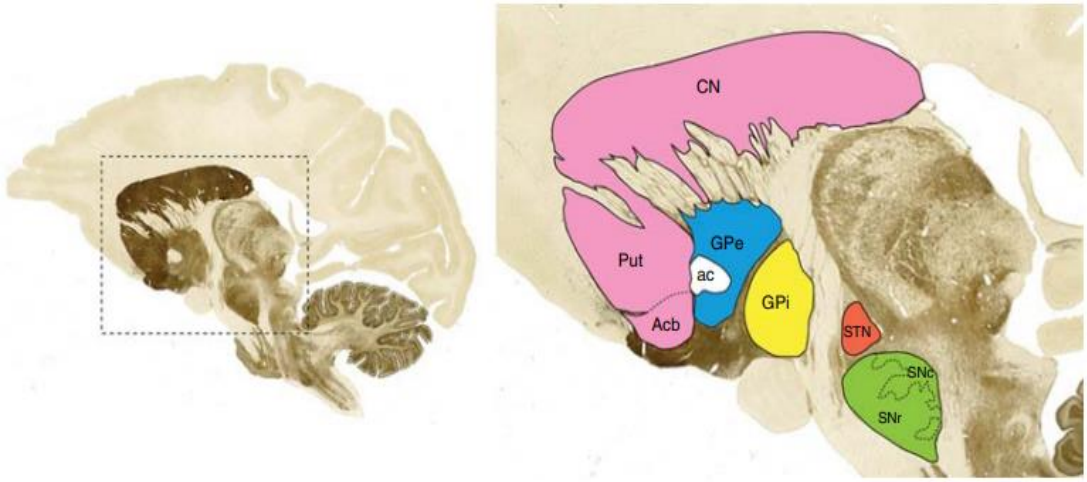

Figure 6. **Basal ganglia nuclei.** Parasagittal section through the monkey brain (stained with the acetylcholinesterase method) showing the localization and boundaries of all major components of the basal ganglia system. Figure from (Lanciego et al., 2012).

Input nuclei are the caudate nucleus (CN), the putamen (Put), and the accumbens nucleus (Acb) and they receive incoming information mainly from cortical, thalamic, and nigral structures. The output nuclei consist of the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (Snr) and they send information to the thalamus. Finally, intrinsic nuclei such as the external segment of the globus pallidus (GPe), the STN and the substantia nigra pars compacta (SNc) act as relay sites in the input-output stream. Cortical and thalamic efferent information reaches the striatum (CN, Put, and Acb) to be elaborated further within the basal ganglia system. The output nuclei (GPi and SNr) project mainly to the thalamus (ventral nuclei), which, in turn, project back to the cerebral cortex (mainly frontal lobe). The proper functioning of the whole BG system is ensured by dopamine released at the input nuclei. After briefly describing the anatomical organization of the BG, the functional one will follow.

1.8.1 Functional organization of basal ganglia: the canonical model

The functional organization of the BG formulated in the 1980s to understand the pathophysiology of movement, established that neuronal signals from the cortex flow to the striatum, through the GPi and SNr, and project back to the cortex via the thalamus, forming parallel cortico –basal ganglia – thalamo –cortical loops. The main assumption of the model concerned the opposite functional effect on BG output of direct and indirect striato-pallidal projections (Albin et al., 1989; DeLong, 1990) (Figure 7).

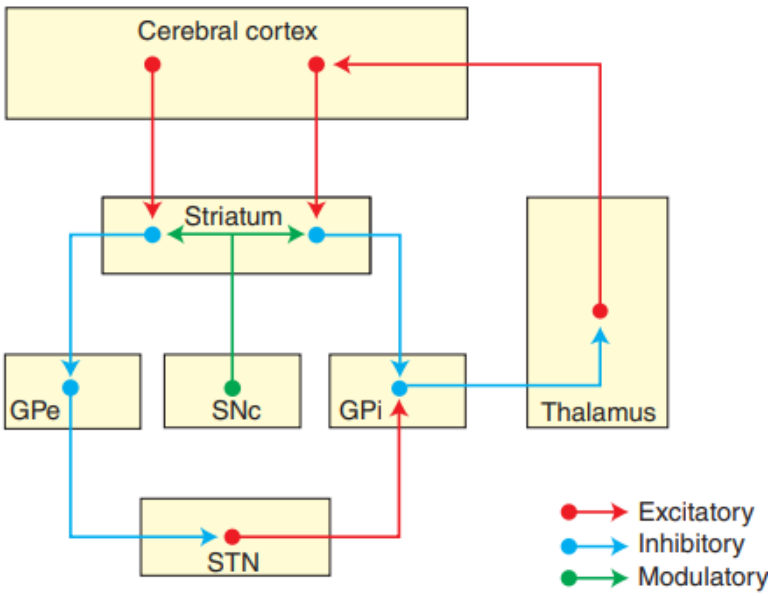

Figure 7: **Schematic summary of the original basal ganglia model**. The motor circuit is composed of a corticostriatal (putaminal) projection, two major striatofugal projection systems giving rise to the direct and indirect pathways, and the efferent pallido – thalamo – cortical projections to close the motor loop. The thickness of arrows represents the functional state of a given circuit. Thicker arrows illustrate hyperactive pathways, whereas thinner arrows represent hypoactive circuits. Figure from (Lanciego et al., 2012).

In accord with this model, different BG territories encode and process different functional information throughout distinct territories of the BG output structures (GPi and SNr) and back to specific cortical areas by the thalamus. This model further suggested BG involvement in cognitive and motivational functions. This revolutionary model of cortico-BG network organization was also strengthened by nonhuman primates anatomical data using rabies virus tracing (a retrograde trans-

synaptic tracer) that showed: (1) the BG output pathways to the cortex are truly organized in distinct parallel circuits, where different functional domains could be processed independently, and (2) the BG output pathways indeed project to the motor cortex, but also to the prefrontal cortex related to cognitive and motivational information processing (Tremblay et al., 2015).

To sum up, the BG and cortical regions together constitute a loop, in which the former are featured as a "go through" station within the motor loop, aimed at facilitating (or inhibiting) motor activity. By the way, now this model is out to date.

1.8.2 Functional Subdivisions: Basal Ganglia Domains

Current thinking has modified the functional model mentioned above on several fronts and in fundamental aspects. It is now known that the basal ganglia have several loops, where cortical and subcortical projections interact with internal reentry loops forming a complex network, ideally designed for selecting and inhibiting simultaneously occurring events and signals (Lanciego et al, 2012).

Based on their projection to specific areas, the BG are functionally subdivided into motor, associative, and limbic/emotional domains. Indeed, advances knowledge in this field (besides motor control) allowed a better appreciation of other functions, such as attention and time estimation, implicit learning and habit formation, reward-related behavior and emotions, all of which are associated with the activation of cortical loops that connect with the caudate or putamen nuclei (Hikosaka et al., 2002; Buhusi and Meck, 2005; Yin and Knowlton, 2006).

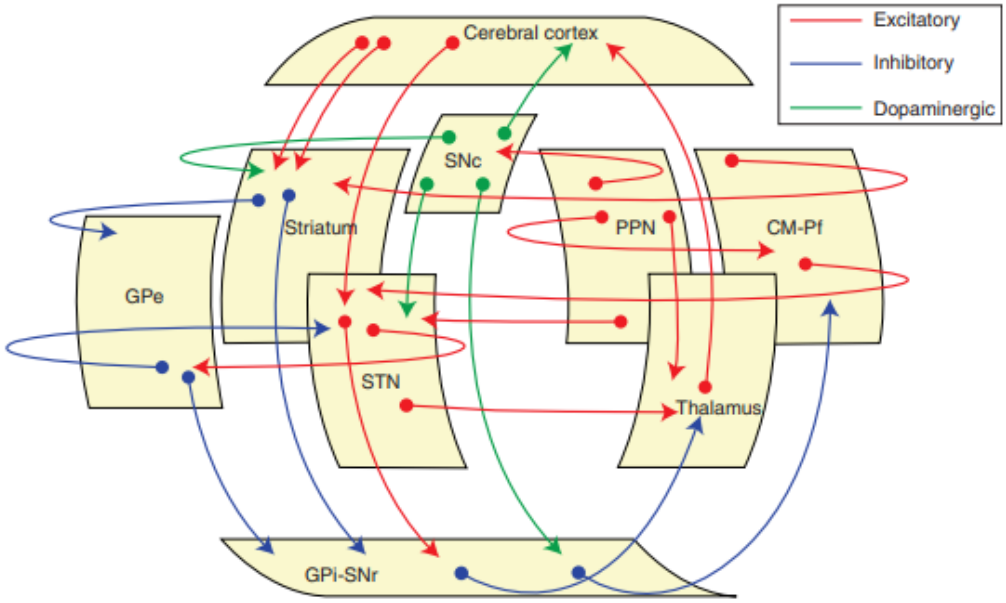

Figure 8: **Basal ganglia circuits**. Cartoon showing the main circuits linking the basal ganglia nuclei. Besides traditional cortico-basal ganglia-thalamocortical circuits, several transverse loops have been described in the last few years, most of them with a putative modulatory role. Figure from (Lanciego et al., 2012).

It is possible to conceive the BG network as a set of multiple, parallel loops and reentering circuits, through which motor, associative, and limbic regions are involved in controlling movement, behavior, and emotions. According to this model, the same basic architectural and functional organization underlies (1) selection and facilitation of prefrontal-striato-pallidal activity during the performance and acquisition of new activities and tasks (goal directed system); (2) reinforcement learning to create habitual responses automatically performed by the motor circuit (habit system); and (3) stopping an ongoing activity and switching to a new one if necessary, which is mainly mediated by the inferior frontal cortex/STN cortical circuit (Lanciego et al., 2012).

At this point, given the variety of data discussed so far, it is necessary to dwell more in depth on the current literature about putamen, in order to finalize the theoretical background of the present study.

1.8.3 Putamen: somatotopy and functional proprieties

The putamen (Put), together with the globus pallidus, constitutes the lentiform nucleus and with the caudate nucleus, it forms the striatum (Ghandili and Munakomi, 2020) (Figure 9). Ontogenetically (in humans) it develops by the end of the fifth week of gestation after the prosencephalon differentiates to the diencephalon and the telencephalon, when the latter gives rise to the components of the BG (Mortazavi et al., 2014).

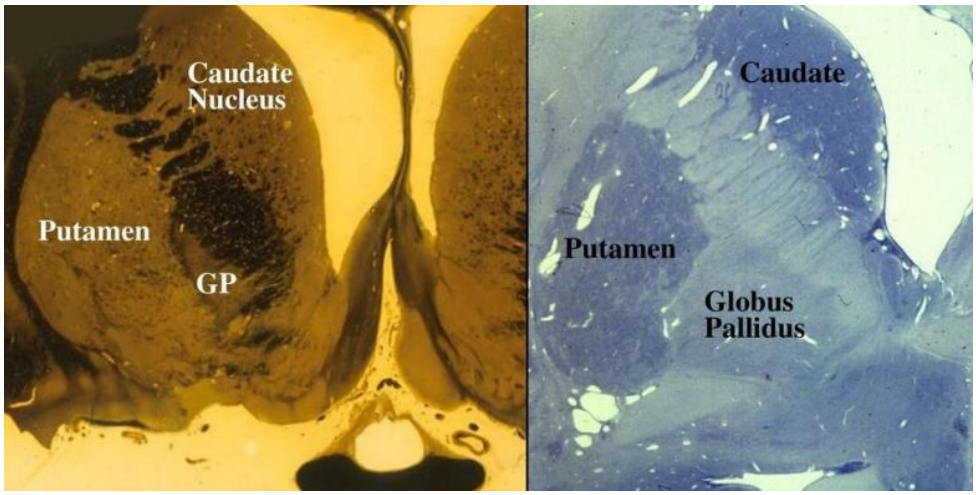

Figure 9. **Striatum: Caudate Nucleus and Putamen, GP Globus Pallidus also visible** (Left). In a Nissl-stained section the caudate and putamen are seen as histologically the same structure, separated by the anterior limb of the internal capsule (Right) Figure from Leichnetz.

The striatum is accounted for the primary input site of the BG with the subthalamic nucleus as well. Both these nuclei receive most of their afferent projections from the cortex and send efferent projections to the nuclei of the BG, the internal globus pallidus or the substantia nigra pars reticulata (Mannella and Baldassarre, 2015). Moreover, the Putamen in primates corresponds widely to the "motor" section of the neostriatum (Alexander, 1987). Takada and coworkers (1998a, b), injecting anterograde tracers showed that the forelimb region of M1 projects chiefly to the lateral part of the Putamen, while that of SMA projects mainly to the medial one. Futhermore, they indicated that the terminal zones from M1 and SMA partially overlap in the Putamen, particularly in its mediolateral central zone. It is yet to unveil if inputs from M1 and SMA converge onto the same neurons or not

(Nambu, 2002). Based on somatosensory responses, evoked movements by microstimulation (Alexander and DeLong, 1985a, 1985b), neuronal activity related to movements (Crutcher and DeLong, 1984), and corticostriatal projections (Kunzle, 1975; Liles, 1975; Takada et al., 1998a, 1998b), it was possible to define the somatotopic organization of the Putamen (Figure 10).

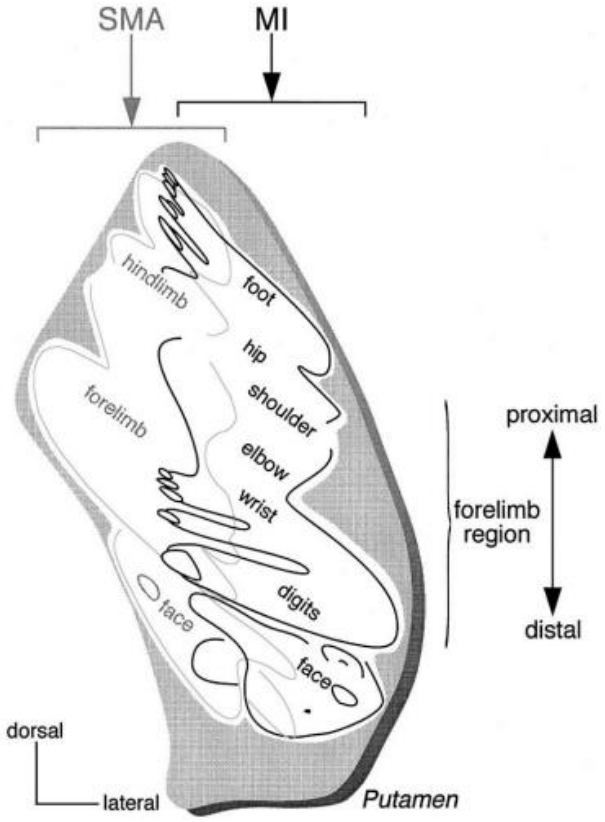

Figure 10. **Somatotopic organization of the Putamen according to cortical motor inputs from the M1 and SMA**. Drawings in black lines represent somatotopically arranged cortical inputs from the M1, whereas those in gray lines roughly represent somatotopic inputs from the SMA. Inputs from both the M1 and SMA converge onto the mediolateral central part of the Putamen. There is a distal-proximal somatotopic organization in the M1- and M1 SMA-recipient forelimb regions. Figure from (Nambu et al., 2002).

