Context-Dependent Duration Signals in the Primate Prefrontal Cortex

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Abstract

The activity of some prefrontal (PF) cortex neurons distinguishes short from long time intervals. Here, we examined whether this property reflected a general timing mechanism or one dependent on behavioral context. In one task, monkeys discriminated the relative duration of 2 stimuli; in the other, they discriminated the relative distance of 2 stimuli from a fixed reference point. Both tasks had a pre-cue period (interval 1) and a delay period (interval 2) with no discriminant stimulus. Interval 1 elapsed before the presentation of the first discriminant stimulus, and interval 2 began after that stimulus. Both intervals had durations of either 400 or 800 ms. Most PF neurons distinguished short from long durations in one task or interval, but not in the others. When neurons did signal something about duration for both intervals, they did so in an uncorrelated or weakly correlated manner. These results demonstrate a high degree of context dependency in PF time processing. The PF, therefore, does not appear to signal durations abstractedly, as would be expected of a general temporal encoder, but instead does so in a highly context-dependent manner, both within and between tasks.

Key words: dorsolateral prefrontal cortex, duration, executive function, monitoring, periprincipal prefrontal cortex, temporal processing, timing

Introduction

Some neurons in the primate prefrontal (PF) cortex show activity modulation that distinguishes among elapsed time intervals. This signal appears as a phasic modulation that follows the termination of an event of variable duration, during a transition to the next event. In our previous study, PF neurons distinguished short, long, and intermediate cues, even though their duration was irrelevant to the task (Genovesio, Tsujimoto, et al. 2006). Here, we explored the context dependency of this PF signal. Like our previous study, there was no task requirement for estimating the duration of the task periods in question.

Various forms of temporal information processing have been observed in the PF cortex (Niki and Watanabe 1979; Brody et al. 2003; Sakurai et al. 2004; Tsujimoto and Sawaguchi 2005; Genovesio, Tsujimoto, et al. 2006; Oshio et al. 2006, 2008; Lebedev et al. 2006; Ohmae et al. 2008; Jin et al. 2009), along with the motor and premotor cortex (Lucchetti and Bon 2001; Renoult et al. 2006; Ohmae et al. 2008; Mita et al. 2009; Kilavik et al. 2010; Merchant et al. 2013), the basal ganglia (Chiba et al. 2008), and the thalamus (Tanaka 2007). Neuropsychological (Harrington et al. 1998; Mangels et al. 1998), neuroimaging (Onoe et al. 2001; Rao et al. 2001), and transcranial magnetic stimulation (Koch et al. 2003; Jones et al. 2004) studies also support the idea that PF plays a role in temporal perception. For example, patients with right PF lesions show deficits in timing tasks (Harrington et al. 1998; Kagerer et al. 2002; Koch et al. 2002; Danckert et al. 2007), and transcranial magnetic stimulation to the right PF impairs performance (Koch et al. 2003; Jones et al. 2004).
Temporal processing in PF might underlie the ability of human participants to estimate durations both when they are aware that they should do so (prospective time estimation) and when they become aware of the need to do so only after the timed event has ended (retrospective time estimation). Retrospective judgments have greater variance (McClain 1983), tend toward underestimates (Block and Zakay 1997), and are relatively variable intertrial interval of 700–1000 ms followed both correct and incorrect choices. The 2 tasks were run in blocks with no fixed order.

Surgery

Recording chambers were implanted over the exposed dura matter of the left frontal lobe, along with head restraint devices, using aseptic techniques and isoflurane anesthesia (1–3%, to effect). Monkey 1 had two 18 mm diameter chambers, and Monkey 2 had a single 27 × 36 mm chamber.

Methods

Two adult male rhesus monkeys (Macaca mulatta), 8.5 and 8.0 kg, used their left hands to perform 2 discrimination tasks, and all procedures were approved by the NIH ACUC.

The monkeys were situated 29 cm from a video monitor, with 3 touch-sensitive switches (3 × 2 cm) within reach. The switches were arrayed from left to right directly beneath the monitor. The stimulus material consisted of a white circle (0.6° diameter, visual angle), a blue circle (3° diameter), and a red square (3° × 3°).

