Neurosci Bull December 1, 2012, 28(6): 693–703. http://www.neurosci.cn
DOI: 10.1007/s12264-012-1291-x

·Original Article·

Anticipatory activity in rat medial prefrontal cortex during a working memory task

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Abstract: Objective Working memory is a key cognitive function in which the prefrontal cortex plays a crucial role. This study aimed to show the firing patterns of a neuronal population in the prefrontal cortex of the rat in a working memory task and to explore how a neuronal ensemble encodes a working memory event. **Methods** Sprague-Dawley rats were trained in a Y-maze until they reached an 80% correct rate in a working memory task. Then a 16-channel microelectrode array was implanted in the prefrontal cortex. After recovery, neuronal population activity was recorded during the task, using the Cerebus data-acquisition system. Spatio-temporal trains of action potentials were obtained from the original neuronal population signals. **Results** During the Y-maze working memory task, some neurons showed significantly increased firing rates and evident neuronal ensemble activity. Moreover, the anticipatory activity was associated with the delayed alternate choice of the upcoming movement. In correct trials, the averaged pre-event firing rate (10.86 ± 1.82 spikes/bin) was higher than the post-event rate (8.17 ± 1.15 spikes/bin) (P <0.05). However, in incorrect trials, the rates did not differ. **Conclusion** The results indicate that the anticipatory activity of a neuronal ensemble in the prefrontal cortex may play a role in encoding working memory events.

Keywords: anticipatory activity; working memory; rat; medial prefrontal cortex; neuronal ensemble

1 Introduction

Working memory is a key cognitive function, defined as the process of holding relevant representations when behavioral events are separated by temporal delays. These active representations are short-lived, but can be maintained and used to plan future behaviors[1-4].

It is well-recognized that the medial prefrontal cortex (mPFC) participates in several high-order processes including working memory, selective attention, decision making, and goal-directed behaviors[3,5-8]. Several reports have also suggested its crucial role in working memory[9,10]. The mPFC in rat consists of four main subdivisions, the medial agranular, anterior cingulate (AC), prelimbic (PL) and infralimbic cortices[10-12]. Inactivation of the ventral mPFC (PL and AC cortices), produces marked deficits in delayed-response tasks involving short or long delays[13-20]. Recent evidence indicates that the PL cortex is directly involved in limbic/cognitive functions, homologous to the dorsolateral prefrontal cortex (DLPFC) in primates[21], which is necessary for delayed-response tasks[2,22]. But how neuronal activity in the mPFC encodes behavior during a working memory task is still an open question.

In 1949, Hebb published the Cell Assembly Theory

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Article ID: 1673-7067(2012)06-0693-11
Received date: 2012-03-12; Accepted date: 2012-07-14

and assumed that assemblies of synchronously activated neurons are elementary to information processing in the brain. He also hypothesized that memory encoding is implemented by a neuronal population in which individual neurons participate in different cell assemblies during multiple cognitive functions. After several decades, it is increasingly recognized that the investigations of neuronal ensemble coding mechanisms are effective for exploring and understanding the neuronal basis of behavior[23-28]. According to Hebb's rule, memory formation involves the strengthening of synaptic connections between neurons. After training, synaptic connections between mPFC neurons are strengthened and neuronal ensembles form. Previous research showed that neuronal activity in the PFC increases throughout the training of animals to remember past events and prepare for future behavior, suggesting that working memory is mediated by neuronal activity[29]. However, it is still unclear how working memory is encoded within the PFC population[29].

In the present study, we analyzed the characteristics of neuronal ensemble activity in rat mPFC during a working memory task, to explore the mechanism by which such activity encodes and predicts behavior during working memory.

2 Materials and methods

2.1 Animals Male Sprague-Dawley rats weighing 300–350 g at the start of the experiment were used. They were first acclimatized to the handling procedures for two days. Then, food access was limited to 2 h per day. The quantity of food was adjusted to maintain body weight at 85% of individual baseline free-feeding weight, adjusted for growth. Water was freely available. All surgical and experimental procedures conformed to the Guideline for the Care and Use of Laboratory Animals and were approved by the Tianjin Medical University Animal Care and Use Committee.

