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Three-lever operant behavior for rats measured with accelerometer and animal model for motor learning

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ABSTRACT

In this study, we measured a three-lever operant behavior for rats with an accelerometer and evaluated similarity of acceleration waveforms by standardizing them for quantification, in order to establish an animal model for motor learning and review its effectiveness. The operant task to press three levers in order and within an established timeframe was imposed on male wistar rats at the age of nine weeks, and their physical movements were measured with an accelerometer. One experiment was as frequent as five times a week and lasted for 60 minutes a day, totaling 80 times. The number of reinforcement, the efficiency compared with the reinforcement number, the required time and similarity of waveforms were reviewed. The reinforcement number remained 150 or more after the 5th experiment. The efficiency remained at 50% or more after the 15th experiment. The required time was shortened by repetition of experiments, and became more or less constant after the 10th experiment. As for acceleration waveforms, after 50 waveforms were overlapped for each experiment, the similarity of waveforms was confirmed due to visual overlapping. By further standardization of acceleration waveforms in order to review the similarity of acceleration waveforms with mutual correlation coefficient, the correlation coefficient increased through repetition of experiments and settled at 0.5 or higher after the 30th experiment. By quantitatively understanding the motor learning process in the three-lever operant behavior with acceleration waveforms, effectiveness as an animal model was indicated. It was indicated that motor learning in this model converged in the order of increase in the number of success, increase in efficiency, shortening of hours, and increase in correlation coefficient of acceleration waveforms. Although there was no animal model for motor learning in the past that utilizes behavior, we can expect this motor learning model utilizing operant behavior to be applied to fundamental research as a new animal model.

KEY WORDS

Motor learning; Three-lever operant; Acceleration waveform; Animal model; Correlation coefficient

Introduction

Learning[1-4] necessary for our living supposedly means to obtain new intellectual abilities (language and knowledge) and physical capabilities (skill and movement). In rehabilitation medicine, treatment and training is performed for the purpose of recovering or regaining intellectual and physical abilities lost due to disease or disorder. The subject of learning in this case is acquisition of the ability to live in the society (daily living and work), mainly based on motor learning[5,6]. Many studies about learning attempt to understand behaviors. Although learning in essence accompanies change in brain, it is common to assume and judge learning based on behaviors.

Singer[7] used performance as indication of the amount of learning occurred, and determined that

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the motor learning process was based on observation of changes in performance. A skill indicated by performance is one indicator of what is learned, and muscle activity or physical movement necessary to perform certain required activities well is expressed as motor skills. Johnson[8] noted that it was necessary to consider four parameters of speed, accuracy, form and adaptability in order to describe skills.

By measuring the movement of forearms at the time of work operation for humans, Seki et al.[9] indicated that in regards to motor learning for humans, the process of proficiency in movements converged nearly at a constant level in terms of time and amplitude for acceleration waveforms and that convergence was not confirmed for acceleration waveforms for schizophrenic patients, indicating disorder of motor learning. Thus, it was indicated that motor learning was regulary repeated with proficiency. However, Johnson's four parameters were not fully discussed as a method to analyze waveforms.

On the other hand, fundamental research utilizing animal models was often performed in order to understand clinical conditions for disease, to develop therapeutic medication, and to search for fundamentals of neuroscience[1]. However, in regards to motor learning, tasks mainly include utilization of startle reflex for rats or mice as well as working memory, and nothing utilizes behavioral tasks as far as we researched.

Therefore, we attempted to create a motor learning model for animals by incorporating an accelerometer used by Seki, et al.[9] in operant experiments that had been previously performedt. For this purpose, we developed the three-lever operant task to understand motor learning with an accelerometer, and examined whether acceleration waveforms for rats' operant behavior can lead to the same results as humans' in consideration of four parameters of speed, accuracy, form and adaptability.

Methods

1. Experimental Animal

16 male Wister rats (SPF/VAF Wistar, Charles River Japan, Inc., Yokohama, Japan) at the age of nine weeks.

2. Rearing Method

Each rat was raised in a stainless steel cage (N-627, Natsume Seisakusho Co., Ltd., Tokyo, Japan). The environment was maintained at 23 degrees of room temperature and 45% humidity, and in regards to lighting, 12-hour light/dark schedule (Light turned on at 22:00) was used. Food was consumed at a certain volume and weight control was not given. Water was freely given with water bottle (KN-670, Natsume Seisakusho Co., Ltd., Tokyo, Japan).

