

# Functional differences between macaque prefrontal cortex and caudate nucleus during eye movements with and without reward

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**Abstract** The prefrontal cortex and the basal ganglia form mutually connected networks and are thought to play essential roles together in guiding goal-directed behaviors. Yet, these structures seem to have independent pathways to motor outputs as well, suggesting differential contributions to goal-directed behaviors. We hypothesized that the prefrontal cortex guides actions to a direction required by external demands and the basal ganglia guide actions to an internally motivated direction. To test this hypothesis, we used a task in which monkeys were required to make a memory-guided saccade to a direction indicated by a visual cue while only one direction was associated with reward.

We observed a functional dissociation between the lateral prefrontal cortex (LPFC), which commonly represented the cue direction, and the caudate nucleus (CD), which commonly represented the reward-associated direction. Furthermore, cue-directed and reward-directed signals were integrated differently in the two areas; when the cue direction and the reward direction were opposite, LPFC neurons maintained tuning to the cue direction, whereas CD neurons lost the tuning. Different types of spatial tuning in the two brain areas may contribute to different types of goal-directed behavior.

**Keywords** Basal ganglia · Primate · Single-neuron recording · Working memory

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## Introduction

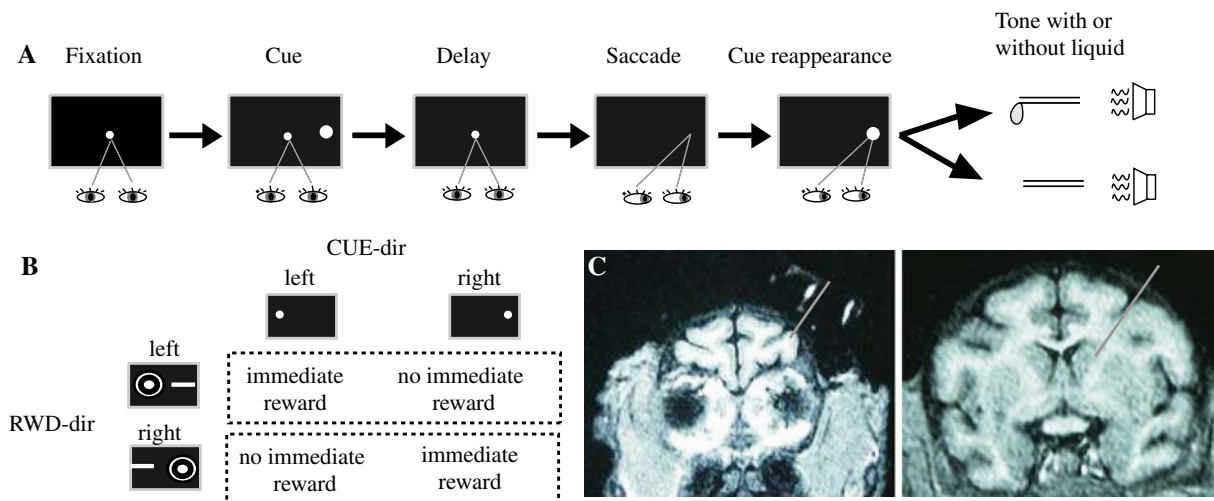
In primates, behavior is influenced, at least to some extent, by the currently expected reward value. For example, when the reinforcement ratio is different for each choice position, choice behavior is biased to a position where reward is expected with a higher probability (Herrnstein 1961). The basal ganglia have been suggested to play an important role to interface motivation and action (Mogenson et al. 1980; Hikosaka et al. 1989; Schultz et al. 1992; Bowman et al. 1996). Animal behavior can also be guided by externally instructed demand. For example, a spatial working memory task requires a subject to memorize a location in order to make a correct response. Various lines of research using trained monkeys showed that the lateral prefrontal cortex (LPFC) plays a crucially important role in spatial processing under task demand (Jacobsen

1935; Fuster and Alexander 1971; Kubota and Niki 1971; Funahashi et al. 1989).

Recent studies have suggested that the task demand can come into conflict with mechanisms of reward expectation (Takikawa et al. 2002a; Watanabe et al. 2003). For instance, monkeys were instructed to perform a spatial response in one direction while reward was associated with a spatial response in the other direction (1-direction reward task, or 1DR; Kawagoe et al. 1998). It was found that neurons in the caudate nucleus (CD) were spatially tuned to the reward-associated direction (Kawagoe et al. 1998; Lauwereyns et al. 2002a, b; Takikawa et al. 2002b). This activity, however, does not explain the actual behavior of the monkey, which is to make a saccade to the instructed direction as opposed to the rewarded direction. Activity tuned to the instruction cue, as reported in the LPFC (Funahashi et al. 1989), may guide behavior to the instructed direction. In most previous studies on the LPFC, however, the animal's correct performance was consistently followed by reward. To test the influences of an external instruction and reward association on the activity in the LPFC, neuronal activity must be examined under a task in which these factors are independently controlled. Although we reported the influence of reward on the LPFC by directly indicating presence or absence of reward (Kobayashi et al. 2002), the role of the LPFC in a situation with a potential motivational conflict has not been studied.

Comparing single-neuron activity during 1DR between the LPFC and the CD would be important to understand functional relationship between the two areas. It has been proposed that the LPFC and the basal ganglia form a functional continuum through LPFC–CD–internal segment of the globus pallidus/substantia nigra pars reticulata–thalamus circuit (Alexander et al. 1990), based on anatomical evidence that the LPFC sends a dense projection to the CD (Goldman and Nauta 1977; Yeterian and Van Hoesen 1978; Selemon and Goldman-Rakic 1985) and that lesions in the two brain structures often cause similar symptoms (Brozoski et al. 1979; Brown and Marsden 1988; Jahanshahi et al. 2002). On the other hand, some studies showed that the LPFC and the basal ganglia have different contributions, for example, in attentional set-shifting (Owen et al. 1993), associative learning (Pasupathy and Miller 2005), and distractibility (Aron et al. 2003).

In the current study, we recorded single-unit activity in the LPFC using 1DR task that we used in our previous basal ganglia research. In this task, the monkeys were required to remember and make a saccade to a cue direction (CUE-dir) while the same or opposite direction was associated with reward (RWD-dir) (Fig. 1a, b). To be able to compare LPFC and CD data in the most optimal way, we recorded from both LPFC and CD in two monkeys, and added a previously collected CD database from three other monkeys (Lau-



**Fig. 1** Behavioral task and the recording areas. **a** Temporal sequence of the memory-guided saccade task. **b** Trial conditions. A memory cue was presented in one of two directions (CUE-dir), e.g. left or right. Within a block of trials, immediate reward was mapped consistently onto one direction, designated as RWD-dir (bull's eye mark), whereas the alternative direction was associated with no immediate reward (*horizontal bar*). In another block of trials, the direction-reward mapping was

reversed. Note that neither the reward-associated direction nor the reward-non-associated direction was indicated by any visual cue (the bull's eye mark and the horizontal bar are shown just for illustrative purposes). The direction-reward mapping rule had to be learned within a block of trials. **c** Coronal magnetic resonance images of monkey HA with indication of the angle of penetration to the lateral prefrontal cortex (A 35) and the caudate nucleus (A 18)

wereyans et al. 2002a; Takikawa et al. 2002b) in this study.

## Materials and methods

### General

The subjects for this study were five adult male Japanese monkeys (*Macaca fuscata*), weighing between 6 and 11 kg. The monkeys were kept unrestrained in individual primate cages in an air-conditioned room where food was available ad libitum. Each monkey had controlled access to fluids and received most of its intake during the behavioral sessions. Their body weight and appetite were checked and supplementary water, vegetables, and fruits were provided daily. 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 the Care and Use of Animals.

### Surgical procedures

Single-unit activity was recorded from the LPFC of two monkeys (HA and ZO) and from the CD of five monkeys (GA, HA, HO, KI, and ZO). Before the recording experiments started, we implanted a head holder for head fixation, a chamber for unit recording, and a scleral eye coil for monitoring eye position. 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/h) with butarphanol tartrate (0.02 mg/kg/h).