2.2 Apparatus The Y-maze was made of gray plastic sheeting, and consisted of three arms that extended at 120° from the central point. Removable guillotine doors were used to control access to certain parts of the maze. One arm (arm A) was set as the starting point while the others were the goal arms (arms B and C). Food cups were placed at the ends of the goal arms. Small pieces of food were placed in the food cups as a reward for correct responses.

2.3 Habituation Two days after initiation of food restriction, rats were habituated to the Y-maze and the smell of food over two consecutive days. Rats received 30-min free access to all maze areas and were permitted to collect food pieces from all food cups twice daily. Beginning on the second day of habituation, movement of the guillotine doors was introduced into the experiment.

2.4 Working memory task Following habituation, rats were given two training sessions per day. Each trial consisted of a free choice and a delayed alternation. At the beginning of a trial, small pieces of food reward were placed in the food cups in arms B and C. The rat was placed at the start arm A and required to have a 'sample run', that is, a free choice between arms B and C. After consuming the reward, the rat returned to the start A by itself. After a 5-s delay, it underwent a 'choice run', in which it would receive a reward only if it entered a previously unexplored arm (that is, the arm was alternated). If the rat entered the arm visited already in the 'sample run', an error was recorded and it received no reward. After a trial, the animal was allowed to return to A to start the next trial. Training continued until the animals reached an acquisition criterion of at least 8 correct out of 10 trials on two consecutive days.

2.5 Chronic implant surgery Once the rats reached the acquisition criterion, chronic implant surgery was performed[30,31]. Briefly, the rat was anesthetized with chloral hydrate (350 mg/kg), and a 16-channel microelectrode array was implanted under aseptic conditions into the mPFC at a target location at the PL cortex, according to the rat brain stereotaxic coordinates (2.5–4.5 mm anterior to bregma, 0.2–1.0 mm lateral to midline, 2.5–3 mm deep from cortical surface). The size of the implanted array was 2×0.3 mm^2, with 0.25 mm interelectrode spacing. After recovery, neuronal activity was recorded during the working memory task. To check the accuracy of location of the implant, perfusion, fixation and histological examination were performed after recording. All the experimental pro-

cedures are shown in Fig.1.

2.6 Data preprocessing Wideband signals were recorded during trials with a Cerebus data acquisition system (Cyberkinetics, Foxborough, MA). The occurrence of behavioral events was marked online by an infrared sensor in the Y-maze. Local field potentials (low-pass filter 0.3–500 Hz) were extracted from each wideband channel *via* digital filters in the Neural Signal Processor. Spikes (high-pass filter 250–7 500 Hz) exceeding the voltage threshold were sampled at 30 kHz per channel and stored with time stamps. Single neurons with a signal-to-noise ratio of <3.0 and a very low baseline firing rate (<30 spikes/min) were discarded. The recorded signal was in fact an integrated signal produced by several neurons near the tip of the microelectrode, rather than that produced by a single neuron. Therefore, spike-sorting was performed to classify different neuronal firings. Here, an offline sorter was used to separate the activity of single neurons. The flow from raw data to spatio-temporal trains is illustrated in Fig. 2.

3 Results

We recorded neuronal ensemble activity from the rat mPFC during the performance of a working memory task. All the sessions were divided into training sessions (before surgery) and recording sessions (after surgery).

3.1 Behavioral results The rats were trained to perform the Y-maze working memory task on continuous days before surgery. Improvement in behavioral performance was indicated by a gradual increase in the percentage of trials completed correctly. The criterion of at least 8 correct out of 10 trials on two consecutive days generally stabilized after 7 days of training (Fig. 3).

All the trials in the task were sorted by four conditions: LR (sample run: left arm; choice run: right), RL (sample run: right; choice run: left), LL (sample run: left; choice run: left) and RR (sample run: right; choice run: right). Specifically, LR and RL were correct trials, whereas LL and RR were incorrect trials. From a total of 128 tri-

