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

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Abstract

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

New & Noteworthy

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

Introduction

Interaction with the world is fundamental in the evaluation and coding of magnitudes such as distance, duration and numerosity. The estimation of temporal and spatial magnitudes are correlated (Mendez et al., 2011) and can interfere with each other, generating errors in perception in both humans and monkeys (Basso et al., 1996; Casasanto and Boroditsky, 2008; Merritt et al., 2010; Mitchell and Davis, 1987) and leading to the idea that both magnitudes are processed in a general magnitude system (Walsh, 2003). For example, humans perform better in binding pairs of tones and lines when their durations and lengths, respectively, correlate positively (Srinivasan and Carey, 2010). Stimulus dimension affects duration perception very specifically making the perception of larger stimuli also longer (Xuan et al. 2007; Ono and Kawahara, 2007). A similar result was obtained with a timing reproduction task (Rammsayer and Verner, 2014). One hypothesis that could explain these results is that this effect reflects a shared common coding scheme for different magnitudes. At the neural level, this could depend on neurons having congruent coding schemes. When a neuron increases activity for higher values of a magnitude, it would do the same for other magnitudes. Conversely, when a neuron decreases its activity for higher values it would do the same when tested for other magnitudes. Further, estimations of time and space are similarly compressed by saccadic eye movements when stimuli are briefly presented just before or after the movement (Ross et al., 1997; Morrone et al., 2005). In contrast, Lambrechts et al. (2013) did not find any interference by number or space on the perception of duration on a task in which numeric and spatial information accumulated over time.

Several recent studies have reported the involvement of the PF in processing duration (Genovesio et al., 2006a; Lebedev et al., 2008; Ohmae et al., 2008; Oshio et al., 2006, 2008; Sakurai et al., 2004; Tsujimoto and Sawaguchi, 2005; Jin et al., 2009; Brody et al., 2003: Yumoto et al., 2011), in addition to other widespread cortical and subcortical areas, including the motor and premotor cortex (Mita et al., 2009; Lucchetti and Bon, 2001; Ohmae et al., 2008; Merchant et al., 2011b, 2013; Renoult et al., 2006; Kilavik et al., 2010), parietal cortex (Janssen and Shadlen, 2005; Schneider and Ghose, 2012), and basal ganglia (Chiba et al., 2008; Bartolo et al., 2014). At the single-cell level, PF neurons encode time and space (Hoshi et al., 2000; Saito et al., 2005; Merchant et al., 2011a; Genovesio et al., 2006a,b; Genovesio et al., 2012; Genovesio and Tsujimoto 2014; Lebedev et al., 2004) and numbers (Nieder et al., 2002). Based on these proprieties and its importance in domain-general processing (Baars et al., 2003; Duncan, 2010; Wilson et al., 2010), we examined timing and spatial representations at the single-cell level in the PF. Specifically, we recorded from the individual neurons in duration and distance discrimination tasks, which required monkeys to determine which of the 2 stimuli, presented sequentially on a screen, was greater either in duration of presentation or in distance from a reference point, respectively.

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

Materials and Methods

Behavioral task

Two adult male rhesus monkeys (*Macaca mulatta*, 8.5 and 8.0 kg) performed 2 tasks: a duration discrimination task and a distance discrimination task (Figure 1A). In both tasks, 2 stimuli were presented sequentially, and the monkeys had to select which one had the greatest magnitude —duration in the duration task and distance from a reference point in the distance task. The monkeys sat in a chair, with their heads fixed 29 cm from a video screen. Three infrared switches, measuring 3x2 cm each, were placed in front of them, within reach, and used as an interface between the monkeys and the experimental task. All procedures conformed to the Guide for the Care and Use of Laboratory Animals (1996) and were approved by the NIMH Animal Care and Use Committee.