### Behavioral paradigm

The monkey was seated in a primate chair with its head fixed inside a completely enclosed sound-attenuated room. For monkeys HA and ZO, visual stimuli were presented on a computer display placed at 70.5 cm in front of the monkey. For monkeys GA, HO, and KI, visual stimuli were back-projected on a tangential screen using LED projectors. A trial started with the onset of a central fixation point. If the monkey gazed at the fixation point for 500 ms (Monkeys HA and ZO) or 1 s (Monkeys GA, HO, and KI), a peripheral cue appeared for 200 ms (Monkeys HA and ZO) or 100 ms (Monkeys GA, HO, and KI). The cue direction was pseudo-randomized such that two directions were randomly assigned to a sub-block of four trials. Two diagonally opponent directions were selected out of

eight candidates at a constant distance from the center of the display (usually 6.5 degrees for monkeys HA and ZO; between 5 and 30 degrees for monkeys GA, HO, and KI). When the neuron had spatial preference, one of the two positions was selected to be within the neuron's response field. The monkey had to remember the cue position during a delay period of random duration between 0.9 and 2.1 s for monkeys HA and ZO and between 1.0 and 1.5 s for monkeys GA, HO, and KI. The disappearance of the fixation point after the delay period signaled the monkey to make a saccade to the previously cued position. An auditory tone followed if the monkey made a correct saccade. If the monkey made an error, the same trial was repeated. In one block, one direction (e.g. left) was associated with immediate reward and the opponent direction (e.g. right) was not associated with immediate reward. In the next block, the direction-reward mapping was reversed (i.e., in the given example, right was now associated with immediate reward and left was not associated with immediate reward). A block consisted of at least 60 correct trials. The cue that indicated the future saccade direction was randomly presented at one of the two locations on every trial (Fig. 1b). By taking these two blocks together, we applied a  $2 \times 2$  factorial design with cue direction and reward direction.

### Recording procedures

Single-unit recordings were performed using tungsten electrodes (diameter, 0.25 mm; 1–5 M $\Omega$ ; measured at 1 kHz; Frederick Haer). The electrode was inserted into the brain through a stainless steel guide tube (diameter, 0.8 mm). Microelectrodes were advanced vertically to the cortical surface, using an oil-driven micro-manipulator (MO-95-S, Narishige, Tokyo). A grid system (holes 0.6 mm wide and 1.0 mm apart from center to center; Nakazawa, Tokyo) was used for LPFC recordings. The action potentials were amplified, filtered (500 Hz to 2 kHz) and processed by a window discriminator (MDA-4 and DDIS-1, BAK Electronics, Germantown, MD, USA). Neuronal discharges were converted into standard digital pulses and continuously monitored on an oscilloscope together with the waveform. A PC generated raster displays of neuronal activity. The times of discharge occurrences were stored on PC with a resolution of 1 ms. Eye positions were recorded at 500 Hz stored continuously in an analog file during each block of trials, using the magnetic search-coil technique (MEL-25, Enzanshi-Kogyo, Tokyo) (Robinson 1963; Judge et al. 1980). LPFC neurons were recorded from a wide area in the

LPFC. We recorded CD activity of presumed projection neurons, which show very low spontaneous activity, but not of presumed interneurons, which show irregular tonic activity (Aosaki et al. 1994).

#### Data collection and analysis

Conventional extracellular single-unit recording was conducted. We sampled neuronal activities that were related to the task. We analyzed only trials in which the monkey made a correct response. Single-unit activity was classified based on 2-way analysis of variance (CUE-dir  $\times$  RWD-dir,  $P < 0.01$ ). Activity with and only with a significant main effect of the cue direction was defined as “CUE-dir type”. Activity with and only with a significant main effect of the reward-associated direction was defined as “RWD-dir type”. In 1DR, reward availability on each trial was not directly instructed; the information of reward availability could be obtained by combining CUE-dir information with RWD-dir information on each trial. When CUE-dir and RWD-dir were both in the same direction A (denoted as RWD<sup>A</sup>–CUE<sup>A</sup>), or both in the same direction B (RWD<sup>B</sup>–CUE<sup>B</sup>), immediate reward was available. When CUE-dir and RWD-dir were in different directions (RWD<sup>B</sup>–CUE<sup>A</sup> and RWD<sup>A</sup>–CUE<sup>B</sup>), there was no immediate reward available and instead reward would be given in a later trial. Activity with a significant interaction effect ( $P < 0.01$ ) in 2-way ANOVA was further examined by post-hoc multiple comparison ( $P < 0.05$ , Scheffé test). If the test indicated a significant result in all the comparisons between immediately rewarded conditions (RWD<sup>A</sup>–CUE<sup>A</sup> and RWD<sup>B</sup>–CUE<sup>B</sup>) and the conditions without immediate reward (RWD<sup>B</sup>–CUE<sup>A</sup> and RWD<sup>A</sup>–CUE<sup>B</sup>), the activity was defined to be selective with respect to reward availability, and called “EXPECT type”. Finally, two other types of activity were called “HYBRID” type: (1) activity that showed significant main effects for both CUE-dir and RWD-dir without a significant interaction effect, and (2) activity that showed a significant interaction effect indicating that the cue-related activity changed according to reward availability. The cue direction that elicited the highest mean discharge rate was defined as the preferred cue direction. Similarly, the reward direction that elicited the highest mean discharge rate was defined as the preferred reward direction. For each neuron, activity in the pre-cue period (–500 ms to 0 ms from cue onset), the cue period (100–400 ms after cue onset), the delay period (400–900 ms after cue onset), and the saccade period (–300 ms to 0 ms from saccade onset) was submitted to the analysis to classify the activity.

To quantify the effect of CUE-dir and RWD-dir across neurons, spike counts were first normalized into  $z$  score and the following two indices were computed.

$$\begin{aligned} \text{CUE-dir index} &= |R_{\text{CUE}}^{\text{A}} - R_{\text{CUE}}^{\text{B}}|, \\ \text{RWD-dir index} &= |R_{\text{RWD}}^{\text{A}} - R_{\text{RWD}}^{\text{B}}|, \end{aligned} \quad (1)$$

where,  $R_{\text{CUE}}^{\text{A}}$  and  $R_{\text{CUE}}^{\text{B}}$  are normalized discharge rates ( $z$  scores) when cue direction is A and B, respectively, and  $R_{\text{RWD}}^{\text{A}}$  and  $R_{\text{RWD}}^{\text{B}}$  are normalized discharge rates when reward direction is A and B, respectively.

To quantify the effects of interaction between cue-directed signals and reward-directed signals in EXPECT-type and HYBRID-type neurons, we performed a multiple linear regression procedure using the following linear equation form,

$$\hat{Y} = b_0 + b_1 \times X_1 + b_2 \times X_2 + b_3 \times X_3, \quad (2)$$

where,  $Y$  is the spike count in a fixed time window (the cue period, the delay period, or the saccade period),  $X_1$  is the reward direction,  $X_2$  is the cue direction,  $X_3$  is the interaction between the reward direction and cue direction,  $b_0$  is a constant, and  $b_1$ ,  $b_2$ , and  $b_3$  are weights. We computed the coefficient of partial determination, which is the proportion of variation in firing rate explained by the interaction between CUE-dir and RWD-dir, holding CUE-dir and RWD-dir terms constant. We used the coefficient of partial determination as an indicator of non-linearity of integrating the reward direction and the cue direction information.

We carefully isolated and maintained single-unit activity throughout the experiment. Still, it is possible that the main effect of the reward-associated direction derived from a change in recording condition across blocks, due to drift of the neuron relative to the electrode. To avoid such artifacts, we checked the reproducibility by repeating the block with the same reward condition.

A part of the CD data appeared in previous papers that were focused exclusively on the pre-cue anticipatory activity (Lauwereyns et al. 2002a; Takikawa et al. 2002b). In the current paper, we analyzed the CD database in all time periods in 1 DR to compare with the LPFC activity. None of the LPFC data have been published previously.

