Proposal of Novel Experimental Methodology for Studies on Alzheimer's Disease using Rat and Small Mobile Robot

H. Ishii, A. Komura, Y. Masuda, S. Miyagishima, A. Takanishi, N. Iida, H. Kimura

Abstract— **WHO reports that more than 18 million people are suffering from AD in the world today. Therefore, many studies on AD have been conducted not only in clinical medicine but in basic medical science. These studies contribute to clarifying molecular biological mechanism of AD. Psychological factors such as stress or satisfaction from interaction with other people plays important part in onset of AD as well as molecular biological factor. However, comparing to studies on AD in molecular biology, psychological factors have not been well studied. We then propose a novel experimental methodology to study AD from psychological view point. Applying robotics to animal psychology, we developed an experimental setup to investigate rat's characteristic related with AD through the interaction experiment between a rat and a small mobile robot.**

In the experiment, young rat learned the task three times faster than old one. Learning curve of young rats look stair like while that of old rat looks gentle slope. Concerning only this result, our experimental setup has little novelty. However, each rat shows different kinds of interaction with the robot. For instance, young rat bit and pulled the robot several times before to learn to push the lever while old one had not exhibited that. Consequently, we believe proposed experimental setup can be a novel experimental methodology to evaluate "learning ability" and "sociality" of rats. In future work, we will evaluate "learning ability" and "sociality" of AD model rats in this experimental methodology.

I. Introduction

In aging society, many elderly people suffer from Alzheimer's disease (AD). WHO reports that more than 18 million people are suffering from AD in the world today [1]. Therefore, many studies on AD have been conducted not only in clinical medicine but also basic medical science. After, Glenner reported that amyloid had been deposited in the brain of AD patients [2], several researchers started to develop AD model animals by injecting amyloid into their brains [3][4][5] or knocking out the genes associated with amyloid protein formation [6][7][8]. These studies contribute to clarifying molecular biological mechanism of AD. Psychological factors such as stress or satisfaction obtained from interaction with other people play important part in onset of AD as well as molecular biological factor. However, comparing to studies on AD in molecular biology, psychological factors have not been well studied.

On the other hand, we have been studying interaction between a rat and a small mobile robot as a basic model of interaction between a human and a robot [9][10][11]. In this study, we have developed several kinds of small mobile robots and experimental setups [12]. Using these setups, we have been performing several kinds of interaction experiments between a rat and a robot collaborating with animal psychologists. We then consider this methodology can be useful to evaluate learning ability and sociality of rats. Therefore, we propose to apply this methodology to studies on AD. In this paper, we introduce a small mobile robot, WM-6 and an experimental setup. An interaction experiment where the robot taught a simple task to rat is described as one of the methods to evaluate learning ability and sociality.

II. Small Mobile Robot WM-6

We developed a small mobile robot WM-6 (Waseda Mouse No. 6) as shown in Figure 1. The mobility and dimensions are almost equal to those of mature rats as shown in Table 1. WM-6 is wirelessly controlled by a PC and consists of two levers, two driving wheels, a microcontroller, a Bluetooth wireless communication module, and a Li-ion battery.

A. Mobile Mechanism

WM-6 has 2 drive wheels and 1 passive omni-directional ball caster. Each drive wheel is actuated by a DC motor with planetary gear reduction. They are mounted on the left and right sides of the rear portion while the ball caster is mounted on the center of the front end. Due to this mobile