It shows a dorsolateral to ventromedial topography of representations from hindlimb to face, with the representation of the forelimb in an intermediate region. Data from the existing literature report that activity of Putamen neurons depends on movements of the limbs and other body parts, with laterally and medially located neurons firing differently in relation to distinct aspects of motor behavior (Alexander and Crutcher 1990a, b; Liles, 1983). Simple movement activate lateral portions of the Putamen, while complex movements are related to activity in medial ones, which could be due

to different cortical inputs of these regions (M1 vs. SMA, respectively) (Nambu, 2002).

Furthermore, similar differences in terms of activity modulation between medial and lateral parts of the Putamen are related to different aspects of motor tasks. Findings coming from animal research are in line with those arising from functional magnetic resonance imaging (fMRI) studies in humans, which showed topographical segregation according to the requested task and underlying functions. Indeed, Lehericy and coworkers (2005) reported that the execution of previously learnt movements correlated with activity in the posterior (i.e., sensorimotor) putamen and that this region presented a somatotopical organization, with the leg lying dorsal, face ventral, and arm in between (Figure 11). Moreover, changes of activity have been observed in the basal ganglia at different stages of the acquisition of motor abilities. In this study fourteen right-handed healthy volunteers had to practice 15 min daily a sequence of eight moves using the left hand. MRI sessions were performed on days 1, 14 and 28. In both putamen, activation decreased with practice in rostrodorsal (associative) regions. In contrast, there was a significant signal increase in more caudoventral (sensorimotor) regions of the putamen.

The results suggest that there was a dynamic shift of activation from the associative-premotor to the sensorimotor territories of the striato-pallidal complex during sequence learning. The associative cortico–basal ganglia circuit is thus believed to be engaged at the beginning of learning and to contribute to the acquisition of an accurate representation of the sequence, whereas the sensorimotor circuit is thought to maintain a speedy representation of that skill when it is well learned and has become automatic.

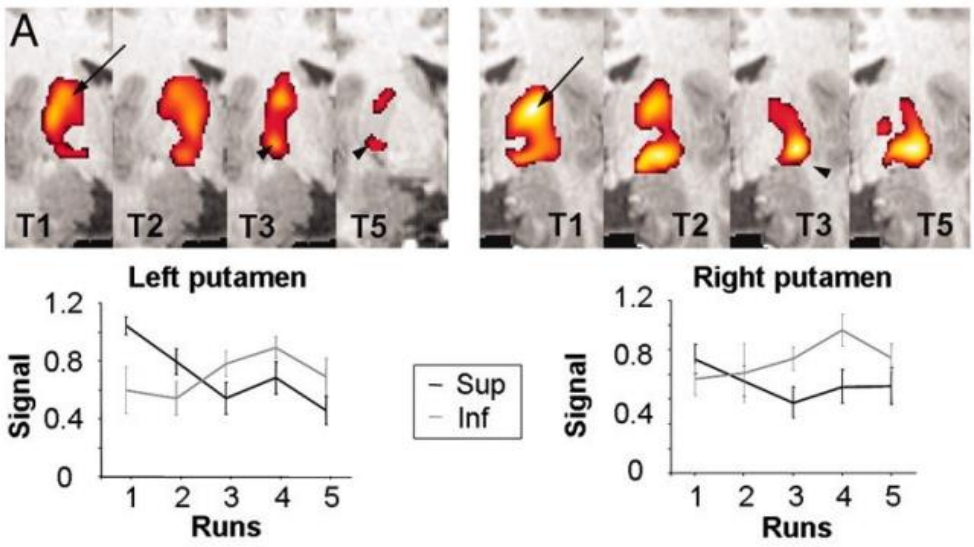

Figure 11. **Activation patterns in the basal ganglia**. (A Upper) Activation maps obtained in the putamen. There was a progressive activation decrease in the dorsal part of the putamen (arrows) and an increase in a more ventrolateral area (arrowheads) bilaterally, which persisted after 4 weeks of training. (Lower). Figure from (Lehericy et al., 2005).

1.9 Hypothesis and aim of the study

The literature described above indicates that the parieto-frontal regions containing MNs are connected both to specific areas of the VLPFC, namely areas 46v and 12r, and to specific sectors of the putamen, suggesting that also these territories can be involved in encoding of actions made by others. In addition, areas 12r and 46v are known to play a fundamental role in guiding behavior based on the contextual cues available as well as to processes many typologies of visual information, such as observation of actions, also during simple passive task in which the monkey is not required to use this information to guide behavioral responses (Nelissen et al., 2005; Simone et al., 2017; Falcone et al., 2016; Sliwa & Freiwald, 2017, Rozzi & Fogassi, 2017). Therefore, one can hypothesize that the prefrontal cortex exploits social information in order to guide one's own behavior. This function requires the integration of the prefrontal cortex with other nodes of the MN system, and in particular of the premotor area F5 and basal ganglia. The specific role of these regions of the network in this general function is at present largely unknown.

To address these issues, in the present study we recorded neural activity simultaneously in prefrontal areas 46v and 12r, in premotor area F5 and in the sectors of BG connected to these cortical areas, during a task in which abstract and biological cues are used to guide.

More in details, we aim to verify whether and to what extent the different recorded territories can exploit to guide actions information related:

a) to the presence/absence of biological information about others' actions;

b) to stimulus-response association, regardless of their visual features;

c) to the general rule instructing behavior.

2. MATERIALS AND METHODS

One female rhesus monkey (Macaca mulatta), weighing about 7 kg, aged 11 years was used in the present experiment. The animal handling, and the surgical and experimental procedures, complied with European guidelines (2010/63/EU) and Italian laws in force on the care and use of laboratory animals, and were approved by the Veterinarian Animal Care and Use Committee of the University of Parma (Prot. 78/12 17/07/2012, and Prot. 91/OPBA/2015) and authorized by the Italian Health Ministry (D.M. 294/2012-C, 11/12/2012 and 48/2016-PR,20/01/2016).

2.1 Surgical procedures

We planned to record neural activity from the hand field of ventral premotor area (F5), from the region of ventrolateral prefrontal cortex (VLPF), from which movement related neurons have been recorded (Hoshi et al. 1998; Simone et al. 2015) and from the putamen sector. In the putamen we aimed to implant in the sector classically considered as “motor putamen” (Alexander, 1987) and recently described as anatomically connected with the VLPF and F5 (Gerbella et al., 2016). The F5 hand sector is located just ventral to the spur of the arcuate sulcus and extends over the cortical convexity and in the posterior bank of the inferior arcuate sulcus (Rizzolatti et al., 1996). The prefrontal region is a quite large sector of VLPF extending over two anatomic fields that are part of the "lateral grasping network" (Gerbella et al 2013; Borra et. al 2011, Borra et al., 2017: Rozzi and Fogassi, 2017). More specifically, this cortical region includes the caudal part of area 46 ventro-rostral (cPF) and the intermediate sector of area 12r (rPF). Considering the basal ganglia region, according to Gerbella and coworkers (2016), we adopted a stereotaxic vertical approach aiming at three different AP levels calculated respect to the anterior commissure (AC). The planned locations were in correspondence of the anterior commissure (AC0), 2 mm rostral (AC+2), and 3 mm caudal to it (AC-3). On the medio-lateral axes, based on the MRI the coordinate was +13 for AC+3, +14 for AC0 and +15 for AC-3. Before surgical procedures, the monkeyunderwent a MRI scan with a General

Electric 7-T tomograph, under general anesthesia (described below). The MRI scan allowed identifying the anatomical reference points and to calculate the position on the brain of the planned stereotaxic coordinates. Figure 12 shows the planned location of the cortical and BG recording devices on a 3D reconstruction of the frontal lobe and on three selected coronal slices based on MRI.

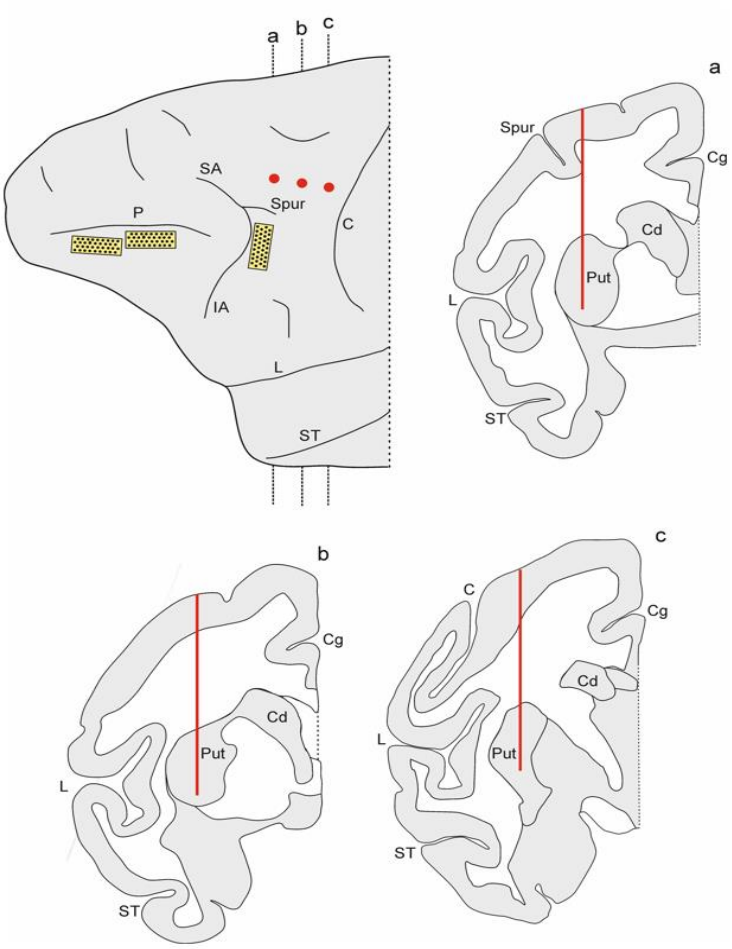

Figure 12: **Anatomical location of recording devices**. Upper part-left: drawing of the 3D reconstruction of the left frontal lobe of the monkey based on the MRI scan. The yellow rectangles represent the location of the cortical arrays and the black circles on them indicate the electrodes spacing; the red dots indicate the penetration site through which the BG probes were inserted. a,b,c represent coronal section taken at the homologue location shown on the 3d reconstruction. In each coronal section, the red line represents the planned position of recording probes. C: central sulcus; Cd: caudate nucleus; Cg: cingulate sulcus; IA: inferior arcuate sulcus; L: lateral fissure; P: principal sulcus; Put: Putamen; Sa: superior arcuate sulcus; ST: superior temporal sulcus;

All surgical procedures were carried out under general anesthesia. Specifically, the anesthesia was preceded by the administration of Atropine, 0.03 mg/kg i.m., followed after about 10 minutes by

sedation with i.m. injection of Ketamine hydrocloride, 5-10 mg/kg and Medetomidine hydrocloride, 40-60 μg/kg. An intravenous catheter was then placed for administration of isotonic solutions (NaCl 0.9% saline 3-5 ml/kg/h). Induction of general anesthesia was performed with sodium thiopental 1.25% at a dose of 1-3 mg/kg i.v. General anesthesia was maintained with isoflurane vaporized in oxygen after orotracheal intubation with Magill's tube. General anesthesia was followed by postsurgical antibiotic and pain medications (Fogassi et al., 1996; Rozzi et al., 2006).

2.2 Training and Experimental Apparatus

Before recordings, the monkey was habituated to sit comfortably in a primate chair, to interact with the experimenters, and to become familiar with the experimental setup. Subsequently, the monkey was trained to perform the tasks described below, using the right hand.

During training and recording, a headband was fixated to the primate chair, in which the monkey was previously seated, and then attached to the head-fixation system. In front of the monkey a shelf (80x60cm) was placed, at the level of the abdomen. Above this shelf, at about 6 cm from the monkey's chest, there was an aluminum cylinder, which constituted the starting position. At 26 cm from the chest of the monkey there was a transparent plexiglass box hosting on top an aluminum sphere (diameter 1 cm), centered with respect to the box. Behind the box, at 34 cm from the chest of the monkey, a 19-inch screen with a resolution of 1440 x 900 pixels was placed. The aluminum cylinder and sphere were connected to two different contact detection circuits. The plexiglass box contained a LED which could produce a green or red light, serving as an instructive cue relative to the type of task to perform, and a photodiode, i.e., a device that converts light into an electrical signal, that allowed to accurately detect the onset and offset of the stimuli presented on the monitor. Above the monitor there was an infrared camera (resolution 120Hz), connected to a dedicated computer, part of the ISCAN ETL-200 system (I-scan inc., Cambridge, MA, USA; 120hz). This system allows to constantly monitor the eye's position. On the right side of the monitor a laser device was located, that could

project a light beam into the center of the screen, used as fixation point. Before beginning each training and recording session, a cannula was placed near the mouth of the animal to administer fruit juices or water, to reinforce correct trials.

Eye position calibration

To precisely assess the eye position, it is necessary to make a preliminary calibration of the instrument. The calibration procedure, repeated at the beginning of each training and recording session, consisted in presenting a set of five light points, at the center and in the four corners of a virtual 10 x 10 degrees square window.

The position of the pupil was detected and recorded following the fixation of each presented individual point. At least 16 acquisitions per point were performed, after which the software automatically calculated the average and standard deviation of the recorded signal, in volts. Based on known parameters (i.e., the distance between the eyes and the monitor and the distance among copies of the presented points) the signal acquired by the oculometer can be transformed into eye position, expressed in degrees with respect to the center of the screen/fixation point, by a program created *ad hoc* in the Lab View environment. Subsequently, an 8 x 8 degrees window, inside which the monkey had to keep fixation during the task, was defined around the central fixation point.

2.3 Stimuli

The database of stimuli used during the experiment consisted of a set of "biological" videos and another set of "non-biological" video clips (Figure 13). All videos had a size of 12x12 degrees and a duration of 880 milliseconds. They were projected at the center of the screen, in a 10 x 10 degrees window, with "the area of interest" of the video (in which the object was grasped/touched or the square/triangle moved) falling the 8 x 8 degrees fixation window previously defined.

As a “biological stimulus” was presented a human subject touching or grasping an object placed

in front of him. The action was presented in an allocentric (third person) perspective, i.e., as observed by an executant located in front of us looking toward us, depicted on a black background; the face of the agent was obscured, since it is known that there are prefrontal neurons sensitive to face.

The “non-biological stimuli” consisted in two yellow geometric shapes, a triangle and a square (1 x 1 degrees of size), moving vertically on the screen from a central starting position to a final position corresponding to that occupied by the object in the biological condition. Each non-biological stimulus included, in the bottom left part, a white circle (non-visible to the monkey) placed perfectly in line with the photodiode, that has allowed us to accurately track the timing of presentation of the stimuli, specifically detecting the onset and offset of the stimuli.

