Feature-Based Anticipation of Cues that Predict Reward in Monkey Caudate Nucleus

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Summary

A subset of caudate neurons fires before cues that instruct the monkey what he should do. To test the hypothesis that the anticipatory activity of such neurons depends on the context of stimulus-reward mapping, we examined their activity while the monkeys performed a memory-guided saccade task in which either the position or the color of a cue indicated presence or absence of reward. Some neurons showed anticipatory activity only when a particular position was associated with reward, while others fired selectively for color-reward associations. The functional segregation suggests that caudate neurons participate in feature-based anticipation of visual information that predicts reward. This neuronal code influences the general activity level in response to visual features without improving the quality of visual discrimination.

Introduction

A biological organism increases its likelihood to live long and generate offspring if it can guide its behavior toward obtaining energy resources, avoiding hazardous situations, and finding a suitable partner for mating. Successful organization of behavior requires the ability to anticipate and exploit opportunities that may lead to desirable internal physical states (Bindra, 1968; Dickinson and Baleine, 1994; Tinklepaugh, 1928). Primates are equipped with neural circuits that predict the availability of such rewards, most notably in the prefrontal cortex (Amador et al., 2000; Kobayashi et al., 2002; Leon and Shadlen, 1999; Rolls et al., 1996; Thorpe et al., 1983; Tremblay and Schultz, 1999; Watanabe, 1996) and in the basal ganglia (Bowman et al., 1996; Hikosaka et al., 1989c, 2000; Kawagoe et al., 1998; Rolls et al., 1983; Schultz et al., 1992, 1997; for comprehensive reviews, see Rolls, 1999, and Schultz, 2000). Previous research has shown

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how neuronal activity in these areas changes following the presentation of reliable reward-predictive information. It is not known how these circuits operate before receipt of reward-predictive information. Yet, motivated behavior does not wait until a rewarding object arrives on the scene. In natural environments, individuals will actively search for opportunities to obtain a reward, even without any guarantee of reward availability.

In the monkey caudate nucleus, there exists a subset of neurons that may be involved in reward-oriented control of visual information processing. Previous studies have identified caudate neurons that selectively increase their discharge rate right before the expected appearance of a task-relevant visual cue (Apicella et al., 1992; Hikosaka et al., 1989c; Rolls et al., 1983). For instance, in a memory-guided saccade task (Hikosaka and Wurtz, 1983; see Figure 1A), some caudate neurons fire in advance of the peripheral visual cue, which indicates the target location for the subsequent saccadic eye movement (Hikosaka et al., 1989c). These neurons are believed to be projection neurons with a medium-spiny dendritic structure (Kawaguchi et al., 1990) and GABAergic neurotransmission (Fisher et al., 1986). Their anticipatory activity typically has variable onset latency but shows a time-locked peak around the time when the peripheral cue is expected to appear (see Figure 2A for an example in the present data). Such anticipatory activity has been labeled "expectation of the cue" (Hikosaka et al., 1989c; see Apicella et al., 1992, for a similar conclusion from a manual-response task). However, caudate nucleus also receives reward-predictive information (Kawagoe et al., 1998), most likely through its heavy dopaminergic innervation (Groves et al., 1994; Kato et al., 1995; Smith and Bolam, 1990). Thus, the "expectation of the cue" could actually reflect a reward-oriented process relating to the fact that the peripheral cue entails information about reward availability.

Consistent with this hypothesis, we recently found that caudate neurons selectively increase or decrease their anticipatory activity depending on which spatial position, out of four candidates, is associated with reward in a memory-guided saccade task with an asymmetric reward schedule (Takikawa et al., 2002). This finding indicates that the anticipatory activity cannot be due to factors that affect the general activation level such as arousal. Instead, individual neurons show a unique preference among different associations between position and reward. In our previous study, however, the reward-predictive feature (position) also indicated the direction of the required eye movement, making it difficult to tease apart reward-oriented processes from processes relating to the memory-guided eye-movement task. To examine the hypothesis that the selective anticipatory activity in caudate nucleus reflects a reward-oriented mechanism, we therefore needed to adapt the memory-guided saccade task with asymmetric reward schedule to include a condition in which the reward-predictive feature (color) was dissociated from the task-relevant feature (position) (see Figure 1C). Given that caudate nucleus receives nonspatial visual
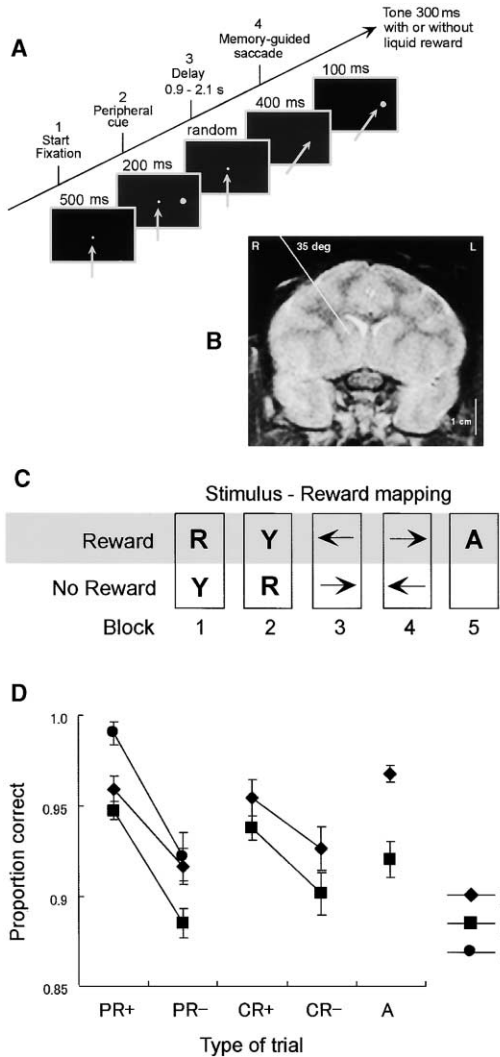
Figure 1. Experimental Design and Behavioral Data

