Different Contribution of the Monkey Prefrontal and Premotor Dorsal Cortex in decision-making supported by inferential reasoning

Ramawat Surabhi[1,2], Mione Valentina[1], Di Bello Fabio[1,] Bardella Giampiero[1,2], Genovesio Aldo[1], Pani Pierpaolo[1], Ferraina Stefano[1], Brunamonti Emiliano[1]

[1]Department of Physiology and Pharmacology, Sapienza University, Sapienza University of Rome, P.le Aldo Moro 5, 00185 Rome

[2]PhD Program in Behavioral Neuroscience, Sapienza University of Rome, P.le Aldo Moro 5, 00185 Rome

Corresponding author: Dr. Emiliano Brunamonti, PhD

Department of Physiology and Pharmacology

Sapienza University

P.le Aldo Moro 5, Rome, Italy

email: emiliano.brunamonti@uniroma1.it

Phone: 06 4969 0389

Abstract

Several studies reported similar neural modulations between brain areas of the frontal cortex, such as the dorsolateral prefrontal (DLPFC) and the premotor dorsal (PMd) cortex, in tasks requiring encoding of the abstract rules for selecting the proper action. Here, we compared the DLPFC and PMd neuronal activity of monkeys trained in choosing the highest-ranking image of pair (target item), selected from an arbitrarily rank-ordered set (A>B>C>D>E>F) in the context of a transitive inference task. Once acquired by trial-and-error, the ordinal relationship between pairs of adjacent images (i.e. A>B; B>C; C>D; D>E; E>F), monkeys were tested in inferring the ordinal relation between items of the list not paired during learning. During inferential decisions, we observed that the choice accuracy increased and the reaction time decreased as the rank difference between the compared items enhanced. This result is in line with the hypothesis that after learning, the monkeys built an abstract mental representation of the ranked items, where rank comparisons correspond to the item position comparison on this representation. In both brain areas, we observed higher neuronal activity when the target item appeared in a specific location on the screen, with respect to the opposite position and that this difference was particularly enhanced at lower degrees of difficulty. By comparing the time evolution of the activity of the two areas, we revealed that the neural encoding of target item spatial position occurred earlier in DLPFC than in PMd, while in PMd the spatial encoding duration was longer.

Keywords: transitive inference, prefrontal cortex, premotor cortex, monkey, decision making

INTRODUCTION

When reaching toward a target, visual information about the target properties and location must be transformed in spatially oriented motor acts. Cortical circuits behind these transformations embed neurons that show spatial preference, i.e. higher neuronal activity for a specific target position compared to others (Wise et al., 1992; Caminiti et al., 1998; Ferraina et al., 2001; Lebedev and Wise,

2001). When more potential targets are simultaneously presented, neurons with different spatial preferences compete for signaling the proper target location and reaching direction (Cisek and Kalaska, 2005). An open question is whether and how perceptual or cognitive factors, affect this competing process. The manipulation of perceptual factors variables, such as visual discriminability, demonstrated that the difficulty in encoding the target position was reflected in less sharp spatial preference in different brain areas (Coallier and Kalaska, 2014; Coallier et al., 2015; Chandrasekaran et al., 2017). However, how cognitive variables influence spatial preference-related activity in brain areas involved in visuomotor transformation is still poorly investigated. It has been recently demonstrated that in the dorsal premotor cortex (PMd), a brain area with a key role in visuomotor transformation in primates (Johnson et al., 1996; Boussaoud et al., 1998), neurons express their spatial preference depending on the cognitive difficulty in selecting the target when simultaneously presented with a non-target (Mione et al., 2020). In the quoted work, by using a Transitive Inference (TI) protocol, monkeys were firstly required to create a mental representation of a rank-ordered set of visual items as A> B> C> D> E > F, and then to use this representation to select the higher-ranking item (target-item) within all possible pairs, including never experienced ones (e.g., B-E) by performing a reaching movement. In different trials, the target item was randomly presented to the left or the right side of a computer screen and paired with a non-target-item presented at the opposite spatial position. Within this experimental design, the cognitive difficulty was modulated by pairing target and non-target items as a function of their degree of overlapping in the mental representation of their ordinal position. The degree of overlapping of pairs of items is quantified by their difference in rank and referred to as Symbolic distance (SDist). Depending on the symbolic distance, target selectivity for the item B - for example - was easier when paired with the non-target item E (low degree of overlapping corresponding to SDist = 3) and more difficult when paired with non-target item C (high degree of overlapping corresponding to SDist = 1). The authors found that this cognitive difficulty affected the neural spatial preference (spatial selectivity) in PMd.

Several neurophysiology studies have revealed comparable neural activation between PMd and DLPFC while encoding a given task-relevant variable, thus suggesting an overlapping competence of the two brain areas (Cromer et al., 2011; Yamagata et al., 2012; Fine and Hayden, 2021). It is

known that the prefrontal cortex can flexibly encode different task-relevant variables (Donahue and Lee, 2015; Fusi et al., 2016; Astrand et al., 2020), including the position of the target in oculomotor delayed visual search and delayed-response tasks (Iba and Sawaguchi, 2002). Here we first asked if target position selectivity of DLPFC emerges during the execution of a TI task, then we tested for differences between DLPFC and PMd.

We observed that the spatial selectivity of the DLPFC and PMd neurons was modulated by cognitive difficulty on target selectivity. Importantly, the comparison between the time evolution of neuronal activity in the two brain areas revealed that the selection of target position occurred with different timings in DLPFC and PMd. In this work, in line with previous studies (Cromer et al., 2011; Yamagata et al., 2012), we support the idea of a tight interplay between the lateral PFC and PMd in the target position encoding for action execution.

MATERIALS AND METHODS:

Subjects and Data Acquisition:

Animals: Neuronal activity was recorded from the DLPFC and the PMd of three male rhesus monkeys (Macaca mulatta), weighing 5.50 kg (Monkey 1), 6.50 kg (Monkey 2), and 10.0 kg (Monkey 3) respectively, while performing a TI task.

DLPFC Recording: In Monkey 1 and Monkey 2, the cells in the dorsal area of the prefrontal cortex (DLPFC) were targeted and the neural activity from these cells was recorded extracellularly using a five-channel multielectrode recording system (Thomas Recording, Germany). The recording chambers were surgically implanted in the left frontal lobe at the stereotaxic coordinates: anterior-32, lateral-19 in Monkey 1 and anterior-30, lateral-18 in Monkey 2, along with the head restraining devices. At the end of the neurophysiological experiment, the location of the electrodes was confirmed by visual examination following the surgical opening of dura for the implantation of a chronic array in Monkey 1 (given the following recording from PMd neurons), while in Monkey 2, the electrodes' location was confirmed using a structural MRI scan.

PMd Recording: The neural activity was recorded extracellularly from the left PMd of Monkey 1 and Monkey 3 using chronic electrode arrays (96-channels; Blackrock Microsystems, Salt Lake City, Utah).

The surgical procedures in all three monkeys were performed under aseptic techniques while keeping the animal under a general anesthesia (1-3% isloflurane-oxygen, to effect).

The monkeys were housed and cared for following the European (Directive 2010/63/EU) and Italian (D.L. 26/2014) laws, regulating the use of non-human primates in scientific research. The Italian Ministry of Health approved the research protocol. Housing conditions and experimental procedures were in line with the Weatherall report (use of non-human primates in research).

Behavioral data recording and task implementation: The task was controlled using the Cortex Software package (https://nimh.nih.gov/) and administered by presenting the task stimuli on a touchscreen (MicroTouch, sampling rate of 200 Hz) connected to the computer through serial port to detect the response. An RX6 TDT recording system (Tucker-Davis Technologies) was employed during the DLPFC recording sessions, which was synchronized to the behavioral events in order to detect and record the neuronal activity during each trial. During the PMd recording sessions, an RZ2 TDT system (Tucker-Davis Technologies, Alachua, FL, USA) was used, since a higher number of simultaneously recorded channels were dealt with.

Test stimuli and task design:

For this study, at the beginning of every session, six stimulus images were randomly selected from a database of 80 abstract black and white images (16° X 16° visual angle, bitmaps) and arbitrarily ordered to form a ranked series (Figure 1A). To avert the familiarity of the stimulus/rank association, any of the stimuli were not repeated or assigned to the same rank for a significant number of consequent sessions (Brunamonti et al., 2014, 2016; Mione et al., 2020). The monkeys were trained to learn the relationship among all the items of this ranked series.

Each experimental session (for both DLPFC and PMd neural recordings) comprised a learning phase, requiring the monkeys to learn the novel relationship between all the adjacent items (Figure

1B: SDist1) in the ranked series, and a test phase in which the monkeys were asked also to infer the relationship between novel pairings of non-adjacent items (Figure 1B; SDists >1). The learning phase was accomplished by the means of two different methods: 1) sequential learning, and 2) chained learning procedure as reported in our previous works (Brunamonti et al., 2016; Mione et al., 2020). More specifically, in the sequential learning sessions monkeys were required to progressively learn the reciprocal rank order of pairs of items adjacent in the sequence, while in the chained learning procedure monkeys were required to link two lists of 3 rank-ordered items previously acquired by the sequential learning.

The sequential learning was implemented in two steps, learning phase 1 and learning phase 2. During learning phase 1, the monkeys were presented with the pairs comprising adjacent items sequentially, and they were required to identify the higher ranking item by trial and error in blocks of 15 (Monkey 1: DLPFC recording) or 20 (Monkey 2: DLPFC recording; and Monkey 1 and Monkey 3 PMd recording) trials. Each block was repeated until the monkey achieved a performance of at least 90% (DLPFC recording) or 80% (PMd recording) for the pair. Once the desired performance was reached for every pair in the series, the learning phase 2 (consolidation) followed, where the previously experienced pairs were presented in a random order in larger blocks of trials, and a different criterion (> 60% correct trials) was used.

