

Detection of Fixed and Variable Targets in the Monkey Prefrontal Cortex

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Behavioral significance is commonly coded by prefrontal neurons. The significance of a stimulus can be fixed through experience; in complex behavior, however, significance commonly changes with short-term context. To compare these cases, we trained monkeys in 2 versions of visual target detection. In both tasks, animals monitored a series of pictures, making a go response (saccade) at the offset of a specified target picture. In one version, based on "consistent mapping" in human visual search, target and nontarget pictures were fixed throughout training. In the other, based on "varied mapping," a cue at trial onset defined a new target. Building up over the first 1 s following this cue, many cells coded short-term context (cue/target identity) for the current trial. Thereafter, the cell population showed similar coding of behavioral significance in the 2 tasks, with selective early response to targets, and later, sustained activity coding target or nontarget until response. This population similarity was seen despite quite different activity in the 2 tasks for many single cells. At the population level, the results suggest similar prefrontal coding of fixed and short-term behavioral significance.

Keywords: association memory, behavioral category, target detection, unit activity

Introduction

In the behaving monkey, many studies show how neurons of the prefrontal cortex (PFC) code stimuli in terms of their behavioral significance, i.e. the role that they play in the context of a particular task (e.g., Watanabe 1986; Sakagami and Niki 1994; Freedman et al. 2001; Neider et al. 2002). In some cases, the significance of a stimulus remains fixed throughout learning. After long training in search for a specific target object, for example, many PFC cells respond selectively to that target (Everling et al. 2002, 2006). The behavioral significance of a stimulus, however, can also be established by short-term context, changing from one trial to the next (see e.g., Watanabe 1986; Miller et al. 1996).

It is often proposed that the PFC is especially important in dynamic or context-dependent behavior (Miller and Cohen 2001). In both human and monkey imaging studies, several regions of PFC respond strongly during task switches, or when a new task context is established (Dove et al. 2000; Nakahara et al. 2002; Dosenbach et al. 2006). PFC lesions are especially harmful when task rules change or when a current stimulus must be interpreted in light of preceding context (Dias et al. 1996; Gutnikov et al. 1997; Rossi et al. 2007). In electrophysiological studies, many frontal cells carry "working memory" signals (e.g., Fuster et al. 1985; Funahashi et al. 1989), potentially providing short-term context for subsequent decisions and behavior (Miller and Cohen 2001).

Here, we compared PFC activity for stimuli with short-term, context-specific and long-term, fixed behavioral significance. To this end we adapted a well-known distinction from research in human visual search (Schneider and Shiffrin 1977; for neurophysiological data see Bichot et al. 1996). In "consistent mapping," the definition of target and nontarget stimuli is fixed across trials. In this case, performance is determined by long-term association between individual stimuli and their behavioral significance. In "varied mapping," a cue at the start of each trial defines the target. Here, the behavioral significance of each stimulus (i.e., its role as target or nontarget) depends on the short-term context provided by the cue. With practice, consistent mapping search becomes increasingly rapid and efficient; even with very extended training, however, varied-mapping search remains slow and effortful (Schneider and Shiffrin 1977). In the behavioral literature, these 2 types of search have been taken as paradigm cases of automatic versus attentional processing (Schneider and Shiffrin 1977).

For neurophysiological study in the monkey, we extended previously used temporal search tasks (Miller et al. 1996; Everling et al. 2002, 2006; see also paired-associate tasks used in many previous studies of inferotemporal cortex, e.g., Sakai and Miyashita 1991; Takeda et al. 2005). In the fixed-target (consistent mapping) version (Everling et al. 2002, 2006), monkeys had long training in monitoring a sequence of pictures for a particular, highly familiar target. In the cued-target (varied mapping) version, in contrast, each picture could serve sometimes as a target and sometimes as a nontarget, a cue before each sequence defining the target for this trial (cf. Miller et al. 1996, Sigala et al. 2008). To compare PFC coding of fixed and short-term behavioral significance, we examined responses to cue stimuli at trial onset, activity in delay periods between one stimulus and the next, and coding of fixed or variable behavioral status for individual choice stimuli.

Materials and Methods

Subjects

Subjects were 2 male rhesus monkeys (*Macaca mulatta*) weighing 11 and 12 kg. All experimental procedures were approved by the UK Home Office and were in compliance with the guidelines of the European Community for the care and use of laboratory animals (EUVD, European Union directive 86/609/EEC).

Task and Stimuli

Two types of visual target detection tasks were used (Fig. 1A,B). Each trial began with a red central fixation point (FP) and 2 dim gray spots (location markers) 6° to left and right on the horizontal meridian. Once fixation was acquired and held for 500 ms, a stimulus sequence was presented over either the left or the right location marker. Left or right

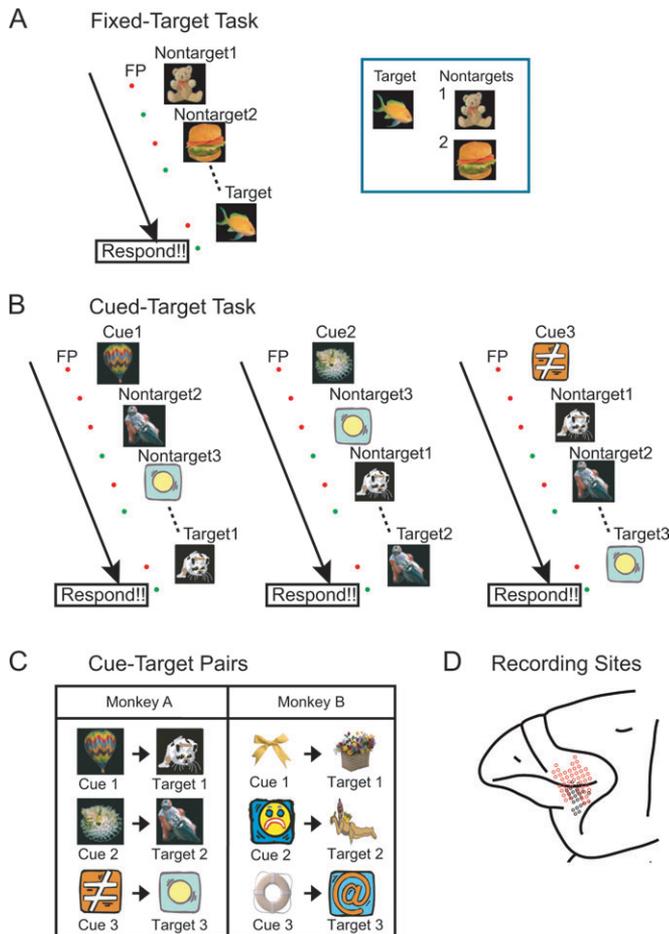


Figure 1. Tasks and recording locations. (A, B) Schematic drawings of tasks used. For details see text. (C) Cue-target pairs for each animal. (D) Schematic diagram of recording sites, illustrated by red and blue symbols for monkey A and B, respectively. Recording sites for monkey A (right hemisphere) have been transferred to the left.

stimulus location was random between trials, but fixed within a trial. Stimuli, $2^\circ \times 2^\circ$ in size were each presented for 500 ms, with a random interval of 400–800 ms intervening between each stimulus and the next. The FP remained red during stimulus presentation but changed to green during interstimulus delays. The monkey's task was to hold fixation until a target appeared, and then at its offset (FP change to green) to make an immediate saccade to its location for juice reward (required latency < 500 ms). Both central fixation and target location windows were set to $3.5^\circ \times 3.5^\circ$ for approximately 86% of the recorded cells, $2.5^\circ \times 2.5^\circ$ for the remainder.

In the fixed-target task (Fig. 1A), the target throughout training was a fish, whereas nontargets were teddy-bear and burger (Fig. 1A, inset). On each trial, the stimulus sequence consisted of 0–3 nontargets (random mixture of teddy-bear, burger), followed by a single target. The probabilities of different sequence lengths were set at 0.30, 0.21, 0.15, and 0.34 for, respectively, 0, 1, 2, and 3 nontargets, so that the probability of target appearance in each of the first to third stimulus presentations was 0.30. For the cued-target task (Fig. 1B), each animal was trained before recordings began with 3 cue-target pairs. Picture sets were different for the 2 animals, but for each animal remained fixed throughout the experiment. Each trial began with one of the 3 possible cue pictures (Fig. 1B, cues 1–3), indicating the target picture for this trial (Fig. 1B,C, targets 1–3). Again, the cue was followed by a sequence of 0–3 nontargets preceding the target. This time, the majority (two thirds) of nontargets following any given cue were the same pictures serving as targets on other trials (Fig. 1B, nontargets 1–3). For the remaining one third of nontargets we used a fourth picture, typically fixed for several recording sessions and never serving as a target. This

fourth nontarget was included simply as a check on monkey behavior for a stimulus whose meaning did not change with short-term context; for all physiological analyses, we included just the set of 3 pictures that were targets on some trials but nontargets on others. Different trial types (fixed-target, cued-target cues 1–3, each in left or right hemifield) were randomly intermixed in each trial block.