The sequence of events during a trial is described in Figure 1A and was similar in each task. A trial started when the monkeys pressed the central switch. Then, a central stimulus (white circle of 0.6º of diameter) appeared for 400 or 800 ms and was followed by the presentation of the first stimulus (S1: a blue circle of 3º of diameter or red square of 3ºx3º dimensions) at the center of screen. In the duration task, S1 lasted from 200 ms to 1200 ms, in increments of 200 ms (ie, 6 conditions). In the distance task, S1 always lasted 1000 ms and was presented 8-48 mm (1.6°-9.4° of visual angle) above or below the central stimulus in steps of 8 mm (ie, 6 conditions). The duration of each S1 stimulus could be followed by each of the other different durations with equal probability. The same was true in the distance task but in terms of distances (Figure 1B). The first delay (D1) of 400 or 800 ms separated the disappearance of S1 from presentation of the second stimulus (S2). In the duration task, S2 was presented in the same range of durations as S1, appearing at the center of the screen, but could be longer or shorter than S1. In the distance task, S2 lasted 1000 ms and was presented above the reference point when S1 appeared below it; otherwise, it was displayed below. The distance of S2 varied in the same range as that of S1 and could be farther or closer than S1 to the reference. Subsequently, a second delay (D2) of 0, 400, or 800 ms preceded the reappearance of the 2 stimuli. S1 and S2 reappeared 7.8º to the left and 7.8º to the right of the central reference pseudorandomly determined, and their appearance served as "go" signal. The "go" signal instructed the monkeys to select, within a maximum of 6 s, the stimulus that had lasted longer or was presented farther from the reference point in the duration or distance tasks, respectively. In the duration task, fixation on the center of the screen was required from the appearance of the central stimulus until the “go” signal. In the distance task, fixation requirements were not imposed.

An important feature of the task design for both the distance and the duration tasks was that the monkeys could not plan any motor response until after the go signal. Correct responses were rewarded with 0.1 ml of fluid, whereas incorrect responses were followed by acoustic feedback. An intertrial period of 700-1000 ms separated 2 consecutive trials. All variables in the task, such as the duration of D1 and D2 and the features of the stimuli, were pseudorandomly determined. For a detailed description of the duration and distance tasks, see Genovesio et al. (2009) and Genovesio et al. (2011), respectively.

Surgery

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

Histological Analysis

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

Data Collection

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

Neural analyses

Neural stability

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

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

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

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

$$I' = log(I)$$

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

where μ_{pos} and μ_{neg} are the mean score values of true-positives and true-negatives, Σ_{pos} and Σ_{neg} are their 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 neuron is considered to be stable between sessions if its combined score (S) is lower than a threshold (T). We used the values of μ_{pos}, μ_{neg}, Σ_{pos}, Σ_{neg} and T obtained from Dickey et al. (2009). From the original dataset (Genovesio et al., 2009; Genovesio et al., 2011; Marcos et al., 2016), we identified 428 neurons that were recorded and stable in both behavioral tasks. From these neurons, 192 neurons were recorded in the dorsolateral PF (PFdl) and 236 neurons in caudal periarcuate (PA).

Neural selectivity

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

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

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

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

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

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

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

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

To assess how well the neural populations represented the duration or distance of S1, we implemented a classification procedure with neuron-dropping analysis based on the peri-stimulus time histogram (PSTH) (Foffani and Moxon, 2004; Lebedev et al., 2004). We divided the trials by condition, ie. long or short duration of S1 in the duration task or far or near distance of S1 in the distance task, and used the neural activity in the early D1 period as the predictor variable. In brief, to assess the robustness of the magnitude representation, we randomly selected one trial from the same condition for each neuron (test trials set) in the population and calculated a response template for each neuron and condition using the mean activity of all remaining trials. Then, the Euclidean distance between the response in each trial of the test set and the corresponding neuron's template was calculated. The selected trials were classified as belonging to the condition with the lowest sum of calculated distances. The neuron-dropping analysis consisted of randomly eliminating one neuron from the population in each iteration and computing the decoding accuracy using the subset of remaining neurons. This procedure was performed 1000 times for each condition and each specific number of neurons. The neural populations consisted of the neurons uniquely selective for duration (n_{dur}-n_c) of S1 and those uniquely selected for its distance (n_{dist}-n_c).

Results

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

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

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

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

Figure 3A shows an example of neurons with a preference for long (preferred) versus short durations (nonpreferred). The inset panel shows its mean firing rate in the early D1 period, sorted by duration of S1. Its activity rose exponentially with increasing durations of S1 and became saturated for the longest cases at approximately 20 spikes/s. Figure 3B shows the activity of the same neuron, divided by the distance of S1 in the distance task. The neuron did not exhibit significant difference in activity between near (8-16 mm) and far (40-48 mm) placements of S1. The inset panel shows the mean firing rate of the neuron during the early D1 period along all distances of S1. In contrast to the modulation in its response in the duration task, in this case, the neuron exhibited a similar mean firing rate along all distances of S1.