#### Anatomical methods

Cylinder position was verified in all monkeys using magnetic resonance imaging. The monkey was anesthetized with ketamine, and scanned in a 0.3 T Magnetic

Resonance Scanner (AIRIS, Hitachi Tokyo, Fig. 1c). The recorded location has been verified histologically in three monkeys (GA, HO, and KI). At the end of some recording experiments, electric microlesions ( $5 \mu\text{A}$  for 200 s) were made. After recording was completed, the monkeys were deeply anesthetized with an overdose of pentobarbital sodium and perfused through the heart with 4% paraformaldehyde. The brain was blocked and equilibrated with 20% sucrose. Frozen sections were stained with cresyl violet. Individual recording sites were estimated on the basis of the microlesions.

## Results

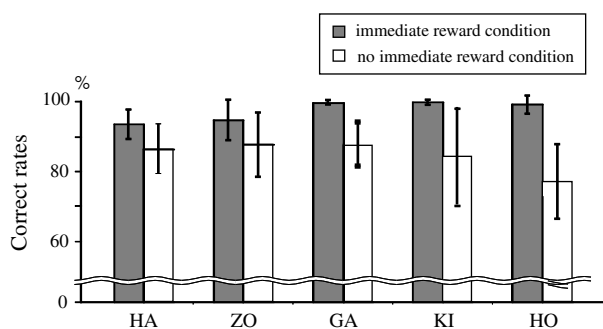
### Behavioral measures and neuronal database

In all monkeys, the rate of correct performance was higher when cue presentation and reward association were in the same direction (condition with immediate reward) than when they were opposite (condition without immediate reward) (Fig. 2;  $P < 0.01$ , paired  $t$ -test). The results indicate that the monkeys basically followed the task requirements by making saccades to the cue direction, but reward direction or availability of immediate reward certainly influenced their behavior.

We recorded single-unit activity of 189 LPFC neurons from two monkeys and 381 presumed projection neurons in the CD from five monkeys while they performed 1DR (see [Materials and methods](#) and Fig. 1c).

### Coding of cue direction versus reward direction

By using 1 DR, we could dissociate spatial tuning to the cue direction and reward direction. Figure 3a



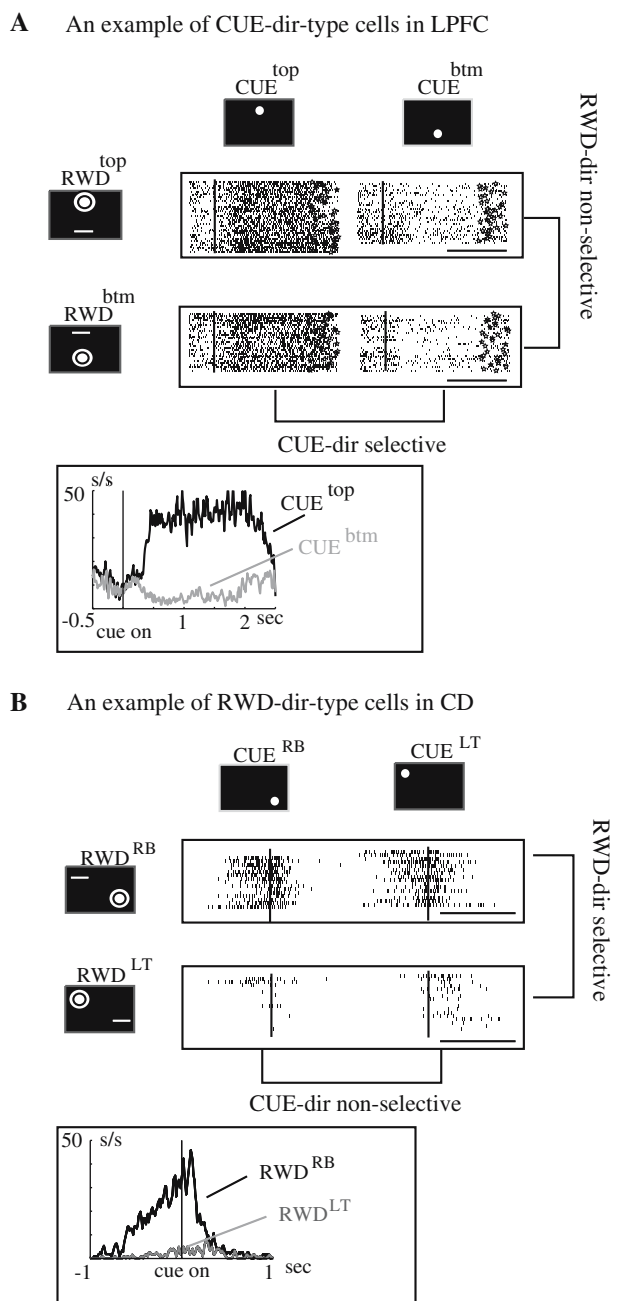
**Fig. 2** Behavioral performance. Correct performance rates of five monkeys averaged across blocks are shown for the two conditions; when the cue direction was associated with immediate reward (gray bars), correct rates were higher than when cue direction was not associated with immediate reward (white bars). Error bars SD

shows an example of activity tuned to the cue direction, which was recorded in the LPFC. When the cue was presented at the top, this prefrontal neuron showed sustained activity until a saccade was executed. When the cue was presented at the bottom, the activity during the delay period was much weaker. The activity did not change significantly by the reward direction in any period. So, this neuron had the preferred cue direction at the top and it was not sensitive to the reward direction. We call this type of activity “CUE-dir type”.

Figure 3b shows an example of activity tuned to the reward direction, which was recorded in the CD. This neuron showed vigorous pre-cue activity in the first block when reward was associated with right bottom. When we changed the reward direction to left top in the next block, the discharge rate of this neuron was high in the first couple of trials, but became much lower thereafter. We repeatedly confirmed that the pre-cue activity appeared when the reward direction was in the right hemi-field, and the pre-cue activity disappeared when the reward direction was in the left hemi-field (data not shown). We call this type of activity “RWD-dir type”, as it was tuned to the reward direction during the pre-cue period.

### Population analysis on the effects of cue direction and reward direction

To examine the effects of the cue and reward directions on the population of LPFC and CD neurons, we introduced the CUE-dir and RWD-dir indices, which represent the spatial preference to the cue direction and reward direction, respectively (see [Materials and methods](#)). We calculated these indices for all neurons that showed at least one significant effect in 2-way ANOVA (RWD-dir  $\times$  CUE-dir,  $P < 0.01$ ). Figure 4 shows that mean CUE-dir index was significantly larger in the LPFC population (blue spots) than the CD population (red spots) during the cue period (LPFC  $0.76 \pm 0.51$ , CD  $0.56 \pm 0.38$ ,  $P < 0.01$ ,  $t$ -test). RWD-dir index was significantly larger in the CD than the LPFC in all task periods (pre-cue period, LPFC  $0.25 \pm 0.15$  vs. CD  $0.45 \pm 0.24$ ,  $P < 0.001$ ; cue period, LPFC  $0.16 \pm 0.13$  vs. CD  $0.37 \pm 0.24$ ,  $P < 0.001$ ; delay period, LPFC  $0.15 \pm 0.11$  vs. CD  $0.34 \pm 0.26$ ,  $P < 0.001$ ; saccade period, LPFC  $0.14 \pm 0.09$  vs. CD  $0.31 \pm 0.23$ ,  $P < 0.001$ ,  $t$ -test). Of these neurons, those with and only with a significant main effect for RWD-dir were defined as RWD-dir type, and activities with and only with a significant main effect for CUE-dir were defined as CUE-dir type. RWD-dir type activity appeared mainly in the pre-cue period and was significantly more

