Neurons in the primate dorsolateral prefrontal cortex (dIPFC) filter attend targets distinctly from distracters through their response rates. The extent to which this ability correlates with the organism’s performance, and the neural processes underlying it, remain unclear. We trained monkeys to attend to a visual target that differed in rank along a color-ordinal scale from that of a distracter. The animals’ performance at focusing attention on the target and filtering out the distracter improved as ordinal distance between the stimuli increased. Importantly, dIPFC neurons also improved their filtering performance with increasing ordinal target-distracter distance; they built up their response rate in anticipation of the target-distracter onset, and then units encoding target representations increased their firing rate by similar amounts, whereas units encoding distracter representations gradually suppressed their rates as the interstimulus ordinal distance increased. These results suggest that attentional-filtering performance in primates relies upon dIPFC neurons’ ability to suppress distracter representations.

INTRODUCTION

The primate dorsolateral prefrontal cortex (dIPFC) is thought to play an important role in executive functions such as working memory, response inhibition, preparation for action, goal selection, planning, and decision making (Tanji and Hoshi, 2008). Previous studies in nonhuman primates have reported that dIPFC neurons selectively respond to stimuli that are relevant to a given task, suggesting that these units play a role in attentional filtering of behaviorally relevant signals from irrelevant ones (Boussaoud and Wise, 1993; di Pellegrino and Wise, 1993; Everling et al., 2002; Lebedev et al., 2004; Rainer et al., 1998). However, a similar response pattern is shown by neurons in other brain areas such as the frontal eye fields (FEFs) (Thompson and Bichot, 2005), area lateral intraparietal (LIP) (Bisley and Goldberg, 2003; Goldberg et al., 2006), and the superior colliculus in the brainstem (Fecteau and Munoz, 2006; Ignashchenkova et al., 2004), raising the question of what are the specific roles of the dIPFC and each one of these areas in attentional filtering.

A recent study has shown that during voluntary allocation of attention to a visual target in the presence of distracters, dIPFC and FEF neurons selectively represent the target location through their firing patterns earlier than neurons in area LIP (Buschman and Miller, 2007, 2009), suggesting that top-down attentional signals may emanate first in the prefrontal cortex and then propagate throughout the rest of the brain (but see Schall et al., 2007 and Buschman and Miller, 2009). Moreover, it has been suggested that the FEF plays a role in shifting attention toward a target location, regardless of whether the target is present or absent, whereas the dIPFC signals the current target position (Buschman and Miller, 2009). However, because data comparing the specific roles of dIPFC and FEF in generating attentional signals are scarce, this issue remains poorly understood.

Over the last decade, studies in monkeys have reported that microstimulation of the FEF causes enhanced detection performance at selected locations in the visual field (Moore and Fallah, 2001) as well as increases in the firing rate of V4 neurons with receptive fields at that location (Moore and Armstrong 2003). Additionally, the strength of FEF activation correlates with changes in the animals’ performance during attentional tasks (Armstrong et al., 2009; Gregoriou et al., 2009). In the dIPFC, although it has been reported that attentional filtering by single neurons is strong and shows selectivity not only for spatial locations but also for stimulus type (Everling et al., 2002), it is unclear to which extent the strength of this filtering mechanism correlates with changes in behavioral performance during attentional tasks.

Here, we explored the latter issue by recording the responses of dIPFC neurons of two macaque monkeys during a task that yielded measurable changes in the animals’ behavioral performance at filtering out a target from a distracter. The experimental design was based on the previous observation that when comparing the ranks of two stimuli within an ordinal scale (e.g., numbers or quantities), humans and monkeys respond faster and more accurately the greater the interstimulus ordinal distance (distance effect: Buckley and Gillman [1974]; Dehaene et al. [1998]; Jou and Aldridge [1999]; Moyer and Landauer [1967]; Nieder et al. [2002]). We hypothesized that when monkeys select and sustain attention on a target stimulus that differs in ordinal rank from a nearby distracter, changes in the animals’ ability to do so would be accompanied by corresponding changes in the activity of dIPFC neurons.
We found that animals better detected changes in the target as the ordinal distance to the distracter increased (distance effect). More importantly, neurons in the dlPFC better filtered out the target from the distracter through their response rate as ordinal distance between the two stimuli increased. The latter effect was due to a gradual suppression of responses to distracters as a function of ordinal distance to the target.

RESULTS

Behavioral Performance and Ordinal Distance

We trained two adult monkeys (Macaca mulatta, Se and Ra) to hold gaze on a fixation spot at the center of a projection screen, and to attend to one of two moving random dot patterns (RDPs) appearing to the left and right of the spot. The dots in the two RDPs moved in the same direction but differed in their color (Figure 1). The attended (target) and ignored (distracter) RDPs were defined according to a color/rank-order selection rule (gray < pink < green < blue < red < turquoise). The animals were rewarded for releasing a button after a change in the target’s direction of motion while ignoring similar changes in the distracter (see Figure 1 inset and Experimental Procedures).

Within 3–5 months of training, both animals reached stable performances in the task. First, we tested the hypothesis that they did so by learning, from the pattern of hits and errors, the position of the different colors in the ordinal scale according to our color/rank-order selection rule. As an alternative hypothesis, the animals may have learned, for each color pair, which RDP was the target and which one the distracter. The former hypothesis predicts a distance effect in the pattern of reaction times and proportion of correct button releases (hits). The latter predicts no systematic relationship between reaction time and proportion of hits, and rank/ordinal distance between the colors.

