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BRIEF COMMUNICATION

Medial prefrontal cortex stimulation disrupts observational learning in Barnes maze in rats

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Abstract

Observational learning, which improves one's own behavior by observing the adaptive behavior of others, has been experimentally demonstrated in primates and rodents in several behavioral studies, including our previous study. However, its neural mechanisms remain unclear. We electrically stimulated the brain regions of rats and disturbed their neural activities during observation periods in the observational learning task using Barnes maze. According to comparison of escaping latencies of the observer and model rats, the observer rats with stimulation of the medial prefrontal cortex (mPFC) showed no observational learning, whereas both of the observer rats with stimulation of the dorsal hippocampus and with no stimulation (control) showed observational learning. These results suggest that mPFC stimulation disrupts observational learning and confirms that the mPFC is an important brain region for it in rats.

Keywords Observational learning · Medial prefrontal cortex · Barnes maze · Rat

Introduction

Observational learning, defined as the ability to acquire new information by observing the behavior of others (Bandura 1977), is crucial for behaving efficiently in social communities. Several different behavioral experiments have demonstrated that various species can learn discrimination tasks through observation (Darby and Riopelle 1959; John 1968; Vanayan et al. 1985). However, the neural mechanisms involved in observational learning remain unclear. A few studies have investigated potential mechanisms using functional magnetic resonance imaging (fMRI) in human participants, and analyzed their brain activities while they were learning visual information (Burke et al. 2010; Frey and Gerry 2006). Although these results revealed rough brain maps related to learning ability, the problem was that fMRI did not have time and space resolution high enough to detect neural and/or circuitry activities.

To clarify the neural mechanisms involved in observational learning in detail, it is necessary to develop animal models for experiments wherein brain activity can be directly controlled and the effects of such control on observational learning can be quantified. We consider that rodents are appropriate as the subjects because more invasive neurological methods have been developed for them than those for other species, e.g., administration of activity inhibitors into targeted brain regions, electrical or chemical stimulation of them, and/or electrophysiological recording of their neural activity.

We had developed an observational learning task for rats using the Barnes maze, and confirmed that the rats (observers) showed faster escaping behavior after they observed behavior of the other rats (models) escaping into the goal box in the maze (Yamada and Sakurai 2018). Using this observational learning task, the present study investigated brain regions that were necessary for observational learning in rats. A previous study suggests that electrical stimulation is a useful tool, by showing that stimulation of the medial prefrontal cortex (mPFC) canceled the benefit of observation in mice (Jurado-Parras et al. 2012). In that study, mice improved their acquisition of a simple operant conditioning task (lever pressing) by observing other mice pressing a lever in the next room.

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Electrical stimulation of the observer's mPFC at a key moment during observation (when the model presses a lever to obtain a reward) canceled the benefits of observation. That study used an operant conditioning task in a small chamber, and the animals were preliminarily trained to obtain food reward as reinforcement. However, as Mitchel et al. (1999) pointed out, a variety of cues, such as odor of the food reward or saliva secreted by other conspecifics, were present in the chamber and observational learning sometimes depended on the training period.

To overcome these problems, the present study included an observational learning task in rats using the Barnes maze and not an operant learning task. This spatial maze task is based on the nature of rats: they dislike bright lights and tend to escape to dark places. This task is generally employed in behavioral and pharmacological experiments (e.g., Gawel et al. 2016). We consider the Barnes maze task to be more advantageous for investigating observational learning in rats compared to the operant learning tasks because the former depends on the innate behavior of rats, does not require training periods for shaping operant behaviors, and does not need food reward, which allows easy elimination of cues other than the behaviors of other conspecifics. We used electrical stimulation, similar to that used by Jurado-Parras et al. (2012), and tested whether the mPFC was really important for observational learning in the spatial task using the Barnes maze.