(A) Temporal sequence of the memory-guided saccade.
(B) Coronal MRI scan of monkey H with indication of the angle of penetration to the caudate nucleus.
(C) Reward schedule. Within a block of trials, reward was mapped consistently onto a stimulus feature (top row: R = red; Y = yellow; ← = left; → = right; A = all), whereas the alternative feature was associated with no reward (bottom row).
(D) Behavioral performance of the three monkeys, proportion correct as a function of type of trial. PR+ refers to rewarded trials in the position-reward condition; PR− refers to nonrewarded trials in the position-reward condition. Similarly, CR+ and CR− refer to, respectively, rewarded and nonrewarded trials in the color-reward condition. The letter A refers to trials in the neutral (all-rewarded) condition.
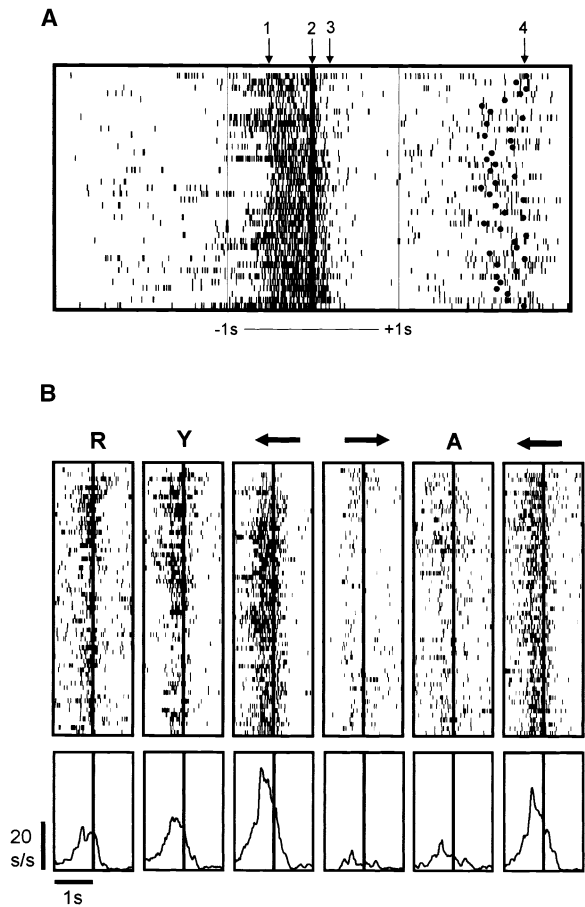
Figure 2. Anticipatory Activity in Caudate Nucleus

(A) Example of precue activity in a caudate projection neuron during a memory-guided saccade task. Each raster represents one trial, aligned on cue onset; trials are shown in order presentation from top to bottom; each tick represents a neuronal impulse. The thick black horizontal line in the middle indicates cue onset. The thin horizontal lines indicate the temporal window shown in following figures. The numbers above the rasters indicate the different events during a trial and correspond with the numbering in Figure 1A (1, start fixation; 2, onset of peripheral cue; 3, start of delay period; 4, memory-guided saccade).
(B) Caudate neuron with anticipatory bias for the contralateral position. Each vertical pair of rectangles represents one block of trials (top, rasters; bottom, histogram); the blocks are shown in sequence from left to right. The symbol above the top rectangle represents the stimulus feature associated with reward (R = red; Y = yellow; ← = left; → = right; A = all). All trials (rewarded and nonrewarded trials randomly interleaved) are shown in order of appearance from top to bottom.

information through afferents from both frontal and temporal association cortices, including color-sensitive areas (Divac et al., 1967; Levy et al., 1997), we speculated that there may be a functional segregation of anticipatory activity depending on whether color or position predicts reward availability.

In each trial, the monkey was required to direct and maintain his gaze at a central fixation spot during a first fixation ("precue") period. Then, a peripheral cue was presented briefly while the monkey had to keep gazing at the fixation spot. Following a delay period, the fixation spot disappeared, at which time the monkey had to saccade to the remembered cue position. The monkey had to make a correct memory-guided saccade in every trial but was rewarded for a correct saccade in only half of the trials. Within a block of trials, reward delivery was mapped consistently onto a feature of the peripheral cue, either a particular position in position-reward blocks or a particular color in color-reward blocks. Here, we show that the caudate anticipatory activity does indeed reflect a reward-oriented mechanism with different

groups of neurons involved in color-based versus position-based anticipation of reward-predictive information. Some of the findings presented here have appeared in abstract form (see J. Lauwereyns et al., 2000a, Neurosci. Soc., abstract).

Results

Behavioral Performance

Among behavioral parameters, the monkey's performance rate (proportion of trials performed correctly) yields the most sensitive and most consistent measure of reward modulation in the memory-guided saccade task (see Kobayashi et al., 2002). The performance rates of all three monkeys in the present study were strongly affected in a very similar way by the cued presence or absence of a reward ($p < 0.001$, χ^2 test for each monkey; see Figure 1D). These results indicate that the monkeys derived an incentive value from the peripheral cue such that they were highly motivated to perform the required saccade in case of reward, but not in case of no reward. Collapsed across monkeys, the performance rates were 0.960 $\pm$ 0.009 (mean $\pm$ 95% confidence interval) in rewarded trials versus 0.903 $\pm$ 0.013 in nonrewarded trials in position-reward conditions. In color-reward conditions, the performance rates were 0.946 $\pm$ 0.012 in rewarded trials versus 0.913 $\pm$ 0.017 in nonrewarded trials, even though the color feature was entirely irrelevant to the performance of the memory-guided saccade task (see Lauwereyns et al., 2000b for a behavioral study on the processing of task-irrelevant visual features by macaques). The performance rate in neutral (all-reward) trials was 0.942 $\pm$ 0.007. The effect of reward modulation (the performance rate in rewarded trials minus that in nonrewarded trials) was stronger ($p < 0.02$, χ^2 test, data from monkeys H and Z) in position-reward conditions than in color-reward conditions (0.054 $\pm$ 0.011 versus 0.033 $\pm$ 0.007).