In animal Se, we found that the hit rate ((number of hits – number of false alarms)/number of trials) increased (p < 0.000001, Kruskal Wallis one-way analysis of variance [ANOVA]), and the reaction time decreased (p < 0.000001, one-way ANOVA) as the ordinal distance between the stimuli increased (Figure 2A, left panels). For animal Ra, we found a similar effect on reaction times (p = 0.0113, one-way ANOVA), and a trend in the median performance to increase with distance; however, this latter effect did not reach statistical significance (p = 0.3401, Kruskal Wallis one-way ANOVA) (Figure 2A, right panels). One explanation for this latter result is that Ra was more extensively trained than Se, which resulted in hit rates above 96% for all distances producing a ceiling effect. In order to test this hypothesis, we examined Ra’s data obtained during early training sessions following the acquisition of the color-rank rule prior to the recordings. Here, Ra showed a strong distance effect, not only for distances 1–3 but also for other tested distances (see Figure S1A available online). However, as training progressed Ra’s performance increased, and differences between distances became gradually smaller.

In both animals the observed main effect of distance in the reaction times was due to significantly shorter reaction times for distance 3, whereas no significant differences were obtained between distances 1 and 2. We examined reaction times as a function of target change time and observed that reaction times were longer the shorter the trial duration (i.e., the earlier in the trial the target change happened), and the difference between distances was more pronounced (one-way ANOVA, Ra: p = 0.0004; Se: p = 0.0001; Figure S1B). These results suggest that both length of training and trial duration modulate the intensity of the distance effect.

Moreover, we initially trained Ra using the combinations “red-blue,” “blue-green,” and “red-green” (rule: green < blue < red). When hit rates for the three pairs visibly increased above chance (50%) we introduced gray as the color with the lowest rank. Ra...
was first presented with the novel combination "green-gray" and was rewarded for choosing green as the target. During the first few trials, Ra appeared to have chosen the target randomly, but quickly hit rate increased indicating that it learned which pattern was the target, and which one the distracter. Then, Ra was presented with two novel pairs, "blue-gray" and "red-gray." Almost instantaneously, the animal chose blue and red over gray (Figure 2B, upper panels), indicating that it generalized the previously acquired knowledge, i.e., because gray was lower in rank than green, and green was lower than blue and red, then gray must be lower than blue and red. In rank-ordered representations this phenomenon is called transitive knowledge (e.g., whenever A < B and B < C, then also A < C). This effect has been previously demonstrated in macaques when building representations of lists of objects (Treichler and Van Tilburg, 1996), and it seems to involve activation of the frontal and parietal cortices in humans (Acuna et al., 2002).

A similar behavior was observed when introducing the novel color pink. Ra learned the combination "green-pink" and showed successful transition to blue and red. However, when presented
with the novel pair “pink–gray”— wherein no transitive knowledge could be applied because both were equally likely to be lower in rank than the previously seen colors —Ra’s performance showed a random pattern of hits and errors that eventually stabilized above chance once the animal learned the new combination. A statistical analysis of these data is shown in Figure S1C.

In order to determine whether differences between responses to targets and distracters were task specific, we trained the animals in a condition during which they ignored both RDPs and responded to a change in the luminance of the fixation spot (one-way ANOVA with task period as factor, p < 0.05). From these task-related neurons, 122 (82%, 64 in Ra and 58 in Se) showed clear preference for target stimuli in one of the two hemifields (three-way ANOVA with target hemifield, color combination, and distance as factors, p < 0.05, see Table S1 for details). These units responded more strongly to the target at a preferred position (i.e., left [n = 73] or right [n = 49] of the fixation spot) than to the distracter at the same position following color-change onset (Figure 3B). The upper panels in Figures 3C and 3D show responses of two example neurons preferring the target on the left (Figure 3C) and right (Figure 3D) of the fixation spot.

In sum, based on the animals’ performances during training and the recording sessions, we concluded that they learned the ordinal rank of the colors and used the color-rank order rule to select the target. The data analysis in the next section focuses on neuronal responses preceding direction changes in the target and distracter. This ensured that any response modulation was due to the allocation of attention to the target rather than to changes in a stimulus direction, or to exogenous allocation of attention to such direction changes (Busse et al., 2008).

**Target Selection in dIPFC Neurons**

While the animals performed the tasks, we recorded the responses of a total of 222 neurons in the right dIPFC (106 in Ra, and 116 in Se; Figure 3A). A total of 147 (66%) units showed significant changes in firing rate during task trials relative to a 200 ms interval preceding the stimulus onset, during which the animals were only fixating the central spot (one-way ANOVA with task period as factor, p < 0.05). From these task-related neurons, 122 (82%, 64 in Ra and 58 in Se) showed clear preference for target stimuli in one of the two hemifields (three-way ANOVA with target hemifield, color combination, and distance as factors, p < 0.05, see Table S1 for details). These units responded more strongly to the target at a preferred position (i.e., left [n = 73] or right [n = 49] of the fixation spot) than to the distracter at the same position following color-change onset (Figure 3B). The upper panels in Figures 3C and 3D show responses of two example neurons preferring the target on the left (Figure 3C) and right (Figure 3D) of the fixation spot.

In sum, based on the animals’ performances during training and the recording sessions, we concluded that they learned the ordinal rank of the colors and used the color-rank order rule to select the target. The data analysis in the next section focuses on neuronal responses preceding direction changes in the target and distracter. This ensured that any response modulation was due to the allocation of attention to the target rather than to changes in a stimulus direction, or to exogenous allocation of attention to such direction changes (Busse et al., 2008).