Recordings

Each monkey was implanted with a custom-designed titanium head holder and recording chamber (Max Planck Institute, Tuebingen, Germany). The chamber was placed over the right hemisphere of monkey A at AP = 32, ML = 22.2 (AP, anterior-posterior; ML, medio-lateral), and over the left hemisphere of monkey B at AP = 25.8, ML = 21.2, positioned over the principal sulcus and anterior to the arcuate sulcus. Recording locations are shown in Figure 1D. Implants were fixed on the skull with stainless steel screws. When task training was completed, a craniotomy was made for physiological recording. All surgical procedures were aseptic, and carried out under general anesthesia.

We used arrays of tungsten microelectrodes (FHC, Bowdoinham, ME) mounted on a grid (Crist Instrument Co., MD) with 1 mm spacing between adjacent locations inside the recording chamber. The electrodes were independently controlled by a hydraulic, digitally controlled microdrive (Multidrive 8 Channel System, FHC, Bowdoinham, ME). Neural activity was amplified, filtered and stored for offline cluster separation and analysis with the Plexon MAP system (Plexon, Dallas, TX). Eye position was sampled at 100 Hz using an infrared eye tracking system (Iscan, Boston, MA) and stored for offline analysis. We did not preselect neurons for task-related responses; instead we advanced microelectrodes until we could isolate neuronal activity before starting the search tasks.

At the end of the experiments, animals were deeply anaesthetized with barbiturate and then perfused through the heart with heparinized saline followed by 10% formaldehyde in saline. The brains were removed for histology, and recording locations were confirmed to lie on dorsal and ventral frontal convexities and within the principal sulcus.

Data and Analysis

Recordings started after the animals were adequately trained in both tasks. Except for specific analyses of error responses, physiological data were analyzed just from successfully completed trials, typically including more than 15 repetitions for each combination of trial type (fixed-target, cued-target cues 1–3), stimulus type (target or nontarget), and hemifield. We excluded data from the fourth stimulus presentation on a trial (a target following the presentation of 3 nontargets), because in this case the upcoming stimulus was 100% predictable. For the cued-target task, all analyses of responses to the choice stimuli (targets and nontargets) concerned just those 3 pictures serving as targets on some trials but nontargets on others, that is, stimuli whose behavioral significance changed with short-term context. We grouped together data from dorsal and ventral recording locations as we found no differences between them. All statistical analyses were done using MATLAB (The MathWorks Inc., Natick, MA).

Delayed-Saccade Task

As a control for saccade-related activity, about 80% of cells were also tested with a delayed-saccade task in separate blocks. While the animal was fixating a central FP, a small red spot of the same size as FP appeared 6° to left or right. After 500 ms, the peripheral spot disappeared and the color of FP changed from red to green, at which point the animal was rewarded for a saccade to the peripheral spot location. Saccades were thus matched in spatial and temporal parameters to those required by targets in the main tasks.

Results

Behavior

Behavioral data appear in Figure 2. For targets, the figure shows separately the percentages of correct responses (saccade to

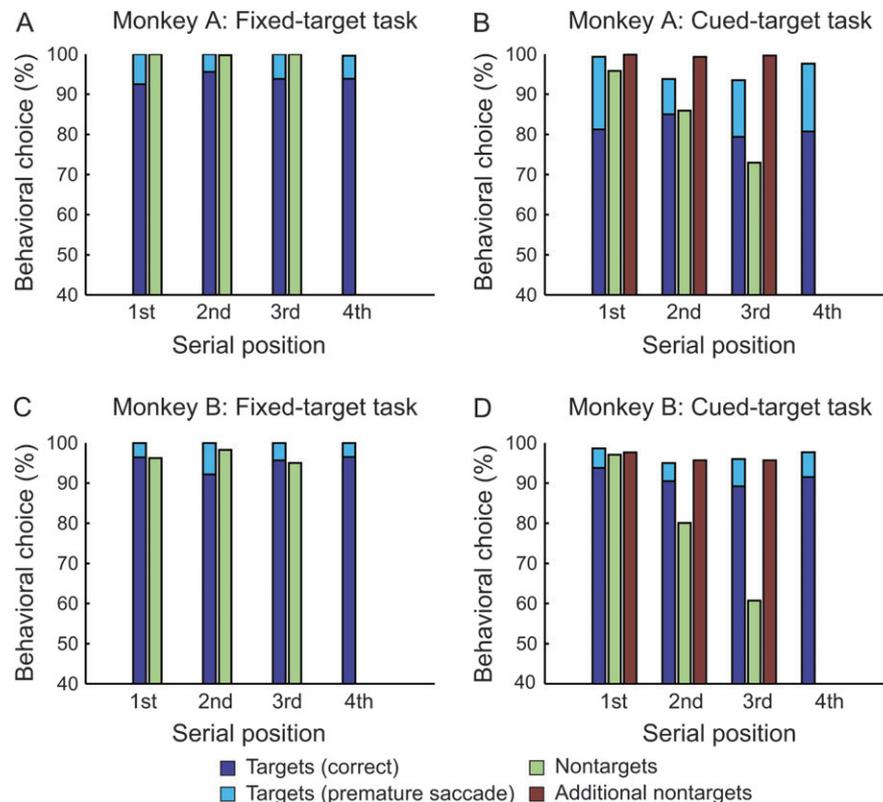


Figure 2. Behavioral data. Blue bars show percentage of correct responses (dark blue) and premature saccades (light blue) to target pictures. Green bars show percentage of correct responses (maintained fixation) to nontargets; for cued-response task, these data concern just nontargets that were targets on other trials. Equivalent data for the additional nontarget (never used as target) are shown by red bars. Data are shown separately for first, second, third and fourth serial positions within a trial; in the fourth serial position, the stimulus was always a target. (A, C) Fixed-target task. (B, D) Cued-target task.

target location at offset) and premature saccades (saccade to target location during target presentation). For nontargets, data are simply percentage correct (maintained fixation throughout stimulus presentation and the following delay). The primary nontarget data (green) for the cued-target task concern just those nontargets that were targets on other trials; data are given separately for the additional nontarget never serving as a target (red). Fixation breaks (saccade to location outside the target window) were discarded before calculation of response percentages. In both animals, correct saccades to targets were almost all made within 200 ms of stimulus offset (98% monkey A, 92% monkey B).

Except that responses to targets were sometimes made prematurely (Fig. 2, pale blue bars), the performance of both animals was uniformly accurate in the fixed-target task. In the cued-target task, a more complex picture emerged. For targets, again, >95% of responses were either correct or premature saccades. For the nontargets that were targets on other trials (primary nontarget data; green bars), percentage correct was high for the first stimulus following the cue, then progressively decreased as the trial continued. For the additional nontarget that never served as a target, in contrast, accuracy remained high throughout the trial (red bars).

These data reveal the expected behavioral difference between consistent and varied stimulus-response mapping. Accuracy was reduced in the cued-target task, specifically for those nontargets that were targets on other trials. As the trial progressed, there was an increasing tendency for monkeys to respond to these stimuli as though they were targets; at the

same time maintaining good accuracy when actual targets appeared.

Population Activity in Fixed- and Cued-Target Tasks

Of 254 recorded cells (153 from monkey A and 101 from monkey B), stimulus-related activity was seen in 217 (131 from monkey A and 86 from monkey B). To define stimulus-related activity, each spike was smoothed with a Gaussian kernel ($\sigma = 10$ ms; width 3 σ), followed by ANOVA comparing each 1-ms bin of poststimulus activity with equivalent data sampled from the prestimulus period (20, 1-ms samples prior to each stimulus onset, spaced 10 ms apart over the period 10- to 200-ms prestimulus). Cells were regarded as stimulus-related if, for any target or nontarget in either task, this test showed a significant difference (t -test, $P < 0.01$) in at least 50 successive poststimulus bins. Just these 217 stimulus-related cells were selected for further analysis.

As a first indication of the population PFC response in fixed- and cued-target tasks, Figure 3 shows mean activity at each task phase, across the full set of 217 stimulus-related cells. In both tasks, data are shown separately for choice stimuli (targets and nontargets) in first, second and third serial positions within a trial. In the cued-target task, data are also shown for the cue at trial onset.