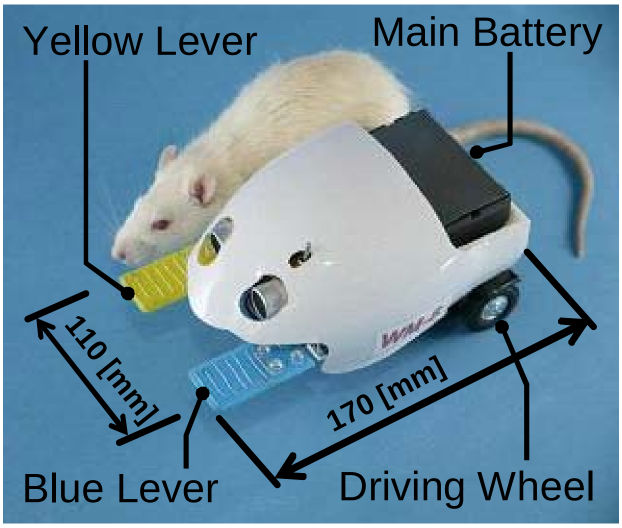

Fig. 1 A rat and a small mobile robot: WM-6

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Table 1 Specification of WM-6

Dimension	mm	175 x 100 x 85
Weight	g	540
Max Speed	m/s	1.0
Max Rotation Speed	rad/s	0.75
Operating time	min	120

mechanism, mobility of WM-6 is non-holonomically constrained.

B. *Power Supply*

A Li-ion battery is selected as the power supply unit for WM-6, since it is simple to measure the remaining battery level using the battery voltage. WM-6 has a Li-ion battery pack (7.2 [v], 1500 [mAh]). WM-6 operates constantly for a minimum of 120 [min] with one fully charged battery. In addition, the battery exchanger (described in Chapter III) automatically exchanges the battery on the robot without human handling. Therefore, it is possible to perform the interaction experiments for over 120 [min] without human interruption to exchange the battery.

C. *Electronic System*

WM-6 has a microcontroller PIC (16F877, 20 MHz, Microchip ltd.) and a Blue-tooth communication module. The microcontroller controls the directions and velocities of the left and right wheels separately (via DC motors) according to instructions sent from the PC. In addition, the microcontroller measures the battery voltage and states of each lever (described later) before sending these data to the PC every 100 [ms].

D. *Interaction Module; Levers*

WM-6 has two levers to interact with rats. Since Skinner's experiment, levers have been used in many experiments with rats. Pushing levers is not an innate behavior of rats, meaning that it is highly likely that pushing the levers observed in experiments is an intentional behavior.

The dimensions of the levers are 20 x 30 [mm] identical to the Skinner box, and they are colored blue and yellow respectively for image processing. These levers consist of touch sensors that are electrically connected to the microcontroller and the logic level of each touch sensor is also sent to the PC through the microcontroller. It is possible to use these data as variables on the operation generator module in the PC. For example, in Figure 3, WM-6 moves to the front of the food-feeding machine when the lever is pushed. We consider these two levers are input devices of WM-6.

III. EXPERIMENTAL SETUP

We developed an experimental setup as shown in Figure 2. The interaction experiments between the rat and WM-6 are conducted in an "open field," 1000 [mm] square flat area surrounded by a wall of 450 [mm] high (Figure 3). The food-feeding machine, water-feeding machine and the battery exchanger are mounted on the wall. A CCD camera is positioned above the open field and sends images of the experiment to the PC every 30 [ms]. The PC automatically

