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ORIGINAL ARTICLE

Neurons in rat orbitofrontal cortex and medial prefrontal cortex exhibit distinct responses in reward and strategy-update in a risk-based decision-making task

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Abstract

The orbitofrontal cortex (OFC) and the medial prefrontal cortex (mPFC) are known to participate in risk-based decision-making. However, whether neuronal activities of these two brain regions play similar or differential roles during different stages of risk-based decision-making process remains unknown. Here we conducted multi-channel in vivo recordings in the OFC and mPFC simultaneously when rats were performing a gambling task. Rats were trained to update strategy as the task was shifted in two stages. Behavioral testing suggests that rats exhibited different risk preferences and response latencies to food rewards during stage-1 and stage-2. Indeed, the firing patterns and numbers of non-specific neurons and nosepoking-predicting neurons were similar in OFC and mPFC. However, there were no reward-expecting neurons and significantly more reward-excitatory neurons (fired as rats received rewards) in the mPFC. Further analyses suggested that nosepoking-predicting neurons may encode the overall value of reward and strategy, whereas reward-expecting neurons show more intensive firing to a big food reward in the OFC. Nosepoking-predicting neurons in mPFC showed no correlation with decision-making strategy updating, whereas the response of reward-excitatory neurons in mPFC, which were barely observed in OFC, were inhibited during nosepoking, but were enhanced in the post-nosepoking period. These findings indicate that neurons in the OFC and mPFC exhibit distinct responses in decision-making process during reward consumption and strategy updating. Specifically, OFC encodes the overall value of a choice and is thus important for learning and strategy updating, whereas mPFC plays a key role in monitoring and execution of a strategy.

Keywords Risk-based decision-making · Orbital frontal cortex · Medial prefrontal cortex · Multi-channel units recording

Introduction

Decision-making is a cognitive process in which the risks and benefits of action choices are evaluated so that a choice with maximal value can be made. Risk-based decision-making is a cognitive process in which a choice is made on the known probability of every possible outcome (Levy et al. 2010). Previous studies have proposed five steps for risk-based decision-making, which includes learning the existing practical choices and the potential value of each choice, making an action selection choice, evaluating the outcome of an action and comparing it with expected outcome, updating and memorizing the strategy, and forming expectations of subsequent tasks (Floresco 2015; Rangel et al. 2008; Stott and Redish 2014). Although various brain regions are involved in risk-based decision-making, the orbital frontal cortex (OFC) and the

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medial prefrontal cortex (mPFC) are of particular importance to this process.

The OFC is known to participate in various aspects of risk-based decision-making. Lesion or inactivation of OFC compromised strategy learning and updating. In a probability discounting task (PDT) or rat gambling task (RGT), lesion of OFC blocked the formation of strategy selection before, (Pais-Vieira et al. 2007) but not after, task-learning (St Onge and Floresco 2010; Zeeb and Winstanley 2011). Moreover, lesion of OFC caused the rat to fixate on a certain choice and lose the ability to switch strategy from the very beginning of the task (Rivalan et al. 2011). However, how OFC neurons encode strategy switch in a risk-based decision-making process remains unclear. In addition, OFC is involved in the representation of external variables that influence the outcome's value. OFC neurons encoded information about the size and possibility of an expected positive outcome (Kahnt et al. 2010; Kennerley et al. 2009; Sescousse et al. 2010; Sul et al. 2010; van Duuren et al. 2009). Lesion of OFC significantly reduced a risk-taking action when the task involved risk of punishment (Orsini et al. 2015). Moreover, OFC neurons also provide a behaviorally relevant signal that reflects inferences about both value-relevant and value-neutral information (Stalnaker et al. 2014).

In contrast, the mPFC plays an important role not only in the processing of decision execution but also in strategy learning and updating (Euston et al. 2012; Jentsch et al. 2010; St Onge et al. 2012). Lesion of mPFC had a very similar effect on risk-based decision making to lesion of OFC, except that lesion of mPFC after task-learning decreases the number of selections for the advantageous choices in RGT task. This is largely due to the reduction of sensitivity to negative outcomes after the lesion of mPFC (Likhtik and Paz 2015; Paine et al. 2013). Because mPFC is also involved in the executive functions such as attention, working memory and planning, it is believed that the role of mPFC in risk-based decision-making is more complicated than previously thought.

Indeed, recent studies have demonstrated that OFC and mPFC play different roles in making a decision in tests such as the PDT task and rodent betting task (Barrus et al. 2017; St Onge and Floresco 2010). While OFC is responsible for the coupling of stimulus event and outcome, the mPFC plays a more important role in the coupling of behavioral response and outcome. Currently, it remains unclear whether these two brain regions play different roles in reward choice and risk-taking probability in a RGT task. In addition, their roles in strategy learning and updating during risk-based decision making remains to be investigated. In this study, the neuronal activities of rat OFC and mPFC were simultaneously recorded, and the changes of neuronal discharging patterns were observed when rats were performing a risk-based decision-making task. The changes of neuronal activity accompanying the changes of strategies in a risk-based decision-making task were carefully observed and analyzed. We hypothesized that the OFC and mPFC contain neurons with different discharging properties and these neurons participate in encoding risk and value of reward; further, when rats updated their strategy, some of those neurons would change their discharging preference. We tested this hypothesis with multi-channel unit recording in behaving animals performing a risk-based decision-making task. We found that although OFC and mPFC shared some similar properties in neuronal firing patterns, these two brain regions displayed distinct responses in reward and strategy updating in a decision-making process.

Experimental procedures

Animals

Ten male adult Sprague-Dawley rats (body weight 300–350 g) were purchased from the Academy of Military Medical Science (Beijing, China) and were housed with two rats per cage (standard cage for rats: 45 cm × 30 cm × 20 cm). The animals were maintained under standard housing conditions at room temperature (24–26 °C) with a 12 h light/dark cycle (lights on at 7:00 A.M.) and all behavioral experiments were performed during the light phase of the cycle. Each rat was allowed access to food and water ad libitum. All experimental procedures were carried out in accordance with the National Institutes of Health (USA) Guide for the Care and Use of Laboratory Animals. The experimental procedures were approved by the Local Committee of Animal Use and Protection at Capital Normal University, China.

Rats were food-restricted for 14 days before the experiments and maintained at 85% of their free-feeding body weight throughout the experiment with water available ad libitum. Each training or test session lasted 30 min per day.

Experimental apparatus

Behavioral test

All behavioral tests were performed in a five-hole nose poke chamber (30.5 cm × 24 cm × 21 cm, Med Associate, Inc. VT, USA). A food-consumption receptacle was located on the opposite wall of the five holes, which allowed animals to retrieve reward (45 mg pallet). Illuminating lights were used as cues to initiate behavioral response and an infrared beam for the recording of animal activity was placed in all nose-poking apertures and the receptacle. A monitor light was hung over the chamber wall. The operation chamber was placed in a soundproof box with a miniature fan to create white noise background. All behavioral data were collected and sampled using a workstation computer.

Electrophysiological settings

The discharge of a single neuron was recorded using the multi-channel single units recording system (Cerebus, Blackrock Microsystem, UT, USA). Signals were acquired using a 16-channel digital headstage connected to the electrode array. Spikes were amplified, filtered (500–7500 Hz) and sampled (30 KHz) into the workstation computer. Local field potential was amplified, filtered (0.5–500 Hz), and sampled (1 KHz) into the same workstation computer.