Differently, during the chained learning procedure the six-item list was divided into two smaller three-item lists (A>B>C and D>E>F). The rank order of the two three-item lists was learned independently by the sequential learning method in separate blocks until the monkeys achieved a criterion of at least 80% correct trials. The two lists were then linked by learning the association C>D in blocks of 20 trials.

For the DLPFC experiment, 45 and 47 sessions were recorded respectively for Monkey 1 and Monkey 2, using the sequential learning only; whereas during the PMd recording, Monkey 1 and Monkey 3 were tested for 7 sessions each, using different learning procedures: the chained-list learning in 6 (Monkey 1) and 4 (Monkey 3) sessions, and sequential learning in 1 (Monkey 1) and 3 (Monkey 3) sessions (see Brunamonti et al., 2016; Mione et al., 2020 for further details).

In the test phase, all the possible pairs of items were presented in a random order i.e. the pairs comprising adjacent items from the ranked series, in addition to the pairs with non-adjacent items (Figure 1B; SDist1 – SDist5). Each pair was presented at least 14 or 18 times during the DLPFC and PMd experiments respectively, with an equal probability of the target item to be presented on the left or the right position of the screen.

The time course of each trial was identical for the learning phase and the test phase during all the recording sessions from DLPFC and PMd (Figure 1C). At the beginning of each trial, a red dot (central target) was presented at the center of the screen and the monkey had to respond within 5s by pressing a button fixed on the monkey chair (DLPFC sessions) or by touching the red dot on the screen (PMd sessions; as depicted in Figure 1C) until the appearance of pair of items on the screen. The monkey was required to maintain the touch (or the button pressed) for a random variable Delay period (600-1200 ms) after the Pair Onset until the red spot disappeared from the screen (Go Signal). The Go Signal instructed the monkeys to select (to reach) the higher-ranking item on the screen to obtain the reward.

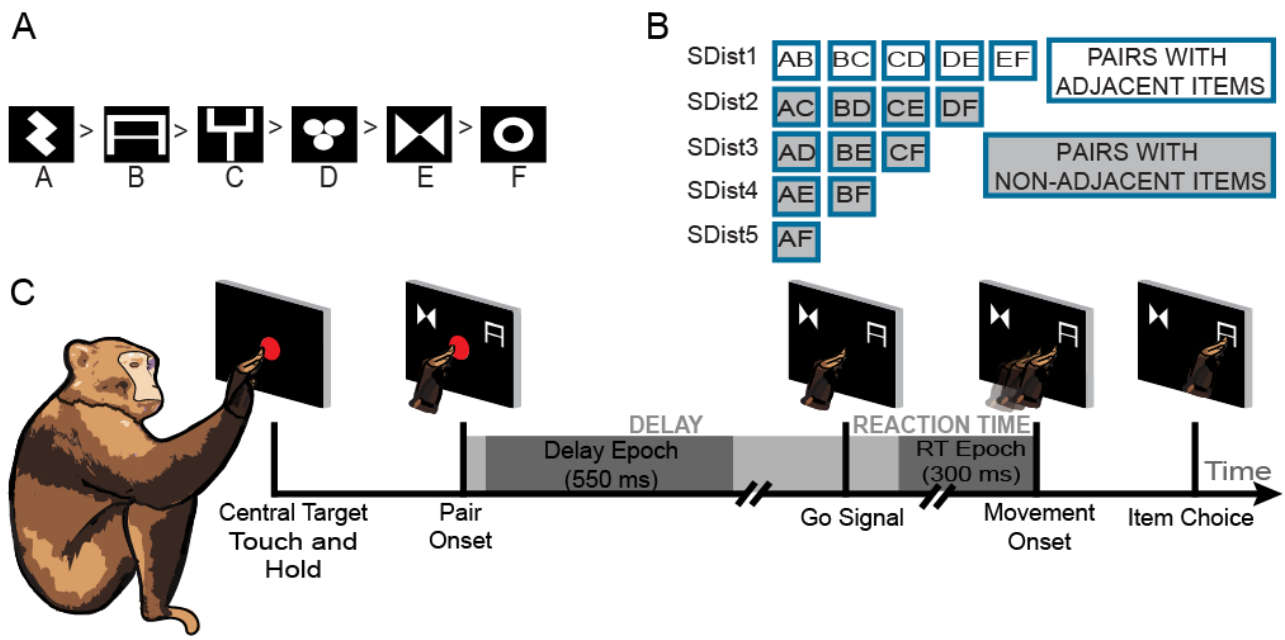


Figure 1. Task design and Analysis Epochs: A. An example of a 6-item ranked series chosen at the beginning of the experiment. **B.** All the possible combinations of pairs from the items of the ranked series and their symbolic distances (SDist) associated to each combination. **C.** Time course of a single trial during each session for learning phase and test

phase through all DLPFC and PMd recording sessions and the epochs were chosen for analysis of neuronal activity (marked in dark grey).

Data Analysis:

Selection of DLPFC and PMd recording sessions:

One of the goals of the present work is to compare the temporal evolution of the neuronal encoding of the target position between DLPFC and PMd while performing a TI task. Since this comparison was performed by analyzing the neuronal activity recorded in different experimental sessions, we first assessed that differences in the time evolution of the brain activity between the two areas were independent of different levels of accuracy and response time of monkeys in different sessions. To this aim, we studied DLPFC and PMd neuronal activity from the sessions in which the accuracy and the reaction time (RT; calculated as the time from the Go Signal to the Movement Onset) in performing the task was comparable across monkeys. By this procedure, we selected 14/45 sessions of Monkey 1 and 22/47 sessions of Monkey 2 DLPFC recording, respectively.

While exploring these behavioral parameters, we observed that the RT of Monkey 1, from both the DLPFC and the PMd sessions, were significantly faster than Monkey 2 and Monkey 3, respectively recorded in DLPFC and PMd only. To account for these differences, in the following analyses data obtained from Monkey 1 were analyzed independently from that obtained in recording sessions with Monkey 2 and Monkey 3. As a result of a two-sample t-test, we found comparable accuracies and RT between Monkey 1 DLPFC and PMd sessions ($p>0.05$), Monkey 2 DLPFC, and Monkey 3 PMd sessions ($p> 0.05$; see Table 1 for details).

	DLPFC	**PMd**	**Two- sample t-test**
	Monkey 1	**Monkey 1**	
Average accuracy (SD)	0.90 (0.05)	0.86 (0.08)	$t(19) =1.28$, $p=0.21$
Average Reaction Time (SD)	350 (75) ms	386 (32) ms	$t(19) = -1.99$, $p=0.24$
	Monkey 2	**Monkey 3**	
Average accuracy (SD)	0.92 (0.10)	0.85 (0.09)	$t(1,27) = 1.77$, $p=0.08$

Average Reaction Time (SD)	433 (46) ms	437 (60) ms	t(27) = -0.19, p=0.85

Table 1: Comparative analysis of Average Behavior in selected sessions; SD-Standard Deviation

Behavioral correlates of TI at test: We first investigated if the behavior during the selected sessions from DLPFC (Monkey 1: 14; Monkey 2: 22) and PMd (Monkey 1: 7; Monkey 2: 7) recordings, was modulated by the SDist. This analysis was performed to assess whether the monkeys' ability to select the target item over the simultaneously presented non-target item depends upon the degree of overlapping of the two items in their mental representation. To this aim, we tested if the probability of selecting the correct item significantly increased and the corresponding RT significantly decreased with the rising of the symbolic distance.

Neuronal correlates of TI at test: We studied 141 neurons from DLPFC (Monkey 1: 56, Monkey 2: 85) and 186 neurons (Monkey 1: 59, Monkey 3: 127) from PMd obtained during the selected recording sessions. To address the question, whether the activity of DLPFC neurons correlated with the difficulty in selecting the position of the target item, we first studied spatial preference for the target that emerged in the neuronal activity of DLPFC, and then we tested if this preference was modulated by the SDist. As a further step of the analysis, we compared the pattern of activation of neuronal activity in DLPFC and PMd to evaluate how it differed between the two brain areas, during different epochs of the task. In doing so, we studied the neuronal activity from each neuron during two task epochs, 1) the Delay epoch, lasting from 50 ms to 600 ms after the Pair Onset; 2) the Reaction Time epoch, lasting for 300 ms before the Movement Onset (Figure 1C). For each neuron, we calculated the mean spike rate from the correct trials corresponding to each of the two target positions (left and right) at every SDist (SDist1-SDist5). Further, we normalized the mean spike rate across different task conditions by applying a z-score transformation.

To quantify the degree of preference of each neuron for the left or right target position, we first represented the neuronal activity as a point in a 2-dimensional space having the neuronal activity for the right and left positions of the target as x and y coordinates, respectively (Figure 3,4). Then, we

computed the Shortest Distance (D_n) of each point from the Equality Line (representing a preference or a lack of preference for any of the two target positions) as follows:

$$D_n = \frac{\mathrm{Right}_n - \mathrm{Left}_n}{\sqrt{2}}$$

where Left_n and Right_n are the coordinates of the nth neuron in the defined space, representing the normalized mean neuronal activity during the trials with the target located on the left and right position respectively. D_n can assume both positive and negative values, representing the points lying on either side of the equality line, where the negative values represent the neuronal preference for the left target position and positive values for the right target position. A high magnitude of D_n (positive or negative) indicates a greater degree of preference for one of the two positions of the target. We used the magnitude of D_n to identify the neurons showing a significant target position preference. Across the population of neurons from each area, we calculated the maximum range of variation during the two analysis epochs: $D_{population} = (D_{n_max} - D_{n_min})$, then we defined a neuron to be significantly selective for the left or the right target position respectively, if the corresponding positive or negative value D_n was lower (if $D_n < 0$) or higher (if $D_n > 0$) than the 10% of the total range of excursion ($D_{population}$). To study how the preference for the target position was modulated by the task difficulty, we first identified the DLPFC and PMd neurons displaying a target position selectivity at SDist5 (the easier condition of the task), and then we observed how this selectivity changed across other SDists. We used a linear model fit to test if the target position selectivity was significantly modulated by the rising of SDist.

