

1 **Independent coding of absolute duration and distance magnitudes in the prefrontal cortex**

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17

18 **Abstract**

19 The estimation of space and time can interfere with each other, and neuroimaging studies have shown  
20 overlapping activation in the parietal and prefrontal cortical areas. We used duration and distance  
21 discrimination tasks to determine whether space and time share resources in prefrontal cortex (PF)  
22 neurons. Monkeys were required to report which of 2 stimuli, a red circle or blue square, presented  
23 sequentially, was longer and farther, respectively, in the duration and distance tasks. In a previous study,  
24 we showed that relative duration and distance are coded by different populations of neurons and that the  
25 only common representation is related to goal coding. Here, we examined the coding of absolute duration  
26 and distance. Our results support a model of independent coding of absolute duration and distance metrics  
27 by demonstrating that, not only relative magnitude, but also absolute magnitude is independently coded in  
28 the PF.

29

30 **New & Noteworthy**

31 Human behavioral studies have shown that spatial and duration judgements can interfere with each other.  
32 We investigated the neural representation of such magnitudes in the prefrontal cortex. We found that the  
33 two magnitudes are independently coded by prefrontal neurons. We suggest that the interference between  
34 magnitude judgements might depend on the goal rather than the perceptual resource sharing.

35

36 **Introduction**

37 Interaction with the world is fundamental in the evaluation and coding of magnitudes such as distance,  
38 duration and numerosity. The estimation of temporal and spatial magnitudes are correlated (Mendez et al.,  
39 2011) and can interfere with each other, generating errors in perception in both humans and monkeys  
40 (Basso et al., 1996; Casasanto and Boroditsky, 2008; Merritt et al., 2010; Mitchell and Davis, 1987) and

41 leading to the idea that both magnitudes are processed in a general magnitude system (Walsh, 2003). For  
42 example, humans perform better in binding pairs of tones and lines when their durations and lengths,  
43 respectively, correlate positively (Srinivasan and Carey, 2010). Stimulus dimension affects duration  
44 perception very specifically making the perception of larger stimuli also longer (Xuan et al. 2007; Ono  
45 and Kawahara, 2007). A similar result was obtained with a timing reproduction task (Rammsayer and  
46 Verner, 2014). One hypothesis that could explain these results is that this effect reflects a shared common  
47 coding scheme for different magnitudes. At the neural level, this could depend on neurons having  
48 congruent coding schemes. When a neuron increases activity for higher values of a magnitude, it would  
49 do the same for other magnitudes. Conversely, when a neuron decreases its activity for higher values it  
50 would do the same when tested for other magnitudes. Further, estimations of time and space are similarly  
51 compressed by saccadic eye movements when stimuli are briefly presented just before or after the  
52 movement (Ross et al., 1997; Morrone et al., 2005). In contrast, Lambrechts et al. (2013) did not find any  
53 interference by number or space on the perception of duration on a task in which numeric and spatial  
54 information accumulated over time.

55         Several recent studies have reported the involvement of the PF in processing duration (Genovesio  
56 et al., 2006a; Lebedev et al., 2008; Ohmae et al., 2008; Oshio et al., 2006, 2008; Sakurai et al., 2004;  
57 Tsujimoto and Sawaguchi, 2005; Jin et al., 2009; Brody et al., 2003; Yumoto et al., 2011), in addition to  
58 other widespread cortical and subcortical areas, including the motor and premotor cortex (Mita et al.,  
59 2009; Lucchetti and Bon, 2001; Ohmae et al., 2008; Merchant et al., 2011b, 2013; Renoult et al., 2006;  
60 Kilavik et al., 2010), parietal cortex (Janssen and Shadlen, 2005; Schneider and Ghose, 2012), and basal  
61 ganglia (Chiba et al., 2008; Bartolo et al., 2014). At the single-cell level, PF neurons encode time and  
62 space (Hoshi et al., 2000; Saito et al., 2005; Merchant et al., 2011a; Genovesio et al., 2006a,b; Genovesio  
63 et al., 2012; Genovesio and Tsujimoto 2014; Lebedev et al., 2004) and numbers (Nieder et al., 2002).  
64 Based on these properties and its importance in domain-general processing (Baars et al., 2003; Duncan,  
65 2010; Wilson et al., 2010), we examined timing and spatial representations at the single-cell level in the  
66 PF. Specifically, we recorded from the individual neurons in duration and distance discrimination tasks,

67 which required monkeys to determine which of the 2 stimuli, presented sequentially on a screen, was  
68 greater either in duration of presentation or in distance from a reference point, respectively.

69 We have previously shown that in the decision phase, relative duration and spatial metrics (i.e.  
70 difference between specific values of the same magnitude) are represented independently in the PF, and  
71 only the goal was coded commonly by the same population (Genovesio et al., 2012). The goal was  
72 defined as the object or location that an animal choose as a target for its action (Passingham and Wise,  
73 2012), corresponding to the blue or red stimuli in our tasks. We have advanced the hypothesis that some  
74 of the interference effects between different magnitudes could reflect the sharing of goal information in  
75 the PF. To support this hypothesis, however, we must exclude the possibility that interferences reflect  
76 common coding of each absolute magnitude in the PF as described before, in which the neurons have the  
77 same preference for low or high values of various magnitudes. To address this question, we analyzed the  
78 activity of PF neurons during the delay that followed the presentation of an initial stimulus (S1). We  
79 identified the populations of neurons that encoded the absolute duration and spatial distance of S1 in this  
80 period and examined whether the 2 groups of neurons significantly overlapped in coding the 2 metrics  
81 more than expected by chance or showed independence.

82

## 83 **Materials and Methods**

### 84 **Behavioral task**

85 Two adult male rhesus monkeys (*Macaca mulatta*, 8.5 and 8.0 kg) performed 2 tasks: a duration  
86 discrimination task and a distance discrimination task (Figure 1A). In both tasks, 2 stimuli were presented  
87 sequentially, and the monkeys had to select which one had the greatest magnitude —duration in the  
88 duration task and distance from a reference point in the distance task. The monkeys sat in a chair, with  
89 their heads fixed 29 cm from a video screen. Three infrared switches, measuring 3x2 cm each, were  
90 placed in front of them, within reach, and used as an interface between the monkeys and the experimental

91 task. All procedures conformed to the Guide for the Care and Use of Laboratory Animals (1996) and were  
92 approved by the NIMH Animal Care and Use Committee.