Tasks

The monkey began each trial by touching the central switch, which led to the appearance of the white circle at the center of the video screen. The monkey then achieved and maintained visual fixation on the circle, and an interval of either 400 or 800 ms elapsed (Fig. 1A,B). At the end of this interval, called “interval 1,” either the blue circle or the red square appeared as the first discriminant stimulus (S1). Another interval, called “interval 2,” intervened between the offset of S1 and the onset of the second discriminant stimulus (S2). Like interval 1, interval 2 lasted either 400 or 800 ms. In the duration task (Fig. 1A), the 2 stimuli differed in duration but not in location. In the distance task (Fig. 1B), they differed in location but not in duration. The durations of intervals 1 and 2 were randomized independently, such that both durations of interval 2 could follow with the same probability, regardless of the duration of interval 1.

Figure 1C shows the stimulus durations used in the duration task. When we used the “square set,” the stimulus intervals varied between 200 and 1200 ms. S2 differed in both duration and color (as well as in shape) from S1, and the monkey’s task was to choose—after a “go” cue—the stimulus that had lasted longer. The go cue consisted of the red square and blue circle, one to the left and one to the right of the white circle (pseudorandomly selected). When we used the “V set,” the durations varied as shown in Figure 1C. For either distribution, the 2 discriminant stimuli had an equal likelihood of lasting longer on any given trial.

In the distance task (Fig. 1B), the central white circle served as a reference point. On each trial, one stimulus appeared one above the reference point and the other below it (pseudorandomly selected). Both stimuli lasted 1.0 s and ranged from 8 to 48 mm from the reference point, in steps of 8 mm (1.6°, 3.2°, 4.7°, 6.3°, 7.9°, and 9.4° of visual angle). The monkey’s task was to choose the stimulus that had been farther from the reference point. The durations of intervals 1 and 2 and the “go” cue matched those for the duration task (Fig. 1A).

In both tasks, an acoustic feedback signaled an error and a variable intertrial interval of 700–1000 ms followed both correct and incorrect choices. The 2 tasks were run in blocks with no fixed order.

Neurophysiological Analysis

Our previous reports used the same neuronal dataset to analyze activity during the duration and distance tasks (Genovesio et al. 2009, 2011, 2012; Genovesio, Tsujimoto, et al. 2014). The present analysis compares duration signals within and across tasks, using only correctly performed trials that followed other correctly performed trials. For the present analysis, we measured activity 80–400 ms after each interval ended. For interval 1, this occurred during the presentation of S1. Accordingly, we included only trials with an S1 duration of at least 400 ms. Note, however, that all of the trials are plotted in the rasters, including some with an S1 duration of <400 ms. Gray shading shows the trials used for analysis in the raster plots. During the S1 period, which intervened between intervals 1 and 2 (Fig. 1A), we measured activity only for stimulus durations of 400 and 800 ms (green dots in Fig. 1C). Of the S1 durations that occurred, Figure 1A shows the ones used for analysis in black type and the ones excluded in gray type. For interval 2, the measurements were made during the presentation of S2, again restricted to trials with an S2 duration of at least 400 ms. To identify cells with activity that distinguished the 2 interval durations, we performed an one-way ANOVA.

To compare the selectivity of cell preferences, we calculated a dimensionless modulation index, \( I = (A_{400} - A_{800})/A_{400} + A_{800} \), where \( A_{400} \) was the mean discharge rate on trials when the preceding interval had lasted 400 ms, and \( A_{800} \) was the mean rate when it had lasted 800 ms. For the stimulus interval, we calculated the modulation index using only S1 durations of 400 and 800 ms. As a measure of context dependency, we calculated Spearman’s rank order correlation between the indices, on a cell-by-cell basis, for different intervals and tasks.
Histological Analysis
Near the end of recording, we made electrolytic marking lesions (15 μA for 10 s). Ten days later, the monkeys were deeply anesthetized and perfused with formal saline. We plotted recording sites on coronal Nissl-stained sections, by reference to the recovered marking lesions, pins inserted during the perfusion, and structural magnetic resonance images. Although, the entry points for more posterior recordings (Fig. 1D) make it appear that many cells were located in the postarcuate cortex, track reconstructions based on the angle and depth of penetrations indicated that nearly all recordings came from prearcuate cortex, which corresponds to area 8.

