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Neurons in the macaque orbitofrontal cortex code relative preference of both rewarding and aversive outcomes

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Abstract

Many studies have shown that the orbitofrontal cortex (OFC) is involved in the processing of emotional information. However, although some lines of study showed that the OFC is also involved in negative emotions, few electrophysiological studies have focused on the characteristics of OFC neuronal responses to aversive information at the individual neuron level. On the other hand, a previous study has shown that many OFC neurons code relative preference of available rewards. In this study, we aimed to elucidate how reward information and aversive information are coded in the OFC at the individual neuron level. To achieve this aim, we introduced the electrical stimulus (ES) as an aversive stimulus, and compared the neuronal responses to the ES-predicting stimulus with those to reward-predicting stimuli. We found that many OFC neurons showed responses to both the ES-predicting stimulus and the reward-predicting stimulus, and they code relative preference of not only the reward outcome but also the aversive outcome. This result suggests that the same group of OFC neurons code both reward and aversive information in the form of relative preference.

Keywords: Orbitofrontal cortex; Monkey; Aversive outcome; Relative preference; Reward; Electrical stimulus

1. Introduction

A previous study has shown that a group of orbitofrontal cortex (OFC) neurons code relative preference of available rewards (Tremblay and Schultz, 1999). It suggests that the OFC compares the values of available rewards. This is a very important function to perform in making an adaptive decision. However, it remains unclear that the coding style of relative preference in the OFC could be extended to aversive outcomes. In our daily life we compare various types of outcomes, not only rewards, to make a decision. We sometimes compare rewarding outcomes with aversive outcomes at the same time. For example, if we are on a diet we may think over whether or not to eat a sweet cake. Eating the cake is rewarding but at the same time putting on fat is aversive. The brain must compare the various types of outcomes, rewarding and/or aversive, to make an adaptive decision.

Heretofore, many studies have shown that the OFC is involved in the processing of reward information (Tremblay and Schultz, 1999, 2000a,b; Schultz et al., 2000; Roesch and Olson, 2004, 2005; Padoa-Schioppa and Assad, 2006). Although many electrophysiological studies have examined the response properties of OFC neurons to rewards, only a few studies have focused on the response properties of OFC neurons to aversive stimuli (Thorpe et al., 1983; Roesch and Olson, 2004). This is in spite of the importance of negative emotions, which are accompanied by aversive events. Negative emotions are as important as positive emotions to the formation of adaptive behavior in the natural environment, especially personal safety and security behaviors. In order to survive in the natural environment, animals must predict the possibility that a danger occurs and select adaptive behavior to avoid it.

Some lines of evidence have indicated that the OFC is also concerned with aversive information. Firstly, some neuroimaging studies have showed that the OFC is activated by aversive stimuli (Elliott et al., 2000; Frey et al., 2000; O'Doherty et al., 2001; Ursu and Carter, 2005). Secondly, patients with damage to the OFC are unable to use aversive information to modify their behavior (Stuss et al., 1983; Freedman et al., 1998).

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Finally, monkeys with damage to the OFC respond abnormally to aversive objects (Butter and McDonald, 1969b; Ursin et al., 1969; Butter et al., 1970; Butter and Snyder, 1972; Izquierdo and Murray, 2004). These observations suggest that the OFC is processing not only reward information but also aversive information.

In this study, we focused on how the OFC codes aversive information as well as reward information at the individual neuron level. One hypothesis is that reward information and aversive information are coded separately in different groups of neurons in the OFC. Another hypothesis is that they are integrated in the same group of neurons in the way that relative preference is represented. To compare the neuronal response to aversive stimuli with those to rewarding stimuli, we set two stimulus-outcome conditions; one included rewarding and aversive outcomes, and the other included only rewarding outcomes. We examined the response of OFC neurons under these stimulus-outcome conditions in separate experimental blocks, and compared the response properties to aversive-predicting cue stimulus with those to reward-predicting cue stimulus.

2. Materials and methods

2.1. Subjects

Two macaque monkeys (*Macaca mulatta*, monkey P: 5.8 kg, monkey D: 8.9 kg) were used in this study. The experiment was performed in a dark and sound-attenuated room, with the monkey seated in a primate chair facing a 17 in. CRT monitor (PC-KM173: NEC, Tokyo, Japan). During the training and recording sessions, the animals were deprived of water to elevate their motivation for liquid reward. All experiments were carried out in accordance with the "Guide for the Care and Use of the Laboratory Primates" (1986, 1996, 2001) of the Primate Research Institute of Kyoto University and "Guidelines for Care and Use of Laboratory Animals" (1985) of the National Institutes of Health.

2.2. Behavioral task

The monkeys performed a delayed color matching task, in which they learned to memorize the color of a cue stimulus and to choose the same color target after a delay. We used four colored squares as cue and target stimuli (red, yellow, blue, and green) and introduced three trial types; juice trial, water trial, and electrical stimulus avoidance (ESA) trial (Fig. 1(b)). In the juice trial and water trial, grape juice or water was given for a correct response, respectively, and an error response led to no reward. In the ESA trials, electrical stimulus (ES) was applied for an error response and no reward was given for a correct response. In each block, we used two combinations of a color and an outcome. Two outcome types used in one block were either juice and water, or water and ESA. We will call the block with outcomes of juice and water the "Juice–Water condition" and the block with outcomes of water and ESA the "Water–ESA condition". Furthermore, both the Juice–Water condition and Water–ESA condition had two blocks according to the combinations of cue colors and outcomes (a standard block and a reversal block). Therefore, there were four stimulus-outcome combinations in all. In the standard block of the Juice–Water condition, we gave juice as the reward for correct trials with the green cue, and gave water as the reward for correct trials with the blue cue. In the reversal block of the Juice–Water condition, we gave water for correct trials with the green cue and juice for correct trials with the blue cue. In the standard block of the Water–ESA condition, we gave water as the reward for correct trials with the yellow cue and gave ES for error trials with the red cue. In the reversal block of the Water–ESA condition, we gave ES for error trials with the yellow cue and water for correct trials with the red cue. The combinations of cue colors and outcomes are summarized in Fig. 1(b).

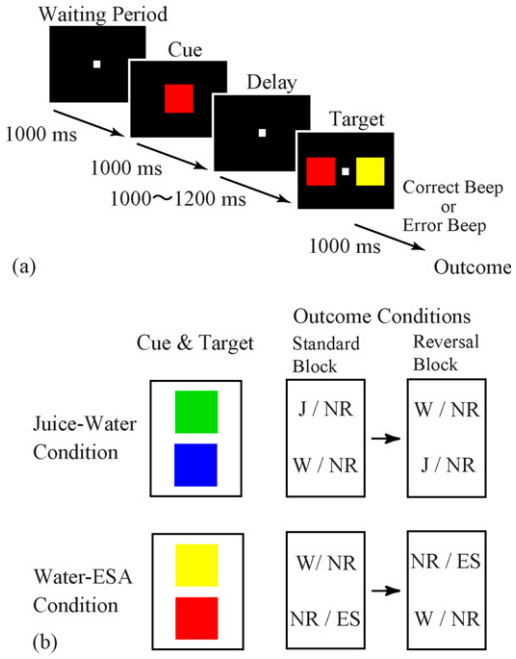

Fig. 1. (a) Temporal sequence of the delayed matching to sample task used in this experiment. See Section 2 for details. (b) The color and outcome conditions. The Juice–Water condition consists of green and blue colors, and the Water–ESA condition consists of yellow and red colors. The outcome that each cue color predicted is shown in the two columns on the right side. The left column shows the outcome types under the standard block, and the right column shows those under the reversal block (J: juice, W: water, NR: no reward, ES: electrical stimulus. The outcome for a correct response is left side, and that for an error response is right side).