Materials and methods

Animals

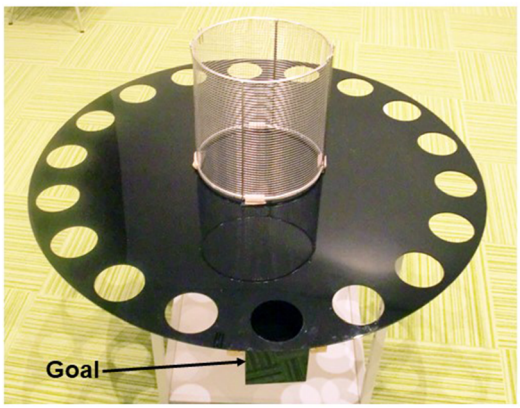
We used 30 male Long Evans hooded rats, weighing approximately 350 g (range, 300–400 g) and aged 10 weeks at the beginning of the experiment. They were housed in pairs (model and observer rats) in cages (25 cm × 30 cm × 25 cm) in a temperature-controlled room (26 ± 2 °C, approximately 55% humidity). All rats were provided ad libitum access to food and water. All experiments were performed in accordance with the Guidelines for Animal Experiments at Doshisha University with the approval of the Animal Research Committee of Doshisha University.

Surgery

Before the experiment, the animals underwent surgery for implantation of stimulation electrodes in the mPFC or dorsal hippocampus (dHPC). The dHPC was selected for comparison because it is the major learning-related brain region and is integral to spatial learning in rodents in the Barnes maze (Gawell et al. 2019). The animals were anesthetized with 2.5–3.0% isoflurane, supplied by an anesthetic vaporizer (MK-AT200, MUROMACHI KIKAI Co., LTD) at a flow rate of 1.5 l/min oxygen. The electrodes were bipolar, made by bundling two tungsten microwires (0.2 mm in diameter) and connected to a two-pin socket through a flexible cable. Some of them were implanted in the left prelimbic area of the mPFC (3.0 mm anterior, 0.3–0.7 mm lateral to the bregma and 3.0 mm from the brain surface, Fig. 2a) and others in the left dHPC (3.0 mm posterior, 2.4 mm lateral to the bregma and 2.0–2.2 mm from the brain surface, Fig. 2b), according to the atlas of Paxinos and Watson (2007). The implanted electrodes were fixed to the skull using implanted small metal screws and dental cement. The animals were allowed to recover from surgery for a week before the start of the experiment. They were also habituated to electrical stimulation on the last day of the recovery week by administration of a 100 μA current (frequency = 100 Hz, duration = 0.1 s, delay = 10 ms) for 1 min in a cage with a stimulus isolator (A365R, World Precision Instruments, Inc.) connected to the two-pin socket on the rat heads, confirming that the current did not cause any body movements. The stimulation parameters were determined according to the previous reports that indicated some behavioral effects of electrical stimulation of the mPFC in rats (Quirk et al. 2003; Mehdipour et al. 2015; Shimizu et al. 2017).

Apparatus

The experimental apparatus and procedures were almost identical to those used in our previous study (Yamada and Sakurai 2018). The apparatus was the Barnes maze, which consisted of a black acrylic circular platform 108 cm in diameter, located 70 cm above the floor (Fig. 1a). It had 18 holes (10 cm in diameter) and one of the holes had a detachable acrylic black box (12 cm × 23 cm × 12 cm), which was the goal box where the rats could escape from the aversive stimulus of bright light in the ceiling (approximately 500 lx). We used a circular, gray translucent cylinder (24 cm in diameter, 28 cm in height) to cover the rats before starting the trials in the Barnes maze. We changed the other circular, metal wire mesh cylinder (20 cm in diameter and 20 cm in height) used in the previous study to a larger cylinder (30 cm in diameter and 30 cm in height, Fig. 1a) with no ceiling, which allowed the cable connected to the rats' heads to move freely.



b

① Surgery

- Receiving surgery to be implanted electrodes in mPFC or dHPC

-2 days-

② Recovery and Habituation

- Being allowed to recover after surgery
- Being housed in pairs and then accustomed to the experimental environment and electrical stimulation