Results
Database
Our database included 1339 neurons recorded in the distance task: 1065 from the caudal PF (PFc) and 274 from the dorsolateral PF cortex (PFdl). This population included 517 neurons from Monkey 1 and 822 from Monkey 2. We recorded a similar number of neurons in the duration task: 1257 neurons, of which 977 came from the PFc and 280 from the PFdl. Of this population, 526 were taken from Monkey 1 and 731 from Monkey 2. In the duration task, 524 neurons were recorded using the “V” distribution and 733 with the “square” distribution of durations. For 726 neurons recorded in the duration task, activity was recorded in the distance task, as well. In this category, 562 cells came from the PFc and 164 from the PFdl; 235 from Monkey 1 and 491 from Monkey 2.

Context Dependency
Figure 2 shows a neuron with strong context dependency across task periods. Figure 2E shows the mean and SEM for the activity in areas shaded gray in Figure 2A–D. This neuron had its highest activity after an interval 2 duration of 400 ms (Fig. 2B) and significantly less activity after an interval 2 duration of 800 ms (Fig. 2D; F = 9.34; df = 1; P = 0.003). Thus, the activity of this cell was modulated by the relative duration of interval 2, with a preference for the shorter duration. This neuron also showed increased activity after interval 1, although it was not modulated by duration in that task period (Fig. 2A,C; F = 0.00; df = 1; P = 0.997).

Figure 1. Task, stimulus durations, and sampled areas. (A) Duration task. (B) Distance task. The black lines corresponding to a stimulus interval of 400 and 800 ms indicate the durations used for the analyses. The durations of intervals 1 and 2 were randomized independently, so that each interval 2 duration followed each interval 1 duration with equal probability. The gray lines indicate the durations of the “square” set excluded from the present analysis, which instead used S1 durations of 400 and 800 ms only. (C) Duration sets. The green dots indicate the stimulus durations used for analyzing duration effects for the S1 interval. (D) Penetration sites. Composite from both monkeys. AS: arcuate sulcus; PS: principal sulcus.
Figure 2. An example neuron recorded in the duration task (with the “square” set of durations) showing context dependency between intervals 1 and 2. This neuron shows significant duration effects for interval 2. The gray background indicates the trials used for analysis, which excluded those with S1 and S2 durations of <400 ms. (A) Trials with an interval 1 duration of 400 ms. (B) Trials with an interval 2 duration of 400 ms. (C) Trials with an interval 1 duration of 800 ms. (D) Trials with an interval 2 duration of 800 ms. Each raster shows activity aligned on stimulus onset. Rasters are aligned on S1 onset in A and C and on S2 onset in B and D. Empty squares indicate the 2 interval durations. The dots to the right of the alignment lines indicate S1 offset in A and C and S2 offset in B and D. (E) Means ± SEM for the data shaded in gray. Asterisk indicates statistically significant difference.

Figure 3. Same neuron as in Figure 2 showing duration effects that were task-dependent. This neuron shows significant duration effects only in the duration task, with higher activity when interval 1 was 400 ms. The rasters of Figure 2B are plotted again for comparison with the duration task. (A) Duration task with an interval 2 of 400 ms. (B) Distance task with an interval 2 of 400 ms. (C) Duration task with an interval 2 of 800 ms. (D) Distance task with an interval 2 of 800 ms. (E) Means ± SEM for the data shaded in gray. Asterisk indicates statistically significant difference.

Figure 3 illustrates another feature of the neuron illustrated in Figure 2. In addition to having context dependency across periods within a task (Fig. 2), it had context dependency across the 2 tasks. As illustrated in Figure 3E, this neuron was modulated by the relative duration of interval 2 in the duration task (Fig. 3A,C; $F = 9.34; df = 1; P = 0.003$) but not in the distance task (Fig. 3B,D; $F = 0.49; df = 1; P = 0.489$), in which the neuron was also less active on average after interval 2.