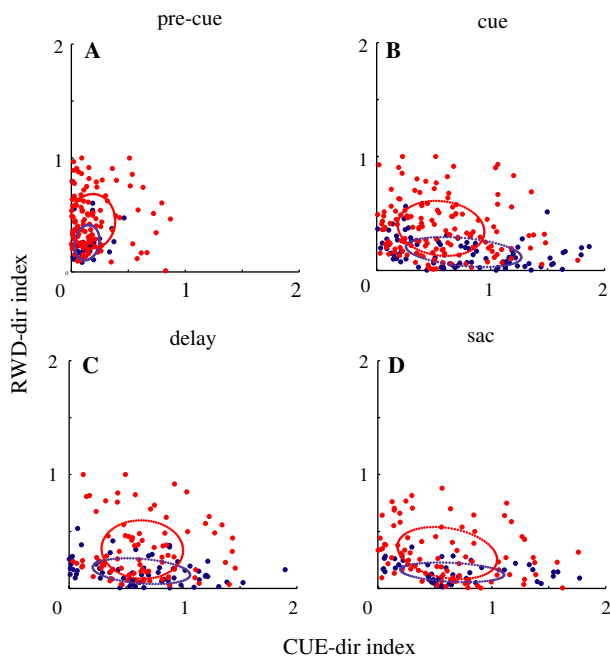


prevalent in the CD than the LPFC ( $P < 0.05$ , chi-square test; Fig. 5a, white bars, LPFC; gray bars, CD). In contrast to RWD-dir type, CUE-dir type activity appeared more commonly in the LPFC than the CD ( $P < 0.01$  during the cue period and  $P < 0.05$  during the delay period, chi-square test; Fig. 5b). Note that many of the CD neurons that had a high CUE-dir index also had a high RWD-dir index. Statistically, CD neurons with a significant main effect of CUE-dir often had a significant main effect of RWD-dir or significant interaction effect, thus not counted as CUE-dir type (classified as HYBRID type, see below).

**Fig. 3** Examples of CUE-dir type cells and RWD-dir type cells. **a** An example of CUE-dir type cells recorded from the right LPFC of monkey HA. Rastergrams are shown for each cue direction and reward direction. For each rastergram, the sequence of trials runs from top to bottom. The *schema on top* indicates the direction in which the cue was presented. The *schema on the left* indicates the direction with which immediate reward was associated (bull's eye mark) and with which no immediate reward was associated (*horizontal bar*). The top two rastergrams (panels  $RWD^{top}-CUE^{top}$  and  $RWD^{top}-CUE^{btm}$ ) are from one block of trials, and the bottom two rastergrams (panels  $RWD^{btm}-CUE^{top}$  and  $RWD^{btm}-CUE^{btm}$ ) are from the other block of trials. The cue was presented at either one of these two positions randomly in one block of trials. The vertical line in the rastergram indicates the time of cue onset. Action potentials are plotted by *black tick marks*. *Asterisks* indicate the time of saccade onset. *Horizontal bar* 1 s. The histogram at the bottom compares mean discharge rates when the cue was in the preferred cue direction (*black line*, corresponding to the activity in panels  $RWD^{top}-CUE^{top}$  and  $RWD^{btm}-CUE^{top}$ ) and when the cue was not in the preferred cue direction (*gray line*, corresponding to the activity in panels  $RWD^{top}-CUE^{btm}$  and  $RWD^{btm}-CUE^{btm}$ ). **b** An example of RWD-dir type cells recorded from the left CD of monkey GA. The same format as (a). *Horizontal bar* 1 s. The histogram at the bottom compares mean discharge rates when immediate reward was associated with the preferred reward direction (*black line*, corresponding to the activity in panels  $RWD^{RB}-CUE^{RB}$  and  $RWD^{RB}-CUE^{LT}$ ) and when immediate reward was not associated with the preferred reward direction (*gray line*, corresponding to the activity in panels  $RWD^{LT}-CUE^{RB}$  and  $RWD^{LT}-CUE^{LT}$ )

“Pure” reward expectation: a specific type of integration

We found that cue-directed and reward-directed signals were integrated in various ways in both LPFC and CD. A specific type of integration generated activity that predicts immediate reward availability, as exemplified in Fig. 6. When the cue was presented in the reward-associated direction, this caudate neuron showed sustained activity during the delay period (panels  $RWD^{top}-CUE^{top}$  and  $RWD^{btm}-CUE^{btm}$ ). When the cue was presented in the direction that was not associated with reward, the activity was much lower (panels  $RWD^{top}-CUE^{btm}$  and  $RWD^{btm}-CUE^{top}$ ). We call this type of activity “EXPECT type”. EXPECT type could predict immediate reward outcome on a trial-by-trial basis, as opposed to the RWD-dir type as it remained fixed throughout an entire block. Differential activity of EXPECT type was either higher in the rewarded trials (3, 8, and 8 cells in LPFC and 48, 57, and 54 cells in CD during the cue, delay, and saccade periods, respectively) or higher in the unrewarded trials (6, 9, and 8 cells in the LPFC and 15, 32, and 20 cells in the CD during the cue, delay, and saccade periods, respectively). EXPECT type was more common in the CD (cue period: 63 cells [16.5%], delay period: 89 cells [23.4%], saccade period:



**Fig. 4** The effects of the cue direction and the reward direction on the LPFC and CD. The scattergrams compare the effect of the cue direction, as measured by CUE-dir index, and the effect of the reward direction, as measured by RWD-dir index in each task period (see [Materials and methods](#)). Each point corresponds to activity of one neuron (blue: LPFC, red: CD). Dotted lines indicate unit standard deviation contour of the population of LPFC (blue) and CD (red) neurons. Note that in the pre-cue period the cue was not presented and its direction was not predictable, so the CUE-dir index was not meaningful in this period

74 cells [19.4%]) than in the LPFC (cue period: 9 cells [4.8%], delay period: 17 cells [9.0%], saccade period: 16 cells [8.5%]) in all periods after cue presentation (Fig. 5c;  $P < 0.01$ , chi-square test).

#### Mixed representation of the cue-directed and reward-directed signals

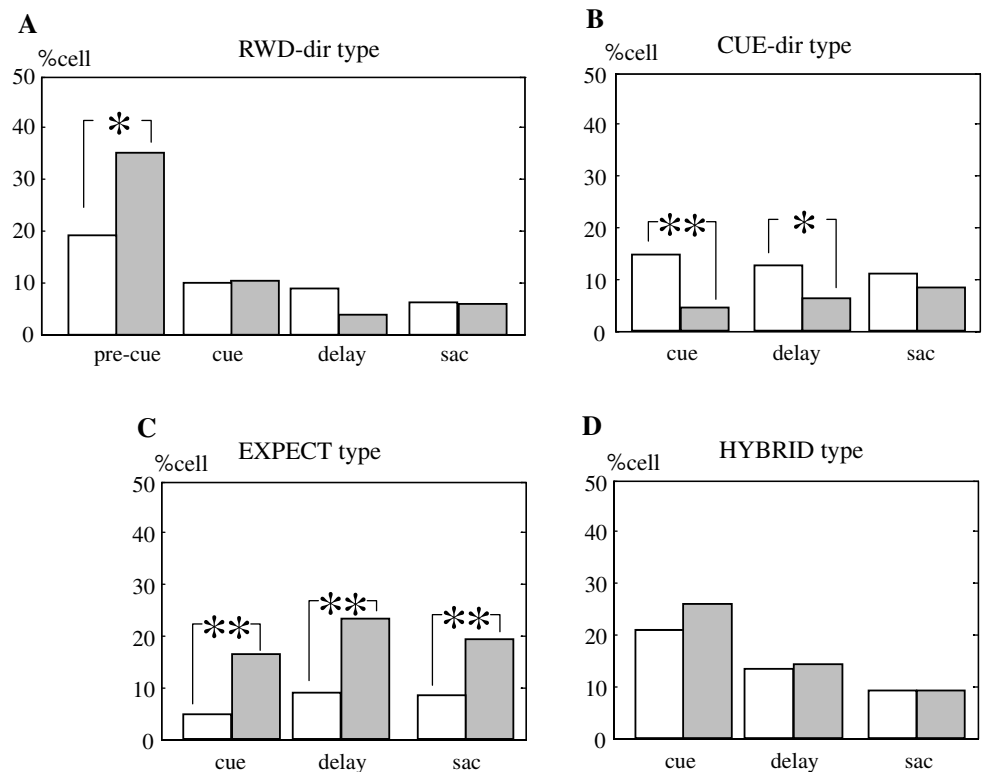
We found other forms of integration. Figure 7a illustrates such an example observed in the LPFC. During the pre-cue and cue periods, the activity of this neuron was higher when reward was associated with left (panels  $RWD^{\text{left}}\text{-CUE}^{\text{left}}$  and  $RWD^{\text{left}}\text{-CUE}^{\text{right}}$ ) than when reward was associated with right (panels  $RWD^{\text{right}}\text{-CUE}^{\text{left}}$  and  $RWD^{\text{right}}\text{-CUE}^{\text{right}}$ ). In addition to the effect of the reward direction, there was an effect of the cue direction: cue presentation at the left strongly activated this neuron during the cue period and the delay period (panels  $RWD^{\text{left}}\text{-CUE}^{\text{left}}$  and  $RWD^{\text{right}}\text{-CUE}^{\text{left}}$ ); when the cue was presented at the right, the activity during the cue period was strongly suppressed, followed by weak activity during the delay

