Short communication

An experimental task to examine the mirror neuron system in mice: Laboratory mice understand the movement intentions of other mice based on their own experience

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ABSTRACT

We developed a behavioral experiment to elucidate the neural mechanisms of intention understanding in mice. In this experiment, the mouse is first trained to acquire food by reaching with its forelimb. The mice that learnt this were placed in an experimental box wherein they can observe the reaching activity of another mouse. We found that trained mice tend to observe the reaching activity of other mice; mice that did not receive any prior training displayed a lower tendency towards observing another mouse’s reaching behavior. In experiment 2, in order to rule out that observing the behaviors of other mice is solely due to interest in the feeding table or the social stimulus itself, we compared exploratory approach behaviors when the box with the feeding table was empty, when the untrained mouse did not reach it, and when another learnt mouse was reaching for the food. The results showed that exploratory approach behaviors to trained mice lasted significantly longer than the exploratory approach behavior to the empty box and untrained individuals. These results suggest that the learning of individuals’ exploration of other reaching individuals may be motivated not only by interest in the presence of the feeding table and other individuals themselves, but also by an associated intentional movement. The tasks developed in our study could be used in the research of the mirror system in behavioral neuroscience to elucidate the mechanism underlying the ability of mice to understand the intent of other mice via motor learning.

The mirror neuron system is one of the major neural circuits associated with understanding the intentions of others [1–3]. Studies have reported the presence of mirror neurons in the ventral premotor cortex and inferior parietal lobe of macaque monkeys [4]. Neurons that demonstrate identical firing patterns during observation and execution of a corresponding behavioral action are referred to as mirror neurons. Following their discovery, human brains have been extensively studied using electroencephalography, functional near infrared spectroscopy, and functional magnetic resonance imaging, and it has been suggested that the mirror system is also present in humans [5–7].

Recently, a few groups have initiated studies investigating rodents for the presence and activity of their mirror neuron system [8,9]. Takano and Ukezono (2014) successfully developed a protocol for a behavioral experiment in laboratory rats similar to that conducted in monkeys to understand the activity of mirror neurons, and demonstrated a method to study the influence of observing other individuals [8]. Carrillo et al. have used a negative emotional contagion scene in laboratory rats to identify neuronal activity with identical firing patterns in the anterior cingulate cortex when experiencing and observing similar negative emotions [9]. Thus, although there have been early attempts to investigate mirror neuron systems in rodents, they were primarily focused on laboratory rats; however, none of these studies used mice as the test subject. Since a significant amount of work in the field of neuroscience involves research in both rats and mice, this study aimed to develop behavioral tasks to study the mirror neuron system in mice.

We attempted to simulate behavioral experiments in monkeys, in which the acts of watching others reach for food and eating by self are used as a trigger for mirror neurons [4]. Additionally, in these scenes, one of the most important interpretations was that the common neural pattern during observation and execution contributed to the understanding of intention, which could be represented by suggesting that it is possible for an observer to understand the intention of another
individual's action if it is can done by the observer. However, this indicates that it might be relatively difficult to understand the intentions of other individuals who are engaged in an activity that has not been experienced or cannot be replicated by the observer. It must be noted that for reaching behavior, training can be performed not only in mice, but also in rats, monkeys, and humans. However, regarding laboratory mice and rats, the reaching behavior to obtain rewards is not a routine behavioral action and requires training from human experimenters.

This study examined the following three points. First, we examined the possibility in mice to observe other individuals reaching for food reward if they have learned the behavior. Reaching for food is not an innate behavior in mice; therefore, unless it is learned, it is possible that the mice will not demonstrate any interest in the reaching behavior of other individuals. Second, we examined the influence of observation by other individuals on reaching behavior using an index of social facilitation. We aimed to demonstrate that it was at least a social context for two individuals. Furthermore, we also consider its influence on the social facilitation that occurs when observing mice reaching for food, depending on whether the observer could be considered a trained individual or a non-trained individual. Considering previous studies, the speed of rotation on the spot before performing the reaching action can be used as an indicator of social facilitation [8]. When a mouse learns, the frequency of the reaching behavior increases despite any lack of rewards. To eliminate the instances of ineffective reaching behavior, we made the mouse learn to turn once on the spot before reaching for food. This turn was beneficial as a behavioral control and could be applied in the field of neuroscience in the near future. Finally, we discuss the effectiveness of studying the mirror neuron system in mice using this developed behavioral task.

In experiment 1 and 2, all animal experiments were performed in accordance with the guidelines for Care of Laboratory Animals of Tohoku University Graduate School of Medicine. This guideline is based on the 8th edition of “Guide for the care and use of laboratory animals” by the National Research Council of the National Academies, USA. The experimental protocols were approved by the ethical review board for animal study of the Tohoku University School of Medicine (No. 2017-334).

