9th International IEEE EMBS Conference on Neural Engineering
San Francisco, CA, USA, March 20 - 23 , 2019

Leading a Rat along a Moving Virtual Reward Circle with "Rattractor", a Closed-loop Deep-Brain Stimulator

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Abstract— **Electrophysiological rewards in the brain have been used to affect animal behavior. We have worked on a closed-loop deep-brain stimulator named "Rattractor", which applies neural rewards in the deep brain to attract a rat toward a virtual reward circle on a flat experimental field so that its range of activity is regulated but without explicit cues. The system is unique in that the rat was not fed with one-way specific instructions on how it should locomote. Instead, the system projected a set of behavioral values that the rat should follow, and the rat tried to get comfortable by searching the virtual reward circle by itself. This paradigm composes a closed-loop cross-interaction system consisting of a rat and the device. In this work, the virtual reward circle was moved with a suitable timing for leading the rat to different places. Although the moving speed had to be low in order not to allow the rat to lose interest in the reward circle, in two trials at least, the rat was led more than 1 meter away from its the initial location. This paper describes these successful trials, and discusses the behavior of the rat in both successful and unsuccessful trials.**

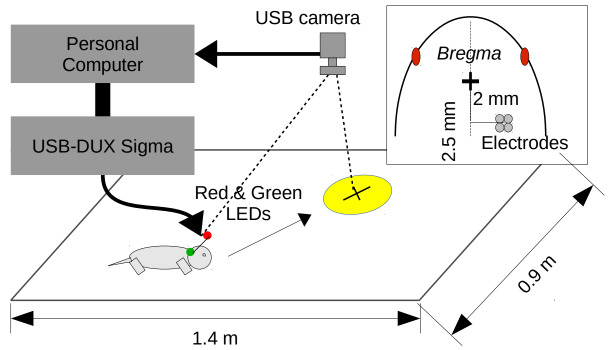

Fig. 1. Hardware schematic diagram of *Rattractor* . The rat had a red LED on its left side, and a green LED on its right side so that the USB camera could track them in a dark room. The electrical stimuli were applied when the rat entered a reward circle, indicated by the yellow circle.

I. INTRODUCTION

Recent advances in neurotechnology have enabled researchers to make a direct connection to neural systems[1], which makes it possible to affect animal behavior by using electrophysiological stimuli in the deep brain as cues and rewards.

For example, a rat navigation system was proposed to navigate a rat in a complex environment including ladders and a bridge [2]. The authors applied electrical stimuli in the primary motor cortex (S1) to instruct the rat to change its direction, and in the medial forebrain bundle (MFB) to supply rewards for following the commands.

A roach biobot called Roboroach[3] is another example of controlling an animal by applying direct electrical stimuli in the neural system. The authors applied electrical stimuli to the antennae of cockroaches to guide them to follow predefined pathways[4]. They also introduced *Microsoft* Kinect to automatically evaluate their behaviors[5].

These preceding works show promise for manipulating small animals instead of small and complex artificial robots. In these systems, the experimenters gave the animals external instructions on which direction they should make a turn. Therefore, the animal behavior was planned by the experimenters outside of the animal's brain.

We took a similar but different approach, where the reward stimuli were instantaneously applied as the animal fulfilled certain behavioral conditions. The animals were *not* controlled by specific instructions, but they followed their own behavior plans, which we actually modified. We implemented this system, which we named *Rattractor* after its ability to *attract a rat*, by developing a closed-loop controller that gave micro-electrical stimuli in the deep brain, most likely the lateral hypothalamus (LH) region, when the rat stayed inside a virtual reward circle[6]-[8]. It is unique in that the system did not feed a rat with one-way specific instructions on how it should locomote. Instead, it projected a set of behavioral values that the rat should follow, and the rat tried to get comfortable by searching the virtual reward circle by itself, composing a closed-loop cross-interaction system of the rat and the device.

In this work, we chose one rat which showed a good response to the stimuli — a rat which was attracted to the virtual reward circle in our recent experiments — and let it follow a moving reward circle, expecting that the rat could be guided toward an arbitrary place on the experimental field.

II. SYSTEM

In our previous studies[6], [7], we implanted four microelectrode wires made of tungsten (W) near the right lateral hypothalamic (LH) region of the rat. These regions are known to be related to the neuronal reward system[9]-[11], and have been historically used for electrophysiological

*This work was partially supported by the Japan Science and Technology Agency (JST) KAKENHI 17K17684, and the Precise Measurement Technology Promotion Foundation (PMTP-F).

The animal experiments were approved by Animal Experiments Committee of the Graduate School of Medicine of the University of Tokyo and followed their guidelines.