period (panels  $RWD^{\text{left}}\text{-CUE}^{\text{right}}$  and  $RWD^{\text{right}}\text{-CUE}^{\text{right}}$ ). So, the effects of the cue direction and the reward direction were independent: a reward association with the preferred direction built a higher baseline activity, and cue presentation in the preferred direction caused an additional increase of activity. There was no significant interaction effect between the cue direction and the reward direction during the cue period ( $P > 0.05$ , 2-way ANOVA [RWD-dir  $\times$  CUE-dir]).

An example observed in the CD is illustrated in Fig. 7b. When reward association and cue presentation were both at right-bottom, the neuron showed sustained activity during the delay period (panel  $RWD^{\text{RB}}\text{-CUE}^{\text{RB}}$ ). In other conditions, the neuron was not activated strongly (panels  $RWD^{\text{LT}}\text{-CUE}^{\text{LT}}$ ,  $RWD^{\text{LT}}\text{-CUE}^{\text{RB}}$ , and  $RWD^{\text{RB}}\text{-CUE}^{\text{LT}}$ ). In short, cue presentation at the preferred direction activated this neuron only when this direction was associated with immediate reward.

Activities exemplified in Fig. 7a and b changed depending on both cue direction and reward direction. We call this type of activity “HYBRID type” as it represented the information of both cue and reward directions. We found HYBRID-type activity commonly in both LPFC and CD (Fig. 5d). Many HYBRID-type cells had a preferred cue direction and a preferred reward direction in the same direction during the cue period (LPFC:  $n = 25/39$  [64.1%], CD:  $n = 58/99$  [58.6%]), delay period (LPFC:  $n = 18/25$  [72.0%], CD:  $n = 34/53$  [64.2%]), and saccade period (LPFC:  $n = 12/18$  [66.7%], CD  $n = 22/35$  [62.9%]) (number of cells with the same preferred cue direction and preferred reward direction/number of all HYBRID-type cells [ratio]). For quantitative evaluation of HYBRID-type activity in each trial condition, we plotted population histograms of HYBRID-type neurons, which had the preferred cue direction and the preferred reward direction in the same direction (LPFC, Fig. 8a; CD, Fig. 8b). In a given trial, immediate reward was either associated with the preferred direction ( $RWD^{\text{Pref}}$ ) or its opposite direction ( $RWD^{\text{Anti}}$ ) and the cue was either presented in the preferred direction ( $CUE^{\text{Pref}}$ ) or its opposite direction ( $CUE^{\text{Anti}}$ ). During the pre-cue period, an association of immediate reward with the neuron’s preferred direction boosted the discharge rate of HYBRID-type cells in both LPFC and CD ( $RWD^{\text{Pref}}$  condition plotted by red line versus  $RWD^{\text{Anti}}$  condition plotted by black line). In the LPFC, cue presentation in the preferred direction caused an additional increase in the discharge rate whether or not reward was associated with the preferred direction ( $CUE^{\text{Pref}}$  condition plotted by thick line versus  $CUE^{\text{Anti}}$  condition plotted by thin line). In

**Fig. 5** Frequency histograms of four types of activity in the LPFC and CD. The figure shows the proportion of each type of activity to the whole database (CD,  $n = 381$ ; LPFC,  $n = 189$ ; see [Materials and methods](#) for classification criteria). \* $P < 0.05$ , \*\* $P < 0.01$ , by chi-square test between LPFC (white bars) and CD (gray bars) for frequency of each type in each period



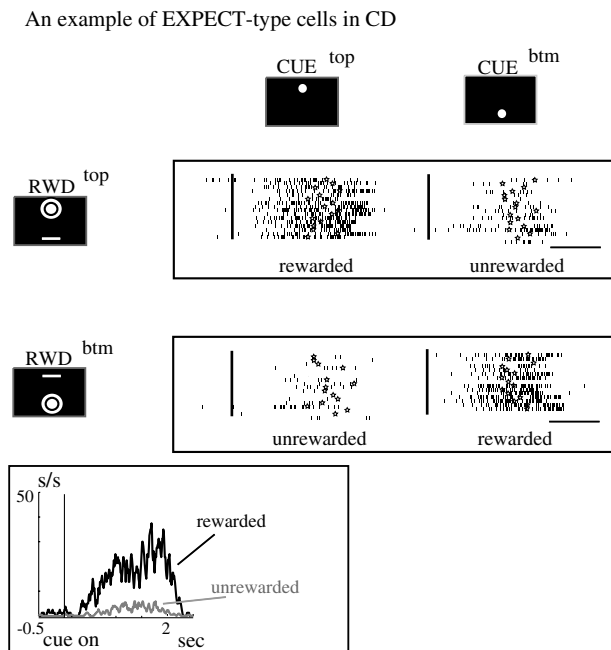
the CD, in contrast, cue presentation in the preferred direction raised the discharge rate only when immediate reward was associated with the preferred direction; cue presentation in the preferred direction hardly affected the discharge rate when reward was not associated with the preferred direction, as if HYBRID-type cells in the CD could not *see* the cue when immediate reward was not expected (RWD<sup>Anti</sup>-CUE<sup>Pref</sup> condition plotted in thick black line).

#### Different mode of integration in the LPFC and the CD

Example neurons of EXPECT type (Fig. 6) and HYBRID type (Fig. 7) demonstrated that separate elements of information, that is, cue direction and reward direction, were integrated in different ways. We found that the mode of integration tended to be different between the LPFC and the CD. Integration by the prefrontal HYBRID type, as exemplified in Fig. 7a, tended to be linear (the activity is characterized by a sum of CUE-dir selectivity and RWD-dir selectivity). On the other hand, integration by the caudate HYBRID type cells, as exemplified in Fig. 7b, and EXPECT-type cells, which were commonly found in the CD, tended to be non-linear (the activity is not characterized by simple addition of CUE-dir selectivity and

RWD-dir selectivity, but must be due to interaction). The difference was statistically supported by the 2-way ANOVA analysis: Neurons that showed a significant interaction effect between CUE-dir and RWD-dir were more common in the CD (cue period, 148 cells [38.9%]; delay period, 138 cells [36.2%]; saccade period, 107 cells [28.1%]) than LPFC (cue period, 38 cells [20.5%]; delay period, 36 cells [19.1%]; saccade period, 30 cells [15.9%]) in all three periods ( $P < 0.01$ , chi square test). To further quantify linearity/non-linearity in the integration process, we fitted the data into a linear regression model and measured the contribution of the interaction between the reward direction and the cue direction by the coefficient of partial determination (see [Materials and methods](#)). Figure 9f shows that the caudate EXPECT/HYBRID-type activity is explained better by the interaction term in the regression model than the prefrontal EXPECT/HYBRID-type cells as indicated by a significantly higher coefficient of partial determination during the cue period (CD: 0.16 vs. LPFC: 0.12,  $P < 0.05$ ), during the delay period (CD: 0.20 vs. LPFC: 0.13,  $P < 0.001$ ), and during the saccade period (CD: 0.17 vs. LPFC: 0.09,  $P < 0.001$ ) by 1-tailed  $t$ -test. The same tendency was observed when the population was limited to the HYBRID type: coefficient of partial determination was 0.23 in the CD versus 0.11 in the LPFC during cue period (n.s.), 0.17 in





