Availability of three-lever operant task as mouse model for studying motor sequence and skill learning

Original Article

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Mitsugu Yoneda*, Yuki Tabata**, Ryosuke Echigo*, Yui Kikuchi*, Takako Ohno-Shosaku*

Abstract

　Human behavior in daily life is based on various brain functions, including cognitive and motor functions. A better understanding of neural mechanisms underlying motor learning is an important prerequisite for the development of treatments and has important clinical implications. Previous studies developed a sequence and skill learning task, called "three-lever operant task," where rats were trained to press three levers in correct order within a given time, and demonstrated that this task is dependent on the basal ganglia. As genetically altered mice have been shown to be useful for studying the molecular mechanisms underlying brain functions, we applied the three-lever operant task to mice and examined whether this task can be used as a mouse model for studying motor sequence and skill learning.

　Experiments were carried out with five C57BL/6NCr male mice at the age of 8 weeks. One training session lasting 60 minutes was given once a day, five times a week. Mice were trained to press any one of active levers for food reinforcement (R) (one-lever task), three levers in a given sequence within a given time (T) (three-lever task), and three levers in the opposite sequence (reverse three-lever task).

　Analysis of the performance in the one-lever task, which was used as a shaping procedure for the three-lever task, demonstrated that mice change their behavior after inactivation of the most frequently pressed lever, and that this behavioral change can be evaluated quantitatively from the inactive lever press ratio. In the three-lever task, the number of sessions required to learn the order without time restriction ranged from 4 to 16 sessions (1 – 3 weeks), which was comparable to that in rats (1 – 4 weeks). In the three-lever task with time restriction, the mice showed good performance (R > 100) even at T = 0.6 s. In the reverse three-lever task, mice relearned the order of lever press within three sessions, indicating that this task can be used to study reversal learning. These results indicate that the three-lever operant task is useful for studying several different aspects of motor learning, including sequence learning, skill learning, adaptation, and reversal learning. We expect that the application of this task to various types of genetically altered mice will yield substantial progress in understanding the neural mechanisms of motor learning.

KEY WORDS

operant task, lever press, sequence learning, motor skill learning, mouse model

Introduction

　Human behavior in daily life is based on various brain functions including cognitive and motor functions. In addition, learning, memory and other aspects of neural plasticity are important for adapting and reacting to changing circumstances. To understand these processes, their neural mechanisms have been investigated in humans[1-6], and more intensively in laboratory animals[7-10].

　Theoretical models of motor learning suggest that three learning modules, which are distributed in different brain

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*　　Faculty of Health Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University
**　　Medical Corporation Juzenkai Juzen Hospital

areas, are specialized for different types of learning[11, 12]. The basal ganglia are specified for reinforcement learning, which is guided by the reward signal encoded in the dopaminergic input[13, 14]. The cerebellum is specified for supervised learning, which is guided by the error signal encoded in the climbing fiber input[15, 16]. The cerebral cortex is specialized for unsupervised learning, which is guided by the statistical properties of the input signal itself or the ascending neuromodulatory inputs[17].

Using rats, Yoneda et al.[18] developed a sequence and skill learning task, called "three-lever operant task". In this task, rats are trained to press three levers in a correct order within a given time. Therefore, this task involves both sequence learning and motor skill learning. The analysis of the performance in this task has shown that the parameters of performance are improved in the following order; the time required for pressing three levers, success rate, and uniformity of movement, indicating that skill learning takes more time than the sequence learning. It was also found that the performance of this task was impaired in Parkinson's disease model rats, suggesting that this task is dependent on the function of basal ganglia[19].

Several tasks have been used for studying motor learning depending on the basal ganglia. For procedural memory, habit formation or response learning, cross-maze task[20], conditional T-maze task[21, 22], and operant vertical head movement[23] have been used. For motor sequence learning, sequential nose poke[24] and treadmill[25] have been used. For motor skill learning, accelerating rotarod training[26, 27] has been used. Compared to these tasks, which are rather specialized to certain aspect of motor learning, the three-lever operant task is unique in targeting several aspects of motor learning at a time.