In the fixed-target task, the data show a phasic response to each choice stimulus, returning approximately to baseline between stimuli. (Note that, for this task, the first choice stimulus was the first event of the trial, so that activity before this stimulus reflects pretrial baseline.) In the cued-target task,

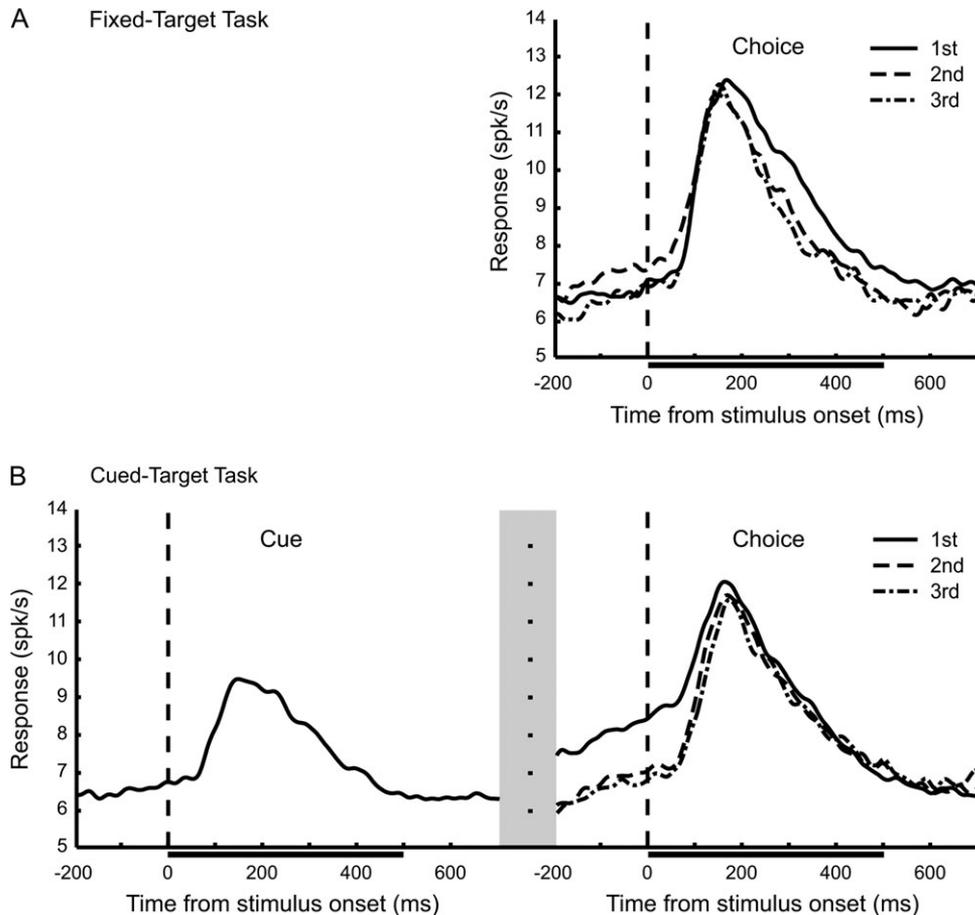


Figure 3. Mean activity across all analyzed cells ($n = 217$). (A) Fixed-target task, choice stimuli (targets and nontargets). (B) Cued-target task, cue stimuli and choice stimuli. In all cases, stimulus duration was 500 ms. For choice stimuli, data are shown separately for first, second and third choice stimuli in a trial.

there were phasic responses to both cue and choice stimuli, the former rather smaller (ANOVA across cells on mean activity in window 50–500 ms from stimulus onset, factors stimulus (cue/choice) \times hemifield, main effect of stimulus $P < 0.001$). The average response to choice stimuli was remarkably similar in fixed- and cued-target tasks, with no hint of significant difference across the cell population (ANOVA across cells on mean activity in window 50–500 ms from stimulus onset, factors task \times hemifield \times serial position, main effect of task $P > 0.2$). In both tasks, the onset latency of response was about 60 ms. In line with previous studies (e.g., Suzuki and Azuma 1983; Funahashi et al. 1989; Sakagami and Niki 1994), the analysis also showed a small but highly significant preference for the hemifield contralateral to the recording location, mean activity 9.8 spikes/s contralateral, 9.1 spikes/s ipsilateral, $P < 0.001$.

Baseline activity between stimuli was also closely similar in the 2 tasks, except for increased firing before the first choice stimulus in the cued-target task, that is, at the end of the first postcue delay. For the window 200 ms before onset of the first choice stimulus, firing was significantly greater in the cued-target than the fixed-target task (ANOVA across cells with factors task \times hemifield, main effect of task $P < 0.001$). As shown by a comparison with mean activity immediately after cue offset (Fig. 3B, immediate postcue period), this result reflects increasing neural activity across the postcue delay, not a sensory aftereffect of the cue stimulus. As the first choice stimulus in the

cued-target task was the second stimulus in the trial, we also compared the preceding delay activity with activity preceding the second choice stimulus in the fixed-target task. Again, the difference between tasks was highly significant ($P < 0.001$).

In terms of mean population PFC activity, fixed- and cued-target tasks differed only before presentation of the first choice stimulus, at the end of the postcue delay. At this time, activity was increased in the cued-target task. Thereafter, however, mean activity was closely similar in the 2 tasks, suggesting similar PFC involvement in target/nontarget decisions.

Cue and Delay Activity

For the next step of analysis, we examined cue- and task-selective activity in single cells. In the first set of analyses, we focused on the cued-target task, asking how cue selectivity evolves as a trial progresses. Data were analyzed from 5 trial periods, shown with data from 2 example cells in Figure 4A: 50–250 ms from cue onset (Cue Early), 300–500 ms from cue onset (Cue Late), 0–200 ms from cue offset (Postcue), 200–0 ms before onset of the first choice stimulus (Prechoice 1), and 200–0 ms before onset of second and third choice stimuli (Prechoice 2/3). For each analysis window, data from each cell were examined by ANOVA with factors cue (cues 1–3) \times hemifield (for Prechoice 2/3, factors cue \times hemifield \times serial position). Note that, in principle, a main effect of cue might reflect a visual code of cue identity, a prospective code of

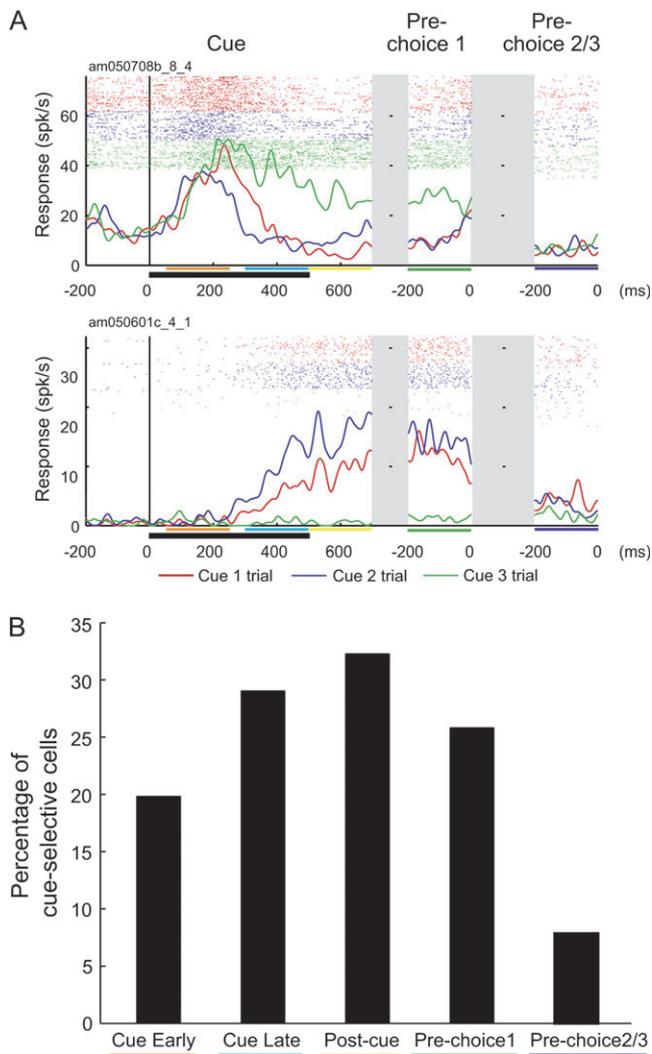


Figure 4. Cue selectivity. (A) Activity of 2 example cells, indicating analysis periods for cue selectivity. To left are data from analysis periods during and immediately following cue: Cue Early (red bar beneath x-axis); Cue Late (blue bar), and Postcue (yellow bar). Heavy black bar indicates time of cue presentation. Zero indicates cue onset. To right are data from periods preceding first (Prechoice 1, green bar) and subsequent (Prechoice 2/3, dark blue bar) choice stimuli. Zero indicates onset of choice stimuli. (B) Percentage of all analyzed cells ($n = 217$) showing significant cue selectivity in different time periods.

target identity, or some other code of short-term context for target/nontarget classification. For convenience here we use the term “cue selectivity” to refer to any of these possibilities (see Discussion).