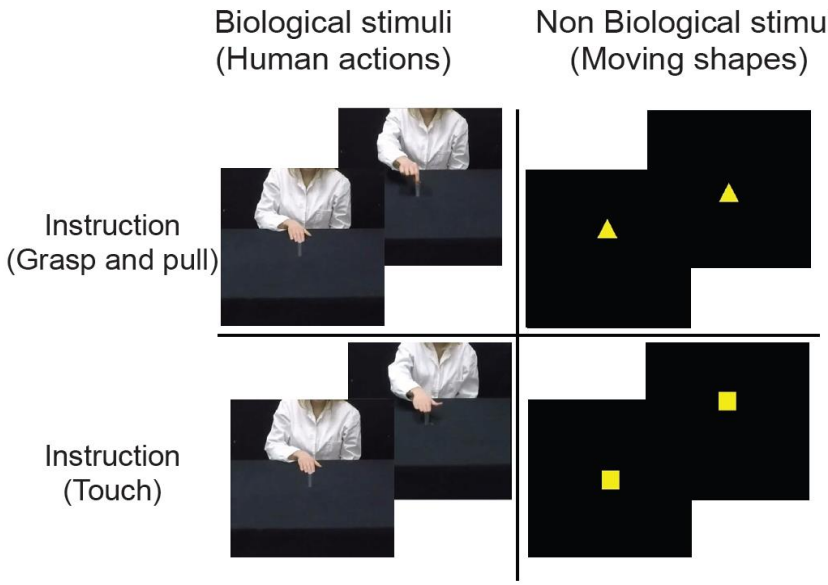

***Figure 13*:** Stimuli proposed within the experimental paradigm.

2.4 Experimental paradigm

The experimental paradigm is characterized by two conditions: "Imitation" and "Observation" (Figure 14). Note that the term "Imitation" was only used to highlight the fact that the monkey was asked to perform an action like that observed (or an action associated to a specific non-biological stimuli), after learning to do so through conditioning. It is not a real process of imitation, which is indeed only found in humans.

A green or red instructive light (produced by the LED contained in the plexiglass box) respectively instructs these conditions. Each trial began when the monkey placed his hand on the starting position, after which the fixation point was projected in the center of the monitor and the monkey had to fixate it. After a randomized time of 500 to 750 ms, if the monkey kept fixating and did not move the hand from starting position, one of the two instructing cues was presented. If the monkey continued to maintain its gaze within the limits of the fixation window, after a further time interval randomized between 500 and 750 ms, one of the four stimuli was presented. Following a randomized time between 500 and 900 ms after stimulus presentation, the cue and fixation point were switched off (Go signal).

In the "Imitation" condition, the monkey had to release the hand from the starting point and touch or grasp and pull the object, starting in less than 1 second. Specifically, the monkey had to grasp the object if it had observed either a video depicting a human subject grasping an object or a vertically moving triangle, whilst it had to reach for it if it had seen either the video depicting a human subject reaching for it or a vertically moving square. In the "Observation" condition, the monkey had to simply release the hand from the starting point and remain, regardless of the presented stimulus.

The order of stimuli presentation was randomized. The trial was considered null if the fixation was not maintained for at least 90 percent of the time during each phase of the task, if the monkey released the hand from the starting position too early (before the go signal) or too late (more than 1s after the go signal) or if the monkey's response was not correct in relation to the instructive cue or the presented stimulus. Under all conditions, every correct test was rewarded with the release of a few drops of fruit juice. If the monkey performed an incorrect trial, reinforcement was not delivered. Incorrect trials were repeated, in a random order, after all the set of stimuli were presented, to ensure a minimum of 11 correct trials for each stimulus/condition.

The experimental paradigm was controlled by a software programmed in LABVIEW (National Instruments, Austin, Texas, USA). This software guides: *appearance* and *disappearance of the fixation point; appearance of the instructive light (cue onset)* and *go-signal (cue offset), stimulus presentation onset and offset* and finally *reward delivery*. Other relevant events were digitalized and

fed to the computer by contact detecting circuits. These devices allowed controlling the presence/absence of the hand on the starting position and the contact of the hand with the sphere and the beginning/end of holding. Finally, the analog signal recorded by the oculometer were also acquired and later sent to this system. All these signals were also sent to the acquisition system (see below).

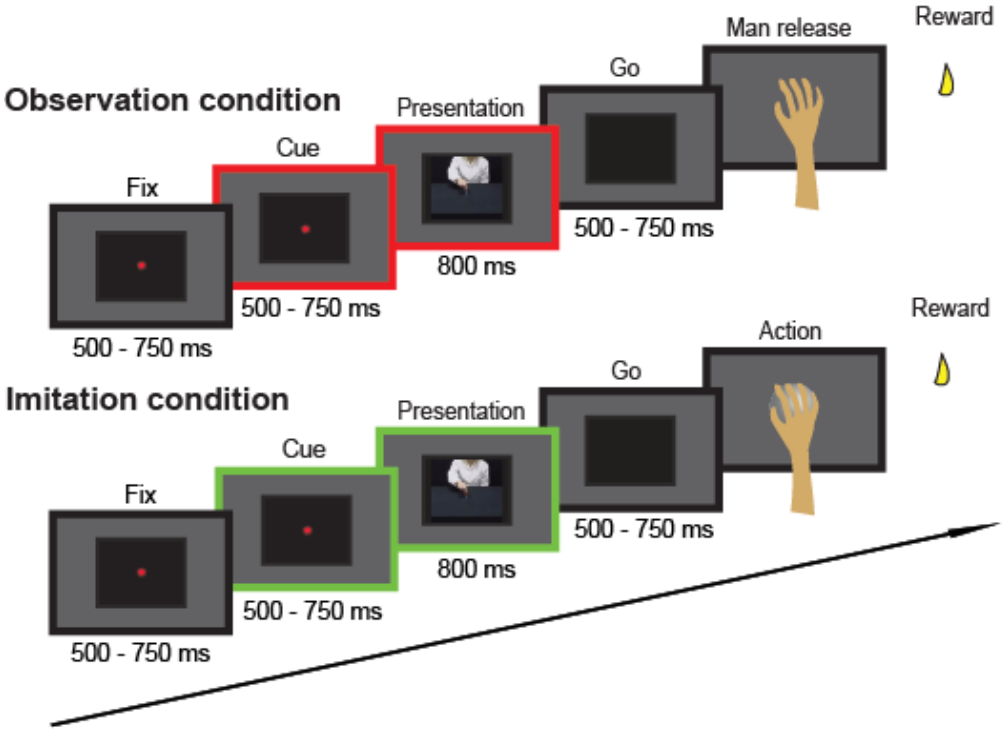

Figure 14: Temporal sequence of events in the "Imitation" and “Observation” condition.

2.5 Recording techniques and signal acquisition

Figure 15 shows an example of the type of arrays implanted in prefrontal and F5 areas, a Floating Microelectrode Array (FMA MicroProbes for Life Science, Gaithersburg, MD, USA). The arrays consist of a ceramic platform of 4 x 1.8 mm, 125 microns thick, containing 36 rigid platinum microelectrodes with a diameter of 25 microns, arranged in triangles 400 µm apart, and with a length comprised between the 0.5 and 5 mm. The different length of the electrodes was chosen in order to cover the different depths of the recorded regions, which include convexities and sulci banks. Out of the 36 microelectrodes of each micro-array, 32 were actual recording microelectrodes with an impedance of about 0.5 mΩ, 2 correspond to reference channels and 2 to ground channels. While the

length of the recording electrodes was such to allow to record in a cortical convexity (ranging from 0.5 to 1.7 mm) or in the bank of sulci (ranging from 0.5 to 5 mm) ground and reference electrodes were longer in order not to record cortical activity: 3 mm for convexity arrays; 5 and 6 mm for mixed convexity sulci arrays.

Figure 15: Microarrayandconnection made of wires insulated by means of a silicone sheath.

Figure 16 shows an example of the type of multielectrode linear array implanted in the BG, which comprised a single probe. The probe shank had pointy tips, as provided by ATLAS Neuroengineering (Leuven, Belgium), to facilitate probe insertion. The probe shanks were 24 mm in length at a width and thickness of 123 μm and 100 μm, respectively. The recording sites had a diameter of 30 µm and were spaced 250 µm from each other. The impedance of the recording sites was in the range of 0.21–026 mΩ measured at 1 kHz.

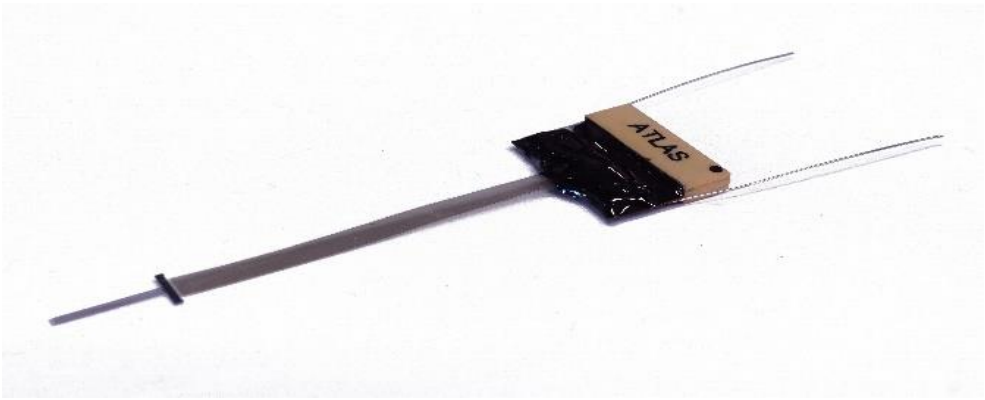

Figure 16: Multielectrode linear array implanted in the BG.

Neuronal activity was recorded and monitored through the integrated hardware-software "Open Ephys" acquisition system (Siegle et al., 2017). The software consists of a downloadable specialized

electrophysiological recording software, the Open Ephys GUI (graphical user interface) which is fully integrated with the acquisition board and implements a plugin-based architecture useful for acquisition, processing and visualization of the activity detected by extra-cellular electrodes. The acquisition board receives signal from the 192 elctrodes and from all the analog and digital signals needed to control the behavioral paradigm (see paragraph Experimental paradigm).

2.6 Data Analysis

2.6.1 Offline processing of the neural signal and extraction of single neurons

A first process allowed to identify and isolate the waveforms of single neurons and digitalize their occurrence. This process was obtained using "Mountainsort", an automatic offline sorting software (Chung et al., 2017) and an open-source Mountainlab plugin package for processing and visualization of the activity. The digitalized single neuron activity was then realigned to the different digital and analog signals using the NeuroExplorer software and custom MATLAB programs. Different digital signals were used to align the single neuron activity. To this aim, we used the following events: the onset and offset of fixation point; the instructive led and stimulus presentation; the detachment of the monkey's hand from the starting position; and, only for the imitation condition, the contact between hand and object. Finally, the neuronal activity, according to the various alignments, was displayed in the form of rasters and histograms and exported in numeric format for subsequent analyses.

2.6.2 Identification of task related neurons

To analyze the neuronal activity, we first defined six epochs based on the acquired digital signals, as follows;

Baseline, 500 ms, before the appearance of the fixation point;

Fixation, 500 ms following the appearance of the fixation point;

Cue, 500 ms following the appearance of the instructive light (cue onset);

Presentation, 500 ms following stimulus presentation onset;

Delay, 500 ms following stimulus presentation offset;

Go, 250 ms following the disappearance of the instructive light (cue offset);

Action, 500 ms following release from the starting point.

To assess whether neurons significantly responded during task unfolding, similar to Hoshi and coworkers (1998), for each neuron we calculated the mean firing rate (expressed in spikes/s) recorded in the *Baseline* epoch and its standard deviation (SD). A neuron was classified as task related if the activity in at least one of the other statistical epochs was > or < than 3 SD of the baseline average discharge for at least 3 consecutive 20-ms bins.

2.6.3 Principal Components Analysis

For each task-related neuron, we aligned neural activity using three different alignments designated as: "*Cue*" consisting in a time period ranging from 500 ms before to 2 second after the appearance of the instructive light; "*Presentation*" consisting in a time period ranging from 500 ms before to 1 second after stimulus presentation onset; "*Action*", consisting in a time period ranging from 500 ms before to 1 second after release of the hand from the starting point. Moreover, we considered the activity from thre different contrasts: both conditions (Imitation vs. Observation), type of stimulus, which in turn can be classified based on its behavioral significance (instruction to Grasp vs. instruction to Touch) or its visual features (Biological vs. Non-biological). Then, we classified the activity according to the eighteeen possible type of trials i.e. combination of contrasts and alignments, and calculated the trial-averaged firing rates in 20-ms bins. The result was smoothed with a 60 ms Gaussian kernel. We applied the "soft-normalization procedure" according to Churchland and coworkers (Churchland et al., 2012). In brief, for each neuron, each 20-ms bin was divided with the maximum firing rate of the eighteen type of trials added with a small costant (+5 spk/s) to reduce the influence of high-firing neurons, thus to preserve a relative range of firing rates. After this pre-processing, the normalized firing rates were considered as an N-dimensional neural population state

space. PCA were performed on a T x N matrix (where T is the bin number, N is the number of neurons), obtaining the scores of N-1 principal components in each time bin of each of the eighteen type of trials. Then, for each type of trial, we plotted the scores of the first two principal components over time, obtaining the "neural trajectories" describing the evolution of the population state.

To mark the time corresponding to specific task events (i.e. Cue, Start presentation, End presentation, Action, Reward) along the trajectories, we calculated their mean time relative to stimulus presentation of each contrasts.

2.6.4 Decoding analysis

In order to assess the functional role of different populations of neurons active in distinct phasses of the task, and make hypotheses about the type of their nural code, we adopted a population decoding approach according to the methodology described by Mayers and coworkers (Meyers et al 2008; url: http://www.readout.info/).

First, for each neuron, the activity was aligned with the main behavioural events (see 'Statystical analysis'). This allowed us to create a mtrix in which the firing rate of each trial was strictly related to an given epoch. Based on these allignments, for each neuron we extracted trials activity expressed in terms of trial bin count (bin=1 ms). Then, for each trial we calculated the average firing rate in bins of 150 ms, sampled at 50 ms intervals. We defined "data point" as the set of 150ms-bins belonging to a trial. Labels were then assigned to each data point to identify the factors to analize (i.e., 40 data points x 2 conditions for Imitation vs Observation decoding; 40 data points x 2 type of stimuli classified based on their visual feautures for Biological vs Non-Biological one decoding; 40 data points x 2 type of stimuli classified based on their behavioral significance for instruction to Grasp vs. instruction to Touch decoding) in an N-dimensional space (where N is the total number of neurons considered for each analysis). Subsequently, we randomly assigned the data points in a number of splits corresponding to the number of data points per factor, with each split containing a "pseudopopulation," that is, a population of neurons that cuold be partially recorded in different days,

but treated as if they were recorded simultaneously. Finally, in order to avoid that neurons with high firing rates do not end up contributing more to the decoding results than neurons with lower firing rates, we normalized the activity by useing a zscore normalization. By using this procedure each neuron activity has approximately zero mean and a standard deviation of 1 over all trials.

Different decoding analyses were performed on specific populations of neurons (e.g. neurons recorded by each array). For each population we trained a "maximum correlation coefficient classifier" using all the splits but one and then tested it on the remaining one. This process (cross-validation) was repeated as many times as the number of splits (i.e., 40 in the case of condition for Imitation vs. Observation decoding; 40 in the case of Biological vs. Non-Biological stimuli decoding; 40 in the case of Grasp vs. Touch stimuli decoding), using a different test split each time. The classification accuracy was then calculated as the percentage of predictions correctly made on trials from a separate test set of data. To increase the robustness of the results, the overall decoding procedure was repeated over 50 resample runs, each with different data in the training and test splits, and the results reported are the average classification accuracy over these 50 runs.

In order to evaluate the dynamics of the population code we applyed a temporal-cross decoding analysis (TCT), which consist in training the classifier at one time bin and testing its decoding performance at either the same or all the other different time bins. This procedure allows one to observe to wich extent the activity recorded in each phase of the task can discriminate the investigated factor (e.g. conditions or type of stimlus) in the other phases.