Experimental procedures

Training session

To acclimate animals to the experimental environment, rats were placed in the operation box 30 min per day for three consecutive days. During the training sessions, animals were first trained to respond to the illuminating light presented in either number 2 or number 4 aperture by poking the corresponding aperture within 10 s in a five-choice serial reaction time task (5CSRTT). The sequence of light in these two apertures was generated by pseudorandom selection. A food pellet was automatically delivered as a reward if the animal made the correct poke. Once the rat was able to correctly respond at a rate ≥ 80%, the experiment proceeded to the risk-based decision-making stage. During this stage, number 2 and number 4 apertures were respectively assigned to different reward values: the small reward (1 food pellet at a probability of 90%) and the big reward (3 food pellets at a probability of 50%), which was balanced between animals. Both options were not accompanied with punishment time (Zeeb et al. 2009). As shown in Fig. 1b, the trial was initiated by illumination of the house light; 5 s later, two apertures were simultaneously illuminated for 10s. Nosepoking into either number 2 or number 4 aperture would lead to the corresponding reward. Failure to choose within 10s would lead to one omission. Each training session lasted for 30 min and contained 100 trials. After 15 days of training sessions, seven rats showed consistent preference to the big reward, and these animals progressed to the next stage of the experiment. The remaining three rats choosing the small reward at a rate ≥ 50% were removed from this study.

Electrode implantation surgeries

The seven rats that chose the big reward were surgically implanted with electrode arrays at both OFC and mPFC ipsilaterally. The surgery was performed under pentobarbital anesthetization (50 mg/kg, i.p.) and sterile conditions. The hair was removed to expose the skin, and then alcohol and iodine were rubbed onto the skin to guard against infection. A 1.5–2.0 cm wound cut was made to expose the Bregma. After the dorsal surface of the skull was exposed, a craniotomy was performed to expose the brain surface for the stereotaxic implantation of electrode arrays. The coordinates of OFC were 2.7–4.7 mm posterior from Bregma, 2.7–3.7 mm lateral from midline, and at a depth of 4.6–5.2 mm from Bregma surface. The coordinates of prelimbic mPFC were 2.5–4.5 mm posterior from Bregma, 0–1.0 mm lateral from midline, and at a depth of 3.5–4.5 mm from the Bregma surface (Paxinos and Watson 1996). Each structure (OFC or mPFC) was implanted with one 2 × 8 microwire electrode array made of sixteen 30 μm-diameter FeNiCr wires (California Fine Wire Co., Grover Beach, USA) and permanently fixed to the skull with dental cement. After surgery, the rats were inspected daily and given Benzylpenicillin Sodium (0.5 mg/kg/day, i.p., North China Pharmaceutical Group Corporation Veterinary Co., Shijiazhuang, Hebei, China) once per day for 3 days. Sterile saline (5–10 ml, s.c.) was given if the rat showed signs of dehydration. After recovering for two weeks with free access to food and water, the rat was food-restricted at 10~15 g of food per day (with free access to water) until its body weight was reduced to 85%–90% of its projected free-feeding body weight.

Test session

The rats were then subjected to a two-stage behavioral test: the risk-taking and reward-seeking test (stage-1, lasting for 3 days) and the gambling test (RGT, stage-2). RGT included a 10-day forced choice task and a 3-day free choice task. Each task lasted 30 min or less. In stage-1, the experimental procedure was identical to the one described previously in the training session. The rat was allowed to freely choose between the big reward and small reward (i.e., performing the free choice task). A simple mathematical calculation would reveal that the big reward was advantageous to the rat at this stage. The rat stayed at stage-1 for three days to learn the values of the two different options. The neuronal activities of OFC and mPFC were simultaneously recorded during these three testing sessions. In the forced choice task of stage-2, a waiting time was introduced as punishment. For one choice, the rat had a probability of 50% to get 3 food pellets or a probability of 50% to get a 35-s waiting time punishment (hole-light flashed for 35 s); while for the other choice, the rat had a probability of 90% to get 1 food pellet or a probability of 10% to get a 5-s waiting time punishment (hole-light flashed for 5 s). Because the introduction of a long waiting time increased the risk in obtaining the big reward, the choice of big reward became disadvantageous to the rat (the small reward became advantageous). The rat would perform the forced choice task for 10 days to learn the changes in values of the two rewards. Then the rat would be moved to the free choice task for 3 days to test how animals executed the new decision-making strategy, and the neuronal activity of both OFC and mPFC were recorded to be compared with those recordings in stage 1.