93           The sequence of events during a trial is described in Figure 1A and was similar in each task. A  
94 trial started when the monkeys pressed the central switch. Then, a central stimulus (white circle of  $0.6^\circ$  of  
95 diameter) appeared for 400 or 800 ms and was followed by the presentation of the first stimulus (S1: a  
96 blue circle of  $3^\circ$  of diameter or red square of  $3^\circ \times 3^\circ$  dimensions) at the center of screen. In the duration  
97 task, S1 lasted from 200 ms to 1200 ms, in increments of 200 ms (ie, 6 conditions). In the distance task,  
98 S1 always lasted 1000 ms and was presented 8-48 mm ( $1.6^\circ$ - $9.4^\circ$  of visual angle) above or below the  
99 central stimulus in steps of 8 mm (ie, 6 conditions). The duration of each S1 stimulus could be followed  
100 by each of the other different durations with equal probability. The same was true in the distance task but  
101 in terms of distances (Figure 1B). The first delay (D1) of 400 or 800 ms separated the disappearance of S1  
102 from presentation of the second stimulus (S2). In the duration task, S2 was presented in the same range of  
103 durations as S1, appearing at the center of the screen, but could be longer or shorter than S1. In the  
104 distance task, S2 lasted 1000 ms and was presented above the reference point when S1 appeared below it;  
105 otherwise, it was displayed below. The distance of S2 varied in the same range as that of S1 and could be  
106 farther or closer than S1 to the reference. Subsequently, a second delay (D2) of 0, 400, or 800 ms  
107 preceded the reappearance of the 2 stimuli. S1 and S2 reappeared  $7.8^\circ$  to the left and  $7.8^\circ$  to the right of  
108 the central reference pseudorandomly determined, and their appearance served as "go" signal. The "go"  
109 signal instructed the monkeys to select, within a maximum of 6 s, the stimulus that had lasted longer or  
110 was presented farther from the reference point in the duration or distance tasks, respectively. In the  
111 duration task, fixation on the center of the screen was required from the appearance of the central stimulus  
112 until the "go" signal. In the distance task, fixation requirements were not imposed.

113           An important feature of the task design for both the distance and the duration tasks was that the  
114 monkeys could not plan any motor response until after the go signal. Correct responses were rewarded  
115 with 0.1 ml of fluid, whereas incorrect responses were followed by acoustic feedback. An intertrial period  
116 of 700-1000 ms separated 2 consecutive trials. All variables in the task, such as the duration of D1 and D2

117 and the features of the stimuli, were pseudorandomly determined. For a detailed description of the  
118 duration and distance tasks, see Genovesio et al. (2009) and Genovesio et al. (2011), respectively.

119

## 120 **Surgery**

121 Recording chambers were implanted over the exposed dura mater of the left frontal lobe, with head  
122 restraint devices, using aseptic techniques and isoflurane anesthesia (1% to 3%, to effect). Monkey 1 had  
123 two 18-mm-diameter chambers, and monkey 2 had a single 27x36-mm chamber.

## 124 **Histological Analysis**

125 Electrolytic lesions (15 mA for 10 s, anodal current) were made at selected locations. After 10 days, the  
126 animal was deeply anesthetized and after perfused through the heart with formaldehyde-containing  
127 fixative. We plotted recording sites on Nissl-stained coronal sections by reference to the recovered  
128 electrolytic lesions and the marking pins inserted when we performed perfusion. PA recordings were  
129 predominantly taken from area 8 and PFdl included area 46 and a small population of area 12. Figure 1C  
130 shows the dividing line between the PFdl and PA recording sites.

131

## 132 **Data Collection**

133 We monitored eye position with an infrared oculometer (Arrington Recording) and recorded single cells  
134 using quartz-insulated platinum-iridium electrodes (0.5–1.5 M $\Omega$  at 1 kHz), positioned by a 16-electrode  
135 drive assembly (Thomas Recording). The electrodes were arranged in a concentric array with 518-mm  
136 spacing. Spikes were discriminated online using Multichannel Acquisition Processor (Plexon) and  
137 confirmed with Off Line Sorter (Plexon).

138

## 139 **Neural analyses**

140 *Neural stability*

141 We assessed the neurons stability between tasks by calculating the similarity of the mean waveform and  
 142 the interspike interval histogram (ISIH) in the two tasks (Dickey et al., 2009). The waveform similarity  
 143 (W) was calculated by obtaining the Pearson's correlation coefficient between the mean waveforms of the  
 144 neurons in each task. The similarity of ISIHs was obtained by first fitting each ISIH with a mixture of  
 145 three log-normal distributions using an expectation-maximization algorithm and then computing a  
 146 similarity score (I) as:

$$147 \quad I(A, B) = \sqrt{\frac{\sum_{i=1}^{i=8} (A_i - B_i)^2}{\sigma_i^2}}$$

148 where A and B are the set of eight parameters used to fit the ISIHs in the duration and distance task,  
 149 respectively, and  $\sigma$  is a normalization factor that represents the variance of the fitting parameters and is  
 150 obtained from a sample set. The two scores were then normalized and combined in one unique score S:

$$W' = \tanh^{-1}(W)$$

$$I' = \log(I)$$

$$S = (x - \mu_{pos})^T \Sigma_{pos}^{-1} (x - \mu_{pos}) - (x - \mu_{neg})^T \Sigma_{neg}^{-1} (x - \mu_{neg})$$

151  
 152 where  $\mu_{pos}$  and  $\mu_{neg}$  are the mean score values of true-positives and true-negatives,  $\Sigma_{pos}$  and  $\Sigma_{neg}$  are their  
 153 covariance obtained from the sample set and  $x$  is a vector with the  $W'$  and  $I'$  for a neuron ( $x = \begin{pmatrix} W' \\ I' \end{pmatrix}$ ). A  
 154 neuron is considered to be stable between sessions if its combined score (S) is lower than a threshold (T).  
 155 We used the values of  $\mu_{pos}$ ,  $\mu_{neg}$ ,  $\Sigma_{pos}$ ,  $\Sigma_{neg}$  and T obtained from Dickey et al. (2009). From the original  
 156 dataset (Genovesio et al., 2009; Genovesio et al., 2011; Marcos et al., 2016), we identified 428 neurons  
 157 that were recorded and stable in both behavioral tasks. From these neurons, 192 neurons were recorded in  
 158 the dorsolateral PF (PFdl) and 236 neurons in caudal periarculate (PA).

159  
 160 *Neural selectivity*

161 To identify neurons that were modulated by the duration or distance of S1, we sorted the trials  
 162 by S1 duration (long or short) in the duration task and by its distance (far or near) in the distance task. In

163 the duration task, we classified durations of S1 of 1000-1200 ms as long and 200-400 ms as short. In the  
164 distance task, we classified distances of S1 of 40-48 mm as far and those of 8-16 mm as near. We  
165 calculated the number of neurons that were selective for these ranges of values in the early D1 period (80-  
166 400 ms), because it is the period in which the absolute duration of S1 in the duration task and its distance  
167 in the distance task are known and should be maintained in memory before it can start the comparison  
168 process. Only correct trials were considered for all analyses.

169 The neural selectivity for duration and distance magnitudes was examined by a one-way  
170 ANOVA test in the early D1 period for activity with long/short durations of S1 and far/near distances of  
171 S1 as factors in the duration and distance tasks, respectively. We also conducted linear regression  
172 analysis, in which we calculated the mean activity for each neuron in the early D1 period for the 6  
173 specific values of duration and distance of S1 in each task and performed linear fitting of the data. Finally,  
174 we calculated the significance of the duration or distance of S1 as a predictor of the calculated firing rate.