**Fig. 6** An example of EXPECT-type cells recorded from the right CD of monkey KI. Rastergrams are in the same format as in Fig. 3. *Vertical line*: cue onset. *Horizontal bar*: 1 s. Cue presentation in the reward-associated direction indicated presence of immediate reward; in this case, the neuron showed sustained activity (panels RWD<sup>top</sup>-CUE<sup>top</sup> and RWD<sup>btm</sup>-CUE<sup>btm</sup>). Cue presentation in the direction not associated with immediate reward indicated absence of immediate reward; in this case, the activity of the neuron was low (panels RWD<sup>top</sup>-CUE<sup>btm</sup> and RWD<sup>btm</sup>-CUE<sup>top</sup>). The histogram compares mean discharge rates in the immediate reward condition (*black line* corresponding to the activity in panels RWD<sup>top</sup>-CUE<sup>top</sup> and RWD<sup>btm</sup>-CUE<sup>btm</sup>) and in the condition without immediate reward (*gray line* corresponding to the activity in panels RWD<sup>top</sup>-CUE<sup>btm</sup> and RWD<sup>btm</sup>-CUE<sup>top</sup>)

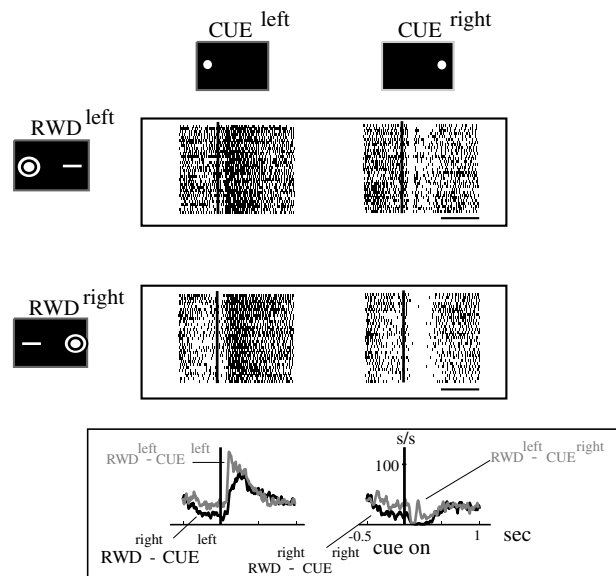
**Fig. 7** Examples of HYBRID-type cells. **a** An example of HYBRID-type activity recorded from the right LPFC of monkey HA. Rastergrams are in the same format as in Fig. 3. Cue presentation at the left increased activity during the cue and delay periods (RWD<sup>left</sup>-CUE<sup>left</sup> and RWD<sup>right</sup>-CUE<sup>left</sup>). In addition to this effect of the cue direction, the activity of this neuron changed by the reward direction. When immediate reward was associated with left in block RWD<sup>left</sup>, the activity during the pre-cue period and cue period was higher than the activity when immediate reward was associated with right in block RWD<sup>right</sup>. *Vertical line* cue onset. *Horizontal bar* 500 ms. Histograms are shown for each cue direction separately (*left* cue at left, *right* cue at right). *Gray lines* and *black lines* indicate mean discharge rates when immediate reward was associated with left and right, respectively. **b** An example of HYBRID-type activity recorded from the left CD of monkey GA. Rastergrams are in the same format as in Fig. 3. *Vertical line* cue onset. *Horizontal bar* 500 ms. This neuron showed sustained activity during the delay period when the cue was presented at right-bottom when that was also the reward direction (panel RWD<sup>RB</sup>-CUE<sup>RB</sup>). In all other conditions, the neuron was not activated strongly (panels RWD<sup>LT</sup>-CUE<sup>LT</sup>, RWD<sup>LT</sup>-CUE<sup>RB</sup>, and RWD<sup>RB</sup>-CUE<sup>LT</sup>). Histograms are shown for each cue direction and each reward direction separately

the CD versus 0.11 in the LPFC during the delay period ( $P < 0.05$ ), and 0.15 in the CD versus 0.08 in the LPFC during the saccade period ( $P < 0.05$ ).

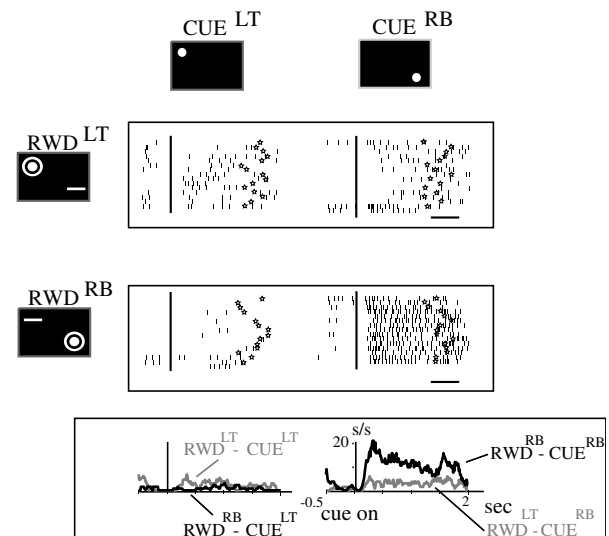
Anatomical locations

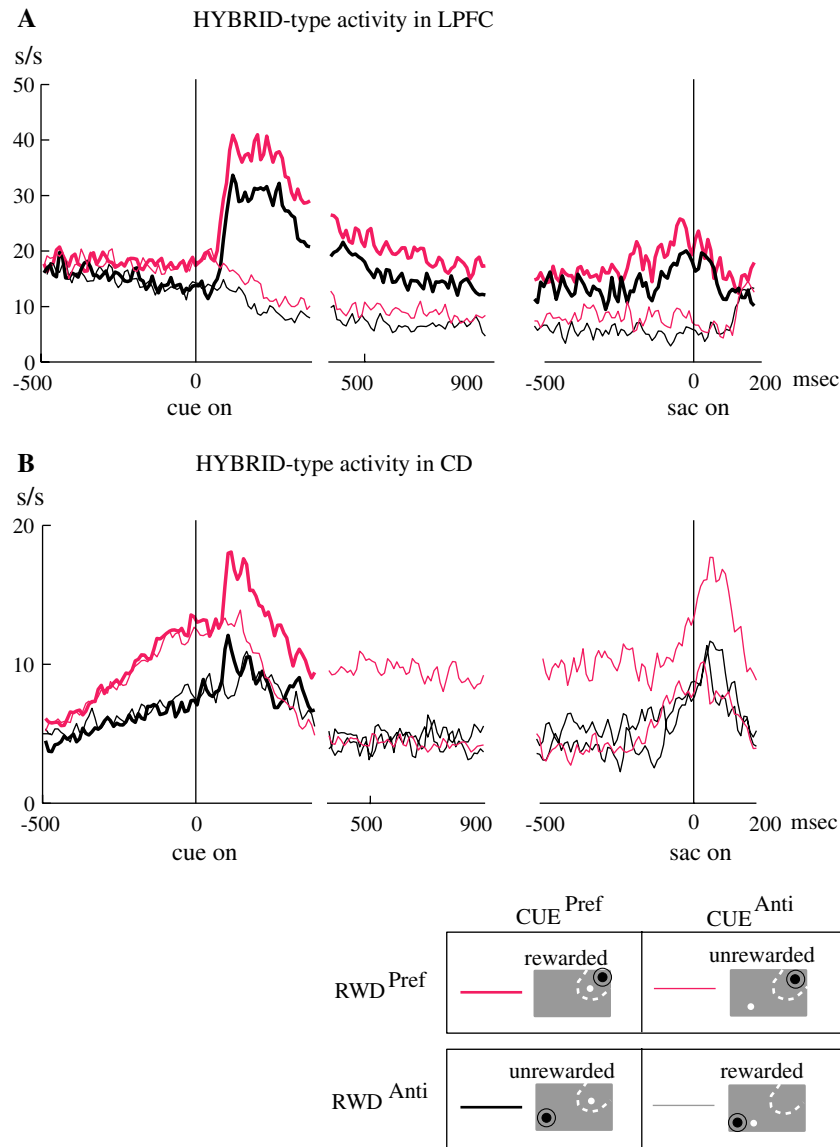
The distribution of each type of neuron from the LPFC is shown in Fig. 10. Neurons recorded from two monkeys (HA and ZO) were superimposed so that the brain landmarks (principal sulcus and arcuate sulcus) overlapped best. The types of neuron were widely distributed, showing no anatomical segregation within the LPFC.

