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Development of Experimental Setup to Create Novel Mental Disorder Model Rats using Small Mobile Robot

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Abstract- **The number of patients with mental disorders is increasing in advanced countries. Many researchers are working to develop mental disorder model animals that contribute to development of new psychotropic drugs. However, we have some doubts about conventional mental disorder models. Therefore, the purpose of this study is to develop an experimental setup to create novel mental disorder model animals. We then developed a small mobile robot and a control system for the robot. Using them, we performed an experiment to develop a mental disorder model rat. In the experiment, we succeeded in developing a new depression model rat and also high activity model rat. These disorder models must be useful in the screening of new psychotropic drugs. In addition, the methodology we developed in this research will contribute to clarifying mechanisms of mental disorders.**

I. Introduction

Recently, the number of patients with mental disorders is increasing in advanced countries such as Japan, USA or European countries. For instance, the number of the patients with mood disorders such as depression doubled in the recent decade in Japan [1]. Therefore, many studies have been performed to develop effective cures for mental disorders not only in clinical medicine but also in basic medicine. These studies have been playing a very important role for clarifying mechanisms of mental disorders and developing new psychotropic drugs. Several researchers have been then studying to develop mental disorder model animals. Mental disorder model animals are living animals that represent phenotypes, such as behavior disorders or plastic changes in the brain, of the human patients with mental disorders. They are created by genetic manipulation, surgical operation on the brain, psychotropic drugs or stressful environment [2]. They are used to screen candidates for psychotropic drugs. Actually, Griebel and Louis found out that Saredutant (SR48968) has anxiolytic-like and antidepressant-like effects [3-5].

In clinical medicine, the stress-vulnerability hypothesis is now well recognized as one of the most suitable ideas to explain how mental disorders occur in humans [6-7]. There are few doubts that stress from the environment plays a very important role when a mental disorder occurs in patients. In this hypothesis, there are individual differences in stress vulnerability, and the mental disorder occurs in the patient when the sever stress exerts on his or her vulnerability. When two people are induced a stress together, it might happen that the mental disorder occurs in one while it doesn't in the other. It can be explained using the stress vulnerability hypothesis.

We recognize how the mental disorder model animals have been contributed to developing psychotropic drugs. However, we consider that studies on how the stress acts on occurrence of mental disorders haven't been well done while those on the vulnerability have been well done in genetics, biochemistry and neuroscience. The stress induced from the environment should be more considered to make more suitable mental disorder model animals. However, there haven't been useful experimental methodology and setups to induce and control the stress from the environment.

On the other hand, we have been developing an experimental system to study interaction between a rat and a small mobile robot [8-10]. We then consider our experimental system can be used to develop novel mental disorder model animals. Therefore, the purpose of this study is to establish the methodology to create more suitable mental disorder model animals. The basic idea is shown in Fig. 1. In this idea, mental disorder models can be created by the stress induced from the robot such as attacking or disturbing. Some changes might be

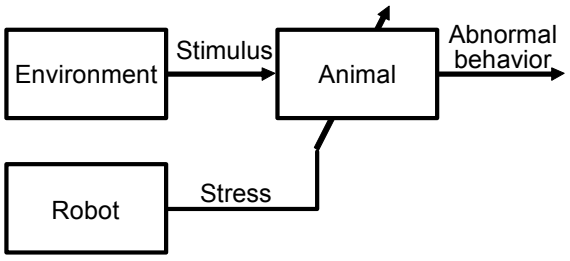

Fig. 1 Basic idea to develop novel mental disorder model.

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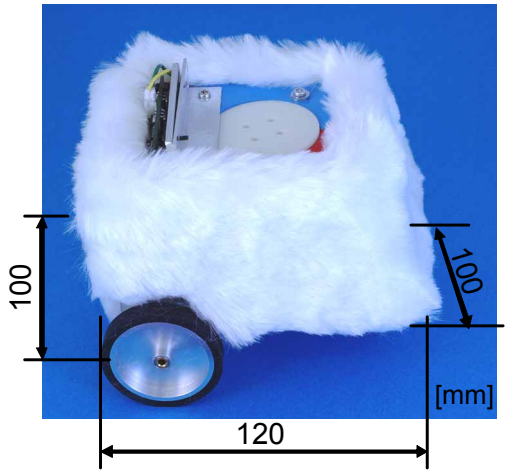


Fig. 2 Small mobile robot WM-8.