175 The significance of the overlap between the distribution of neurons that were selective for the  
176 duration and distance of S1 was determined by hypergeometric distribution test (Casella and Berger,  
177 1990). From the total number of neurons (N), we identified  $n_{dur}$  neurons that were selective for the  
178 duration of S1,  $n_{dist}$  neurons that were selective for its distance, and  $n_c$  neurons that were selective for  
179 both. The significance of  $n_c$  neurons was then calculated as the probability of selecting  $n_{dist}$  neurons from  
180 the original group, N, and obtaining  $n_c$  neurons or more that belonged to the  $n_{dur}$  group of neurons.  
181 Mathematically, the probability of selecting  $n_c$  neurons is calculated as:

$$P(n_c) = \frac{C(n_{dur}, n_c) \cdot C(N - n_{dur}, n_{dist} - n_c)}{C(N, n_{dist})}$$

182 where  $C(n, m) = \frac{n!}{m!(n-m)!}$ . Then, the p-value is estimated as the probability to observe at least  $n_c$   
183 common neurons belonging to the two groups and it is calculated as the sum of the probabilities of  
184 selecting the exact  $n_c$  number of neurons or more:

$$p = \sum_{i=n_c}^{n_{dist}} P(i)$$

185

186 We calculated this value for the group of neurons that were identified as selective for the duration or  
187 distance of S1 by a one-way ANOVA test and for those with its duration or distance as a significant  
188 predictor of mean neural firing rate.

189 The mean firing rates were plotted using a sliding window of 50 ms with steps of 5 ms.  
190 Preferred and nonpreferred durations corresponded to the mean maximum and minimum activity in early  
191 D1, respectively. To compare the activity of the neural population that was selective for the duration of  
192 S1 in the duration task with that of the same neurons in the distance task, we analogized long durations to  
193 far positions of S1 and short durations to its near positions—ie, if a neuron preferred long durations of S1,  
194 we assigned the far distances of S1 as the preferred distances for the distance task and its near distances as  
195 the nonpreferred ones. The same logic applied when short and long durations of S1 were its preferred and  
196 nonpreferred durations, respectively. The statistical significance of the difference in mean firing rates  
197 between conditions at the population level was calculated by a paired-sample t-test with Bonferroni  
198 correction using a nonoverlapping window of 50 ms. Only periods in which the difference between  
199 conditions is significant for at least two consecutive bins are reported.

200 To assess how well the neural populations represented the duration or distance of S1, we  
201 implemented a classification procedure with neuron-dropping analysis based on the peri-stimulus time  
202 histogram (PSTH) (Foffani and Moxon, 2004; Lebedev et al., 2004). We divided the trials by condition,  
203 ie. long or short duration of S1 in the duration task or far or near distance of S1 in the distance task, and  
204 used the neural activity in the early D1 period as the predictor variable. In brief, to assess the robustness  
205 of the magnitude representation, we randomly selected one trial from the same condition for each neuron  
206 (test trials set) in the population and calculated a response template for each neuron and condition using  
207 the mean activity of all remaining trials. Then, the Euclidean distance between the response in each trial

208 of the test set and the corresponding neuron's template was calculated. The selected trials were classified  
209 as belonging to the condition with the lowest sum of calculated distances. The neuron-dropping analysis  
210 consisted of randomly eliminating one neuron from the population in each iteration and computing the  
211 decoding accuracy using the subset of remaining neurons. This procedure was performed 1000 times for  
212 each condition and each specific number of neurons. The neural populations consisted of the neurons  
213 uniquely selective for duration ( $n_{dur-n_c}$ ) of S1 and those uniquely selected for its distance ( $n_{dist-n_c}$ ).

214

## 215 **Results**

216 Two monkeys performed the duration and distance discrimination tasks. Figure 1A shows the sequence of  
217 events in the 2 tasks, and Figure 1B shows the recorded areas. The mean performance of the monkeys was  
218 high in both tasks, with correct trial rates of 81% and 79% in the duration and distance tasks, respectively.  
219 The performance of the two animals was comparable also when examined in more detail (see  
220 Supplementary Figure 2 in Genovesio et al. 2012). Easier discriminations were associated with both faster  
221 responses and higher accuracy. While the monkeys performed the 2 tasks, 428 neurons were recorded  
222 stably in both tasks from PF. From this group of neurons, 51 neurons were recorded in PFdl and 34 in PA  
223 of Monkey 1 and 141 neurons were recorded in PFdl and 202 in PA of Monkey 2.

224 To examine the neural representation of absolute duration and distance, we first divided the  
225 trials by the absolute duration or distance of S1. In the duration task, the trials were split into short (200-  
226 400 ms) and long durations of S1 (1000-1200 ms). From the total set of neurons, we identified 113  
227 neurons ( $n_{dur}=113$ ; 26.4%; 57 in PFdl and 56 in PA) that were significantly modulated ( $p<0.05$ , one-way  
228 ANOVA) by the duration of S1 in the early D1 (80-400 ms). In the distance task, we divided the trials  
229 similarly into far (40 and 48 mm) and near (8 and 16 mm) categories. From the same neural subset, 41  
230 neurons ( $n_{dist}=41$ ; 9.6%; 15 in PFdl and 26 in PA) were significantly modulated by the distance of S1 in  
231 the early D1 ( $p<0.05$ , one-way ANOVA). Thus, the number of neurons that encoded the duration of S1  
232 was more than twice those that encoded its distance. We identified 13 neurons ( $n_c=13$ ; 11.5% and 31.7%

233 of neurons that were selective for duration and distance, respectively; 5 in PFdl and 8 in PA) that were  
234 selective for both the duration and distance of S1 (Figure 2), which is not significantly different than the  
235 expected overlap if 41 neurons were randomly selected from the total of 428 neurons ( $p=0.262$ ,  
236 hypergeometric distribution test; see Materials and Methods). This result indicates that 2 populations of  
237 neurons encoded S1's duration and distance independently but does not indicate that neurons that encode  
238 one magnitude cannot encode another—only that this happens in the proportion that we expect by chance.  
239 The same result was obtained when looking at the number of neurons divided by area, ie. PFdl and PA  
240 ( $p=0.475$  and  $p=0.252$ , respectively, hypergeometric distribution test).

241 In addition to the ANOVA, we also performed a linear regression analysis for each neuron in the  
242 entire population that was recorded, using firing rate as the dependent variable and the duration or  
243 distance of S1 as the predictor. The duration of S1 was a significant predictor of activity in 121 neurons in  
244 the duration task, whereas 47 neurons exhibited the same effect with regard to its distance in the distance  
245 task. In these 2 groups, 81.8% and 72.4% of neurons for duration and distance, respectively, were also  
246 significant by one-way ANOVA. We identified 12 neurons common to both groups, which was, however,  
247 not significant from what was expected by chance ( $p=0.726$  hypergeometric distribution test; see  
248 Materials and Methods). Moreover, the correlation coefficient between the slopes of the common neurons  
249 calculated in the duration task and the ones calculated in the distance task was not significant ( $p=0.120$ ,  
250 Pearson correlation). These analyses confirmed the independence of the coding of duration and distance  
251 in the PF even if we consider not only the magnitude-selective neurons according to one-way ANOVA  
252 but also the neurons with significant linear relationship with the two magnitudes. We used the population  
253 of neurons that were identified by the one-way ANOVA test for the remaining analyses.