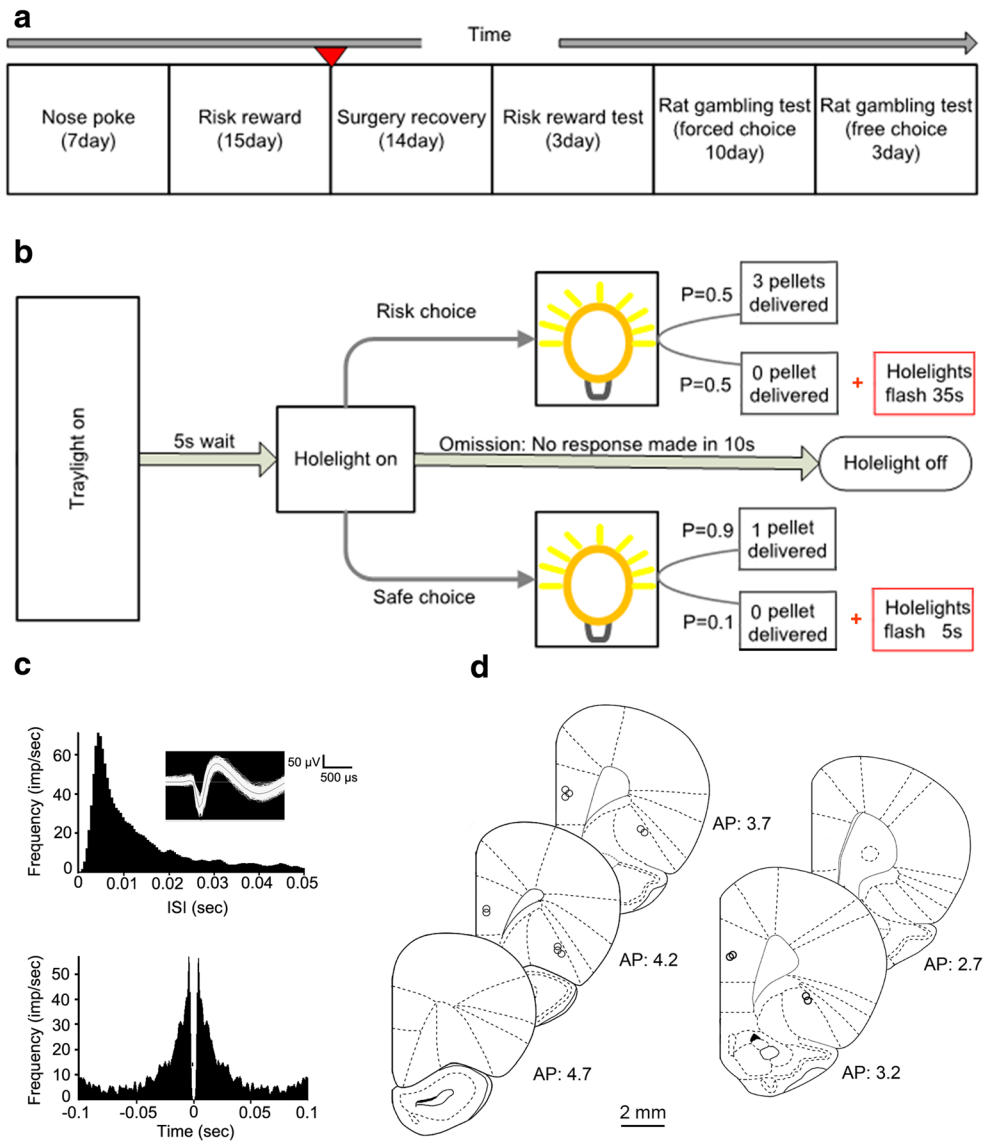

Fig. 1 Schematic diagram showing the experimental paradigms of the risk-based decision-making task, data analysis, and tip localization of the recording electrodes. A: Rats were trained to learn nosepoking for 7 days. Then they were subjected to a 15-day risk-reward task. After the surgical implantation of electrode arrays and a 2-week recovery, rats were subjected to a stage-1 test that lasted 3 days, and then to a stage-2 test that included a 10-day forced choice and a 3-day free choice. B: Experimental paradigm: The rat entered the food reward process when the tray light was turned on. After a nosepoking response was observed, the tray light was turned off and a trial started. After a 5-s delay, the hole light was turned on and the rat got either a food reward or punishment after making a choice. In the stage-1 test, the big reward was defined as 50% chance of getting 3 food pellets and small reward as 90% chance of getting 1 food pellet (the black text box). In the stage-2 test, the punishment was set by waiting time (the red text box). The rat had a probability of 50% to get 3 food pellets or a probability of 50% to get a 35-s waiting time punishment (holelights flashed for 35 s); while for the other choice, the rat had a probability of 90% to get 1 food pellet or a probability of 10% to get a 5-s waiting time punishment (holelights flashed for 5 s). If the rat made no nose poking on the hole within 10s after the holelights were turned on, it was considered as an omission trial. C: An example of a neuronal unit discharge sorted and isolated by an analysis of interspike interval (ISI) histograms and autocorrelograms. D: Tip locations of the recording electrodes, which were histologically verified to be in the mPFC and OFC

Data collection and statistical analysis

As shown in Fig. 1c, autocorrelograms and interspike interval (ISI) histograms were performed on the recorded neuronal unit discharge. In the autocorrelation graph and spike interval graph (Fig. 1c), the absolute refractory period was no shorter than 2 ms. Spikes with absolute refractory periods shorter than 2 ms were considered as noise and were eliminated. The ensemble analysis in the Offline-Sorter software (Plexon, Dallas, Texas, USA) was used for spike sorting.

We recorded a total of 15 sessions in each stage from five rats (two were excluded because of the electrical noise). The total trials, omissions, premature-response trial, reward number, nosepoking time point, and head entry were recorded by

using MEDLAB8 software of the MED Associate System (MED Associates Inc., VT, USA). Statistical analysis of behavioral data and firing frequency of recorded neurons was performed by SPSS19.0. For each session, the preference of choice was calculated as *(trials for choosing big reward - trials for small reward)/total trials*. Then these values of all sessions for each rat were averaged as the final value of preference of choice for one rat. The latency to respond was defined as the time from the cue light being turned on to a nosepoke. The latency to reward was defined as the time from the rat making a nosepoke to the rat obtaining a food reward. The final value of latency to respond for each rat was calculated in the same manner as the final value of preference of choice. Then we compared the latency in big-reward choosing trials vs. that in small-reward choosing trials with repeated two-way ANOVA. All manipulations were specified into 4 experimental conditions: stage-1/big reward, stage-1/small reward, stage-2/big reward, and stage-2/small reward. The decision-making process was divided into four periods with nosepoking at time 0 (0 s): the baseline period (−8 s - -4 s), the nosepoking expectation period (−4 s - 0 s), the reward-expecting period (0 s - 2 s), and the reward period (2 s - 4 s). Each neuron was analyzed in 100 ms bins with the bin as a repeated-measures factor (period), and conditions as an independent-measures factor. Then we determined the type of phasic encoding by comparing the average firing rates over the periods: Neurons with firing frequency significantly higher or lower than baseline ($p < 0.05$, two-way ANOVA with Post-hoc Fisher's LSD test) were grouped as phasic nosepoking-predicting neurons, phasic reward-expecting neurons, and phasic reward-excitatory neurons. Cell firing was normalized to allow population analysis by IBM SPSS Statistics 19.0. The average firing for each cell was grouped into 100 ms bins and the mean and standard deviation of bins were calculated for each baseline. Then each bin was normalized by subtracting the mean firing frequency from the firing frequency in each 100 ms bin and divided by the standard deviation. Unless otherwise stated, results were expressed as mean ± SEM values.

Histology

After all tests, the recording locations in the OFC and mPFC were marked by passing DC current (40-μA) through the recording electrodes for 20s. Then rats were deeply anesthetized with an overdose of pentobarbital (100 mg/kg, i.p.) and were transcardially perfused with 100 ml 0.02 M phosphate buffer and 100 ml 4% paraformaldehyde solution. The brain was removed and sequentially transferred into 10 mM, 20 mM, and 30 mM sucrose solutions. After dehydrating, the brains were transferred into 4% paraformaldehyde for three days. Coronal sections at 50-μM thickness were cut on a freezing microtome (SM2010R, Leica, Nussloch, Germany). The sections were counterstained with Nissl, and the tips of the recording electrodes were confirmed to be located within the OFC and mPFC in all 7 rats (Fig. 1d).

Results

Behavioral testing suggests that rats exhibit different risk preferences and response latencies to food rewards during stage-1 and stage-2

The difference between risk preferences in the two stages was significant ($t_4 = 8.86$, $p < 0.01$, Fig. 2a). Rats showed a significantly decreased interest in the big food reward which was bonded with punishment in stage-2, suggesting that they could identify the preferred choice (i.e., the big reward in stage-1 and small reward in stage-2). Although rats modified their decision-making strategy, the total food amount acquired in stage-2 was less than in stage-1 ($t_4 = 3.48$, $p < 0.05$) (see Table1). Further analysis suggested that the decrease might not be attributable to reduced motivation because the omission rate between in stage-1 and in stage-2 was not significantly different (Wilcoxon test, $z = -1.753$, $p = 0.08$, Table 1).

The experimental design was 2 (stage: stage-1 or stage-2) × 2 (choice: big or small food reward choices), and the response time was recorded under each condition. Repeated two-way ANOVA analysis of latency to respond showed that the interaction effect between stages and choices was not significant ($F_{(1,\ 4)} = 4.71$, $p = 0.096$). The main effect of the experimental stages was significant ($F_{(1,\ 4)} = 78.95$, $p < 0.01$). The latency of stage-2 was significantly shorter than the stage-1 (Fig. 2b). The main effect of choices was marginally significant ($F_{(1,\ 4)} = 6.18$, $p = 0.07$, $p < 0.05$). Post-hoc (LSD) test showed that latency to respond for big food reward was longer than that for small food reward in stage 1 ($p < 0.01$) without significant difference in stage 2 ($p = 0.93$; Fig. 2b). Two-way ANOVA analysis of the latency to reward showed that both the main effect of stages ($F_{(1,\ 4)} = 14.19$, $p < 0.05$) and the main effect of choices ($F_{(1,\ 4)} = 271.44$, $p < 0.001$) were significant (Fig. 2c), whereas the interaction was not significant ($p = 0.15$). LSD test showed that choosing the big-reward option took a shorter time than choosing the small reward option in both stage-1 and stage-2 ($p < 0.001$ for stage-1 and $p < 0.001$ for stage-2).