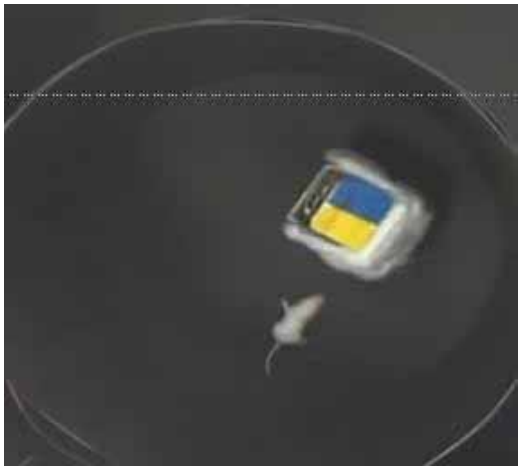


Fig. 4 Open-field, a robot and a rat are there.

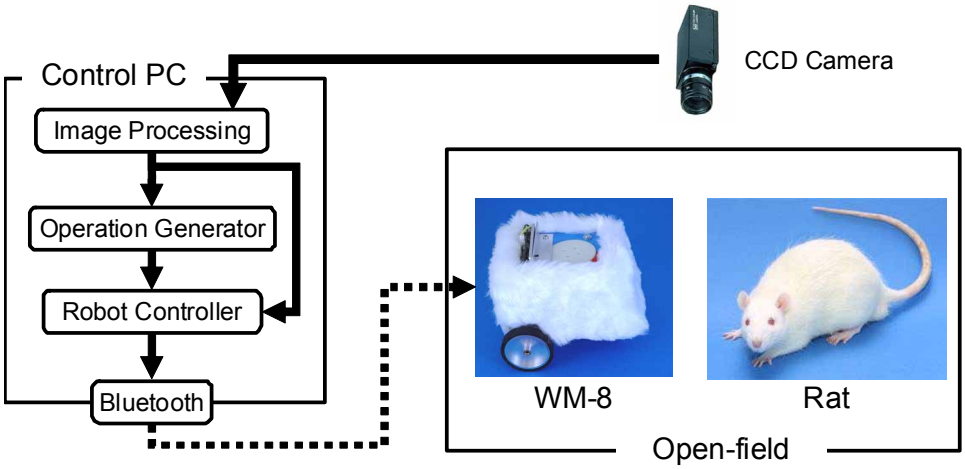


Fig. 3 Overview of experimental setup [8][9].

then occurred in their neural circuit or biochemical system, and they become to behave like patients with mental disorders.

We developed a small mobile robot that interacts with a rat and a control system for the robot. We then performed an experiment based on the concept as shown in Fig. 1. In this experiment, the robot chased the rat with two different conditions in immature period. Characteristics of the rat, validity and reliability of the mental disorder models, were evaluated in the behavior tests. In these tests, the rat that had been chased and attacked by the robot in immature period expressed low activity like the patient with depression while that was chased softly by the robot expressed high activity. Thus, we considered that the small mobile robot can be used to create not only disorder model animals but also high performance animals.

II. Robot and Experimental Setup

A. Small Mobile Robot: WM-8

The small mobile robot, WM-8 (Waseda Mouse No. 8) was developed. A photo of the robot is shown in Fig. 2 and its specifications are shown in Table 1. Dimensions and performance are equal to a mature rat. A Li-ion battery is mounted on WM-8 and it keeps operation for 120 [min]. During the experiment, WM-8 is covered with white fake fur with a color sheet (red and blue) for image processing.

WM-8 has two drive wheels and a passive omni-directional caster. The drive wheels are mounted at right and left side of rear end and a passive omni-directional caster is placed at the front end. Therefore, motion of WM-8 receives non-holonomic constraint.

A microcontroller, a Bluetooth wireless communication module and motor control drivers are implemented in WM-8. The motion of WM-8 is controlled by the PC via Bluetooth wireless communication. The PC sends the instruction of the velocity of each motor. When it receives an instruction from the PC, the microcontroller sends a target value of the velocity of each motor to each driver. Each driver then controls the velocity of each DC motor via virtual velocity feedback control. This driver controls the velocity of the motor with a

circuit to calculate velocity of the motor from the back electromotive force.