For each analysis window, Figure 4B shows the proportion of all 217 cells with a significant main effect of cue. In all single cell ANOVAs in this and subsequent sections, significance was evaluated at $P < 0.05$. The data show clear evolution of cue-selective activity. Beginning at around 20% immediately after cue onset (Cue Early), the incidence of cue selectivity increased to a peak of $>30\%$ in the immediate postcue delay, and remained high to the end of this delay. In later delays (Prechoice 2/3), in contrast, the percentage of cells with significant selectivity (7.8%) was only slightly higher than the 5% expected by chance ($P < 0.05$, 1-tailed, binomial test). Low selectivity in these later delays was also seen when they were analyzed separately.

Delay activity was also examined for task selectivity, that is, for significant main effects of fixed- versus cued-target tasks. Again we used separate ANOVAs for periods Prechoice 1 (factors task \times hemifield) and Prechoice 2/3 (additional factor of serial position). For Prechoice 1, in line with the overall activity levels shown in Figure 3, many cells showed a significant main effect of task, 72/217 with cued-target $>$ fixed-target, 29/217 the reverse. For Prechoice 2/3, the main effect of task was significant in 61/217 cells, this time more equally divided between cued-target $>$ fixed target (23 cells) and the reverse (38 cells).

For the cued-target task, the results show strong cue selectivity or coding of short-term context before the first choice stimulus. Such coding built to a maximum in the period immediately following cue offset, and remained strong to the end of the postcue delay. In this period, too, single cell activity strongly distinguished between cued-target and fixed-target tasks. Later in the trial, both task and cue selectivity remained, but at much reduced levels.

Target/Nontarget Discrimination

Next we turned to choice stimuli, and to the discrimination between targets and nontargets. Across cells we observed a variety of response patterns, with both early (phasic) and late (sustained) components that could differ between fixed-target and cued-target tasks. Examples are shown in Figure 5. In the first cell (Fig. 5A,B), a phasic response at stimulus onset was somewhat greater for targets, significantly so in the fixed-target task. In the cued-target task, sustained activity following this phasic response was also significantly greater for targets. In the second cell (Fig. 5C,D), the fixed-target task showed a similar, phasic response to targets and nontargets, followed by an extended period of response just to targets. In the cued-target task, activity was low and unrelated to stimulus presentation. In the third cell (Fig. 5E,F), there was again target-selective activity, both starting earlier and lasting for longer in the cued-target task. The fourth cell (Fig. 5G,H) showed selective response to nontargets, again greater in the cued-target task.

For each cell, periods of significant target/nontarget selectivity were separately identified for each task. After Gaussian smoothing of spike trains ($\sigma = 10$ ms, width 3 σ), we used ANOVA to examine data for each separate 1 ms bin from -200 to $+700$ ms from stimulus onset. For the fixed-target task, the factors were stimulus (target/nontarget) \times hemifield \times serial position in trial; for the cued-target task, there was an additional factor of cue. The distinction between targets and nontargets was coded as significant throughout any time period of ≥ 30 ms during which the main effect passed a threshold of $P < 0.05$. This criterion produced an acceptably low false alarm rate in the prestimulus period (see Fig. 6A,B); analyses using a range of other criteria (10–60 ms) gave qualitatively similar results. Figure 6A,B shows percentages of all cells showing significance at each time bin, separately for the fixed-target (Fig. 6A) and cued-target (Fig. 6B) tasks.

In the fixed-target task, the number of target/nontarget-selective cells increased quickly from about 100 ms after stimulus onset and reached its peak at around 200 ms (Fig. 6A, blue line). This peak consisted predominantly of target-selective cells (red), with a substantially smaller proportion of nontarget-selective cells (green). In Figure 6A, time periods in which the proportion of target-selective cells was significantly

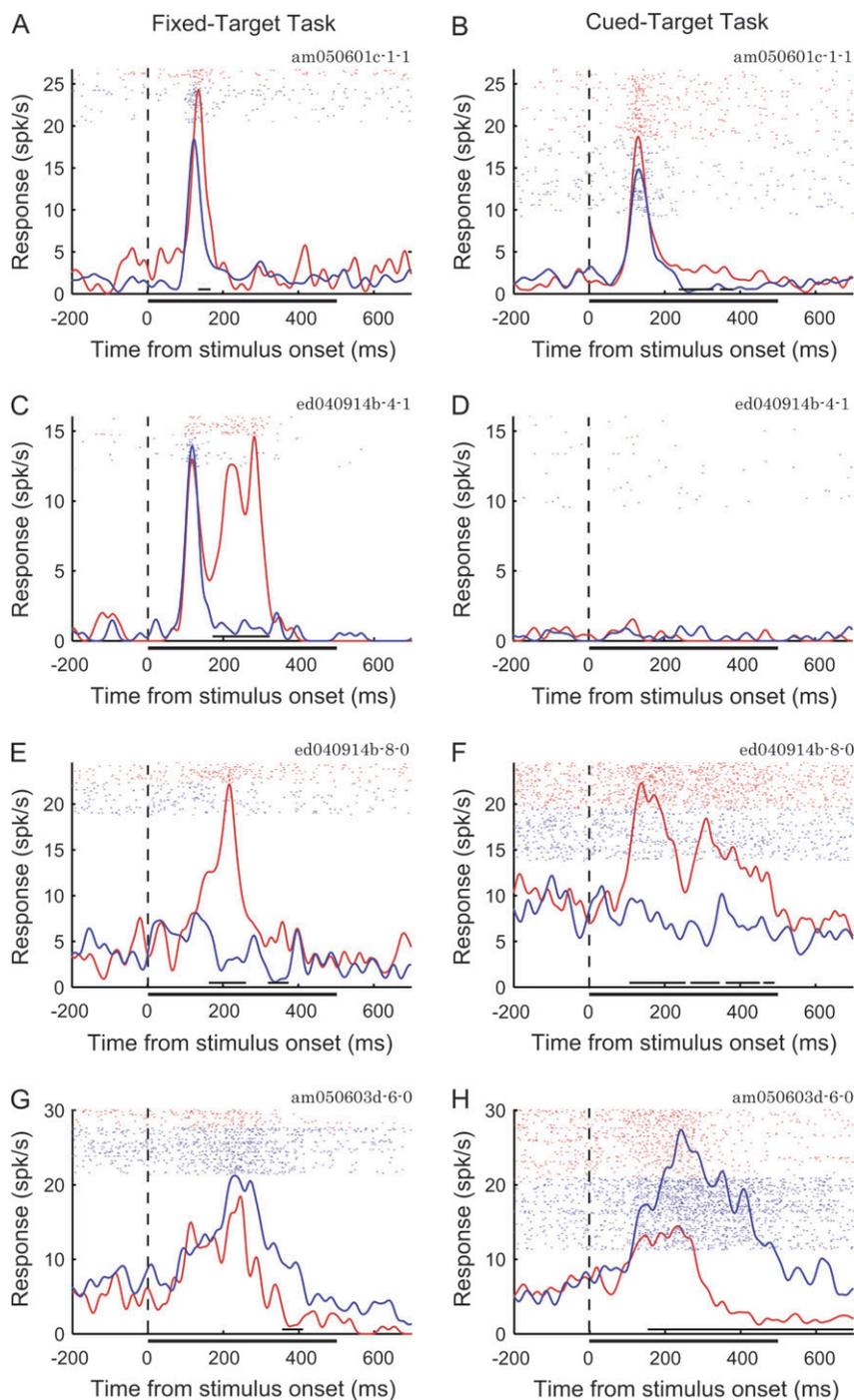


Figure 5. Responses to targets and nontargets in single cells. Data are shown for 4 cells (panels AB, CD, EF, GH). Within each pair, left and right panels show data for fixed-target and cued-target tasks, respectively. Each panel shows a raster display (top) and spike density functions (bottom). Density functions are based on smoothed spike trains ($\sigma = 10$ ms, width 3 σ). Red dots and lines—response to targets; blue dots and lines—response to nontargets. Black horizontal line below panels shows stimulus presentation period. Thin black horizontal lines above x -axis show periods in which responses to targets and nontargets were significantly different (see text).

greater than the proportion of nontarget-selective cells (binomial test, $P < 0.05$) is shown by the thin black line above the x -axis. Later in the stimulus period, the number of target-selective cells decreased, approaching the number of nontarget-selective cells. In the cued-target task, the number of selective cells also started to increase about 100 ms after stimulus onset (Fig. 6B, blue line). Again there was a significant early preponderance of target-selective cells, followed by conver-

gence of target and nontarget selectivity toward the end of the stimulus period. At least qualitatively, these data suggest similar target detection processes in fixed- and cued-target tasks.