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operant conditioning[12], [13].

The electrodes were placed in the brain according to the stereotaxic coordinates [14] listed in Table I. Out of five rats that we prepared, we selected one rat that showed the best performance in following a virtual reward circle in our previous work[6], [7]. A pair of electrodes LA & LP was used to apply a differential electrical current in the brain — assuming that the stimulation current was focused around a position 3.3 mm lateral, and 2.5 mm posterior (caudal) from the *bregma* point, and 8.0 mm ventral from the dura (i.e., the brain surface).

Figure 1 shows a hardware schematic diagram of the *Rattractor* system. An awake rat was placed on a field of 1.4 m wide and 0.9 m deep. Note that the left, right, and deepest end of the field consisted of walls, and the one in front was a descending cliff without barriers. The rat had red and green LEDs attached to its head. It also had a connector on the head which was wired to a in-house designed voltage-current converter circuit after a general purpose I/O unit (*Incite Technology* USB-DUX Sigma). A personal computer controlled the experimental operation, and detected the head position of the rat on the field using a generic USB webcam placed on the ceiling to decide when to apply stimuli in the brain.

The camera captured raw images of the illuminated LEDs on the rat's skull at 5–15 frames per second. The experiment was conducted in a dark room to avoid interference from environmental light. We built a C program using the OpenCV library[15] to filter colors in the HSV color space, followed by denoising and centroid calculation to detect the position coordinates of the LEDs on a complex plane ($r_{\mathrm{R}}, r_{\mathrm{G}} \in \mathcal{C}$). Then, the head position, r, and the heading direction of the rat, θ, were calculated as follows;

$$\begin{aligned} r &= \frac{r_{\mathrm{R}} + r_{\mathrm{G}}}{2} \\ \theta &= \angle(r_{\mathrm{R}} - r_{\mathrm{G}}) \end{aligned}$$

Figure 2 shows a captured monitor image of the UI of the software. The rat position r is shown as a white circle with a line representing the heading direction θ. In this image, for demonstration purposes, a reward circle of with radius $R = 0.1$ m was manually placed at the position of the mouse cursor p to provide the rat with stimuli. More generally, the reward stimulation in the LH region was applied when

$$|r - p| < R$$

was satisfied, indicated as a red circle covering the rat. The software was designed to allow the operator to arbitrarily set

TABLE I

ELECTRODE COORDINATES RELATIVE TO BREGMA

Elec-trode	**Lateral** (Right side)	**Posterior** *Caudal*	**Ventral from dura**
MA	0.7 mm	1.3 mm	8.0 mm
MP	0.7 mm	3.7 mm	8.0 mm
LA	3.3 mm	1.3 mm	8.0 mm
LP	3.3 mm	3.7 mm	8.0 mm

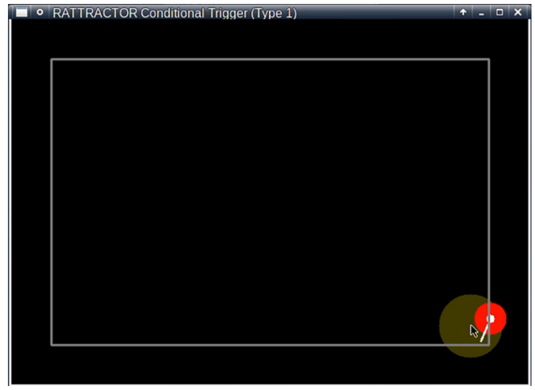

Fig. 2. Software showing the rat head position r (a small white circle) and the heading direction θ (white line sticking out of the white circle). The yellow circle and the large rectangle represent the virtual reward circle and the edge of the experimental field, respectively. The red circle covering the rat indicates that the rat's brain is currently being stimulated in the reward circle.

the position and the size of the reward circle. They could be temporarily updated as follows,

- Gradually increase or decrease the radius,
- Smoothly displace the position at a specified velocity in any direction,
- Randomly displace the position at a specified velocity following a Poisson distribution.

When the software decided to provide stimulation to the rat, it generated 10 biphasic pulses, which were applied to an analog output channel of the USB-DUX Sigma unit using the Comedi library[16]. Finally, the output voltages were converted into current stimuli of 80 μA in amplitude. The whole process was developed on Gentoo Linux running on a customized desktop computer (*Intel* Core i3-7100 3.9 GHz CPU; 2 GB Memory).