We applied a Receiver Operating Characteristic (ROC) analysis on neuronal activity recorded during the selected sessions to study the time course of target position selectivity in DLPFC and PMd (Thompson et al., 1996; Mione et al., 2020). Once identified the preferred target position of each neuron at SDist5 we computed the area under the ROC (auROC) in consecutive time bins (lasting 20ms) in a time epoch starting 500 ms before to1300 ms after the Pair Onset using a moving time window of 200 ms with a 20 ms step. Thus, for each time window of every neuron, we obtained a probabilistic measure of encoding the target when it was presented on the preferred position

compared to the opposite position. We estimated the latency of target position discrimination by calculating the time when the auROC value crossed the threshold of 0.6 for 60 ms (3 consecutive time bins) in the trial time ranging from 80ms to 1300ms after the Pair Onset. We repeated this estimate for the comparisons at SDist lower than 5 to test if the latency of spatial discrimination changed in pairs comparisons of increasing degrees of difficulty in both, DLPFC and PMd. The auROC values were calculated for a balanced number of trials for all the task conditions, corresponding to the minimum number of correct trials across all the task conditions. On average, the number of trials for each position of the target was 17(SD=5) for DLPFC sessions and 31 (SD=16) for PMd sessions.

To account for the differences in RT detected in Monkey 1 and the other two monkeys (see previous section), we performed the latency estimates of target position selectivity in different groups of neurons: 1) neurons obtained by Monkey 1 in which the RT in DLPFC (47 neurons) and PMd (55 neurons) recording sessions was not statistically different; 2) neurons obtained by Monkey 2 in DLPFC (79 neurons) sessions and neurons recorded in Monkey 3 PMd (119 neurons) sessions with RT not statistically different.

Latency of target position discrimination in neurons measured in Monkey 1 and those measured in Monkey 2 and Monkey 3 were analyzed separately. To test for the differences between latencies across different task conditions and different areas, we calculated the probability of observing latencies in the initial 75% of the distributions (< 900ms). Consequently, we applied a Kolmogorov Smirnoff test to identify the inter-area differences between these probabilities if any. A t-test was used to compare the inter-area differences between the average latencies across the different SDists. To explore further, how the neuronal populations of two areas encode target position with varying difficulties, we computed the fraction of cells showing a sustained coding for the target position (auROC>0.6 for more than 70% of the total time) as a function of SDist. The differences for the measures between the two areas were tested using a Kolmogorov Smirnoff test. All data analyses were performed using custom-made functions developed in MATLAB (The MathWorks) and Wolfram Mathematica.

RESULTS:

Choice difficulty modulates the ability to select the target position during TI task:

The accuracy and RT for target position selection exhibited a significant SDist effect during the pair comparisons of the test phase, in both the DLPFC and PMd recording sessions (Figure 2). A linear regression analysis revealed a significant increase in the proportion of correct to incorrect choices and a decrease in the RT with the rising SDist (see table 2 for details on the regression analysis) for each monkey. These results are in line with the hypothesis that, at the end of the learning phase, ranked items are arranged on a mental line, and the difficulty in pair comparisons depends on the degree of overlapping of the items' representation on this line (Brunamonti et al., 2011, 2016; Mione et al., 2020).

DLPFC Sessions	**Monkey 1**	**Monkey 2**
Accuracy (left target)	P_{left}=-0.51(SDist)+0.76, $p<0.05$	P_{left}=-0.037(SDist)+0.80, $p<0.05$
Accuracy (right target)	P_{right}= 0.50(SDist)+0.78, $p<0.05$	P_{right}=0.022(SDist)+0.89, $p<0.05$
RT (left target)	RT_{left}= 0.10(SDist)+0.32, $p<0.05$	RT_{left}= 0.22(SDist)+0.67, $p<0.01$
RT (right target)	RT_{right}= -0.15(SDist)+0.42, $p<0.05$	RT_{right}=-0.20(SDist)+0.60, $p<0.01$
PMd Sessions	**Monkey 1**	**Monkey 3**
Accuracy (left target)	P_{left}=-0.056 (SDist)+0.74, $p<0.01$	P_{left}=-0.075 (SDist)+0.66, $p<0.01$
Accuracy (right target)	P_{right}=0.058 (SDist)+0.71, $p<0.01$	P_{right}=0.067 (SDist)+0.69, $p<0.01$
RT (left target)	RT_{left}= 0.46 (SDist)+1.37, $p<0.01$	RT_{left}= 0.46(SDist)+1.38, $p<0.01$
RT (right target)	RT_{right}= -0.49(SDist)+1.48, $p<0.01$	RT_{right}= -0.42(SDist)+1.25, $p<0.01$

Table 2. Linear Correlation Coefficients of SDist with Behaviour of each monkey during DLPFC and PMd recording sessions

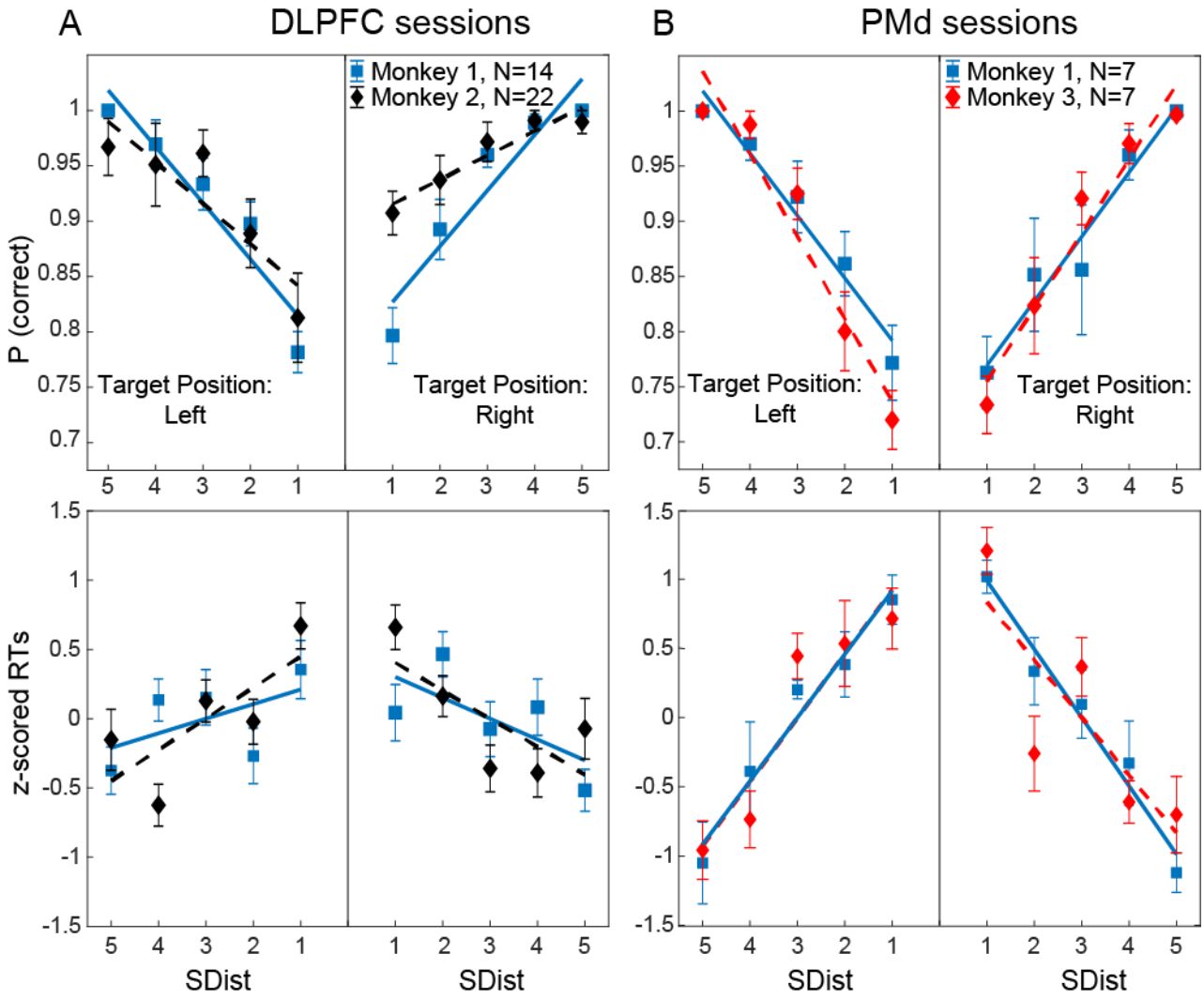


Figure 2. Influence of SDist on behavioral performance: Proportion of correct choices (top plots) and corresponding z-scored RT (bottom plots) for target selection at every SDist when the target was presented on the left and the right position of the screen during 'N' recording sessions from DLPFC (A: Monkey 1 and Monkey 2) and PMd (B: Monkey 1 and Monkey 3). Squares and diamonds correspond to the average performance and z-scored RT across the sessions, vertical bars represent the S.E.M. Linear regression fit across sessions is reported in table 2.

Populations of DLPFC and PMd neurons encode the task difficulty while differentiating between the target positions

Here we investigated if the neuronal correlates of target position selectivity in the population of DLPFC (n=141) and PMd (n=186) neurons were modulated by the difficulty of the task.

Figures 3 and 4 display the scatterplots of the normalized neuronal activity in response to the presentation of the target on the left (y-axis) or right (x-axis) position on the display for each SDist, during the Delay (Figures 3A and 4A) and Reaction Time (Figures 3B and 4B) epochs. By representing the activity of each neuron as a point in such 2-dimensional space, we quantified the degree of preference of the target position as the distance from the equality line. According to this criterion, a neuron was classified as spatially selective if its distance from the equality line exceeded 10% of the total range of excursion of the distances calculated across all the neurons and SDists. DLPFC neurons were considered as target selective for the left or right position of the target during the Delay epoch, if their distance from the equality line was lower than -0.49 or higher than 0.49, respectively. The same criterion in the RT epoch identified -0.51 and 0.51 as the threshold for left and right target selectivity. Similarly, a PMd neuron was distinguished to be spatial selective if the magnitude of the distance from the diagonal exceeded ±0.54 and ±0.46 during the Delay and the RT epochs respectively. For each neuron we first identified the left (blue dots) or right (red dots) preference for the target position, then we tested if the encoding of target location changed as the difficulty in pairs comparisons gradually increased, i.e. during the pairs comparisons from SDist5 to SDist1.