Electrophysiological results

The firing patterns and numbers of non-specific neurons and nosepoking neurons were similar in OFC and mPFC. But there were no reward-expecting neurons and significantly more reward-excitatory neurons in the mPFC

As shown in Tables 2, 171 neurons (99 from the OFC and 72 from the mPFC) were recorded in stage-1 and 143 neurons (82

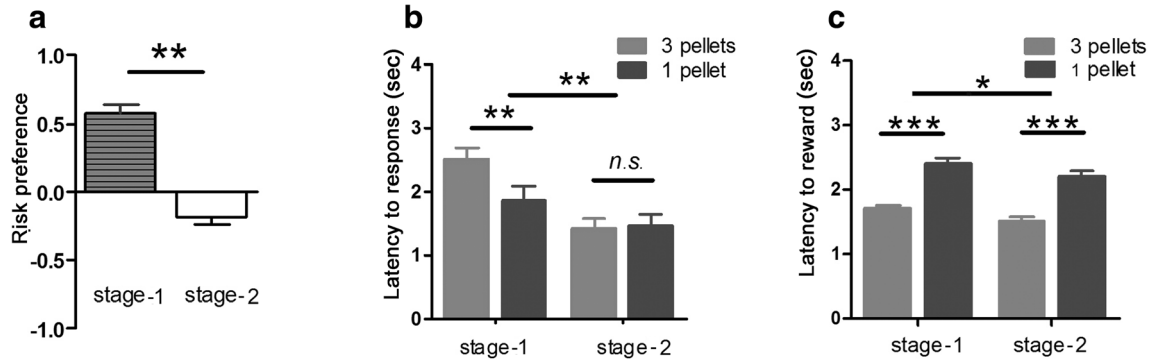

Fig. 2 The rats showed different risk preferences and response latencies to food rewards during stage-1 and stage-2. Data is presented as mean ± SEM. A: The risk preference of stage-1 was significantly higher than that of stage-2. B: Repeated two-way ANOVA analysis showed that the overall latency to response for both big and small rewards during stage-1 was significantly longer than the latency during stage-2. Moreover, post-hoc (LSD) test showed that the latency to big reward choice was significantly longer than the latency to small reward choice during the stage-1 but not during the stage-2. C: Repeated two-way ANOVA analysis ($n = 5$ per group) showed that the overall latency to reward during stage-1 was significantly longer than the latency during stage-2. Post-hoc (LSD) test showed that the latency to 3-pellet reward was significantly shorter than the latency to 1-pellet reward during both stage-1 and stage-2. * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$

from OFC and 61 from mPFC) were recorded in stage-2. In the OFC, about half (53.54% or 53/99) of the neurons recorded were *non-specific* neurons, whereas 46.46% of the neurons (46 out of 99) showed characterized firing patterns, including 19 (19.19%) nosepoking-predicting neurons, 22 (22.22%) reward-expecting neurons, and 5 (5.05%) reward-excitatory neurons. In contrast, in the mPFC, although a similar percent (45.83% or 33/72) of the cells were *non-specific* neurons ($\chi^2 = 0.49$, $p = 0.48$), 54.17% of the neurons (39 out of 72) showed characterized firing patterns, including 19 (26.34%) nosepoking-predicting neurons, and 20 (27.78%) reward-excitatory neurons. There was no difference in nosepoking-predicting cells between the two brain areas ($\chi^2 = 0.98$, $p = 0.32$), but mPFC had no reward-expecting cell and significantly more reward-excitatory neurons ($\chi^2 = 14.73$, $p < 0.01$). Similarly, in stage-2, the majority of the cells (50/82 or 60.98%) were *non-specific* neurons and about one-third of the neurons (32/82 or 39.02%) were characterized by firing patterns in the OFC, including 14 (17.07%) nosepoking-predicting neurons, 16 (19.51%) reward-expecting neurons, and 2 (2.24%) reward-excitatory neurons. This distribution pattern was similar in the mPFC, with about 34/61 (55.74%) *non-specific* cells and 27/61 (44.26%) characterized firing cells, including 10 (16.39%) nosepoking-predicting neurons and 17 (27.87%) reward-excitatory neurons (see Table 2).

Table 1 Behavioral testing results (*Mean* ± *SE*)

	Stage-1 ($n = 5$)	Stage-2 ($n = 5$)
Total trials	83.47 ± 4.95	77.30 ± 4.59
Premature	7.60 ± 3.13	14.46 ± 1.89
Omission rate	6.40 ± 1.32	2.52 ± 0.86$^{\#}$
Food amount	122.06 ± 7.91	83.07 ± 7.13*
Risk preference	0.58 ± 0.11	−2.16 ± 0.85**

Again, no reward-expecting cells were found in the mPFC in stage-2. Chi-square tests showed no significant difference between the two brain areas in nosepoking-predicting cells in stage-2 ($\chi^2 = 0.01$, $p = 0.92$), as well as the total neuron numbers of *non-specific* neurons from stage-2 ($\chi^2 = 0.16$, $p = 0.69$).

Nosepoking-predicting neurons in OFC encode the overall value of reward and strategy

Nosepoking-predicting neurons were recorded in both stage-1 and stage-2. A representative neuron is shown in Fig. 3a-d. The standardized firing reactions of all nosepoking-predicting neurons were shown in Fig. 3e for stage-1, and in Fig. 3F for stage-2. The nosepoking-predicting neurons exhibited more robust firing activity to big reward (the preferred choice at this stage) than to small reward ($t_{36} = 20.22$, $p < 0.001$) in stage-1 (Fig. 3e). However, in stage-2, the same group of neurons exhibited more robust firing to small reward (the preferred choice at this stage) than big reward ($t_{26} = 11.90$, $p < 0.001$, Fig. 3f). Apparently, OFC nosepoking-predicting neurons exhibited stronger response (increase in firing frequency) to the preferred choice in the corresponding stage, indicating that these neurons not only represented the amount of reward or probability, but also the overall values of the rewards.

Reward-expecting neurons show more intensive firing to big food reward in OFC

As shown in Fig. 4, reward-expecting neurons displayed characteristic firing in the reward-expecting period (2 s after a nosepoking). Either in stage-1 (Fig. 4a-c) or stage-2 (Fig. 4d-f), the firing of reward-expecting neurons gradually decreased from big reward to small and then to no reward. In stage-1, the overall neuronal firing activity of reward-

Table 2 Neuronal firing patterns in OFC and mPFC

	OFC		mPFC	
	Stage-1	Stage-2	Stage-1	Stage-2
Nosepoking-predicting neurons	19 (19.19%)	14 (17.07%)	19 (26.34%)	10 (16.39%)
Reward-expecting neurons	22 (22.22%)	16 (19.51%)	–	–
Reward-excitatory neurons	5 (5.05%)	2 (2.44%)	20 (27.78%)	17 (27.87%)
Non-specific neurons	53 (53.54%)	50 (60.98%)	33 (45.83%)	34 (55.74%)
Total	99	82	72	61

expecting neurons was standardized (in Fig. 4g). One-way ANOVA analysis showed that these neurons exhibited a significantly different response to the three different reward sizes (big/small/no food reward) ($F_{(2,\ 63)} = 33.27$, $p < 0.001$). LSD test showed that the neuronal firing activity was significantly different between the three reward sizes ($p < 0.01$ for small reward vs. no reward; $p < 0.001$ for big reward vs. small reward and $p < 0.001$ for big reward vs. no reward). Fig. 4h shows the overall standardized neuronal firing activity of reward-expecting neurons in stage-2. One-way ANOVA analysis indicated that reward-expecting neurons exhibited a significantly different response to the three different reward sizes (big/small/no food reward, $F_{(2,\ 45)} = 43.43$, $p < 0.001$). LSD test showed that the neuronal firing activity was significantly different between any of the two rewards.