254 Figure 3A shows an example of neurons with a preference for long (preferred) versus short  
255 durations (nonpreferred). The inset panel shows its mean firing rate in the early D1 period, sorted by  
256 duration of S1. Its activity rose exponentially with increasing durations of S1 and became saturated for  
257 the longest cases at approximately 20 spikes/s. Figure 3B shows the activity of the same neuron, divided  
258 by the distance of S1 in the distance task. The neuron did not exhibit significant difference in activity

259 between near (8-16 mm) and far (40-48 mm) placements of S1. The inset panel shows the mean firing  
260 rate of the neuron during the early D1 period along all distances of S1. In contrast to the modulation in its  
261 response in the duration task, in this case, the neuron exhibited a similar mean firing rate along all  
262 distances of S1.

263           Next, we examined the neural population response for cells that were selective by ANOVA for  
264 the duration of S1 but not for its distance. Left panel of Figure 4A shows the mean activity of these  
265 neurons (100 neurons) during the duration task. This group had a significantly higher firing rate for the  
266 preferred versus nonpreferred duration of S1 that began approximately 200 ms before the end of its  
267 presentation and was maintained during the D1 period ( $p < 0.05/24$ , paired-sample t-test with Bonferroni  
268 correction). In contrast, when we analyzed the activity of the same neurons in the distance task, matching  
269 far distances with long durations and near ones with short ones to assign preferred and nonpreferred  
270 conditions (see Materials and Methods), the neurons did not show any significant differences in activity  
271 between conditions. Right panel of Figure 4A shows the flat response that characterized the activity of the  
272 neurons for the preferred and nonpreferred conditions and their lack of selectivity for distance of S1. We  
273 performed the same analysis with the neurons that were selective for the distance of S1 in the spatial task  
274 but not for its duration in the duration task (28 neurons). Left panel of Figure 4B shows a lack of  
275 modulation in the activity of the neurons for the duration of S1 in the duration task. In contrast, as  
276 expected, they encoded its distance during the D1 period (Right panel of Figure 4B). Thus, these  
277 population analyses confirm that the sharing of the representation of duration and distance for PF neurons  
278 does not exceed what is expected by chance.

279           To rule out the possibility that the observed lack of neural representation of distance in the  
280 neurons that were selective for duration, and vice versa, was caused by averaging of the activity of the  
281 population, we used a PSTH-based classification method with neuron-dropping analysis (Foffani and  
282 Moxon, 2004; Lebedev et al., 2004; see Materials and Methods). The method does not assume a matching  
283 of preferences (long/short duration with far/near distance) and does not average the activity across trials  
284 and neurons but, instead, considers the individual responses to single trials and sums up the contribution

285 of the set or subsets of neurons. We observed that the long or short duration of S1 could be decoded from  
286 the activity within the early D1 period of the neurons selective for the duration of S1 in the duration task  
287 (100 neurons). The classification accuracy increased with the number of neurons considered, reaching a  
288 value of 95% of correct decoding when all neurons were used (Figure 5A). Likewise, the far or near  
289 distance of S1 could be decoded with an accuracy of 84% using the activity from the early D1 period  
290 activity of the neurons selective for the distance in the distance task (28 neurons; Figure 5B). However,  
291 when the same groups of neurons were tested in the distance and the duration tasks, respectively, the  
292 classification accuracies were close to chance levels in both cases regardless of the number of neurons  
293 considered. This result confirms the lack of common magnitude coding in these two groups of neurons.

294         Among the small population of neurons selective for both duration and distance of S1 (13  
295 neurons), one group changed preference between tasks whereas the other group, instead, maintained same  
296 preference between the two tasks. Specifically, 9 neurons had the same preference for duration and space  
297 (long duration and long distance or short duration and short distance), whereas 4 neurons showed a  
298 change in preference (long duration but short distance or short duration but long distance). Although the  
299 difference in the proportion of neurons was significant (binomial test,  $p < 0.01$ ), overall our results show a  
300 small proportion of neurons with a common magnitude coding scheme which is not significantly different  
301 from chance.

302

### 303 **Discussion**

304 In this study, we focused on the period of the first delay after the presentation of an initial stimulus to  
305 examine the encoding and decoding of absolute magnitude and found that PF neurons encoded absolute  
306 distance and duration independently. Whereas past studies addressed the function of several brain areas in  
307 the representation of duration, we report the first examination of the possible conjunctive representation  
308 of absolute duration and space by individual neurons in the PF.

309 Two studies (Tudusciuc and Nieder, 2009; Eiselt and Nieder, 2015) assessed the  
310 representation of space and numbers. The former study, using a match-to-sample task, reported that 20%  
311 of selective neurons that were recorded in the PF represented numbers and line length, pointing to a  
312 generalist function of the PF in the representation of magnitude (Tudusciuc and Nieder, 2009).  
313 Subsequently, Eiselt and Nieder (2015) evaluated the representation of numbers, line length, and spatial  
314 frequency, adopting a more demanding paradigm than the match-to-sample task of Tudusciuc and Nieder  
315 (2009). In this new task (Eiselt and Nieder, 2015), monkeys were required to report whether a test  
316 quantity was “greater than” or “less than” a sample quantity, depending on the rule that was cued. In  
317 contrast to their previous study, they found no overlap between populations of neurons that encoded each  
318 magnitude. The authors attributed this discrepancy to the difference in demand between tasks, which was  
319 higher in the second experiment, in which monkeys were required to flexibly switch between rules during  
320 its performance.

321 Although our current tasks did not require any rule-dependent switch, the monkeys were  
322 required to base their decision on the comparison of the 2 stimuli. Given that the domain specificity was  
323 consistent with that of Eiselt and Nieder (2015), the key aspect is likely to be whether the subject can  
324 simply match the stimulus to the other or compare their relative values within each magnitude—not the  
325 demands of flexible rule-switching. To compare the relative magnitudes without interference (Genovesio  
326 et al., 2015b), independent neural magnitudes are more efficient than a general network—a model  
327 consistent with childhood development of neural networks from holistic to fractionated, fine-tuned  
328 systems (Tsujimoto et al., 2007; Tsujimoto, 2008).

329 Conversely, later in the task, once the goal is selected based on the comparison, the modality-  
330 specific, independent systems might become redundant. Our previous findings (Genovesio et al., 2012)  
331 concur with this hypothesis. In this earlier study, we investigated the representation of relative magnitudes  
332 in the PF and showed that neuronal activity develops over time along a specificity-generality axis, ending  
333 with generalist neurons that encode the same goal, regardless of the sensory domain that had guided the

334 goal. In that study, however, we did not examine whether the values of the two magnitudes were coded  
335 independently before the decision process.