We quantified the proportion of neurons significantly exhibiting a target position selectivity at each SDist. The colored density distributions on the top of diagonals in both Figure 3 and 4 show that the proportion of target position selective neurons identified in DLPFC and PMd during the Delay epoch gradually decreased as the difficulty in pairs comparisons increased (see Table 3 for details). At the same time the proportion of neurons not showing a significant target position selectivity gradually increased from SDist5 to SDist1 (gray density distributions). This effect was not observed during the RT epoch in either area.

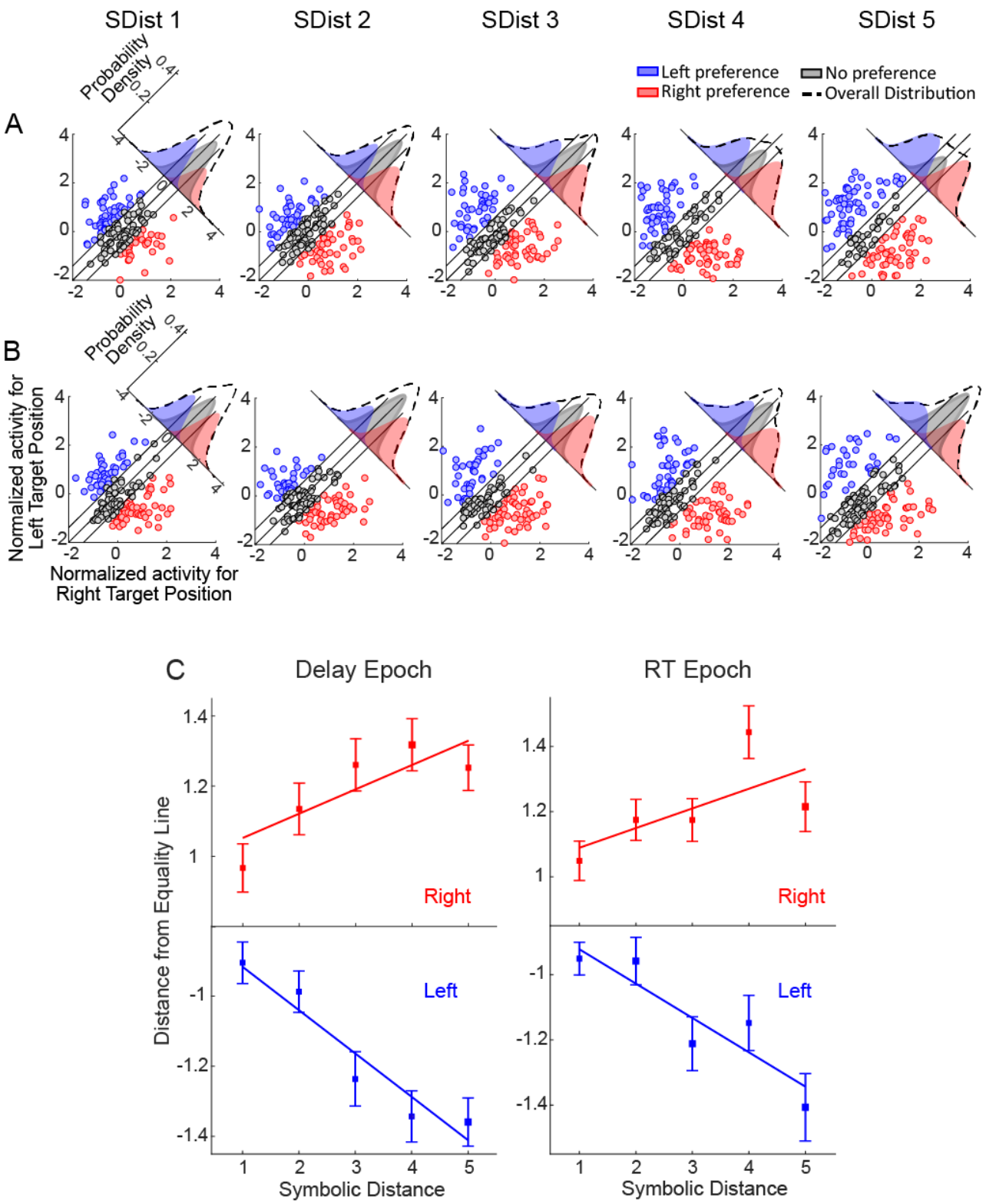
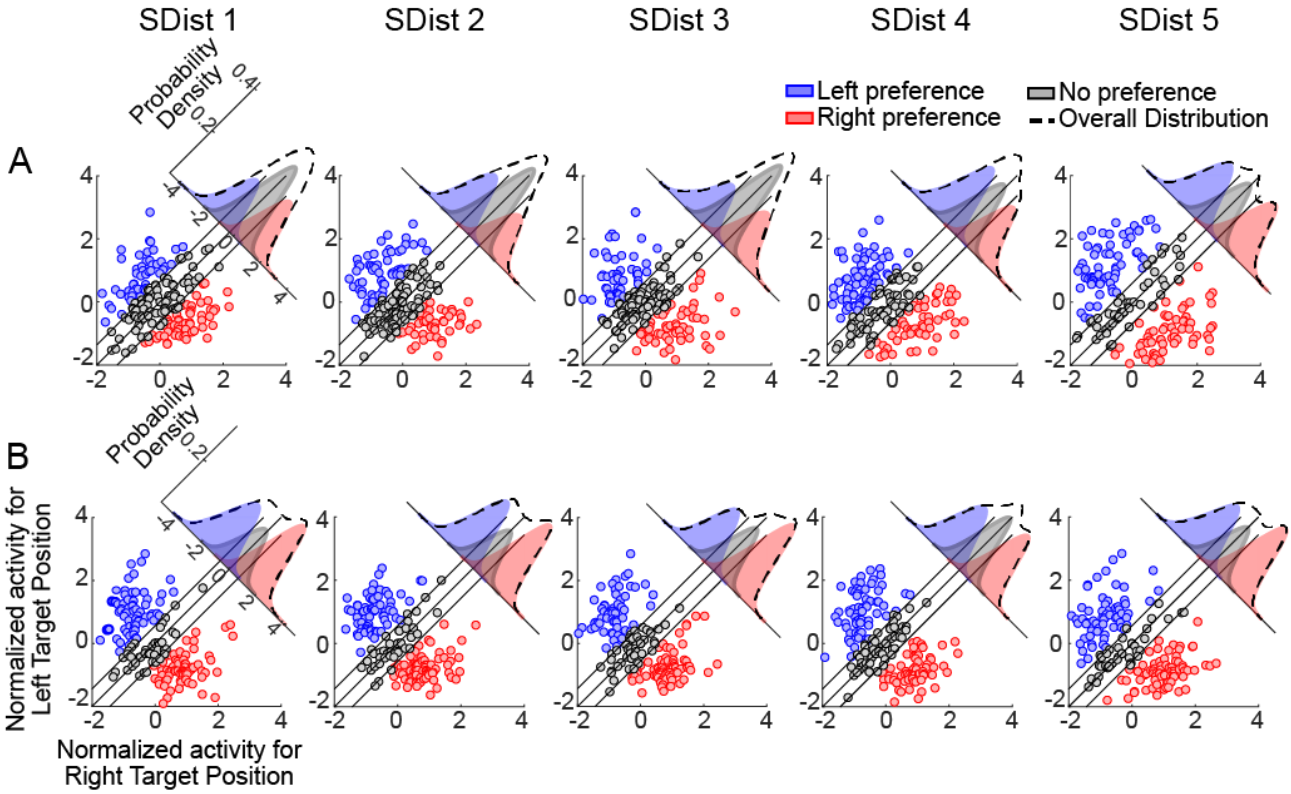


Figure 3. Encoding of target position in the population of DLPFC neurons

A-B, Scatter plots comparing the normalized mean neuronal activity from 141 DLPFC neurons during the Delay (A) and RT epoch (B), calculated across all the SDists when the target was presented on the left (y-axis) and the right (x-axis) position on the screen. Each dot in the plots represents a single neuron. The preference for left (blue dots) or right (red dots) target position of each neuron has been detected as its distance from the equality line (diagonal in each plot). Neurons

with a distance lower than 10% of the total range from the equality line were labeled as non-selective for the target position (grey dots). The density plots (dotted line) on the top of each diagonal show the distribution of the spatial-selectivity of neurons at each SDist, while the colored density plots represent the corresponding sub-distributions for the neurons showing selectivity for left, right, or no target preference. **C.** Mean distances of all the DLPFC neurons from the diagonal at each SDist and their linear correlation with the SDist during the Delay and RT epochs. They represent the strength of selectivity for left and right target positions exhibited collectively by all the neurons and the regression lines indicate a modulation of target position selectivity during Delay ($p<0.01$) and the RT epochs ($p<0.01$). Vertical bars indicate the Standard Error of Mean.