In experiment 1, thirty-two male C57BL/N mice were purchased (CLEA Japan, Inc.) at the age of 6 weeks. The animals were separated into groups of four mice and housed in a temperature-controlled (approximately 23 °C) animal room under a 12-h light/dark cycle (light from 08:00 to 20:00). We randomly sorted the mice into a “learning group” and “unlearning group,” with each group containing sixteen mice. Prior to the experiments, the mice were provided with food (CE-2, CREA Japan Inc.) and tap water ad libitum as preliminary breeding for one week. During the behavioral experiments, approximately 1 g of food per day was given to each mouse after the day’s experiment. Tap water was continuously available in their home cages.

The apparatus included a reaching room and observation room (Fig. 1a). Both compartments were 10 cm depth × 19 cm wide × 20 cm height and were made of transparent acrylics, with a feeding table between the two sides. In the reaching room, a slit (10 mm) was prepared near the feeding table to allow mice to reach for and grasp a piece of pasta. In the observation room, a slit (1 mm) was prepared facing the feeding table. The design of the reaching room followed Farr and Wishaw [10]. Using a stick that could hold pasta, the experimenter was able to place pasta in front of the slits. We placed two video cameras both above and in front of the apparatus and recorded the animal

Fig. 1. Apparatus and Training. a. The apparatus included a reaching room and observation room made of transparent acrylic. Between the two sides, there was a table for placing the stick of pasta. The reaching room has a 10 mm slit from which the mouse was able to take pasta. b. Schedule of learning the reaching task and test session. c. Learning curve for reaching. Dashed line represents the results of the linear regression.
behaviors (60 fps).

A summary of the experimental procedure is presented in Fig. 1b. Approximately, one to two days before the first training session, the mice were given pasta and habituated. The pasta was cut into a length of approximately 2–3 mm and each piece weighed 10 mg. The mean weight of mice on the day before the training began was 21.25 g (SD = 1.12) at the age of 7 weeks. We trained the mice in the learning group twice a day in the reaching room. Twenty rewards were provided to the mice to accurately perform the act of reaching and grasping the food in a session, with each session being maximum 20 min in length. The intertrial interval in a session depended on individual mouse behavior. In the first and second sessions, the mice were trained to reach and grasp for the pasta with the forepaw. In the third or fourth session, the experimenter did not present pasta when the mouse was sitting in front of the slit but did so when the mouse was situated away from the slit. This resulted in the mice reaching for the pasta after performing a complete turn on the spot. Therefore, the mouse did not perform the reaching movement in the absence of the trigger but did so in the presence of it. Additionally, the movement before reaching can be standardized. In the 5th to 7th sessions, we trained the mice to reach and hold the pasta after ensuring that all the mice have rotated. Fig. 3a shows the mouse spinning in front of the slit before reaching. In the unlearning group, the mice were put in the observation room for 10 min while keeping the reaching room empty during each session. As the training times in the learning and unlearning groups were therefore different, these data were obtained in front of the slit before reaching. In the unlearning group, the mice were observed once by both the learning and the unlearning groups. The occurrence rate of “not paying attention” for unlearning non-cage mates was significantly higher than that for the other conditions. Error bars represent the standard error of the mean. **p < .01.

We calculated the percentage of trials in which the mouse did not drop the pasta as the success rate during training sessions. In the case of the observation test, we classified the reaching situations into three different categories using a previous study as a reference [8]. The first was “face to face” based on the two heads being in a straight-line though the slits. The second group was termed as “not paying attention,” in which the head of the observer was positioned ≥90° away from that of the reaching individual. Examples of “face to face” and “not paying attention,” are shown in the Data in Brief Figs. 2 and 3. The third was “ambiguous” and did not meet the criteria of “face to face” or “not paying attention”. Data on “ambiguous” situations is only shown in Table 4 and 5 in the Data in Brief.

We measured the time required to complete a single spin before performing the reaching action. The starting point was the first frame in the video in which the mouse started spinning after sitting in front of the slit, and the end point was the frame before the one in which the front paws of the mice were away from the ground. We measured the time using a stopwatch. Furthermore, we examined whether there was a difference in the time spent close to the slit for the mice in the observation room between the learning and unlearning groups in the test session (Data in Brief Fig. 4). We measured the time using images from the upper camera using a stopwatch.