Nosepoking-predicting neurons in mPFC show a close correlation with decision-making strategy

Figure 5a-d display the firing patterns of a representative nosepoking-predicting neuron during stage-1 (Fig. 5a, b) and stage-2 (Fig. 5c, d) big and small rewards, respectively. The standardized responses of all nosepoking-predicting neurons were summarized in Fig. 5e, f. The mPFC nosepoking-predicting neurons exhibited more intensive firing to the expectation of small food reward than to big reward in both stage-1 and stage-2, although this did not reach significance (main effect of reward size, $F_{(1,54)} = 0.64$, $p = 0.429$). Furthermore, the firing frequency to either big food reward or small reward in stage-2 was similar to the values in stage-1 (main effect of stage, $F_{(1,54)} = 0.40$, $p = 0.529$). These results indicate that nosepoking-predicting neurons in the mPFC are specialized in monitoring the encoding of clues but not in switching the decision-making strategy.

The response of excitatory neurons to reward is inhibited in nosepoking stage in the mPFC

Figure 6 shows the firing pattern of a representative rewarding neuron in stage-1 (Fig. 6a-c) and stage-2 (Fig. 6e-g), and the standardized overall neuronal activity of all reward neurons (Fig. 6d, h). One-way ANOVA analysis showed that the neuronal firing frequencies were significantly different among the three reward sizes in both stage-1 ($F_{(2,\ 57)} = 152.45$, $p < 0.001$; Fig. 6d) and stage-2 ($F_{(2,\ 48)} = 172.51$, $p < 0.001$; Fig. 6h). LSD test showed that the rewarding neurons could distinguish whether there was food reward, but not the differences between the big and small rewards in either stage 1 or stage 2 (stage1: $p = 0.15$ for 3 pellets vs. 1 pellet, $p < 0.001$ for 3 pellets vs. 0 pellet, $p < 0.01$ for 1 pellet vs. 0 pellet; stage2: $p = 0.13$ for 3 pellets vs. 1 pellet, $p < 0.001$ for 3 pellets vs. 0 pellet, $p < 0.01$ for 1 pellet vs. 0 pellet). Another characteristic of reward-excitatory neurons was that their activities were reduced during the nosepoking period. Each trial was divided into pre-nosepoking (−4–2 s), nosepoking (−2–2 s), and post-nosepoking (2–4 s) periods. In both stage-1 and stage-2, the firing frequencies among the three periods were significantly different (stage-1: Fig. 6i, j, $F_{(2,\ 57)} = 25.32$, $p < 0.001$. LSD test: $p < 0.001$ for pre- vs. during- nosepoking period; $p < 0.001$ for during- vs. post-nosepoking period, $p < 0.01$ for pre- vs. post-nosepoking periods; stage-2: Fig. 6k, l,$F_{(2,\ 48)} = 10.02$, $p < 0.001$. LSD test: $p < 0.001$ for pre- vs. during- nosepoking period; $p < 0.001$ for during- vs. post-nosepoking period, $p = 0.48$ for pre- vs. post-nosepoking periods; one-way ANOVA). All of these neurons were inhibited during nosepoking.

Discussion

In this study, three rats were excluded based on our exclusion criteria. The remaining 7 rats could effectively identify the more valuable strategic choice for an optimal decision; that is, a selection of greater reward in stage-1, and a selection of lesser reward in stage-2, suggesting that rats can evaluate the integral value of choice (Zeeb et al. 2009). Previous studies in human subjects have used the two-stage Iowa Gambling Task (IGT), in which stage-1 is described as a stage of selection, a period from the appearance of signal to the making of a selection. The stage-2 is the results appraisal stage, a period during which the results are experienced (Christakou et al. 2009). The RGT task used in our study is similar to the IGT task. With this test, we found that neurons in the OFC and mPFC encoded

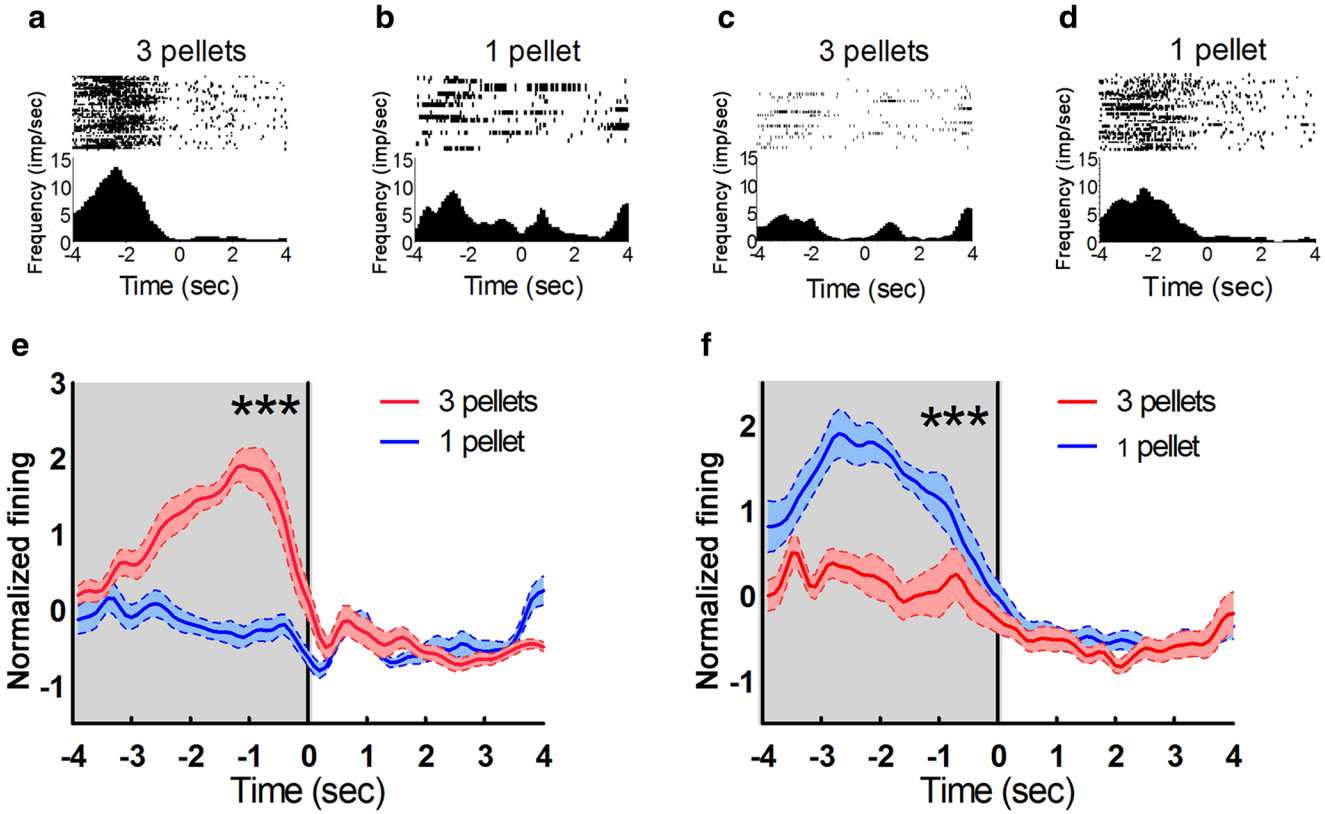

Fig. 3 Nosepoking-predicting neurons in the OFC exhibited a significantly stronger response to big reward than to small reward in stage-1, but an increased response to small reward and reduced response to big reward in stage-2. Bin: 100 ms. Nosepoking at time 0 s on the X-axis. Data is presented as mean ± SEM. A–D: Perievent raster analysis of a single nosepoking-predicting neuronal firing recorded from OFC. During stage-1 (**a** and **b**) this neuron exhibited more robust firing to big food reward (**a**) than to small food reward (**b**). However, during stage-2 (**c** and **d**), this same neuron exhibited more robust firing to small food reward (**d**) than to big food reward (**c**). **e** and **f**: Normalized and averaged firing response of all OFC nosepoking-predicting neurons to food rewards during stage-1 (**e**) and stage-2 (**f**). Neurons exhibited a significantly stronger response to big food reward than to small food reward in stage-1, but an increased response to small reward and no response to big reward in stage-2. Student's *t* test, stage-1 $n = 19$, stage-2 $n = 14$, *** $p < 0.001$. This reversed response suggests that in the early stage of the task, nosepoking cells' response is motivated by food reward, but these same cells will also increase the firing strength to drive the animals to re-evaluate the reward value by punishment. These data indicate that nosepoking-predicting cells in the OFC are associated with both reward and punishment

both reward and strategy-updating signals in a risk-based decision process during the two stages of the task. We observed both similarities and differences in the firing types and characteristics of these neurons. Specifically, the discharge changes of the characteristic neurons were correlated with rats' behavioral selection preferences. Moreover, neurons in the OFC and mPFC could also predict the potential reward even without the cue signal: for instance, based on memory only, which is different from the previous findings reported in the cue-prediction tasks (Ogawa et al. 2013; Roitman and Roitman 2010).