Figure 4 shows a different type of cell, one that was context-independent across tasks for the interval 1, but highly context-dependent for the 2 intervals within a task. This neuron was modulated by interval 1’s duration in both the distance (Fig. 4A) and duration (Fig. 4B) tasks, preferring the short interval (400 ms) in both cases. This signal occurred for interval 1 but not for interval 2, indicating a strong context dependency for the 2 intervals within a task.
Population Analysis

In the distance task, we found that 303 neurons were selective for at least one interval duration. Like the neuron illustrated in Figure 4, the majority of cells that distinguished whether an interval was short or long in the distance task did so for one interval or the other, but not both (281/303, 93%). Only 7% (22/303) of the population had activity that significantly distinguished between the short and long durations for both intervals 1 and 2. Table 1 presents the results for the distance task divided by cortical area. It shows that a similar percentage of neurons was modulated by the duration of interval 1 (12% in the PFdl and 13% in the PFc) and interval 2 (13% in the PFdl and 11% in the PFc).

Table 2 summarizes analogous results for the duration task. A smaller proportion of neurons was modulated by the relative duration of interval 1 (7% in the PFdl and 10% in the PFc) than for interval 2 (14% in the PFdl and 13% in the PFc), and only a small minority of neurons was modulated for both intervals (21/260, 8%).

The number of neurons that preferred the shorter interval differed little from those that preferred the longer interval. For interval 1, slightly more cells preferred the long interval 1 in both the distance (56%) and duration (58%) tasks. For interval 2, short duration preferences were a slight majority: 54% for both tasks.

Like the neuron illustrated in Figure 3, the majority of cells that distinguished between short and long interval durations did so for one task or the other, but not for both. As with context dependency across task periods, there were exceptions, and Table 3 displays these results. Of the 152 cells modulated by the
duration effects in both tasks (green data points in Fig. 7). For that interval 1 or 2 versus the stimulus interval: for S1 versus S1 period, which we have described previously (Genovesio et al. 2009). The same analysis could not be performed for the distance task because in that task the S1 stimulus had a short versus long durations for intervals 1 and 2, these were not trials that had S1 durations of either 400 or 800 ms. There was no significant correlation between the modulation indices for either interval 1 or 2 versus the stimulus interval: for S1 versus S1 interval 1 (Fig. 6A, $r = 0.01; P = 0.93$) for S1 versus interval 2 (Fig. 6B, $r = 0.21; P = 0.12$). These results indicate that while some neurons were, at least to a degree, involved in distinguishing short versus long durations for intervals 1 and 2, these were not the same neurons that distinguished stimulus durations during the S1 period, which we have described previously (Genovesio et al. 2009). The same analysis could not be performed for the distance task because in that task the S1 stimulus had a fixed duration.

Figure 7 compares the modulation indices across tasks. For the total population, we found a significant population-level correlation for both interval 1 ($r = 0.21, P = 0.009$) and interval 2 ($r = 0.36, P \ll 0.0001$). These results indicate, at the single-cell level, a degree of context independence in duration sensitivity across tasks, especially for the small population of cells with significant duration effects in both tasks (green data points in Fig. 7). For that subpopulation, between-task correlations were higher for both interval 1 ($r = 0.71, P = 0.002$) and interval 2 ($r = 0.46, P = 0.027$) than for the overall population. For interval 1, the cells with significant duration effects in both tasks accounted for the significance of the correlation for the overall population. When these cells were removed, the remaining correlation failed to reach significance ($r = 0.11, P = 0.23$). For interval 2, the correlation was still significant after removal of the cells with significant duration effects in both tasks ($r = 0.30, P \ll 0.0001$).

### Magnitude of the Effect

Figure 8A–D shows the population activity for cells modulated by interval duration in the distance task, for intervals 1 (Fig. 8A,C) and 2 (Fig. 8B,D), further divided by their preference for the shorter or longer intervals. Figure 8E–H shows comparable results for

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**Table 1** Number and percentage of cells with significant effects of interval duration, by ANOVA, in the distance task

<table>
<thead>
<tr>
<th>Intervals</th>
<th>PFdl</th>
<th>PFC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval 1</td>
<td>32 (11.7%)</td>
<td>139 (13.0%)</td>
<td>171 (12.8%)</td>
</tr>
<tr>
<td>Interval 2</td>
<td>37 (13.5%)</td>
<td>117 (11.0%)</td>
<td>154 (11.5%)</td>
</tr>
<tr>
<td>Both</td>
<td>5 (1.8%)</td>
<td>17 (1.6%)</td>
<td>22 (1.6%)</td>
</tr>
<tr>
<td>N</td>
<td>274</td>
<td>1065</td>
<td>1339</td>
</tr>
</tbody>
</table>

Note: Percentage of neurons recorded in each area (N) and combined (total). The cells with significant effects in both intervals are included in the totals for intervals 1 and 2.