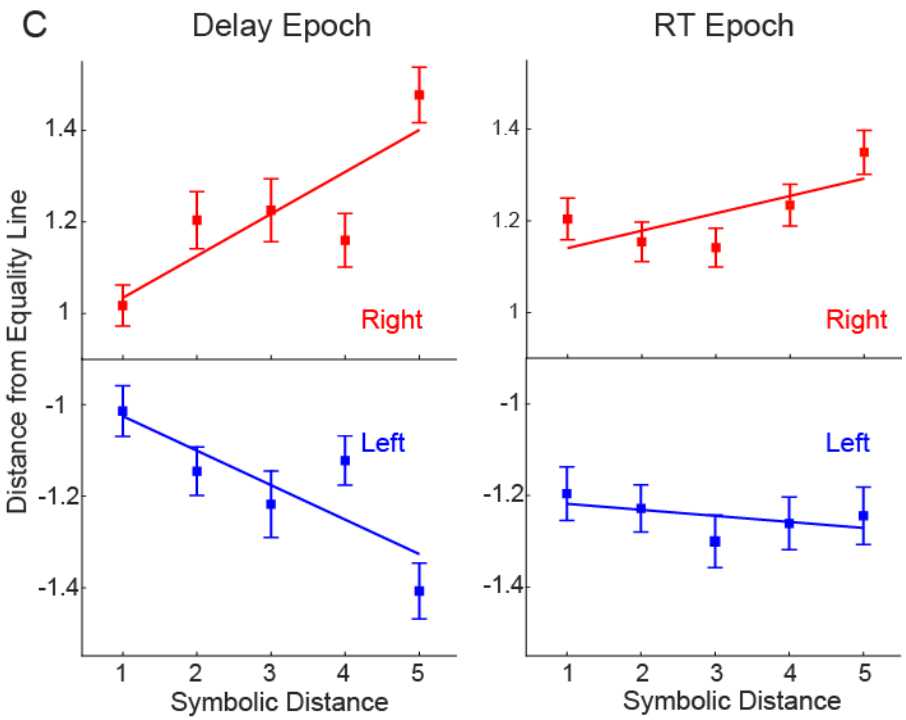


Figure 4: Encoding of target position in the population of PMd neurons

A-B, Scatter plots comparing the normalized mean neuronal activity for two target positions in 186 PMd neurons at each SDist during the Delay(A) and RT(B) epochs. The modulation of the neuronal activity is represented with the same codes as in Figure 3. **C.** The plots show the average strength of target position selectivity by overall PMd neurons at each SDist during the Delay and RT epochs. It indicates a linear correlation between the strength of selectivity with the SDist during the Delay ($p<0.01$), while a weaker modulation for the right target position and no modulation ($p>0.05$) for the left target position during RT by the SDist.

	SDist 1	**SDist 2**	**SDist 3**	**SDist 4**	**SDist 5**
Delay Epoch (DLPFC neurons)					
Target Preference	84 (59.6%)	85 (60.2%)	91 (64.5%)	101 (71.6%)	111 (78.7%)
No Preference	57 (40.4%)	56 (39.7%)	50 (35.4%)	40 (28.3%)	30 (21.2%)
RT Epoch (DLPFC neurons)					
Target Preference	91 (64.5%)	82 (58.1%)	96 (68.1%)	93 (65.9%)	81 (57.4%)
No Preference	50 (35.5%)	59 (41.8%)	45 (31.9%)	48 (34.0%)	60 (42.5%)
Delay Epoch (PMd neurons)					
Target Preference	105 (56.4%)	107 (57.5%)	104 (55.9%)	127 (68.2%)	134 (72%)
No Preference	81 (43.5%)	79 (42.7%)	82 (44.1%)	59 (31.7%)	52 (27.9%)
RT Epoch (PMd neurons)					
Target Preference	142 (76.3%)	144 (77.4%)	138 (74.2%)	129 (69.3%)	142 (76.3%)
No Preference	44 (23.7%)	42 (22.6%)	48 (25.8%)	57 (30.6%)	44 (23.7%)

Table 3: DLPFC (n=141) and PMd (n=186) neurons showing directional target preferences at varying choice difficulties

We further investigated the strength of target position selectivity as a function of the degree of difficulty in comparing the pairs of items by quantifying the variance of the density distribution of the distances from the equality line (dashed lines in figure 3 A-B and Figure 4 A-B; Table 4). This analysis highlighted a gradual and significant increase of the width of the distribution of the distance from the equality line with the increasing of SDist in both the analysis epochs overall DLPFC neurons and in the Delay epoch overall PMd neurons (Bartlett's test for the equal variances: all $p<0.01$; see table 4). Additionally, for the DLPFC and PMd spatially-selective neurons we measured the average distance from the equality line for each SDist (leftward and rightward shifting of the blue and red sub-distributions in Figure 3 A-B and Figure 4 A-B). By the means of regression analysis we detected that for both left and right target position selective neurons, the distance from the baseline significantly increased with the increasing SDist in DLPFC neurons during the Delay and the RT epochs ($p<0.05$; Figure 3C). Whereas, in the PMd neurons (Figure 4C), this effect was mainly detected only in the Delay epoch ($p<0.05$), but not in RT ($p>0.05$) epoch.

Variance	SDist1	SDist2	SDist3	SDist4	SDist5	Bartlett's test for equalvariances
DLPFC neurons (Delay)	0.65	0.83	1.20	1.48	1.56	$\chi^2(4)= 35.12$, $p<0.01$
DLPFC neurons (RT)	0.77	0.79	1.13	1.35	1.17	$\chi^2(4)= 15.57$, $p<0.01$
PMd neurons (Delay)	0.70	0.93	1.02	1.05	1.70	$\chi^2(4)= 39.90$, $p<0.01$
PMd neurons (RT)	1.26	1.23	1.22	1.22	1.46	$\chi^2(4)= 2.22$, $p=0.69$

Table 4: Variance of the distribution of distances from the equality line at every SDist.

Figure 5 (A and B) displays the pattern of activity from four representative neurons from DLPFC and PMd. Figure 5A shows the temporal evolution of the activity of two different DLPFC neurons during the time around the Pair Onset (upper panels) and the time around the Movement Onset respectively (lower panels). In these neurons, the average neuronal activity during the corresponding epochs was higher for the right position of the target and it increased with the rising of SDist. Figure 5B

displays a similar plot for two PMd neurons. The first of the PMd neurons (upper panels) displays a preference for the left position of the target during the Delay epoch that increased with the growth of SDist, while the second neuron (lower panels) displays a preference for the right position of the target during the time around the movement onset, but this preference was not modulated by the SDist.

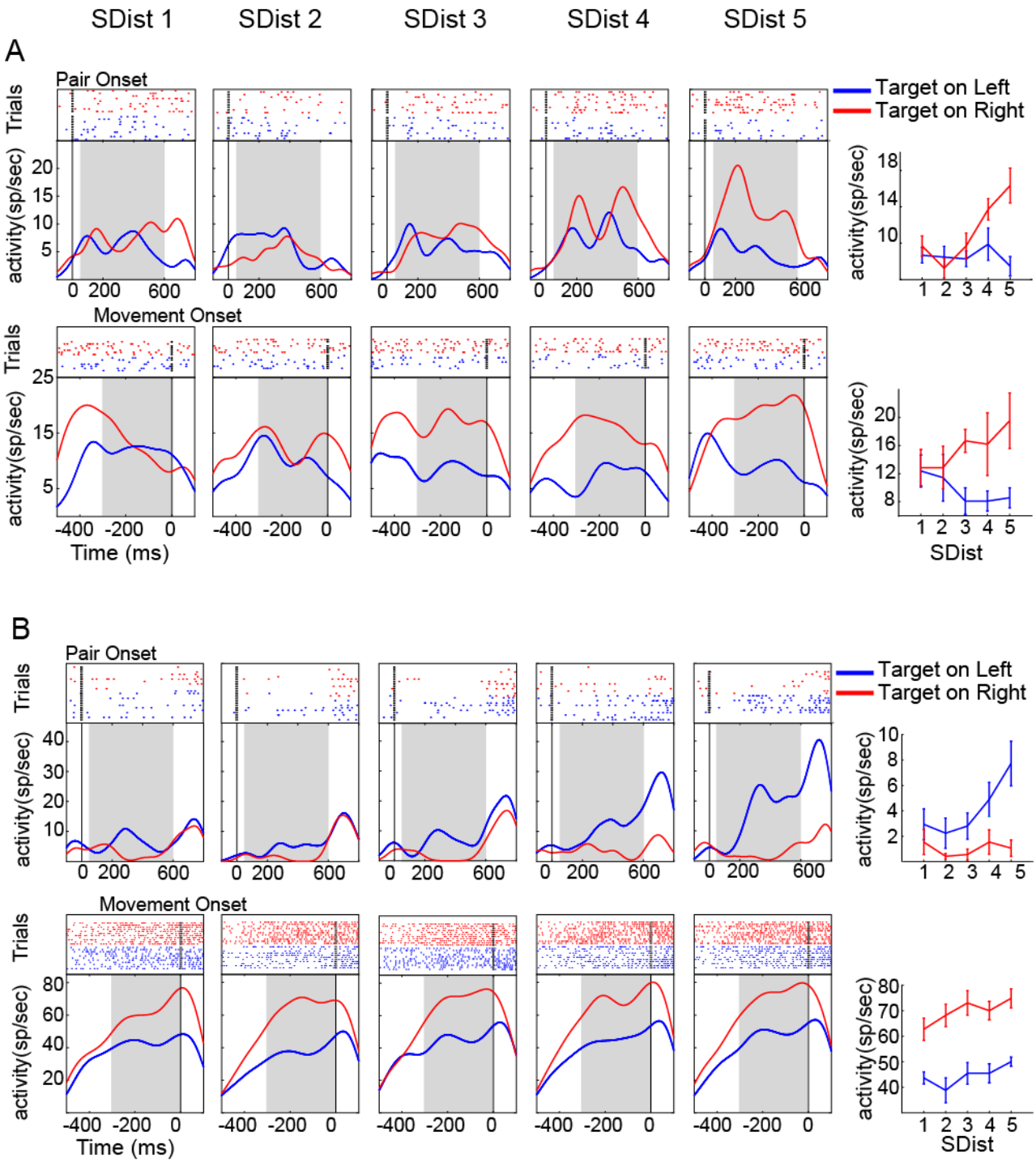


Figure 5: Modulation of activity in DLPFC and PMd neurons during pairs comparisons: Time evolution of the neuronal activity of four different neurons recorded from DLPFC (Panel A) and PMd (Panel B), exhibiting a target position selectivity during the Delay epoch (from 100 ms before to 800 ms after the pair onset; first row) and Reaction Time epochs (from 600 ms before to 200 ms after the movement onset; bottom row), respectively. For comparisons at each SDist the raster plots (upper part) and the corresponding spike density functions (lower part) are plotted for correct trials grouped according to left (blue) and right (red) target positions. The rightmost panels show the mean spike rate as a function of SDist, calculated during the Delay and RT analysis epochs (shaded area). Both the DLPFC example neurons exhibit a preference for the right target position (red) and an increasing difference in neuronal activity for the left and right target position with the rising of SDist. Differently, only one of the PMd example neurons (top one) modulated its preference for the left position with the rising of the SDist.