**Figure 3. Recording Sites and Neuronal Selectivities**

(A) Chamber location (top) and recording sites (middle) in monkey Ra and Se, respectively.

(B) Classification of neuronal populations into task-related and target-selective (see Experimental Procedures for details).

(C and D) Single-cell examples illustrating responses (ordinate) to targets positioned to the left (red) or right (blue) of the fixation cross in the main task (top) and fixation (bottom) conditions as a function of trial event onset (abscissa).
Target Selection as a Function of Ordinal Distance

For each one of the 122 target selection units, trials were grouped according to the ordinal distance between target and distracter colors, and to the stimulus position (Figure 4A). During the task the example neuron u26 increased its firing rate at stimulus onset (Figure 4B, left panel). Shortly after the color change, the unit similarly responded to all stimuli, but after ~200 ms, responses started diverging for targets and distracters. Responses to targets at the preferred location (see Experimental Procedures) were similar regardless of target-distracter distance (solid lines). However, responses to distracters were differentially suppressed as the distance increased (i.e., stronger suppression for distance 3 [d3, black dashed line], followed by distance 2 [d2, blue dashed line] and distance 1 [d1, red dashed line]). At about 400 ms, all responses (to targets and distracters) appeared to decrease; however, the pattern of response differences remained similar.

During the fixation condition (Figure 4C, right panels), both units showed lower firing rates; however, u26 still showed differences between responses to targets and distracters. Thus, this unit selected the target even during fixation where both RDPs were irrelevant. On the other hand, the second unit (u79) shows some response after the color change, mostly to targets, and no response to distracters. A common finding in most units was a progressive buildup of responses after the onset of the two white RDPs during the main task relative to fixation.

In order to examine the trend across the recorded neural population, we normalized in each unit responses to targets and distracters (to targets and distracters) appearing to decrease; however, the pattern of response differences remained similar.

This behavior was similar although not as dramatic for neuron u79 (Figure 4C, left panel). Thus, for both cells, responses to targets and distracters at the preferred location increased after the onset of the two white RDPs, reached a certain level, and at about 200 ms after the color change, started diverging with similar increases for targets and variable decreases for distracters depending on ordinal distance.

During the fixation condition (Figure 4C, right panels), both units showed lower firing rates; however, u26 still showed differences between responses to targets and distracters. Thus, this unit selected the target even during fixation where both RDPs were irrelevant. On the other hand, the second unit (u79) shows a constant low firing rate for both targets and distracters during the entire fixation period. These two units represent extreme cases in our fixation data set. The average neuron showed some response after the color change, mainly to targets, and no response to distracters. A common finding in most units was a progressive buildup of responses after the onset of the two white RDPs during the main task relative to fixation.

In order to examine the trend across the recorded neural population, we normalized in each unit responses to targets and distracters corresponding to the different distances to the mean response during a 300 ms time window prior to the color-change onset during main task trials. We aligned all units to their preferred target location, and pooled responses across cells to obtain normalized population responses (Figure 4D). In agreement with the single-cell data, the population responses showed a pattern intermediate between the two example neurons. During the main task (Figure 4D, left panel), responses to all stimuli gradually increased following the onset of the two white RDPs (see Temporal Dynamics of the Response Modulation). During the interval of 100–400 ms after the color-change onset, responses to targets increased while those to distracters decreased.
onset, responses to targets increased by similar amounts ($p = 0.83$, one-way ANOVA), whereas responses to distracters were differentially suppressed as a function of ordinal distance ($p = 0.043$, one-way ANOVA). The results were similar in both animals (see Figures S3A and S3B for population responses corresponding to Ra and Se). During fixation there was no response buildup after the onset of the two white RDPs, but only a slight response increase to targets after the color change (Figure 4D, right panel). In this condition we did not observe differences in response as a function of distance for any of the stimuli ($p = 0.062$ for targets and $p = 0.696$ for distracters, one-way ANOVA).

**Temporal Dynamics of the Response Modulation**

In order to characterize the dynamic of response changes during the tasks across the population of neurons, we computed for each unit and distance a modulation index (MI) between the responses to each stimulus (target and distracter), and the average response across the 300 ms preceding the onset of the two white RDPs (baseline; see Experimental Procedures). During the task condition, MIs corresponding to both stimuli and the three distances departed from zero (horizontal dashed line) toward more positive values at the onset of the color change (Figure 5A). After the color change, the MIs corresponding to targets at the preferred location increased transiently for all distances, whereas the MIs corresponding to distracters gradually decreased. As anticipated from the results shown in Figure 4D, this decrease was fastest for d3 (black dotted line), followed by d2 (blue dotted line) and d1 (red dotted line).

The color plots appearing in the lower panels of Figure 5A quantify these findings. The colors represent probability values associated with the null hypothesis that the responses are not different from baseline. Dark red indicates probability values lower than the level required (Student’s t tests, evaluated at Bonferroni-corrected $p < 0.05$/number of comparisons across time) for rejecting the null hypothesis. Blue and green indicate values higher than that level. Shortly after stimulus onset, responses became significantly higher than baseline for all stimuli and distances. However, after color-change onset, responses to targets remained significantly higher than baseline, but responses to distracters dropped to baseline levels, losing significance faster for d3, followed by d2 and d1.