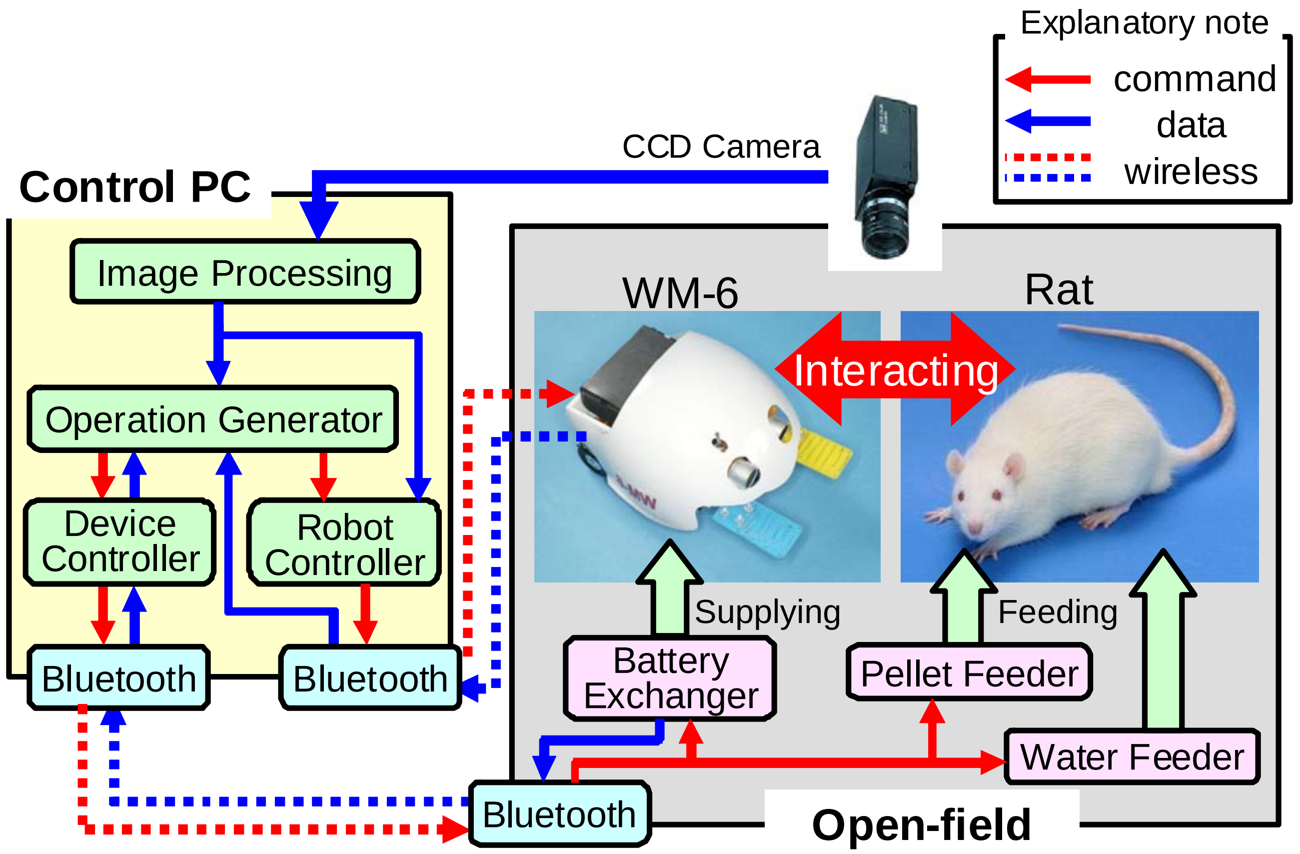


Fig. 2 Experimental Setup that the robot and the rat interact in the open field

controls WM-6, the food-feeding machine, the water-feeding machine and the battery exchanger.

A. *Food-feeding Machine and Water-feeding Machine*

The food-feeding machine releases a food pellet of 45 [mg] into a small tray on the field when it receives an instruction from the PC. The water -feeding machine shows a tap connected with a water bottle for 3 [sec] when it receives an instruction.

B. *Battery Exchanger*

The battery exchanger consists of a microcontroller PIC (16F877, 20 [MHz]), electromagnets for attracting the batteries, 2-DOFs arm and a charger. WM-6 moves to the front of the battery exchanger when the battery on the robot is running low. The PC then sends an instruction to the battery exchanger. After that, the arm catches the dead battery on the robot via electromagnets and exchanges it for a fully charged battery on the charger.

C. *Control PC*

Software that automatically controls WM-6 and all the machines is installed in a PC (CPU; Pentium IV 3.4 GHz, OS; Windows XP) that has an image-processing board and two Bluetooth communication units. This software consists of some soft-ware modules involving an image-processing module, operation generator module, robot controller module and device controller module. Therefore, it automatically conducts the interaction experiments and records the data without human intervention.

The image-processing module receives images from the CCD camera via the image-processing board. This module then computes the gravity points of the rat and the robot respectively every 100 [ms]. This module also saves the positions of the rat and the robot, and their movement distances respectively every 1 [sec].