To investigate neural mechanisms of motor learning in the three-lever operant task, we first used pharmacological methods. However, daily injection of pharmacological agent for weeks or months, which is necessary because motor sequence and skill learning takes a long time, is stressful for animals, and not recommended for ethical reasons[28]. Furthermore, pharmacological agent such as a receptor antagonist sometimes lacks the specificity to the target (e.g., receptor), and causes side effects. Recently, genetically engineering techniques have been applied to animals, and developed genetically altered animals, typically knockout animals that completely lack certain gene products, such as receptors and enzymes. Whereas the number of types of knockout rats available is limited, numerous types of knockout mice have already been produced, and proved to be useful for studying functions of each subtype of receptors or enzymes[29-31]. So, we planned to apply the three-lever operant task to mice. In the present study, we analyzed the performance of wild-type mice in this task, and examined whether the three-lever operant task can be used as a mouse model for studying motor sequence and skill learning.

Methods

1. Experimental set-up

Experiments were performed in an operant chamber (225 × 240 × 200 mm, OP-3101K, O'HARA & Co., Ltd.) placed in a sound-attenuating box (495 × 750 × 685 mm). Three levers (18 × 15 mm) were protruded into the chamber, and the right (A), center (B) and left (C) levers were positioned 2, 4 and 2 cm above the floor, respectively (Fig. 1). The B-lever was set 2 cm higher than the other two levers, so that the mouse can press the lever with a forelimb by standing up on the hind legs. Execution of experiments and data collection were
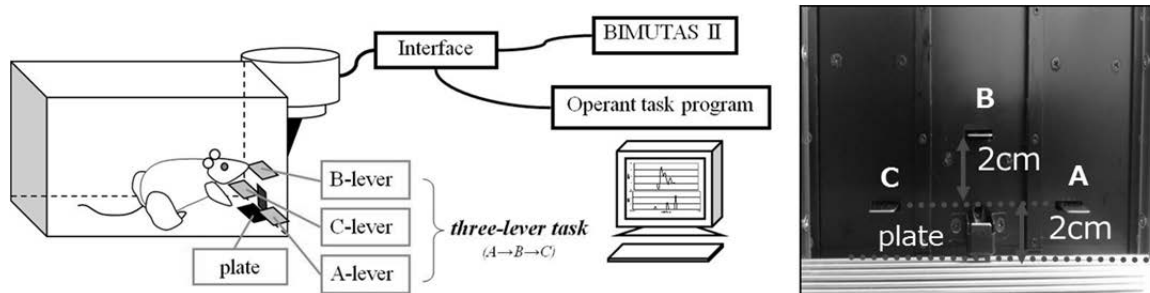

Figure 1. Experimental set-up for three-lever operant task. The operant test panel consists of three levers (A, B, and C), which are positioned 2, 4, and 2 cm above the floor, respectively. Execution of experiments and data collections are controlled by operant task program installed in a personal computer.

Table 1. Experimental schedule.

Age	Type of task	Level	T(s)	Criterion (R)		
6wk	Carrying-in and habituation					
7	Handling					
8	Shaping	0		(A- or B- or C-lever)		<100
		1				≧100
		2		(ex. B- or C-lever)		<100
	One-lever task	3				≧100
		4		(ex. B-lever)		<100
		5				≧100
10～13		6	99.9	(A- ⇒ B- ⇒ C-lever)		<100
		7	99.9			≧100
		8	3.0			
		9	2.5			
		10	2.0			
		11	1.5			
		12	1.0			
	Three-lever task	13	0.9	T=3 to 0.4(s)	≧100	
		14	0.8			
		15	0.7			
		16	0.6			
		17	0.5			
15～21		18	0.4			

Age	Type of task	Level	T(s)	Criterion (R)		
16～21		6	99.9	(C- ⇒ B- ⇒ A-lever)		<100
		7	99.9			≧100
		8	3.0			
	Reverse Three-lever task	9	2.5			
		10	2.0	T=3 to 1.0(s)	≧100	
		11	1.5			
19～24		12	1.0			

T : The time limit for lever press after the preceding lever press.

R : The number of reinforcement per session.

controlled by a program (Operant Task for multi levers, O'HARA & Co., Ltd., Tokyo) installed in a personal computer (Dell, Dimension 210L). When the mouse presses an active lever (one-lever task) or three levers (required load: 4-7 g) in a correct order within a given time (three-lever task), one pellet for reinforcement (AIN-76A, 10 mg, U.S.A.) is delivered from the automatic diet feeder (PD-010D, O'HARA & Co., Ltd.). The numbers of reinforcement and lever press for each lever were recorded in the personal computer through interface (A01040C, O'HARA & Co., Ltd.) by the task program. The lever signals were recorded by Vital Recorder II (Kissei Comtec) installed in the personal computer. In the operant chamber, water was available ad libitum from a bottle (KN-670-5A or KN-671-2B, Natume).