Fig. 1(a) shows the temporal sequence of the task. The primate chair had three levers on the front panel, one hold lever at the center and two response levers on the left and right sides. Each trial started with the monkey pressing the hold lever. After a 1.0 s waiting period, one of the two colored squares was presented at the center of the screen as a cue stimulus for 1.0 s. After the offset of the cue stimulus a random delay period (1.0–1.2 s) intervened. Then after the delay, a target (the same colored square as cue stimulus) was presented on the left or right side, with a distractor (a colored square) presented on the opposite side. The color of the distractor was the other color used under the same condition. When the target and distractor were presented, the monkey had to release the hold lever within 1.0 s and press the response lever of the side on which the target was presented within another 1.0 s. As soon as the monkey pressed the response lever all stimuli disappeared from the screen. We presented an auditory cue after the lever touch, a pip sound for a correct response or a beep for an error response. Under the Juice–Water condition a correct response led to grape juice or water delivery, and under the Water–ESA condition a correct response led to water delivery or no reward. In the ESA trial under the Water–ESA condition an error response led to ES on the calf of the left hind limb. Error responses included an early hold lever release before the target presentation, a failure to respond within the time limit, and a choice of a distractor.

2.3. Aversive stimulus

We used ES as an aversive stimulus. The ES was 60 Hz of alternating constant current of square waves (2.0 mA) delivered via a bipolar electrode plastered on the calf of the left hind limb with elastic tape. The strength of ES was determined in a pilot study. A 2.0 mA of ES reliably elicited a significant increase in the heart rates, indicating that the ES was sufficiently aversive. Researchers involved in this study also received the ES to confirm that the ES was aversive but not harmful. To minimize sensory adaptation, and to reduce the total time of ES exposure, the ES stimulus consisted of two 40 ms trains with a

160 ms interval between them (Greenspan et al., 1986). During the training sessions, we gradually increased the strength of ES up to 2.0 mA as the training advanced. The procedure was approved by the ethical committee of the Primate Research Institute.

2.4. Neuronal recording

After the training had been completed, surgery was conducted. Stainless steel recording cylinders and a head-restraining device were implanted on the skull with dental acrylic under sodium pentobarbital anesthesia (20 mg/kg body weight; i.v.).

Neuronal activities were recorded extracellularly using glass-coated Elgiloy electrodes (1.0–2.5 MΩ). Recording chambers (19 mm in diameter) were placed stereotaxically over the prefrontal cortex, targeting the caudo-lateral part of the OFC (both hemispheres of monkey P, and left hemisphere of monkey D. mainly the area 12 and a part of the area 13; Walker, 1940). An electrode was advanced with a hydraulic microdrive (MO-95; Narishige, Tokyo, Japan) through a stainless steel guide tube. Neuronal activities were converted into pulses using a spike wave-form detector (Multispike Detector, Alpha Omega Engineering, Nazareth, Israel). Pulses and task events were sampled at 10 kHz and stored as digital data on the same personal computer that controlled the behavioral task (PC-9821Xa; NEC, Tokyo, Japan). For on-line analysis, neuronal activities were sent to another personal computer (PC-9821Xe10; NEC, Tokyo, Japan) and peristimulus time histograms were computed and displayed. Neuronal activities and task events were also stored on digital tapes for off-line analysis (PC216Ax; Sony, Tokyo, Japan).

We reconstructed and localized the recording sites within the OFC based on magnetic resonance images and the depth from the surface of the brain. One animal was perfused under deep anesthesia with a solution of 10% formalin and recording sites were confirmed anatomically.

2.5. Data analysis

We examined the neuronal activities during the cue periods (the period from 100 to 400 ms after the cue onset). We compared the magnitudes of neuronal activity between the cue period and the control period (the 500 ms period after the start of the waiting period). If the neuronal activity during the cue period was significantly greater than that of the control period (Mann–Whitney U-test, $p < 0.05$), we considered that the neuron responded during the cue period. We will call these neurons "cue-responsive" neurons.

We further analyzed the cue-responsive neurons that were recorded in both the standard and the reversal blocks of the Juice–Water and the Water–ESA conditions by two-way ANOVA (cue stimulus factor and outcome type factor, $p < 0.05$). The first correct trial after the reversal of each cue stimulus (i.e. two trials in total) was omitted from the analysis to allow the monkeys to recognize the new condition. In this study, we focused on the neurons whose cue responses reflected the outcome information; the neurons that showed a significant main effect in outcome type factor and/or significant interaction.

2.6. Index for the preference of the outcomes in neuronal response

To quantify the preference of the outcomes in neuronal responses, we calculated two indices for each neuron as follows:

$$I_{J/W} = \frac{R_{juice} - R_{water}}{R_{juice} + R_{water}}$$

$$I_{W/E} = \frac{R_{water} - R_{ESA}}{R_{water} + R_{ESA}}$$

where $I_{J/W}$ is the preference index under the Juice–Water condition, $I_{W/E}$ the preference index under the Water–ESA condition, and R_{juice}, R_{water} and R_{ESA} are the average spike rate during the cue period in the juice trials, water trials and ESA trials, respectively. These two indices approached 1 when a neuron responded more vigorously in the trials with a preferable outcome (juice under the Juice–Water condition, or water under the Water–ESA condition), and -1 when in the trials with a less preferable outcome (water under the Juice–Water condition, or ES under the Water–ESA condition). For these indices, we used the neuronal data recorded in the block (the standard block or the reversal block) in which the neuron showed the maximal cue response.

3. Results

3.1. Behavioral reaction time and task performance

We summarized the behavioral reaction time (from target onset to the hold lever release) of each condition in Table 1. The monkeys showed the differential behavioral reaction time depending on the outcomes. Under the Juice–Water condition, the monkeys responded significantly faster in the trials with juice reward than those with water reward in both the standard and the reversal blocks ($p < 0.01$; Mann–Whitney U-test). Similarly, under the Water–ESA condition, they responded significantly faster in the trials with water reward than those with ESA in both the standard and the reversal blocks ($p < 0.01$; Mann–Whitney U-test). These observations suggested that the monkeys' preferences decreased in the order of juice > water > ESA, and they realized the change of the outcome condition in each block and expected the particular outcome type of the current trial. This is consistent with the result of the preference test which we conducted outside the task. We let the monkeys drink juice and water freely in their home cages for several hours a day, and measured the consumed amount. Both monkeys drank juice much more than water (monkey P: juice; average 120 ml/h, water; 20 ml/h. monkey D: juice; 90 ml/h, water; 40 ml/h), suggesting that they preferred juice to water. Although we did not conduct a preference test including ESA or no reward, it is obvious that ESA or no reward is less preferable than juice and water. Thus, we can conclude that the preference of the outcomes is juice > water > ESA.