For quantitative comparison, we need comparable data sets for the 2 tasks. For this purpose, trials of the cued-target task were split into 3 separate sets, one for each cue. For whichever task (fixed-target or cued-target, averaged across cues) had the greater number of stimulus presentations for a given cell, data

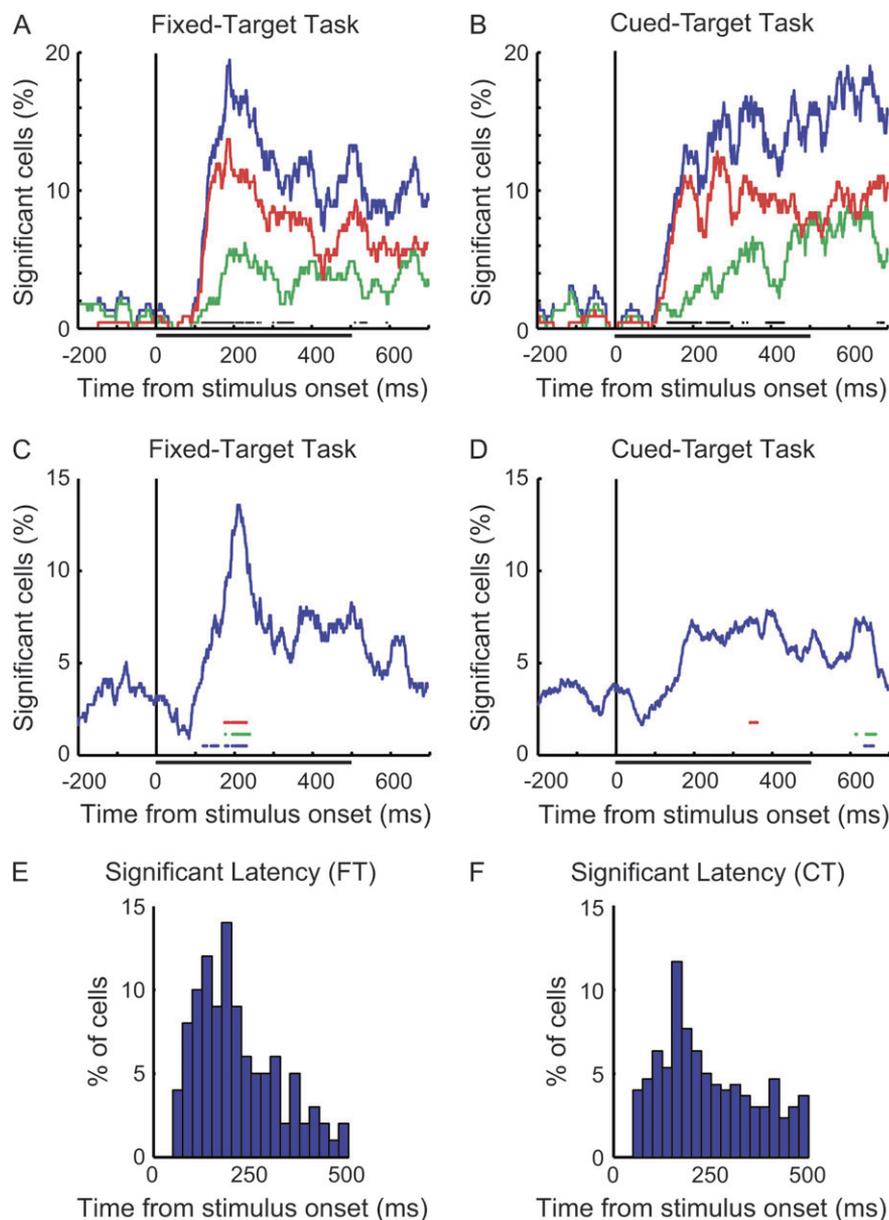


Figure 6. Target/nontarget discrimination. (*A, B*) Percentage of all analyzed cells ($n = 217$) with significantly different response to targets versus nontargets. Blue line is sum of target selective cells (target response > nontarget; red line) and nontarget-selective cells (nontarget response > target; green line). Black horizontal line below panels shows stimulus presentation period. Thin black horizontal lines above x -axis show time bins with number of target selective cells significantly higher than number of nontarget-selective cells. (*C, D*) Percentages of significant target/nontarget discrimination using comparable data from the 2 tasks. For cued-target task, plot shows average data for the 3 separate cues. Colored lines above the x -axis in (*C*) show time periods in which percentage of significant cells in fixed-target task was significantly higher than for cues 1 (red), 2 (green), or 3 (blue) in cued-target task. Equivalent lines in (*D*) show significant time periods for the reverse comparison. (*E, F*) Distribution of onset latencies (see text) for target/nontarget discrimination among all cells in which discrimination was significant. FT, fixed-target; CT, cued-target.

were randomly discarded until numbers were equal. ANOVAs as before assessing target/nontarget selectivity were then repeated on these 4 comparable data sets (1 for fixed-target, 3 for cued-target). The results are shown in Figure 6*C* (fixed-target) and *D* (cued-target; mean across the 3 cues). With comparable data, the early peak of target/nontarget selectivity was significantly stronger in the fixed-target task (see Fig. 6*C*, colored lines above x -axis; proportion of selective cells in fixed-target task compared with data sets for each cue in cued-target task, McNemar's test, $P < 0.05$). Overall, in the fixed-target task, 109/217 of all cells showed significant target/nontarget discrimination at some point during stimulus presentation.

The equivalent figure for the cued-target task (mean across cues) was 104/217. For each case of significant target/nontarget discrimination, the latency was defined as the start of the first period of significant discrimination across the stimulus period from 50 to 500 ms after the onset of stimuli. Latency distributions appear in Figure 6*E* (fixed-target) and *F* (cued-target; mean across cues). Latencies were significantly shorter in the fixed-target task (Mann-Whitney comparison between fixed-target and each cue in cued-target, $P < 0.02$ in each case). Thus target/nontarget discrimination was qualitatively similar in the 2 tasks, but significantly earlier in the fixed-target case.

The results in Figure 6*A,B* suggest somewhat separate early and late phases of response to choice stimuli, with a clear preponderance of target-preferring cells in the early phase, but more balanced preferences in the late phase. To examine this further, for each cell we performed ANOVA on spike rates calculated for 2 analysis windows, 50–250 ms (early) and 300–500 ms (late) from stimulus onset, separately for the fixed-target task with factors stimulus (target/nontarget), hemifield and serial position in trial, and for the cued-target task with an additional factor of cue. In the fixed-target task, the main effect of stimulus was significant in 67 cells (31% of sample) in the early period, and in 60 cells (32%) in the late period. Of these cells, 49 preferred targets in the early period, and 48 in the later period. For the cued-target task, equivalent values were 42 significant cells (19% of sample) in the early period, of which 32 preferred targets, and 92 significant cells (42%) in the late period, of which 50 preferred targets.

Mean normalized activities for these different cell groups appear in Figure 7. As a population, early target cells in both tasks showed a phasic response, beginning around 70 ms from target onset, and complete well before stimulus offset. In early nontarget cells, there was a suggestion of phasic inhibition for targets. Following these phasic target responses, frontal cells as a population maintained the target/nontarget discrimination at least up to the time of the response. This more sustained maintenance of target or nontarget preference is shown in the average histograms for late-selective cells. Again, the results suggest similar choice processes in the 2 tasks, with the quantitative difference that early target-selective activity was somewhat greater for fixed-target.

As shown by the examples in Figure 5, however, this similarity between tasks at the population level often did not hold for single cells. To test such differences statistically, data from early and late windows were examined by ANOVA as before, but with an additional factor of task. In the early window, there were 31 cells (14% of cell sample) with a significant interaction between stimulus (target/nontarget) and task. In the late window, this number increased to 56 (26%). To compare preferences in the 2 tasks, for each cell and task we calculated a target selectivity index, $TSI = (R_t - R_{nt}) / (R_t + R_{nt})$ where R_t = response to target, R_{nt} = response to nontarget. R_t and R_{nt} were mean firing rates, separately calculated for early (50–250 ms) and late (300–500 ms) analysis windows. The analysis was conducted on the full population of 217 cells. The distributions of TSIs in early and late phases of the fixed-target and cued-target tasks are shown in Figure 8. In both analysis windows, TSIs for the 2 tasks were only modestly correlated (early, $r^2 = 0.17$; late, $r^2 = 0.28$).