Influences of Reward Context on Caudate Precue Activity

We focus on caudate projection neurons that showed increased activity during the first fixation period, that is, between onset of the fixation point and onset of the peripheral cue (precue neurons, or neurons that exhibited activity previously labeled as "expectation of the cue"). We recorded a total of 63 precue neurons; 15 of these neurons were removed from the data set because they showed signs of drift in responsiveness (see Experimental Procedures). Forty-eight precue neurons provided sufficient data for present analyses. All but one of these neurons showed statistically reliable effects ($p < 0.01$, see Experimental Procedures) in the precue firing rate as a function of different types of stimulus-reward mapping. Figure 2B shows an example of a precue neuron with spatial selectivity in its anticipatory activity (40 out of 48 neurons [83%] showed a similar spatial bias). For this neuron, initially the color red was associated with reward, leading to a moderate and rather erratic precue firing rate. The same pattern was observed in the next block of trials, when the alternative color, yellow, was associated with reward. Marked changes in the precue firing rate occurred in the subse-
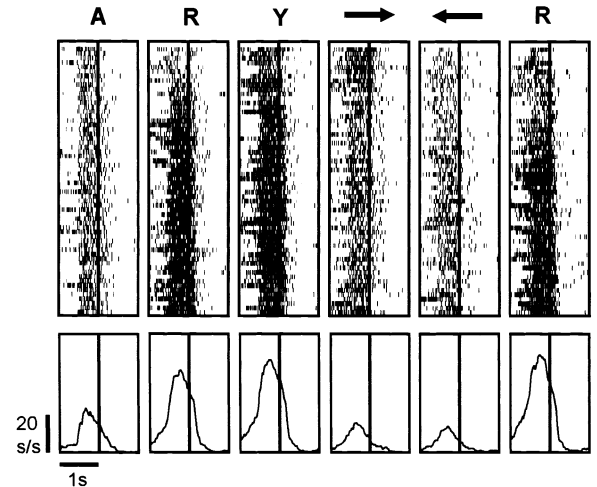

Figure 3. Caudate Neuron with Cross-Dimensional Bias for Color-Reward Associations

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quent blocks with position-reward mapping. When the left (contralateral) position was associated with reward, the precue firing rate became stronger and less variable than in the color-reward conditions, but when the right (ipsilateral) position was associated with reward, the precue firing tended to disappear entirely. In the neutral (all-reward) condition, the firing rate of this neuron remained rather low, but when the position-reward association was changed again to link the contralateral position with a positive incentive value, the neuron's precue activity recovered, confirming the reproducibility of the spatial bias. Among the 40 precue neurons with a significant spatial bias in their anticipatory activity, 30 neurons (75%) showed a higher firing rate when the contralateral position was associated with reward than when the ipsilateral position was associated with reward.

In addition to effects of position-reward mapping, we observed effects of color-reward mapping on the anticipatory activity of precue neurons. Figure 3 shows an example of a precue neuron that increased its firing rate specifically in conditions with a color-reward association ($p < 0.01$). Among the 40 neurons tested with color-reward mapping, 12 neurons (30%) exhibited a similar general bias for color-reward associations. In the neuron shown in Figure 3, we first tested the neutral (all-reward) condition, followed by a condition in which the color red was associated with reward. A few trials after the change of the stimulus-reward condition, the neuron increased its precue firing rate. The anticipatory activity remained high throughout the next condition in which the color yellow was associated with reward. Excluding the initial trials when the neuron was adapting to the reversed color-reward mapping, we found no difference in the precue firing rate between the two color-reward conditions. The precue firing rate decreased, however, in the following two position-reward conditions, falling back to a level of activity not much higher than that in the neutral condition. Changing the reward condition back to an association between the color red and reward, we found that the neuron's precue activity increased again,
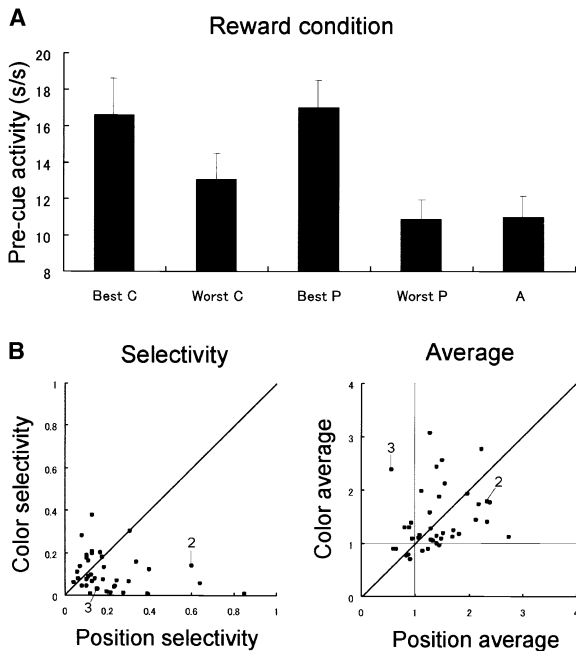
A

B

Figure 4. Population Analyses of Precue Neurons

(A) Average precue firing rate as a function of different stimulus-reward conditions. Best C refers to the color-reward condition in which each neuron showed its highest precue activity; Worst C refers to the alternative color-reward condition. Similarly, Best P and Worst P refer to position-reward conditions with each neuron's highest and lowest precue activity. The letter A refers to the neutral (all-rewarded) condition.

(B) Box plots of selectivity indices (left panel) and average indices (right panel). Selectivity indices were defined as the difference of best minus worst precue activity (normalized by dividing by the sum), separately in color-reward conditions (color selectivity) and in position-reward conditions (position selectivity). Average indices were defined as the average activity in position-reward conditions divided by the activity in the neutral condition (position average) and as the average activity in color-reward conditions divided by the activity in the neutral condition (color average). Example neurons are indicated with numbers corresponding to figure numbering.

confirming this neuron's general preference for color-reward associations.

We also observed color selectivity among color-reward associations (p < 0.01) in 16 out of the 40 precue neurons (40%) tested with both color- and position-reward mapping. The effect of color selectivity shows up as well in the population data for all 40 precue neurons that were tested with both types of stimulus-reward mapping (see Figure 4A, "Best C" versus "Worst C"). For each neuron, we added the data from the color-reward condition in which it showed the highest precue activity to be in the Best C group and the data of the alternative color-reward condition to be in the Worst C group. The average precue firing rate was reliably higher (p < 0.01, paired t test) in the Best C group (16.62 ± 1.96 spikes per second [s/s]; mean ± 95% confidence interval) than in the Worst C group (13.05 ± 1.47 s/s). Similarly, we divided the data from the position-reward conditions into a "Best P" and "Worst P" group (see Figure 4A, Best P versus Worst P). The average precue firing rate was reliably higher (p < 0.01, paired t test) in the Best P group

(16.98 ± 1.50 s/s) than in the Worst P group (10.90 ± 1.04 s/s).