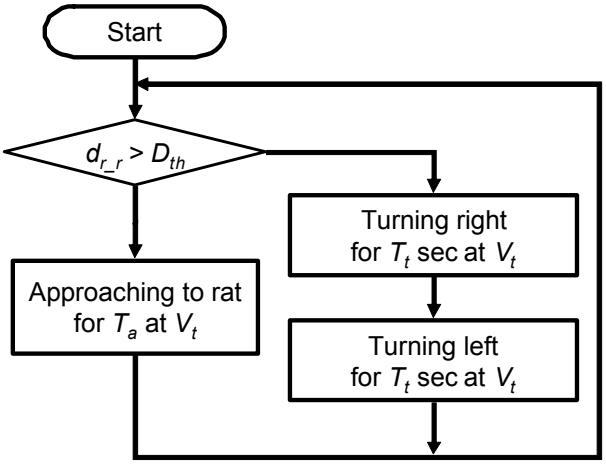
Table 1 Specification of WM-8.

Dimension	mm	100x100x120
Weight	g	585
Max translational vel.	m/s	1.0
Max rotational vel.	rad/s	10.0

B. Experimental Setup

This setup consists of an open-field, a CCD camera and a control PC as shown in Fig. 3. The CCD camera is placed above the open-field. The experiments with a rat and WM-8 are performed in the open-field. A picture of the open-field taken by the CCD camera is shown in Fig. 4.

The robot is controlled by a control PC with software that consists of an image processing module, an operation generator module and robot controller module. In this software, the positions of the rat and the robot are calculated every 50 milliseconds. Motion of the robot is generated based on the algorithm in operation generator module. It is implemented using a format as shown in Fig. 5.



d_{r_r}: Distance between the rat and the robot
D_{th}: Threshold of d_{r_r}
V_t: Velocity of the robot
T_a: Time the robot approaches to the rat
T_t: Time the robot rotates

Fig. 5 Algorithm of the robot motion.

III. Experiments

A. Objective

A person who has experienced much stress, such as violence or lack of affection, during childhood has a higher risk to suffer from mental disorders after growing up [11-12]. On the other hand, the person who grows up in rich environment, surrounded many playful items and moderate stimulus, tends to be active and clever after growing up. Therefore, we aim to develop two opposite kind of model rats, one is the mental disorder model and the other is high performance model by putting the rat in the stressful or rich environment in immature period using WM-8.

B. Method

1) Subject: In this experiment, we choose F344 rats as subjects [13]. These rats arrived at the laboratory when they were two weeks old with their mother. Since then, each litter was bread in a cage with their mother. They were then divided into 4 groups and experienced different situation.

2) Procedure in Immature period: The rats in each group were experienced the experimental situation as shown in Table 2 for 5 days from when they were 2 weeks old. During these 5 days, all the rats were put in the open-field and experienced experimental situation. The experiment with each rat is performed for 30 minutes. After these 30 minutes, the rat put back in the breeding cage.

Group A is a control group. They were just put into the open-field and released there alone. They weren't induced any specific stress in the open-field

Group B is an experimental group. The rats in this group were induced sever stress by WM-8. They were put into the open-field with WM-8. In the open-field, WM-8 was controlled to keep the distance between it and the rat under 50 [mm]. When the distance is under 50 [mm], the robot also kept turning right and left by turns.

Group C is also an experimental group. The rats in this group were chased gently by WM-8. They were put into the open-field with WM-8. In the open-field, WM-8 was

Table 2 Experimental condition of 4 groups.

		Group A	Group B	Group C	Group D
Number of rats		6	4*	6	6
Experimental condition	State of the open-field	Circular (d=450mm)			Rectangular (350mm×200mm)
	Robot	No	Chasing rapidly with attack	Chasing Slowly	No
	Other stressor	No	No	No	Electric shock (30 V, 3 mA)

*2 rats died before being mature

controlled to keep the distance between it and the rat around 300 [mm]. When the distance is under 300 [mm], the robot kept turning right and left by turns.

Group D is a kind of control group. The rats in this group were induced stress by conventional experimental setup. They were put into the box set in the open-field and provided the electric shock from the floor of the box. The electric shock was provided 5 seconds in every 30 seconds.

3) Procedure in Mature period: Characteristics of the rats in each group were evaluated when they became 8 weeks old. We used 5 conventional behavior test protocols for it.

Open-field test is a test to evaluate activity of a rat. In this test the rat is released into the open-field and left there for 10 minutes. The rat's locomotion distance is measured by image processing.