Task performance of the monkey P was better than the monkey D, although there was a tendency that task performance decreased in a preference dependent manner in both monkeys. The monkey P performed the task with over 95% accuracy in all trial types (juice: 99.6%, water: 98.9%, ESA: 96.1%), while the monkey D erred more in the ESA trials (juice: 94.3%, water: 88.7%, ESA: 80.4%). The monkeys were choosing the distractor in most of error trials (92.9–100% of error trials).

Table 1
Behavioral reaction time (median)

	Outcome	Standard block	Reversal block
Monkey P			
Juice–Water condition	Juice	401 ms (green)	451 ms (blue)
	Water	514 ms (blue)	521 ms (green)
Water–ESA condition	Water	392 ms (yellow)	392 ms (red)
	ESA	544 ms (red)	531 ms (yellow)
Monkey D			
Juice–Water condition	Juice	295 ms (green)	351 ms (blue)
	Water	362 ms (blue)	472 ms (green)
Water–ESA condition	Water	338 ms (yellow)	372 ms (red)
	ESA	495 ms (red)	472 ms (yellow)

The performance of the monkey P in the ESA trials was so high that it received ES only up to 10 times a day at most. Then, the question arose whether the monkey P considered the ESA trials simply as no reward trials. To answer this question, we trained the monkey P under a new condition, which included four trial types with new four colors: gray: juice trial (juice for a correct response/no reward for an error response), white: water trial (water for a correct response/no reward for an error response), dark green: ESA trial (no reward for a correct response/ES for an error response), and cyan: no reward trial (no reward for a correct response/no reward for an error response). The monkey developed differential behavioral pattern depending on the type of outcomes. The monkey responded significantly faster in the reward trials (juice or water) than in the ESA or no reward trials (juice trials: 485 ms, water trials: 516 ms, ESA trials: 608 ms, no reward trials: 657 ms, median, Mann–Whitney U-test, $p < 0.001$). Furthermore, the reaction time in the ESA trials was significantly faster than that in the no reward trials (Mann–Whitney U-test, $p < 0.001$). In the no reward trials, the performance was worse than those in the other trial types (juice: 94.2%, water: 95.3%, ESA: 93.7%, no reward: 75.4%). Since the performance in the ESA trials was much better than that in the no reward trials, the monkey must be more motivated in the ESA trials than in the no reward trials to avoid ES, and the monkey did not consider ESA trials simply as no reward trials.

3.2. Neuronal responses to cue stimulus

We recorded 211 OFC neurons, 132 of which were recorded in all four blocks (the standard and the reversal blocks of both the Juice–Water and the Water–ESA conditions), 95 of which showed significant cue responses under either the Juice–Water or the Water–ESA conditions. Of these 95 neurons, 65 were revealed to have cue responses reflecting the outcome information by two-way ANOVA; namely the main effect of the outcome type factor was significant and/or the interaction was significant (see Section 2). In the following analysis, we focused on these 65 neurons.

3.3. Cue responses reflecting the relative preference of the outcomes

Of 65 neurons that showed cue responses reflecting the outcome information, many neurons showed selective cue responses under both of conditions and their cue responses seem to reflect the relative preference of the outcomes. Fig. 2 shows an example of a neuron that showed selective responses reflecting the relative preference of the outcomes. This neuron showed the relatively high spontaneous firing rate and phasic activation after cue onset. Under the Juice–Water condition, this neuron showed phasic response to the green cue in the standard block and to the blue cue in the reversal block, suggesting that it responded to the juice-predicting cue stimuli. Under the Water–ESA condition, the neuron showed phasic response to the yellow cue in the standard block and to the red cue in the reversal block, suggesting that it responded to the water-predicting cue stimuli. Thus, this neuron responded more strongly to the cue stimuli that predicted the preferable outcomes.

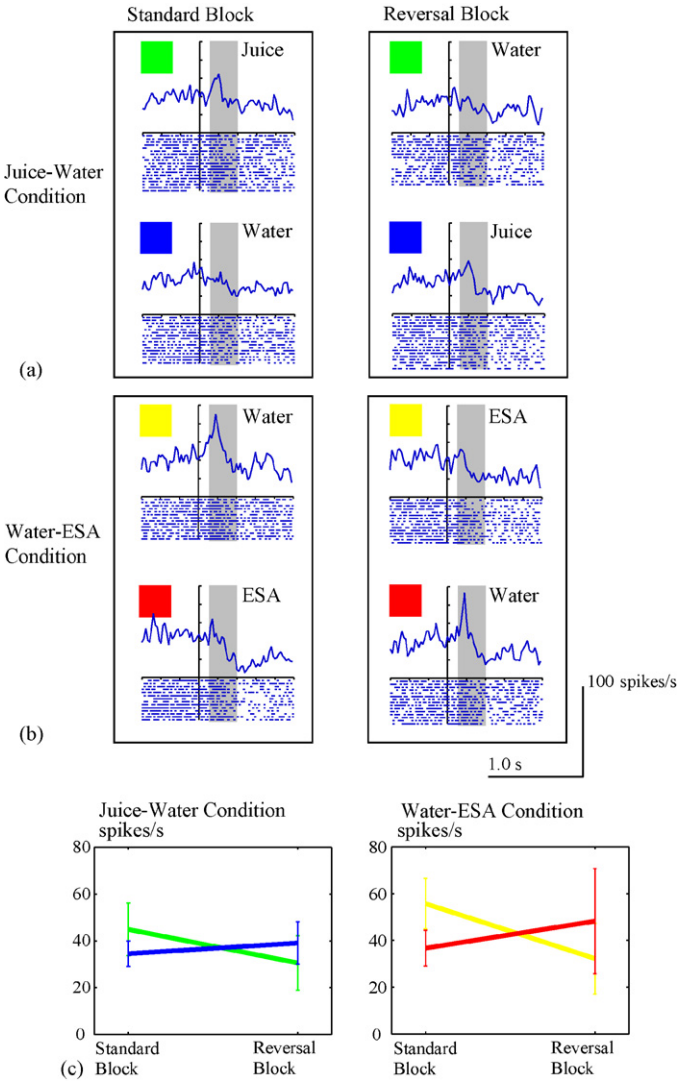

Fig. 2. An example of a neuron that showed selective cue responses reflecting the relative preference of the outcomes. (a) The neuronal responses during the cue period under the Juice–Water condition. The standard block is in the left column and the reversal block in the right column. The cue color and outcome type are shown above each histogram. The vertical line in each histogram represents the cue onset. The neuronal data of the shaded period was used for the analysis (the period from 100 to 400 ms after the cue onset). Ticks in the vertical axes mark 20 spikes/s and ticks in the horizontal axes mark 200 ms. Bin width of each histogram is 20 ms. (b) The neuronal responses during the cue period under the Water–ESA condition. Figure configurations are the same as (a). (c) Average spike rates for each condition (mean ± S.D.). We showed the average spike rates of the Juice–Water condition on the left and those of the Water–ESA condition on the right. The color of each line represents the cue color.