**Table 2** Number and percentage of cells with significant effects of interval duration in the duration task

<table>
<thead>
<tr>
<th>Intervals</th>
<th>PFdl</th>
<th>PFC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval 1</td>
<td>21 (7.5%)</td>
<td>94 (9.6%)</td>
<td>115 (9.1%)</td>
</tr>
<tr>
<td>Interval 2</td>
<td>39 (13.9%)</td>
<td>127 (13.0%)</td>
<td>166 (13.2%)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (1.1%)</td>
<td>18 (1.8%)</td>
<td>21 (1.7%)</td>
</tr>
<tr>
<td>N</td>
<td>280</td>
<td>977</td>
<td>1257</td>
</tr>
</tbody>
</table>

Note: The cells with significant effects in both intervals are included in the totals for intervals 1 and 2. Format as in Table 1.

**Table 3** Number and percentage of cells with effects of interval duration, by task, in interval 1

<table>
<thead>
<tr>
<th>Task</th>
<th>PFdl</th>
<th>PFC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>19 (11.6%)</td>
<td>78 (13.9%)</td>
<td>97 (13.4%)</td>
</tr>
<tr>
<td>Duration</td>
<td>14 (8.5%)</td>
<td>58 (10.3%)</td>
<td>72 (9.9%)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (0.6%)</td>
<td>16 (2.8%)</td>
<td>17 (2.3%)</td>
</tr>
<tr>
<td>N</td>
<td>164</td>
<td>562</td>
<td>726</td>
</tr>
</tbody>
</table>

Note: The cells with significant effects in both intervals are included in the totals for the 2 tasks. Format as in Table 1.

**Table 4** Number and percentage of cells with effects of interval duration, by task, in interval 2

<table>
<thead>
<tr>
<th>Task</th>
<th>PFdl</th>
<th>PFC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>25 (15.2%)</td>
<td>73 (13.0%)</td>
<td>98 (13.5%)</td>
</tr>
<tr>
<td>Duration</td>
<td>25 (15.2%)</td>
<td>84 (15.0%)</td>
<td>109 (15.0%)</td>
</tr>
<tr>
<td>Both</td>
<td>7 (4.3%)</td>
<td>16 (2.8%)</td>
<td>23 (3.2%)</td>
</tr>
<tr>
<td>N</td>
<td>164</td>
<td>562</td>
<td>726</td>
</tr>
</tbody>
</table>

Note: The cells with significant effects in both intervals are included in the totals for the 2 tasks. Format as in Table 1.

The same analysis could not be performed for the distance task because in that task the S1 stimulus had a short versus long durations for intervals 1 and 2, these were not trials that had S1 durations of either 400 or 800 ms. There was no significant correlation between the modulation indices for either interval 1 or 2 versus the stimulus interval: for S1 versus S1 interval 1 (Fig. 6A, $r = 0.01; P = 0.93$) for S1 versus interval 2 (Fig. 6B, $r = 0.21; P = 0.12$). These results indicate that while some neurons were, at least to a degree, involved in distinguishing short versus long durations for intervals 1 and 2, these were not the same neurons that distinguished stimulus durations during the S1 period, which we have described previously (Genovesio et al. 2009). The same analysis could not be performed for the distance task because in that task the S1 stimulus had a fixed duration.