2. Animals

Five C57BL/6NCr male mice (17.6 ± 0.9 g at the age of eight weeks) were used. At the age of six weeks, mice were transferred from the colony room to the testing area. Mice were kept separately in plastic cages with four compartments (KN-606, 230 × 300 × 130mm, Natume)

at 23 ±2℃ on a 12h light/dark cycle (lighting on at 1:00 am). Water was available ad libitum from a bottle (No. 6A, Natume). Mice were provided a limited amount of food (CRF-1, Charles River Laboratories; CE-2, Wako). Mice were killed at the end of the experiments by an overdose of isoflurane. All experiments were performed in accordance with the guideline set by the animal welfare committee of Kanazawa University.

3. Training procedures

1) Time schedule

The time schedule of training is shown in Table 1. Before training, mice were allowed to habituate to the testing area for one week, and handled for approximately 10 min/day to habituate to the experimenter for one week. Experiments were carried out at the age of eight weeks. One training session lasting 60 min was given once a day and five times a week (from Monday to Friday).

2) One-lever task

One-lever task was used as shaping procedure for three-lever task. In this task, the mouse was trained to press any one of active levers for a food reward (fixed ratio 1, FR1).

Learning levels of 0-5 were set according to the number of active levers and the number of reinforcement (Table 1). The number of active levers was three at level 0-1, two at level 2-3, and one at level 4-5. At each condition, the mouse was required to press any one of active levers more than 100 times. When the mouse pressed the same active lever more than 100 times per session in two consecutive sessions at level 1 or 3, the lever was inactivated in the subsequent session (at level 2-3 or 4-5, respectively). When the mouse pressed the active lever more than 100 times per session in two consecutive sessions at level 5, one-lever task was completed.

3) Three-lever task

After the completion of the one-lever task, the mouse was trained to press three levers in a given sequence (A→B→C) with or without time restriction. In the task with time restriction, the mouse was required to press the second (or third) lever within a given time (T) after the onset of the first (or second) lever press. Learning levels of 6-18 were set according to the time T and the number of reinforcement per session (R) (Table 1). The time T was set to 3 sec initially, then decreased by 0.5 or 0.1 sec steps when R was >100 in two consecutive sessions. When R was <100 or when success rate was <10%, T was returned to 1 sec in two sessions before completion of the three-lever task.

4) Reverse three-lever task

After the completion of the three-lever task, the mouse was trained to press three levers in the opposite sequence (C→B→A) with or without time restriction. Like the original three lever task, learning levels of 6-12 were set according to T and R (Table 1). The time T was set to 3 sec initially, then decreased by 0.5 sec steps when R was >100 in one session.

4. Food

The total amount of food per day was needed to set to 1.5, 1.5, 2.0, and 2.5 g on Monday, Tuesday, Wednesday and Thursday, respectively, to minimize the different in the number of lever press from Monday to Friday, but decreased by 0.5 g when the number of lever press was small (<100). Mice were provided food ad libitum after the end of the fifth session (Friday) in each week, and deprived of food for approximately 10 hours before the first session (Monday) in the next week.

5. Data analysis

Recorded values by the task program include the numbers of lever press of A-lever (A), B-lever (B), and C-lever (C), the total number of lever press (A+B+C), and the number of reinforcement (R) per session. From these values, we calculated the success rate ($R \times 3/(A+B+C)$), inactive lever press ratio ($I/(A+B+C)$), and disparity ratio ($((A+B+C)/Max-1)/2$), where I is the number of inactive lever press and Max is the maximum value among A, B and C.

Data are expressed as mean ± S.E.M., or median and interquartile range for the number of sessions or lever press. Statistical significance was evaluated by Kruskal-Wallis test (nonparametric analysis of variance), followed by Steel-Dwass test (nonparametric multiple comparisons) to compare the number of sessions, inactive lever press ratio, and disparity ratio between different conditions (learning level, or session no.). Shirley-Williams nonparametric test was used to compare the number of lever press, the number of reinforcement, and success rate between the first session (or T=1.0 sec) and the following sessions (or other T values < 1.0 sec). The differences with $P < 0.05$ were taken as significant.