The OFC nosepoking-predicting neurons could promptly change their discharging pattern during stage-2, indicating that this type of neuron encoded the integral value of the choice, including numerical information or probability information in addition to waiting time information. This is a very interesting and novel finding, although it is in discrepancy with a previous report. Burton et al. (2014) reported the existence of neurons in OFC representing reward amount and reward delay (Burton et al. 2014). However, in their study, each type of these neurons could only encode one dimension of the reward choice. We noticed that in their experiment, the waiting time and reward were derived from different trials. Therefore, the choice only included one-dimensional information. As a result, they concluded that different choices were encoded by different neurons. In the present study, we found that one type of neurons could encode two different choices. This is because, in our experiment, the waiting time was mixed with the amount of food reward, and rats had to make a decision based on the overall value of a choice. In addition, previous studies suggested that the OFC encodes abstract information (e.g. representative, behavioral and rewarding related information) in complex situations (Stalnaker et al. 2015; Wilson et al. 2014). Our findings were in support of this assumption. Indeed, during the context change, OFC updates the strategy in encoding value information.

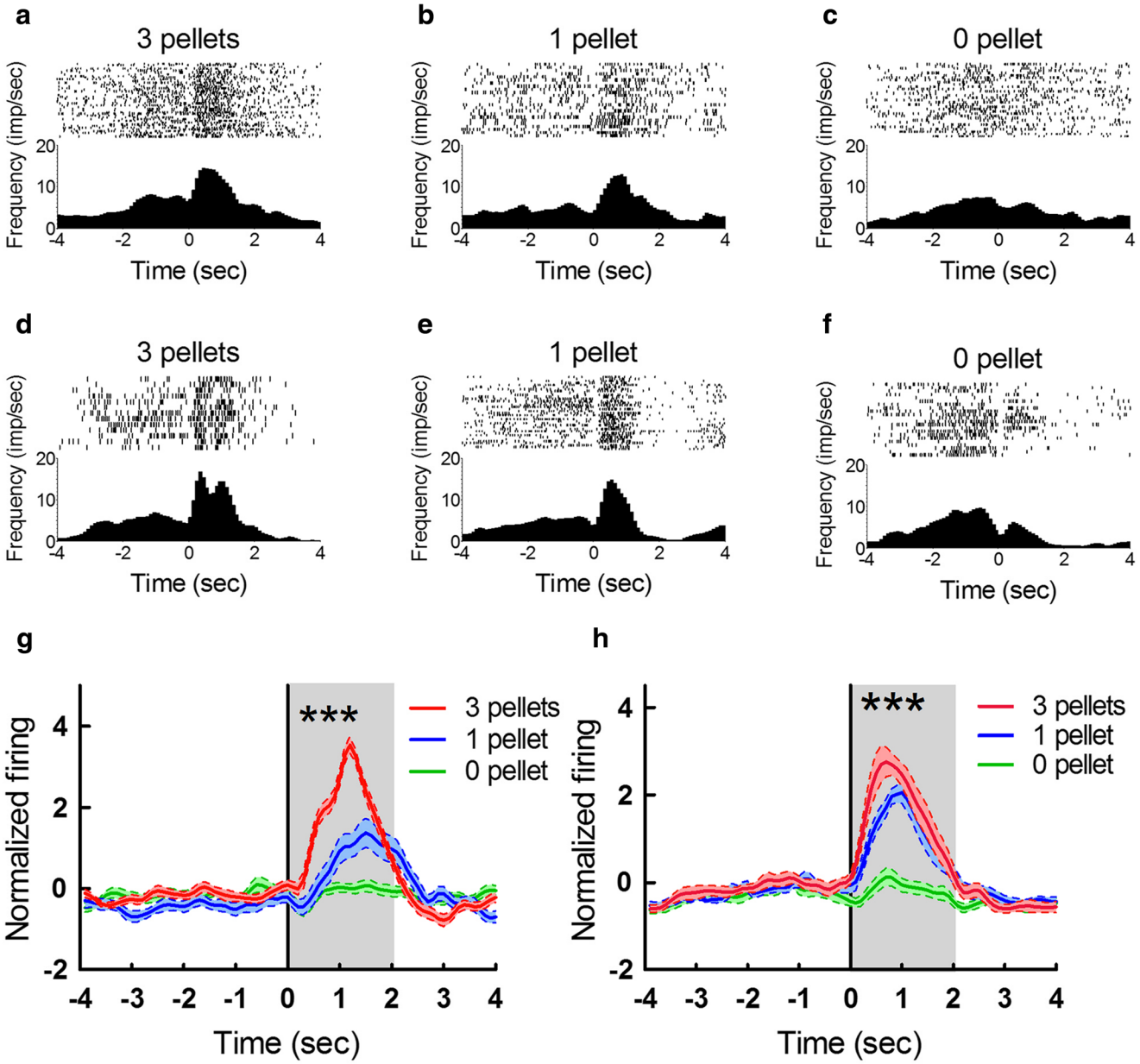

Fig. 4 Reward-expecting neurons in the OFC exhibited reward dependent responses in both stages. Nosepoking at time 0 s on the X-axis. Data is presented as mean ± SEM. A-F: Perievent raster analysis of a single reward-expecting neuronal firing recorded from OFC during stage-1 (**a**-**c**) and stage-2 (**d**-**f**). Bin: 100 ms. **g**-**h**: Normalized and averaged firing responses of all reward-expecting neurons during stage-1 (**g**) and stage-2 (H). Two-way ANOVA with post hoc Fisher's LSD, stage-1 $n = 22$, stage-2 $n = 16$, *** $p < 0.001$. During both stage-1 and stage-2, the reward-expecting neurons exhibited significantly stronger responses to big food reward and smaller responses to no reward. However, the neuronal responses in stage-2 were weaker in differentiating the reward size

Reward-expecting neurons were also recorded from the OFC. We found that the firing frequencies were significantly higher than baseline during the period from nosepoking to food reward. In both stage-1 and stage-2, the firing frequencies increased as the reward was increased. In the Pavlovian over-expecting task, OFC was involved in the outcome expectation. When the rat was expecting a bigger reward, the OFC neuron activity intensified and the expectation to reward would promote further behavioral response and learning (Takahashi et al. 2011). Although OFC could characterize the reward expectation information, it could not directly encode the outcome-related action information (Rushworth et al. 2007). The role of OFC is thus to utilize the expected outcome to guide the subsequent behavior (Schoenbaum et al. 2006). In our study, in both stage-1 and stage-2, reward-expecting neurons did not change their firing patterns when the strategy was updated, suggesting that this type of neuron probably only represented the information of expected food amount. Another explanation is that the nosepoking action changed