To examine the extent of selectivity on the basis of color versus position, we computed for each neuron the difference of best minus worst precue activity (normalized by dividing by the sum) in color-reward conditions (color selectivity) and in position-reward conditions (position selectivity). Figure 4B (left panel) shows the box plot of these data. On average, we found that the position selectivity (0.209 ± 0.053) of these neurons was reliably higher (p < 0.01, paired t test) than the color selectivity (0.106 ± 0.027). This result is evident from the box plot as most data points are located below (to the right of) the diagonal. The relative strength of the modulation on the basis of position as compared to color may be due to the fact that position constitutes a task-relevant visual feature whereas color constitutes a task-irrelevant feature in the present behavioral paradigm, or it may be due to the fact that position was sampled more finely than color (eight positions versus four colors).

To compare the general preference for either position or color, we computed for each neuron the average activity in the position-reward conditions (position average) and the average activity in the color-reward conditions (color average). These values were divided by the activity in the neutral condition to yield normalized indices (data from all 40 precue neurons tested with both color- and position-reward mapping). Figure 4B (right panel) shows the box plot of these data. Nineteen neurons showed a reliable general preference for position, whereas 12 neurons showed a reliable general preference for color. Considering the box plot, however, we find that there are about equally as many data points situated above (to the left of) the diagonal in the box plot (n = 19; higher color average than position average) as there are data points situated below (to the right of) the diagonal (n = 21; higher position average than color average). The mean values of the color and position averages are not significantly different from each other (paired t test), indicating that there is no general preference across the population of caudate neurons for either position- or color-reward associations.

To examine the possibility of anatomical segregation among the neurons that preferred color- versus position-reward conditions, we split the population of neurons in two groups by their position and color average: position-anticipation neurons with a higher position average (n = 21) and color-anticipation neurons with a higher color average (n = 19). We found no significant difference in the anatomical distribution of color-anticipation versus position-anticipation neurons.

Relation between Caudate Precue and Postcue Activity

Intriguingly, all of the influences of stimulus-reward mapping are seen at a time when the monkey can have no idea about which cue will follow, that is, at a time during a trial when the monkey is entirely ignorant about whether he will receive reward for a correct saccade. Given that caudate anticipatory neurons often appear to have also a visual response (Hikosaka et al., 1989b, 1989c), one possibility is that the precue activity has a
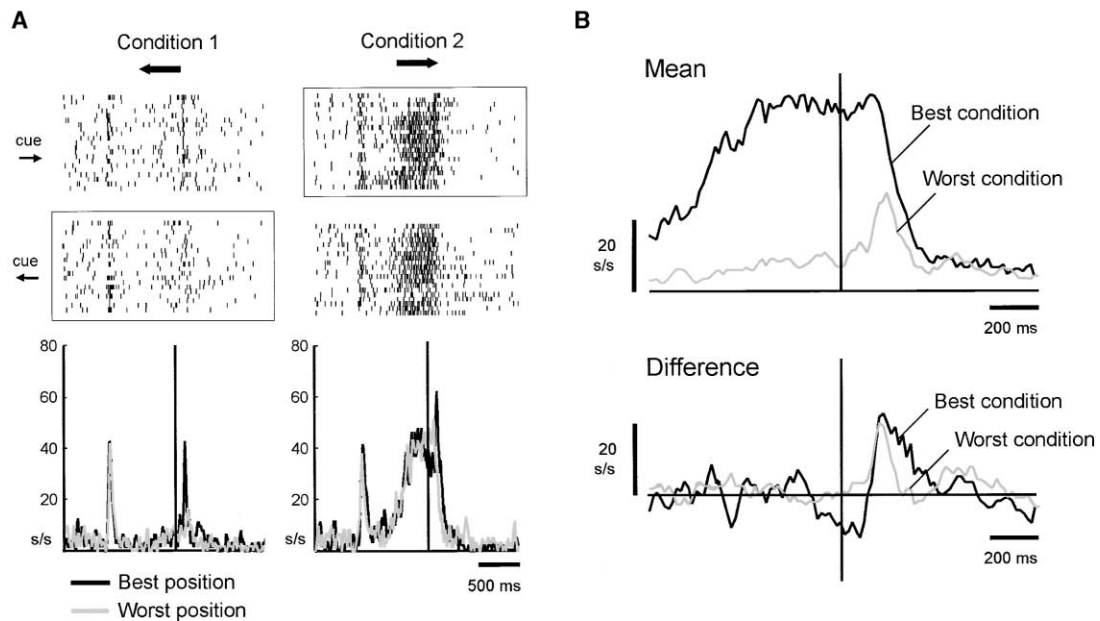
Figure 5. Caudate Neuron with Position Bias and Discriminative Postcue Response

(A) Large symbols above the rasters (here, arrows) indicate the stimulus-reward association. The trials are separated depending on the type of cue, indicated by small symbols. The rewarded condition is indicated by a rectangle around the rasters. The rasters and histograms are aligned with cue onset. Black histograms indicate activity in response to the best feature; gray histograms indicate activity in response to the worst feature.

(B) Mean activity (top panel) and difference of activity (bottom panel) in the best condition (black curve) versus worst condition (gray curve). Best or worst condition is defined by the neuron's precue firing rate. Mean activity is defined as the average of the activity in best-feature and worst-feature trials. Difference of activity is defined as the activity in best-feature trials minus the activity in worst-feature trials.

preparatory function related to the reception of reward-predictive information. To examine this possibility, we analyzed the responses following cue presentation in the population of precue neurons. Most precue neurons showed reliable cue-discriminative responses (in a temporal window from 50 to 250 ms after cue onset): 42 out of 48 precue neurons (87.5%) showed statistically significant discrimination on the basis of cue position ($p < 0.01$); 27 out of these 42 neurons (64%) consistently preferred one position to another, whereas 15 neurons (36%) reversed their preference depending on the reward value of the position. 34 out of 40 precue neurons (85%) showed statistically significant discrimination on the basis of color ($p < 0.01$); 14 of these 34 neurons (41%) consistently preferred one color to another, whereas 20 neurons (59%) reversed their preference depending on the reward value of the color. Across the entire population of neurons, the responsiveness to the reward-predictive feature (e.g., position in a position-reward condition) was reliably stronger ($p < 0.01$) than that to the alternative feature (e.g., color in a position-reward condition). These observations are consistent with previous reports (Rolls et al., 1983; Kawagoe et al., 1998), suggesting that the visual responses of caudate neurons are sensitive to stimulus-reward mapping. In this report, we therefore concentrate on the visual responses to the reward-predictive feature.