In experiment 2, fifty male C57BL/N mice were purchased (CLEA Japan, Inc.) at age 5–7 weeks and the experiment was performed at 7–8 weeks of age. The animals were housed in groups of two or four animals. The duration of the preliminary breeding was 1–14 days. The food and water breeding methods were identical to those of experiment 1. The mean weight at the start of training was 19.25 g (SD: 1.12 g).

We randomly assigned ten animals to a trained group, ten to an untrained group, and ten to an empty group. Thirty animals were used to obtain experimental data, and twenty animals were used to examine reaching behaviors during the test session (Data in Brief: Table 8 and 9). The thirty animals in the observation room and ten of the twenty animals in the reaching room were trained in reaching behaviors using the same methods as those in experiment 1 (Data in Brief: Table 11–13). The remaining 10 animals only spent 10 min in the apparatus for habituation, since the individuals not trained in the test session were used as social stimuli.

A summary of the experimental procedure is presented in Fig. 1b. Approximately, one to two days before the first training session, the mice were given pasta and habituated. The pasta was cut into a length of approximately 2–3 mm and each piece weighed 10 mg. The mean weight of mice on the day before the training began was 21.25 g (SD = 1.12) at the age of 7 weeks. We trained the mice in the learning group twice a day in the reaching room. Twenty rewards were provided to the mice to accurately perform the act of reaching and grasping the food in a session, with each session being maximum 20 min in length. The intertrial interval in a session depended on individual mouse behavior. In the first and second sessions, the mice were trained to reach and grasp for the pasta with the forepaw. In the third or fourth session, the experimenter did not present pasta when the mouse was sitting in front of the slit but did so when the mouse was situated away from the slit. This resulted in the mice reaching for the pasta after performing a complete turn on the spot. Therefore, the mouse did not perform the reaching movement in the absence of the trigger but did so in the presence of it. Additionally, the movement before reaching can be standardized. In the 5th to 7th sessions, we trained the mice to reach and hold the pasta after ensuring that all the mice have rotated. Fig. 3a shows the mouse spinning in front of the slit before reaching. In the unlearning group, the mice were put in the observation room for 10 min while keeping the reaching room empty during each session. As the training times in the learning and unlearning groups were therefore different, these data were obtained in front of the slit before reaching. In the unlearning group, the mice were observed once by both the learning and the unlearning groups. The occurrence rate of “not paying attention” for unlearning non-cage mates was significantly higher than that for the other conditions. Error bars represent the standard error of the mean. **p < .01.

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A summary of the experimental procedure is presented in Fig. 1b. Approximately, one to two days before the first training session, the mice were given pasta and habituated. The pasta was cut into a length of approximately 2–3 mm and each piece weighed 10 mg. The mean weight of mice on the day before the training began was 21.25 g (SD = 1.12) at the age of 7 weeks. We trained the mice in the learning group twice a day in the reaching room. Twenty rewards were provided to the mice to accurately perform the act of reaching and grasping the food in a session, with each session being maximum 20 min in length. The intertrial interval in a session depended on individual mouse behavior. In the first and second sessions, the mice were trained to reach and grasp for the pasta with the forepaw. In the third or fourth session, the experimenter did not present pasta when the mouse was sitting in front of the slit but did so when the mouse was situated away from the slit. This resulted in the mice reaching for the pasta after performing a complete turn on the spot. Therefore, the mouse did not perform the reaching movement in the absence of the trigger but did so in the presence of it. Additionally, the movement before reaching can be standardized. In the 5th to 7th sessions, we trained the mice to reach and hold the pasta after ensuring that all the mice have rotated. Fig. 3a shows the mouse spinning in front of the slit before reaching. In the unlearning group, the mice were put in the observation room for 10 min while keeping the reaching room empty during each session. As the training times in the learning and unlearning groups were therefore different, these data were obtained in front of the slit before reaching. In the unlearning group, the mice were observed once by both the learning and the unlearning groups. The order of learned or unlearned was subsequently randomized. The pair of the observation tests, which we used to determine if mice in the observation room paid attention to the mice in the reaching room. The pair of the observer and reaching mouse in the two observation tests were grouped with the same methods as those in experiment 1 (Data in Brief: Table 11–13). The thirty animals in the observation room and ten of the twenty animals in the reaching room were trained in reaching behaviors using the same methods as those in experiment 1 (Data in Brief: Table 11–13). The remaining 10 animals only spent 10 min in the apparatus for habituation, since the individuals not trained in the test session were used as social stimuli.
Following the 7th training session, we conducted an observational test on the situation in which non-cage-mate learned individuals were reaching, unlearned individuals were in the reaching room, and the empty box was with no mouse. We examined whether the mice trained in the reaching behavior in the observation room were close to the slit when learning mice, unlearning mice, and empty box were in the reaching room. The test session for the learning group was conducted the same as that in experiment 1. For the untrained and empty group, the experimenter moved a stick to set pasta in front of the slit every 30 s.