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

To rule out the possibility that the observed lack of neural representation of distance in the neurons that were selective for duration, and vice versa, was caused by averaging of the activity of the population, we used a PSTH-based classification method with neuron-dropping analysis (Foffani and Moxon, 2004; Lebedev et al., 2004; see Materials and Methods). The method does not assume a matching of preferences (long/short duration with far/near distance) and does not average the activity across trials and neurons but, instead, considers the individual responses to single trials and sums up the contribution of the set or subsets of neurons. We observed that the long or short duration of S1 could be decoded from the activity within the early D1 period of the neurons selective for the duration of S1 in the duration task (100 neurons). The classification accuracy increased with the number of neurons considered, reaching a value of 95% of correct decoding when all neurons were used (Figure 5A). Likewise, the far or near distance of S1 could be decoded with an accuracy of 84% using the activity from the early D1 period activity of the neurons selective for the distance in the distance task (28 neurons; Figure 5B). However, when the same groups of neurons were tested in the distance and the duration tasks, respectively, the classification accuracies were close to chance levels in both cases regardless of the number of neurons considered. This result confirms the lack of common magnitude coding in these two groups of neurons.

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

Discussion

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

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

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

Conversely, later in the task, once the goal is selected based on the comparison, the modality-specific, independent systems might become redundant. Our previous findings (Genovesio et al., 2012) concur with this hypothesis. In this earlier study, we investigated the representation of relative magnitudes in the PF and showed that neuronal activity develops over time along a specificity-generality axis, ending with generalist neurons that encode the same goal, regardless of the sensory domain that had guided the goal. In that study, however, we did not examine whether the values of the two magnitudes were coded independently before the decision process.

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

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

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

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

Our results show that there is a small proportion of neurons exhibiting a common magnitude coding scheme and that the proportion is not significantly different from chance. Therefore, it is unlikely that such a small population of neurons could generate the magnitudes interference that has been reported (Mendez et al., 2011; Casasanto and Boroditsky, 2008; Mitchell and Davis, 1987; Basso et al., 1996). Moreover, the proportion is very low when compared to the neurons that have shown to be selective for the goal in the two tasks (see Fig. 2 in Genovesio et al., 2012). This previous study not only showed a larger overlap of goal coding in the two tasks but also found that such neurons mostly share the same goal preference just with few exceptions. Nevertheless, it is important to mention that not all ranges of magnitudes might interfere with each other. Indeed, only the classification of specific ranges of duration and distance into “long” and “short” categories are correlated (Mendez et al., 2011). In particular, the categorization of spatial distances within 3.7º and 8.2º correlated with the classification of durations within 200 ms and 1520 ms. The range of magnitude values used in our experiment substantially overlap with the reported ranges providing a suitable framework to investigate the possible common neural representation of the two magnitudes. Nevertheless, we cannot completely rule out the possibility of a higher overlap in the neural coding of distance and duration if a different set of magnitude ranges was used.