Fig. 3 shows another example of neurons that showed selective responses reflecting the relative preference of the outcomes. This neuron showed stronger responses to the water-predicting cue stimuli under the Juice–Water condition, and to the ES-predicting cue stimuli under the Water–ESA condition. We examined the same neuron under a new condition that included three trial types: green: juice trial

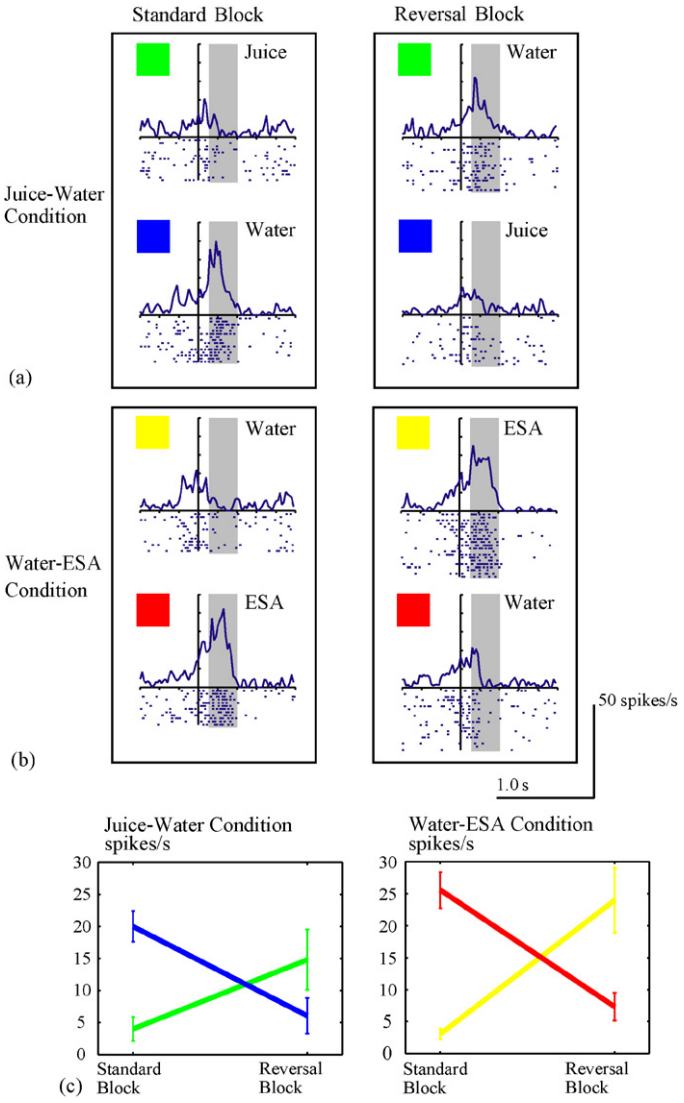

Fig. 3. Another example of a neuron that showed selective cue responses reflecting the relative preference of the outcomes. (a) The neuronal responses during the cue period under the Juice–Water condition. Ticks in the vertical axes mark 10 spikes/s. (b) The neuronal responses during the cue period under the Water–ESA condition. (c) Average spike rates for each condition. (a)–(c) The configurations of this figure are the same as Fig. 2.

(juice for a correct response/no reward for an error response), blue: water trial (water for a correct response/no reward for an error response), and red: ESA trial (no reward for a correct response/ES for an error response). This result is shown in Fig. 4. Under this condition, the neuron responded in a preference dependent manner; it responded most strongly to the red cue that predicted ES stimuli (least preferable), intermediately to the blue cue that predicted water reward (moderately preferable), and most weakly to the green cue that predicted juice reward (most preferable). Thus, this neuron responded more strongly to the cue stimuli that predicted the less preferable outcomes.

Of 65 neurons that showed cue responses reflecting the outcome information under either the Juice–Water or the Water–ESA condition, 24 neurons (36.9%) showed cue responses that reflected relative preference of the outcomes. Of these 24 neurons, 9 showed significantly greater responses to the cue stimuli that predicted the preferable outcomes under both the Juice–Water and the Water–ESA conditions (juice under the Juice–Water condition and water under the Water–ESA condition, Mann–Whitney U-test, $p < 0.05$). Fifteen neurons showed significantly greater responses to the cue stimuli that predicted the less preferable outcomes under both the Juice–Water and the Water–ESA conditions (water under the Juice–Water condition and ESA under the Water–ESA condition, Mann–Whitney U-test, $p < 0.05$).

3.4. Selective cue response under one condition

The neurons that we have viewed above showed selective cue responses under both the Juice–Water and the Water–ESA conditions. We also found 26 neurons that showed selective cue responses under one condition, either the Juice–Water or the Water–ESA.

Fig. 5 shows an example of a neuron that showed the selective cue response under one condition. This neuron responded more strongly to the cue that predicted water reward under the Juice–Water condition. However, the neuron did not show the differential cue responses under the Water–ESA condition. Thus, this neuron responded to the cue that predicted water reward only under the Juice–Water condition, even though there were water-predicting cue stimuli under the Water–ESA condition. This result suggests that the neuron did not respond simply to the water-predicting cue stimulus, but its response was dependent on both the outcome type and the combination of current available outcomes.

Fig. 6 shows another example of a neuron that showed selective cue response under one condition. This neuron responded more strongly to the cue that predicted ES under the Water–ESA condition. However, the neuron did not show the differential cue responses under the Juice–Water condition. Because we used ES only under the Water–ESA condition, we could not determine whether the neuron responded to the ES-predicting cue stimulus under any conditions or only under the Water–ESA condition.

Of 65 neurons that showed cue responses reflecting the outcome information under either the Juice–Water or the Water–ESA condition, 26 neurons (40.0%) showed selective cue responses under one condition. Of these 26 neurons, 13 neurons showed significant differential cue response under only the Juice–Water condition; 4 neurons showed significantly greater response to the juice-predicting cue, and 9 neurons showed significantly greater response to the water-predicting cue (Mann–Whitney U-test, $p < 0.05$). The remaining 13 neurons showed significant differential cue response under only the Water–ESA condition; 6 neurons showed significantly greater response to the water-predicting cue and 7 neurons showed significantly greater response to the ES-predicting cue (Mann–Whitney U-test, $p < 0.05$). We found no neurons that responded selectively to water-predicting cue stimuli under both the Juice–Water and the Water–ESA conditions.