The neuron shown in Figure 5 combined spatially biased precue activity with a discriminative postcue response. The neuron showed higher precue activity ($p < 0.01$) in the block of trials when the right (contralateral)

position was associated with reward (condition two) than when the left position was associated with reward (condition one). The neuron also showed a phasic visual response for a cue appearing at the right, which was reliably higher than the activity following a cue at the left in both position-reward conditions ($p < 0.01$, in a temporal window of 50 to 250 ms after cue onset). The effect of the precue bias appears to be to generally increase the activity level until the time of the visual response without affecting the quality of the discrimination. This can be seen clearly in Figure 5B as the mean activity level is higher in the best condition (condition two) than in the worst condition (condition one) until more than 250 ms after cue onset (top panel), whereas the differential activity between best and worst position remains about the same in the two conditions (bottom panel).

Similar observations were made in color-reward conditions. The neuron shown in Figure 6 combined a color-selective precue bias with a discriminative postcue response on the basis of color. The neuron showed higher precue activity ($p < 0.01$) in the block of trials when the color yellow was associated with reward (condition two) than when the color red was associated with reward (condition one). In addition to the precue component, there was also a color-discriminative response ($p < 0.01$, in a temporal window from 50 to 250 ms after cue onset). Again, the precue bias appears to lead to a general increase in the activity level with a higher mean in the best condition than in the worst condition until more than 250 ms after cue onset (Figure 6b, top panel), whereas the differential activity between best and worst
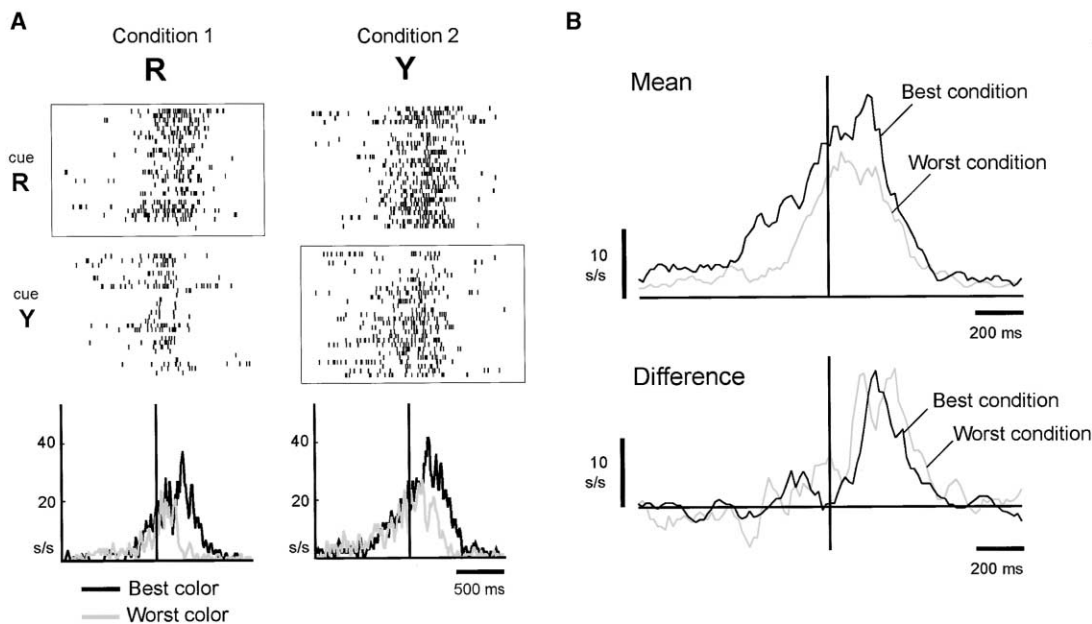
Figure 6. Caudate Neuron with Color Bias and Discriminative Postcue Response
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color remains about the same in the two conditions (bottom panel).

To examine the relation between precue and postcue activity at the population level, we divided the data into four groups: best/worst condition and best/worst feature. Note that "feature" refers to the reward-predictive feature: position in position-reward conditions and color in color-reward conditions. For each neuron, the data from the condition in which it showed the highest precue activity were added to the best condition; the data from the alternative condition were added to the worst condition. Similarly, the data were also divided according to the neuron's cue response: best feature or worst feature. Figure 7A illustrates alternative hypotheses concerning the effect of precue bias on visual responses. The two overlapping distributions at the left represent the neuronal firing rates to the best and worst feature in the worst condition (i.e., a situation without precue bias). Relative to this situation, elevated activity due to precue bias in the best condition could lead to improved discrimination by separating the two distributions further apart; that is, an interaction between condition and feature discrimination (Figure 7A, top right). Alternatively, the precue bias could lead to a general increase in the firing rates so that the two distributions merely shift to higher values without a change in the distance between them, that is, a main effect from condition but no interaction with feature discrimination (Figure 7A, bottom right).

Figure 7B presents the data separately for position-reward mapping (left panel) and for color-reward mapping (right panel). It is easy to see that the population data for the best condition (black lines) shows higher activity than for the worst condition (gray lines) until well after cue onset. The effect of best versus worst condition is statistically reliable ($p < 0.01$; sliding temporal window of 10 ms, paired t test) until 420 ms after cue onset for

position-reward mapping and until 330 ms after cue onset for color-reward mapping. The difference between best versus worst feature, however, remains virtually unchanged regardless of the condition. To illustrate this, Figure 7C shows the average firing rates in the time window during which the population of neurons shows the strongest visual response (from 50 to 250 ms, indicated by a gray background in Figure 7B). For both position- and color-reward mapping, there is a main effect of best condition versus worst condition ($p < 0.0001$; two-factor analysis of variance, condition × feature), as well as of best feature versus worst feature ($p < 0.005$), but no interaction between condition and feature ($F < 1.3$). This can be seen in Figure 7C as the black lines (best condition) appear to be shifted upward relative to the gray lines (worst condition) without affecting the slope between best feature and worst feature.