**A** An example of HYBRID-type cells in LPFC



**B** An example of HYBRID-type cells in CD





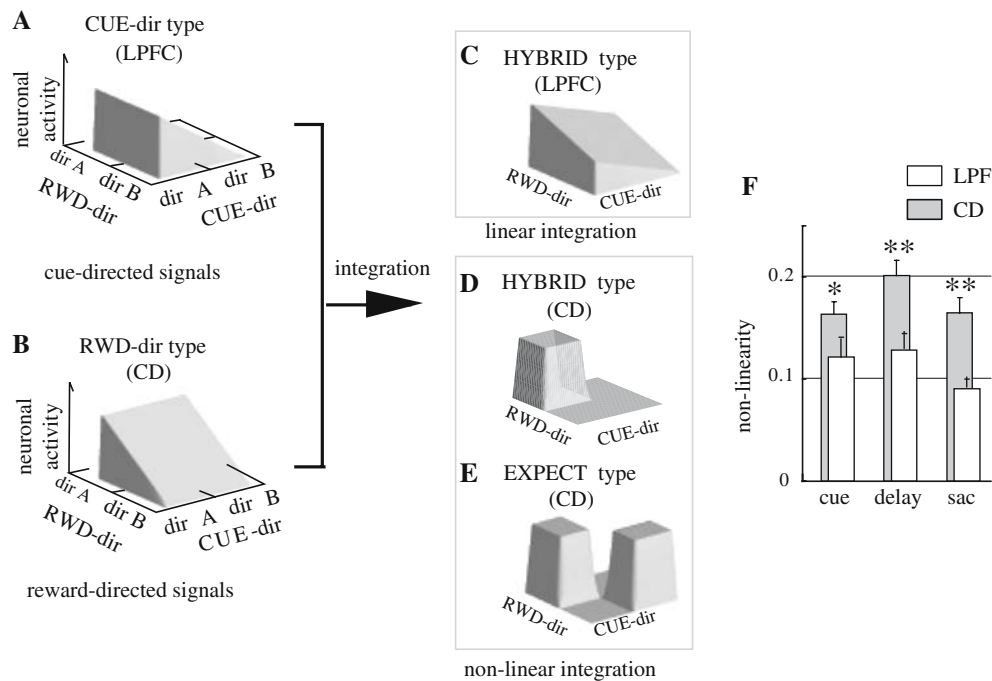
**Fig. 8** Population histograms of HYBRID-type cells. Averaged discharge rates of HYBRID-type cells, which had a preferred direction for cue and reward in the same direction, are shown for the LPFC population (**a**) and CD population (**b**). A *white dashed line* in an inset schema indicates the preferred direction. The cue was presented either in the preferred direction (CUE<sup>Pref</sup>, white circle inside the *white dashed line* in the schema; thick line in the histograms) or anti-preferred direction (CUE<sup>Anti</sup>, white circle out of the *white dashed line* in the schema; thin line in the histograms). Immediate reward was associated with the

preferred direction (RWD<sup>Pref</sup>, bull's eye mark inside the *white dashed line* in the schema; *red line* in the histograms) or non-preferred direction (RWD<sup>Anti</sup>, bull's eye mark out of the *white dashed line*; *black line* in the histograms). Immediate reward was available in the CUE<sup>Pref</sup>-RWD<sup>Pref</sup> condition and the CUE<sup>Anti</sup>-RWD<sup>Anti</sup> condition, whereas immediate reward was not available in the CUE<sup>Pref</sup>-RWD<sup>Anti</sup> condition and the CUE<sup>Anti</sup>-RWD<sup>Pref</sup> condition. The *left vertical line* indicates the time of cue onset and the *right vertical line* indicates the time of saccade onset

## Discussion

We studied single-neuron activity in the LPFC and CD using 1DR, a variant of the conventional memory-guided saccade task. In this task, we presented a cue in one direction as a future saccade target, and activity in the LPFC was commonly tuned to the cue direction.

We associated one direction with reward, and activity in the CD was commonly tuned to the reward-associated direction. Cue-directed and reward-directed signals were integrated in both LPFC and CD, but in different forms: in general, signals of cue and reward directions were added linearly in the LPFC, and non-linearly in the CD. We discuss two hypotheses that



**Fig. 9** Linear and non-linear integration of the cue-directed signals and the reward-directed signals. **a** A schema illustrating CUE-dir type activity, commonly found in the LPFC. The activity changes depending on CUE-dir and is independent of RWD-dir. **b** A schema illustrating RWD-dir type activity, commonly found in the CD. The activity changes depending on RWD-dir and is independent of CUE-dir. **c–e** Various patterns of post-integration activity, which changes depending on both

CUE-dir and RWD-dir. The area in the brain in *parenthesis* indicates in which brain area each type of activity was found most commonly. **f** Non-linearity of integration measured by the coefficient of partial determination in a linear regression model (see [Materials and methods](#)). Error bar SE. Significant difference of the coefficient of partial determination between LPFC and CD by one-tailed *t*-test is shown by \* ( $P < 0.05$ ) and \*\* ( $P < 0.01$ )

explain distinct processes between the LPFC and the CD that might guide behavior based on different policies.

#### Functional interpretations of cue-directed and reward-directed signals

As a variant of working memory task, 1DR required the monkeys to maintain the cue direction during the delay period. Tuning of the LPFC neurons to the direction of instruction cue is consistent with the well-established concept that the LPFC is involved in spatial working memory process (Fuster and Alexander 1971; Kubota and Niki 1971; Funahashi et al. 1989). On the other hand, to predict immediate reward outcome, the monkeys have to learn and maintain the direction-reward mapping in every block of trials. Reward-directed tuning commonly found in the CD might reflect this process.

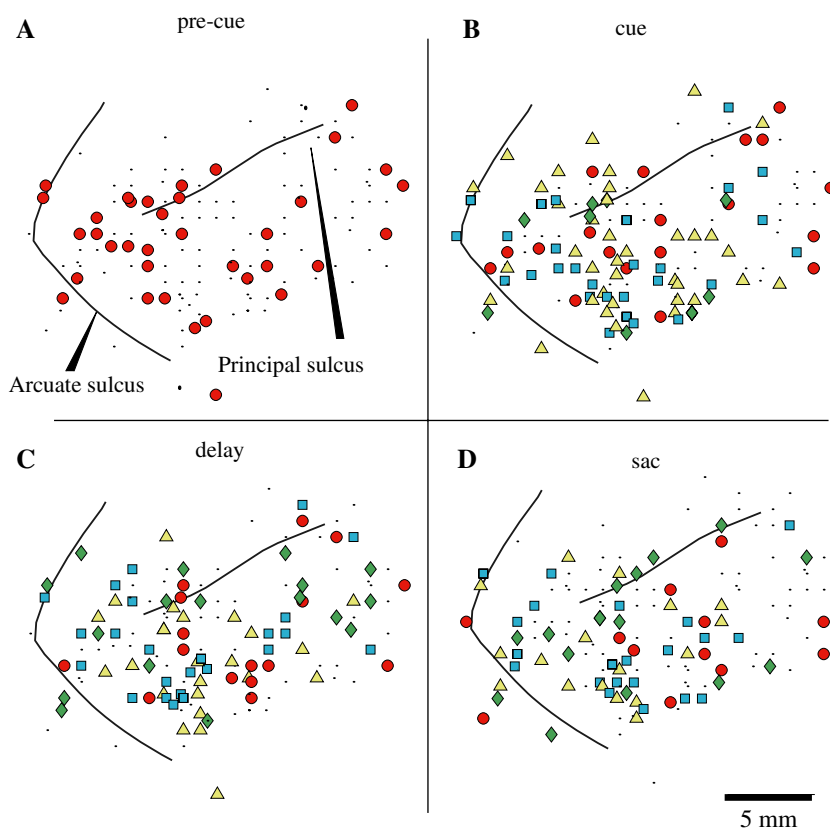
As we indicated the cue direction by a visual cue and reward direction without any explicit cue, it is possible that the CD processed internally generated information and the LPFC processed externally instructed

information ('internal vs. external' hypothesis). Cue-directed and reward-directed activities in the CD may correspond to previously reported striatal activity during externally- and internally-triggered movements, respectively (Schultz and Romo 1992; Romo et al. 1992). Our results emphasize the role of the CD in processing internally-triggered movements. Reward-directed signals generally built up during the pre-cue period and disappeared after the cue presentation, perhaps because the external trigger suppressed the internally-triggered signals.