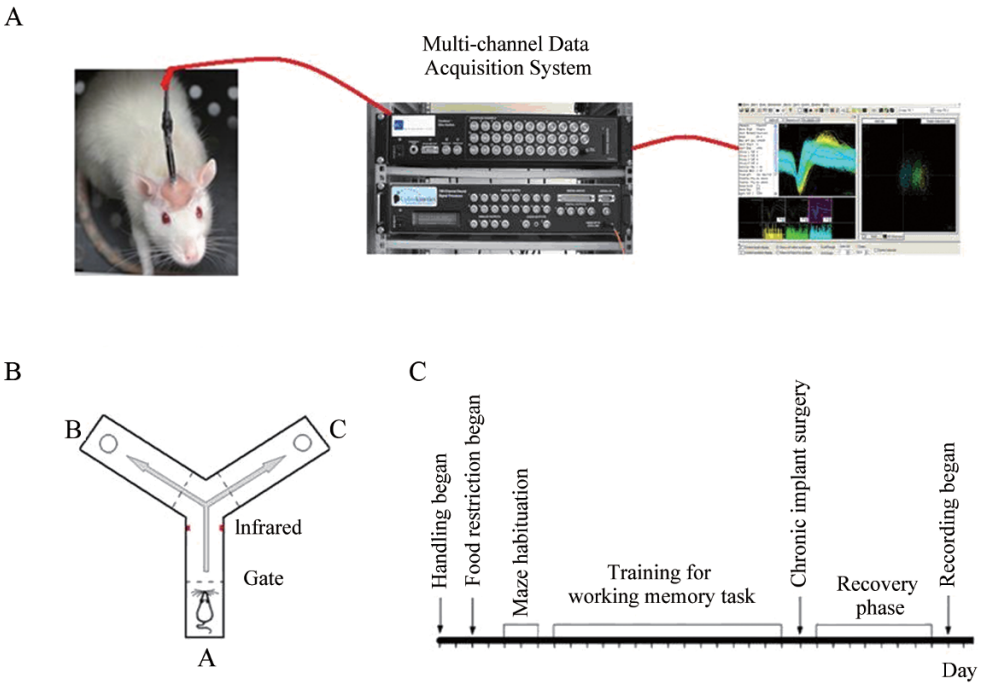

Fig. 1. Experimental setup and procedures. A: Experimental setup, consisting of microelectrode implantation, the Cerebus data acquisition system and analysis software. B: Schematic drawing of the Y maze. Dashed lines represent the removable guillotine doors. The occurrence of behavioral events was detected by an infrared sensor. A was the starting position. Food cups, which were used for reward delivery, were located at the ends of arms B and C. Arrows show possible correct paths. C: Timeline of the experiment.

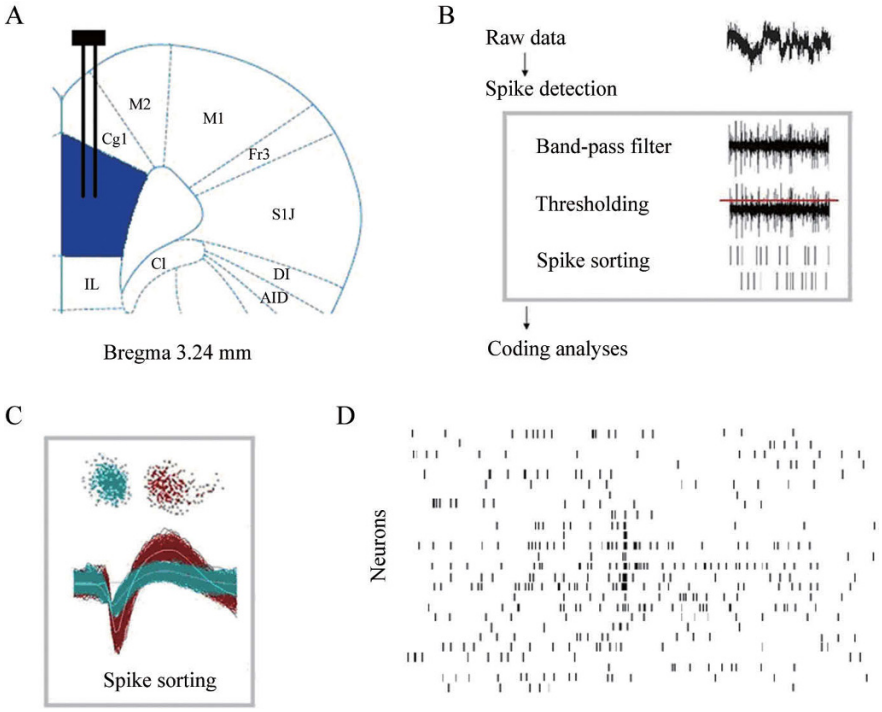

Fig. 2. Flow of preprocessing from raw data to spike trains. A: Location of cortical implant in rats. B: Flow of preprocessing. C: Schematic representation of spike sorting. D: Rastergram of medial perfrontal cortex neurons recorded during a trial in the Y-maze task.