Saccadic Activity

As shown in Figure 7, for no group of target-selective cells was there activity immediately after stimulus offset, at the time of the monkey's saccade. These data suggest little direct involvement in saccade production. To confirm this conclusion, many cells were also tested in a standard delayed-saccade task (see Materials and Methods) with the same saccade parameters as the main tasks. In both tasks, saccades were required to a location 6 deg to left or right of fixation, at the offset of a 500 ms target stimulus at that location. Mean saccade endpoints were $\pm 5.5^\circ$ (horizontal) from fixation in the main tasks, and $\pm 5.7^\circ$ deg in the delayed-saccade task. For analysis we

selected all those target- and nontarget-selective cells (Fig. 7) for which delayed-saccade data were also available.

The results are shown in Figure 9. In these cell groups, there was no suggestion that delayed-saccade data resembled target responses in the main tasks. In particular, population activity in the delayed-saccade task was closely similar for main-task target and main-task nontarget cells. It seems unlikely that, in our tasks, target-selective activity was directly linked either to saccade preparation or execution.

Errors

In the fixed-target task, there were too few errors for meaningful analysis. In the cued-target task, however, there were frequent errors in which a nontarget stimulus was treated as a target (saccade to target location).

Data from 4 example cells appear in Figure 10. For each cell, the figure shows data for target corrects (saccade at offset; red), nontarget corrects (maintained fixation; blue), and nontarget errors (saccade; green). In Figure 10*A,B* are 2 cells with significantly greater response to targets in the late phase of the response. In both cells, the late response for nontarget errors resembled that for target corrects. Such results suggest activity related to behavioral outcome, that is, to the final target/nontarget decision. More striking results are shown by the 2 cells in Figure 10*C,D*. Here there was significant discrimination between targets and nontargets in both early and late phases. In the late phase, as before, nontarget activity reflected behavioral outcome. In the early phase, in contrast, nontarget errors resembled nontarget corrects, suggesting activity driven not by outcome but by correct stimulus classification.

To analyze these data quantitatively, we took all those cells (Fig. 7*E-H*) with significant discrimination between targets and nontargets. For 42 cells with early discrimination (50–250 ms from stimulus onset; Fig. 7*E,G*), we compared mean activity in this early analysis period for target corrects, nontarget corrects, and nontarget errors. In this analysis period, response to nontarget errors was frequently different from response to target corrects (20 cells), somewhat less frequently different from response to nontarget corrects (11 cells). These results suggest early activity driven more by actual stimulus category than behavioral outcome. A similar analysis examined activity in the late analysis period (300–500 ms) for the 92 cells showing significant target/nontarget discrimination in this period (Fig. 7*F,H*). Now nontarget errors were significantly different from nontarget corrects in 50 cells, as compared with only 27 cells in which nontarget errors differed from target corrects. At this late phase, accordingly, responses in a majority of cells were most closely related to final decision and behavioral outcome.

Discussion

In this experiment we compared PFC activity in 2 kinds of target detection task. In the fixed-target version, the same picture served as target throughout training. Here, the behavioral significance of each stimulus was established by long-term stimulus–response association, analogous to “consistent mapping” in human visual search. In the cued-target version, the same pictures served sometimes as targets, sometimes as nontargets, with the current target defined by a cue at trial onset. Here, behavioral significance was determined by the short-term context provided by the cue, analogous to “varied mapping” in human visual search.

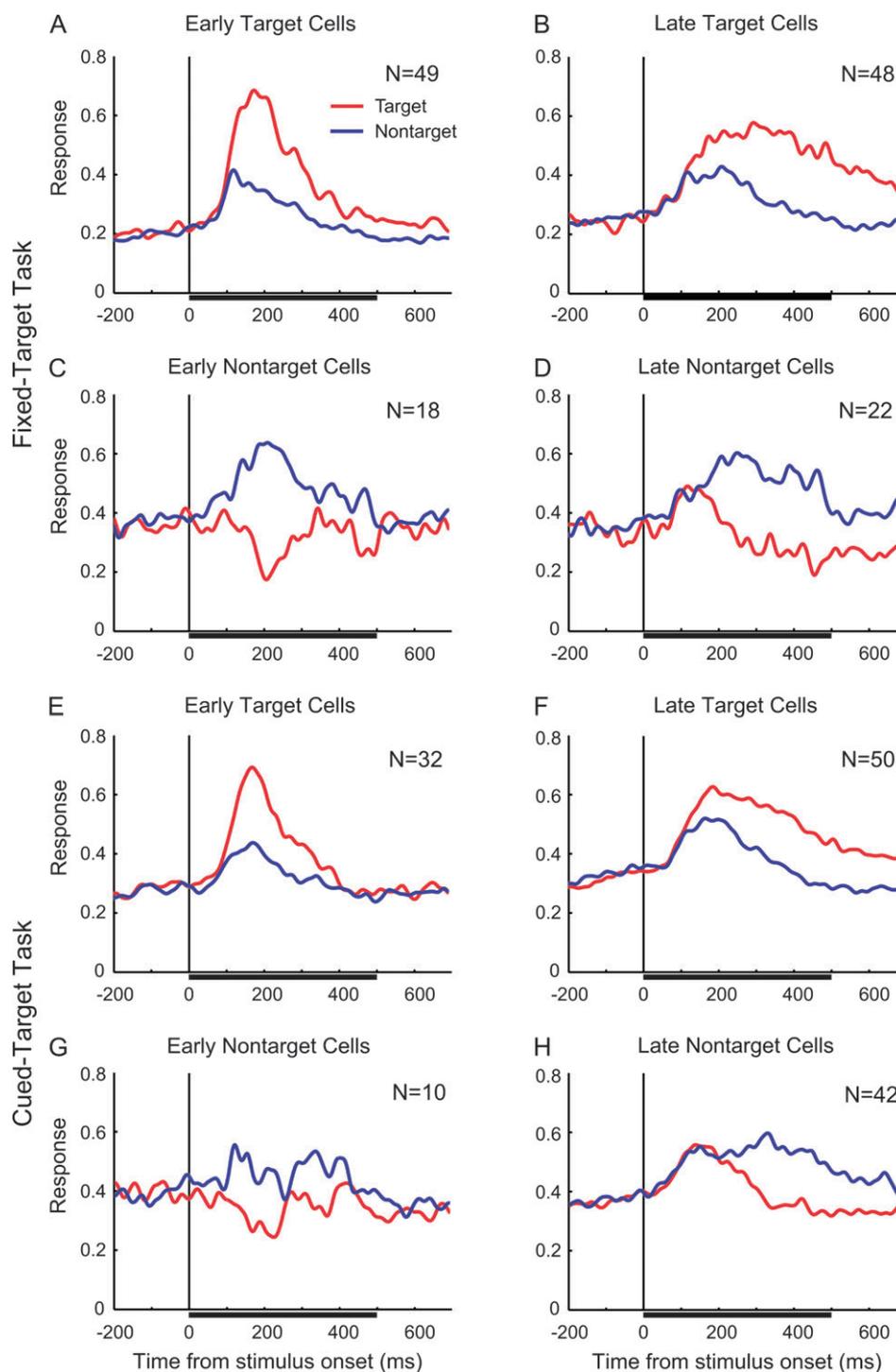


Figure 7. Population activity for target- and nontarget-selective cells. Mean normalized spike density functions for target- and nontarget-selective cells in early and late response periods, separately for fixed-target (*A–D*) and cued-target (*E–H*) tasks. For each cell, normalization was performed by dividing the 2 spike density functions (target and nontarget) by the maximum value in either one. Responses to targets and nontargets are shown with red and blue lines, respectively. Black horizontal line below each panel shows stimulus presentation period.