336 Our current findings fill this gap, demonstrating that absolute magnitudes signals develop in a  
337 domain-specific manner in the early stages of the task—not only in the decision phase. The neurons code  
338 duration and distance metrics independently or, in other words, the number of neurons that encode both  
339 distance and duration is not higher than the one expected by chance. The independence of coding of the 2  
340 absolute magnitudes thus originates as early as their initial representation and is maintained while  
341 calculating the relative value (Genovesio et al., 2012, 2015b). In this series of studies, goal encoding  
342 appears as the first magnitude-independent representation, consistent with goal generation and monitoring  
343 being an important function of the PFdl (Genovesio et al., 2006b, 2008, 2014a, 2014b ; Genovesio and  
344 Ferraina 2014; Rainer et al., 1999; Tsujimoto, 2008; Kusunoki et al., 2009; Falcone et al., 2015; Marcos  
345 and Genovesio 2016) and with the proposed function of goal coding as a general organizational principle  
346 in the PF (Stoianov et al., 2015).

347 A similar trend in the PF—from specific to general—in terms of sensory modalities rather than  
348 magnitudes was also reported in our previous study, using a strategy task (Tsujimoto et al., 2012). The  
349 cues instructed 1 of 2 strategies: “stay” with the previous response or “shift” to the alternative one. The  
350 cue could be drops of fluid reward or a visual stimulus. We found that in the PFdl, the spatial goal or  
351 response preference was represented in a modality-specific manner during the presentation of the cue.  
352 Only later in the delay period did we observe a transition from modality-specific to modality-general  
353 activity in neurons that started to share the spatial goal preference. The current findings also support our  
354 previous data on the selectivity of duration coding in a context-dependent manner (Genovesio et al.  
355 2015a), but the earlier study compared the coding of durations in the same task period between tasks and  
356 between task periods in the same task and did not compare the coding of various magnitudes. Our current  
357 findings are consistent with the traditional view of the function of the PF in bridging sensory information  
358 and motor responses (Takeda and Funahashi, 2002; Wang et al., 2015) and apply to a more granular  
359 model: the modality-specific representation of absolute magnitude; comparison of relative magnitudes

360 based on such independent absolute coding systems; and goal generation and representation that are  
361 domain-general.

362 In our task, the period of interest is the working memory period. In contrast to other  
363 experimental designs, in which the studied property of a stimulus is not its duration but alternative ones,  
364 such as space or numbers (Dehaene et al., 1998; Tudusciuc and Nieder, 2009; Eiselt and Nieder, 2015),  
365 the duration of the stimulus can only be determined after its presentation. Thus, the working memory  
366 period is the only epoch in which the neural representation of duration and distance can be compared.

367 It is still possible that there is partial overlap of computational resources for various magnitudes  
368 at the level of the parietal cortex, in which several magnitudes have been hypothesized to share a common  
369 representational format along a common spatially organized line (Dehaene et al., 2003; Hubbard et al.  
370 2005). Limiting the discussion to space and time, in support of a parietal representation of magnitudes,  
371 brain-imaging studies have shown parietal activation in tasks that require orienting one's attention to time  
372 intervals and spatial locations (Coull and Nobre, 1998) and in collision tasks in which the subjects are  
373 required to integrate spatial and temporal information to predict a collision (Assmus et al., 2003). Based  
374 on our task and our collective findings, although we noted an additional level of resource sharing for goal  
375 and response (right and left) representations in the PF, we did not find evidence of absolute or relative  
376 common representation of 2 different magnitudes.

377 Our results show that there is a small proportion of neurons exhibiting a common magnitude  
378 coding scheme and that the proportion is not significantly different from chance. Therefore, it is unlikely  
379 that such a small population of neurons could generate the magnitudes interference that has been reported  
380 (Mendez et al., 2011; Casasanto and Boroditsky, 2008; Mitchell and Davis, 1987; Basso et al., 1996).  
381 Moreover, the proportion is very low when compared to the neurons that have shown to be selective for  
382 the goal in the two tasks (see Fig. 2 in Genovesio et al., 2012). This previous study not only showed a  
383 larger overlap of goal coding in the two tasks but also found that such neurons mostly share the same goal  
384 preference just with few exceptions. Nevertheless, it is important to mention that not all ranges of  
385 magnitudes might interfere with each other. Indeed, only the classification of specific ranges of duration

386 and distance into “long” and “short” categories are correlated (Mendez et al., 2011). In particular, the  
387 categorization of spatial distances within 3.7° and 8.2° correlated with the classification of durations  
388 within 200 ms and 1520 ms. The range of magnitude values used in our experiment substantially overlap  
389 with the reported ranges providing a suitable framework to investigate the possible common neural  
390 representation of the two magnitudes. Nevertheless, we cannot completely rule out the possibility of a  
391 higher overlap in the neural coding of distance and duration if a different set of magnitude ranges was  
392 used.

393           Our study supports our initial hypothesis that interference between different kinds of  
394 magnitudes, such as size or duration (Xuan et al., 2007), occurs at the level of goal coding—not at the  
395 perceptual level (Genovesio et al. 2012). In support of this hypothesis, Yates et al. (2012) showed that  
396 larger stimuli are perceived longer in comparative judgments but not in equality judgments in which no  
397 goal or decision interference is possible. Further experiments are needed to confirm the generality of our  
398 results in other tasks, such as less demanding or similar tasks in which the distance and duration of the  
399 same stimulus are varied simultaneously, to determine whether the independence of space and time is  
400 maintained.

401

402

403 **Figure Legends**

404 **Figure 1.** Experimental tasks and penetration sites for the two monkeys. **(A)** Sequence of events during a  
405 trial for the duration (left panel) and distance tasks (right panel). In both cases, 2 stimuli are presented  
406 sequentially, and the monkeys are required to later select the one that lasted longer (duration task) or was  
407 presented farther from a reference point at the center of a screen (distance task). **(B)** Stimulus set for the  
408 duration (left) and the distance (right) tasks. **(C)** Composite of both monkeys, relative to sulcal landmarks.  
409 Vertical blue line: division between periarculate (right) and dorsolateral prefrontal (left) areas.  
410 Abbreviations: AS, arcuate sulcus; PS, principal sulcus.

411  
412 **Figure 2.** Venn diagram (not to scale) of the number of neurons that encode the duration and distance of  
413 S1 in the duration (black) and distance (gray) tasks, respectively. The neurons shared by the 2 groups are  
414 reported in the intersecting area (n=13), whereas the noncommon ones are shown in their respective areas.