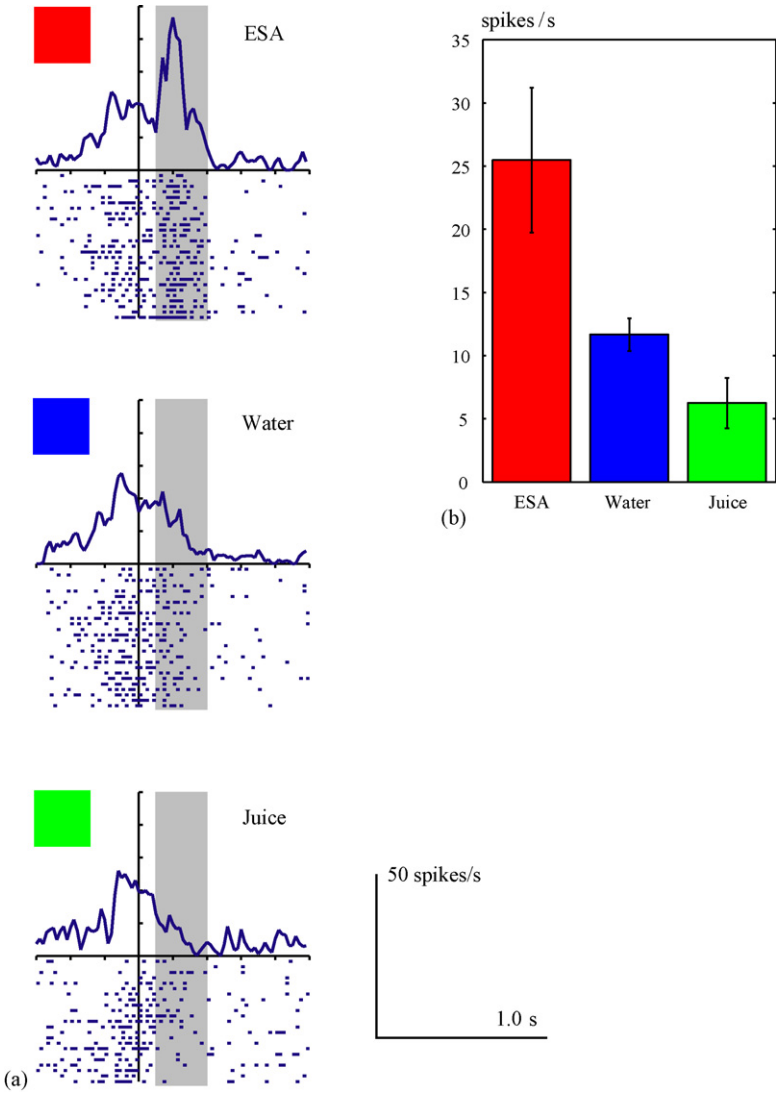

Fig. 4. (a) The cue responses of the same neuron in Fig. 3 under a condition that three cue colors predicted three outcomes. Under this condition, red, blue, and green cues predicted ESA, water, and juice, respectively. The cue color and outcome type are shown above each histogram. The vertical line in each histogram represents the cue onset. The neuronal data of the shaded period was used for the analysis (the period from 100 to 400 ms after the cue onset). (b) Average spike rates for each cue stimulus (mean ± S.D.). The color of each bar represents the cue color.

3.5. Index for the preference of the outcomes in neuronal response

To compare the characteristics of the cue responses between the Juice–Water condition and the Water–ESA condition, we calculated two indices for the preference of the outcomes in neuronal response (see Section 2). The result was shown in Fig. 7. The indices under the Water–ESA condition ($I_{W/E}$) were highly predictable from those under the Juice–Water condition ($I_{J/W}$) (simple linear regression analysis, $p < 0.0001$). The majority of neurons were positioned around the diagonal line, indicating that the selectivity for the preference of the outcomes is matched between the Juice–Water condition and the Water–ESA condition. This result suggests that the OFC neurons that responded to the cue stimulus that predicted the more preferable outcome (juice) under the Juice–Water condition also responded to the cue stimulus that predicted the more preferable outcome (water) under the Water–ESA condition and vice versa.

3.6. Summary of each type of neuron

We summarized each type of neurons in Table 2. The population histograms of each type of neurons were shown in Fig. 8(a and b: ‘‘relative preference selective’’ neurons, c–f: ‘‘selective under one condition’’ neurons). In Fig. 8, we used the neuronal data recorded in the block (the standard block or the reversal block) in which the neuron showed the maximal cue response. We normalized the neuronal responses to the maximal cue response of each neuron.

As for the neurons that were selective under one condition, it seems that there is a qualitative difference in the response properties of neurons according to whether the neurons strongly responded to preferable outcomes or less preferable outcomes,

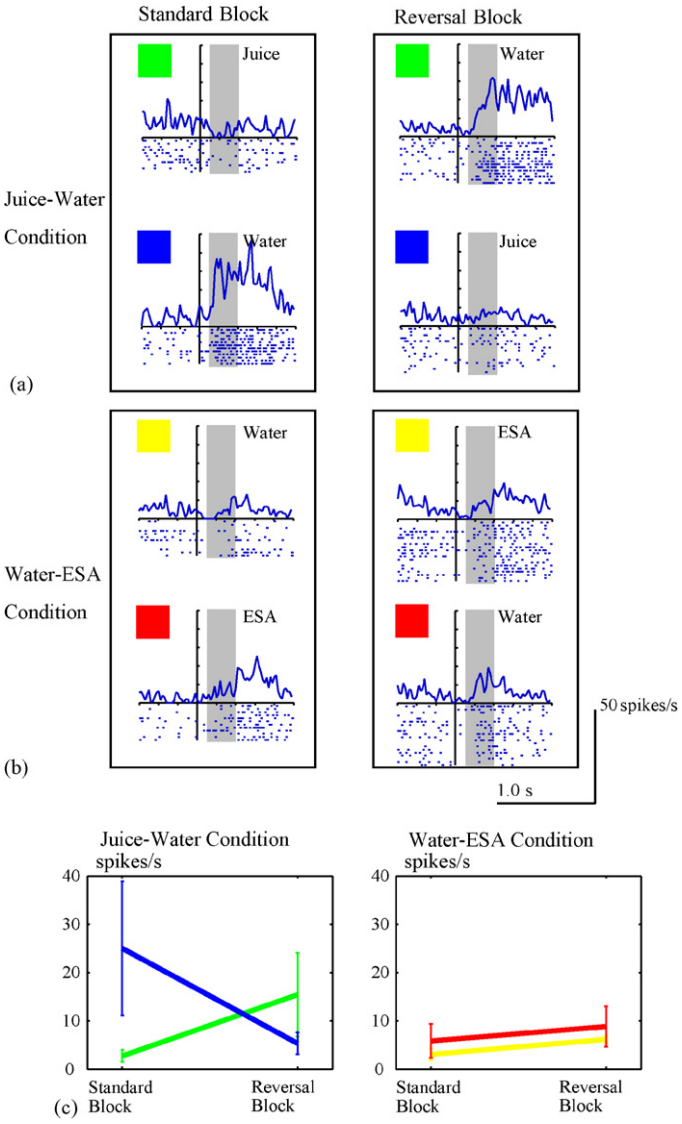

Fig. 5. An example of a neuron that showed the selective cue responses under one condition. (a) The neuronal responses during the cue period under the Juice–Water condition. Ticks in the vertical axes mark 10 spikes/s. (b) The neuronal responses during the cue period under the Water–ESA condition. (c) Average spike rates for each condition. (a)–(c) The configurations of this figure are the same as Fig. 2.