In line with a role in setting context, many neurons in PFC showed an initial, strong cue selectivity. Though cue selectivity began early, during the phasic response to cue onset (see Fig. 3), it reached its maximum several hundred ms later, immediately after cue offset (Fig. 4). The results suggest a role for this activity not just in cue identification, but in preparation for subsequent decisions. In the immediate postcue delay, activity was

selectively modulated by cue identity in around one third of all PFC cells. Following this early cue coding, choice-related PFC activity was remarkably similar in cued- and fixed-target tasks. At the population level, PFC showed similar overall activity in the 2 tasks, and similar patterns of phasic and tonic target/nontarget selectivity. This population similarity occurred despite many differences between tasks in single cells. With some quantitative

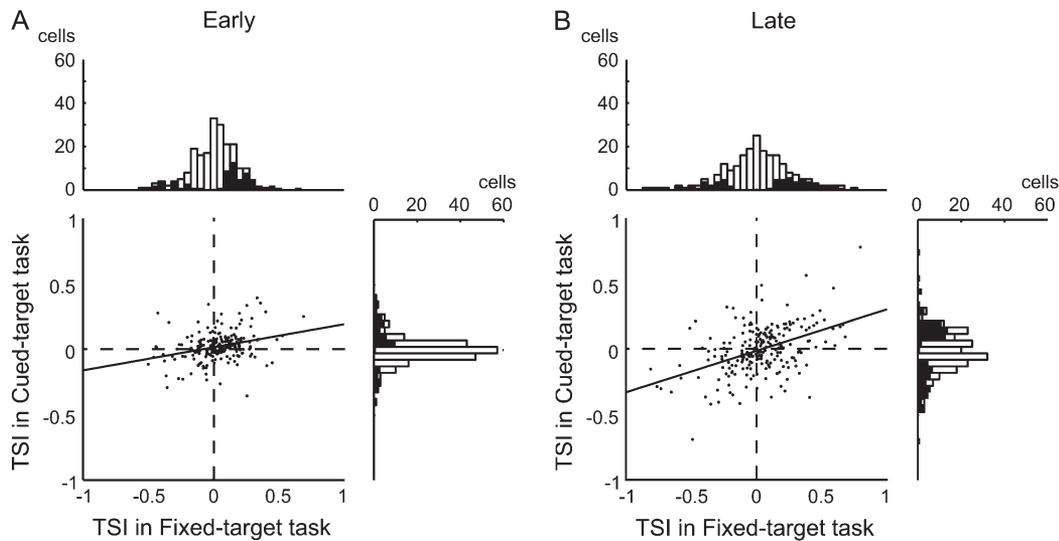


Figure 8. TSIs. (A) Early window (50–250 ms). Panels to top (fixed-target) and right (cued-target) show distributions of TSI across all 217 cells (filled columns—significant difference between target and nontarget responses; open columns—all cells). Scatter plots show relation between TSI in fixed-target and cued-target tasks. (B) Late window (300–500 ms).

differences, PFC cells show similar coding of fixed and context-dependent behavioral significance.

Strong cue selectivity in the first postcue delay resembles many previous demonstrations of “working memory” activity in PFC neurons. In delayed match to sample (DMS), for example, the monkey must decide whether 2 successive stimuli are identical; in many studies, PFC cells have been shown to maintain the identity of the first stimulus over the delay leading up to the second (e.g., Fuster et al. 1985; Miller et al. 1996; Freedman et al. 2001). In our task, as we have noted, cue selectivity in working memory could take various forms. One simple possibility is a visual memory of the cue itself. A second is a prospective visual code of the corresponding target. A third is some more abstract code reflecting current context for target/nontarget classification; such a code would be important, for example, in determining which subsequent stimulus will produce a target-selective response. Evidence against a simple memory of cue identity is provided by similar delay activity following different cues that indicate the same target (Rainer et al. 1999). Previously we have shown that, in our task, working memory codes in prefrontal neurons are only weakly related to visual codes of either cues or targets; for a given cell, the pattern of cue selectivity during interstimulus delays, for example, preference for cue 1 over cue 2 trials, is only weakly related to the pattern of selectivity during actual cue or target presentation (Sigala et al. 2008). Such results suggest that, at least in some tasks, the prefrontal code of short-term context may be somewhat more abstract than a simple visual memory of cue or visual prediction of target.

In our task, some cells retained cue-selective delay activity after the first choice stimulus; compared with the strong coding of cue identity in the first postcue delay, however, this later signal was much reduced. Reduced cue coding as the trial progressed might relate to reduced performance accuracy. As the trial progressed, monkeys increasingly responded to nontargets as though they were targets, perhaps reflecting a weakened working memory for the current cue or task context. That said, performance accuracy averaged across targets and nontargets remained >75% until the end of the trial, and analyses of neural

activity were based only on correctly completed trials (requiring a series of 1–4 correct decisions). Evidently, reduced cue selectivity in later delays is not incompatible with maintained accurate behavior. Our results contrast with those from a previous study of DMS, in which strong, cue-selective delay activity survived across a number of successive choice stimuli (Miller et al. 1996). In that study, such cue-selective activity was substantially stronger if, on some trials, the series of stimuli contained the potential distraction of repeated nontargets; in that task, the monkey withheld response to repeated nontargets, awaiting a repetition of the specific sample presented at trial onset. Either this or other differences could explain the discrepancy between the earlier DMS results and ours.

Many experiments have examined switching of task context or set in the human brain. Analogous to cue-related activity in our study, these experiments show strong PFC activity when an instruction defines the new context (Dove et al. 2000; Dosenbach et al. 2006). There are also several parallels between context-related activity in our data and behavioral results on human task switching. In task switching experiments (Allport et al. 1994; Rogers and Monsell 1995), stimuli can be classified by alternative rules (task sets). Rules for each trial can be instructed by an explicit cue (Meiran 1996), as in our study, or can follow some regular pattern of repetition and alternation (Rogers and Monsell 1995). Typically, performance improves with increasing time to prepare for the forthcoming rule, reaching an asymptote after 500 ms or more (Rogers and Monsell 1995). This result mirrors our finding that cue-selective delay activity reached a maximum during the immediate postcue delay, >500 ms from cue onset. A second striking result in human behavior is the substantial difference between rule repeats and switches (Allport et al. 1994). Performance is best when the same rule is applied to 2 successive stimuli. Even with maximal preparation time, performance is worse when the current rule changes from the previous trial (Rogers and Monsell 1995). The results suggest that, once a rule has been used, its repetition does not require the same active, preparatory support necessary after a new task cue. In our data, a reduction in active preparation

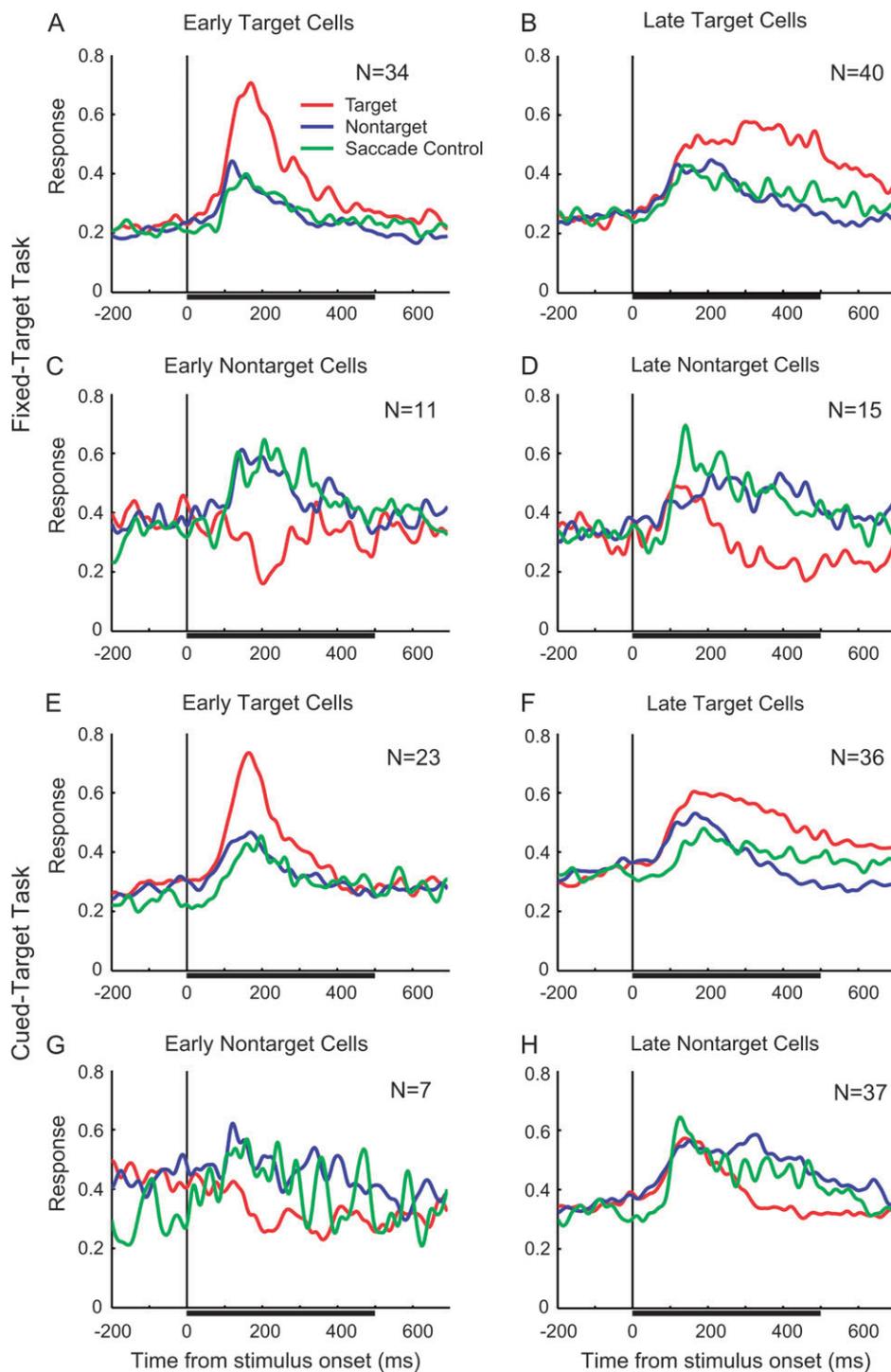


Figure 9. Responses of target and nontarget cells in delayed-saccade control task. Format as Figure 7. Responses to search task targets and nontargets are shown in red and blue, respectively; responses in saccade control task are shown in green.

could be reflected in reduced cue-selective delay activity following the first choice stimulus.