3. RESULTS

3.1 Behavioral results

Since the beginning of the recordings, behavioral analyses have been carried out with the aim to constantly monitor the progress made by the monkey in each recording session. We recorded the neural activity during 41 sessions in 34 days. For this analysis, we considered the first session of every day. In all the considered sessions, the monkey was required to perform at least 44 correct trials for each condition. We calculated the ratio between the number of the correct tests (see Methods) for each condition and the total of trials performed (including errors) expressed as percentage. We aimed at reaching a successful criterion of performance >80% considering the trials of the two conditions together. However, the two task conditions were analyzed separately. The monkey achieved the performance >60% of correct trials in the Imitation condition and >93% of correct trials in the Observation condition (Figure 17).

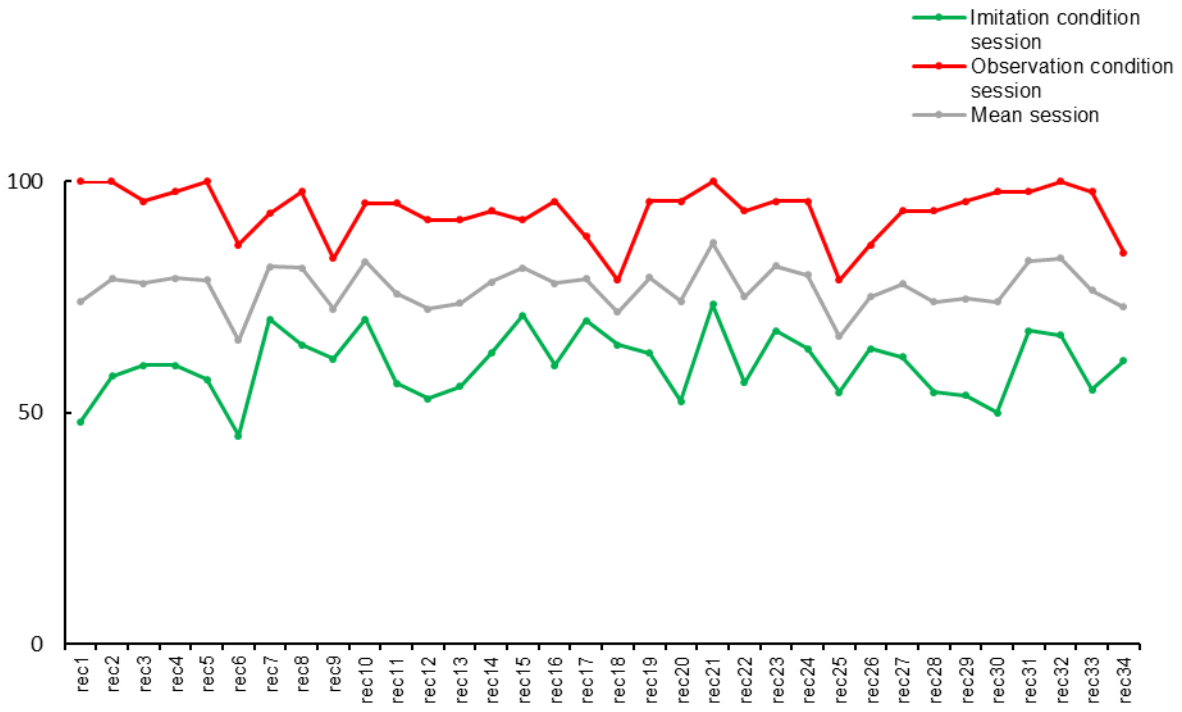

***Figure 17*: Monkey performance in different recording sessions.** Abscissa: recording sessions. Ordinate: monkey performance.

3.2 General properties of single neurons

We recorded neural activity by employing 192 electrodes in different cortical sectors and in the basal ganglia (see Methods). Note that surgical implantation in the BG took place after the first 31 recording sessions. Therefore, initially the recording channels were 96, located only in the cortex, but with the addition of electrodes in BG, the last 10 recordings had 192 recording channels. Out of these 192 electrodes, 62 allowed us to record at least one single unit during at least one recording session and were therefore classified as active. Of the active electrodes, 23 were in rPF array, 12 in cPF array, 7 in F5 array and 20 in the BG.

We isolated 703 single units, 278 (39,5%) were recorded from the rPF array, 280 (39,8%) from the cPF array; 72 (10, 2%) from the F5 array; 73 (10,4%) were recorded from BG probes.

Four hundred-twenty-six neurons (60,6% of the total single units isolated) were classified as task related based on the statistical criterion defined in the Methods section. In details, 183 neurons were recorded from rPF array, 175 from cPF array, 44 from F5 array and 24 from BG probes (Figure 18 a).

Each neuron can discharge (activity exceeding 3SD of the baseline mean, see Methods) in one or more epochs. Figure 18 b shows a classification of neurons based on the number of epoch in which the discharge is significantly above baseline. The number of neurons responding in 6 epochs (n=96, 22,5%) is the largest, immediately followed by neurons responding to 5 (n=83, 19,5%) and 3 (n=71, 16,66% of the total) epochs. Finally, a smaller number of neurons responds in 4 (n= 63, 14, 80%), 1 (n=60, 14, 08%) and 2 (n=54, 12, 70%) epochs.

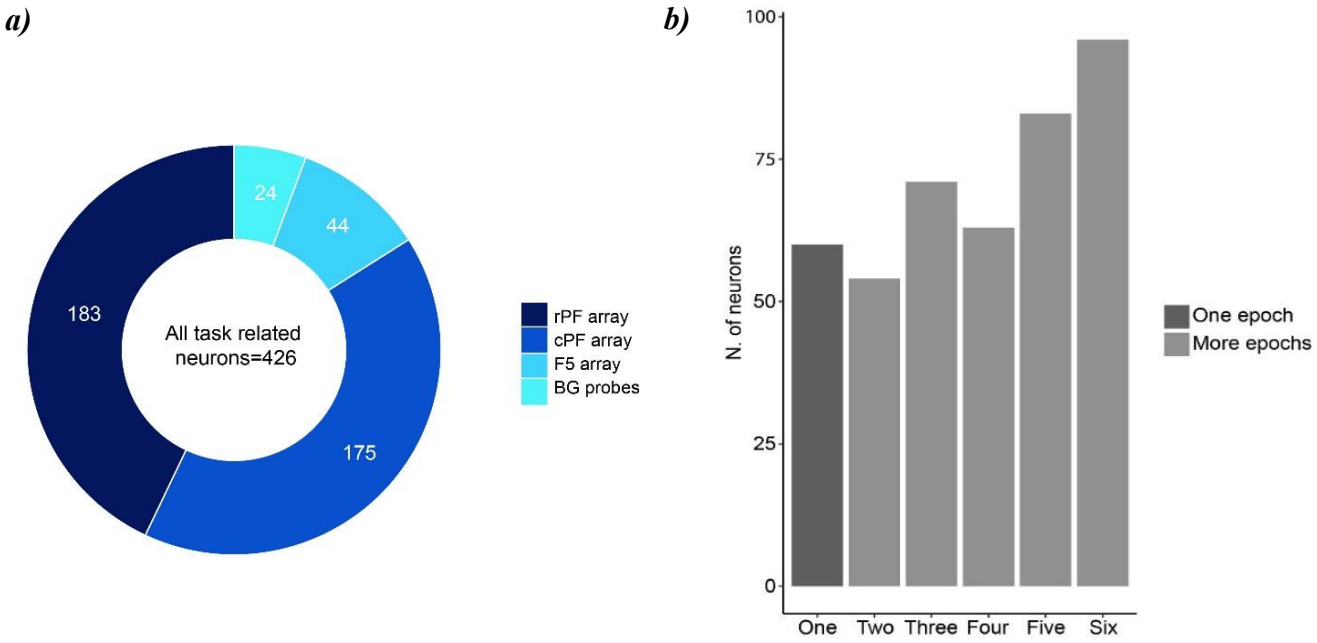

Figure 18: **a)** Number of task-related neurons in each array. **b)** Number of task-related neurons responding in one or more epoch.

3.3 Influence of behaviorally relevant factors on neural activity

3.3.1 Imitation vs. Observation

In order to evaluate how the neural population encodes the general rule represented by the two cues (to imitate or to observe), we carried out a principal component analysis. To this aim, we discarded the information relative to the two types of visual features (biological and non-biological) and to the two behavioral goals (instruction to reach or to grasp). Figure 19 shows the projections of neural trajectories corresponding to the two different instructive cues (green and red) onto the plane of the two first principal components. Note that these two components capture >50% of the total variance. It is evident the presence of a separation between the activity related to the two cues in each of the three analyzed epochs, in the activity recorded in each array, except for the F5 population in the *Cue* epoch.

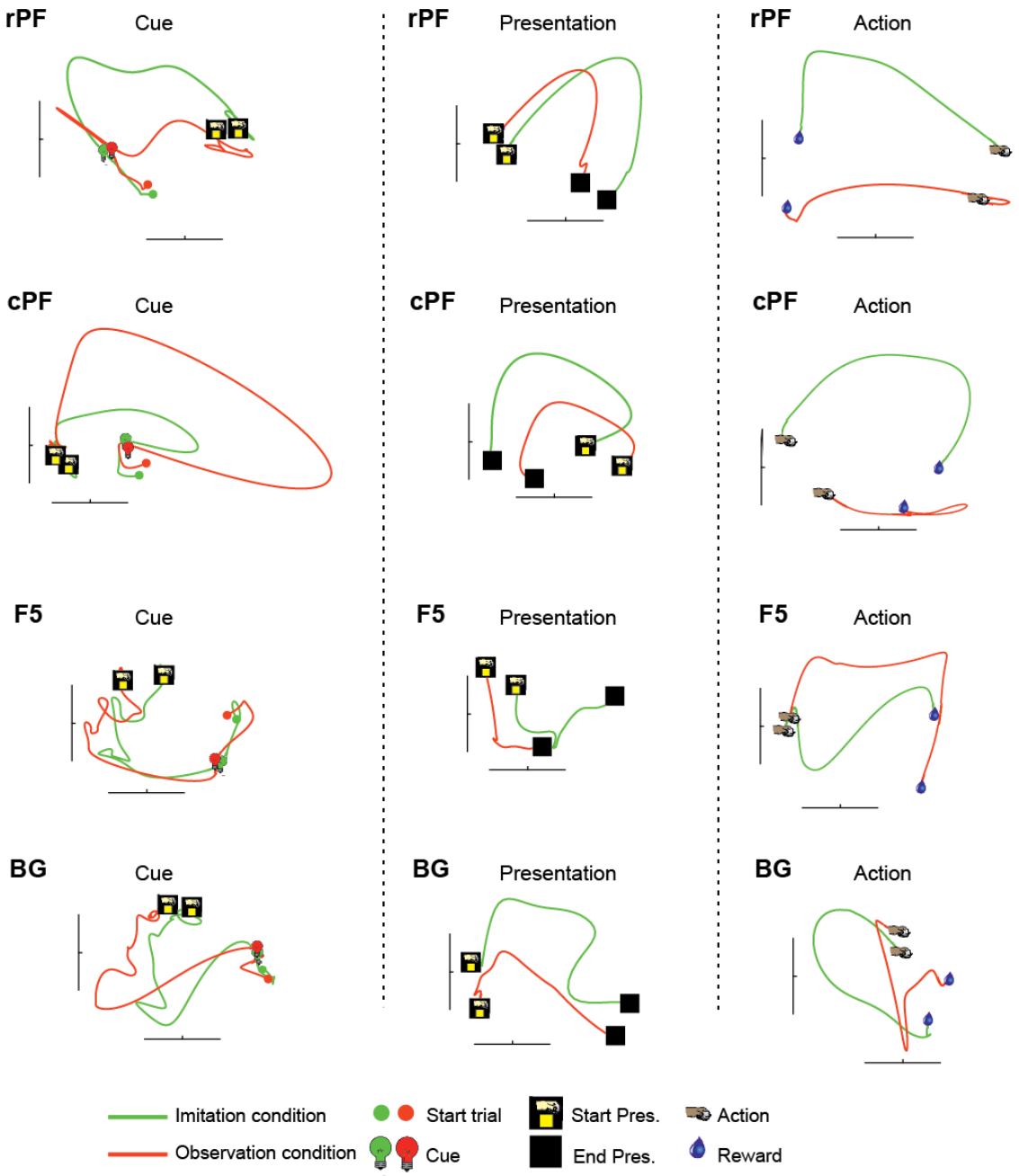

***Figure 19*: Imitation vs. Observation comparison, all arrays.**

PCA is an exploratory method analysis that allowed us to demonstrate that the condition influences the population activity. This analysis, however, cannot describe the actual population dynamics. For example, a wider trajectory in one condition than in the other does not mean that the neural activity is stronger in that condition. To shed light on this issue, we also analyzed single neurons activity and found that several neurons differentially code the two cues (Imitation vs. Observation). The statistical analysis of single neuron activity has not been completed yet,

accordingly we will present two paradigmatic examples of neurons. Figure 20 a) shows the discharge of a cPF array neuron displaying excitatory activity in the *Cue* epoch and differentially coding the Imitation and Observation conditions in this epoch. In particular, the neuron starts firing just after cue onset, both in the Imitation and Observation conditions, but in this latter, the peak is more than two times higher. In contrast, the neuron shown in Figure 20 b) presents an opposite behavior. In this case, the neuron starts firing after the appearance of the fixation point, with no difference between conditions, and reaches its peak on cue onset, which is higher in the Imitation than in the Observation condition.

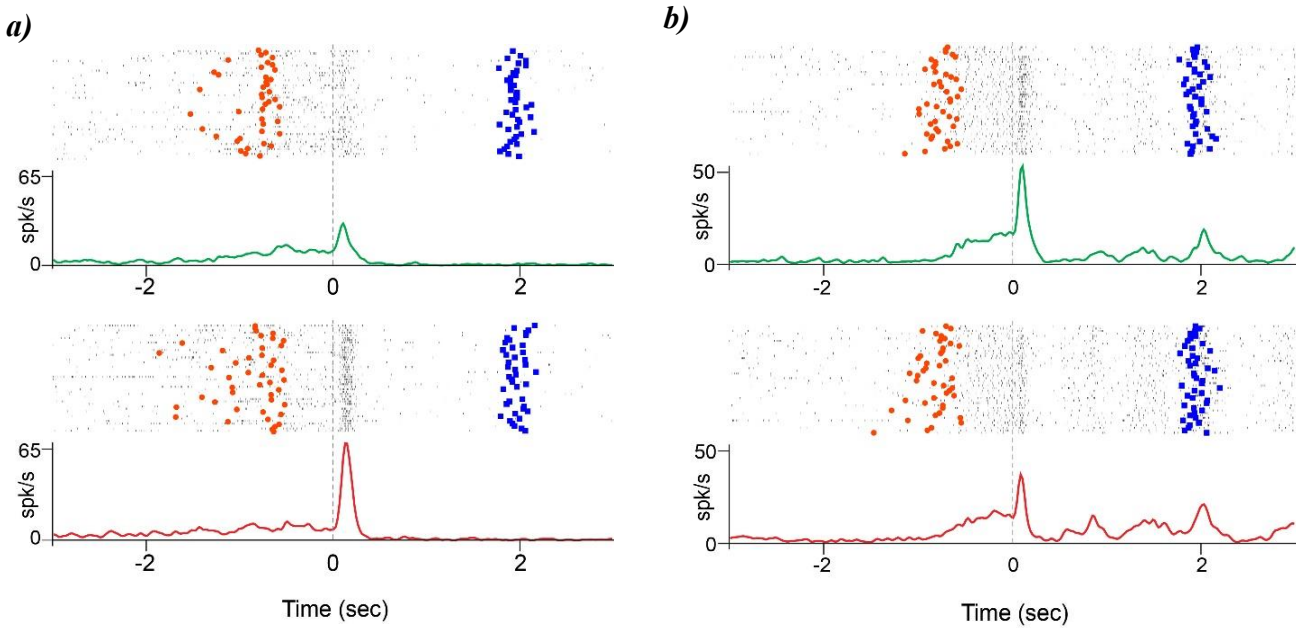

Figure 20: **Neurons differentially coding Imitation vs. Observation conditions.** Raster and histogram showing the activity of the neurons, recorded respectively by cPF (a) and rPF (b) arrays, recorded in 88 correct trials of the behavioral task aligned on the cue onset, shown by vertical dashed gray line, during Imitation (green waveform) and Observation (red waveform) conditions. Red circle: appearance of the fixation point; blue squares: stimulus presentation onset. Abscisse: time (s). Ordinate: firing rate (spikes/s).