Results

1. One-lever task

1) Time courses of the learning level

The results of the one-lever task are shown in Figures 2-4. In Figure 2A, we plotted the learning level as a function of session number for each mouse. The total number of sessions required for level 0-5 was 10 (10-11) sessions (median and interquartile range) (Fig. 2B, Total). The numbers of sessions spent at level 0, 1, 2, 3, 4 and 5 were 4 (4-5), 2 (2-2), 0 (0-0), 2 (2-2), 0 (0-0), and 2 (2-2) sessions, respectively. The number of sessions at level 0 was significantly higher than that of other levels ($P < 0.05$). Figure 2C shows the time course of total number of lever press (A+B+C). The number of lever press was significantly larger after the fourth session than in the first session ($P < 0.05$).

2) Inactive lever press and disparity ratio

When the most pressed lever was inactivated, the mouse was required to change the behavior. Figure 3A shows an example of such a behavioral change. In this figure, lever signals obtained from the seventh (level 1) and eighth (level 3) sessions. Each vertical bar
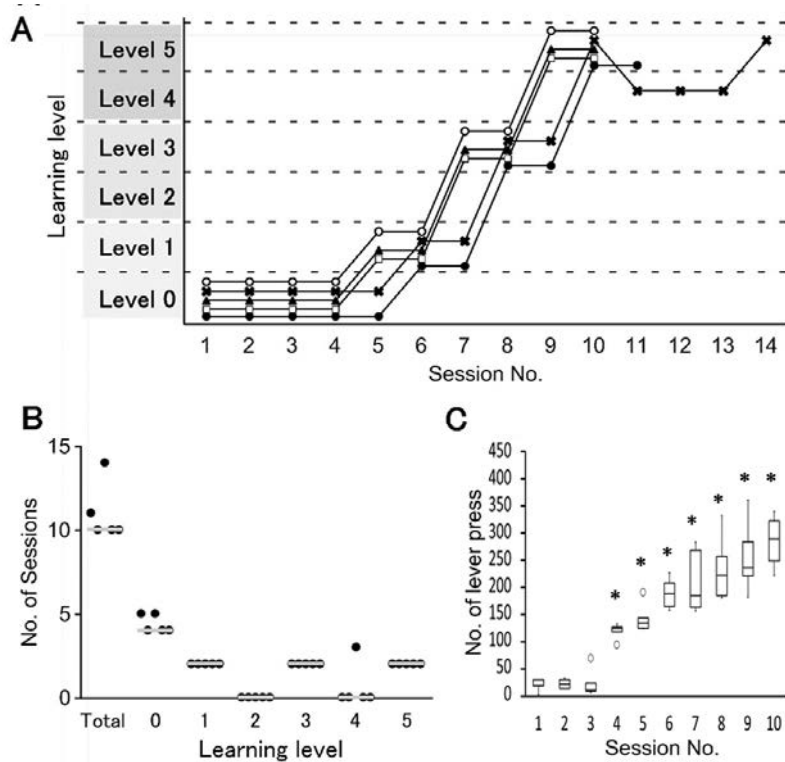
Figure 2. Performance of one-lever task. A: Time courses of the learning level in one-lever task. Each symbol represents the data from each mouse. B: The number of sessions spent in one-lever task and at each level. The number of sessions spent at level 0 was significantly larger than the others. C: The total number of lever press in each session between the 1st and 10th sessions. The number of lever press was significantly larger after the 4th session than in the 1st session. Single asterisks indicate P < 0.05.
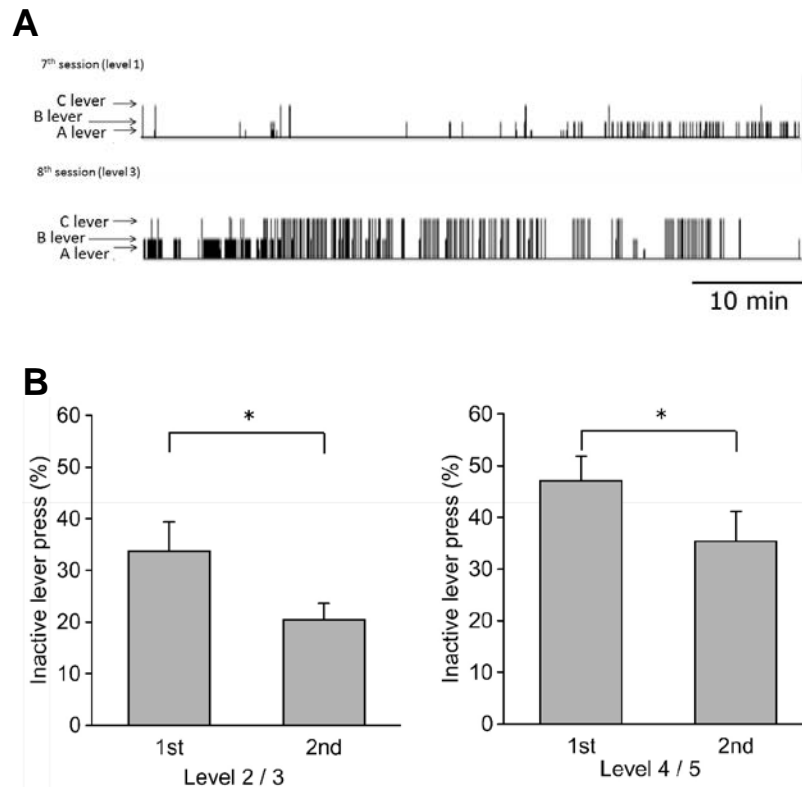
Figure 3. Behavioral change after inactivation of the most pressed lever. A: Examples of lever signals during the 7th (level 1) and 8th (level 3) sessions. In the 7th session, B-lever was most frequently pressed. In the 8th session, where B-lever was inactivated, the most frequently pressed lever was shifted from B-lever to C-lever. B: The rate of inactive lever press (no food reward) in total number of lever press just after inactivation of the most pressed lever. Single asterisks indicate P < 0.05.