3. Experimental Apparatus

Experiments were performed in an operant box (OP-3301K, O'HARA & Co., Ltd., Tokyo, Japan) placed in a soundproof box (560 × 420 × 370 mm), and execution of experiments and data collection was controlled by a program (operant scheduler Ver1.00, O'HARA & Co., Ltd., Tokyo, Japan) installed in a personal computer (PC-9821/Xa13, NEC). There are three levers in the operant box, and their height can be adjusted voluntarily within the range of 3 - 8.5 cm (vertical interval: 5.5cm). Levers take the height into consideration for rats to be able to press levers using front legs in the state of standing (with only back legs). Rats press three levers in the established order (required load: 10g), and if the order is correct, one pellet for reinforcement (CE-2 50mg, Wakan Kenkyusho, Tokyo, Japan) is given from the automatic diet feeder (PD-50, O'HARA & Co., Ltd., Tokyo, Japan). The number of lever pressing responses as well as the reinforcement number was recorded in a personal computer through interface (A01040C, O'HARA & Co., Ltd., Tokyo, Japan). Water was given freely from water bottle (KN-670, Natsume Seisakusho Co., Ltd., Tokyo, Japan) during experiments.

Data on the accelerometer (ADXL50, Analog Devices INC., Tokyo, Japan) was amplified with DC amplifier (NEC, AL1301, Tokyo, Japan) and recorded on a digital recorder (RD135-T, TEAC CORRPORATION, Tokyo, Japan). Recording was performed with the accelerometer by dressing a rat in a jacket made of Vercro placed in order to detect acceleration in a vertical direction, and wiring of accelerometer was through the slip ring (SPM-50, MUROMACHI KIKAI Co., Ltd., Tokyo, Japan) to minimize restriction to movements in the experiment box. In order to clearly match the movement of lever pressing by rats with the data on the accelerometer, three electric signals for each lever were recorded at the same time as a marker.

4. Experimental Method

One experiment lasted 60 minutes a day and was conducted during the lights-out time. Rats received handling and habituation to the experimental box from the age of six weeks, and were reinforced by pressing any of the three levers as shaping to form lever pressing response from the age of eight weeks. From the age of nine weeks when the response number of 100 or more was maintained for any lever, the three-lever operant experiment began, which continued until the age of 26 weeks, with one session as frequent as five times a week, totaling 80 times.

In the three-lever operant task, three levers with height changed at random were pressed in the established order and at the same time the interval between the time when one lever was pressed and the time when the other was pressed is determined; therefore rats were reinforced by pressing levers in a correct order and at the same time by pressing them within the determined interval. This time, the order was determined with right lever (Lever 1), central lever (Lever 2) and left lever (Lever 3), from the right to the left facing the panel. Regarding the height difference of the levers, Lever 2 was set 1cm higher than other the two levers when the reinforcement number of lever pressing exceeds 100 times, and the difference was eventually fixed at 5.5cm. It means that the positional relationship among levers gradually turned into the convex shape (0 ~ 5.5cm), and rats move as if describing a triangle in order to receive food by performing tasks; therefore vertical movement to press Lever 2 increases and the change in acceleration can be understood clearly. The time interval between pressing Levers 1 and 2 as well as between Levers 2 and 3 was shortened from 99.9 seconds according to the experiment schedule, and eventually set at 0.9 ~ 1.0 seconds.

5. Method of Data Analysis

Figure 1 indicates the data obtained from the experimental device as well as the flow sheet for analysis.

In accordance with the reinforcement number recorded in the operant program as well as the sum of lever pressing numbers for each lever and their reinforcement numbers, the efficiency of lever pressing for the reinforcement number was determined {reinforcement number x 3 / (the number for Lever 1 + the number for Lever 2 + the number for Lever 3); hereafter the "efficiency"}.