**Selectivity Analysis**

Figure 5 compares the modulation indices for intervals 1 and 2. This index measures how selective a neuron was for the short versus long intervals. There are 2 versions of this analysis. The first used cells showing significant duration effects in one or both intervals, taken from a population of neurons recorded in either or both tasks (Fig. 5A,B). The second restricted the analysis to the 726 neurons recorded in both tasks (Fig. 5C,D), provided that there was a significant duration effect in at least one interval for at least one task. These inclusion criteria had little effect on the results other than altering the overall size of the cell population. In the distance task, there was no correlation in the duration selectivity between the 2 intervals for the total population (Fig. 5A, $r = -0.03; P = 0.97$) or for cells recorded in both tasks (Fig. 5C, $r = -0.06; P = 0.42$). That is, a neuron that preferred the shorter duration of interval 1 to a given degree was as likely as not to prefer the longer duration of interval 2, and to some different degree. In the duration task, however, there was a weak but significant correlation between the modulation indices for the 2 intervals, both for the total population (Fig. 5B, $r = 0.20; P = 0.001$) and for the cells recorded in both tasks (Fig. 5D, $r = 0.23; P = 0.003$).

In the duration task, we could also test for a correlation between the interval 1 or 2 modulation indices and those obtained for the S1 stimulus interval. For this analysis, we used only the trials that had S1 durations of either 400 or 800 ms. There was no significant correlation between the modulation indices for either interval 1 or 2 versus the stimulus interval: for S1 versus S1 interval 1 (Fig. 6A, $r = 0.01; P = 0.93$) for S1 versus interval 2 (Fig. 6B, $r = 0.21; P = 0.12$). These results indicate that while some neurons were, at least to a degree, involved in distinguishing short versus long durations for intervals 1 and 2, these were not the same neurons that distinguished stimulus durations during the S1 period, which we have described previously (Genovesio et al. 2009). The same analysis could not be performed for the distance task because in that task the S1 stimulus had a fixed duration.

Figure 7 compares the modulation indices across tasks. For the total population, we found a significant population-level correlation for both interval 1 ($r = 0.21, P = 0.009$) and interval 2 ($r = 0.36, P \ll 0.0001$). These results indicate, at the single-cell level, a degree of context independence in duration sensitivity across tasks, especially for the small population of cells with significant duration effects in both tasks (green data points in Fig. 7). For that subpopulation, between-task correlations were higher for both interval 1 ($r = 0.71, P = 0.002$) and interval 2 ($r = 0.46, P = 0.027$) than for the overall population. For interval 1, the cells with significant duration effects in both tasks accounted for the significance of the correlation for the overall population. When these cells were removed, the remaining correlation failed to reach significance ($r = 0.11, P = 0.23$). For interval 2, the correlation was still significant after removal of the cells with significant duration effects in both tasks ($r = 0.30, P \ll 0.0001$).
Figure 5. Scatter plots of modulation indices, as calculated for both intervals 1 and 2. Only cells with significant duration effects are included. (A) Interval 1 versus interval 2 for the distance task. (B) Interval 1 versus interval 2 for the duration task. (C and D) As in A and B, but only for the subpopulation of cells recorded in both tasks. The regression line is plotted for significant correlations only. Blue circles show the modulation indices for cells with significant duration effects only for interval 1; magenta circles represent cells with duration effects only for interval 2; and green circles represent cells that had duration effects for both intervals.

Figure 6. Scatter plots of the modulation indices for cells with significant duration effects for either interval 1 or 2. (A) Interval 1 versus S1. (B) Interval 2 versus S1.
the duration task. Of course, being so highly selected, these population averages do not demonstrate much about the occurrence of duration modulation. Unlike ANOVA, however, they demonstrate the time course and magnitude of duration selectivity, both within and between tasks. In both tasks, the duration signal dissipated approximately 0.5 s after the end of the variable interval. These data also show a small degree of activity build-up before the end of the interval, but only for interval 2.

Discussion

Context Dependency

We found that virtually all of the sampled PF neurons showed a high degree of context dependency. Neurons that distinguished between short and long intervals did so only for some task periods and not others, and for one task and not the other. With only one exception, no neuron simply distinguished between the short and long intervals across both tasks (distance and duration) and all 3 intervals (interval 1, interval 2, and the S1 interval).