III. Demonstration

A. Procedure

We adopted a procedure in which we waited for the rat to voluntarily reach the corner of the experimental field before starting each session for leading the rat to other places. When the rat reached any one of the four corners of the rectangular field, a reward circle of $R = 0.1$ m radius was automatically set at the current position of the rat. Then, the circle was moved along the diagonal line of the field toward the other end. Its velocity was selected from 0.05 m/s (5 cm/s), 0.02 m/s (2 cm/s), and 0.01 m/s (1 cm/s).

B. Coordinates Alignment

Since the starting position and the moving direction of the reward circle in each trial varied depending on four corners of the field, we applied the following conversion to align them on a complex plane:

$$r' = \mathrm{j}\frac{r[k] - r[1]}{p[K] - p[1]} \tag{1}$$

where $k = 1, \ldots, K$ is an index of the processed frames, and j is the imaginary unit ($\mathrm{j}^2 = -1$).

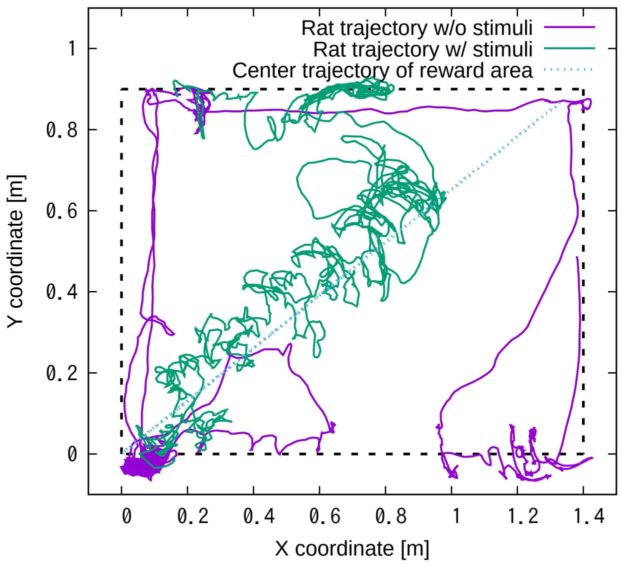

Fig. 3. A typical example of a raw trajectory of the rat (solid lines) and the center of the reward circle (dotted line). The dashed lines represent the edges of the experimental field corresponding to the rectangle in Figure 2. Note that the edges on $X = 0$, $X = 1.4$ and $Y = 0.9$ consisted of walls, and the edge on $Y = 0$ was a descending cliff without barriers.

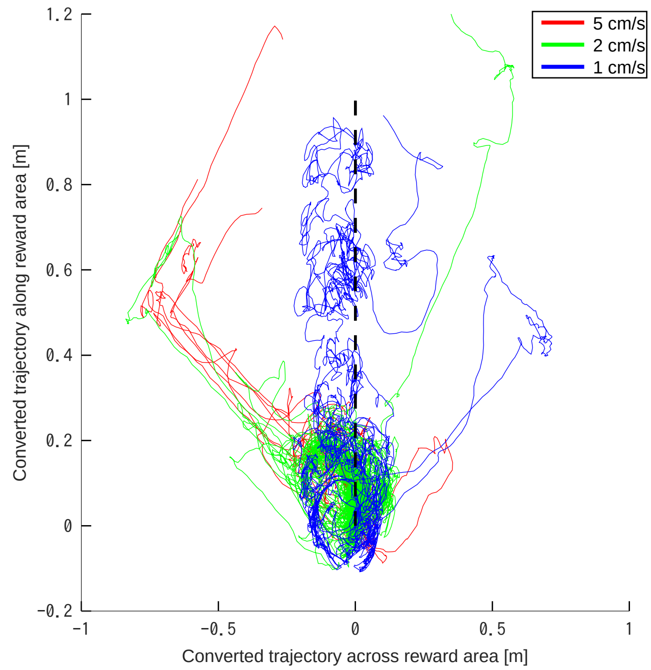

Fig. 4. Converted coordinates of the rat (thin solid lines) corresponding to the different velocities of the moving reward circle. Each line represents one trial. The movement of the reward circle was sorted into a single vertical trajectory (thick dashed line).

C. Results

Figure 3 shows a typical example of the raw trajectory and the center of the reward circle. First, the stimulus was not applied, and the rat tended to locomote along the walls surrounding the field at $r = 0,\ 1.4$ and $r = 0.9\mathrm{j}$. Then, the stimulation function of *Rattractor* system was turned on, and the stimulation session started after the rat voluntarily reached the $X = 0$, $Y = 0$ $(r = 0 + 0\mathrm{j})$ corner. The reward circle was subsequently moved along the diagonal line toward $X = 1.4$, $Y = 0.9$ $(r = 1.4 + 0.9\mathrm{j})$ at a velocity of 0.01 m/s (1 cm/s). The rat wandered around the reward circle and followed it until it suddenly failed to track the area after traveling approximately 1 m.