In contrast, the LPFC neurons showed less activity tuned to the reward direction during the pre-cue period and more activity tuned to the external cue direction. Cue-directed signals may reflect visual input, spatial memory, or saccade preparation, triggered by a visual stimulus, but it was not influenced by reward-associated direction stored internally.

The hypothesis is also consistent with the clinical observation of "paradoxical movement": Parkinsonian patients, who have severe loss of dopamine (DA) neurons and subsequent striatum dysfunction, show a stereotypical motor problem of gait freezing in initiating

**Fig. 10** Anatomical distribution of each type of neurons within the LPFC. Two right hemispheres from two monkeys were superimposed. Each type of neurons is marked separately in each period. RWD-dir type cell, *red circle*; CUE-dir type cell, *blue square*; HYBRID-type cell, *yellow triangle*; EXPECT-type cell, *green diamond*



a step or in attempting to change direction while walking along. Interestingly, such motor problems are often overcome by external stimuli, such as guiding lines on the floor oriented transversely to the direction of walk (Denny-Brown 1968). The symptom might be explained by a dysfunction of the self-generated orienting system in the basal ganglia, with an intact cortical orienting system driven by external stimuli.

#### Pure reward prediction: adaptive integration of cue-directed and reward-directed signals

In 1DR, the cue direction changed trial-by-trial and the reward direction changed block-by-block. To predict immediate reward, the neural system had to adaptively keep track of the changes in the cue-reward mapping by way of non-linear integration of cue-directed and reward-directed signals (Figs. 6, 9d). Predominant expression of EXPECT type in the CD suggests that the CD plays a crucial role in the integration process. Although it remains to be elucidated where and how the integration is realized, a few studies suggested that it is realized on synapses between the cortex and the striatum: (1) anatomically, excitatory corticostriatal glutamatergic projections and dopaminergic nigrostriatal fibers converge onto dendritic spines of striatum

medium spiny neurons (Smith et al. 1994); (2) physiologically, corticostriatal synapses are potentiated by DA release (Reynolds et al. 2001; Centonze et al. 2001); (3) by using a computational model, Gruber et al. (2003) replicated non-linear profiles of caudate activity during 1DR based on neuromodulatory effects of DA inducing bistability of striatum medium spiny neurons through D1 receptor activation.

#### Neural correlates of “motivational conflict”

In 1DR, there is a potential motivational conflict between cue and reward directions. The monkey’s behavioral performance, which was more efficient when the two kinds of directions matched than mismatched, might have come as a result of motivational conflict (Watanabe et al. 2003). This idea is supported by our neurophysiological findings as we found the LPFC and the CD had potentially conflicting spatial tuning.

In human functional imaging studies using conventional conflict paradigms, such as the Stroop color-naming task, the anterior cingulate cortex (ACC) showed greater activation in conflict trials than in non-conflict trials, and its role in “conflict monitoring” has been suggested (Pardo et al. 1990; Carter et al. 2000).

We also found neurons preferentially activated in conflict trials in 1DR (EXPECT-type neurons with activity higher in the unrewarded trials). It is possible that these neurons are involved in detection of motivational conflict, which is important in 1DR as conflict is directly associated with omission of immediate reward.

Caudate HYBRID-type cells might also be linked to motivational conflict; assuming that the excitation of a neuron contributes to the guidance of a saccade to the neuron's preferred direction, caudate HYBRID-type cells could not guide an action in case of conflict (cf. low activity of caudate HYBRID-type cells in the  $RWD^{LT}-CUE^{RB}$  condition in Fig. 7b and in the  $RWD^{Anti}-CUE^{Pref}$  condition in Fig. 8b). Cue-directed tuning of prefrontal HYBRID-type cells also deteriorated in case of conflict, but much less than that of caudate HYBRID-type cells ( $RWD^{Anti}-CUE^{Pref}$  condition in Fig. 8a). Behavior could be guided to the instructed direction best by CUE-dir type cells, which were commonly found in the LPFC, as they did not change spatial tuning by conflict. Our data suggest that in case of conflict (without immediate reward) correct behavior may depend on the LPFC and incorrect behavior may depend on the CD.

#### Functional differences: short-term versus long-term hypothesis

The functional differences between the CD and the LPFC can also be understood in the context of reinforcement learning. The idea of behavioral optimization based on reward has been proposed in the form of reinforcement learning theory (Barto et al. 1983; Watkins and Dayan 1992). Most of the reinforcement learning algorithms are based on value functions that estimate how good it is to perform a given action in a given state. "Goodness" to perform a given action would be different depending on the extent to which future rewards are taken into account. This is particularly the case in 1DR. To make a correct action in a trial without immediate reward was important for the monkey if future rewards are taken into account. First, a correct action in a trial without immediate reward will increase the probability of reward in the next trial. This is because, in 1DR, trials are pseudo-randomized such that cue directions are randomly assigned to a sub-block of four trials (see Nakahara et al. 2004 for a detailed discussion of the implications of this procedure in terms of reward probability). Second, if the monkey makes an erroneous action in a trial without immediate reward, the probability of reward in the next trial is zero. This is because trials without immediate

reward were presented repeatedly until a correct response was made (error correction method).

Let us now consider the activity of CD and LPFC neurons in this context. HYBRID-type activity in the CD appears to show directional tuning only when immediate reward is available. EXPECT-type activity, which was much more common in the CD, was preferentially activated in the condition with immediate reward. From the viewpoint of reinforcement learning, these types of activity would be explained as a result of reinforcement by immediate reward. In contrast, HYBRID-type activity in the LPFC maintained directional tuning even when reward is not immediately available. CUE-dir type activity, which was much more common in the LPFC, maintained directional tuning even more strictly independent of immediate reward outcome. These LPFC neurons could guide a saccade to the cue direction even when it was not associated with immediate reward, which could ensure distant future rewards. These results may suggest that the CD and the LPFC are involved in reinforcement learning processes with short and long time scales of reward outcomes, respectively ('short-term vs. long-term' hypothesis). This hypothesis is in agreement with recent fMRI studies that revealed different brain structures involved in reward prediction at different time scales (McClure et al. 2004; Tanaka et al. 2004). For example, McClure et al. (2004) showed that the limbic system associated with DA system is preferentially activated by decisions involving immediately available rewards and LPFC is engaged uniformly by intertemporal choices irrespective of delay.

#### Conclusion

Our experiments using a memory-guided saccade task with an asymmetric reward schedule revealed overlapping and different functions of the LPFC and the CD in the control of voluntary behavior. The difference between prefrontal activity, basically tuned to the instructed direction, and caudate activity, basically related to reward association, can be interpreted in two ways: (1) the difference may be due to whether behavior is triggered externally (LPFC) or internally (CD); (2) the difference may be due to whether reward outcome is in the distant future (LPFC) or in the near future (CD). Single-unit activity showing a mixture of the two functions was also commonly found in both brain structures, suggesting interactive processes in the cortico-basal-ganglia network, which may possibly underlie a motivational conflict in behavior.

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