The results were very different during fixation (Figure 5B). After stimulus onset, responses did not significantly change. The responses to stimuli corresponding to distracters in the main task condition did not significantly depart from baseline during the whole period. Although responses to stimuli corresponding to targets to the main task appear to slightly increase after the color change, the increase did not reach statistical significance. This result demonstrates that the gradual decrease of responses to distracters in the task condition was dependent on the increase in response preceding the color change. On the other hand, during fixation response decreases were constrained by low firing rates.

In order to test whether the decrease in distracter responses as a function of distance following color-cue onset was related to motor preparation rather than to selecting and allocating attention to the target, we aligned the same normalized responses appearing in Figure 4D to the time of button release. This caused the distance effect to disappear (Figure S3C), suggesting that it was indeed due to processes related to target selection and the allocation of attention triggered by color changes in the RDPs.

We also tested whether the distance effect in the units’ response suppression was caused by the existence of universal distracter and target stimuli (“border” stimuli) in the color scale (i.e., gray and turquoise). It is possible that these stimuli evoked a strong change in response when paired with any other color, and because the proportion of pairs containing universal stimuli is larger for d3 followed by d2 and finally d1, data pooling for pairs of the same distance may result in the pattern observed in Figure 4 (larger effects for d3, followed by d2 and d1). This hypothesis predicts that (1) when removing pairs with universal stimuli from the analysis, the effect will disappear; and that (2) when removing pairs without universal stimuli from the analysis, the effect will also disappear. Our data analysis showed that the effect was still present when removing these stimuli (Student’s t test and one-way ANOVA, respectively, $p < 0.05$ in at least three consecutive time bins; Figure S3D).
Moreover, when comparing the animals’ hit rates between pairs with and without border stimuli we found no significant differences (Wilcoxon signed-rank tests, p > 0.05; Figure S3E). These results show that the distance effect was not due to the influence of pairs containing border stimuli on firing rates and performance.

**Signal Detection Analysis**

In order to examine the impact of the previously isolated changes in firing rate on the neurons’ ability to discriminate between targets and distracters, we applied a signal detection analysis to the population of 122 target-selection units. We obtained for each neuron and target/distracter combination receiver operating characteristic (ROC) curves in bins spanning 10 ms, and in increments of 1 ms during the period from color-change onset to 600 ms after. As a measure of neuronal performance, we then computed the area under the curves (auROCs) and pooled these data across combinations of the same distance (see Experimental Procedures). This analysis takes into account both the differences between mean response levels to targets and distracters, and the variability of the neurons’ response to the stimuli in individual trials (Thompson et al., 1996).

Figure 6 shows the time course (from color-change onset) of the target-distracter discrimination performance (auROC) for each of the 122 units and for the three ordinal distances. Within each color plot dark red indicates chance performance, whereas dark blue represents perfect or almost perfect discriminability (see figure legend). Neurons were sorted from earliest to latest according to their discriminability latency (time from color-change onset at which the auROC value reached 0.64 [discrimination threshold]; see Experimental Procedures). The smaller the ordinal distance, the lower the proportion of neurons that reached the threshold: d1 (n = 47), d2 (n = 66), and d3 (n = 96) (yellow-green contour in each plot).

For each auROC series that reached the discrimination threshold, we determined its latency and its maximal value.

The latter was used as an estimate of the accuracy of the neuronal decision. The mean latency across neurons was significantly lower and the accuracy larger for d3, followed by d2 and d1 (latency: d1, 309 ms; d2, 290 ms; d3, 262 ms; accuracy in auROC values: d1, 0.71 ms; d2, 0.73 ms; d3, 0.75 ms). A Kruskal-Wallis one-way ANOVA for differences in the medians between the groups revealed statistical significance for both latency (p = 0.0155) and accuracy (p = 0.0178) (bar graphs in Figure 6B). Thus, neurons selected the target faster and more accurately the greater the ordinal distance to the distracter. This distance effect in the neuronal performance after the color change resembles the behavioral performance of the animals at detecting a change in the target (Figure 2A).

**DISCUSSION**

The main findings of our study can be summarized as follows. First, when macaque monkeys filtered a target from a distracter based on the ordinal distance between the two stimuli, behavioral performance was better as the distance increased. Second, dlPFC neurons better filtered out the target from the distracter through their response rates as the ordinal distance between the two stimuli increased. Such changes in neuronal performance as a function of distance were due to an increase in baseline activity preceding the color change, followed by, after the change, a further and homogenous increase of responses to targets, and a variable distance-dependent suppression of responses to distracters.

**Behavioral Performance and the Distance Effect**

Previous studies have documented the ability of humans and animals to organize stimulus representations in ordinal scales (Buckley and Gillman, 1974). Probably the most studied ordinal representations are numbers and quantities due to their widespread use by humans. In fact the distance effect was originally reported for situations in which human subjects selected the greatest or smallest of two numbers (Moyer and Landauer, 1967), but it has also been reported when subjects compare the rank of alphabetically ordered letters (Fias et al., 2007).
The distance effect also occurs in monkeys when they compare the number of dots in visual displays (Nieder et al., 2002), or the rank of stimuli in temporal sequences (Orlov et al., 2000). Most of these stimuli, including the ones used in our task, are easily discriminable from each other; thus, the distance effect cannot be due to different degrees of similarity in their sensory properties. Rather, it has been suggested that it results from the way in which ordinal representations are encoded in the primate brain (Nieder et al., 2002), with overlapping tuning curves for neurons encoding nearby representations, and decreases in such overlap for neurons encoding representations located farther apart. In our task, discriminating between two stimuli located nearby in the ordinal scale likely introduced more ambiguity in an animal’s decision to select the target and suppress the distracter relative to when stimuli were farther apart.