Discussion

Using a memory-guided saccade task with an asymmetric reward schedule, we found a separation between color-based and position-based caudate anticipatory activity. The results extend previous findings concerning spatial bias in the anticipatory activity of caudate neurons (Takikawa et al., 2002) and further indicate that some caudate neurons exhibit a nonspatial bias before the onset of reward-predictive information, for instance, firing more for any color-reward association than for any position-reward association (as does the neuron illustrated in Figure 3) or showing a color-selective bias in the precue activity (as does the neuron illustrated in Figure 6). These data suggest that the anticipatory activity in caudate nucleus operates in a feature-based fashion. Note, however, that the present findings of separate color-reward and position-reward signals do not ex-
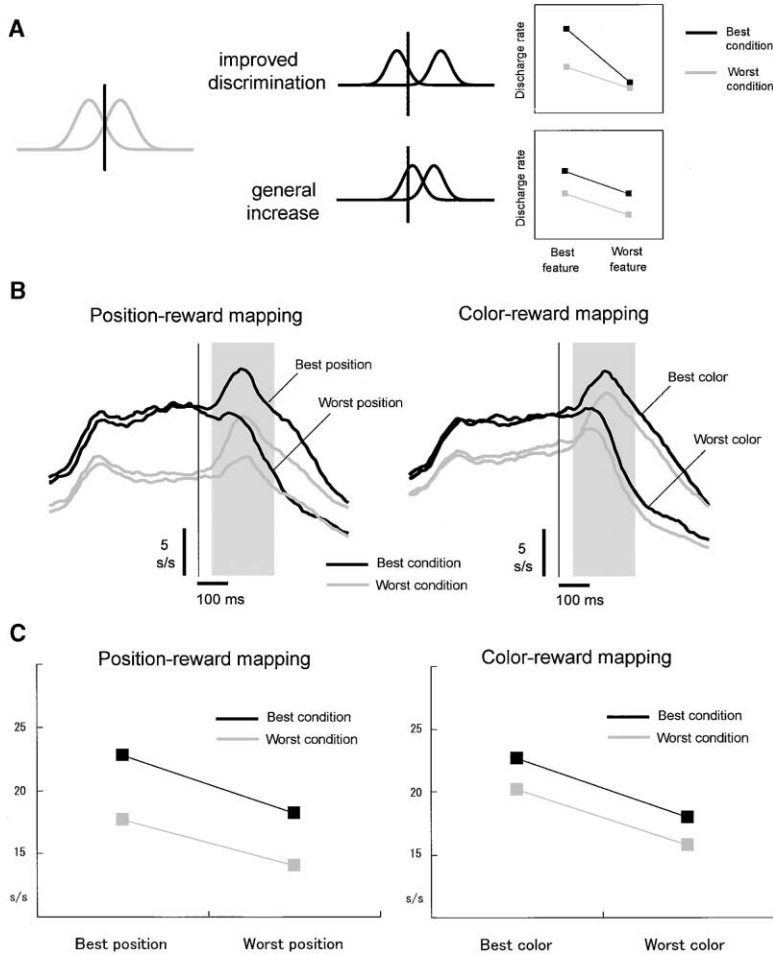
Figure 7. Relation between Precue and Post-cue Activity in Caudate Precue Neurons

(A) Alternative hypotheses about the effect of precue bias on visual discrimination: improved discrimination (top) or general increase (bottom). Explanation in the text.

(B) Population histograms for position-reward mapping (left) and color-reward mapping (right). The data are divided into four groups according to the condition with highest versus lowest precue activity (best condition, black line, or worst condition, gray line) and according to the visual response (best feature versus worst feature). The histograms are aligned with cue onset. The gray rectangle in the background shows the time window of the strongest visual response.

(C) Means of the four groups of data for position-reward mapping (left) and color-reward mapping (right) using the time window indicated in (B).

clude the possibility that both types of signals cooperate or converge under conditions that involve learning associations between color and position. In this regard, perhaps the more important implication of the present functional segregation is that color, as a reward-predictive but task-irrelevant feature, produced any anticipatory bias at all. This observation strongly suggests that the caudate precue activity constitutes a reward-oriented process. Indeed, to perform the memory-guided saccade task correctly, the monkey need not process the color of the peripheral cue. Yet, we found clear effects of color-reward mapping even before the presentation of the peripheral cue. Thus, to understand the function of caudate anticipatory activity, we must study it in the framework of reward-oriented control of neural processing.

Comparison with Feature-Based Attention
An important question with regard to neuronal activity is whether it merely reflects past information, forming a retrospective code, or whether it links past information with anticipated future events, forming a prospective code (Rainer et al., 1999). The time course of the reward-oriented activity by caudate precue neurons becoming more prominent toward the onset of the peripheral cue (e.g., see histograms in Figures 2, 3, 5, 6, and 7) suggests that it has a prospective function. In this view, the pro-

spective activity may influence the reception of the reward-predictive information carried by the peripheral cue. Consistent with this view, we found that most precue neurons also discriminated between different types of cue. Does this mean that the anticipatory activity is involved in the control of visual attention? For instance, the precue component could reflect the prospective recall of information that could subsequently be used for attention. Does caudate activity serve to direct visual attention to the reward-predictive feature?

Single-unit work in monkeys has shown attentional mechanisms in extrastriate visual areas before target onset (Luck et al., 1997). Similarly, functional imaging in humans has identified cortical mechanisms of attention in the absence of visual stimulation, both in the case of spatial attention (Kastner et al., 1999) and in the case of color- or motion-based attention (Chawla et al., 1999; see M.A. Pinsk et al., 2000, Neurosci. Soc., abstract). The operation of visual attention is associated with an improved quality of visual discrimination in terms of behavioral performance (Downing, 1988; Hawkins et al., 1990), as well as in terms of the neuronal coding (McAdams and Maunsell, 1999a, 1999b, 2000; Reynolds et al., 2000; Treue and Maunsell, 1999; Treue and Trujillo, 1999). Specifically, attention in cortical visual areas leads to a stronger increase in responsiveness to a preferred feature than to a nonpreferred or antipreferred

feature. This effect has been termed *multiplicative scaling* or *gain change.* In this view, the effect of attention can be likened to multiplying the neuronal tuning curve by a constant (i.e., the attention factor). For example, multiplying the neuronal response by a constant leads to a null effect in case there is no response in the first place (e.g., in case of an antipreferred feature). Indeed, looking closely at the data on effects of attention in cortical visual areas, we can see in all of the single-unit studies cited above that there is usually no attentional effect for a neuron's antipreferred feature, whereas there can be a strong effect for a neuron's preferred feature. This is precisely the reason why multiplicative scaling can lead to improved discriminability (McAdams and Maunsell, 1999b).