3.3.2 Instruction to Grasp vs. Instruction to Touch

Figure 21 shows the instruction to Grasp vs. instruction to Touch contrast in the Imitation condition. In particular, the Figure illustrates the projections of the neural trajectories corresponding to the two different behavioral meaning associated to the different videos, onto the plane of the two

first PCs. Note that these two components capture >50% of the total variance. The results show that, before stimulus presentation (on the activity aligned on cue onset), there are no differences in the population dynamics of each array, as expected since the cue does not carry the information instructing on which motor act to execute. In the rPF array, the separation between the two motor acts is evident only in the *Presentation* epoch; the cPF and BG populations show a clear trajectory separation in both *Presentation* and *Action* epochs; finally, the F5 array shows a differentiation between trajectories only in the *Action* epoch.

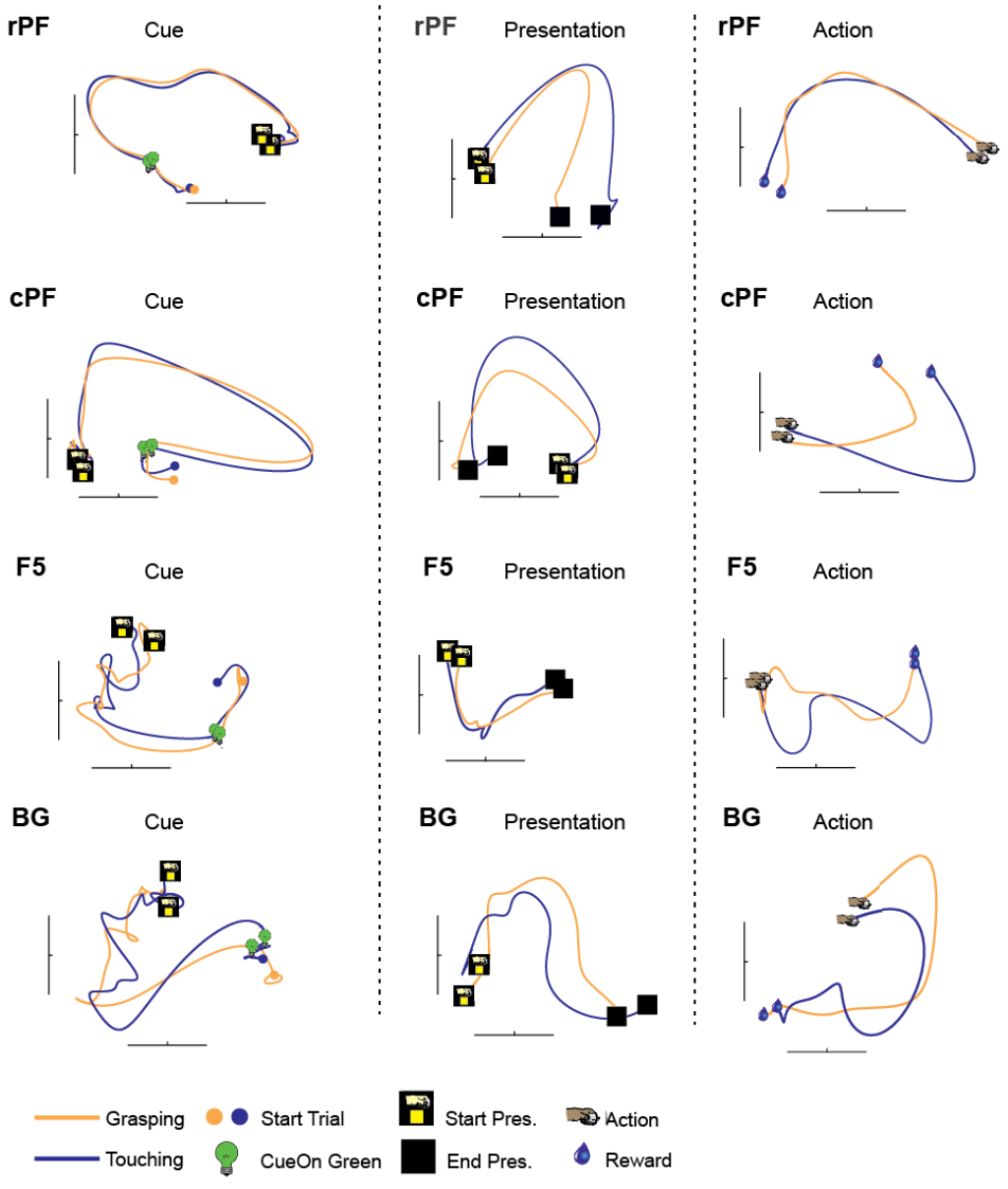

***Figure 21**:* **Grasp vs Touch comparison in the "Imitation" condition, all arrays**.

In line with the above-described neural trajectories, we found several neurons differentially coding the two motor acts, mostly in the *Action* epoch. Figure 22 shows the discharge of a neuron recorded from the cPF array. This neuron, in the Imitation condition, differentially codes the two behavioral goals (Grasp vs. Touch), firing only during the reaching action either when instructed by a biological (reaching action) or non-biological stimulus (moving square), displaying an higher discharge in the latter case.

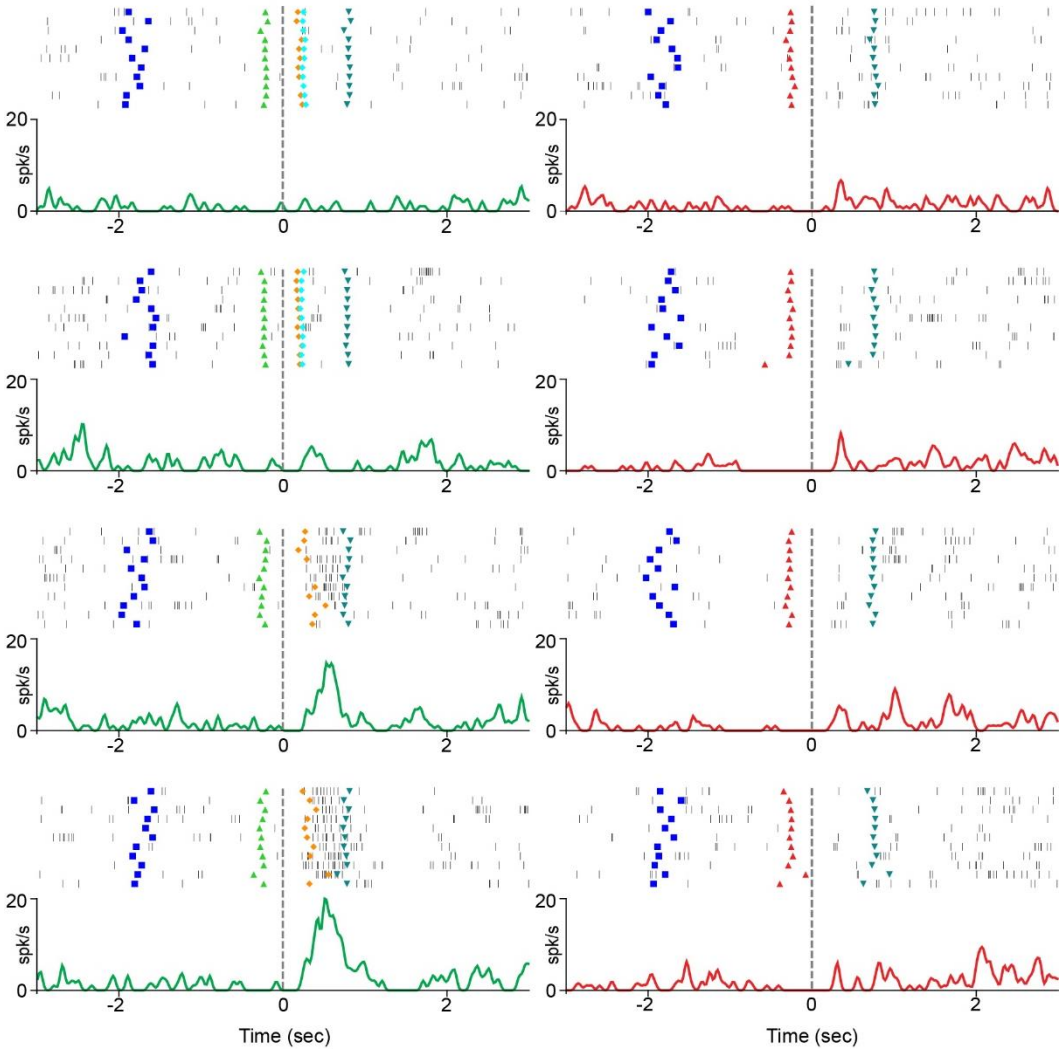

Figure 22: **Neuron differentially coding the instruction to Grasp vs. instruction to Touch contrast.** Raster and histogram showing the activity of a neuron, recorded by cPF array, active during the touching action, recorded in 11 correct trials of the behavioral task and aligned on the release from the starting point, shown by vertical dashed gray line, during the Imitation (green waveform) and Observation conditions (red waveform). Green triangles: disappearance of the green instructive light (go signal in the Imitation condition); red triangles: disappearance of the red instructive light (go signal in the Observation condition); yellow diamond: hand-touching-object contact; light blue diamond: hand-grasping-object contact; light blue diamond: hand-grasping-object contact; dark green triangles: reward delivery. Other conventions as in Figure 20.

On the other hand, Figure 23 shows an rPF neuron that respond in the *Action* epoch only in the Imitation condition. The discharge occurs during grasping-pulling action, independent of the instruction video. In particular, the neuron shows a sustained discharge starting from stimulus presentation, reaching its peak during hand-object interaction and then abruptly returning to baseline level activity.

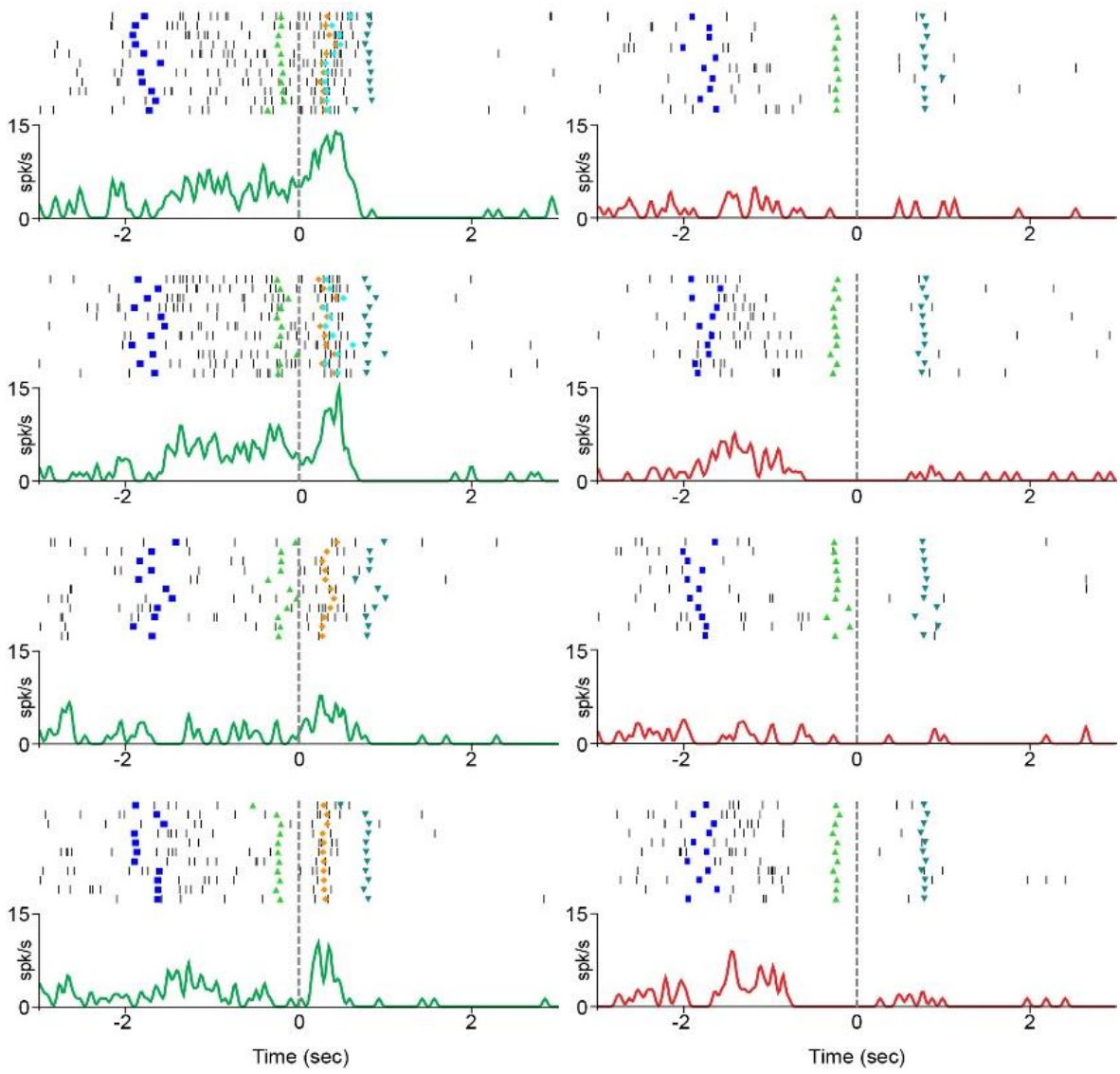

Figure 23: **Neuron differentially coding to Grasp vs. to Touch instructions and Imitation vs. Observation conditions.** Raster and histogram showing the activity of a neuron, recorded by rPF array, active during the grasping action and in the Imitation condition. Other conventions as in Figures 20 and 22.

Figure 24 shows a neuron recorded from cPF array, which does not have a preferential response in the *Action* epoch. The neuron discharges equally well in the two conditions, starting to respond on the release from the starting point in the Observation condition and on hand-object interaction in the Imitation condition and stopping firing at reward delivery. Thus, the neuron discharge during the execution of a simple arm movement (releasing the start point) in the Observation condition, but does not respond to this movement, in the Imitation condition, activating, during the execution of specific motor acts (grasping and touching). Note that in the Imitation condition the neuron discharge equally well during the execution of both reaching and grasping acts.