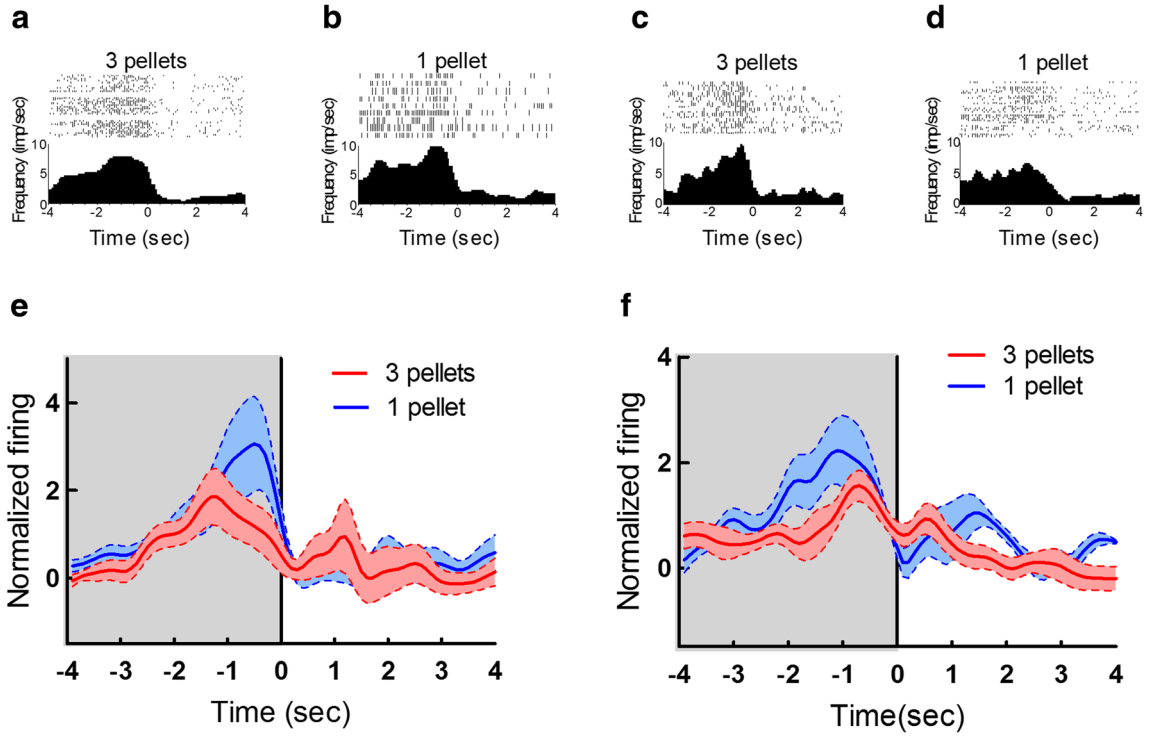

Fig. 5 Nosepoking-predicting neurons in the mPFC exhibited a significantly stronger response to big reward in stage-1 but no difference in stage-2 due to an increased response to small reward and relatively no change in response to big reward in stage-1 vs. stage-2. Nosepoking at time 0 s on the X-axis. Data is presented as mean ± SEM. A-D: Perievent raster analysis of a single nosepoking-predicting neuronal firing recorded from mPFC during stage-1 (**a**-**b**) and stage-2 (**c**-**d**). Bin: 100 ms. E and F: Normalized and averaged firing response of all mPFC nosepoking-predicting neurons to food rewards during stage-1 (**e**) and stage-2 (**f**). The mPFC nosepoking-predicting neurons exhibited more but not significantly intensive firing to the expectation of small food reward than to big reward in both stage-1 and stage-2 (main effect of reward size, $F_{(1,54)} = 0.64$, $p = 0.429$). Furthermore, the firing frequency to either big food reward or small reward in stage-2 was similar to the values in stage-1 (main effect of stage, $F_{(1,54)} = 0.40$, $p = 0.529$)

the decision confidence that was computed in the OFC (Kepecs et al. 2008).

Nosepoking-predicting neurons recorded in mPFC exhibited no correlations with decision-making strategy updating. This type of neuron showed more, but not significantly more, intensive firing to small food reward than to big one in both stage-1 and stage-2. In addition, there was no difference between stage-1 and stage-2 in response to either big or small reward. The reason that this type of neuron had not formed a significant preference was probably attributable to the unstable strategy. Risk-based decision-making depends on retrieval of memory. The mPFC plays a role in memory formation, consolidation, and retrieval (Euston et al. 2012). Previous studies have demonstrated that mPFC encodes information of action and outcome into working memory to further direct a series of action behaviors (Corbit and Balleine 2003). Thus, the nosepoking-predicting neurons might just act to hold the attention instead of encoding specific information.

While a unique population of reward-excitatory neurons was found in mPFC, only a few (5%) were found in OFC and we do not consider them being a specific functional group. The firing of this group of neurons intensified significantly during the period of food-reward, and the discharging pattern remained unchanged between the two stages, indicating that the mPFC participated in the evaluation of outcome information. This group of neurons was suppressed when the rat was performing the holepoking task, suggesting that they would be involved in the control of running action or maintaining attention to get food reward, which is independent of the encoding of outcome information, because there was no difference of firing suppression among the three reward conditions. Based on the learning-enforcement theory, the function of mPFC is to guide current behavior utilizing already-known information (Alexander and Brown 2011), and our findings support this assumption.

The nosepoking-predicting neurons in the OFC and mPFC were mainly involved in the "valuation of each of the potential actions" in the decision-making process. The presence of nosepoking-predicting neurons indicated that the rats predicted the possible outcomes and formed the expected value. Then the actual and subsequent results were compared with each other to evaluate the difference between the outcome and the expected value in the learning of the potential value of the options. This process was conducive to the continuous adjustment of choices to form a better strategy, which played an important role in decision making. Nosepoking-predicting in