-1 week-

③ Training of model rats

- Spatial learning to escape into the goal box in the Barnes maze
- Receiving electrical stimulation twice at random in every trial

-2 days-

④ Training of observer rats

- Spatial learning to escape into the goal box after "observing" the behaviors of model rats
- Receiving electrical stimulation twice when the model rats enter into the goal box

-2 days-

Fig. 1 (**a**) Barnes maze, (**b**) Four successive procedures. The rats were divided into three groups: mPFC stimulation group (n = 14), dHPC stimulation group (n = 8), and control group (n = 8). In the rats in the control group, electrodes were implanted in the mPFC, but they received no stimulation during the experiment. dHPC: dorsal hippocampus; mPFC: medial prefrontal cortex

Experimental procedures

Training of model rats

The total schedule is shown in Fig. 1b. After the last day of the recovery period, the model rats were trained in the spatial learning task in the Barnes maze: escaping the aversive bright lights in the ceiling. One training trial was performed in a session (day). In every trial, the model rat was first taken from its home cage, placed in the center of the platform, and then covered with the metal wire mesh cylinder (Fig. 1a). The rat was then kept waiting for 3 min. During this period, the rat was stimulated by an electrical current identical to that administered on the last day of the recovery and habituation period after the surgery (Fig. 1b), as described above. The model rats were administered the electrical current in their mPFCs or dHPCs twice at random intervals within 3 min. This was because all experimental parameters including the maze, the room, the ceiling light, and the electrical stimulation should be identical between the model and observer rats except for the chance for the observer rats to observe the model rat's behavior during the task. The number of electrical stimulations was based on the observation of the model rats' behaviors in our previous study (Yamada and Sakurai 2018), which showed that the model rats repeated entering into and getting out of the goal box twice on average during the 3 min when the observer rats were waiting. This means that the observer rats, which were stimulated just when the model rats were entering the goal box, were stimulated twice on average in the present study. The model rat was then returned to its home cage, and the platform was cleaned with water so that no olfactory cues or footprints remained. Subsequently, the model rat was again placed at the center of the platform, covered with the gray translucent cylinder, and was kept waiting for 1 min until the cylinder was removed. This was done to randomly change the direction of the rat's head at the start of each trial. Subsequently, the rat was allowed to run and escape into the goal box. When the rat did not enter the goal box within 10 min, the experimenter gently guided the rat to the goal box, and the latency was recorded as 600 + . The reason for setting the upper limit on escape latency is that escaping behaviors in maze and spatial tasks in general vary greatly among individual rats, and there are often some rats that do not escape into the goal for a long time (e.g., Ogren and Stiedl 2013). Therefore, the latencies were statistically analyzed not by parametric tests but by nonparametric rank tests such as the H test and Mann–Whitney U test, both in the present and the previous (Yamada and Sakurai 2018) studies. When 2 min had passed since the rat entered the box, it was returned to its home cage. When a rat fell from the maze, the experimenter quickly retrieved it, returned it to the home cage, and restarted the procedure after 1 h.

Training of observer rats

Subsequent to the days of model rat's training, the observer rat was given the observational learning task in the same Barnes maze. The position of the goal box was consistent during all sessions for each pair of model and observer rats. One training trial was performed in a session (day) like as for the model rats. First, the observer rat was also kept waiting in the metal wire mesh cylinder for 3 min, during which the model rat was walking on the platform to escape into the goal. The observer rat was able to see the model rat's escaping behavior in the metal wire mesh cylinder and was electrically stimulated just when the model rat was entering into the goal. The stimulation was given twice for each observer rat on average because the model rats repeated entering into and getting out of the goal box twice on average during the 3 min when the observer rats were waiting. In other words, some of the observer rats received one stimulation or three stimulations within the 3 min, because some of the model rats entered the goal box only once or repeated entering into and getting out of the box three times within that period. The stimulation parameters were identical between the model and observer rats.