Importantly, by using ordinal representations and a rank-based selection rule, we obtained variations in the animals’ performance in the absence of changes in the spatial proximity between the stimuli, their relative saliency, their number, or their reward value. Such variations reflected changes in the animals’ ability to select and direct attention to the target while filtering out the distracter as a function of ordinal distance between the two stimuli.

**Mechanisms of Attentional Filtering in dlPFC Neurons**

We measured the responses of dlPFC neurons to the same stimulus configuration during the main task, and during fixation. In the 122 units included in the analysis, we observed an increase in firing rate after the onset of the white RDPs. Following the color change, the units further increased firing when the target was at their preferred location but decreased firing when the distracter was at the same location. The speed and level of the response decrease to distracters, but not of response enhancement to targets, produced a distance effect in the units’ filtering performance that preceded the animals’ behavioral response. This later result, together with the similarity between the effects in both neurons’ and animals’ performance, suggests that the degree of response suppression to distracters in dlPFC neurons underlies attentional-filtering performance by the animals during the task.

It is possible that the differential distracter suppression was due to the animals withdrawing more attention away from distracters corresponding to smaller relative to larger distances. However, the fact that increases in response were similar for targets corresponding to all distances suggests that if that was the case, either these resources were not allocated to the target or they were allocated to it, but response increases to this stimulus were not further possible due to response saturation. Alternatively, it is possible that distracter suppression and target enhancement can independently vary depending on task conditions. Supporting the latter idea, responses of parietal cortex neurons to distracters can be differentially suppressed depending on their probability of being a target, whereas responses to targets are always enhanced (Ipata et al., 2006).

Our results differ from reported effects of attention in visual cortex using stimulus configurations comparable to the one in our task (i.e., target and distracter in different hemifields). In such studies the effects of attention have been more modest and have been mainly described as gain increases in response to targets (McAdams and Maunsell, 1999; Treue and Martinez Trujillo, 1999), resembling the physiological and perceptual effects of increasing target contrast (Reynolds et al., 2000; Liu et al., 2009). Our effects were much stronger and, to a large extent, independent of the properties of the visual stimuli (i.e., they virtually disappeared during the fixation task), suggesting a dominant role of task rather than stimulus-related processes in their origin.

Different from the mentioned studies in visual cortex, the suppression of distracter responses observed in our task was dependent on the response increase preceding the color change. During fixation we did not observe this precolor-change activity increase, suggesting that this process was not simply due to the sensory stimulation produced by the two white RDPs but to the engagement of the animals in the main task. This activity buildup, also found in parietal cortex neurons (Janssen and Shadlen, 2005), may be a strategy of attentional systems to expand the dynamic range within which the behavioral relevance of stimuli is encoded in prefrontal cortical maps. When departing from a certain activation level, units can either further increase or decrease their firing. A prefrontal saliency map that uses strong negative (response decreases) and positive (response increases) peaks of about equal height around a mean response level to represent targets and distracters may be more efficient than a visual map mainly using weaker peaks consisting of response increases.

The exact mechanisms of response suppression in dlPFC units are difficult to disentangle with our approach. However, one possibility is competitive interactions between neurons in the area encoding target and distracter representations implemented through inhibitory connections (e.g., interneurons). These interactions have been proposed to underlie the attentional modulation of responses in extrastriate visual neurons (Desimone and Duncan, 1995; Khayat et al., 2010; Lee and Maunsell, 2009; Reynolds et al., 1999; Reynolds and Heeger, 2009).

In our sample of target-selective cells, 60% preferred the target in the left, and 40% in the right visual field. This bilateral representation within the right dlPFC may facilitate competitive interactions between neurons holding representations of stimuli located in different hemifields (e.g., through short-range [intra-area] connections). It may also represent an advantage—at least in the case of stimuli positioned in different hemifields—relative to areas such as the FEF, where neurons have response fields mainly in the contralateral hemifield (Goldberg and Bushnell, 1981; Thompson et al., 2005). In this latter case, although competitive interactions are also possible, they must occur through long-range (interhemispheric) connections. However, because we did not map the entire visual space, we cannot report the extent of the bilateral stimulus representation by the right dlPFC neurons. Further studies are needed to examine this issue in more detail.

Interestingly, a recent study has reported that during visual search, FEF neurons with overlapping RFs (at the target location) positively correlate their firing rates, whereas neurons with nonoverlapping RFs covering targets and distracters, negatively correlate their firing (Cohen et al., 2010). This cooperation-competition pattern may result from competitive interactions...
between units. It is possible that the differential suppression of distracters as a function of distance isolated in our study is due to a modulation in the strength of such interactions by learning of the rank-order rule during training, yielding stronger competition between neurons holding representations of target-distracter pairs more distant along the scale (e.g., d3) relative to units holding representations of closer-by pairs (e.g., d1).

One feature of the dIPFC that may play a role in modulating interactions between units is the convergence of different signals encoding various task components such as reward value (Kim et al., 2009), working memory (Fuster and Alexander, 1971), goal selection (Tsujimoto et al., 2008), planning (Hoshi and Tanji, 2004), decision making (Inoue and Mikami, 2010; Kim and Shadlen, 1999), and stimulus categories (Roy et al., 2010). Such signals can be combined within the area’s circuitry with incoming sensory information into a saliency map that reflects the organism’s priorities and goals. Signals originating within this map can then modulate (via direct or indirect pathways; Petrides and Pandya [2007]) the responses of neurons in sensory areas representing target and distracter features (Ardid et al., 2007; Gregoriou et al., 2009; Olivers, 2008; Rainer et al., 1998).