We further asked how many neurons contributed to the encoding of the same target position at each level of difficulty and if the contribution of a single neuron emerged only for specific levels of difficulty. We observed that a small proportion of DLPFC neurons (8% of all the target position selective neurons) exhibited a preference for the same target position at every difficulty level of the task, while in the PMd, we quantified that 41% of all the target-selective neurons maintained the same directional preferences at every SDist.

To summarize, easier pair comparisons in the TI task are related to the recruitment of a higher percentage of target position selective neurons than for more difficult comparisons both, in DLPFC and PMd. In addition, the spatial selectivity is stronger for the easier pairs comparisons. However, although in PMd neurons this trend occurred during the Delay epoch, in the RT epoch, this selectivity was encoded with comparable strength at each level of difficulty.

The selectivity of target position occurs earlier in DLPFC than PMd

The previous results indicate that the target position selectivity in both DLPFC and PMd was influenced by the task difficulty during different epochs of the task. Here, by using a ROC analysis, we explored the time evolution of spatial selectivity of the target position to determine the time at which it occurred in the selected DLPFC and PMd neurons. Figures 6A and 6B show the temporal evolution of the ROC in the time around the pair onset in 47 neurons recorded from DLPFC and 55 neurons from PMd of Monkey 1 obtained from the recording sessions with comparable RTs (see

methods). Neurons in each plot were sorted according to the time of target position selectivity (See methods for more details). The top histograms on each plot illustrate the distribution of the neuronal estimation of target position selection latencies for each SDist and the corresponding average values. We tested if the latency in the emergence of the spatial selectivity differed between the two brain areas and if it depended on the task difficulty by quantifying the probabilities of observing these latencies during the initial 75% (<900ms) of the distributions at each SDist. We observed a significantly higher probability of finding shorter spatial target selection latencies in DLPFC as compared to the PMd (Figure 6C - Kolmogorov Smirnoff test; $p<0.05$).

Furthermore, we found that the average target position selectivity latency across all conditions was significantly longer in PMd than in DLPFC (DLPFC: 329.2 ms; PMd 403.5 ms; t-test: $t(398) = 2.4079$; $p<0.05$). The probability of observing shorter latencies was also found to be higher with the increase of SDist in both areas. We fitted these trends with a linear model and observed a goodness of fit of 0.78 in DLPC and 0.91 in PMd. Additionally, we detected that the proportion of cells showing a sustained encoding for target position (Figure 6D) was greater in PMD than DLPFC (Kolmogorov Smirnoff test; $p<0.01$). This effect did not depend on the SDist (goodness of fit: DLPFC $R^2 = 0.08$; DLPFC $R^2 = 0.53$).

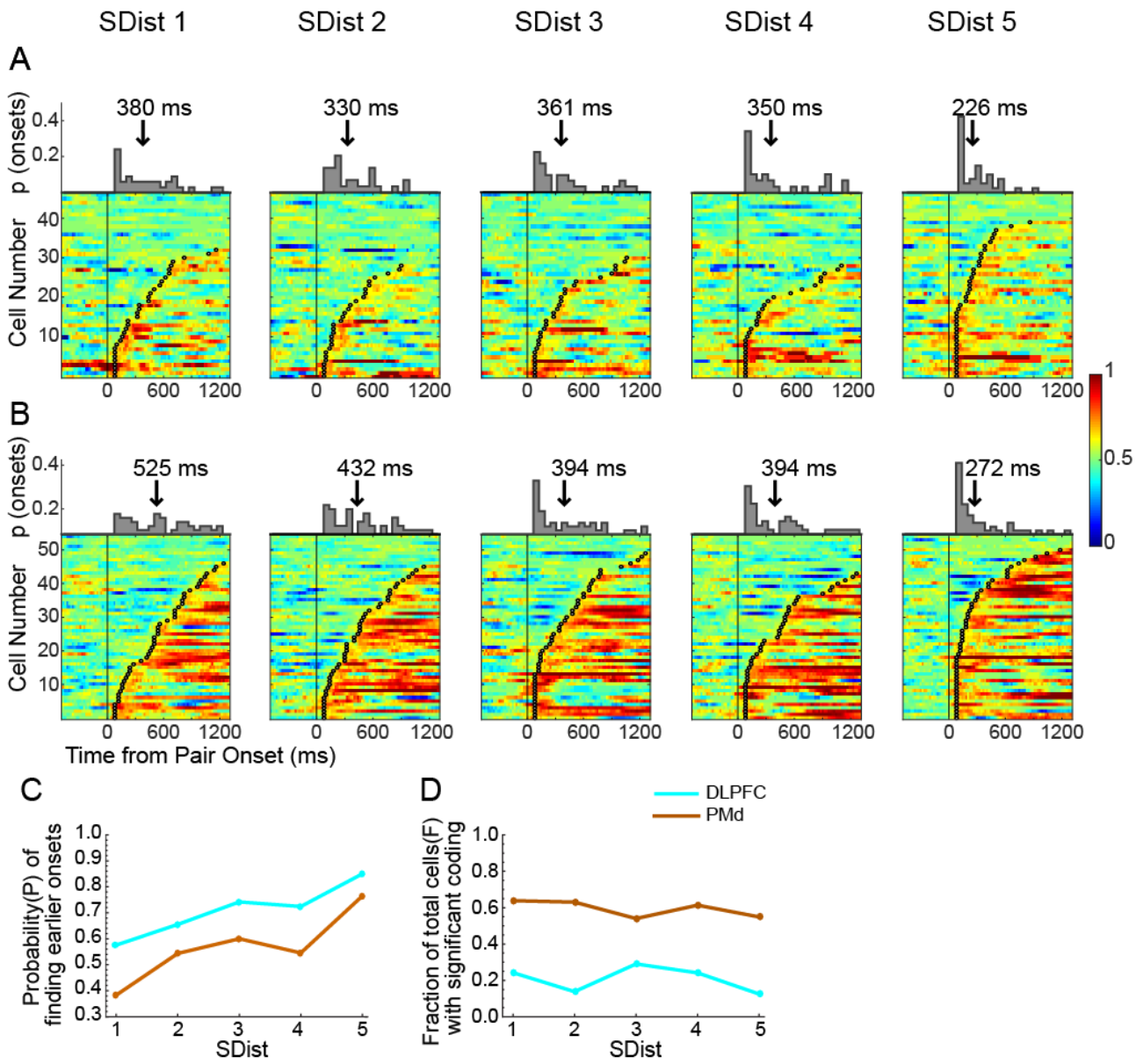


Figure 6. Estimate of the time of target position selectivity in DLPFC and PMd neuronal population from Monkey1: A-B. Time course of target position selectivity, measured as auROC values between the two target positions, in the time from 500 ms before the pair onset to 1300 ms after it, at each SDist from Population of DLPFC neurons(A) and PMd neurons(B). In each plot, the neurons are aligned sorted to the achievement of the set criterion (crossing the threshold value of 0.6 for consecutive 60 ms), highlighted by the black circles in each row. The histograms on the top show the distribution of these onsets of discrimination between target positions over trial time and their mean is represented by a vertical arrow for each SDist. **C.** The probability of observing the target selection onsets in the plots (A and B) before 900 ms after the pair onset (75% of the distribution) as a function of SDist in DLPFC and PMd neurons. **D.** Proportion of total DLPFC and PMd cells in Monkey1 significantly coding the target position for more than 70% of the total time.

These results were confirmed by comparing the evolution of target position selectivity in the neurons recorded from the DLPFC of Monkey 2 (79 neurons) and PMd of Monkey 3 (119 neurons) during the

recording sessions with comparable RT (Figure 7A and 7B) across the same trial epoch. We detected a higher probability of finding lower values of target position selection latencies for DLPFC when compared with PMd (figure 7C; Kolmogorov Smirnoff test, $p<0.01$), with a significant modulation by the SDist in both the brain areas (goodness of fit: DLPFC $R^2 = 0.76$; DLPFC $R^2 = 0.82$). Correspondingly, the mean latencies revealed a significantly earlier target position selectivity in DLPFC than in PMd (DLPFC: 338.0 ms; PMd 552.8 ms; t-test: $t(741) = 9.2980$; $p<0.05$). The fraction of cells encoding the target position was significantly higher in PMd (figures 7D and 7E; Kolmogorov Smirnoff test, $p<0.05$) than DLPFC also in the current comparison, with no significant modulation by the SDist (goodness of fit: DLPFC $R^2 = 0.02$; PMd $R^2 = 0.49$).