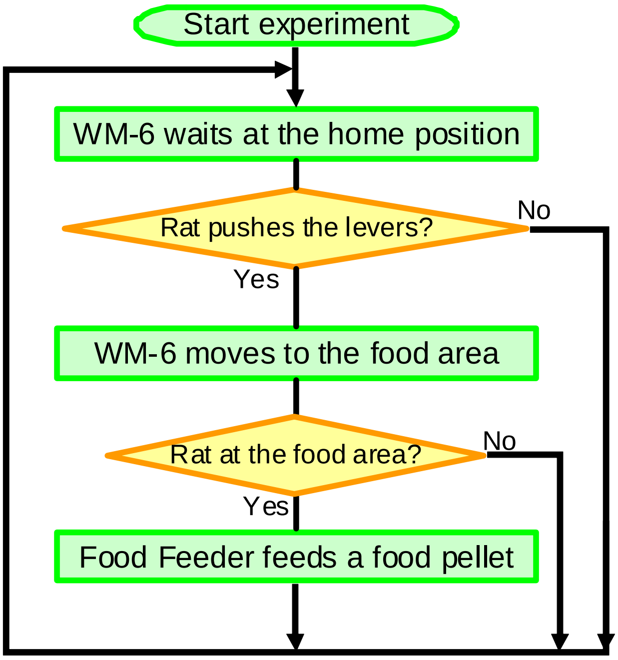
The operation generator module generates the motion of WM-6 and the operation of the experimental setup based on pre-programmed patterns (e. g. Figure 3). For these patterns, experimenters can use variables such as the robot's position, the rat's position, the state of each lever on the robot, and the battery voltage of the robot. The behavior generation algorithm for autonomous teaching is included in this module. It is described in the next chapter.

The robot controller module determines the robot's movements according to the motions generated by the operation generator module. This module then controls WM-6 to move to the target point by controlling the directions and the velocities of each motor according to the distance and angle relative to the target point from the current point.

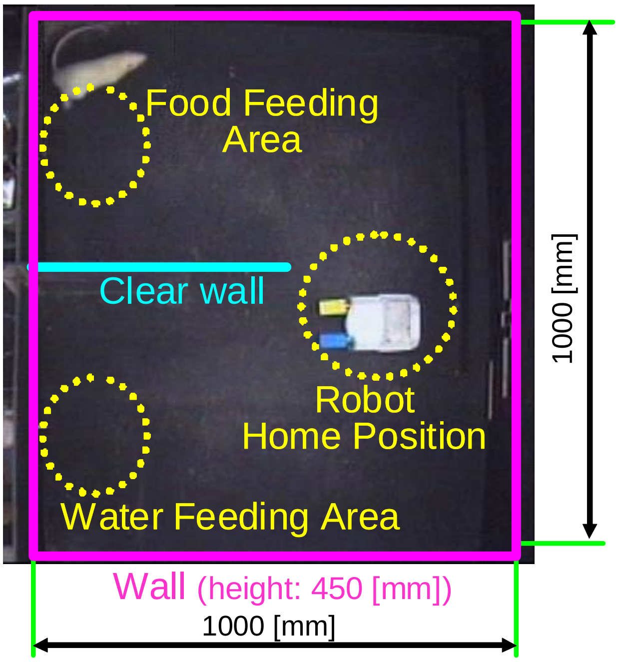
IV. BEHAVIOR GENERATION ALGORITHM FOR TEACHING

A novel behavior generation algorithm that enables WM-6 to autonomously teach a simple task, lever-pushing, to a rat was developed introducing the idea of "shaping [12][13]." The task is shown in Figure 3. In this task, the rat has to push the levers on the robot to obtain food, while the robot usually remains at its home position. When the rat pushes the levers on the robot, the robot moves to the front of the food-feeding machine and then stays there for three seconds. During the time that the robot stays there, the food-feeding machine releases a food pellet if the rat moves there. After these three seconds, the robot returns to the home position.