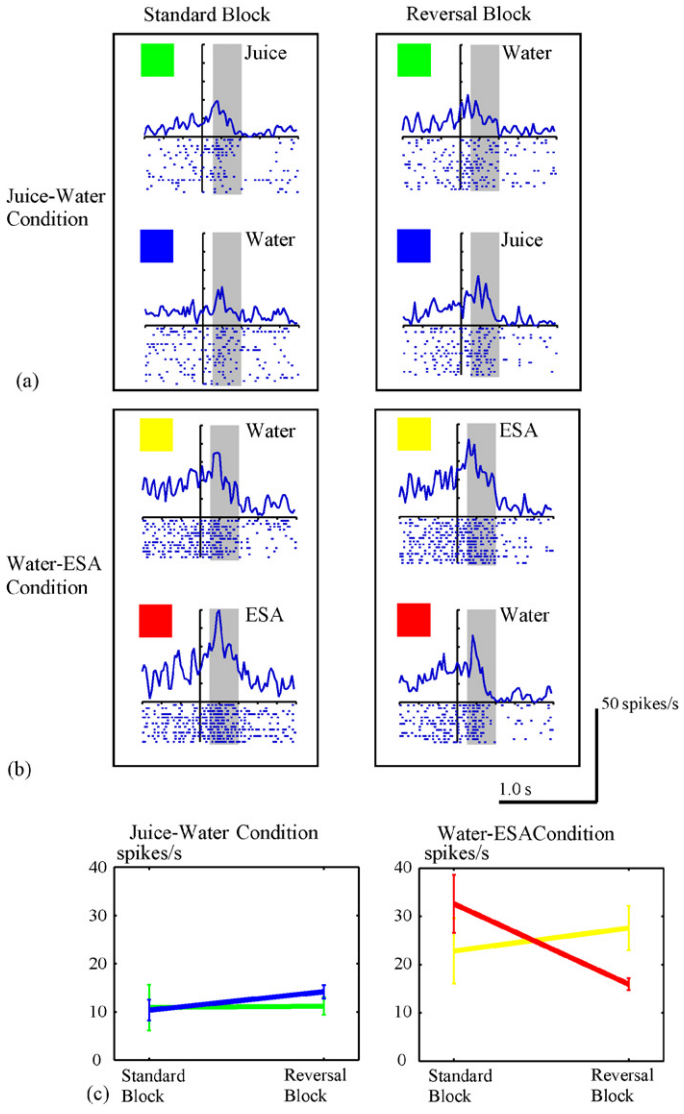

Fig. 6. Another example of a neuron that showed the selective cue responses under one condition. (a) The neuronal responses during the cue period under the Juice–Water condition. Ticks in the vertical axes mark 10 spikes/s. (b) The neuronal responses during the cue period under the Water–ESA condition. (c) Average spike rates for each condition. (a)–(c) The configurations of this figure are the same as Fig. 2.

Table 2
Summary of response types of the 65 neurons whose responses reflect the outcome information during the cue period

Total	65
Relative preference selective	24 (36.9%)
More preferable outcome	9
Less preferable outcome	15
Selective under one condition	26 (40.0%)
Juice under J/W condition	4
Water under J/W condition	9
Water under W/E condition	6
ESA under W/E condition	7
Others	15 (23.1%)

J/W: Juice–Water; W/E: Water–ESA.

although it may be due to the fact that the number of the neurons was small. The neurons that showed greater responses to the cue stimuli predicting the less preferable outcome (water under the Juice–Water condition and ESA under the Water–ESA condition) showed clearly divergent cue responses as seen in Fig. 8(d) and (f). On the other hand, the neurons that showed greater responses to the cue stimuli predicting the preferable outcome (juice under the Juice–Water condition and water under the Water–ESA condition) showed relatively unclear differential cue responses as seen in Fig. 8(c) and (e). For the juice selective neurons under the Juice–Water condition shown in Fig. 8(c), the response to the water-predicting cue seemed to be greater than that to the ES-predicting cue under the Water–ESA condition, although it was not statistically significant. This may suggest that these neurons are the same type of ‘‘more

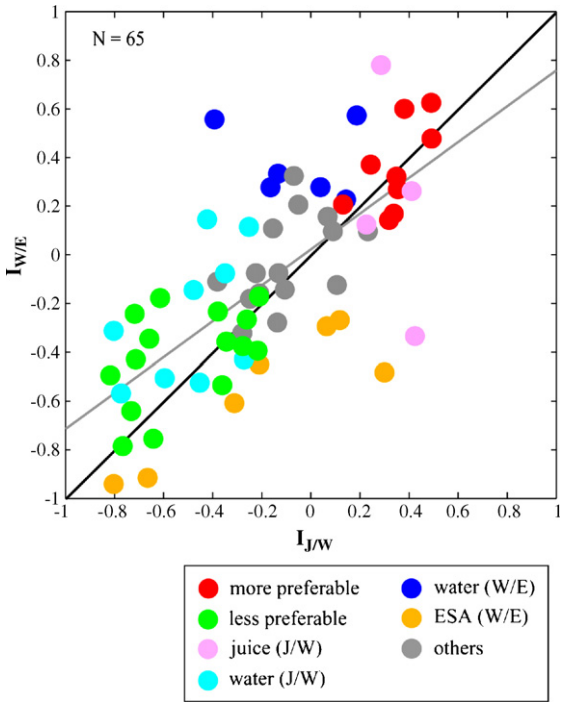

Fig. 7. Index for the preference of the outcomes in neuronal response. The index $I_{W/E}$ was plotted against $I_{J/W}$. Each circle represents one neuron. Neurons were categorized into seven groups depending on their response types (red: more preferable outcomes, green: less preferable outcomes, pink: juice, cyan: water under the Juice–Water condition, blue: water under the Water–ESA condition, yellow: ESA, gray: others) (see Table 2). The gray line is the regression line ($y = 0.736x + 0.022$). $N = 65$. J/W: Juice–Water, W/E: Water–ESA.

preferable neurons'' shown in Fig. 8(a). For the water selective neurons under the Water–ESA condition shown in Fig. 8(e), five out of six neurons showed non-differential cue responses under the Juice–Water condition, suggesting that these neurons may be selective to whether the cue stimuli predicted any reward or not.

Recording sites of ''relative preference selective'' neurons and ''selective under one condition'' neurons are shown in Fig. 9. Most of neurons were recorded in the caudolateral OFC (the area 12). There was no clear division between the recording sites of these two types of neurons. They were intermingled in the caudolateral OFC.

4. Discussion

This study showed that a group of OFC neurons code the relative preference of both rewarding and aversive outcomes. We examined activities of OFC neurons under two conditions, one of which included only reward trials (Juice–Water condition) and the other included reward and aversive trials (Water–ESA condition). Many OFC neurons showed differential cue responses depending on whether the outcome was preferable or not under both conditions. This observation indicates that the same group of OFC neurons code both reward information and aversive information in the way that relative preference is represented. This result suggests that the OFC evaluates relative preference of outcomes including aversive outcomes, and plays important roles in adaptive decision making.