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

Figure Legends

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

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

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

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

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

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

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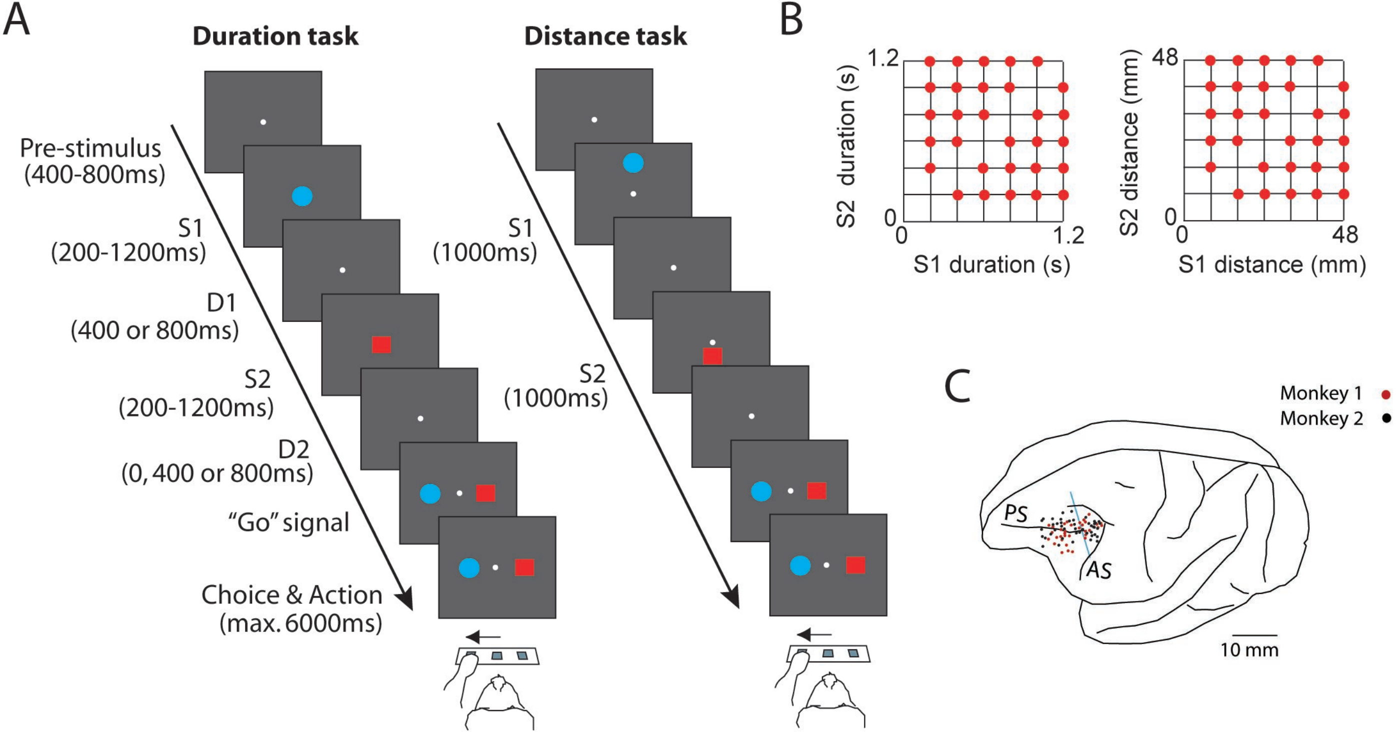
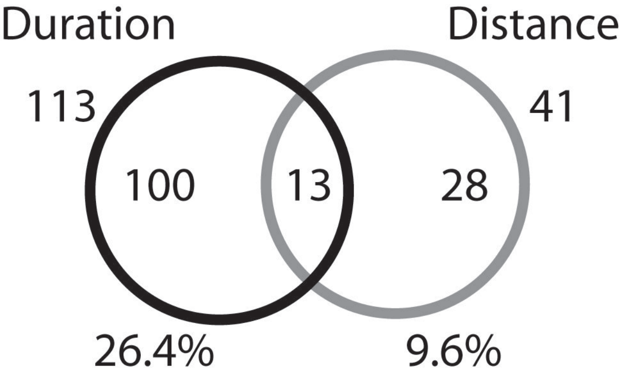
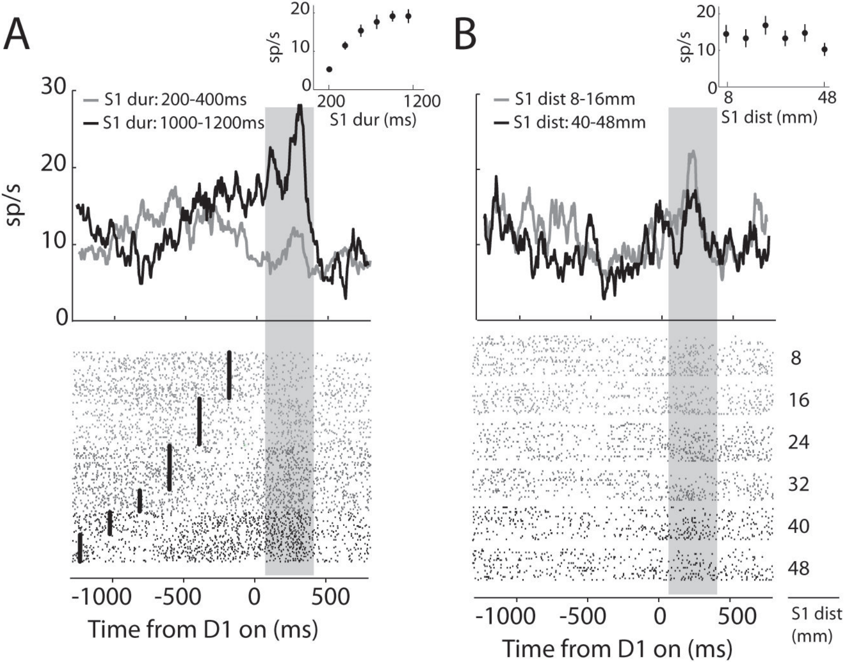
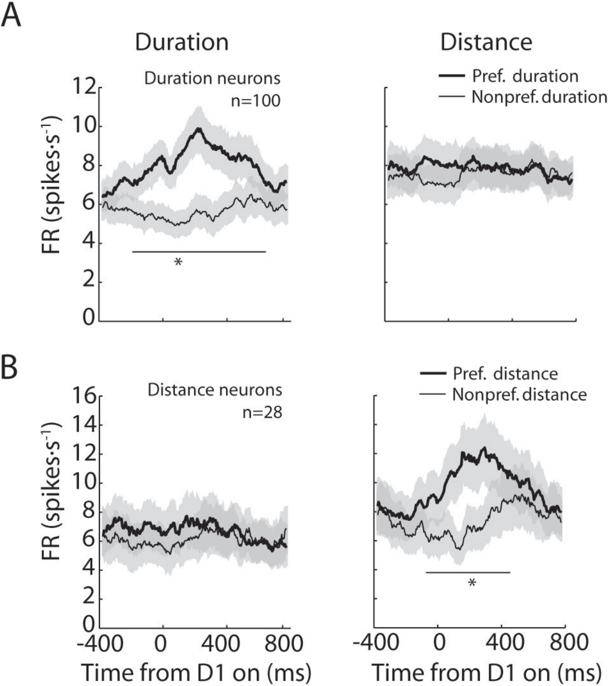