415  
416 **Figure 3.** Example neuron encoding absolute duration of S1 in the duration task but not its distance in the  
417 distance task. Each dot in the raster plot indicates the discharge of the neuron with respect to the start of  
418 D1. Mean firing rate of the neurons is shown above the raster plots. **(A)** Neural response in the duration  
419 task. The neuron shows higher activity (spikes/s) for long (1000-1200 ms) versus short (200-400 ms)  
420 durations of S1. Black marker in the raster indicates the time of S1 presentation. **(B)** Activity in the  
421 distance task. In contrast to **(A)**, the neuron does not differentiate between far (40-48 mm) and near (8-16  
422 mm) distances of S1. Inset panels show the mean activity of the neurons calculated within the 80-400 ms  
423 after presentation of S1 (gray box in the raster plot) for various durations **(A)** and distances **(B)** of S1.

424  
425 **Figure 4.** Population analyses. **(A)** Mean activity of the population of neurons that significantly encode  
426 the duration of S1 in the early D1 period (80-400 ms) in the duration task. *Left panel*, mean activity of the  
427 population for preferred (solid black) and nonpreferred S1 durations (dashed black) in the duration task

428 (\*= $p < 0.05/24$ , paired-sample t-test with Bonferroni correction). *Right panel*, mean activity of the same  
429 neurons in the distance task when far and near placements are considered equivalent to long and short  
430 durations of S1, respectively, and are used as references to compute preferred and nonpreferred  
431 conditions. Error bars are SEM. **(B)** Mean activity of the population of neurons that significantly encode  
432 the distance of S1 in the early D1 period (80-400 ms) in the distance task. *Left panel*, mean population  
433 activity in the duration task for preferred (thick line) and nonpreferred (thin line) conditions when far and  
434 near distances are considered equivalent to long and short durations of S1, respectively. *Right panel*,  
435 mean activity of the same neurons in the distance task (\*= $p < 0.05/24$ , paired-sample t-test with Bonferroni  
436 correction). Error bars are SEM.

437

438 **Figure 5.** Prediction of duration and distance of S1 from neural activity. **(A)** Percentage of correctly  
439 classified cases in the duration (black) and distance tasks (gray) from the mean neural activity in the early  
440 D1 period of neurons selective for S1 duration in the duration task. The percentage of the correct  
441 classification is computed considering groups of 1 to  $n_{dur}-n_c$  neurons. **(B)** Same analyses when the neurons  
442 selective for S1 distance during the distance task are considered (1 to  $n_{dist}-n_c$  neurons). Dashed lines  
443 indicate chance level of the classification (50%).