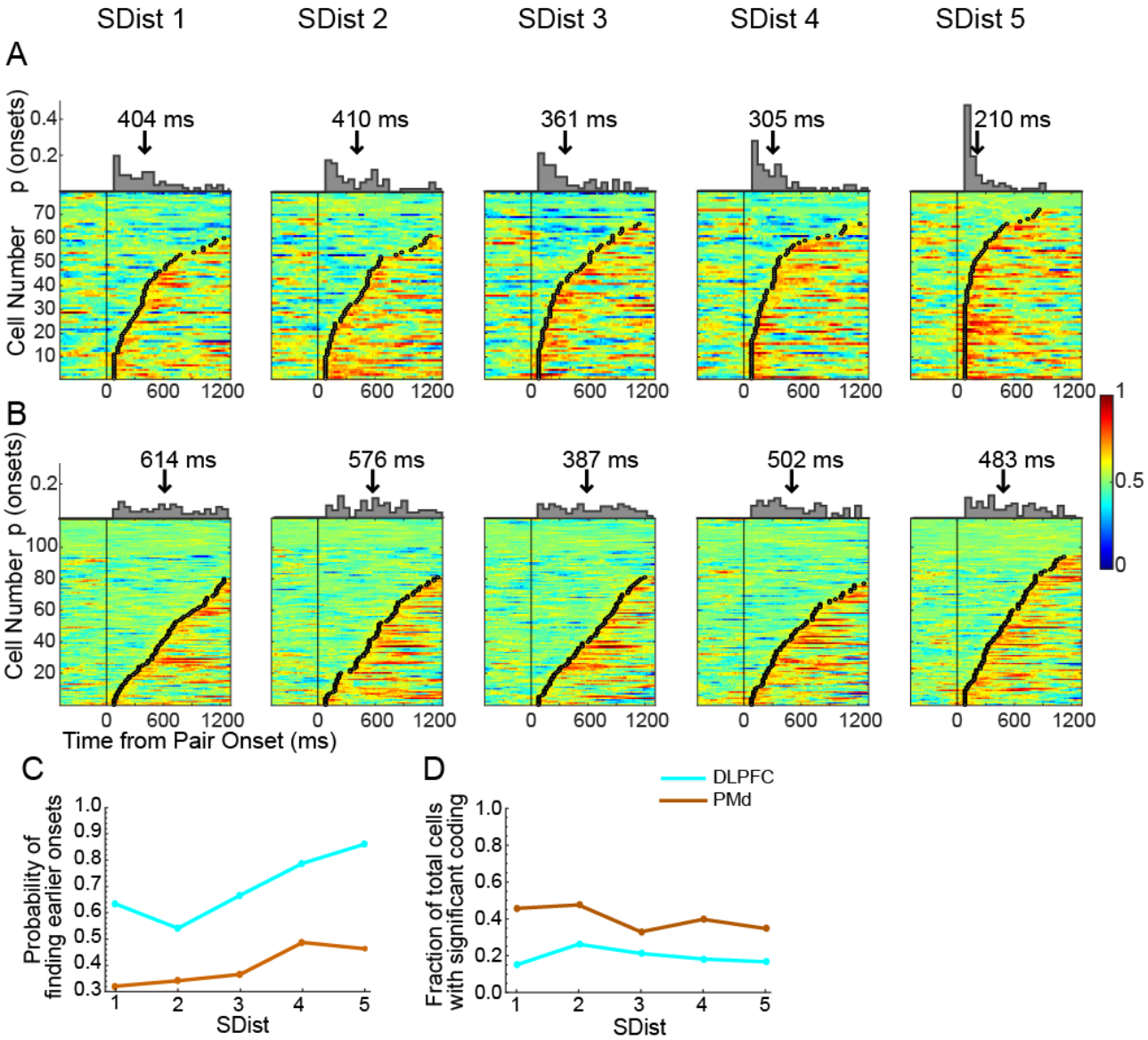


Figure 7. Estimate of the time of target position selectivity in neuronal populations from DLPFC of Monkey2 and PMd of Monkey3: Time course of target position selectivity, measured as auROC values between the two target positions, from the duration of 500ms before the pair onset to 1300 ms after it for each SDist for DLPFC neurons of Monkey2 (A) and PMd neurons of Monkey3 (B). C and D: Comparison of Probabilities of finding shorter target selection onsets and fraction of cells exhibiting significant coding respectively.

Collectively, these results indicate that both the areas, DLPFC and PMd, contribute to target position discriminability decisions in inferential tasks. In both areas, the latencies and the durations of neurons' involvement in spatial selectivity depended upon the degree of task difficulty in detecting the target. More importantly, the two areas partake their role in decision making with an earlier involvement in target position coding of DLPFC neurons over the PMd neurons. PMd neurons

maintained the target position encoding for a longer time, with a higher fraction of cells exhibiting sustained coding.

Discussion

In the present study, we compared the neuronal activity modulation for target position selectivity recorded in DLPF and PMd of monkeys while performing a TI task. The monkeys were required to select a target item presented to the left or the right side of a computer monitor, paired with a non-target stimulus presented at the opposite position. We found that the symbolic distance between the target and non-target item modulated both the monkeys' accuracy and reaction time for identifying the target – suggesting difficulty in target selection - and the neuronal activity related to target spatial selectivity both in DLPFC and PMd.

More specifically, 89% of the DLPFC neurons showed a target position preference, responding with higher levels of activity when the target item was specifically presented at one side of the screen, at least in one of the epochs of the analysis. The proportion of DLPFC neurons, preferring the left (45 %) and right (54 %) direction were comparable and in line with previous studies showing comparable proportions of DLPFC neurons recorded in monkeys performing a motion detection task while the symbolic distance effect modulated the task difficulty (Lennert and Martinez-Trujillo, 2013). Similar proportions of neurons were observed in PMd (92% neurons selective for the target location; 48% left preference; 52% right preference). Within this population of target position selective neurons, we first evaluated how this spatial preference was modulated by the task difficulty in the two brain areas, and then we compared its temporal evolution. By calculating the difference in neuronal activity between the two positions of the target item we detected both, similarities and differences in the patterns of activation of the two brain areas. In both areas, we observed a growing number of neurons increasingly exhibiting the preference for the target position, as the degree of difficulty in distinguishing between the target and the non-target decreased (Figure 3-4). This result indicates a neuronal correlate of the target-position encoding in DLPFC, similarly to what has been observed in PMd (Mione et al., 2020). However, the distribution of the target position selective neurons in the

two epochs of analysis, as well as their corresponding level of activation, was modulated differently in the two brain areas. More specifically, in DLPFC the task difficulty modulated the magnitude of neuronal activity both at the time of target presentation and during the time preceding the onset of movement (Figure 3C), while in PMd the task difficulty modulated the magnitude of neuronal activity only at the time immediately following the pair presentation. For instance, although in the time preceding the movement onset PMd neurons encoded the target position, the magnitude of the encoding was not modulated by the task difficulty. These results reveal that the activity of PMd is more sensitive to the degree of difficulty of the task soon after the pair presentation but not in the later part of the trial.

We also observed differences in the DLPFC and PMd neuronal populations in the way they encoded the effect of task difficulty. In both brain areas, we observed an increasing proportion of neurons recruited for easier pairs comparisons, however, while in PMd about 40% of neurons were engaged in encoding the target position at different SDists, only 8% of DLPFC neurons kept encoding the same target position at each SDist. These results reveal that the neuronal population encoding the task difficulty was more heterogeneous in DLPFC than in PMd. Additionally, the temporal analysis of the target position encoding revealed an earlier involvement of DLPFC neurons over the PMd neurons. Furthermore, PMd cells, after an initial encoding for the target position that depended on task difficulty, kept encoding the target position with higher sustained activity than DLPFC. However, the fraction of cells exhibiting sustained activity was not modulated by the task difficulty in both brain areas (Figure 6D-7D).

All these results are in line with the hypothesis that PMd is mainly involved in managing the task variables related to motor preparation, while DLPFC activity appears more dependent on abstract variables, as the task difficulty (Yamagata et al., 2012).

However, when performing this last analysis, we needed to take into account the different RTs between the three monkeys. This control led us to obtain two separate estimates of the target position encoding time in DLPFC and PMd, one performed by using the brain activity of the same monkey and the other on the brain activity recorded from different monkeys. Even though in both

cases we detected an earlier encoding of target position in DLPFC than in PMd, we observed a larger difference in the time lag in the estimate relaying on the sessions coming from two different monkeys (74.3 ms vs 214.7 ms), likely due to the individual differences. To obtain a reliable estimation of the target selection time of the two brain areas, a simultaneous recording from both DLPFC and PMd would be preferred. A comparable pattern of neuronal activity in PFC and PMd evolving with different timing have been observed during the execution of tasks requiring the encoding of abstract rules in matching to sample or quantity comparisons tasks (Wallis and Miller, 2003; Vallentin et al., 2012), goal selection in conditional visuomotor tasks (Yamagata et al., 2012) or visual categorization tasks (Cromer et al., 2011). In all these tasks PMd cortex was observed to use the task variables to form a motor plan during the time of movement onset and poorly engaged in the encoding task variable not linked to a motor decision (Cromer et al., 2011; Vallentin et al., 2012; Yamagata et al., 2012).

On the contrary, DLPFC is a higher-order brain area involved in encoding abstract variables of decision, such as decision rules (Kim and Shadlen, 1999; Bongard and Nieder, 2010), strategy (Genovesio et al., 2006), behavioral goal (Yamagata et al., 2012; Falcone et al., 2016) or the rank order representation of related information (Brunamonti et al., 2016). There is agreement that DLPFC sends top-down information to downstream motor areas, such as PMd, to convert the processing of these variables in motor decisions commands (Barbas and Pandya, 1987, 1989; Luppino et al., 2003). According to this model, the involvement of DLPFC in decision making should occur earlier than PMd.

However, it has been also found an earlier involvement of PMd compared to DLPFC in the encoding the characteristics of the task (Wallis and Miller, 2003; Cromer et al., 2011). These authors ascribe this early involvement to the familiarity of the monkeys with the task demands and stimuli, that would allow solving the task without the need of an abstract manipulation of the information, a competence supported by PFC (Muhammad et al., 2006). Our experimental protocol hinders such an eventuality. For instance, the monkeys were required to learn the ranked series from a set of never-experienced items, randomly selected at the beginning of each experimental session. Thus this protocol aimed to reduce to get familiar with the tasks' stimuli and increased the involvement of PFC in driving the

decision-making related activity of PMd. On the contrary to the discussed results (Wallis and Miller, 2003; Muhammad et al., 2006; Cromer et al., 2011), the time course of the decision-making related activity of PFC and PMd observed here fits more with the proposed anatomo-functional model of the relationship between the two brain areas (Barbas and Pandya, 1987, 1989; Luppino et al., 2003).