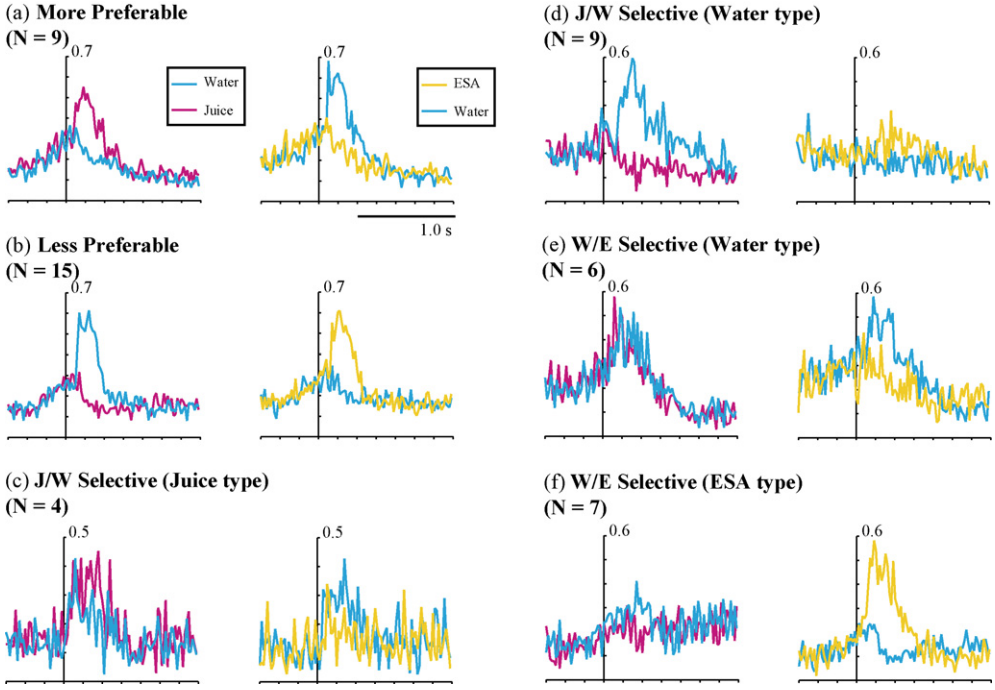

Fig. 8. (a) and (b) Population histograms of the neurons that showed the selective cue responses reflecting the relative preference of the outcomes. (c)–(f) Population histograms of neurons that showed the selective cue responses under one condition. (a)–(f) The population histograms on the left represent the cue responses under the Juice–Water condition. The magenta line is the population histogram of the trials with juice reward, and the blue line is that of the trials with water reward. The population histograms on the right represent the cue responses under the Water–ESA condition. The blue line is the population histogram of the trials with water reward, and the yellow line is that of the trials with ESA. The vertical line represents the cue onset. Responses were normalized to the maximal cue response of each neuron. J/W: Juice–Water condition, W/E: Water–ESA condition.

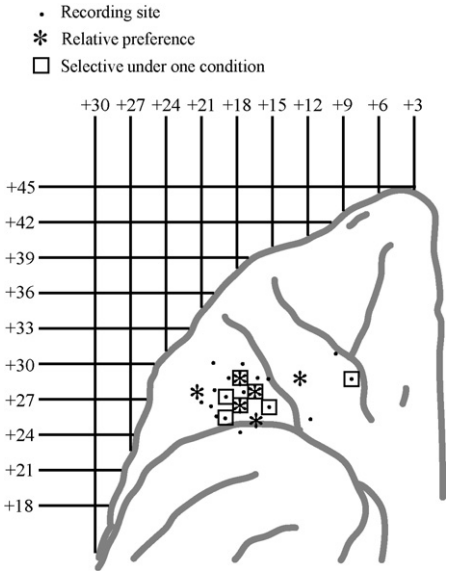

Fig. 9. The ventral view of the OFC is shown. Recording sites from three hemispheres were mapped onto comparable locations in the right hemisphere. The numbers on the left side represent the distance (mm) from the interaural plane, and those on the top represent the distance (mm) from the midline. An asterisk represents the recording site where the relative-preference neurons were recorded. A square represents the recording site where the neurons that were selective under one condition were recorded.

4.1. Outcome preference

The difference of behavioral reaction time reflects the animal's motivational level and preference for outcomes (Holland and Straub, 1979; Sage and Knowlton, 2000; Watanabe et al., 2001). As the behavioral reaction time and the result of the preference test indicated, the monkeys preferred juice to water and water to ESA. The monkeys consistently responded faster in the trials with juice reward under the Juice–Water condition and in the trials with water reward under the Water–ESA condition, even when the relationships between the cue color and the outcome type were changed. This result suggests that the monkeys were aware of the changing of the blocks and were expecting the outcome type of the current trial.

4.2. Electrical stimulus

One may wonder why in the ESA trials the monkeys erred more and did not respond as fast as in the reward trials to avoid ES, and may suspect that the monkeys considered the ESA trials as no reward trials. In fact, no reward trial is also aversive and undesirable for monkeys because they had to do an unremunerative work and wait for subsequent trials to get a reward. The fact that a timeout could be a punisher (Nader and Morgan, 2001; Roesch and Olson, 2004) supports this idea. However our monkey behaved differently in no reward trials and in ESA trials. The ES strength used in this study (2.0 mA) is 4–6 fold weaker than that which elicits painful sensation (7–12 mA, Koyama et al., 1998, 2000, 2001). Probably the monkeys were hardly desperate to avoid ES because it was not painful, albeit aversive. Thus, the monkeys were not motivated in the ESA trials as much as in the reward trials. A similar result was repeated in a previous study, in which monkeys made more errors in aversive air-puff trials (Yamada et al., 2004). However, as shown in the additional behavioral test, the performance in the ESA trials was much better than that in the no reward trials, and the reaction time in the ESA trials was significantly faster than that in the no reward trials. Since a correct or error auditory cue was presented, the monkeys knew whether their response was correct or not even in the no reward trials. Considering that the performances of trials other than no reward trials were above 90%, the reason why the performance in the no reward trials was less satisfactory is probably that the monkey was not motivated in the no reward trials as much as in other trials. On the other hand, the observation that the performance in the ESA trials was maintained suggests that the monkey was aware that ES would be applied if it made an error, and motivated to avoid ES. Thus, we believe that the ESA trials were much more aversive than the no reward trials.

4.3. Ethical matter of using ES

One may be concerned about the ethical problem of using ES as an aversive stimulus. There are some other methods more moderate than ES such as air-puff and timeouts (Nader and Morgan, 2001; Roesch and Olson, 2004; Yamada et al., 2004; Kobayashi et al., 2006). However, because the main point of this study was to investigate how aversive information is coded in the OFC, we wanted to use a reliable aversive stimulus. It is important that we could precisely control the strength of aversive stimuli in order to study the effect of them and to maintain monkeys' motivation when using a task involved aversive stimuli. If the strength of an aversive stimulus is too weak, we cannot investigate its effect, and if it is too strong, monkeys will stop doing the task and it may be harmful. For this point, ES is more advantageous than other aversive stimuli because it is possible to control its strength, onset time, and duration precisely. We used weak strength of ES at early stages of the training, and gradually increased the strength up to 2.0 mA, which was sufficiently aversive, as the training advanced. When completed the training, the monkeys made only several errors a day and they hardly received ES. Thus, the procedure of this study is ethically acceptable.

4.4. Cue responses coding the relative preference of the outcomes

Many OFC neurons showed significant cue responses under the two stimulus-outcome conditions used in this study; one included both rewarding and aversive outcomes (the Water–ESA condition) and the other included only rewarding outcomes (the Juice–Water condition). Furthermore, the characteristics of these cue responses were similar between these conditions in that they reflected the relative preference of the outcomes. For about one-third of the neurons that showed cue responses reflecting the outcome information, their cue responses coded the relative preference of the outcomes. The

neuron that responded to the cue predicting the preferable outcome (juice) under the Juice–Water condition also responded to the cue predicting the preferable outcome (water) under the Water–ESA condition. Likewise, the neurons that responded to the cue predicting the less preferable outcome (water) under the Juice–Water condition also responded to the cue predicting the less preferable outcome (ES) under the Water–ESA condition. These results suggest that a group of OFC neurons code the relative preference of the rewarding and aversive outcomes, not the outcome type itself; in other words they code how desirable the outcome is, not what outcome will be given.