This task looks simple and easy to learn. However, it is much harder for rats than the lever-pushing task in the Skinner box due to the movement of the robot. In fact, the rats never learned this behavior task without any teaching in our previous experiments.



(a) Procedure of robot motion and food releasing



(b) Arrangement of each area in the open field

Fig. 3 Task conditioned to the rat

A. *Design of Behavior Generation Algorithm*

In psychology, the method of “shaping” is used for this kind of complex task learning. We designed the behavior generation algorithm for the robot introducing the idea of “shaping.” Therefore, the learning process until the rats learn the lever-pushing task is divided into three steps (Step 1, Step 2, and Step 3). We then determined the target behavior or task in each step. We also constructed operational patterns of the setup and robot in each step to increase the chances of the target behavior appearing in the rats as shown in Figure 4.

Step 1; Reinforcement of the rat’s motivation

The target behavior of this step is active movement, the simplest kind of behavior. Rats rarely move in an environment that they have never previously experienced due to their natural sense of caution. Therefore, in this step, the food-feeding machine routinely releases ten food pellets every 1 hour. In our previous experiment, the rats that had obtained food in the open-field moved actively compared to those that had not. Therefore, we believe that these routine feedings are effective in reinforcing the rat’s motivation to move. When the total movement distance of the rat exceeds 50 [m], this step is finished and the next step is started.

Step 2; Conditioning the rat to approach to WM-6

The target behavior of this step is the approach to the robot. To attract the rat’s interest in WM-6, the robot routinely moves to the front of the food-feeding machine and this machine then releases a food pellet when the robot arrives. We believe that the rat learns the relationship between the robot and the feedings through these routine movements and feedings. It is then expected that the rat would be interested in WM-6 and hence approach it.

The rat’s approach to the robot is detected by image processing. When d_{rr}, the distance between the rat and the robot, is less than D_{ap}, the threshold of approach detection, the approach is detected. When the rat’s approach to WM-6 is detected, the robot moves to the front of the food-feeding machine. To reinforce the approach of the rat to the robot, the food-feeding machine then releases a pellet. After that, the robot returns to the home position. When the number of detections and reinforcements of approaches exceeds 200, this step is finished and the next step is started.

Step 3: Conditioning the rat to push the levers

The target behavior of this step is pushing the levers on WM-6. At the beginning of this step, when the rat approaches the robot, the robot moves to the front of the food-feeding machine and this machine then releases a pellet. After 200 reinforcements, D_{ap}, the threshold of approach detection, is reduced every time the rat approaches the robot. We believe that the rat would then approach the robot more closely, and it is subsequently expected that the rat would occasionally push the levers on the robot.

When the rat pushes the levers on WM-6, the robot moves to the front of the food-feeding machine and this machine releases a pallet. In this way, the rat would be conditioned to push the levers on the robot. When the number of times that the lever is pushed exceeds 200, this step is finished. In this way, we believe that rat can be conditioned to push levers to obtain food.

B. *Implementation*

This behavior generation algorithm is implemented in the operation generator module in the PC. The behavior of WM-6 and the operation of the setup are automatically generated according to this algorithm. The PC then automatically controls the experimental setup and WM-6 without any human operation or intervention. Thus, the experimenter has to just release the rat that has no experience of experiment into the experimental setup. The setup and the robot then autonomously condition the rat to perform lever-pushing task in a couple of days.