represents one lever press, and long, middle, and short bars represent the lever press of C-lever, B-lever, and A-lever, respectively. In this example, the mouse pressed B-lever most frequently in the seventh session where all three levers were active. In the eighth session where B-lever was inactivated, the mouse preferred B-lever at the beginning of the session, but changed to C-lever 10 min later.

To analyze this behavioral change more quantitatively, we calculated the inactive lever press ratio (Fig. 3B). In the first session after inactivation of the most pressed lever, the inactive lever press ratio of the latter half was significantly lower than that of the first half (P < 0.05) at both level 2/3 (level 2 or 3) and level 4/5.

We also calculated the disparity ratio as an index of preference for one lever (Fig. 4). This ratio has a value between 0 and 1, equaling 0 if the mouse presses only one lever and 1 if the mouse presses three levers equally. At level 0, the disparity ratio decreased as sessions progress, and was 0.68 ± 0.14, 0.55 ± 0.01, 0.27 ± 0.06, and 0.39 ± 0.12 in the first, second, third, and fourth sessions, respectively (Fig. 4). The difference between the first session and the second, third or fourth session was significant (P < 0.05). At level 1, 2/3 and 4/5, the disparity ration was small and not significantly different between the first and second sessions.

2. Three-lever task
1) Time courses of the learning level
The results of the three-lever task are shown in Figures 5 and 6. In Figure 5, we plotted the learning level (A), total number of lever press (B), number of reinforcement (C), and success rate (D) as a function of session number.

The number of sessions required for reaching level 7 ranged from 4 to 16 sessions. The number of sessions required for level 6-12 was 13 (13-16) sessions (median and interquartile range) (Fig. 5A). The total number of lever press was high even in the first session, and did not change until the thirteenth session (700-1200) (Fig. 5B). By contrast, the number of reinforcement and success rate were small in the first session, significantly increased at the third session, and remained high until the thirteenth session (Fig. 5C, 5D).

2) Time restriction
After the level 12 (T = 1.0 sec), T was decreased by 0.1 sec steps. Figure 6 shows the number of reinforcement and success rate at each T value. Although the success rate significantly decreased at T<0.8 sec, all five mice still showed good performance at T=0.5 sec. At T=0.4 sec, however, mice could not perform the task and the number of reinforcement was less than 100 except for one session. When T was returned to 1 sec, the mice showed good performance again (Fig. 6, rightmost bars).