Tremblay and Schultz (1999) reported that many OFC neurons code relative preference of different rewards. They introduced three rewards with different preferences and used two of them in one experimental block. They showed that many OFC neurons strongly responded when a more or less preferable reward was expected, suggesting that these neurons code the relative preference of the rewards. Other studies also support the view that activities in the OFC reflect relative preference of outcomes. It has been reported that OFC neurons stop responding to the reward and to the cue stimuli that predict it once a monkey has had enough of the reward (Rolls et al., 1989; Critchley and Rolls, 1996). These neurons continue to respond to other kinds of rewards with which the monkey is not satiated. Satiated rewards become less preferable for animals. Thus, the response characteristics of these neurons indicate that they reflect the relative preference of the rewards, not the fixed physical properties of the rewards. Our result is consistent with these results and has extended them; OFC neurons code the relative preference of the outcomes, not only rewarding outcomes but also aversive outcomes.

4.5. Biological significance of relative preference coding

The result of this study suggests that the same neuron codes both reward information and aversive information in the manner that it codes the relative preference of outcomes. What is the biological significance of the coding style of relative preference? In the natural environment, foods available at a time are restricted and changing with time. In this situation, it is important to compare the relative value of available foods. Thus, the coding style of relative value is more advantageous than that of absolute value. Furthermore, it is necessary to compare the various types of outcomes, rewarding and/or aversive, to make an adaptive decision. For example, in a situation that getting some food is accompanied by danger, animals must compare the reward value of getting the food with the risk of braving the danger at the same time. A common scale may be necessary to decide what behavior to make in such a situation. Without a common scale, it is very difficult to compare the relative value of different types of outcomes. As shown in this study, many OFC neurons showed non-categorical responses reflecting the relative value of the outcomes, suggesting that the OFC may provide a common scale to compare the relative value of various types of outcomes. This notion is consistent with the study of a theoretical model. Montague and Berns (2002) have advocated a predictor-valuation model of decision making in which the OFC integrates reward information relating to rewards and punishments and their predictors to produce a common neural currency that is used to compare and select actions based on the value of future outcomes.

Although it is a speculative argument, the deficits found in OFC-lesioned animals may be due to the loss of the ability to compare relative values. Both monkeys and rats with OFC damage are unable to modify their behavior when the reward contingencies changed in extinction and reversal learning (Butter, 1969a; Jones and Mishkin, 1972; Meunier et al., 1997; Baxter et al., 2000; Ferry et al., 2000; Quirk et al., 2000; Schoenbaum et al., 2002, 2003; Pears et al., 2003). Animals are required to note the change in biological significance of cue stimuli in order to behave adaptively in these learning tasks. To note the change in biological significance, the ability to compare relative value between the current and past significance of cue stimuli may be necessary. Besides, it is well known that the monkeys with damaged OFC show maladaptive social behavior in their group (Butter et al., 1970). The society of macaque monkeys has a hierarchical relationship between individual monkeys. Each monkey becomes superior or inferior in relation to the other monkeys and must behave in recognition of their relative relationship among the group. The fact that the monkeys with OFC damage are unable to establish appropriate relationship with other monkeys in the social environment indicates that they are not able to recognize their relative relationship within the society. These observations suggest that the OFC-lesioned animals are not able to compare relative values, and this inability may lead to the deficits that are commonly found in OFC-lesioned animals.

4.6. Cue responses selective under one condition

In addition to the relative preference neurons shown above, about one-third of neurons showed the selective cue responses under one condition, either the Juice–Water or the Water–ESA condition. Of these neurons, the neurons that responded to the water-predicting cue under one condition did not respond to the water-prediction cue under the other condition. This fact suggests that they did not respond simply to the water-predicting cue. The responses of these neurons depend on both the outcome type and the combination of the current available outcomes. These responses may be important to judge what outcomes are available now and evaluate the relative preference of the current available outcomes.

As for the neurons that showed the juice-selective response and those that showed the ESA-selective response, we could not determine whether these neurons responded to the juice- or the ES-predicting cue stimulus under any stimulus-outcome conditions because juice and ES were used under only the Juice–Water or the Water–ESA conditions respectively. However, considering that we did not find any neurons showing water-selective responses under both the Juice–Water and the Water–ESA conditions, it is likely that these neurons

also depend on both the outcome type and the combination of the current available outcomes.

4.7. Recording area

We recorded neurons in the caudolateral part of the OFC (mainly the area 12), which differs from the recording areas in a previous study (Tremblay and Schultz, 1999). They have recorded neurons in more anterior and medial region of the OFC (the areas 11, 14, and rostral 13). We chose the caudolateral region of the OFC as the recording site because some neuroimaging studies have shown that the caudal and lateral region of the OFC is especially involved in aversive information (Frey et al., 2000; O'Doherty et al., 2001; Ursu and Carter, 2005). As it is known that anatomical differences exist among different regions of the OFC (Morecraft et al., 1992; Carmichael and Price, 1994; Cavada et al., 2000) and imaging studies have suggested that different regions of the OFC are involved in different functions (O'Doherty et al., 2001; Schnider et al., 2005; Ursu and Carter, 2005), there are possibilities that neurons in other regions of the OFC have different coding style other than that seen in this study. Further studies are necessary to examine the response characteristics of neurons in different regions of the OFC to various types of aversive stimuli.

4.8. Relationship with other brain areas

Although it has not been studied in terms of relative preference, some brain regions other than the OFC (amygdala, striatum, cingulated cortex, and dorsolateral prefrontal cortex) are also involved in reward and aversive information (Ono et al., 1983; Nishijo et al., 1988; Koyama et al., 2001; Yamada et al., 2004; Kobayashi et al., 2006). Since all of these regions have reciprocal connections with the OFC (Pandya et al., 1981; Vogt and Pandya, 1987; Morecraft et al., 1992; Cavada et al., 2000), it is likely that relative preference neurons would be found also in these regions. However, some functional differences have been shown between the OFC and these brain regions (Schultz et al., 2000; Elliott et al., 2003; Pickens et al., 2003; Schoenbaum et al., 2003; Wallis and Miller, 2003; Ichihara-Takeda and Funahashi, 2006; Rudebeck et al., 2006). Thus, it is interesting to compare the temporal dynamics and functional roles between the OFC and these regions in the current task situation. Actually, we are recording amygdala neurons in the same task. Considering that the OFC is critical for adaptive behavior (Butter, 1969a; Ferry et al., 2000; Quirk et al., 2000; Beer et al., 2006), the flexible responses of the relative preference neurons may be originated in the OFC, then, transmitted to the other brain regions. Thus, the cue response latency of the relative preference neurons may be shorter in the OFC than in the other brain regions.

4.9. Concluding remarks

As the results of this study indicated, the OFC codes the relative value of predicted outcomes, not only rewarding outcomes but also aversive outcomes. The OFC integrates visual information with outcome information and determines the relative value of future events by providing a common scale. This characteristic of OFC neurons may enable animals to select adaptive behavior according to the relative value of the future events.

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