One question that remains to be answered is whether there is a distinctive role for dIPFC and FEF neurons in attentional control. One possibility is that the dIPFC plays a role in forms of attentional modulation that require selectivity for nonspatial features of visual stimuli (i.e., feature-based-attention; Bichot et al., 2009; Treue and Martinez Trujillo [1999]; or object-based attention; Roelfsema et al. [1998]), whereas the FEF plays a role in allocating spatial attention (Moore and Armstrong, 2003). Favoring this hypothesis, selectivity for nonspatial features such as motion direction has been documented in dIPFC neurons (Zaksas and Pasternak, 2006). A second possibility is that the dIPFC integrates signals from different sensory modalities into a single saliency map and then signals FEF neurons the target and distracter locations. Favoring this idea, it has been recently reported that neurons in the ferret prefrontal cortex shape the flow of auditory information during a behavioral task (Fritz et al., 2010).

In sum, our results agree with previous studies reporting that dIPFC neurons encode the allocation of attention through their firing patterns (Boussaoud and Wise, 1993; di Pellegrino and Wise, 1993; Everling et al., 2002; Lebedev et al., 2004; Rainer et al., 1998). Importantly, they further support a role of the primate prefrontal cortex on inhibitory control of behavior (Aron et al., 2004; Hasegawa et al., 2004; Sakagami et al., 2006). We found that the response suppression of distracter representations in these units produces changes in their filtering performance similar to the ones observed in the organism’s behavior. It remains to be determined what the exact neuron-to-neuron interactions within dIPFC networks underlying the observed patterns of response suppression, are as well as whether manipulating such interactions leads to changes in behavioral performance.

**EXPERIMENTAL PROCEDURES**

**Animals**

Two young adult male monkeys (Macaca mulatta, Ra: 7 kg; Se: 9 kg) participated in the experiments. During the training and testing periods, the animals received their daily amounts of fluids (fruit juice) as reward for correctly performing the task. The average fluid intake during a session was between 300 and 400 ml. We also gave the animals fresh fruits as supplement when finishing a session. Body weights were measured on a daily basis to monitor health and growth. All procedures complied with the Canadian Council of Animal Care guidelines and were approved by the McGill animal care committee.

**Visual Stimuli**

The stimuli were back projected on a screen using a video projector (NEC WT610, 1024 x 768 pixel resolution, 85 Hz) and custom-made software running on an Apple G4 Power PC. The animals viewed the screen at a distance of 57 cm (1 cm = 1° of visual angle). The RDPs were generated by plotting colored dots (white, 13 cd/m²; gray, 1.9 cd/m²; pink, 5.4 cd/m²; green, 0.9 cd/m²; blue, 1.58 cd/m²; red, 0.6 cd/m²; turquoise, 8 cd/m²) on a dark background (black-gray, 0.02 cd/m²) with a density of three dots per degree² within a circular stationary virtual aperture. All dots within one RDP moved coherently at a speed of 15°/s and were replotted at the opposite side when they crossed the border of the aperture. The radius of the aperture was 4°, and its center was 8° away from the fixation spot.

**Color-Rank Task**

The animals started a trial by pressing a button and keeping gaze within a circular window of 2° diameter centered on a small fixation spot (0.06 degrees²). After 353 ms, two moving RDPs appeared, one located to the left and the other to the right of the spot. The patterns were composed of white dots on a dark background that moved either up or down relative to the vertical. After a variable interval, from 294 to 646 ms following the RDPs’ onset, the dots in each pattern changed to a different color (e.g., in one pattern to red and in the other to blue). The task for the animals was to select and covertly attend to one RDP (the target) while ignoring the other (the distracter), wait for a brief motion direction change (176 ms duration, 32° intensity clockwise from the current direction) in the target, and release the button within 100–650 ms from the change onset. Target direction changes could occur within a time window ranging from 752 to 2940 ms after color-change onset. In order to correctly select the target, the animal had to learn over several training sessions a color-rank selection rule (gray < pink < green < blue < red < turquoise). Each correctly performed trial was rewarded with a drop of juice.

To guarantee that the animal correctly selected the target, on half of the trials, the distracter pattern located in the opposite visual hemifield changed direction. The monkey had to ignore this distracter change and wait for the target change. Trials in which the monkey responded to the distracter change (false alarms), or did not respond to the target change within the reaction time window (misses), or broke fixation before the target change onset (fixation breaks), were terminated without reward. The different trial types were presented in random sequence. Only correctly performed trials were included in the analysis. Due to limitations in the number of trials that the animals performed during one recording session, we tested only four different colors at a time (instead of six). The sets used were turquoise/red/blue/green, red/blue/pink/grey, and blue/green/pink/grey, all of which yielded distances 1, 2, and 3 (d1, d2, and d3, respectively).

Behavioral data were obtained in 46 recording sessions for monkey Se, and 57 for monkey Ra. Note that in this task, the chance-hit rate depends on the probability of a given stimulus to be the target (p = 0.5), and on the time window given to the animal to respond relative to the time of target-distracter presentation (p = (550 ms/2940 ms) = 0.18). Thus, if the animal chooses to respond to any change either in the target or distracter and does that within the 550 ms time window, chance-hit rate would be 50%. If the animal chooses to release the button at any time after the color change, chance-hit rate would be 18%.