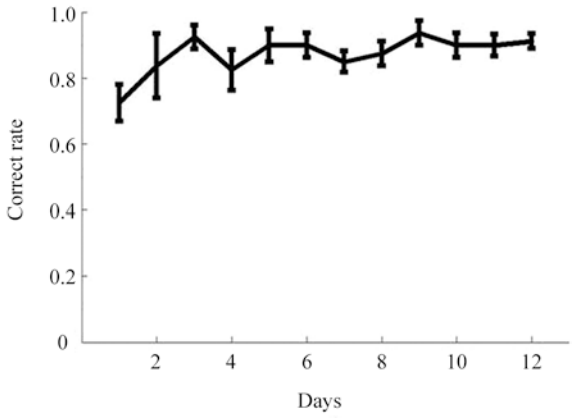

Fig. 3. Y-maze performance. Correct rates (proportion of trials performed correctly) of the delayed alternate choice for eight rats. Error bars indicate SEM.

als in the recording sessions, the percentages were LR 41%, RL 35%, LL 16% and RR 8%. Importantly, the average percentage of correct trials in recording sessions was slightly lower than that in training sessions. One interpretation of this decline is that the rats were affected, to some extent, by the surgery.

3.2 Neuronal responses to a working memory event We recorded 98 well-isolated neurons from the mPFC of four rats (32 neurons from rat 1, 26 from rat 2, 19 from rat 3, and 21 from rat 4) during their performance of the working memory task and analyzed the neuronal activity collected from 118 trials (38 trials from rat 1, 36 from rat 2, 30 from rat 3, and 14 from rat 4).

The activity from three representative neurons is shown in Fig. 4. All showed clear anticipatory activity before the working memory event. Neurons #1 and #2 had sharply increased discharge rates while neuron #3 showed persistent activity during the delay period. In this experiment, "anticipatory activity" referred to neurons with elevated activity in the delay interval when working memory was active, but no behavior occurred.

We assessed neuronal ensemble activity with both correct and incorrect responses during the working memory task. In correct trials, a proportion of mPFC neurons exhibited anticipatory activity corresponding to the working

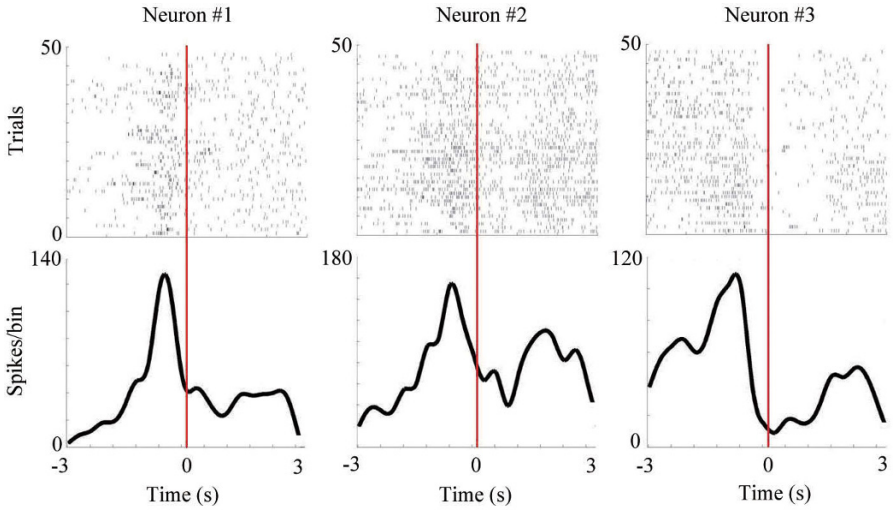

Fig. 4. Peri-event time curves (lower panels) and rasters (upper panels) from three medial prefrontal cortex neurons in 50 correct trials of the delayed alternation task. Red lines indicate the tripping time of the infrared sensor in the Y-maze.

memory task, as manifested by sharply increased discharge rates during the delay period (Fig. 5); however, in incorrect trials, neuronal ensemble activity was irregular and no significant change occurred (Fig. 6).