The model rat was then returned to its home cage and the platform was cleaned with water so that no olfactory traces remained on it. The observer rat alone was subsequently trained according to the same procedure as used for the model rat. We measured the latency period starting from the time of removal of the cylinder until the whole body and tail of the model and observer rats entered into the goal box. Training of both the model and observer rats was carried out for two successive sessions (days). Except for surgery and electrical stimulation, all rats followed the same schedule and training procedures as in our previous study. However, we shortened each of the training sessions for model and observer rats from 5 days employed in our previous study to 2 days because the rats had shown successful observational learning on the first day of training.

Data analysis

We compared the escape latencies between the model and observer rats in the mPFC stimulation group (n = 14, seven pairs of models and observers), dHPC stimulation group (n = 8, four pairs of models and observers), and control group (n = 8, four pairs of models and observers) using the Mann–Whitney U test. To determine whether the observer rats showed shorter latencies than the model rats, we mainly focused on the comparison in the first session (session 1), as in our previous study (Yamada and Sakurai 2018). This is because the escape latencies of the observer rats in the second session (session 2) might have been affected by learning through their own experiences in the first session. We also compared the latencies of the model and observer rats in session 1 among the three groups, using the Kruskal–Wallis H test.

Histology

After the experiment was completed, the rats were deeply anesthetized with sodium pentobarbital.

and perfused with phosphate-buffered saline (PBS) and 4% paraformaldehyde. The brains were removed and post-fixed in 4% paraformaldehyde, and 50 μm coronal sections of the brains were stained with DAPI (4′,6-diamidino-2-phenylindole; Nacalai Tesque, Japan) diluted in PBS (1 μg/ml) for 5 min. After removing the excess DAPI, sections were mounted in 50% glycerol in PBS. The locations of electrode tips in the brain were identified with the aid of the stereotaxic atlas (Paxinos and Watson 2007).

Results

Figure 2 shows the areas of electrical stimulation in the mPFC and dHPC. There was no difference in the distribution of stimulation sites (tips of implanted electrodes) in the mPFC between the model and observer rats. We compared the escape latencies between the model and observer rats in the first session (see Data analysis). The results showed no significant difference between the model and observer rats in the mPFC stimulation group ($U = 110.00$, $P > 0.1$) (Fig. 3a). In contrast, the dHPC stimulation group showed significant differences in latencies between the model and observer rats, similar to our previous study, and the observer rats escaped faster than the model rats ($U = 57.00$, $P < 0.05$) (Fig. 3b). The same differences were observed in the control group. ($U = 53.00$, $P < 0.05$) (Fig. 3c).

We also compared the escape latencies of the observer rats in the first session among the mPFC stimulation, dHPC stimulation, and control groups. The results showed a significant difference among the groups ($H = 7.765$, $P < 0.05$). Furthermore, using the Mann–Whitney U test, we found a significant difference between the mPFC stimulation and the dHPC stimulation groups ($U = 87.00$, $P < 0.05$) and between the mPFC stimulation and control groups ($U = 99.00$, $P < 0.01$), but no significant difference was found between the dHPC stimulation and the control groups ($U = 36.50$, $P > 0.1$). In the model rats, no significant differences were found among the three groups ($H = 2.431$, $P > 0.1$).