**Mapping Task**

To assess the cells’ tuning for different stimulus attributes, we also included a set of trials in which we presented a single RDP on the screen and varied its color (the four colors used in a session and white), motion direction (up/down), and location (left/right of the fixation spot). The animals had to release the button in response to a motion direction change in the RDP, which could occur randomly between 400 and 2000 ms following stimulus onset (Figure S2A).
Fixation Task
We also included “fixation” trials in which sensory stimulation was identical to the main task trials, but the RDPs were irrelevant to the animal. A slightly enlarged fixation point (0.167 degree²) at trial onset indicated a fixation trial. The timing of the stimuli, color change, and response-event onsets were identical to task trials. However, no target and/or distracter change occurred, instead, the animal was required to release the lever upon detection of a small luminance change in the fixation spot. During a recording session, for each distance the monkeys performed half as many fixation trials as task trials. Both trial types were randomly interleaved.

Surgical Procedures
The animals were implanted with titanium head posts and CILUX recording chambers (Crist Instruments, TX, USA). A description of the surgical procedures and techniques appears elsewhere (Khayat et al., 2010). In both animals the recording chamber was implanted on top of a circular craniotomy (20 mm diameter) of the frontal bone that provided access to the right prefrontal cortex, to the region anterior to the arcuate sulcus, posterior and around the principalis (Figures 3 and S2C). The center of the chamber was positioned at the center of the craniotomy; its stereotactic coordinates were 24 mm anterior and 17 mm lateral in Ra, and 30 mm anterior and 17 mm lateral in Se. The chambers were circular, 20 mm in diameter, with 20° and 35° base angle, respectively. In monkey Ra the chamber was positioned with a lateral tilt of 12° from the vertical, and in monkey Se the chamber was positioned parallel to the vertical. In the anteroposterior plane both chambers were parallel to the vertical (the vertical and the horizontal planes were defined in stereotactic coordinates).

Electrophysiological Recordings
We recorded from the right dlPFC of both animals. During each experimental session, transdural penetrations were made with standard epoxy-insulated extracellular tungsten electrodes (FHIC inc., Bowdoin, ME, USA; shank diameter, 500 μm; impedance, 2–4 MΩ at 1 kHz). A guide tube positioned at 5–10 mm distance from the recording electrode—tochuting but not penetrating the dura—served as the reference. We used a Plexon data acquisition system (MAP) to record and store spike and LFP data simultaneously (Plexon Inc., Dallas). The electrode signal was passed through a headstage with unit gain and then split into the spike and the LFP components. For spike recordings the signal was filtered between 250 and 6000 Hz, amplified, and digitized at 40 kHz. Single-unit spiking activity was then isolated using Plexon online and offline sorting software.

Data Analysis
Analysis of spike data (firing rates) and statistical tests were performed using MATLAB (MathWorks, Natick, MA, USA). The activity/response of each neuron was plotted as a spike density function, generated by convolving a spike train with a function that resembled a postsynaptic potential, i.e., the time constant of the growth phase and the time constant of the decay phase were 1 and 150 ms, respectively (Murthy et al., 2007). The mean firing rate at different stages of the task was analyzed by computing the mean number of action potentials over a given epoch in repeated presentations (trials). Where indicated, firing rates of each neuron were normalized to the mean activity within a 300 ms time window prior to color-change onset during task trials. Typically, we obtained 12–20 trials per condition during the main task, six to ten during the fixation task, and six during mapping. In order to examine target selection as a function of ordinal distance, we grouped trials according to the distance between target and distractor colors and to the stimulus position. This resulted in six groups: target at the preferred location-distance 1, 2, and 3; and distracter at the preferred location-distance 1, 2, and 3 (the preferred location is defined as the position where the target produced the strongest response). Because distance 1 comprised more color combinations than distances 2 and 3, we corrected for the number of trials through a randomization procedure (i.e., if one condition had 20 trials and the other 15, we randomly chose 15 trials of the former condition to match the number in the latter).

ANOVA
All statistical tests were evaluated at p < 0.05. We performed a one-way ANOVA to test for possible effects of task period in the main task. Firing rates within four different task periods were computed: during 200 ms before stimulus onset while the animal was fixing (baseline); during 400 ms preceding the color-change onset when both RDPs were white; and during two 400-ms windows—one starting 50 ms, and the other 550 ms after color-change onset. If the ANOVA revealed a significant main effect of task period, a post hoc test for multiple comparisons was performed. Neurons were classified as task related if the test revealed a significant difference between baseline responses and responses in one of the other three analysis windows.

For each task-related neuron, we then performed a three-way nested ANOVA with target position, distance, and color combination as factors using mean activity within a 100 ms window starting from color-change onset and slid along the trial in steps of 10 ms. If neuron revealed a main effect of target position in at least three consecutive time bins, it was classified as a target-selection unit (Figure 3). (See Table S1 for the results.) The position (left or right) at which the unit produced the stronger response to the target was considered the neuron’s preferred location.