The neuronal activity was different between pre- and post-event times in correct trials (*t*-test, $P < 0.05$) while there were no changes in incorrect trials (*t*-test, $P > 0.05$). Furthermore, the neurons showed a distinctly higher discharge rate in correct trials (mean ± SD, 10.86 ± 1.82 spikes/bin) than in incorrectly performed trials (8.17 ± 1.15 spikes/bin) during the delay period. Average firing rates of neuronal population in the correct and incorrect trials were also compared during the period (repeated measures ANOVA, $P < 0.01$) (Fig. 7).

Surprisingly, ~13.3% neurons recorded in the experiments showed a significantly high discharge rate after the choice run (about 1.5 s after the event time), and rarely discharged during the delay period or running time. According to the statistical results, at that time, the rats had finished the choice and would be consuming the reward. Two examples of this type of neuron are shown in Fig. 8. They had similar and consistent patterns; their discharge rates were unchanged throughout the trials except for the reward time. One interpretation of these results is that these neurons are reward-activated. It is well recognized that the PFC is also involved in reward processing[32-37]. Moreover, similar activity was also found in the rat nucleus accumbens, which is implicated in a wide range of reward-related functions, in reward prediction, and behavioral allocation during reward-seeking behavior[38].

4 Discussion

Our data showed anticipatory activity in the mPFC of rats when performing a delayed-alternation task. These results are consistent with previous reports that showed anticipatory activity from the PFC in delayed working memory tasks. It is well documented that mPFC neurons in rats show sustained activity during the delay period of delay tasks[29,39-41]. In nonhuman primates, the region responsible for working memory is mainly located in the caudal DLPFC[3]. Experimental lesions of the DLPFC in primates disrupt performance on delayed response tasks[42-44] and DLPFC cells maintain elevated rates of discharge during the delay period of delayed response tasks[45-48]. Moreover, recent evidence indicates that the PL of rats is homologous to the DLPFC of primates[21].

We also found that a subset of neurons had persistent activity during the delay period in the alternate choice, which is also accord with reports that show persistent activity in the PFC during working memory tasks. Single-