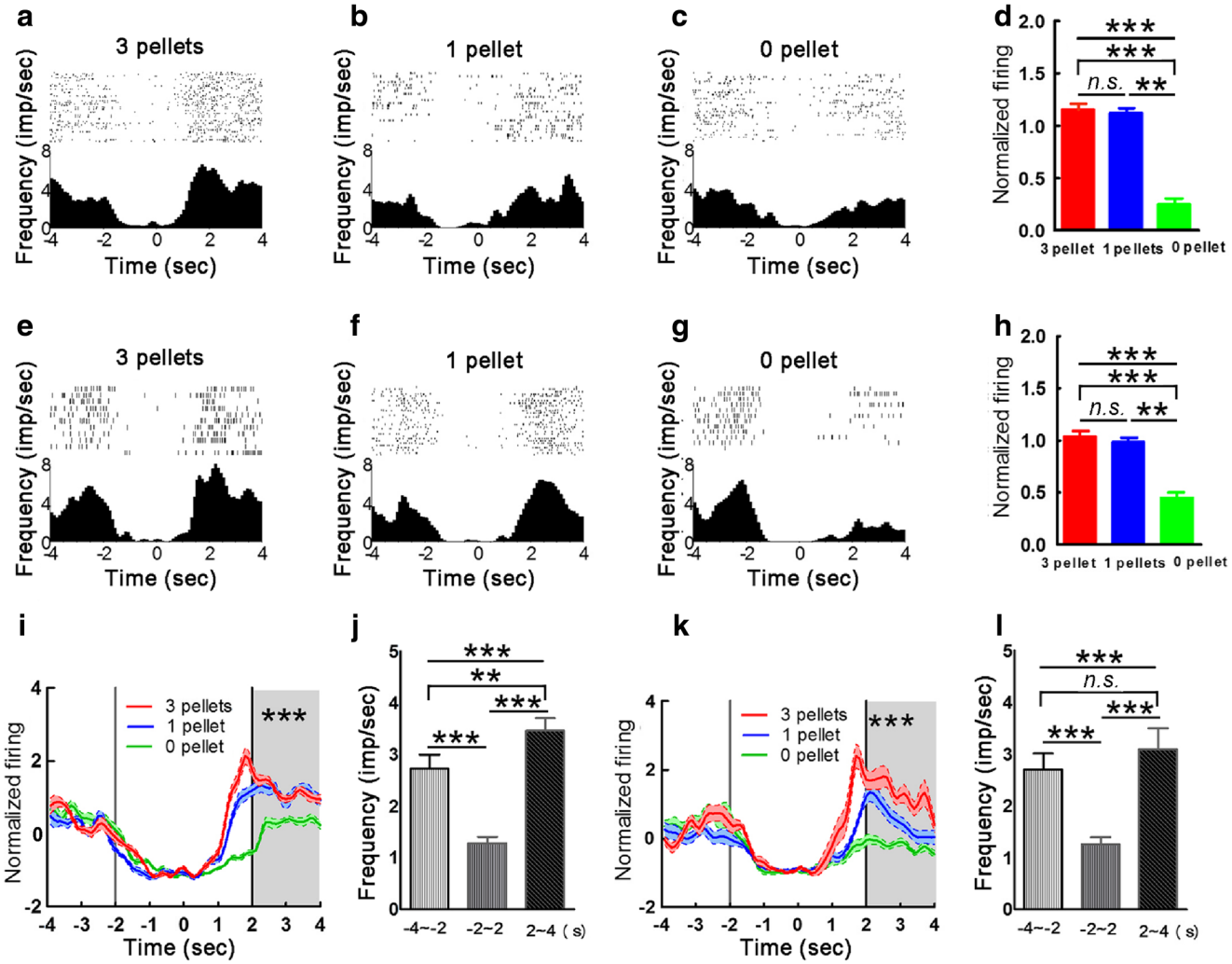

Fig. 6 Responses of reward-excitatory neurons in the mPFC were significantly inhibited by the action of nosepoking and activated by post-nosepoking rewards in both stages. Bin: 100 ms. Nosepoking at time 0 s on the X-axis. Data is presented as mean ± SEM. **a**-**c**: Perievent raster analysis of a single reward-excitatory neuronal firing recorded from mPFC during stage-1. **d**: Normalized and averaged firing response of all trials ($n = 20$) during stage-1. Post-hoc (LSD) test noted that the response was not significantly different between the big and small food rewards ($p > 0.1$) but both significantly stronger than no food reward (*** $p < 0.001$). **e**-**g**: Perievent raster analysis of the same rewarding-excitatory neuronal firing during stage 2. **h**: Normalized and averaged firing response of all trials ($n = 17$) during stage-2. Similar to stage-1, the responses were not significantly different between the big and small food rewards ($p > 0.1$) but both significantly stronger than no food reward (*** $p < 0.001$). **i**-**l**: Normalized and averaged firing response of all mPFC rewarding-excitatory neurons ($n = 54$) in pre- (−4–2 s), during (−2–2 s), and post- (2–4 s) nosepoking periods. Post-hoc (LSD) test showed that the neuronal firing frequency was significantly reduced during nosepoking period (I: stage-1, $p < 0.001$; **k**: stage-2, $p < 0.001$) and significantly increased during reward period (J: stage-1, $p < 0.001$; L: stage-2, $p < 0.001$) in both stage-1 and stage-2 (*** $p < 0.001$)

the OFC also participated in the updating of strategy; that is, it updated memory and made future expectations. In addition, there were reward-expecting neurons in the OFC. The reward-expecting neurons were related to reward seeking. Reward-expecting neurons were found in monkey and rat striatum, orbitofrontal cortex, and amygdala (Schultz 2000). When the expected reward was delayed in the future, the neurons extended their activities. The reward-expecting neurons of the orbitofrontal cortex encoded an expectancy for the consequences of the response based on experience in the task and participated in the evaluation of differences between the outcome and the expected value so that the reward-expecting neurons could guide the next decision by correcting current decisions (Schultz 2000; Shadlen and Shohamy 2016).

Both OFC and mPFC participate in the formation and execution of risky decision-making. However, the OFC is more involved in the representation of the learning process of risky decision-making, while the mPFC participates in both learning and execution processes of risky decision-making. The OFC nosepoking-predicting neurons predicted the overall value of rewards, and the OFC also played a role in strategy switching as the task was updated. Although the mPFC nopokeing-predicting neurons predicted the coding of the reward outcome, they did not help to switch the strategy as the

task was updated. The results suggested that the mPFC could only predict whether there was a reward. For the functional differences in the recognition of rewards in the two brain regions, a probable reason is that the OFC is involved in stimulus-outcome coupling (Ostlund and Balleine 2007; Pickens et al. 2003). Therefore, the OFC might be related to the coding of integrated value of rewards and the learning of strategies. While the mPFC is more important in response-outcome coupling, it is also important in executive functions such as attention, working memory, and planning. Therefore, the mPFC mainly participated in the judgment of reward results and the learning and maintenance of strategies. It also played an important role in the execution of strategies. In short, the OFC might act as a "computing center" in the process of risky decision-making, but the mPFC acts more like an "executive center". Besides the prefrontal cortex structures such as mPFC and OFC, the basolateral amygdala and nucleus accumbens of the subcortical nucleus were also reported to play a crucial role in risk decision-making (Stopper and Floresco 2015; Wenqiang et al. 2016). In particular, the prefrontal cortex - basolateral amygdala - nucleus accumbens neural circuit is the key in determining the choice of risk decision-making (St Onge et al. 2012).

There are a few limitations in this study that need to be addressed. First, because of the technical difficulties, the sample size of this study was relatively small, in which only 7 (out of 10) rats completed the behavior tests and the neuronal recording data of 5 (out of these 7) rats are presented in this article. Despite of the small sample size, our conclusions are supported by statistical tests revealing significances between key values. Second, our rodent gambling task is similar to sections of the IGT in the primate animals (Zeeb and Winstanley 2011; Visser et al. 2011). The difference was that we used a primary reinforcer (food pellets) in our rat RGT. As shown in our study, the primary reinforcer is equally effective as the secondary reinforcer (money) used in the primate IGT (Visser et al. 2011). Third, although a general gambling task was used in this study, we revealed the contributions of OFC and mPFC in risky/probabilistic decision-making. The same paradigm can be applied to animal disease models to explore the abnormalities in OFC and mPFC in schizophrenia, attention deficit hyperactivity disorder (ADHD), addiction, and eating disorders.

Conclusions

Neurons in the OFC and mPFC exhibit distinct responses in the decision-making process during reward consumption and strategy updating. Neuronal activity in the OFC represents the overall value of choice for directing a strategy, while neuronal activity in the mPFC plays a key role in monitoring and execution of a strategy. The existence of reward-associated neurons in both OFC and mPFC indicates that their functions are based on the evaluation of outcomes. The OFC plays an important role in expecting a reward, whereas the mPFC evaluates the outcome to identify whether there is a reward.

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Authors Contributions Wen-Qiang Huang, Ai-Ai Ji, Sha-Sha Yang and Ke-Yi Sun conducted the experiments, Dan-Dan Hong, Wen-Qiang Huang and Ai-Ai Ji analyzed the data. Dan-Dan Hong, Wen-Qiang Huang, Sha-Sha Yang, Hui Xu and Aihua Cao wrote the results and manuscript. Wen-Jun Gao revised the paper. Ning Zhou conceived and supervised the project. Ping Yu conceived and supervised the project and wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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