For the analysis of acceleration waveforms, the personal computer (NetVistaA40P, IBM) equipped with

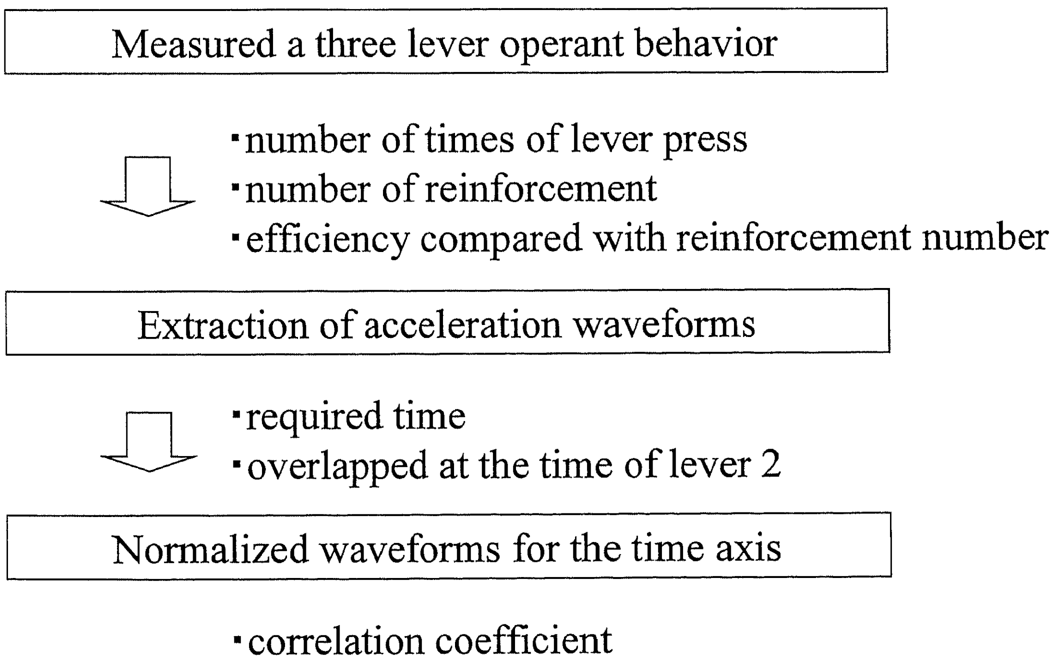

Fig. 1: Flow sheet of an experiment procedure and data analysis.

BIMUTAS-II (KISSEI COMTEC CO. LTD., Matsumoto, Japan) and Excel 2000 (Microsoft, U.S.A.) was used. Data was related to the lever marker, and 50 acceleration waveforms at the time of performing the three-lever operant task were extracted at the beginning of each experiment and overlapped at the time of pressing Lever 2. Furthermore, BIMUTAS-II was used to standardize acceleration waveforms for the time axis (Figure 2) and calculate the mutual correlation coefficient.

6. Statistical Analysis

The measured data was indicated as mean value ± standard deviation in the case of mean value. Regarding changes in the reinforcement number, the success rate, the required time and correlation coefficient, ANOVA was used, and if there is a significant difference among sessions, they were evaluated with the multiple comparison test. Review was conducted with 5% or less of significant level.

Results

1. Reinforcement Number and Success Rate

The transition of reinforcement number for one session (five experiments a week) and the transition of success rate are indicated in Figures 3 and 4 respectively. The reinforcement number was maintained at 100 or more at all times. The success rate reached 50% at the third session, then gradually showed increase and remained at 60% or higher. No significant differences were observed after the 3rd session by comparison with the next session. However, differences were observed at some

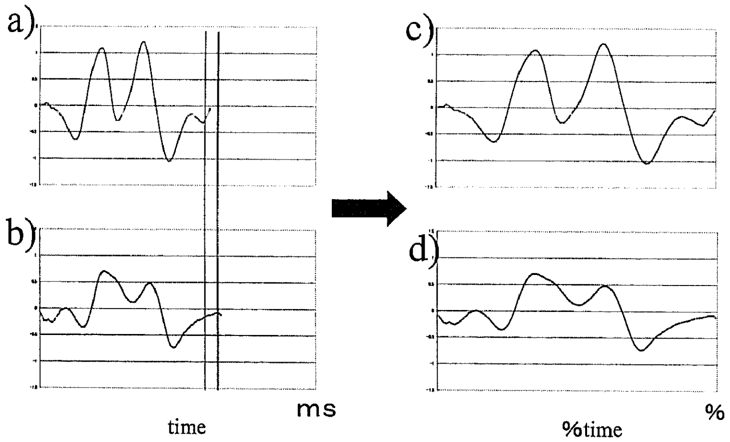

Fig. 2: Normalized waveforms for the time axis. The waveform of a) and b) were each normalized c) and d).