3. Reverse three-lever task
1) Time courses of the learning level
The results of the reverse three-lever task are shown in Figure 7, where we plotted the learning level (A), number of reinforcement (B), and success rate (C) as a function of session number. The number of sessions required for
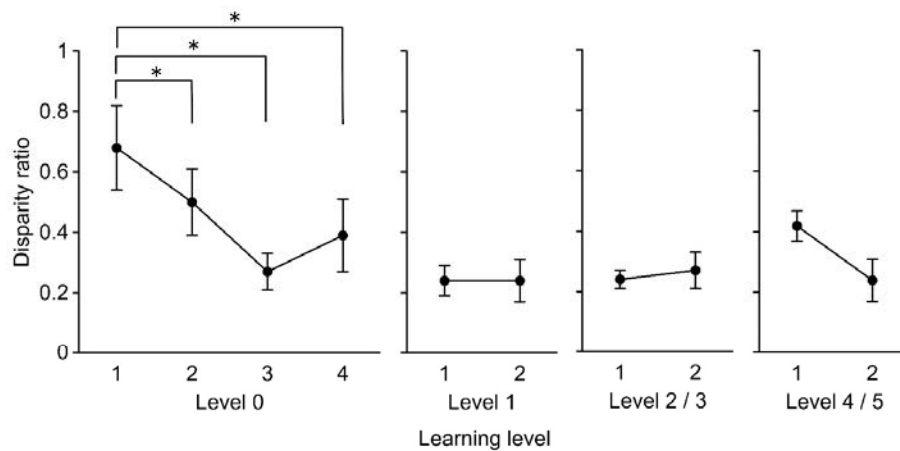

Figure 4. Changes in disparity ratio after inactivation of a lever in one-lever task. Disparity ratio, which was used as an index of preference for one lever, has a value between 0 and 1, equating 0 if only one lever is pressed and 1 if three levers are pressed equally. At level 0, the disparity ratio decreased as sessions progress. Single asterisks indicate P < 0.05.
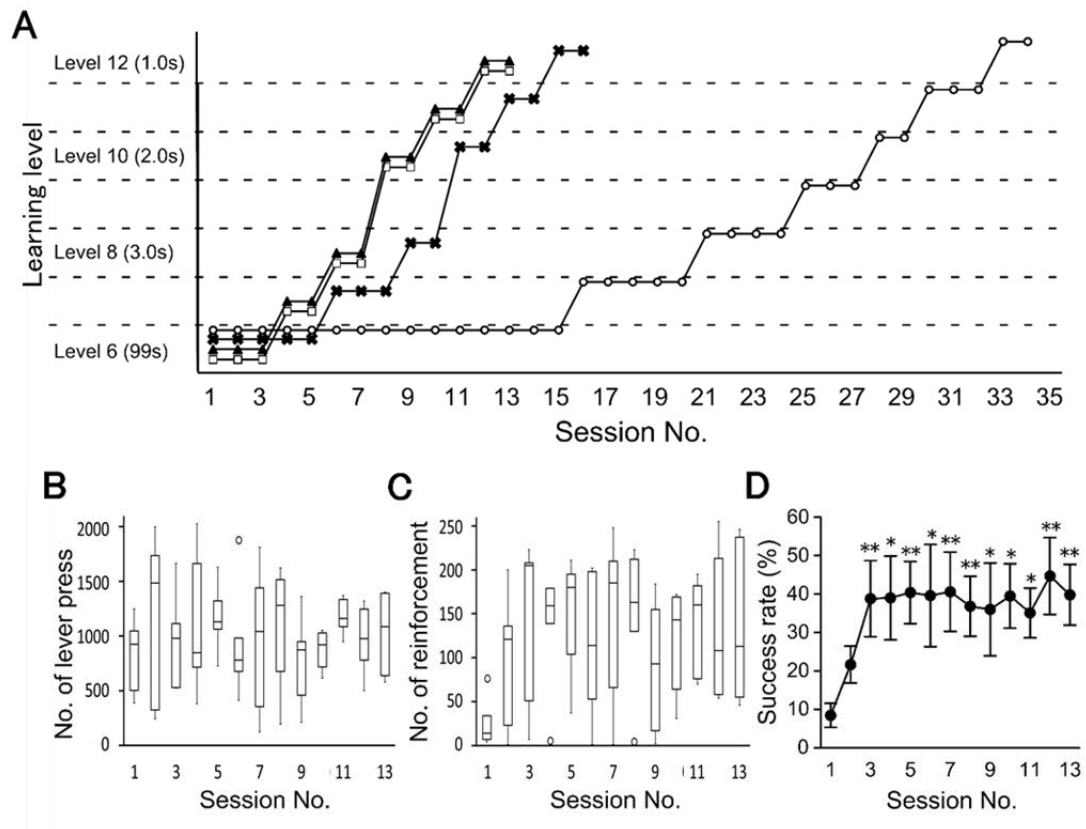
Figure 5. Performance of three-lever task. A: Time courses of the learning level in three-lever task. Each symbol represents the data from each mouse. B-D: Time courses of the number of lever press (B), reinforcement (C) and success rate (D) during the 1st-13th session. The number of reinforcement and success rate were significantly larger after the 3rd session than in the 1st session. Single and double asterisks indicate P < 0.05 and P < 0.01, respectively.
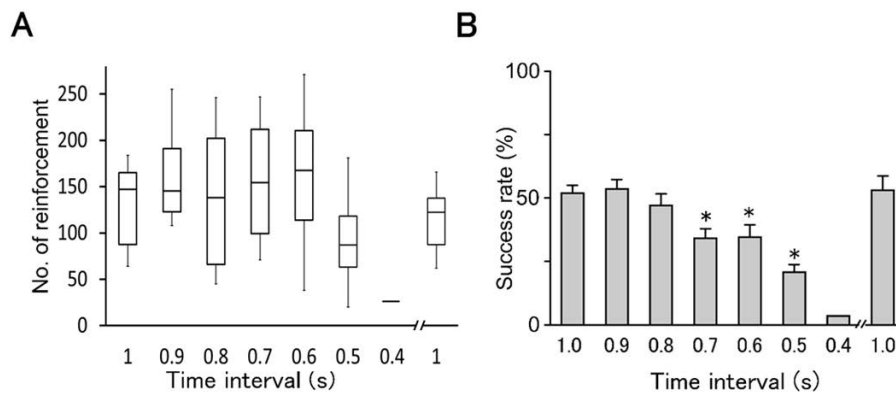