Once current context was established, our data suggest similar processes of stimulus classification in cued- and fixed-target tasks. In both cases, the period 50–250 ms from stimulus onset was characterized by many cells with selective, phasic response to targets. Thereafter, numbers of target- and nontarget-selective cells were more balanced, especially in

the cued-target task. In both tasks, sustained activity maintained target/nontarget discrimination beyond stimulus offset, at least to the time of the response.

For the fixed-target task, phasic target responses resemble those previously reported for the same animals (Everling et al. 2002, 2006). For the cued-target task, the phasic target response resembles “match enhancement” in DMS (Miller et al. 1996). Neuroimaging also shows strong responses to

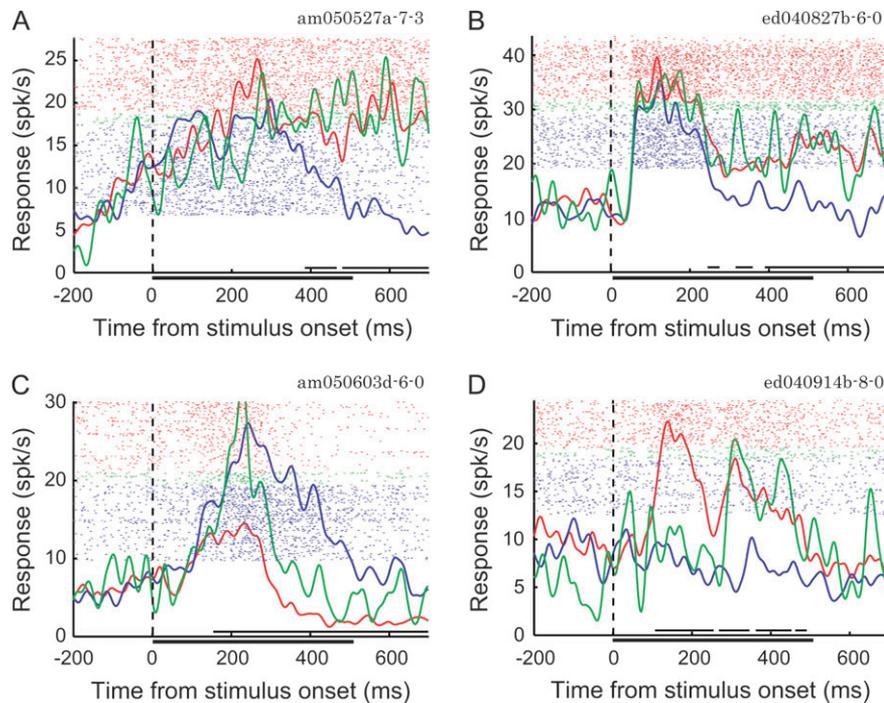


Figure 10. Cued-target error activity in single cells. Target correct (red), nontarget correct (blue) and nontarget error (green) responses in 4 example cells (A–D). Conventions as in Figure 5.

target stimuli in the human PFC (Jiang et al. 2000; Hampshire et al. 2007). In the fixed-target case, selective responses to the target—seen in >25% of all cells in our sample—could be established by fixed training in search for this stimulus. In the cued-target task, a somewhat similar configuration of target-detecting cells must instead be established by the short-term context imposed by the cue. In this case, the same stimulus produces target-selective activity when preceded by the appropriate cue, but not on other trials.

Despite the qualitative similarity of early target detection in the 2 tasks, there were quantitative differences. When tested on comparable data, the early peak of target-selective response was significantly stronger in the fixed-target task. Related to this, a previous report has shown decreased detection latencies in cells of the frontal eye field following long training in search for a fixed-target stimulus (Bichot et al. 1996).

The late phase of stimulus processing was reflected in cells with sustained activity, selective either for targets or for nontargets. A plausible interpretation is that activity in these cells maintained the target or nontarget decision until the time of the go/no-go response. Notably, even cells with this late-phase activity showed no hint of additional activity at the time of the saccade (Fig. 7). Neither did target-selective cells show evident activity linked to saccade preparation or execution in a delayed-saccade control task. The results suggest little role of simple motor processes in target-selective activity.

Despite broadly similar population responses in cued- and fixed-target tasks, differences were seen in many single cells. Across cells, target preferences in the 2 tasks were only modestly correlated. At the population level, there is similar PFC coding of fixed and variable behavioral significance. At the single cell level, however, target and nontarget preferences controlled by short-term context do not necessarily match those established by long-term, fixed-target training.

Error data add some insight into phasic and tonic components of stimulus selectivity. Specifically we examined errors in the cued-target task, when the animal sometimes treated nontargets as targets. At least in some cells, errors were not reflected in early target-related activity (Fig. 10). In the early phase, neural activity followed actual stimulus identity, not forthcoming behavior. The results confirm that, even on error trials, cue information was not entirely lost in the PFC, continuing to shape the correct stimulus classification. Previously we reported similar results for the fixed-target task (Everling et al. 2002, 2006). In the late phase, however, neural activity predicted behavior, with similar activity for nontarget errors and target corrects. This pattern suggests activity related to the final target/nontarget decision. In a variety of previous tasks, PFC activity on error trials has been shown to reflect the response actually made, not the response that would have been correct (e.g., Watanabe 1986; Genovesio et al. 2006). Our data suggest that this result may depend on timing within the task, with initial correct stimulus classification followed by incorrect final decision.

A question for future work is the relation between phasic and tonic components of the target/nontarget response. Very likely, the late pattern of prefrontal activity—reflected in sustained maintenance of a target or nontarget decision—is established at least in part by input from those cells with early, target-selective activity. As the trial progresses, however, this link may be weakened, with the late decision pattern increasingly independent of the early target pattern.

It is often proposed that the PFC is especially important in context-dependent behavior (Miller and Cohen 2001). In target detection tasks, PFC lesions have little effect when target identity remains fixed, in contrast to major impairments when the target changes trial by trial (Rossi et al. 2007). Our results suggest that, nevertheless, physiological activity in PFC is rather similar for fixed and changing targets. Certainly, parallel neural

systems contribute to much decision making. Many studies, for example, document similar neural properties in PFC, premotor cortex, basal ganglia and other structures (e.g., di Pellegrino and Wise 1991; Wallis and Miller 2003). Parallel systems provide a plausible basis for protection from impairment after PFC lesion. A key difference between cued- and fixed-target tasks may lie not in PFC involvement, but in the ability of other systems to support correct behavior when PFC input is impaired.

A second common proposal is that PFC is especially important in novel or unpracticed behavior (e.g., Norman and Shallice 1980). In both cued- and fixed-target tasks, our animals had long training before recordings began. Quite possibly, different PFC properties might be revealed by recordings earlier in task experience.

For context-dependent behavior, one requirement is a signal of current context. In our data, there was strong, sustained context coding—reflected in main effects of cue identity—at least up to the time of the first choice stimulus. A second requirement is that current context must determine behavioral significance. In this respect, our data showed surprising similarity between fixed- and cued-target tasks, with phasic activity linked to early target detection, followed by sustained coding of target or nontarget till the time of response. Often, responses in the 2 tasks were different for single cells; at the population level, however, the broad similarity of the 2 tasks was evident. In the cued-target task, target/nontarget coding occurred despite use of the same physical stimuli as targets on some trials, nontargets on others; in this task, behavioral role could be determined only by combining stimulus information with a signal of current context. The results show that, in PFC, choice processes are closely similar for tasks with or without this short-term context dependence.

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Notes

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