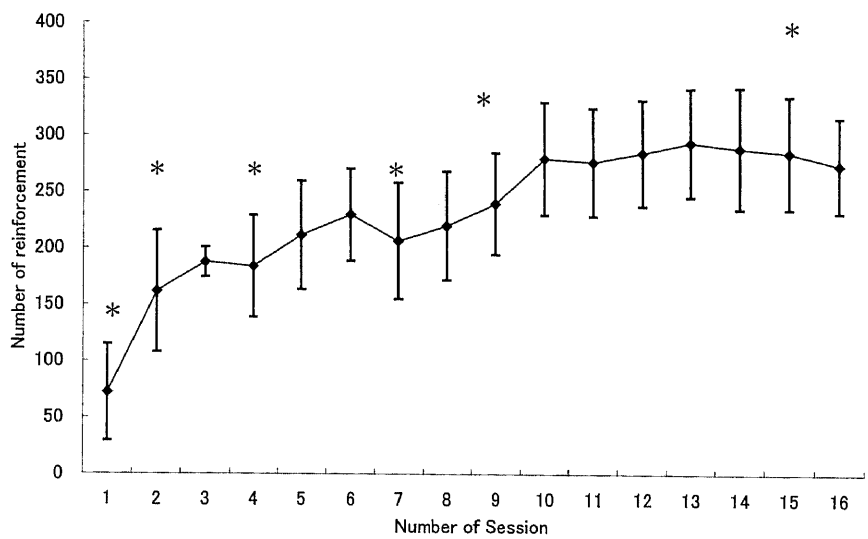

Fig. 3: Reinforcement number. One session is five experiments. N=16. An asterisk (*) showed significant difference in comparison with the next session ($P < 0.05$).

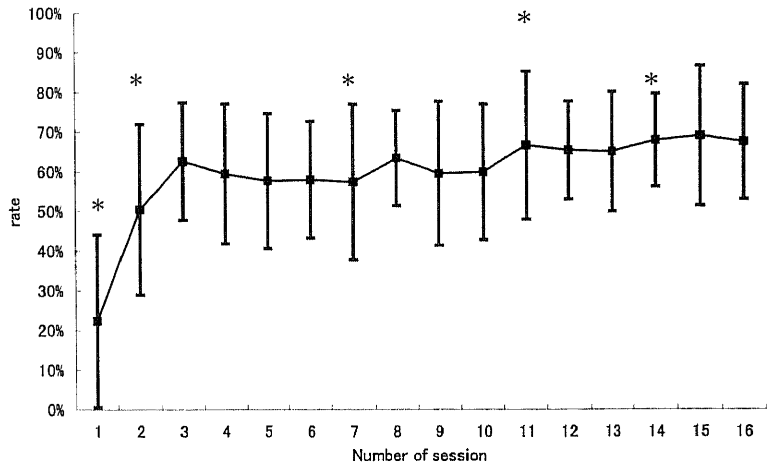

Fig. 4: Efficiency rate. One session is five experiments. N=16. An asterisk (*) showed significant difference in comparison with the next session (P < 0.05).

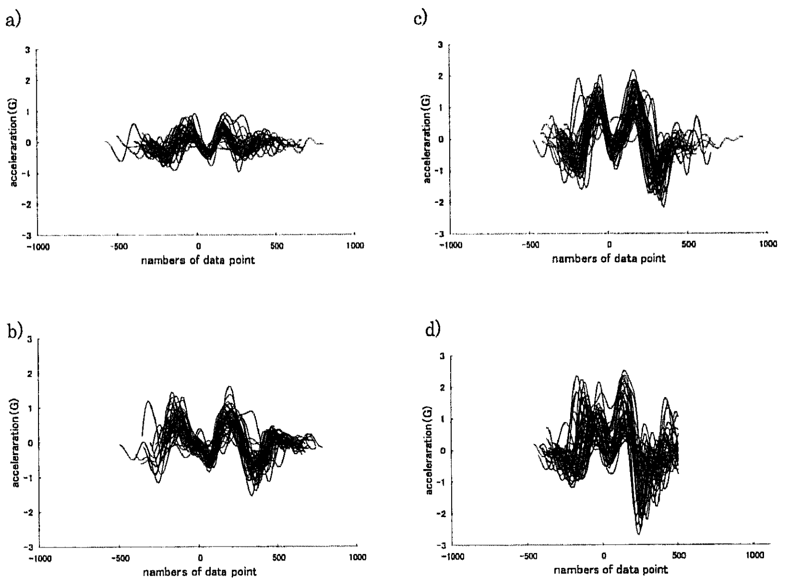

Fig.5: Acceleration waveforms and visual evaluation (a representative exapple). Four graphs are things of the experiment number of times with the same rat. a) the 20th experiments, b) the 40th experiments, c) the 60th experiments, d) the 80th experiments.

points when 7th, 11th and 14th session by similar comparison.