Figure 6. Performance of three-lever task with time restriction. The number of reinforcement (A) and success rate (B) at each condition of time restriction (T=1.0, 0.9, 0.8, 0.7, 0.6, 0.5 and 0.4 sec) in three-lever task. After T was decreased by 0.1 sec steps, T was returned to 1.0 sec (rightmost bars). The success rate was significantly smaller at T=0.7, 0.6 and 0.5 than at T=1.0 sec. The number of mice used was five, except for T=0.4. The data for T=0.4 was obtained from only one mouse, and not used for evaluation of statistical significance. Single asterisks indicate P < 0.05.
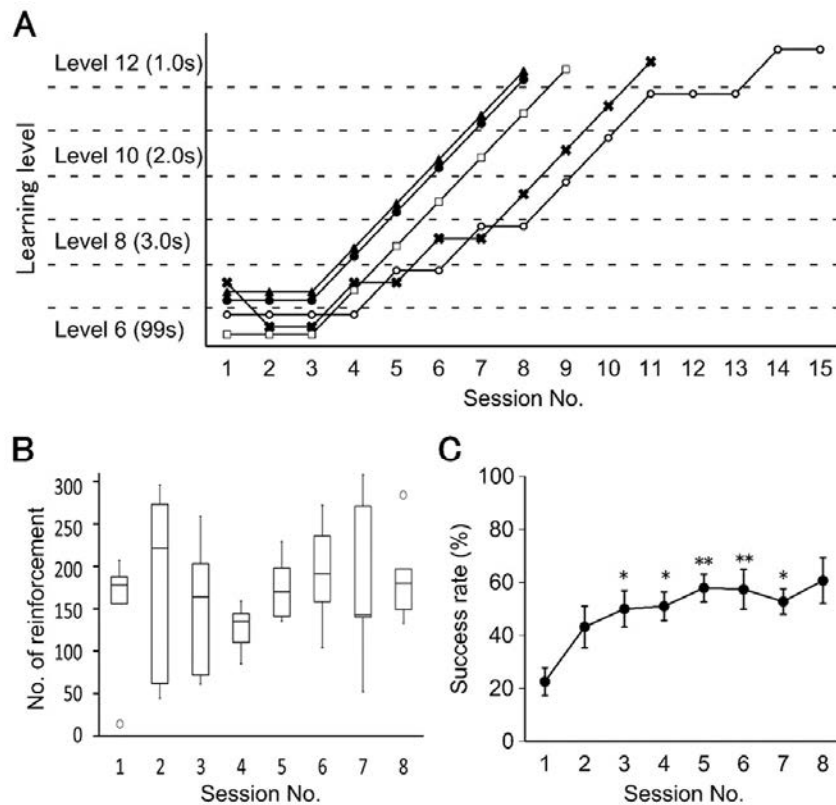
Figure 7. Performance of reverse three-lever task. A: Time courses of the learning level in reverse three-lever task. Each symbol represents the data from each mouse. B, C: Time courses of the number of reinforcement (B) and success rate (C) during the 1st-8th session. The success rate was significantly higher during the 3rd to 7th sessions than in the 1st session. Single and double asterisks indicate P < 0.05 and P < 0.01, respectively.