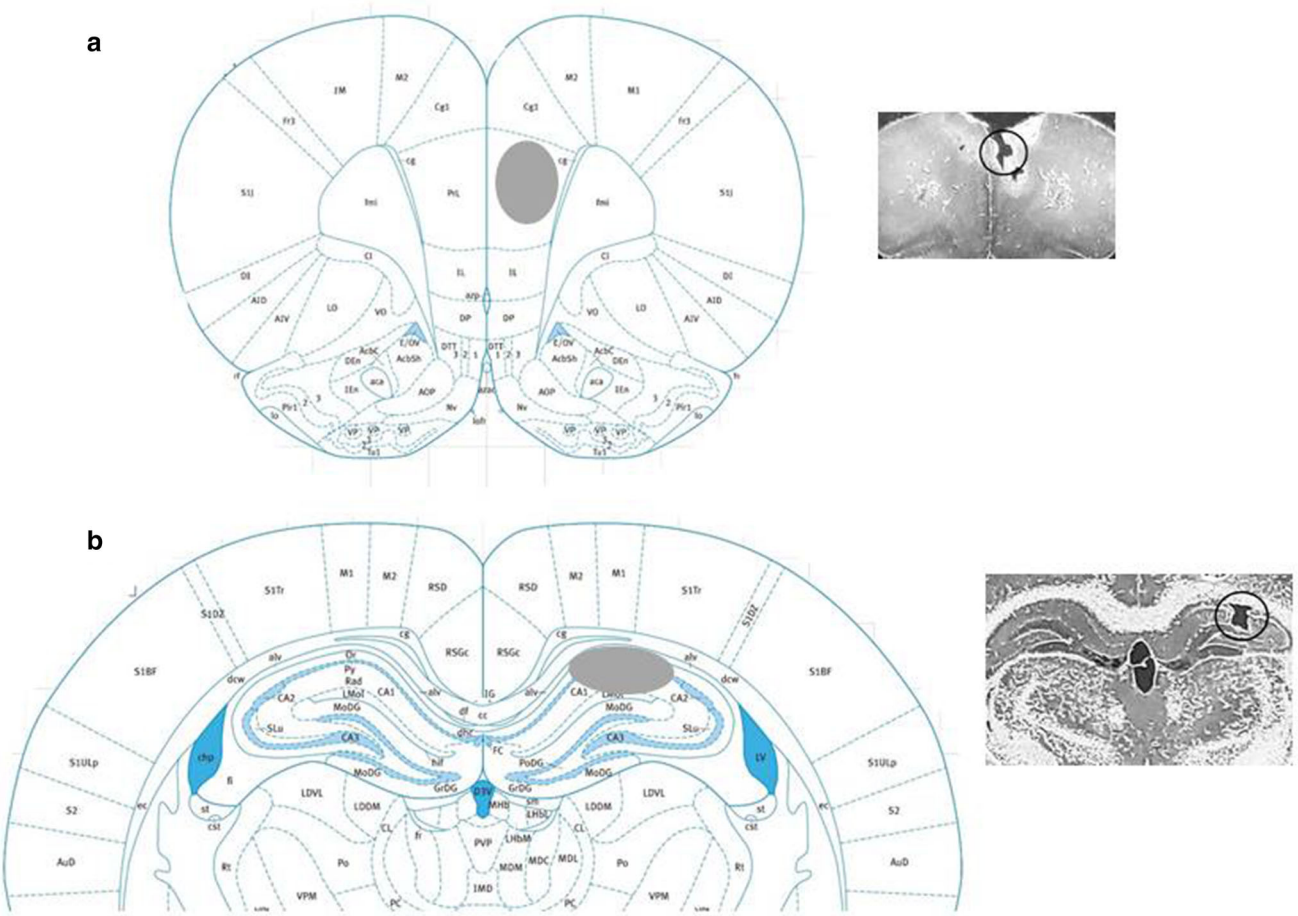


Fig. 2 Areas of electrical stimulation by implanted electrodes (**a**) The gray circle represents the area of the tips of the implanted bipolar electrodes in the rats of the mPFC stimulation group. A photo example of the lesion made by electrodes is shown at the right. (**b**) The gray circle represents the area of electrode tips in the rats of the dHPC stimulation group. A photo example of the lesion made by electrodes is shown at the right. From Paxinos and Watson (2007) with permission. dHPC: dorsal hippocampus, mPFC: medial prefrontal cortex