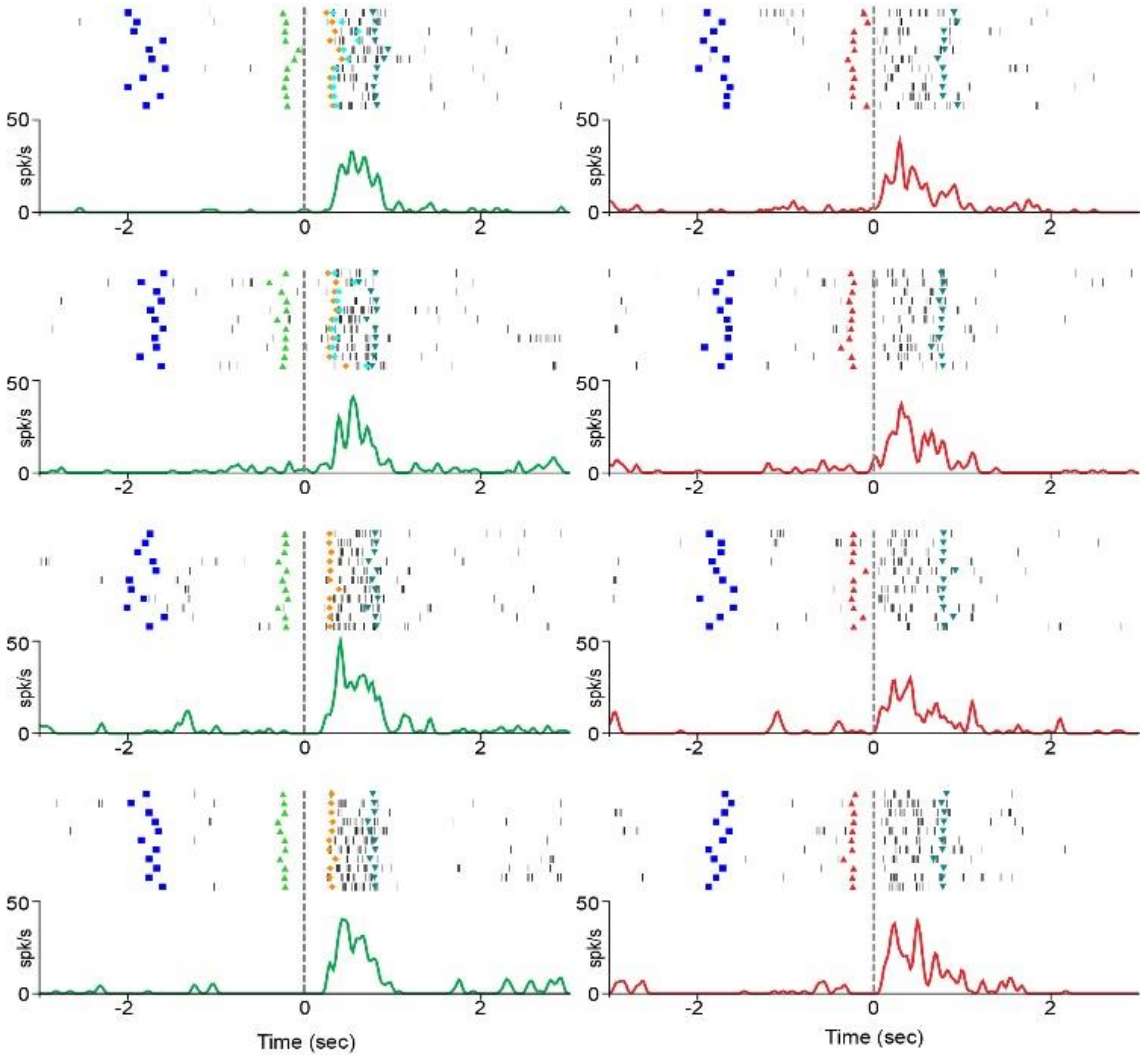

Figure 24: **Neuron does not differentially code to Grasp vs. to Touch instructions and Imitation vs. Observation conditions.** Raster and histogram showing the activity of a neuron recorded by cPF array. Red triangles: disappearance of the instructive light (go signal in the Observation condition). Other conventions as in figure 23.

3.3.3 Biological vs. Non-Biological stimuli

Figure 25 shows the comparison between the neural discharge observed during the conservation of Biological and Non-Biological visual stimuli. More in detail, the Figure illustrates the projections of the neural trajectories corresponding to the two different visual stimuli onto the plane of the two first PCs. Note that these two components capture >50% of the total variance. The results show that, on the activity aligned on cue onset, there are no differences in the population dynamics of each array, as obvious since the cue does not inform the monkey about the type of video that monkey will see. The neural trajectories corresponding to the two types of stimuli run well distinct only during the *Presentation* epoch in the two prefrontal and in the BG populations, but not in F5. In contrast, during the *Action* epoch the neural trajectories corresponding to all the arrays does not show any differentiation between the trajectories representing the type of stimuli presented.

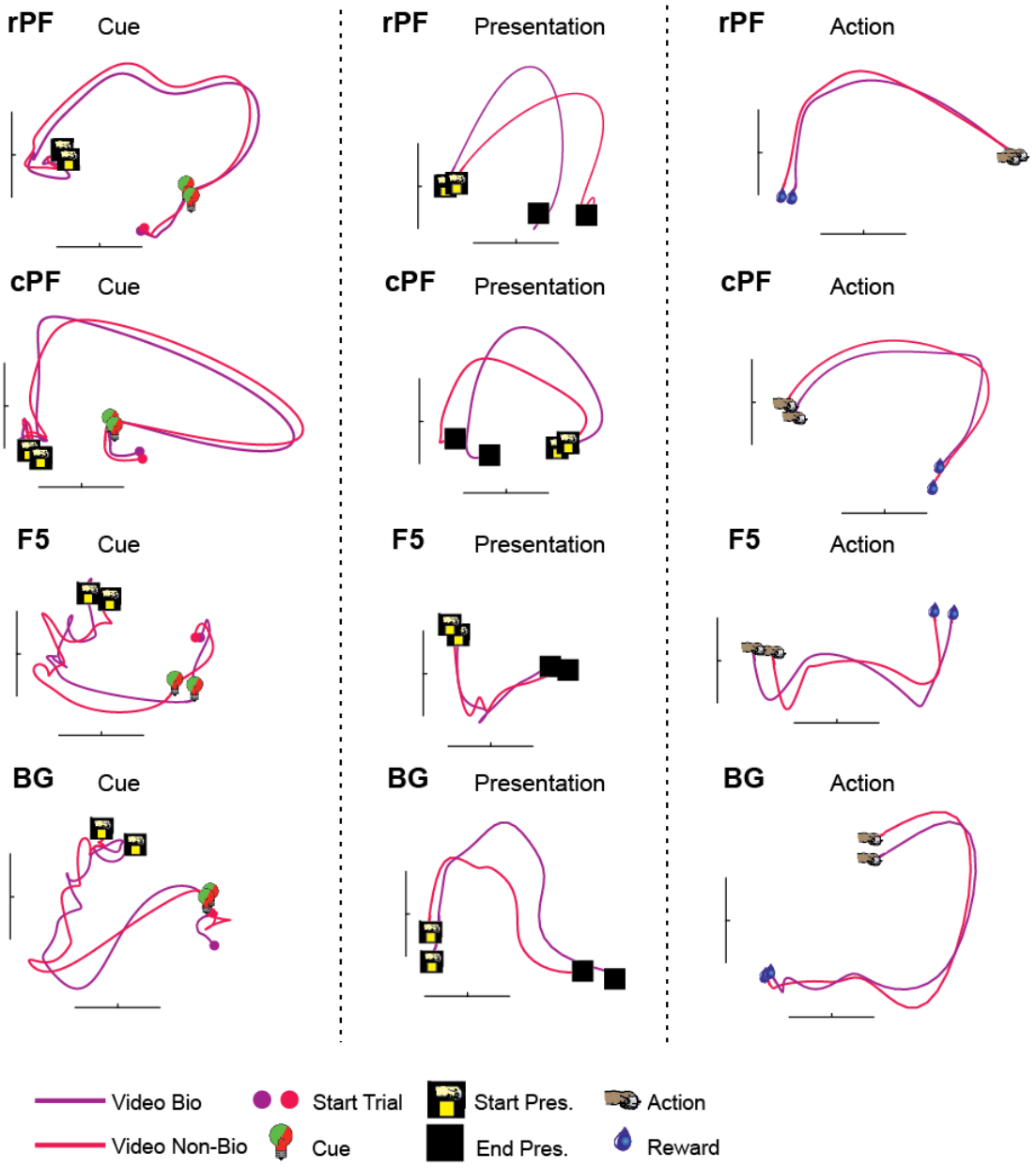

Figure 25: **Biological vs Non-biological stimuli comparison, all arrays.**

In line with the above-described neural trajectories, we found several neurons differentially coding the type of visual stimuli presented. Figure 26 shows the discharge of an rPF neuron showing an excitatory activity in the *Presentation* epoch and differentially coding the type of visual stimulus (Biological vs. Non -Biological). It is evident that, in both Imitation and Observation conditions, the neuron has a strong discharge during the presentation of video representing the biological stimuli but does not fire during the observation of the moving shapes.

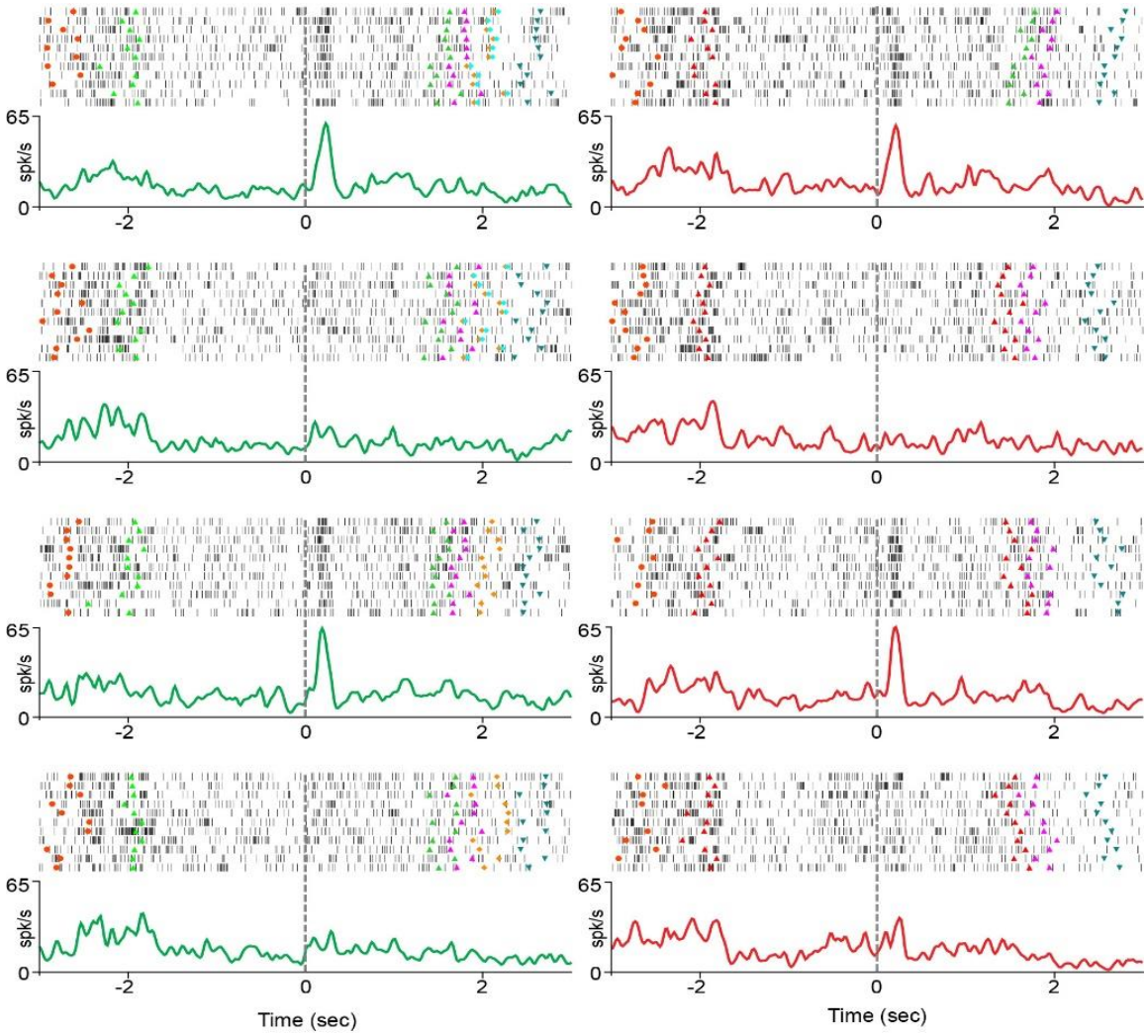

Figure 26: **Neuron differentially coding Biological vs. Non-Biological contrast.** Raster and histogram showing the activity of neuron, recorded by rPF array, active during the presentation of biological stimuli, in both conditions, recorded in 11 correct trials of the behavioral task aligned on stimulus presentation onset, shown by vertical dashed gray line. Fluorescent green triangles: cue green onset. Other conventions as in Figure 25.

On the other side, Figure 27 shows a neuron with the opposite behavior discharging higher during the presentation of the moving shapes than during the observation of the biological stimuli.

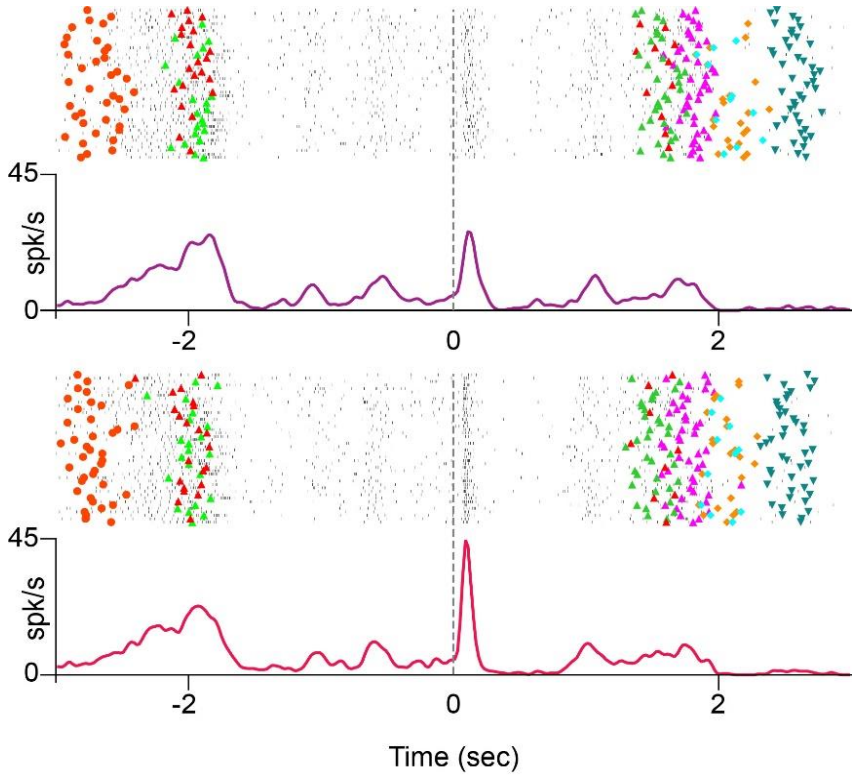

Figure 27: **Neuron differentially coding Biological vs. Non-Biological contrast.** Raster and histogram showing the activity of cPF array neuron firings higher during the presentation of non-biological stimuli, recorded in 88 correct trials of the behavioral task aligned on stimuli presentation onset, shown by vertical dashed gray line. Other conventions as in Figure 26.