level 6-12 was 9 (8-11) sessions (median and interquartile range) (Fig. 7A). As seen in the original three-lever task, the success rate was low in the first session (22.6 ± 5.2%), significantly increased at the third session (50.0 ± 6.9%), and remained high (40-60%) in subsequent sessions (Fig. 7C). The number of reinforcement was, however, high even in the first session, and remained high (>100) in subsequent sessions (Fig. 7B).

Discussion

In the present study, we examined whether the three-lever operant task is applicable to mice, by analyzing the performance of wild-type mice. The number of sessions required for completing one-lever task ranged from 10 to 14 sessions (2-3 weeks), which is comparable with that of rats (2-3 weeks)[32]. In three-lever task, the number of sessions required for reaching level 7 (without time restriction) ranged from 4 to 16 sessions (1-3 weeks), which is also comparable with that of rats (1-4 weeks)[19]. These results indicate that this task is applicable to mice

and can be used as mouse model of motor sequence and skill learning.

The analysis of the performance in one-lever task, which was not analyzed in previous studies on rats, demonstrated that mice changed the behavior after inactivation of the most pressed lever, and that this behavioral change can be quantitatively analyzed by calculating the inactive lever press ratio. Therefore, this task is expected to be useful for studying behavioral adaptation to varying conditions. Our results of reverse three-lever task, which was not reported in previous studies on rats, also revealed that this task is useful for studying reversal learning.

These results show that three-lever operant task including one-lever, three-lever, and reverse three-lever parts, can be used for studying several different aspects of motor learning including sequence learning, skill learning, adaptive change, and reversal learning. Sequence and skill learning can be evaluated from success rate in the three-lever task with or without time restriction. Adaptive change in behavior can be

evaluated from inactive lever press ration in the one-lever task. Reversal learning (or flexibility) can be evaluated from the performance of the reverse three-lever task. We have already applied this task to cannabinoid receptor knockout mice as well as wild-type mice, and found several differences in the performance between wild-type and knockout mice[33, 34]. We might expect that the application of this task to various types of genetically altered mice would result in substantial progress in understanding neural mechanisms of motor learning.

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運動の順序およびスキル学習のマウス・モデルとしての３レバー・オペラント課題の利用可能性

米田　　貢 *, 田端　佑樹 **, 越後　亮介 *, 菊池　ゆひ *, 少作　隆子 *

要　　旨

　リハビリテーションにおいて運動学習は重要な要素の１つであり、その仕組みの解明の臨床的意義は高い。 現在、運動学習の脳内回路として、大脳基底核、小脳、大脳皮質の３つのモジュールが考えられている。ラットを用いて、大脳基底核に依存した運動学習課題として、３レバー・オペラント課題（以下、３レバー課題）が報告されているが、この課題を今後遺伝子改変マウスに適用することを想定し、本研究では、３レバー課題をマウスに適用可能かどうか検討した。実験には C57BL/6 系統の野生型マウス雄５匹（実験開始時８週齢）を使用した。有効レバーを１回押すと強化子（餌）が与えられる１レバー課題（シェイピングとして）、３つのレバーを一定の順序で制限時間内に押すことで強化子が与えられる３レバー課題、順序を逆に設定したリバース３レバー課題の順で行った。１レバー課題では、有効レバーを無効に切り替えるとマウスの行動が変化する様子を定量的に解析することが可能であった。３レバー課題では、マウスは１〜３週間で順序を学習することが可能であり、ラットの場合とほぼ同様であった。リバース３レバー課題では、マウスは押す順を逆にしても３日で学習可能であり、リバース学習の課題としても使用可能であることが示された。以上より、３レバー・オペラント課題は、マウスの運動学習のさまざまな要素（順序学習、スキル学習、適応、リバース学習）を調べることが可能な課題であることが確かめられた。今後は、さまざまな遺伝子改変マウスを用いることにより、運動学習の仕組みの解明が進むことが期待される。