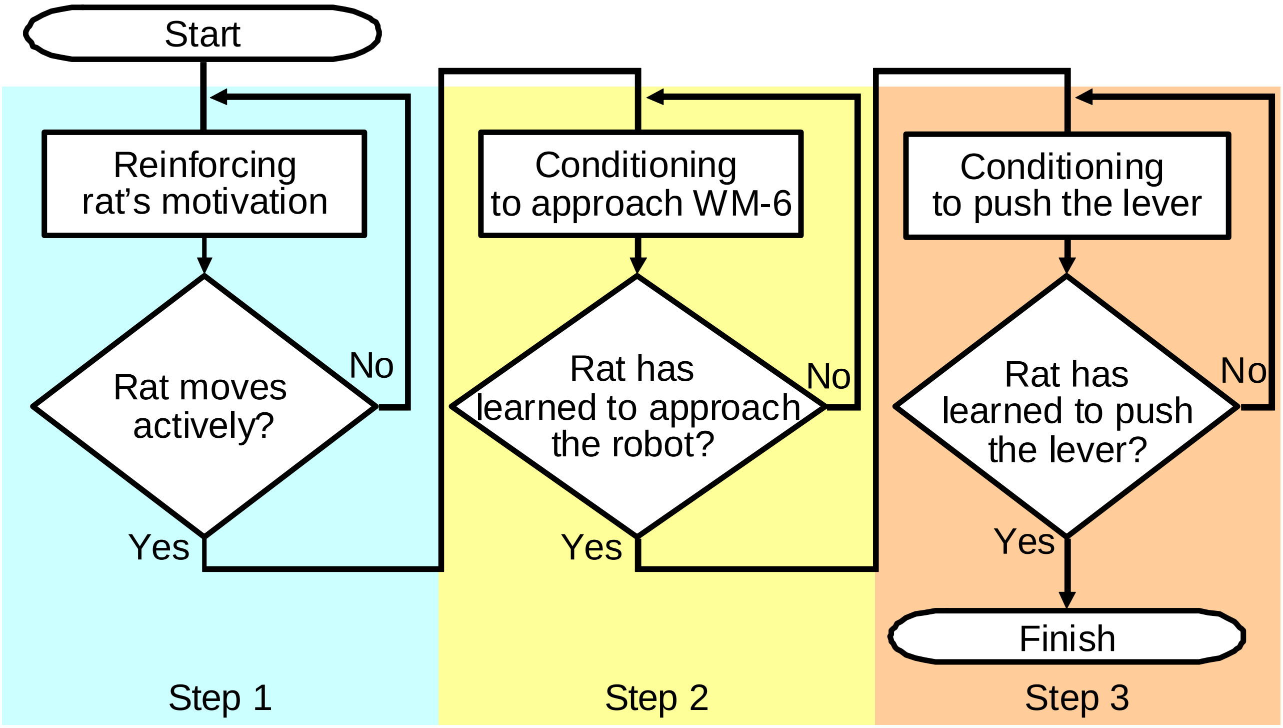


Fig. 4 Behavior generation algorithm for teaching lever-pushing task

V. EXPERIMENT

An experimental evaluation for the behavior generation algorithm for teaching was performed with the experimental setup.

A. *Procedure*

The experiment is performed autonomously using the experimental setup implementing the behavior generation algorithm for teaching. Three rats were used in this experiment. They were male albino rats without any experimental experience and bred singly in breeding cages. Before the experiment, they were made hungry by food restriction.

Each trial was autonomously conducted using a single rat without any human intervention. The rat was released into the experimental setup at the start of each trial. Until the number of times that the lever was pushed exceeded 200, the rat was left there.

B. *Results*

In this experiment, all three rats learned to push the levers on WM-6 to obtain food. Time required to finish each step is shown in Table 2. Cumulative recodes of movement distance, number of approaches to WM-6 and number of lever pushes are shown in figure 5.

C. *Consideration*

All three rats learned the lever-pushing task to obtain food. Therefore, the behavior generation algorithm for teaching was verified.

The times required to learn the lever-pushing task are different from each rat. Comparing to the old rat, Rat 1, the young rats, Rat 2 and 3, required shorter time to acquire lever pushing behavior as shown in Table 2. As shown in figure 5, shape of the learning curve is different from each others, especially between the old rat and the young rats. We consider differences in the shape of the learning curve represent the differences in learning ability. In addition, we consider shape of the learning curve of the approaches represent the interest of the rat to the robot. For instance, young rat bit and pulled the robot several times before to learn to push the lever while old one had not exhibited that. Therefore, we consider it might be represent the sociality of the rat.