A
Duration task
Pre-stimulus
(400-800ms)
S1
(200-1200ms)
D1
(400 or 800ms)
S2
(200-1200ms)
D2
(0, 400 or 800ms)
"Go" signal
Choice & Action
(max. 6000ms)
Distance task
S1
(1000ms)
S2
(1000ms)
B
S2 duration (s)
1.2
0
0
1.2
S1 duration (s)
S2 distance (mm)
48
0
0
48
S1 distance (mm)
C
Monkey 1
Monkey 2
PS
AS
10 mm


Duration
Distance
113
41
100
13
28
26.4%
9.6%


A
B
S1 dur: 200-400ms
S1 dur: 1000-1200ms
S1 dist 8-16mm
S1 dist: 40-48mm
sp/s
30
20
10
0
S1 dur (ms)
200
1200
S1 dist (mm)
8
48
8
16
24
32
40
48
-1000
-500
0
500
Time from D1 on (ms)
S1 dist (mm)


A
Duration
Distance
Duration neurons
n=100
Pref. duration
Nonpref. duration
FR (spikes·s⁻¹)
12
10
8
6
4
2
0
*
B
Distance neurons
n=28
Pref. distance
Nonpref. distance
FR (spikes·s⁻¹)
16
14
12
10
8
6
4
2
0
*
-400
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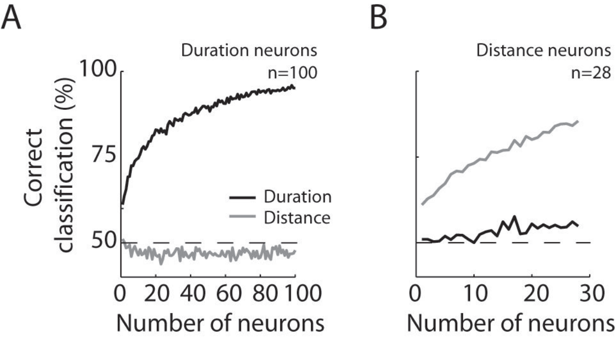
Time from D1 on (ms)


A
Duration neurons
n=100
100
75
50
Correct
classification (%)
Duration
Distance
0
20
40
60
80
100
Number of neurons
B
Distance neurons
n=28
0
10
20
30
Number of neurons