Discussion

In the present study, the observer rats with electrical stimulation of the dHPC and only electrode implantation in the mPFC showed observational learning similar to the intact observer rats in our previous study (Yamada and Sakurai 2018), whereas the observers with electrical stimulation of the mPFC showed no observational learning. These results suggest that electrical stimulation of the mPFC during the observation periods prevented observers from observing the learned behavior of the models and resulted in no observational learning. This observational learning is thought to be based on visual observation of the model's behavior, because the platform was cleaned with water prior to the trials of the observers to remove olfactory traces of the models. Further, we confirmed these findings in a supplementary experiment, using three pairs of model and observer rats, in which the observer rats were kept waiting in an opaque acrylic cylinder when the model rats were escaping into the goal. The results showed that the observer rats, which had been unable to see the escape behavior of model rats, did not show any shorter escape latencies than the model rats, indicating no observational learning for the observer rats (Yamada 2021). This implies that the observational learning in the present Barnes maze was based on visual observation only, and olfactory and other trajectory traces of the models, even if there were, did not affect the escape behavior of the subsequent observer rats.

The three experimental groups did not have the same number of animals because we added more animals to the mPFC stimulation group to confirm that the lack of statistical difference between the models and observers was not due to the small sample size, which could cause a low level of statistical power. This is also related to the fact that the rats could move freely in the Barnes maze and escaping