Figure 4 shows converted coordinates of the rat corresponding to the different velocities of the moving reward circle (red for 5 cm/s, green for 2 cm/s, and blue for 1 cm/s) according to equation (1). Note that the movements of the reward circle were sorted into a single vertical trajectory, because equation (1) constantly gives a direction toward the Y axis (r=j). With this figure, we can evaluate the accumulated trajectory of the rat around the reward circle.

The result shows that when the reward circle was moved at a velocity of 5 cm/s or 2 cm/s, the distance that the reward circle had moved at the point when the rat failed to follow it was 0.2 meter or less. However, at the moving velocity of 1 cm/s, the rat succeeded in staying inside the reward circle at least for two trials.

The result was quantitatively confirmed by drawing the difference between the rat position and the center of the reward circle (Figure 5) over the displacement of the reward circle from the initial position which was at the corner of the field. In the two successful trials with the reward circle moving at a velocity of 1 cm/s, the difference remained around 0.1 m, which was as small as the radius of the reward circle, with some short exceptional periods in which the rat temporarily missed the circle. It is also notable that the difference between the head position of the rat and the reward center did not increase in all trials until the travel displacement of the reward circle reached 0.2–0.3 m, assuming that the stimuli did not cause such a level of discomfort that the rat tried to avoid them immediately.

IV. DISCUSSION

We succeeded in leading a rat to follow a reward circle which was moved in a straight line from one corner of the experimental field, to the diagonally opposite corner, by applying the electrical stimuli in the deep brain, most likely the lateral hypothalamus (LH). The LH region is related to self-feeding and rewarding of rats, motivating themselves to reinforce specific behaviors[9], [10], and has been used for electrophysiological conditioning[12]. Our method inherited the traditional approach, while at the same time introducing recent digital instruments to realize a closed-loop cross-interaction system consisting of a rat and the device.

It is notable that the enforcement of a restricted behavior in the rat compared to its free behaviors was a kind of "loose" intervention, whereby the rat could choose whether or not to follow the value to earn presumably comfortable stimuli. We assume that the rat followed the reward circle of its own volition without us tampering with the natural neural systems.

The rewarding area in which the rat was given the stimuli

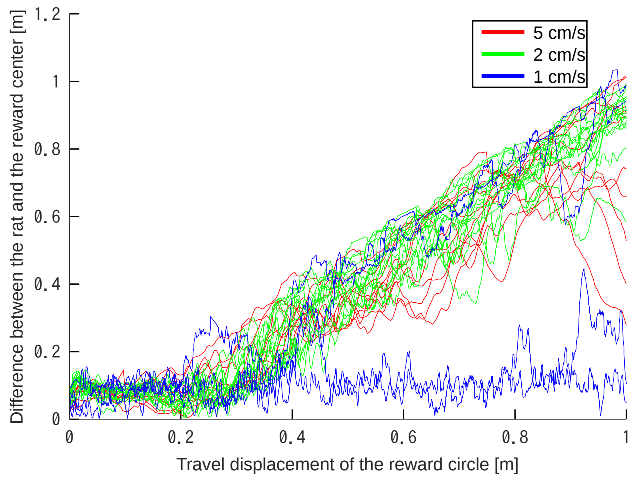

Fig. 5. Difference between the rat position and the center of the reward circle, corresponding to the different velocities, plotted over the the displacement of the reward circle. Each line represents one trial.

could be moved over time, allowing the rat to follow it. However, its movement speed had to be very slow, no faster than 1 cm/s, otherwise, the rat got lost from the circle. The rat occasionally showed reflexive behavior or involuntary twitches possibly caused by the stimuli, which diminished the success rate in following the target.

In the successful trials in which the rat continuously followed the rewarding circle, sometimes the rat followed the area even until reaching the diagonally opposite corner of the field, but it typically gave up along the way, approximately 1 meter from the start point, for example, even though the moving velocity of the rewarding area was at its lowest. Possible explanations for these results include

- the rectangular shape and the size of the experiment field affected the natural (or "baseline") behavior of the rat,
- the wires for supplying the stimuli worked as a unintended tether and obstructed the rat from moving freely,
- or a possible nature of the rat to give up early or to avoid a certain area on the experimental field.

These explanations could be examined further by increasing the number of rats and trials, and varying the experimental conditions. However, we must also emphasize the difficulty of repeating the trials with a rat under controlled conditions. Actually, the rat was very uncertain in its behavior, and in many trials, the rat did not enter the reward circle at all.