The time spent by mice in the observation room close to the slit during the test session was then calculated using images from the upper camera. When the animal was in the half of the observation box that was closer to the slit, we defined it as being close to the slit. We calculated the percentage of time that the observer’s position was close based on the total time in each test session.

The success rate of reaching from session 3 to session 7 in the learning group was presented in Fig. 1c. A simple regression analysis was performed to examine the learning tendency based on the success rate, which indicated that the success rate positively correlated with the total time in each test session.

We subsequently categorized mice in the observation room as cage mates or non-cage mates of the mice in the reaching room and the occurrence of the two situations, “face-to-face,” and “not paying attention,” during the test was counted. The rate of occurrence was calculated based on the number of trials with each situation divided by 20, which was the total number of trials in a session (Fig. 2a). The mean occurrence rate of the “face-to-face” situation for cage mates was 26.25 % (SD = 19.32) and 51.75 % (SD = 7.81) for non-cage mates for observers in the learning group, and 11.25 % for cage mates (SD = 16.45) and 23.75 % (SD = 5.63) for non-cage mates for those in the unlearning group (Fig. 2b). Two-way ANOVA (2 [cage mate/non-cage mate] × 2 [cage mate/non-cage mate]) was performed on the averaged occurrence rate of not paying attention. The results show a significant main effect of learning ([F(1, 28) = 19.53, p < .01], a significant main effect of cage mate status ([F(1, 28) = 6.68, p < .05], and interaction of learning and cage mate status ([F(1, 28) = 5.85, p < .05], SD = .19), and interaction of learning and cage mate status ([F(1, 28) = 5.85, p < .05], SD = .17). The results of the simple main effect test showed that the rate of “not paying attention” in non-cage mates without learning was significantly higher than that in other conditions (p < .01).

In the test, the rat of time that the observed individuals stayed on the side close to the slit in the observation room was calculated for each of the learning group (mean = 56.1 %, SD = 10.69) and unlearned group (mean = 48.4 %, SD = 11.83) mice. As a result, the time spent on the side near the slit was significantly longer for observers in the learning group than for those in the unlearning group (t(30) = 2.35, p < .05).

We subsequently compared the speed of spins in reaching individuals depending on the absence of observers (mean = 1.5 s, SD = 0.22), the presence of an unlearning observer (mean = 1.3 s, SD = 0.13), or the presence of learning observer (mean = 1.1 s, SD = 0.17) (Fig. 3b). Since the main effect was statistically significant in the one-factor repeated ANOVA (F(2, 30) = 37.38, p < .01), multiple comparisons using the Bonferroni method were performed. There were significant differences between the mean values of the no observer and unlearning observer conditions (p < .05), the no observer and learning observer condition (p < .01), and the unlearning and learning observer conditions (p < .01).

In experiment 2, there were three conditions: learning, unlearning, and empty reaching room (Fig. 4a). All animals put in the observation room learned the reaching behavior before the test. To confirm that we were able to train in the same way as in Experiment 1, the success rate for each individual during the training session, the appearance rate of “face to face” and “not paying attention” in the test, and the rotation speed of reaching individuals in the test are shown in Tables 12 and 13 in “Data in Brief”. The time mice in the observation room spent close to the slit of the test session was then calculated from the upper camera. We calculated the percentage of time the observer’s position was close to slit.
of the total time in each test session (Fig. 4b), and compared these using a one-way ANOVA. The results revealed a significant difference among conditions $F(2, 27) = 12.73, p < .01, \eta^2 = .49$. A multiple comparison using the Bonferroni method indicated that proportion of time the observer spent close to the slit in the learning group was greater than that in the unlearning group ($p < .01$) and in the empty group ($p < .01$).

In experiment 1, the mice successfully learned the reaching behavior. The trained mice were more likely to observe the reaching behavior of the other mouse (Fig. 2a). Furthermore, when the mouse was not trained in the reaching behavior, there was a tendency not to observe the reaching behavior of other individuals. If the mice did not receive training, they acquired the rewards directly using their mouth and not their forepaw when placed in an identical situation. For this reason, the mice in the untrained group may not understand that the other mouse is getting a reward and may not have paid attention to the reaching behavior. This is suggested by the decrease in time spent close to the slit in the untrained group (Data in Brief: Fig. 4). Therefore, it is possible to extrapolate that the mice may understand the intent of the reaching behavior of other individuals based on their own motor learning.