3.4 Decoding analysis results

3.4.1 Imitation vs Observation decoding analysis results

To investigate how different populations of task-related neurons (recorded from rPF, cPF, F5 and BG arrays) code the information related to the two general rules (Imitation vs Observation decoding analysis) employed in the task, we performed different decoding analyses. Figure 28 shows the results of the decoding analysis performed on the neural activity of task related neurons recorded in rPF array. The red line represents the classification accuracy, which is very high, above chance level, during all task unfolding, except for the *Baseline* epoch. More in details, accuracy reaches 100% during the *Cue* epoch, slightly decreases during the *Presentation* epoch, raising again during the *Delay* epoch touches 100% accuracy in the *Action* epoch.

In order to evaluate if the activity recorded in each time bin of the task allows the classifier to discriminate between conditions in other phases of the task, we trained it on each point in time and tested its decoding performance in all the considered time points of the task (*Temporal-crossing decoding training*, TCT, see Methods). The results (Figure 28) show that the highest decoding accuracy is present along the diagonal, indicating that the best decoding performance is achieved when training and testing is done using data that have the same timing. More interestingly, when the classifier is trained using the activity from the *Cue* epoch (especially from the second part of this epoch), the decoding accuracy tested on the *Go* epoch is high (around 80%), and further increases until 100% when tested on the *Action* epoch.

When the classifier is trained using the activity recorded in the *Delay* epoch, it discriminates condition-related activity with very high accuracy (reaching 100%) during the *Cue* and *Action* epoch, with a slightly lower, but well above chance level accuracy, during the final part of the *Presentation* epoch and initial part of the *Go* epoch. Finally, training the classifier with the condition-related activity recorded in the *Action* epoch and testing during the previous epochs, the accuracy is very high (until 100%) only during the *Cue* epoch.

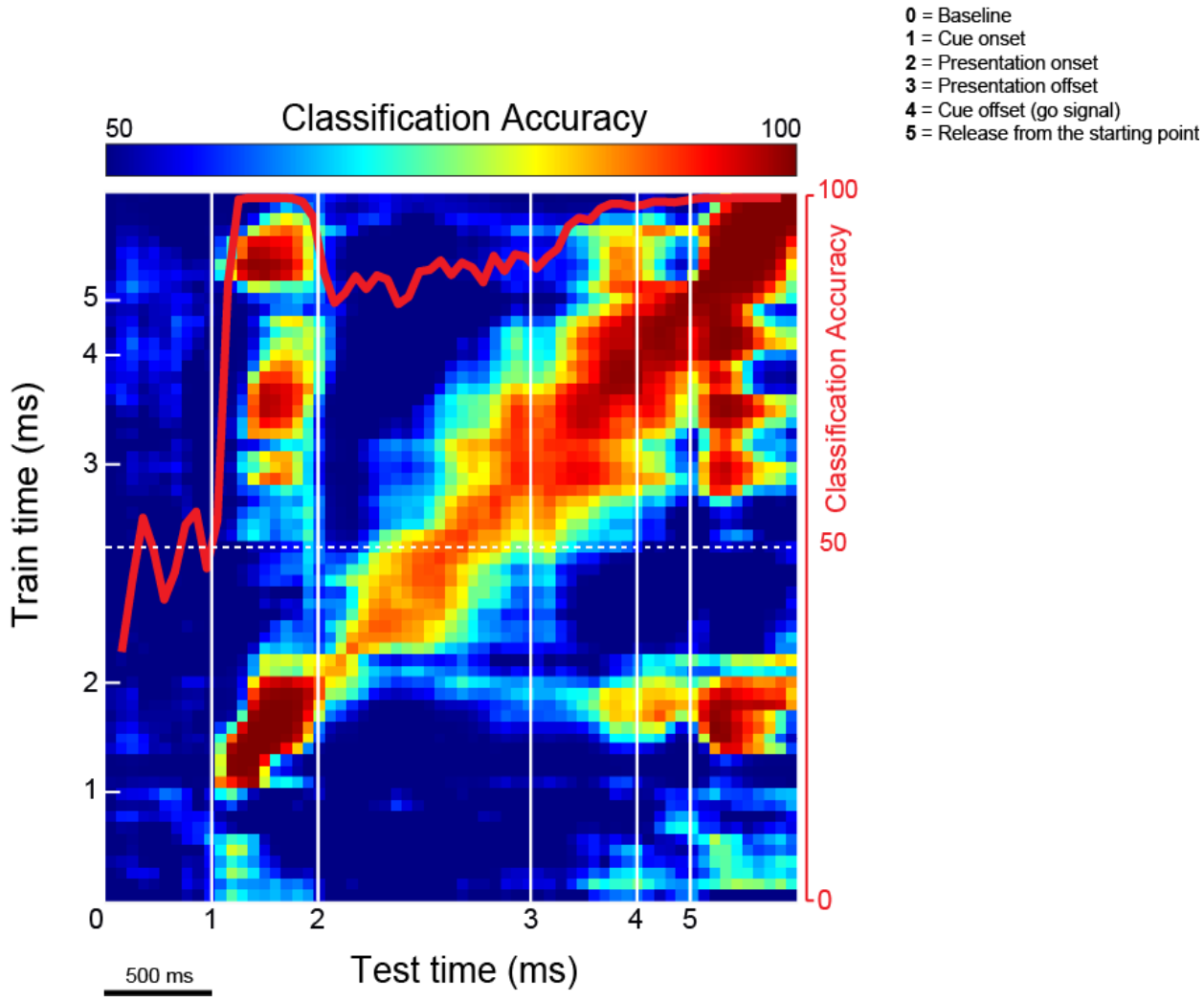

***Figure 28*: Decoding of the Imitation vs. Observation conditions in population of neurons in rPF array.** The red line represents the classification accuracy when the classifier is trained and tested on the same time bin (The scale of the accuracy is shown by the red scale on the right). The color-coded matrix represents the results of TCT. In each row, the time bin represented on the diagonal is used as train bin and each bin of the row shows the accuracy of testing in the bin shown on the X axis. The accuracy is expressed in color code (right scale).

The same analysis was performed on the neural activity recorded in cPF array, and the results are shown in Figure 29. Like the rPF array, the classification accuracy (red line) is 100% during almost all the duration of the *Cue* Epoch, decreases during the *Presentation* epoch and increases slowly during the *Delay* epoch, reaching again an accuracy very close to the maximum of 100% in *Go* and *Action* epochs.

Similarly, the TCT, when the classifier is trained and tested on the same bins, shows that the decoding accuracy is high during *Cue*, *Delay*, *Go* and *Action* epochs and lower during the *Presentation* epoch. When the classifier is trained using the activity recorded in the bins belonging to the *Delay* epoch, the decoding accuracy is constantly high only during the *Action* epoch. Note that, similarly to the rPF array, an above chance decoding occurs also in the *Cue* epoch, but both the accuracy level and the duration in time are much lower.

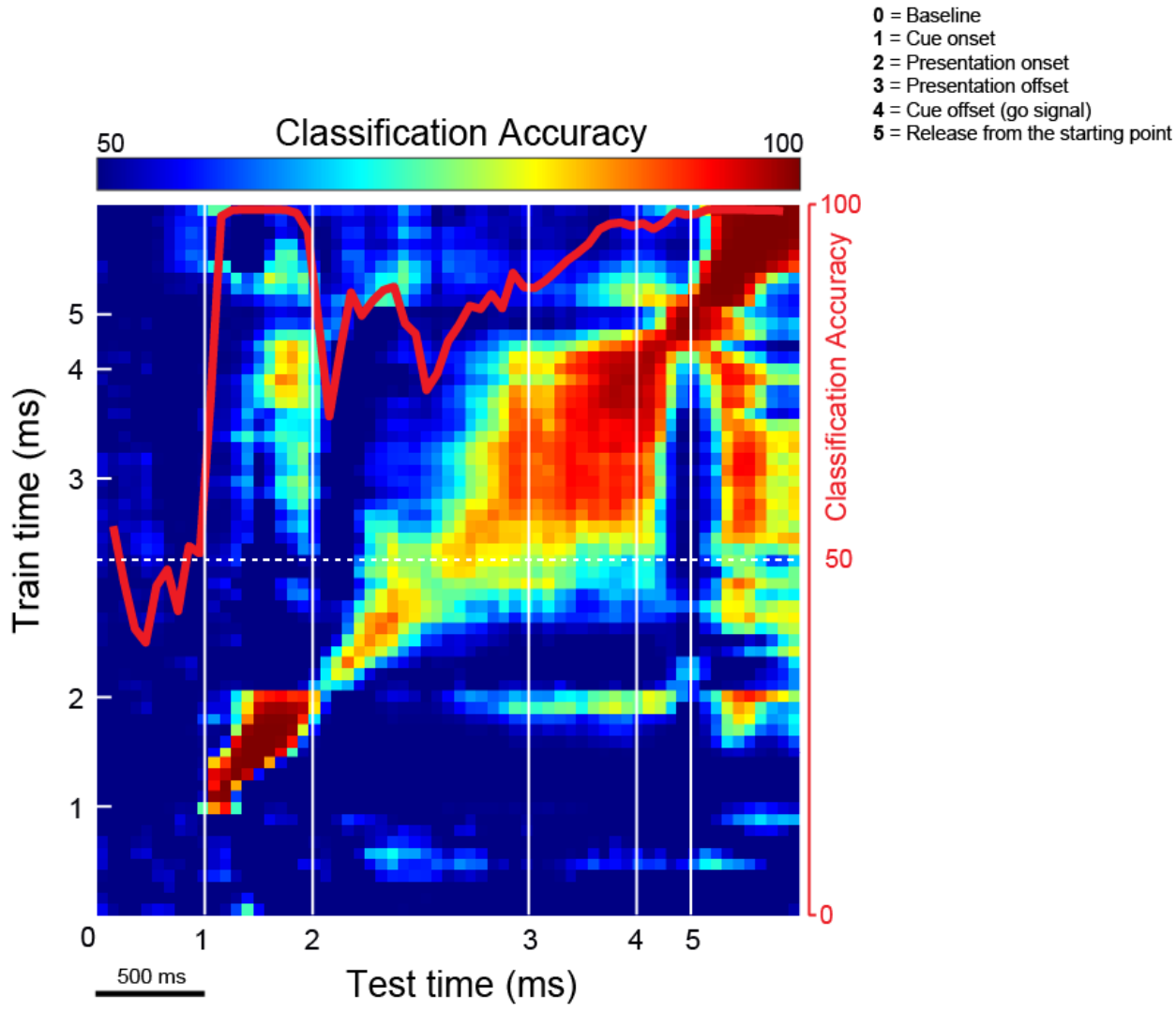

***Figure 29*: Decoding of the Imitation vs. Observation conditions in population of neurons in cPF array.**

Other conventions as in Figure 28.

Concerning the neural activity recorded in the F5 array, the results of the decoding analysis are shown in Figure 30. The red line shows that the decoding accuracy starts increasing during the *Presentation* epoch, sharply decreasing at the end of the *Delay* epoch and reaching 100% accuracy in the *Action* epoch. The results of the TCT analysis show that the highest decoding accuracy is present when the classifier is trained and tested on the same action bins, while training and testing on the *Cue* bins produce a lowest level of decoding, close to chance level. Interestingly, however, training the classifier using the activity recorded during *Cue* epoch and testing with the activity from the *Action* epoch, the decoding performance is quite high (above 70%) in the initial part of the *Action* epoch.

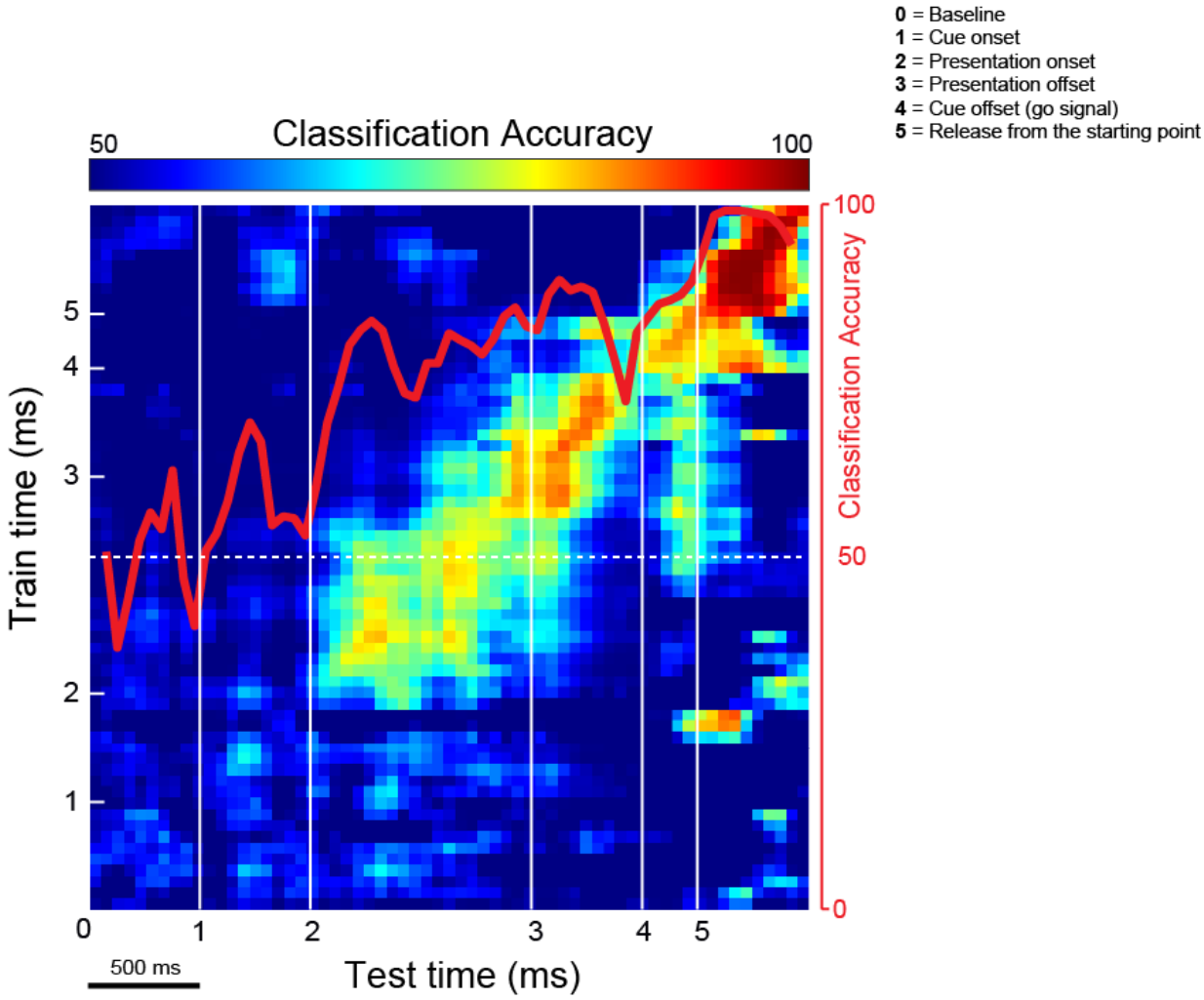

***Figure 30*: Decoding of the Imitation vs. Observation conditions in population of neurons in F5 array.**

Other conventions as in Figure 28.