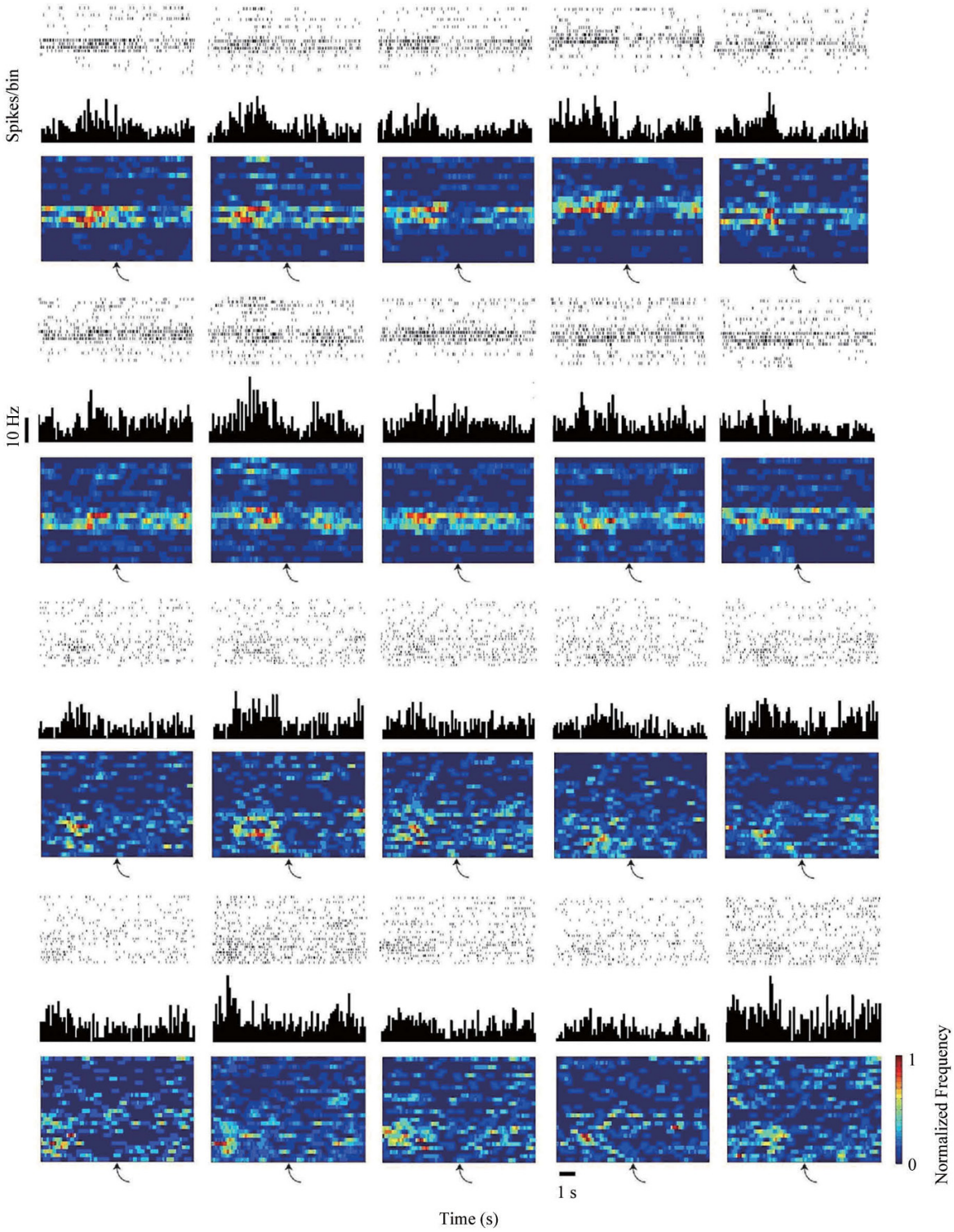

Fig. 5. Neuronal population activity with correct responses during the working memory task (20 representative trials). Dynamic maps present results of neuronal ensemble coding. Firing rates were calculated over a sliding 500 ms window, moving in steps of 125 ms. The histograms show spikes/bin (total number of spikes in each 500-ms bin) of neurons recorded during the working memory task. The rasters show the timestamps of spikes. Arrows indicate the tripping time. Normalized frequency is color-coded on a linear scale.

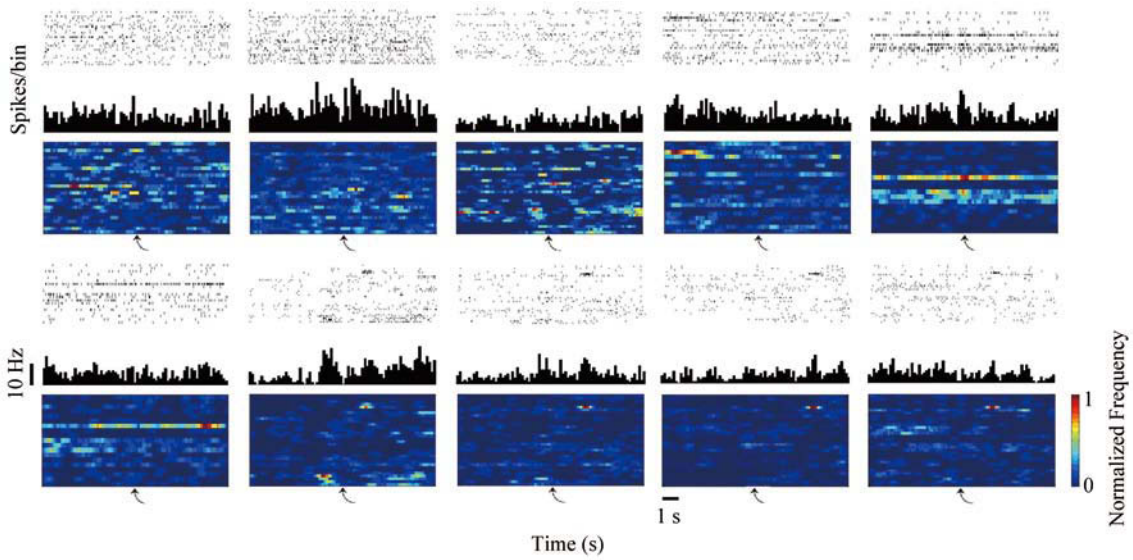

Fig. 6. Neuronal population activity with incorrect responses during the working memory task (10 representative trials). Dynamic maps present results of neuronal ensemble coding. Firing rates were calculated over a sliding 500 ms window, moving in steps of 125 ms. The histograms show spikes/bin (total number of spikes in each 500-ms bin) of neurons recorded during the working memory task. The rasters indicate the timestamps of spikes. Arrows indicate the tripping time. Normalized frequency is color-coded on a linear scale.