We conducted Experiment 2 because the observed behavior of the trained individuals may not be because of the motor intentions of the other mouse but simply because of the social stimulus or the presence of the feeding table. We found that training significantly increased the mice’s proximity-seeking behavior over that in the untrained and empty box conditions (Fig. 4b). In addition, the experimenter performed the pasta presentation action in the untrained and empty box conditions. These results suggest that learning individuals’ exploration of other reaching individuals may be motivated not only by interest in the presence of the feeding table and the other individuals themselves, but also by an intentional movement that is associated with them. The developed behavioral task has made it possible to comprehend the movement intentions of other individuals using mice.

It was shown that mirror neurons can be found in monkeys and their activity was associated with a visually based understanding of the intentions of other individuals’ actions [4,11]. Building on this, it was found that mirror neurons fired when they learned to associate sound information, such as peanut shelling, with eating peanuts [1]. Subsequently, it was reported that not only behavior-based intention understanding, but also emotion-related behavior was affected [12,13]. On the other hand, in rats, the only current discovery is of an emotional mirror [9]. The emotional mirror was used as a behavioral paradigm from studies of emotional contagion in rats [14–16]. De Waal and Preston (2017) suggest that intention understanding is a hierarchical system based on emotion transmission, action-based intention understanding, and cognitive intention understanding [17]. The reaching task used in this study was related to the emotional system because it dealt with rewards, but it was a methodology that focused on intention understanding such as in the monkey task. Although action-based intention understanding research in rodents is just beginning, the neural basis supporting cognitive intention understanding may be more different between rodents and primates than the neural basis of emotional intention understanding. In this regard, rodent models have some limitations. However, as an advantage of the rodent model, we have succeeded in modeling in a short period of time from completely unlearned behavior to the intent of the behavior through training.

Regardless of the amount of evidence on what the animal is actually observing, the outcomes depend on our interpretation. Moreover, since animals cannot interact socially with the help of a spoken language like humans, we have used social facilitation as an index to confirm whether there is any form of relationship between the individuals. When developing the behavioral task to examine rats’ mirror neuron system, it has been objectively reported that there is an influential relationship between two individuals that results in social facilitation when performing the reaching behavior in the presence of an observer compared with that in the absence of an observer [5]. Social facilitation refers to the phenomenon in which being with other individuals enhances behavior performance [18]. Since the appearance of social facilitation is evaluated based on the performance level, it could have been used to quantitatively evaluate the presence of a social context if it were possible to be used as an index of the behavioral task (Fig. 3b). Here, the spin speed before reaching was faster in the presence than in the absence of observers. Furthermore, the speed was faster when there were attentive observers from the trained group than when there were observers from the untrained group. Therefore, it can be suggested that the developed experimental situation is a social context for the mouse. The remarkable results were that all mice demonstrated social facilitation in this context, similar to rats in a previous study [8]. Additionally, it suggests that the attentive observation of trained observers results in more powerful social facilitation than just the presence of untrained individuals. The experimental results in these mice are consistent with those observed in the cases of human social facilitation. [19,20].

However, this research procedure has some limitations. First, the order was not counterbalanced for cage mates and non-cage mates in Experiment 1. No effect of this factor was detected in the learning group, the habituation time of the apparatus was fixed in the un-learning group, there was a statistically significant difference between the training time of the learning group and that of the un-learning group (Data in Brief: Fig. 5). However, in pairs of reaching individuals, training time had no effect on the frequency of face-to-face on subsequent tests (Data in Brief: Fig. 6), suggesting that the time spent in this
apparatus had little influence on the test.

Finally, we wish to discuss the convenience of the application of the developed behavioral task in neuroscience. First, the short training period of approximately 4 days should be considered an advantage. The mean success rate of the reaching behavior was approximately 77% in the experiment. In a previous study of reaching in mice [21], the success rate was approximately 70%, suggesting that the training in this study facilitated learning with a similar success rate. In addition, the mean occurrence rates of face-to-face was approximately 25% in Experiment 1, which was similar to that of rats in a previous study [8]. In Experiment 2, the number of pairs was small, but the mean frequency of face-to-face was as high as 40% (Data in Brief: Table 13). To compare the neural activity during execution and observation, it would be necessary to accumulate data from several trials. For example, repeating the test with one pair three times will mean that face-to-face can be recorded approximately 18 times in total, which is predicted to be sufficient for statistical validation of a raster plot of neural activity. Therefore, we successfully developed a new behavioral task to study the mirror neuron system in mice.

Author contribution

Y.T. and M.U. designed the experiments, and M.U. performed the experiments. Y.T. and M.U. performed data analysis. Y.T. and M.U. wrote the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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