In the distance task, we found that duration selectivity was fully independent for the intervals 1 and 2. This finding indicates that in this task, one outside the temporal domain, duration modulation was entirely context-dependent (Fig. 5A,C). In the duration task, even though there was strong context dependency, at the population level, there was a weak correlation in neuronal preferences between intervals 1 and 2 (Fig. 5B,D). Notwithstanding these small correlations and shared preferences, our results point to a pervasive context dependency.

The high level of specialization seen here for duration effects contrasts with a generalist role reported for many PF neurons. Examples include the encoding of rank order in a serial object and an action task (Berdyyeva and Olson 2010) and in line-length and numerosity tasks. In the latter, a substantial proportion of PF cells (34%) encoded these metrics in a generalized, context-independent manner (Eiselt and Nieder 2013). Task differences and task relevance might account for these results, but the lack of generalized duration effects in our data might indicate a computational feature characteristic of duration processing. We also note 2 relatively strong correlations in our data, but only for the cells with significant duration selectivity in both tasks. These cells tended to have common selectivity and preferences for intervals 1 and 2 across tasks (green points in Fig. 7A,B) with only few cells having opposing preferences.

Coding Irrelevancies

As mentioned in the Introduction section, human participants can estimate duration “retrospectively,” as an automatic process that does not require awareness of that task requirement. Neurons modulated by irrelevant durations could contribute to that capacity. Note that although the durations of intervals 1 and 2 were irrelevant to task performance, the monkeys had extensive experience with these durations, making the 2 possibilities highly predictable. Like several previous results (Mann et al. 1988; Chen et al. 2001; Lauwereyns et al. 2001; Genovesio, Tsujimoto, et al. 2006; Kim et al. 2008; Tsujimoto et al. 2012; Genovesio, Tsujimoto, et al. 2014), the present results provide another example of PF neurons that encode stimuli and other events that are irrelevant to task performance.

Not only does PF encode irrelevant parameters, but there are instances in which PF fails to encode task-relevant information (Lara and Wallis 2014). In this experiment of Lara and Wallis, PF neurons failed to encode the color of the item in working memory, which was relevant to the task, and instead signaled an irrelevant parameter: location.

Using the same database as the one used in this report, we have previously described duration encoding in PF when this metric was relevant to task performance (Genovesio et al. 2009, 2012). Taken together with the present analysis, we can conclude that PF neurons are modulated by both relevant and irrelevant durations, much as human subjects can estimate intervals both prospectively and retrospectively.

Single Versus Multiple Timing Mechanisms

One of the debates in the literature on cortical timing mechanisms involves whether there is a single, common mechanism or several, perhaps in different brain areas. Some behavioral studies have supported the presence of a common timing mechanism. These studies demonstrate the generalization of duration discrimination learning across sensory modalities (Wright et al. 1997; Nagarajan et al. 1998) and from time perception to time production (Meegan et al. 2000). However, the level of generalization has thus far been limited to trained durations and does not generalize to other durations (Merchant et al. 2008). Not only has the existence of a general timing mechanism been proposed, but some evidence suggests an even more abstract mechanism for encoding all magnitudes (Walsh 2003), including duration, number, and distance (Burr et al. 2010).
In contrast to theories of common magnitude or timing mechanisms, which can be applied across tasks and different events, some psychophysical experiments have shown that the perception of duration occurs through several, parallel mechanisms. In our previous study, we have shown that PF neurons do not seem to participate in a shared magnitude system. Instead,
PF neurons encode potential goals, whether on the basis of metric contexts or other ones (Genovesio et al. 2012; Genovesio and Tsujimoto 2014; Genovesio, Wise, et al. 2014).

In a study of the pre-supplementary motor area (pre-SMA), Merchant et al. (2013) found that many neurons share the same duration preference in 2 different tasks: A synchronization–continuation tapping task and a duration–reproduction task. This could reflect a special role for the pre-SMA in timing. For example, the pre-SMA might function together with the basal ganglia and the thalamus in general timing, with the PF functioning in a context-dependent way. However, Merchant et al. (2013) also found that duration selectivity for tapping was encoded in conjunction with the ordinal position of the tapping movement, which resembles the ordinal dependency of intervals 1 and 2 in our study. Therefore, the context dependency of the timing mechanism in the pre-SMA might be much like one we observe in the PFdl and PFC, with differences depending on which contexts are tested.