444

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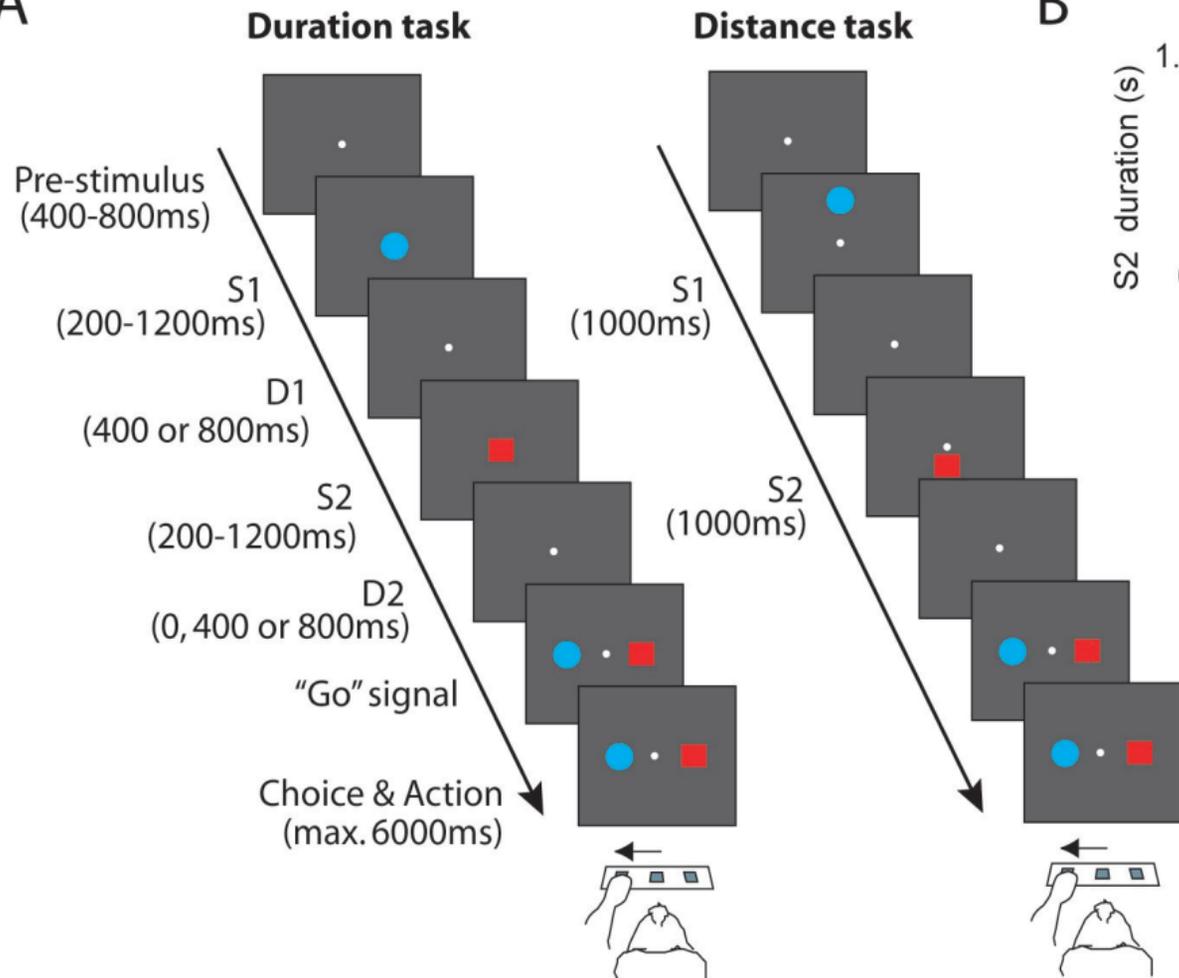
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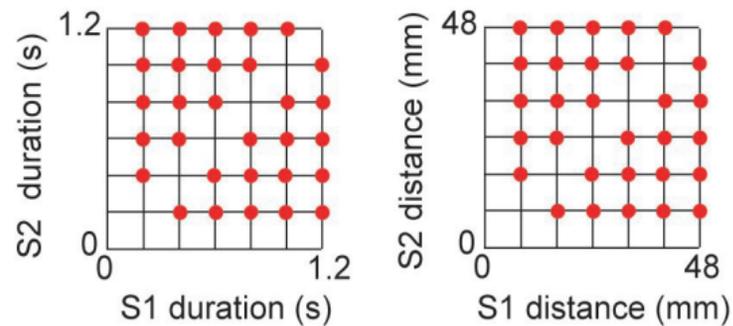
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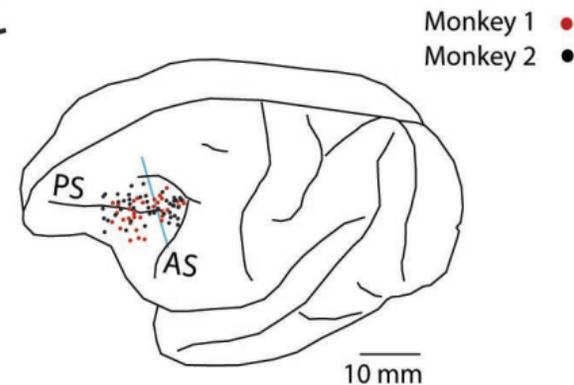
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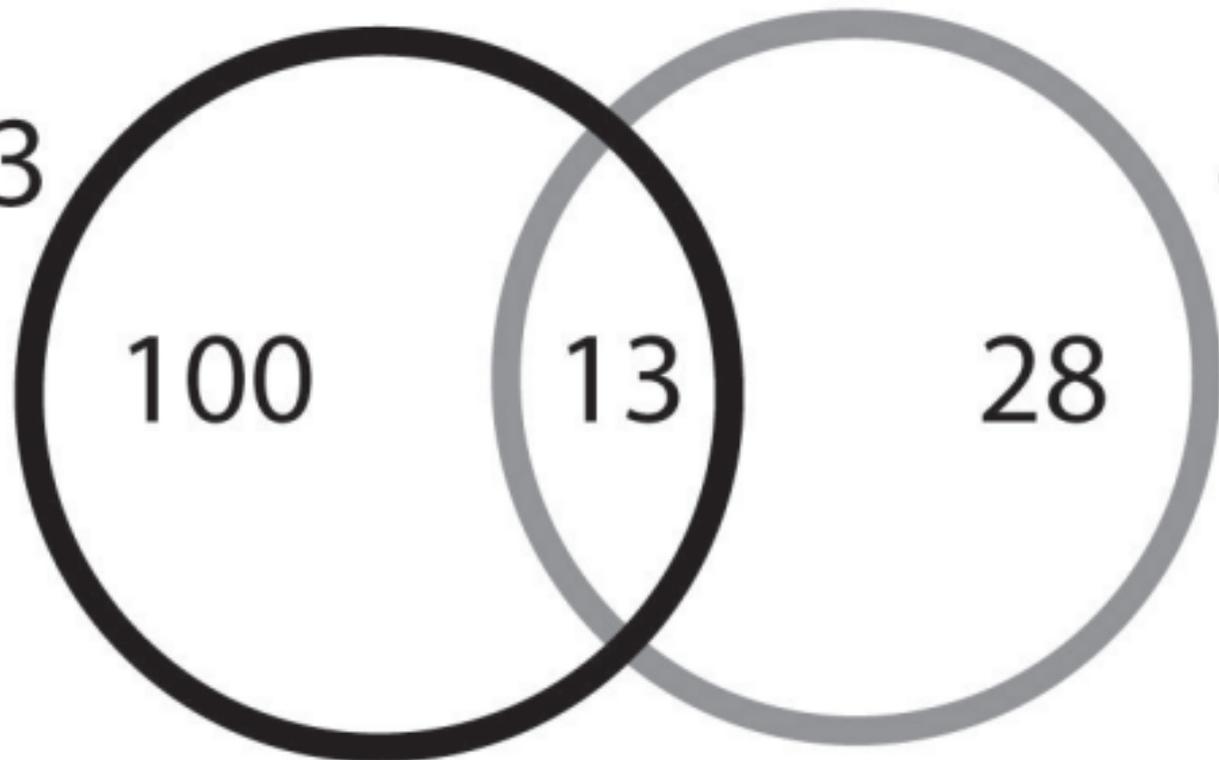
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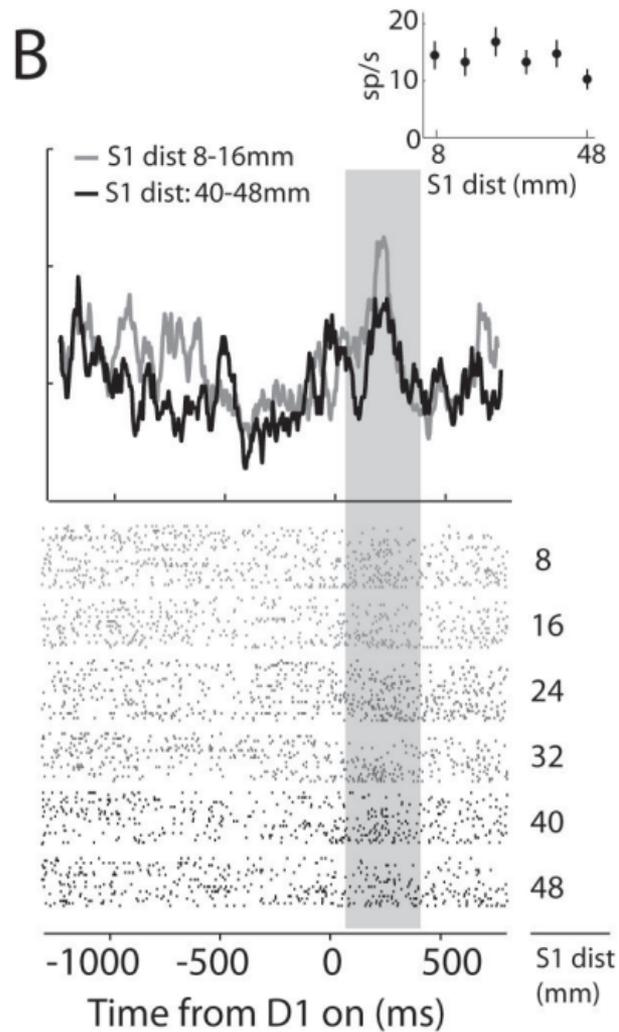
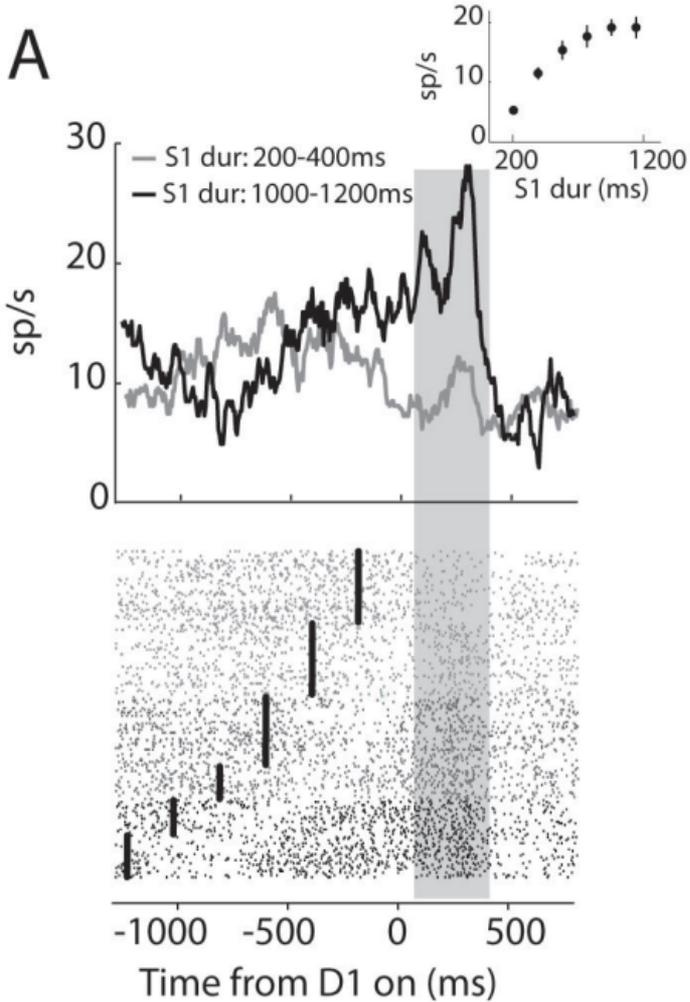
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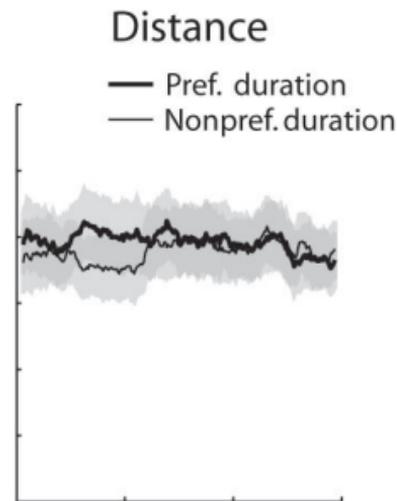
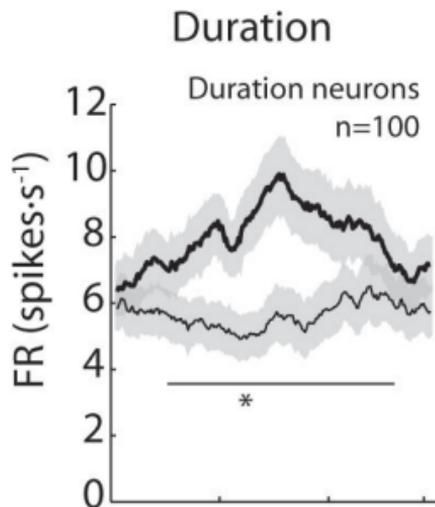
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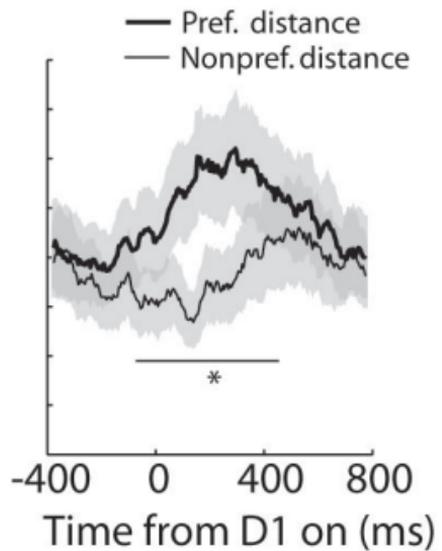
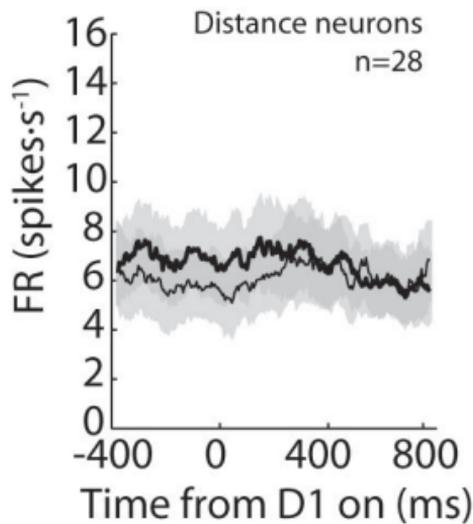