Social interaction test is a test to evaluate sociality and anxiety of a rat. In this test two rats are released into the open-field together for 10 minutes. The distance traveled by the rat is measured by image processing. The rat with high anxiety rarely moves and interacts with the other.

Robot chasing test is a test to evaluate the response of a rat to the robot chasing. In this test the rat is released into the open-field with WM-8 for 10 minutes. WM-8 is controlled to chase the rat as described in procedure of Group C. The distance traveled by the rat is measured by image processing.

Fear conditioning test is at test to evaluate sensitivity of a rat to anxiety. This test consists of two days. In the first day, the rat is released into the box set in the open-field and then provided electric shock for 10 minutes. After the electric shock the rat was put back into the breeding cage. Next day, the rat is released into the box again without electric shock to evaluate sensitivity to anxiety. The distance traveled by the rat is measured by image processing. The rat with high sensitivity to anxiety rarely moves in the second day while one with low sensitivity moves actively.

Forced swimming test is a test to evaluate depression level of a rat. In this test the rat is drooped in a water pool and left there for 10 minutes. The radius of the water pool is 50 [cm] and its depth is 20 [cm]. Immobility time (the rat doesn't move spontaneously) is measured. The rat with high depression rarely swims and just floats on the surface while one without depression swims actively. Thus, immobility time represents depression level.

C. Result

Experimental results of 5 behavior tests are shown in Fig. 6 to 10. In Fig. 6 to 9, bars represent average locomotion distance of the rats in each group. In Fig. 10, the bars represent average immobility time of the rats in each group. Significant differences between each group are confirmed by student's t-test using excel 2003 and shown with * marks in each figure. In Table 3, comparison of the results between group A and other 3 groups are shown.

IV. Discussion

As you can see in Fig. 6 to 9, the locomotion distance of group B is smaller than those of group A and C. The significant differences between group A and B are confirmed in chasing test and social interaction test. Thus, we consider activity of group B was inhibited by WM-8's attack during immature period. It is well known that people with depression are not as active as normal people. Therefore, we considered a rat that experienced attack by the robot can be a depression model.

On the other hand, as you can see in Fig. 6 to 9, the result of group C is quite different from those of group B. The rats in group C move much more active than those in group B. The significant differences are confirmed in all the tests except for the forced swimming test. In fear conditioning test, the traveled distance of the rat of group C is significantly higher than that of group A. Thus, we consider activity of group C was activated by WM-8's gentle chasing during immature period. As described in chapter III, the person who grows up with playful items and moderate stimulus tends to become active and clever. Therefore, we considered the rat that experienced the gentle chase by the robot can be a high activity model.

We would like to compare between group B and C. The rats in both group B and C experienced the interaction with WM-8 in the experimental setup. Only behavior generation algorithm for the robot is different while the results are quite different each other. We consider that the robot had positive (friendly) meaning to the rat in the experiment of group C while it had negative (enemy) meaning in that of group B. Conventional stress inducing setups such as electric shock, water pool, big sound or cat voice only have negative meaning to rats and never have positive meaning. We consider only robot, especially mobile robot can have both negative and positive meaning to the animals. Furthermore, the robot changes its meaning to the rats by only changing behavior generation algorithm.

V. Conclusions and Future works

The purpose of this study is to develop novel mental disorder model animals. We then developed a small mobile robot and an experimental setup. Using them, we performed an experiment to develop not only mental disorder model but also high performance model. In the experiment, we succeeded in developing a new depression model and a high performance model. These disorder models will be able to be used in the screening of new psychotropic drugs. In addition, the methodology we used in this research will contribute to clarifying mechanisms of mental disorders.

To confirm the suitableness of the new depression model, we should do additional experiments using anti-depressant drugs. The suitableness will be confirmed if depression-like behavior is not observed in the experiment when the anti depressant drug is given to the rat. Biochemical analysis should be done too. In patients with depression, the amount of serotonin in the brain is decreased. It occurs in some depression model animals. Therefore, we should confirm if it occurs in our depression models.

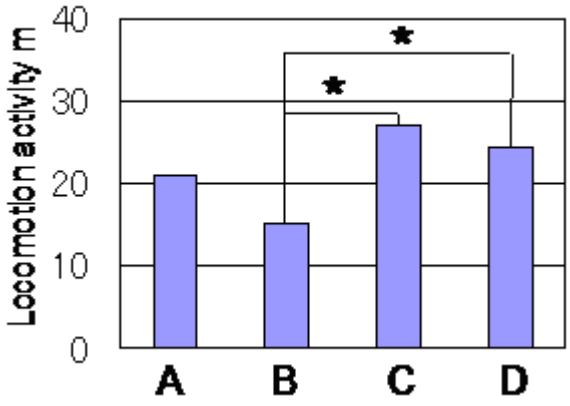


Fig. 6 Locomotion activity in open-field test.