Adaptive Coding

Previous studies have shown that time-dependent modulation can flexibly adapt to duration changes (Komura et al. 2001; Lucchetti and Bon 2001; Brody et al. 2003). In PF, for example, Brody et al. (2003) have shown in a somatosensory discrimination task that the time-dependent PF neurons have anticipatory activity that changes when the delay was varied from 3 to 6 s. They found that the neural activity scaled according to the change in delay duration, instead of maintaining a fixed relationship with the delay offset. A cell might, for example, reach its half-maximal activity halfway through an interval, regardless of the interval’s duration. Komura et al. (2001) reported another example of adaptation in duration-related activity, in their case in the thalamus. They found that reward-expected activity changed as a function of the delay preceding reward delivery. In our tasks, we observed a different type of flexibility: PF neurons developed weakly shared timing signals as monkeys switched from the distance to the duration task (Fig. 5B,D). This finding suggests a novel type of flexibility: Dynamic coding based on task demands (Everling et al. 2002; Duncan 2010) rather than on changed durations.

In addition to intervals 1 and 2, which were common to the distance and duration tasks, the latter had a variable stimulus interval. This added interval could have generated more sharing of limited resources (Passingham 1996; Klingberg and Roland 1997; Buschman et al. 2011; Watanabe and Funahashi 2014), as reflected in the weak correlations illustrated in Figures 5B,D. The partial overlap in the cells modulated by both intervals 1 and 2 in the duration task did not, however, extend to the S1 stimulus interval. One possible interpretation of this result is that context specificity could not be maintained for all 3 intervals in the duration task—interval 1, interval 2, and the S1 interval—without generating interference. So, the network segregated the timing related to the S1 period from that related to intervals 1 and 2. Such specificity resembles the segregation of previous- and future-goal signals to distinct the population of PF neurons (Genovesio, Brasted, et al. 2006; Genovesio and Wise 2008; Genovesio, Tsujimoto, et al. 2008). This form of adaptive coding, in which context dependence or independence changes dynamically, could serve to mitigate interference by allocating scarce neural resources to the extent possible in each task.

Other recent studies of PF activity support this idea. Recordings during a categorization task have found that overlap in image representations was more pronounced when different images belonged to unrelated categories, as opposed to conflicting categories, varying from 44% in the former case to 24% in the latter (Cromer et al. 2010; Roy et al. 2010).

Likewise, Yumoto et al. (2011) have recorded from PF area 9 during a time-reproduction task. They trained monkeys to both discriminate the duration of a visual stimulus and reproduce it with a button press. These investigators found a population of neurons that encoded the duration of a discriminant stimulus, similar to our previous reports (Genovesio, Tsujimoto, et al. 2006; Genovesio et al. 2009). They also identified another population of neurons, one modulated by the duration of the button press that the monkeys needed to reproduce. Interestingly, only a minority of neurons belonged to both populations, a finding that also points to a separation of functions between duration decoding and the temporal organization of movements. This finding, too, could reflect the mitigation of interference through adaptive coding.

Conclusions

We found that PF neurons distinguish between short and long intervals in a highly context-dependent way. This finding indicates that temporal processing in the PF, at the single-cell level, is linked to specific past events. In principle, this property could allow PF to keep track of specific intervals as they unfold over time, as opposed to signaling durations in abstract, general, or common terms. Encoding time in a context-dependent way could contribute to making foraging choices based on the different travel times estimated for reaching resources (Genovesio, Wise, et al. 2014).

Our findings also show that task demands can alter the degree of context dependency from absolute independence in the distance task to weak dependence in the duration task, especially, for cells that show duration effects for both intervals. This result suggests that adaptive coding in PF (Everling et al. 2002; Duncan 2010) not only involves recruiting cells in highly demanding conditions, but also changing the degree of neuronal specialization.

Funding

This work was supported by the Division of Intramural Research of the National Institute of Mental Health (Z01MH-01092).

Notes

We thank Dr Andrew Mitzi, Mr James Fellows, and Ms Ping-yu Chen for technical support. Conflict of Interest: None declared.

References