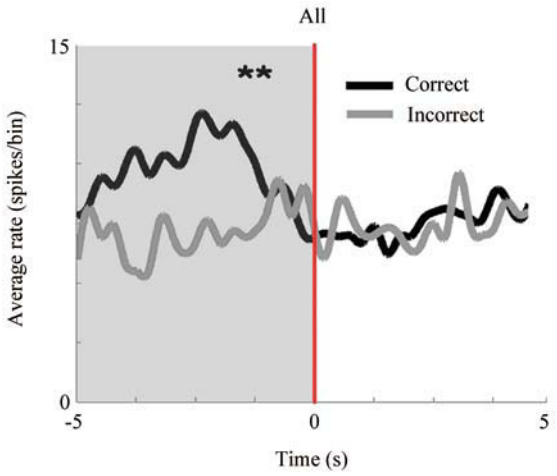

Fig. 7. Averaged population curves (n = 30) representing firing rate (spikes/bin) as a function of time during correct and incorrect trials. The red line marks the event time by the infrared sensor in the Y-maze. The shaded gray area indicates the period used for statistical analysis (P <0.01, ANOVA).**

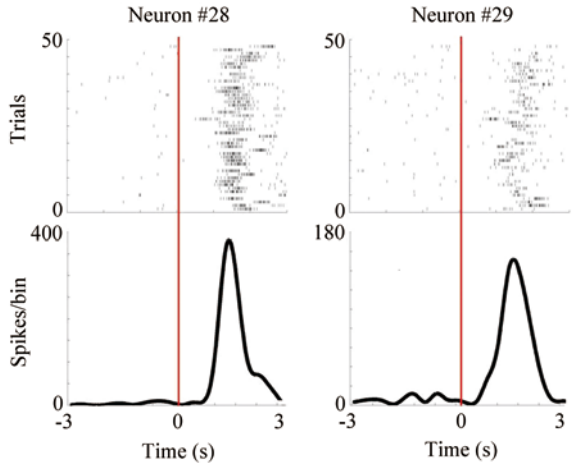

Fig. 8. Single-unit activity of two reward-activated neurons. Red lines mark the tripping time by the infrared sensor in the Y-maze.

unit recordings from the DLPFC often show persistent, sustained levels of neuronal firing during the retention interval of delayed response tasks[49-51]. More recently, event-related functional magnetic resonance imaging (fMRI) studies of humans have recorded persistent activity in the DLPFC during the retention interval of delayed response tasks[52-54]. This persistent anticipatory activity is recognized as a bridge between the stimulus cue and corresponding response.

These reports presented the anticipatory activity in

PFC in a working memory task by showing the spike counts of typical excitatory and inhibitory activity. The present study not only exhibited individual neuronal activity but also showed the firing patterns of the neuronal population to explore the mechanism by which a neural ensemble encodes a working memory event. We found that some PFC neurons showed synchronous and anticipatory excitation during the Y-maze working memory task, and the anticipatory activity was related to the choice of the upcoming movement. Moreover, those neurons that were grouped together as a functional ensemble in correct trials were relatively stable. Therefore, the neuronal ensemble activity may play a role in encoding a working memory event.

We further compared the neuronal activity in correct and incorrect trials and showed that the activity differed during the delay period. In correct trials, the firing rates of some neurons in the PFC significantly increased and evident neural ensemble activity was observed. The averaged pre-event firing rates were higher than the averaged post-event rates. Moreover, the anticipatory activity was related to the choice of the upcoming movement. However, in incorrect trials, the two rates showed no significant difference. These results demonstrated that the anticipatory activity of a neuronal ensemble in the PFC may encode the working memory event.

Since it is insufficient to show average data for correct and incorrect trials, we further analyzed the directional tuning of the neurons to assess directional effects. The data were divided into four categories: "B chosen correctly", "B chosen incorrectly", "C chosen correctly" and "C chosen incorrectly" (Fig. 9). The neuronal activity was significantly different between pre- and post-event times in correct trials, while there was no significant change in incorrect trials. In B-choice trials, the neurons showed a distinctly higher discharge rate in correct trials (~9.2 spikes/bin) than in incorrect trials (~8.4 spikes/bin) during the delay period. In C-choice trials, the neurons also showed a distinctly higher discharge rate in correct trials (~9.8 spikes/bin) than in incorrect trials (~7.1 spikes/bin) during the delay period. It seems that in correct trials, no matter whether B or C was chosen, the anticipatory activity was present. However, in incorrect trials, the two groups showed no change.