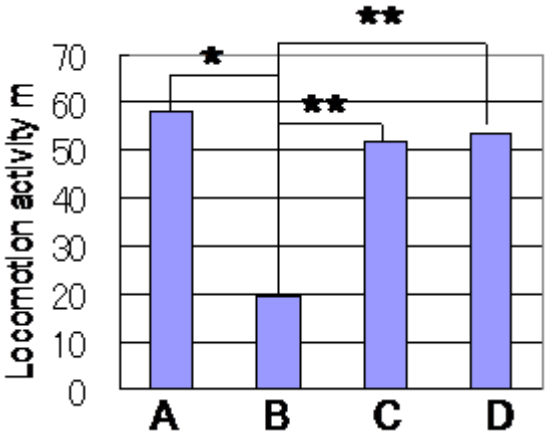


Fig. 7 Locomotion activity in chasing test.

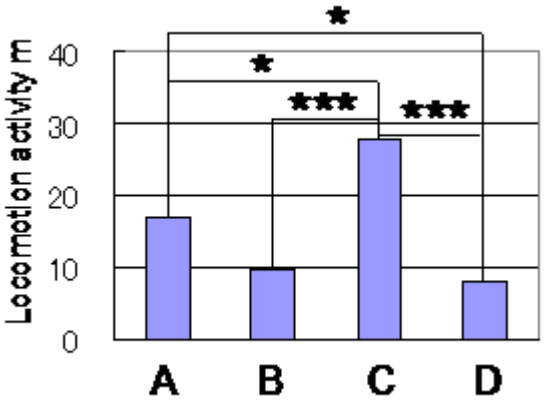


Fig. 8 Locomotion activity in fear conditioning test.

Further more, we will try to clarify mechanisms of mental disorders using the methodology used in the experiment described in this paper. We will change several parameters in robot behavior and obtain experimental results. We'll then analyze the relationship between the robot parameters and the results to develop functions that represent the relationship. We consider that the function can be considered a model of mental disorders.

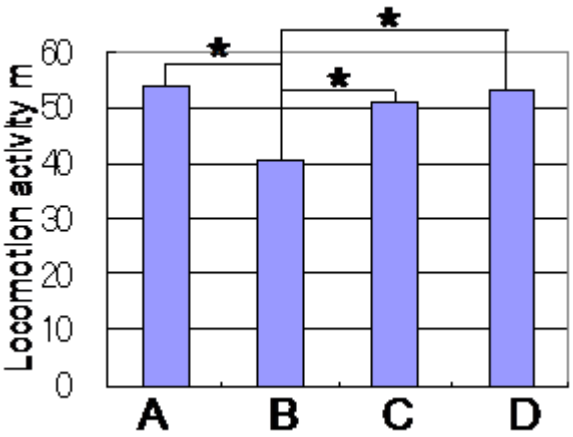


Fig. 9 Locomotion activity in social interaction test.

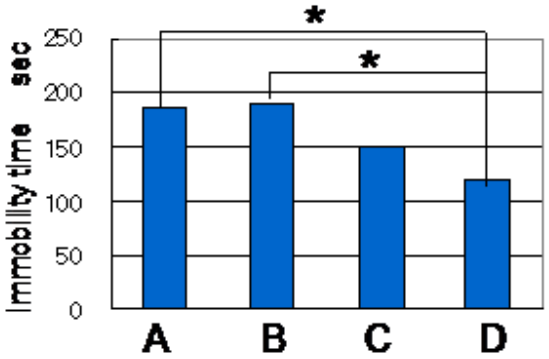


Fig. 10 Immobility time in forced swimming test.

Table 3 Comparison of the results between group A and other 3 groups.

	B	C	D
Open-field test	ns	ns	Ns
Robot chasing test	-	ns	Ns
Fear conditioning test	ns	+	-
Social interaction test	-	ns	Ns
Forced swimming test	ns	ns	-

"+" means significantly large, "-" means significantly small. "ns" means not significantly different. Significant difference is confirmed when p value is lower than 0.05.

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