The rat used in this work and others in general preferred to stay along the walls, especially in the corners of the field. Still, our system led the rat toward the diagonally opposite corner passing through the flat open area which should be not comfortable for average rats, thus overriding their inclination to remain in safer places. Our method may be applied not only to keep a rat in a virtual cage without physical barriers, enforced handling or applying punishments, but also for investigating a rodent model of stress-evoked behaviors[17] and the psychiatric diseases.

V. Conclusion

We succeeded in leading a rat from one corner to a diagonally opposite corner on a planar field along a slowly moving virtual reward circle which was realized by "Rattractor" — a closed-loop deep-brain stimulator. By closing the loop of the rat's behavior and the rewarding cycle, we could override its set of values and systematically change its behavior without giving any forcible or specific instructions.

References

[1] M. Lebedev, and M. A. L. Nicolelis, "Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation," Physiological Reviews, vol. 97, no. 2, 2017, pp. 767–837.

[2] S. K. Talwar, S. Xu, E. S. Hawley, S. A. Weiss, K. A. Moxon, and J. K. Chapin, "Rat navigation guided by remote control," Nature, vol. 417, May 2002, pp. 37–38.

[3] T. Latif, and A. Bozkurt, "Roach Biobots Toward reliability and optimization of control," IEEE PULSE Magazine, vol. 27, Sep. 2017, pp. 2154–2287.

[4] A. Dirafzoon, T. Latif, F. Gong, M. Sichitiu, A. Blzkurt, and E. Lobaton, "Biobotic Motion and Behavior Analysis in Response to Directional Neurostimulation," in Proc. 42nd IEEE Intl. Conf. on Acoustics, Speech and Signal Processing, New Orleans, GA, USA, 2017, pp. 2457–2461.

[5] E. Whitmire, T. Latif, and A. Bozkurt, "Kinect-based System for Automated Control of Terrestrial Insect Biobots," in Proc. 35th Annu. Intl. Conf. IEEE EMBS, Osaka, Japan, 2013, pp. 1470–1473.

[6] N. Sudo, O. Fukayama, and K. Mabuchi, "Study on the deep brain stimulation to induce voluntary locomotion of a rat," in Proc. Society for Neuroscience Annual Meeting, Washington, DC, USA, Nov. 2017.

[7] O. Fukayama, N. Sudo, K. Mabuchi, and T. Isoyama, "Rattractor — Closed-loop Rat Attractor by Deep Brain Stimulation," in Proc. 40th Annu. Intl. Conf. IEEE EMBS, Honolulu, HI, USA, Jul. 2018.

[8] N. Sudo, O. Fukayama, K. Mabuchi, and T. Isoyama, "Modifying behavior of a rat during a Brain-Machine Interface experiment by deep brain stimulation," in Proc. Society for Neuroscience Annual Meeting, San Diego, CA, USA, Nov. 2018.

[9] D. L. Margules, and J. Olds, "Identical "Feeding" and "Rewarding" System in the Lateral Hypothalamus of Rats," Science, vol. 135, Sep. 1961, pp. 374–375.

[10] D. C. Castro, S. L. Cole, and K. C. Berridge, "Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry," Frontiers in Systems Neuroscience, vol. 9, Jun. 2015, pp. 1–17.

[11] Z. -B. You, Y. -Q. Chen, and R. A. Wise, "Dopamine and Glutamate Release in the Nucleus Accumbens and Ventral Tegmental Area of Rat Following Lateral Hypothalamic Self-Stimulation," Neuroscience, vol. 107, no. 4, pp. 629–639, 2001, pp. 629–639.

[12] J. Olds, and P. Milner, "Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain," J. Comparative and Physiological Psychology, vol. 47, no. 6, 1954, pp. 419–427.

[13] J. Olds, P. Travis, and C. Schwing, "Topographic Organization of Hypothalamic Self-Stimulation Functions," J. Comparative and Physiological Psychology, vol. 53, no. 1, 1960, pp. 23–32.

[14] G. Paxions, and C. Watson, The Rat Brain in Stereotaxic Coordinates Compact Third Edition. San Diego, CA: Academic Press, 1997.

[15] Nov. 2018. [Online]. Available: `https://opencv.org/`

[16] Nov. 2018. [Online]. Available: `http://comedi.org/`

[17] A. Saxena, M. Dandekar, G. Scaini, V. Giridharan, Y. Zhou, J. H. Shin, A. Migut, T. Barichello, J. Soares, J. Quevedo, and A. Fenoy, "Effect of Deep Brain Stimulation on Inflammatory Markers in Hippocampus of Rodents Exposed to Chronic Unpredictable Stress — a Model of Depression," Biological Psychiatry, vol. 83, May 2018, pp. S161–162.