Studies have shown that anticipatory activity in many brain areas predicts behavior. For instance, gamma-band synchronization among neurons in the visual cortex predicts the speed of change detection[55]; the temporal structure of neuronal activity in macaque parietal cortex during a working memory task predicts the time of a planned movement[56]; anticipatory activity in primate motor cortex codes memorized movement sequences[57]; anticipatory rate changes in rat mPFC neurons predict different rewards in special working memory; and nucleus accumbens neurons in rats encode predicted and ongoing reward costs[38]. Our data showed that mPFC cells exhibited anticipatory activity in correct trials of the working memory task, but

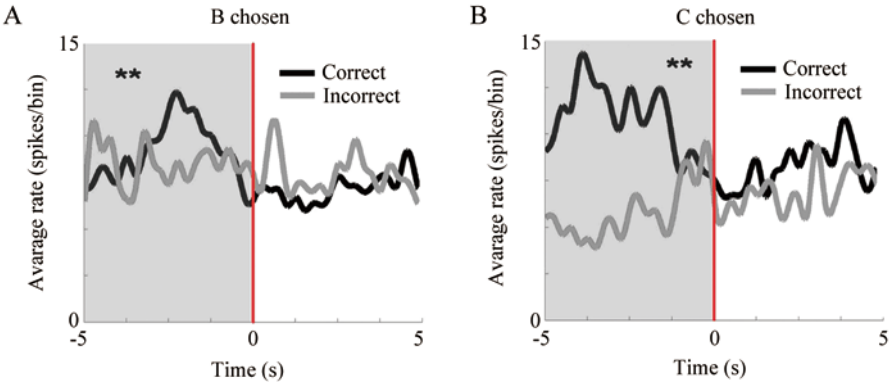

Fig. 9. Averaged population curves (n = 30) of firing rate as a function of time during B- or C-choice trials. The red lines mark the event time by an infrared sensor in the Y-maze. The shaded gray area indicates the period used for statistical analysis (P <0.01, repeated measures ANOVA).**

not in incorrect trials. Recent fMRI studies have identified a network of brain regions that implement working memory and this network temporarily sustains the most relevant internal representations such that they can be used to select adaptive behaviors[2]. We suppose that the anticipatory activity in the mPFC temporarily sustains relevant working memory information, which can be used to plan the upcoming movement. This has a potential use in the field of brain-machine interfaces. The neuronal ensemble decoding method could be used to extract information about the upcoming movement direction from population activity to control external devices, ranging from a computer cursor to robotic prosthetics.

Whether the predictive neuronal activity that we observed before the movement was associated with extensive training in the working memory task merits a comment. In the study, the rats had extensive training and achieved high accuracy before implantation surgery. Therefore, we only recorded neuronal activity in well-learned trials. The changes in neuronal activity during the whole learning process deserve study. Gradually, learning-related changes in neuronal activity have been shown in several brain areas, such as the PFC[58], basal ganglia[59], premotor cortex[60] and supplementary eye field[61]. Experiments in the PFC have shown that learning an arbitrary stimulus-response mapping causes the representation of movement direction to appear earlier in the delay period before the execution of an eye movement. Furthermore, Averbeck and colleagues investigated how neural activity in PFC evolves as the monkey gradually acquires knowledge of the correct movement sequence and found that the sequence predicted by neuronal activity changes gradually from the sequence that had been correct in the previous block to the sequence that is correct in the current block. They showed that the information coded in the ensemble neuronal activity about the correct sequence increases as the monkey discovers it[62]. There is therefore no denying that learning-related changes in neuronal activity during the whole learning processing are more helpful for us to understand the mechanisms of learning and memory.

Acknowledgments: We are grateful to Gary Lehew and Eric Thomson for comments on the manuscript. This work was supported by the National Natural Science Foundation of China (61074131, 91132722) and the Doctoral Fund of the Ministry of Education of China (20101202110007).

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