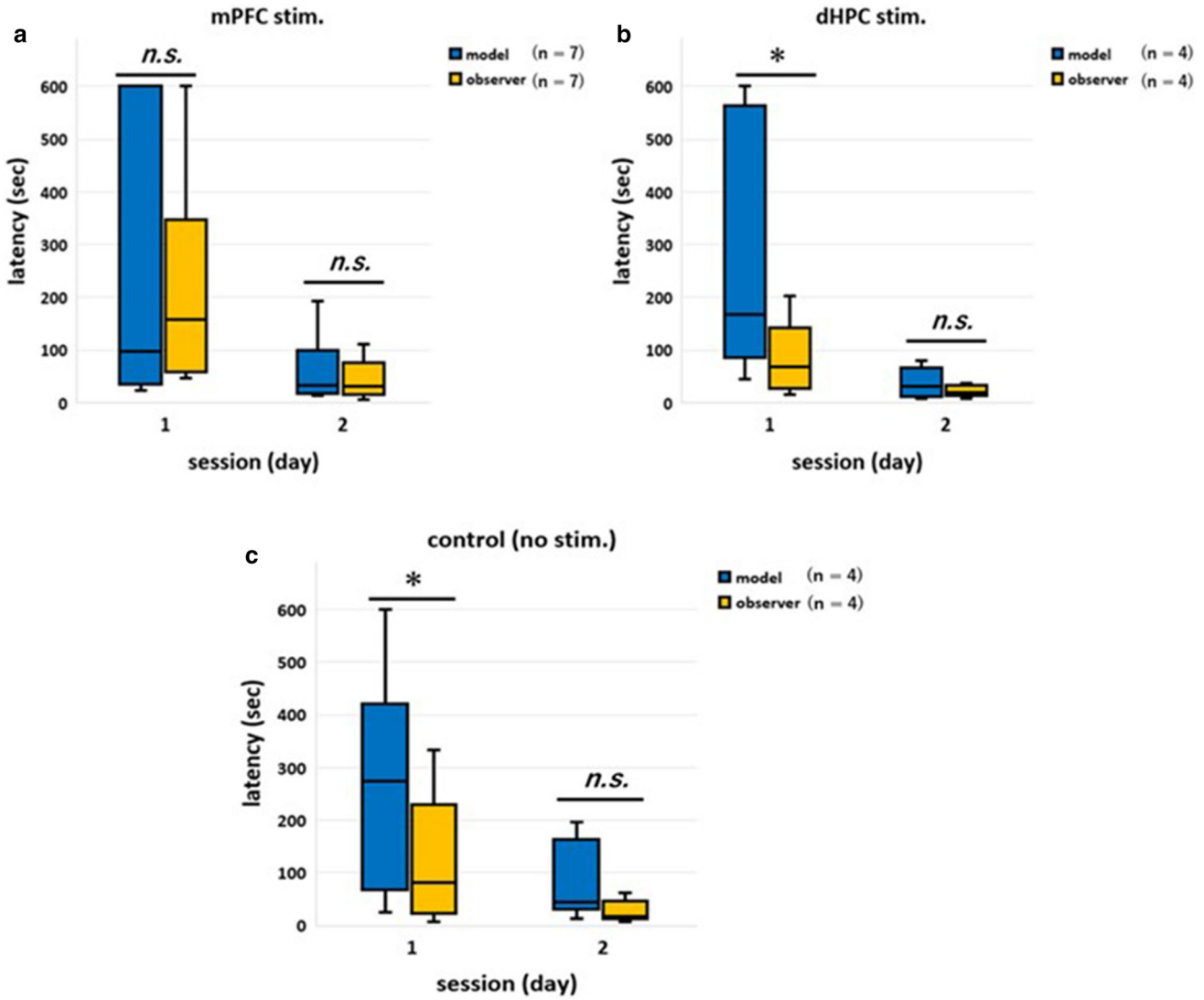


Fig. 3 Median latencies of the escape behavior in mPFC stimulation (**a**), dHPC stimulation (**b**), and control (**c**) groups. In each group, the blue and yellow box-and-whisker plots show the latencies of the model and observer rats, respectively. The box-and-whisker plots in each session included all escape trials of the rats. The crossbars in each box represent the median value. *represents significant difference ($P < 0.05$ or 0.01, U test) between the mPFC and dHPC stimulation groups and between the mPFC stimulation and control groups. Bonferroni correction was applied to avoid errors of significant levels caused by the repeated use of the U test for the second session. dHPC: dorsal hippocampus; mPFC: medial prefrontal cortex; no stim: no stimulation; n.s.: not significant. (Color figure online)

behaviors in the maze sometimes extremely varied among the individual rats, as described in the "Experimental procedures" sub-section. Such varied data could result in a lack of statistical difference when the sample size was small.

The present approach tested whether the behaviors of the observers and models were affected by brain stimulation. Stimulating both models and observers was needed to test the effect of brain stimulation on observational learning. If only observer rats were stimulated, the present results would imply that mPFC stimulation of observer rats had a disruptive effect not only on their observational learning but also on their escape behavior. However, escaping behavior itself was not affected by mPFC stimulation because the comparison of the "models" among the mPFC stimulation, dHPC stimulation, and control groups showed no significant difference. Therefore, the results of the present approach suggest that only observational learning was affected by mPFC stimulation.

Before the task in the maze, we confirmed that the current of electrical stimulation did not cause any body movements. If the current of electrical stimulation to the mPFC had disrupted functions other than observational learning, such as motor movements and/or visual

perception, both the model and the observer rats in the mPFC stimulation group might have had difficulty in escaping to the goal box. However, this was not the case in the present study because the escape latencies of the model rats in the mPFC stimulation group were not different from those of the model rats in the dHPC stimulation and control (no stimulation) groups. This means that electrical stimulation of the mPFC had no specific disruptive effect on motor and/or visual functions compared to stimulation of the dHPC and no stimulation.

As mPFC and dHPC have different after-discharge thresholds (Bandyopadhyay et al. 2005; Racine et al. 1977), electrical stimulation might have caused different electrographic effects in the two areas. We should have examined the ranges of electrical activity in the mPFC and dHPC induced by electrical stimulation in the present study and tested different stimulation parameters for the two areas. However, to see the effect of electrical stimulation on observational learning, we prioritized the equalization of all experimental parameters, including electrical stimulation between the stimulation groups.

The observer rats received electrical stimulation twice during the observation period because the model rats repeated entering into and getting out of the goal box twice on average while the observer rats were waiting. These additional behaviors of the model rats are referred to as exploratory behaviors in and around the goal box. Such exploratory behaviors can be easily demonstrated in free-moving tasks using mazes.