In contrast, the population data for caudate precue neurons (Figures 7B and 7C) clearly support the hypothesis of general increase, not improved discriminability (Figure 7A). Also, the examples of single neurons shown in Figures 5 and 6 suggest that the visual responses are independent of the precue activity, as if they are simply added on top. The function of caudate precue activity, then, appears to be different from the cortical mechanisms of visual attention that interact with signal discriminability. Thus, we propose that the general increase of caudate visual responses can be regarded as a form of *additive*, instead of multiplicative, scaling. Simply speaking, the general increase adds the same number of spikes to the neuronal responses for all visual features regardless of whether a caudate neuron is tuned for a particular feature or not. In other words, the size of the effect of caudate precue bias is the same for all visual features. As a result, discriminability is not improved.

Obviously, more work is required to characterize in detail the differences between reward-oriented anticipation versus visual attention in different brain areas. One possibility is that the reward-oriented anticipatory activity such as seen here in caudate nucleus also affects cortical visual areas. Particularly, caudate nucleus may be part of a network including substantia nigra pars reticulata, thalamus, and prefrontal cortex (see Middleton and Strick, 2000, for a discussion of the anatomical basis of this circuit) that exerts top-down control on stimulus processing in cortical visual areas (see Kastner et al., 1999, for a similar hypothesis). Supporting this general scheme, there already exists evidence suggesting that single neurons in prefrontal cortex show feature-based anticipatory activity (Sakagami and Niki, 1994). Future work should map out to what extent such anticipatory activity is reward-oriented and how it may influence activity in cortical visual areas during and in advance of reward-predictive visual stimulation.

Hypothesis of Motivational Function
In sum, rather than improving visual discriminability, the caudate precue activity tends to lead to a general increase in the activity level of visual responses. This could influence the system's likelihood to detect a specific situation ("the cue indicates reward") independently of any (cortical) information regarding the actual features of the peripheral cue. According to this hypothesis, the precue bias would serve to incorporate the reward value of sensory features in the signal-detection process. For

instance, assuming that the brain makes a perceptual decision by comparing a neuronal response to a criterion value (as suggested in Hanes and Schall, 1996; see also Gold and Shadlen, 2001), the caudate anticipatory activity could bring the neural system closer to reaching the criterion value. Caudate nucleus could exert such influence indirectly, as outlined above, through a network that regulates visual processing in cortical areas. Alternatively, or additionally, caudate nucleus could exert such influence more directly, controlling behavioral output through substantia nigra pars reticulata onto superior colliculus (see Hikosaka et al., 2000, for a comprehensive review of this circuit).

Either way, the function of reward-oriented anticipatory activity would be analogous to the influence of prior probability on the likelihood of detecting a target (Basso and Wurtz, 1996; Carpenter and Williams, 1995; Dorris and Munoz, 1998; Platt and Glimcher, 1999). The precue bias would influence the detection of a rewarding signal by selectively raising its neuronal representation even before it appears. In other words, caudate nucleus would exert motivational control on the detection of a rewarding signal. Specifically, a spatial bias for an association between the left position and reward could lead to an increased likelihood of detecting a cue at the left when the left position happens to be associated with reward. Similarly, a color-selective bias for an association between the color yellow and reward could lead to an increased likelihood of detecting a yellow cue when the color yellow happens to be associated with reward. Alternatively, a general boosting for any color-reward association could speed up the signal-detection process on the basis of color even before the arrival of sensory evidence concerning a particular color feature. We are currently investigating caudate neuronal activity in a paradigm without delay between cue and oculomotor response to provide a direct test of the present hypothesis, that reward-oriented precue bias influences perceptual decision-making.

Experimental Procedures

Subjects and Surgery
We recorded from two right caudate nuclei and one left caudate nucleus in three Japanese monkeys (*Macaca fuscata*), monkeys G, H, and Z. Before the recording experiments started, we implanted a head holder, a chamber for unit recording, and an eye coil under the following surgical procedures: the monkey was sedated with ketamine (4.6–6.0 mg/kg) and xylazine (1.8–2.4 mg/kg) given intramuscularly, and then general anesthesia was induced by intravenous injection of pentobarbital (4.5–6.0 mg/kg/hr) with butorphanol tartrate (0.02 mg/kg/hr). Surgical procedures were performed under aseptic conditions in an operating room. After the skull was exposed, 10–15 acrylic screws were bolted into it. The screws acted as anchors by which a plastic head holder and chamber were fixed to the skull with a dental acrylic resin. The recording chamber, which was rectangular (antero-posterior, 42 mm; lateral, 30 mm; depth, 10 mm), placed over the fronto-parietal cortices, tilted laterally by 35° in the coronal plane, and aimed at the head of the caudate nucleus based on the atlas of *Macaca fuscata* (Kusama and Mabuchi, 1970). The position of the recording chamber was verified with magnetic resonance imagery (Hitachi, AIRIS, 0.3T). A scleral eye coil was implanted in one eye for monitoring eye position (Hikosaka et al., 1993; Judge et al., 1980; Robinson, 1963). The monkey received antibiotics (sodium ampicillin 25–40 mg/kg intramuscularly each day) after the operation. All surgical and experimental protocols were approved by the Juntendo University Animal Care and Use

Committee and were in accordance with the National Institutes of Health Guide for Care and Use of Animals.

Behavioral Paradigm

The monkey sat in a primate chair inside a completely enclosed, sound-attenuated room with its head fixed. A computer display was placed at 70.5 cm in front of the monkey to present the visual stimuli. The monkey performed a memory-guided saccade task (Hikosaka and Wurtz, 1983; see Figure 1A). A trial started with the onset of a central fixation point (0.21° in visual angle). 500 ms after the onset of the fixation point, a peripheral cue (0.53°) appeared for 200 ms randomly at one of two positions. The monkey had to remember the cue position during a delay period of random duration between 0.9 s and 2.1 s. The disappearance of the fixation point after the delay period signaled to the monkey that it should make a saccade to the previously cued position. The monkey had to make the saccade within 400 ms, before the reappearance of the cue, and within 2.6° of the center of the cue position. The cue reappeared after a 400 ms delay for 100 ms at the cue position. An auditory tone of 800 Hz rectangular waveform followed if the monkey made a correct saccade. If the monkey made an error, the same trial was repeated. For monkey G, a tangent screen was used onto which small red spots of light (diameter: 0.2°) were backprojected using two LED projectors, one for the fixation point, and the other for the cue. The position of the cue stimulus was controlled by reflecting the light via two orthogonal (horizontal and vertical) galvanomirrors. For monkey G, the precue period lasted 1 s, cue duration 100 ms, and delay 1–1.5 s.