A further possible role played by the PFC is orienting spatial attention (Lennert and Martinez-Trujillo, 2011; Messinger et al., 2021) before the formation of the proper motor plan. Symbolic distance has been observed to modulate the time and magnitude of target selection-related neuronal activity, by decreasing the intensity of the neuronal response when the distracting item was easily distinguishable from the target (Lennert and Martinez-Trujillo, 2011). In our data, we observed such modulation of the neuronal activity in DLPFC only in a minority proportion of neurons (14.8 %) suggesting that attentional allocation would also act with a different mechanism.

Our results are in accordance with several lines of research on perceptual decision-making in monkeys, converging on the hypothesis that the resolution of the ambiguity of perceptual stimuli supports the selection between competitive motor actions simultaneously available (Cisek and Kalaska, 2005, 2010; Klaes et al., 2011; Kubanek et al., 2013; Shushruth et al., 2018). Enacting this process, higher-order association areas continuously support the motor system on this decisional computation (Pezzulo and Cisek, 2016; Shushruth et al., 2018). Here we show that this mechanism can be valid even when ambiguity relates to the representation of information stored in memory.

In summary, the present results support the hypothesis of a hierarchal organization between brain areas in which the DLPFC encodes the variables for decision processes and PMd uses this information to transform abstract decisions in motor programs.

References

Astrand E, Wardak C, Ben Hamed S (2020) Neuronal population correlates of target selection and distractor filtering. Neuroimage 209:116517 Available at: https://doi.org/10.1016/j.neuroimage.2020.116517.

Barbas H, Pandya DN (1987) Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. J Comp Neurol 256:211–228 Available at: https://doi.org/10.1002/cne.902560203.

Barbas H, Pandya DN (1989) Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol 286:353–375 Available at: https://doi.org/10.1002/cne.902860306.

Bongard S, Nieder A (2010) Basic mathematical rules are encoded by primate prefrontal cortex neurons. Proc Natl Acad Sci U S A 107:2277–2282.

Boussaoud D, Jouffrais C, Bremmer F (1998) Eye Position Effects on the Neuronal Activity of Dorsal Premotor Cortex in the Macaque Monkey. J Neurophysiol 80:1132–1150 Available at: https://doi.org/10.1152/jn.1998.80.3.1132.

Brunamonti E, Genovesio A, Carbè K, Ferraina S (2011) Gaze modulates non-propositional reasoning: Further evidence for spatial representation of reasoning premises. Neuroscience 173:110–115 Available at: http://dx.doi.org/10.1016/j.neuroscience.2010.11.011.

Brunamonti E, Mione V, Di Bello F, De Luna P, Genovesio A, Ferraina S (2014) The NMDAr antagonist ketamine interferes with manipulation of information for transitive inference reasoning in non-human primates. J Psychopharmacol 28:881–887.

Brunamonti E, Mione V, di Bello F, Pani P, Genovesio A, Ferraina S (2016) Neuronal modulation in the prefrontal cortex in a transitive inference task: Evidence of neuronal correlates of mental schema management. J Neurosci 36:1223–1236.

Caminiti R, Ferraina S, Mayer AB (1998) Visuomotor transformations: early cortical mechanisms of reaching. Curr Opin Neurobiol 8:753–761 Available at: https://www.sciencedirect.com/science/article/pii/S0959438898801189.

Chandrasekaran C, Peixoto D, Newsome WT, Shenoy K V. (2017) Laminar differences in decision-related neural activity in dorsal premotor cortex. Nat Commun 8 Available at: http://dx.doi.org/10.1038/s41467-017-00715-0.

Cisek P, Kalaska JF (2005) Neural correlates of reaching decisions in dorsal premotor cortex: Specification of multiple direction choices and final selection of action. Neuron 45:801–814.

Cisek P, Kalaska JF (2010) Neural mechanisms for interacting with a world full of action choices. Annu Rev Neurosci 33:269–298.

Coallier É, Kalaska JF (2014) Reach target selection in humans using ambiguous decision cues containing variable amounts of conflicting sensory evidence supporting each target choice. J Neurophysiol 112:2916–2938.

Coallier É, Michelet T, Kalaska JF (2015) Dorsal premotor cortex: Neural correlates of reach target decisions based on a color-location matching rule and conflicting sensory evidence. J Neurophysiol 113:3543–3573.

Cromer JA, Roy JE, Buschman TJ, Miller EK (2011) Comparison of primate prefrontal and premotor cortex neuronal activity during visual categorization. J Cogn Neurosci 23:3355–3365.

Donahue CH, Lee D (2015) Dynamic routing of task-relevant signals for decision making in dorsolateral prefrontal cortex. Nat Neurosci 18:295–301.

Falcone R, Brunamonti E, Ferraina S, Genovesio A (2016) Neural Encoding of Self and Another Agent's Goal in the Primate Prefrontal Cortex: Human–Monkey Interactions. Cereb Cortex 26:4613–4622 Available at: https://doi.org/10.1093/cercor/bhv224.

Ferraina S, Battaglia-Mayer A, Genovesio A, Marconi B, Onorati P, Caminiti R (2001) Early coding of visuomanual coordination during reaching in parietal area PEc. J Neurophysiol 85:462–467.

Fine JM, Hayden BY (2021) The whole prefrontal cortex is premotor cortex.

Fusi S, Miller EK, Rigotti M (2016) Why neurons mix: High dimensionality for higher cognition. Curr Opin Neurobiol 37:66–74 Available at: http://dx.doi.org/10.1016/j.conb.2016.01.010.

Genovesio A, Brasted PJ, Wise SP (2006) Representation of future and previous spatial goals by

separate neural populations in prefrontal cortex. J Neurosci 26:7305–7316.

Iba M, Sawaguchi T (2002) Neuronal activity representing visuospatial mnemonic processes associated with target selection in the monkey dorsolateral prefrontal cortex. Neurosci Res 43:9–22.

Johnson PB, Ferraina S, Bianchi L, Caminiti R (1996) Cortical Networks for Visual Reaching: Physiological and Anatomical Organization of Frontal and Parietal Lobe Arm Regions. Cereb Cortex 6:102–119 Available at: https://doi.org/10.1093/cercor/6.2.102.

Kim JN, Shadlen MN (1999) Neural correlates of a decision in the dorsolateral prefrontal cortex of the macaque. Nat Neurosci 2:176–185.

Klaes C, Westendorff S, Chakrabarti S, Gail A (2011) Choosing Goals, Not Rules: Deciding among Rule-Based Action Plans. Neuron 70:536–548 Available at: http://dx.doi.org/10.1016/j.neuron.2011.02.053.

Kubanek J, Wang C, Snyder LH (2013) Neuronal responses to target onset in oculomotor and somatomotor parietal circuits differ markedly in a choice task. J Neurophysiol 110:2247–2256.

Lebedev MA, Wise SP (2001) Tuning for the orientation of spatial attention in dorsal premotor cortex. Eur J Neurosci 13:1002–1008 Available at: https://doi.org/10.1046/j.0953-816x.2001.01457.x.

Lennert T, Martinez-Trujillo J (2011) Strength of Response Suppression to Distracter Stimuli Determines Attentional-Filtering Performance in Primate Prefrontal Neurons. Neuron 70:141–152 Available at: http://dx.doi.org/10.1016/j.neuron.2011.02.041.

Lennert T, Martinez-Trujillo JC (2013) Prefrontal neurons of opposite spatial preference display distinct target selection dynamics. J Neurosci 33:9520–9529.

Luppino G, Rozzi S, Calzavara R, Matelli M (2003) Prefrontal and agranular cingulate projections to the dorsal premotor areas F2 and F7 in the macaque monkey. Eur J Neurosci 17:559–578.

Messinger A, Cirillo R, Wise SP, Genovesio A (2021) Separable neuronal contributions to covertly

attended locations and movement goals in macaque frontal cortex. Sci Adv 7:1–15.

Mione V, Brunamonti E, Pani P, Genovesio A, Ferraina S (2020) Dorsal Premotor Cortex Neurons Signal the Level of Choice Difficulty during Logical Decisions. Cell Rep 32:107961 Available at: https://doi.org/10.1016/j.celrep.2020.107961.

Muhammad R, Wallis JD, Miller EK (2006) A comparison of abstract rules in the prefrontal cortex, premotor cortex, inferior temporal cortex, and striatum. J Cogn Neurosci 18:974–989.

Pezzulo G, Cisek P (2016) Navigating the Affordance Landscape: Feedback Control as a Process Model of Behavior and Cognition. Trends Cogn Sci 20:414–424 Available at: http://dx.doi.org/10.1016/j.tics.2016.03.013.

Shushruth S, Mazurek M, Shadlen MN (2018) Comparison of decision-related signals in sensory and motor preparatory responses of neurons in area LIP. J Neurosci 38:6350–6365.

Thompson KG, Hanes DP, Bichot NP, Schall JD (1996) Perceptual and motor processing stages identified in the activity of macaque frontal eye field neurons during visual search. J Neurophysiol 76:4040–4055.

Vallentin D, Bongard S, Nieder A (2012) Numerical rule coding in the prefrontal, premotor, and posterior parietal cortices of macaques. J Neurosci 32:6621–6630.

Wallis JD, Miller EK (2003) From rule to response: Neuronal processes in the premotor and prefrontal cortex. J Neurophysiol 90:1790–1806.

Wise SP, Di Pellegrino G, Boussaoud D (1992) Primate premotor cortex: Dissociation of visuomotor from sensory signals. J Neurophysiol 68:969–972.

Yamagata T, Nakayama Y, Tanji J, Hoshi E (2012) Distinct information representation and processing for goal-directed behavior in the dorsolateral and ventrolateral prefrontal cortex and the dorsal premotor cortex. J Neurosci 32:12934–12949.