Finally, the results of the decoding analysis performed on the neural activity recorded in the BG probes are shown in figure 31. The red line shows that the decoding accuracy starts increasing during the final phases of the *Delay* epoch, reaching its maximum level during the *Action* epoch (100%). The results of the TCT analysis show the higher decoding accuracy is present only when the classifier is trained and tested on the same bins.

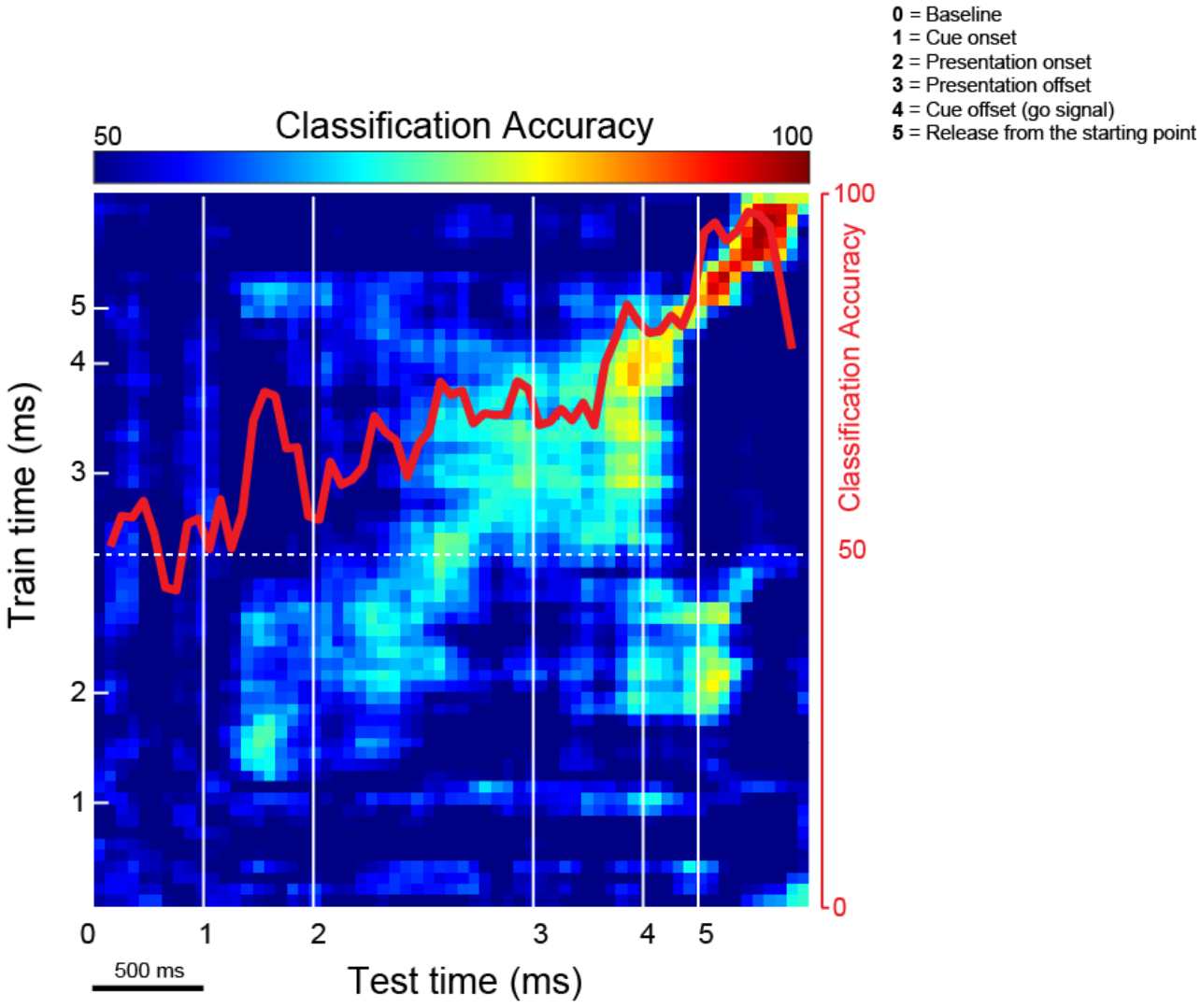

***Figure 31*: Decoding of the Imitation vs. Observation conditions in population of neurons in BG probes.**

Other conventions as in Figure 28.

4. DISCUSSION

The general aim of this work is to assess the specific role of neurons located in different brain regions in linking relevant sensory information to an associated behavioral output. To this aim we recorded simultaneously neural activity from two sectors of the prefrontal cortex (overlapping with the rostral two thirds of ventral area 46 and part of the adjacent area 12), the hand field of the ventral premotor area F5 and the striatal sectors connected with the cortical sectors of a monkey engaged in a behavioral task requiring responding with an overt motor behavior to a specific set of visual stimuli.

The results presented in this thesis represent the preliminary phase of the study. In brief, we identified task related neurons and categorized them based on their pattern of response. In addition, we evaluated how the populations of neurons recorded in the different studied sectors code the task factors relevant for task accomplishment in the different phases of the paradigm. Based on this, evidence we will present more specific hypotheses to be tested with further analyses.

4.1 Neural coding of the main behavioral rule

In order to assess whether and to which extent the recorded neurons have a role in encoding the general, abstract rule of this task (i.e. red cue = pay attention; green cue = act), we performed Principal Component (PCA) and decoding analyses. These analyses were run separately on the neural population recorded in different arrays, to verify whether the rostral prefrontal, the caudal prefrontal, the premotor and the basal ganglia recorded sectors, differently contribute to this type of code.

The decoding analysis showed that the main behavioral rule of the task modulates the neural activity during the entire task unfolding in both prefrontal sectors, and only in the late phases of the task in F5 and in BG. Since the decoding analyses might depend on the number of neurons and neurons sampling, one could hypothesize that increasing the number of neurons in F5 and BG, this

difference could decrease or disappear. We believe that this is unlikely for several reasons. First, the decoding performance reaches 100% accuracy when trained and tested on the cue bins in the two prefrontal arrays, while it is around chance level in F5 and BG, thus it is implausible that this gap will disappear with a different neuronal sample. Second, the results of the PCAs are in line with those of the decoding. In order to demonstrate that the number of neurons is not the reason of the difference in decoding among different areas, we planned to perform a further decoding analysis on the same number of neurons in each sector (by randomly selecting a subsample of prefrontal neurons).

The decoding analysis, also allows to predict, based on the activity recorded at a given time point, how the condition can bias neural activity in different moments of the task. Interestingly, in the rostral prefrontal array, the pattern of activity recorded during the whole task, except for the *Presentation* epoch, allows, to reconstruct the effect of the general rule (condition), in all the other phases of the task. For example, the activity recorded in the *Cue* epoch allows to generalize with a growing accuracy the condition effect in the *Delay*, *Go* and *Action* epochs; similarly, in a sort of bi-directionality of the decoding, the activity recorded during the action performance allows to reconstruct the cue effect in the *Delay* and *Cue* epochs. This suggests that also in the final phases of the task there is a strong representation of the information about the type of behavior to perform, instructed by the cue at the beginning of the task (release starting point or perform a motor act). The TCT analysis indicates that the general rule of the task influences the neural activity during almost the whole task. In turn, this prompts the idea that the neurons activity is not strictly related to what is actually occurring at different times (e.g. cue onset, go signal, action execution), but, instead that there is a common code for the neurons responding in all the epochs. We propose that this common neural code is the process of associating the instruction with the behavior. We will discuss more in detail this proposal later in this section.

This "bi-directional" coding effect, is particularly evident in the rostral prefrontal array, but is also present to a less degree in the caudal one. Here, however, the process seems to be less bi-directional. In fact, while the decoding on the cue activity allows a prediction of the condition effect in the *Action*

epoch, the decoding trained on the *Action* epoch, does not allow reconstructing the condition effect in the *Cue* epoch. This suggests that the general behavioral rule is not the only important factor driving the neuron response in this array, and that the information coded in the *Action* epoch is not strictly related to the information conveyed by the instructing cue. The most likely possibility is that these neurons, even if to some degree are involved in coding whether to release the manipolandum or perform an action, are also involved, to a larger extent, in coding which type of action actually must be performed in the Imitation condition (i.e. to grasp or to touch). Indeed, though indirectly, the results of PCA analyses on the type of stimulus, showing a differential code during *Presentation* and *Action* epochs of the instruction to grasp or touch, support this hypothesis. A further support to this interpretation is represented by the evidence that in the decoding analysis, differently from the rostral array, the *Presentation* activity allows, though quite weakly, a generalization of condition effect on the *Action* epoch, indicating that some information coded in the *Presentation* epoch is important to predict the condition in the *Action* epoch. It is thus very likely that the type of stimulus and the type of specific action to perform in the Imitation condition are also at play in this cortical field. To demonstrate this hypothesis, we plan to decode the effect of the two specific behavioral goals (instruction to touch vs. grasp) on the neurons responding best in the Imitation condition in this array.

Altogether, these observations indicate that the neurons of the rostral prefrontal array encode the general rule of the task, intended as the link between cuing stimulus and behavioral response. This interpretation is in line with previous studies showing that VLPF is crucial for forming associations between the instructing cues and the actions or decisions that they specify (Passingham et al., 2000; White & Wise, 1999; Bussey et al., 2002; Wallis et al., 2001). The rostral prefrontal array is located on the rostral part of area 46v and the rostral part of area 12r, cortical sectors characterized by mostly intrinsic prefrontal connections, and by extrinsic connections mainly with the anterior half of the temporal cortex (Borra et al., 2011; Gerbella et al., 2013; Nelissen et al., 2011; Webster et al., 1994). They are deemed to be involved in coding episodic memory, i.e. the memory about a well consolidate association between sensory stimuli and a rule driving behavior (see Koechlin et al., 2003; Koechlin

and Summerfield, 2007; Rozzi and Fogassi, 2017).This also prompts the idea that neurons of these sector could be deeply involved in the process of associative learning. The caudal prefrontal array, extends over the rostral part of caudal 46v and, to a lesser extent of the intermediate sector of area 12r, strongly connected with the premotor cortex, in particular area F5a, and with inferior parietal areas such as AIP, PFG and SII (Borra et al., 2011; Gerbella et al., 2013; Nelissen et al., 2011), all involved in hand related actions. These connections would support our proposal that, besides coding episodic aspects of the task, this region is involved also in coding the specific behavior associated with contextual information. This interpretation is in line with the cascade model, proposed by Koechlin and coworkers (Koechlin et al., 2003; Koechlin and Summerfield, 2007), suggesting that action selection is guided by hierarchically ordered control signals, processed in a network of brain regions organized along the anterior–posterior axis of the lateral frontal cortex, hypothesizing thus a rostro-caudal organization in which action goal is sequentially encoded from prefrontal to premotor regions. Our posterior prefrontal array would be located in the region involved in the "contextual control" of behavior.

4.2 Neural coding of the two action goals

During the *Imitation* condition, the PCA, and the correspondent single neuron activity, allowed us also to identify differences in the neural dynamics representing the two action goals (i.e. grasp or touch).

The information related to the action goal appears to modulate the neural activity during different epochs depending on the recorded territory. Specifically, in the rostral prefrontal array the population dynamics shows a difference between the trajectories associated to the two action goals only during the *Presentation* epoch, in the caudal prefrontal array, this effect is present in the *Presentation* and in the *Action* epochs, and F5 population only during the *Action* epoch. Note that the visual stimuli associated to each behavioral goal were very different in terms of visual features and complexity (simple moving shapes and complex visual scenes showing a human subject interacting with an

object), indicating that the two action goals are encoded, independently from the visual features of the associated stimuli. This suggest that the role of the input for this type of code is less relevant than the association stimulus-response (rostral and caudal prefrontal sectors) and the behavioral output itself (caudal prefrontal and area F5). Similar to caudal prefrontal, the BG population dynamics shows a difference between the trajectories associated to the two action goals in the *Presentation* and *Action* epochs. This does not necessary mean that the BG and caudal prefrontal recorded sectors are anatomically connected or have the same role. As discussed above, the BG probes allowed to record only a small number of neurons and we pulled together the data from the three probes. Most neurons, however, responded during action execution, suggesting that the sector connected with the motor cortex (see Lanzilotto et al., 2016) was actually included in the recorded area. From this perspective, it is even more interesting that, similar to prefrontal arrays, the PCA allows finding an action goal effect also in the *Presentation* epoch. This suggests that also a prefronto-recipient sector was recorded. The histological evaluation of the recording sites and recording from a second animal are needed to investigate more in details the role of BG in the studied network.

4.3 Neural coding of biological and non-biological stimuli

The PCA and the correspondent single neuron activity allowed us to identify differences in the neural dynamics related to the different categories of stimuli (biological vs. non-biological). This difference was observed only during *Presentation* epoch in the two prefrontal and basal ganglia recorded territories, but not in F5. This indicates that these sectors are likely involved in the description of the visual scene. The visual description of the stimuli could be interpreted as a kind of low level elaboration, considering that the biological stimuli are much more complex than the non-biological ones, in terms of number of colours, three-dimensionality, movement complexity and dynamics. The idea that prefrontal cortex is involved in visual stimuli processing is in line with a large body of functional evidence showing the presence of visual responses in ventral prefrontal cortex (Romanski et al., 2011; Freedman et al., 2001; Rozzi et al., 2021; Seger et al., 2010), and of

anatomical studies describing the connection of ventral prefrontal cortex, and especially of its rostral part, with the inferotemporal cortex (Borra et al., 2011; Webster et al., 1994), that is the apex of the ventral visual stream (Goodale et al., 1992). An alternative interpretation, in line with the studies of Rainer and Miller (2000), is that these neurons are involved in a high level visual coding, contributing to the process of stimulus categorization. Differently from these authors' studies, however, the categorization process, in our case, would be unconscious, since the monkey is not required to exploit the biological and non-biological category in terms of different behaviors. Further analyses and studies specifically aimed to this topic are needed to clarify this issue.

5. CONCLUSION

In this work, we aimed at assessing the specific role of different brain regions in linking relevant sensory information to an associated behavioral output. Our results indicate that each of the studied cortical sectors contains neurons encoding relevant information for the task accomplishment. This type of code is partially different in the various sectors. In particular, the activity of the neurons of F5 area are most often active during action execution. The discharge of F5 neurons in the *Action* epoch, as expected, is not modulated by the visual features of the presented stimuli, but is influenced by the general behavioral rule and by the instruction guiding the selection of the specific act to perform. The neurons of rostral prefrontal areas 46v and 12r discharge in association to most of the task epochs, and in all of them, their discharge strongly depends on the general behavioral rule. The caudal prefrontal area 46v and intermediate area 12r, has a general pattern of activation similar to that of the most rostral sector, but is also strongly involved in coding the specific aspect of motor guidance. The basal ganglia behaves similar to the caudal prefrontal and to the premotor sectors, but, due to the technical limitation we encountered in the study of this subcortical structure, further investigations are needed to precisely assess their specific function.

Altogether, these data confirm the role of ventral premotor cortex in action guidance, support the idea that the rostral prefrontal cortex is involved in the process of associating a stimulus with a specific behavior, and thus, very likely, participate to associative learning, while the caudal prefrontal cortex, would represent a link between the more abstract coding of rules and their actual behavioral implementation.

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