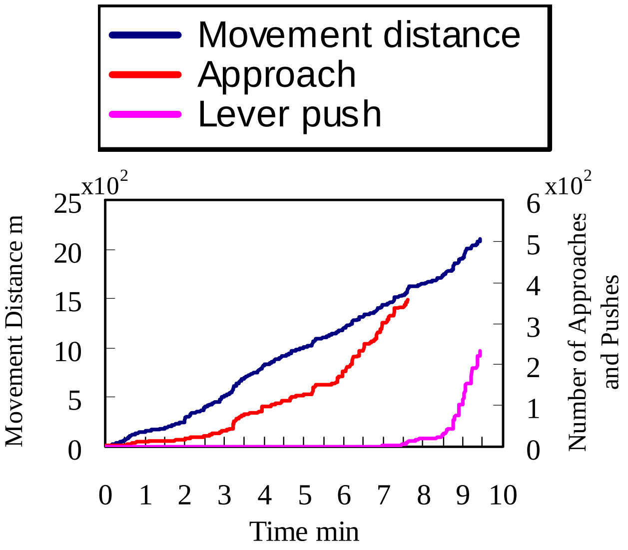
VI. SUMMARY AND FUTURE WORK

We proposed a novel experimental methodology to study learning ability of rats as a method to study Alzheimer's disease. In this methodology, the rat's learning ability is evaluated in the interaction experiment where the robot autonomously taught a simple task. The experimental result suggests that this methodology is useful to evaluate the learning speed of rats decreasing with the age.

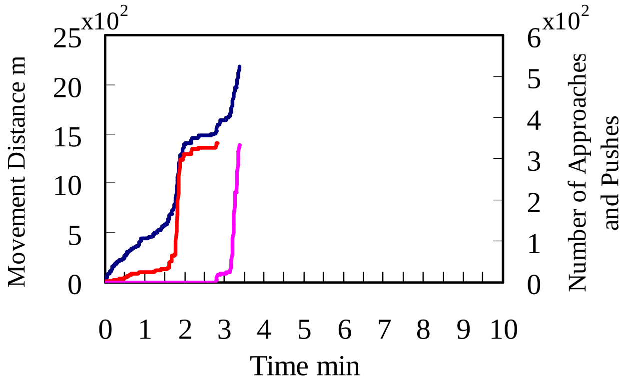
Learning ability can be evaluated using conventional experimental setups such as mazes and Skinner's Box. However, using these conventional experimental setups, sociality can not be evaluated. Using proposed methodology, we consider it can be evaluated. In future work, we will perform an experiment using antianxiety drug to confirm if sociality of rats can be evaluated or not.

Table 2 Experimental result; time required to finish each step [min]

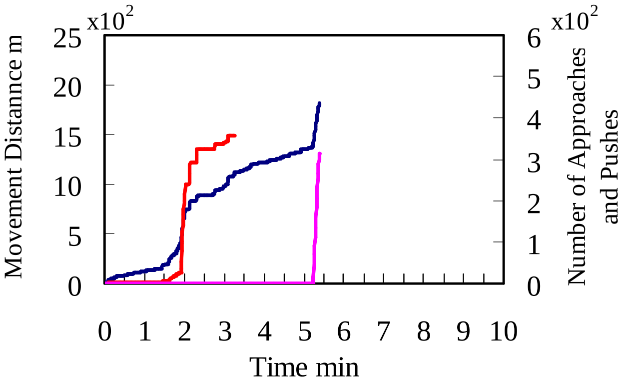
	Rat 1	Rat 2	Rat 3
Weeks old	75	15	15
Step 1	430	50	240
Step 2	6080	1850	1950
Step 3	9360	3260	5320



(a) Rat 1 (75 weeks old)



(b) Rat 2 (15 weeks old)



(c) Rat 3 (15 weeks old)

Fig. 5 Experimental result; cumulative recode of movement distance, number of approaches and pushes

We will also develop other experimental protocols for researches on AD.

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