The present study supports the finding of Jurado-Parras et al. (2012) that electrical stimulation of the mPFC during behavioral demonstration by the models negatively affected observational learning by the observers. In addition to Jurado-Parras et al. (2012) that reported observational learning in mice using a lever-pressing task in an operant chamber, our present study has revealed observational learning in rats in a spatial task. Testing observational learning by rodents using operant chambers sometimes has disadvantages such as multiple cues in experimental situations and complex training for a long time that can sometimes confound the observer rats, resulting in no display of observational learning (Mitchel et al. 1999). On the other hand, the Barnes maze task is a simple spatial task that depends on the innate aversion to bright lights in rodents and requires no long-term and artificial training for shaping operant behaviors. This might be advantageous in testing observational learning in rodents.

The present study describes an initial experiment that only highlighted the mPFC as one of the important brain regions involved in observational learning in rodents. However, it is important to determine whether electrical stimulation of the mPFC prevents the acquisition or expression of observational learning. For example, Leal-Campanairo et al. (2007) examined this point of the question in a well-designed experiment using electrical stimulation of the mPFC and delayed eyeblink conditioning in rabbits. They reported that mPFC stimulation prevents only the expression of conditioned eyeblinks, not their latent acquisition. Therefore, in a future study, we should design another experiment wherein one group receives mPFC stimulation during the observation period, as it was done in the present study, and the other group receives stimulation during escaping behaviors. The former stimulation group can show the effect on acquisition, and the latter can show the effect on the expression of observational learning. Both models and observers should receive mPFC stimulation during the different periods. Similarly, dHPC stimulation performed in the same way would be required for comparison. In the present study, we can only suggest that mPFC stimulation prevented observational learning, in particular its acquisition, because the observers were stimulated during the observation period.

As a similar discussion to that described above, it is important to point out a specific process of the observational learning the mPFC stimulation prevents. Observational learning consists of sensory and memory processes, i.e., observing, acquisition, and retention processes. The present study could not determine which process the mPFC stimulation mainly blocked. As we describe above, it can only suggest that the mPFC stimulation blocked observational learning, in particular its acquisition by observing. A future experiment that systematically operates timings and periods of the mPFC stimulation is needed.

The observers could observe the behavior of the model and the context around the Barnes maze simultaneously. The present study could not precisely evaluate how knowledge about the context improved the spatial learning of the observers. However, learning of the context alone might not improve the escape behavior of the observers, because the goal box could not be seen from the center of the maze where the observers were placed in the mesh cylinder during the observation period. This was confirmed by the fact that most of the models starting from the center of the maze explored the maze for a while and then escaped into the goal box. Only the escape behavior of the models could indicate the location of the goal box for the observers. Therefore, we can only conclude that observing the escape behavior of the model with the context around the maze improved the spatial learning of the observers in consecutive trials.

In future studies, we should also investigate the functions of the mPFC with its connections to other brain regions (e.g., Taber and Fibiger 1993) involved in observational learning, using our behavioral task. For example, investigating the function of the mPFC neuron projections to the anterior cingulate cortex (ACC) is meaningful

because ACC neurons play an important role in processing information about others in social contexts (Apps et al. 2016) such as guessing the mental states of others (Frith and Frith 2006; Hampton et al. 2008), cost–benefit decision making and learning through observation of others (Hillman and Bilkey 2012), and observational fear conditioning in mice (Jeon et al. 2010). Furthermore, neurons in the thalamus, basal ganglia, amygdala, and hippocampus have strong connections with those in the mPFC (Beckstead 1979; Floyd et al. 2001; Hurley et al. 1991; Jay and Witter 1991; Likhtik et al. 2014; Maurice et al. 1998; McDonald et al. 1996, 1998; Motzkin et al. 2015). Therefore, in the near future, we should demonstrate the neural circuits between the mPFC and the brain areas that are activated during the observation periods in our present task, using electrophysiological recording and optogenetics.

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Data availability Data will be made available on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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