To investigate the influences of reward expectation, we used an asymmetric reward schedule in which the monkey was rewarded with a drop of water for a correct saccade in only half of the trials (see Figure 1C). Within each block of at least 60 correct trials, reward delivery was mapped consistently onto a feature of the peripheral cue. The cue could be one of two colors selected out of four candidates (red, yellow, green, and blue; luminance: 5.51, 25.6, 20.1, and 1.6 cd/m^2, respectively) and could appear at one of eight diagonally opponent positions selected out of eight candidates at a constant distance from the center of the display (usually 6.5° for monkeys H and Z; between 5 to 30° for monkey G). If the neuron had a spatial preference, one of the two positions was selected to be within the neuron's response field. Thus, four different types of cue (e.g., red/yellow × left/right) were used within a block of trial; each cue type was repeated at least 15 times and presented in random order in each block. In this way, reward could be mapped, for instance, onto the red color, in which case red cues (no matter which position) were associated with reward (beep + drop of water), whereas yellow cues were associated with no reward (beep only). The stimulus-reward association remained constant within a block but varied systematically between blocks (see Figure 1C). We also used an all-reward block as a neutral condition in which all four types of cue were associated with reward, but the reward magnitude was half of the amount in the other conditions. With monkeys H and Z, present analyses are based on two color-reward blocks, two position-reward blocks, and one all-reward block. With monkey G, present analyses are based on eight position-reward blocks.

We opted for a blocked design to examine the influence of the context of stimulus-reward association. The advantage of a blocked design was that we could vary the context of stimulus-reward association simply by changing the reward schedule without giving any cue to the monkey other than the reward itself. Thus, the monkey could use the history of reinforcement to predict the presence or absence of reward given a specific stimulus. Conversely, designs in which the association rules between stimulus and reward change trial by trial would inevitably require the usage of some type of perceptual cue for the monkey to be able to predict reward. Such designs would be disadvantageous for the present purposes because they make it difficult to tease apart perceptual from motivational processes.

One concern with a blocked design is that results could be contaminated if the neurons show signs of drift in responsiveness. To safeguard against this possibility, we used the following screening procedure for neurons. When we encountered a neuron that appeared to show enhanced activity in the precue period, we estab-

lished its clearest isolation condition by systematically adjusting the position of the electrode in the course of 20–40 trials. The initial criterion for selection was based on visual inspection, which proved to be a conservative criterion, consistently producing significant effects according to our definition of precue neurons (see below). We then proceeded to record the neuron in a sequence of at least six reward blocks of at least 60 trials each. If a neuron showed a change in its activity pattern in the later part of a stimulus-reward block (after 20 trials from the beginning of a block), this was taken as an indication of drift; recording was then aborted for such a neuron. After successful recording of a complete set of data for one neuron (five different stimulus-reward blocks for monkeys H and Z; eight different stimulus-reward blocks for monkey G), we confirmed the reproducibility of the neuron by reapplying the reward block in which the neuron had shown the highest level of precue activity. Reproducibility was judged successful if the neuron's activity increased again to reach its highest level. This procedure is illustrated with the neurons in Figures 2 and 3. Only neurons that passed the test of reproducibility were included in the present data set.

Since effects of drift usually imply that a neuron's activity level decreases or disappears entirely, one should expect an effect of the order of stimulus-reward blocks on the average activity level of the population of neurons if this activity is contaminated by drift. If so, blocks that are recorded first should show a higher activity level than blocks that are recorded later. Thus, by checking the effect of block order on neuronal activity, we could perform an independent test of the presence of drift on the population data from the 48 precue neurons that were judged to show no signs of drift by the above procedure. We found that the average precue activity level in the first position-reward block was not significantly different from that in the second-position reward block; similarly, the average activity level in the first color-reward block was not significantly different from that in the second color-reward block. These tests confirmed that the present data are not contaminated by neuronal drift.

Data Collection and Analysis

During recording sessions, action potentials of single neurons were recorded with tungsten electrodes (FHC, Inc., Bowdoinham, Maine; shank diameter: 250 μm, taper angle: 20°–15°, impedance: 1.5–3 mΩ). Microelectrodes were advanced vertically to the cortical surface, using an oil-driven micromanipulator (MO-95, Narishige, Tokyo). The action potentials were amplified, filtered (500 Hz–2 KHz), and processed by a window discriminator (MDA-4 and DDIS-1, BAK Electronics, Germantown, MD). Neuronal discharges were converted into standard digital pulses by means of an adjustable trigger level, the output of which was continuously monitored on a digital oscilloscope together with the waveform. Eye movements were recorded using the magnetic search-coil technique (MEL-25, Enzanshi-Kogyo, Tokyo). We selected extracellular spike activity of presumed projection neurons, which show very low spontaneous activity (Hikosaka et al., 1989a), but not of presumed interneurons, which show irregular tonic activity (Aosaki et al., 1994).

We analyzed only trials in which the monkey made a correct response. Performance rates were evaluated by means of χ^2 test. Precue neurons were defined as neurons showing a statistically reliable increase in the average number of spikes in the window of −500 to 0 ms from target onset (precue window) as compared to the activity before onset of the fixation spot (from −1 s to −500 ms for monkeys H and Z; from −1.5 to −1 s for monkey G). The first eight trials in each condition were excluded from analyses to remove variability in neuronal activity due to adaptation to the change in stimulus-reward mapping. All pair-wise comparisons of average firing rates were evaluated by two-tailed t tests. For population analyses, we computed a number of indices, which, for ease of exposition, are defined in the Results section before introduction of the data obtained with the respective indices. Temporal windows for computation of the level of neuronal activity were from −500 to 0 ms before cue onset for precue activity and from 50 to 250 ms after cue onset for postcue activity. To examine the temporal pattern of the influence of precue bias on postcue activity, we performed paired t tests in a sliding window of 10 ms following cue presentation. To test the relationship between precue bias and postcue discrimination, we performed two-factor analysis of variance using

condition and feature as within-subject factors with number of neurons as degrees of freedom. To correct for family-wise error with multiple t tests, we used the Bonferroni procedure.

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