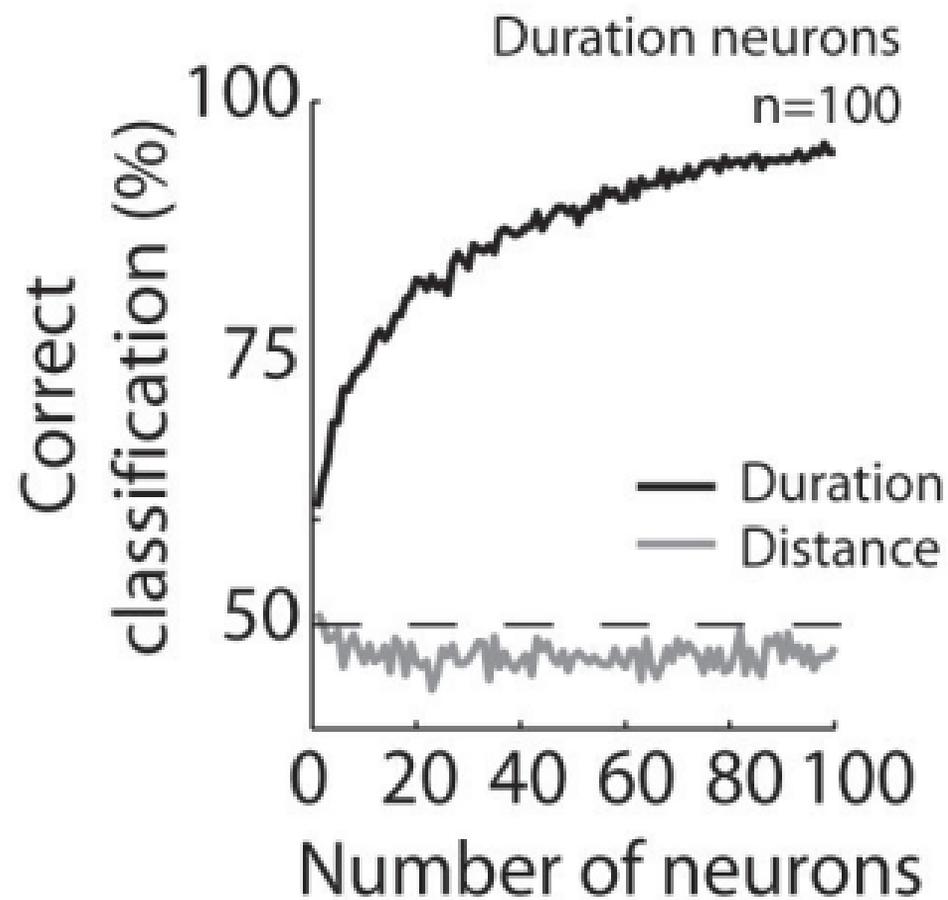


A



B



**A****B**