In 64 out of the 122 target-selective neurons, we obtained data during the mapping task. We conducted in each unit a three-way ANOVA with target position, color, and motion direction as factors using mean firing rates within a 300 ms time window following stimulus onset. The proportion of neurons selective for each factor appears in Figure S2B. In order to determine whether such proportions were significantly different from those expected by chance, we compared them against the ones obtained through a simulation procedure. We simulated for each neuron firing rates for the same amount of trials as during the task. These were obtained through an algorithm that chose for each condition n values (n, number of trials) from a normal distribution of responses with mean equal to the mean firing rate across the entire sample (over the same 300 ms following stimulus onset) and standard deviation equal to the average standard deviation across the sample. For the few cases of negative firing rates, the values were set to zero. We then performed the same three-way ANOVA on the simulated data. We ran the simulation and the ANOVA 100 times and obtained mean estimates of the proportions as well as confidence intervals. The mean proportions of cells that revealed a significant main effect were: 5.1% (color), 5.33% (side), and 5.25% (direction). Confidence intervals for all of them were between 4.5% and 5.82%, considerably overlapping with the real data corresponding to color and direction, but not target position.

Signal Detection Analysis
To quantify the ability of target-distracter discrimination by the group of 122 dlPFC neurons showing differences in firing rate between targets and distracter at the preferred location, we applied an ROC analysis. This analysis takes into account not only the differences in mean response between two conditions but also the response variability of a neuron in individual trials (Thompson et al., 1996). A derived measurement, the auROC, represents the probability with which, on the basis of firing rates, an ideal observer can reliably identify the target in the presence of a distracter. A value of 0.5 indicates that a given firing rate could have been elicited with equal probability by the target or the distracter at the neurons’ preferred location. A value of 1.0 indicates that responses to the target were always greater than responses to the distracter. Conversely, a value of zero indicates that responses to the distracter were always greater than responses to the target.

The auROC values for individual neurons were calculated for a 10 ms window from 0 ms to 600 ms from color-change onset slid in 1 ms increments along the spike train. When calculating auROC values for different distances, we corrected for different number of trials in the conditions through a randomization procedure (see above). For each unit, the auROC values were then plotted as a function of time to describe the time course of neuronal choice probability. The latency with which neurons could distinguish the target from the distracter was defined as the time from color-change onset when the auROC time series reached the criterion value of 0.64. This value is lower than the one used in FEF studies of target selection (0.75) (Thompson et al., 1996) but is substantially higher than 0.5, which is the chance level. The latter has been used in studies of dlPFC neurons’ ability to encode rules (Bongard and Nieder, 2010). However, when increasing our threshold to 0.75 or lowering it to 0.5, the number of neurons reaching the threshold for each distance decreased or increased, respectively, but the relative proportion across...
differences between responses and baseline (evaluated at Bonferroni-cor-
1 ms while correcting for different number of trials, and tested for significant
decrease. We computed Student’s t tests in bins of 50 ms and increments of
following attentional versus intentional cues. Exp. Brain Res. 18,

SUPPLEMENTAL INFORMATION

Cortex 103, 1312–1321.

REFERENCES

parietal lobe activation during transitive inference in humans. Cereb.
Cortex 12, 1312–1321.


Armstrong, K.M., Chang, M.H., and Moore, T. (2009). Selection and mainte-
nance of spatial information by frontal eye field neurons. J. Neurosci. 29,
15621–15629.


Bisley, J.W., and Goldberg, M.E. (2003). Neuronal activity in the lateral intra-
parietal area and spatial attention. Science 299, 81–86.

Bongard, S., and Nieder, A. (2010). Basic mathematical rules are encoded by

following attentional versus intentional cues. Exp. Brain Res. 95, 15–27.

patterns. J. Exp. Psychol. 103, 1131–1136.

of attention in the prefrontal and posterior parietal cortices. Science 315,
1860–1862.

visual search are reflected by the frontal eye fields and correlated with popu-
lation oscillations. Neuron 63, 386–396.

modulation during exogenous and endogenous shifts of visual attention in

Cohen, J.Y., Crowder, E.A., Heltz, R.P., Subraveti, C.R., Thompson, K.G.,
frontal eye field neurons during visual target selection. J. Neurosci. 30, 3227–
3238.

tations of numbers in the animal and human brain. Trends Neurosci. 21,
355–361.


activity in the premotor and prefrontal cortex of a primate. Somatosens.

Everling, S., Tinsley, C.J., Gaffan, D., and Duncan, J. (2002). Filtering of neural
signals by focused attention in the monkey prefrontal cortex. Nat. Neurosci. 5,
671–676.


Fias, W., Lammertyn, J., Caessens, B., and Orban, G.A. (2007). Processing of
abstract ordinal knowledge in the horizontal segment of the intraparietal

Adaptive, behaviorally gated, persistent encoding of task-relevant auditory


responses in monkey cerebral cortex. II. Modulation in frontal eye fields specif-

salience and attention: The role of the lateral intraparietal area in visual
behavior. Prog. Brain Res. 155, 157–175.

specific contribution of the superior colliculus to overt and covert shifts of


Hoshi, E., and Tanji, J. (2004). Area-selective neuronal activity in the dorsolat-
eral prefrontal cortex for information retrieval and action planning. J.
Neurophysiol. 91, 2707–2722.

specific contribution of the superior colliculus to overt and covert shifts of

Inoue, M., and Mikami, A. (2010). Feature to space conversion during target
selection in the dorsolateral and ventrolateral prefrontal cortex of monkeys.

responses to a popout stimulus are reduced if it is overtly ignored. Nat.
Neurosci. 9, 1071–1076.


Khayat, P.S., Niebergall, R., and Martinez-Trujillo, J.C. (2010). Attention differ-
entially modulates similar neuronal responses evoked by varying contrast and

Neuron 70, 141–152, April 14, 2011 ©2011 Elsevier Inc. 151