2. Visual Evaluation and Required Time for Acceleration Waveforms

The example of overlapped acceleration waveforms and their visual evaluation is indicated in Figure 5. By repeating experiments, it is possible to visually confirm the overlaps (unity) of acceleration waveforms. The transition of required time calculated based on these extracted waveforms is indicated in Figure 6. No significant differences were observed after the 4th session by comparison with the next session. However, differences were observed at some points when 7th, 10th, 11th and 15th session by similar comparison. The time was within 1.5 seconds from the beginning, regardless of the experimental setting. The average required time was 871.8 ± 330.8ms at the fifth trial and 769.8 ± 397.6ms at the 80th trial.

3. Similarity of Acceleration Waveforms

Similarity of acceleration waveforms was compared for each session in accordance with the change in the correlation coefficient (Figure 7). The correlation coefficient increased by the time of the sixth session (30 experiments) then remained at a high correlation coefficient of 0.5 ~ 0.7, without significant difference by comparison with the next session. However,

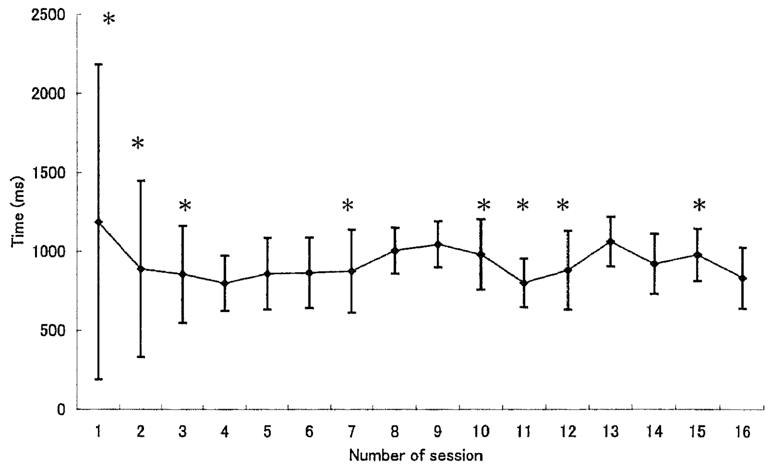

Fig. 6: Required time for Acceleration waveforms. One session is five experiments. N=16. An asterisk (*) showed significant difference in comparison with the next session ($P < 0.05$).

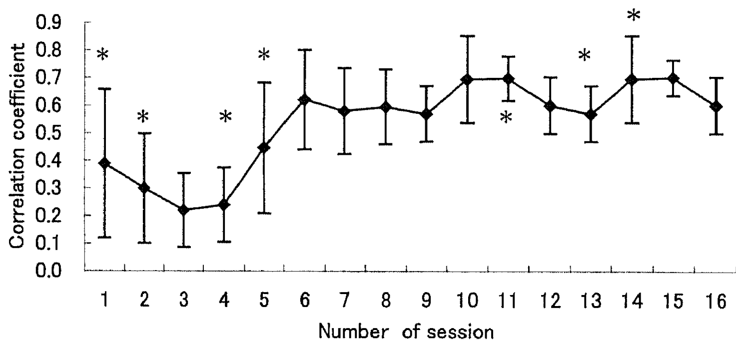

Fig. 7: Correlation coefficient for Acceleration waveforms. One session is five experiments. N=16. An asterisk (*) showed significant difference in comparison with the next session ($P < 0.05$).

differences were observed at some points when 11th, 13th and 14th session by similar comparison.

Discussions

Motor learning is a critical research theme when we consider rehabilitation for physically handicapped people as well as human living. Although many researchers have studied motor learning, its mechanism has not been clarified. The research methods mainly include investigation of error, failure, time, speed, etc. as performance relating to motor learning, as well as recording of activities within a brain at the same time[5,6]. Although they are limited to noninvasive methods in the case of humans, research on experimental animals enable study of the function of brain, genes, etc. directly; therefore it is considered to be very meaningful to develop animal models for motor learning. Model researches using experimental animals for motor learning have been conducted hypothetico-deductively in regards to cerebral localization, neural transmission modification, etc. relating to motor learning, by preparing animals with cerebellar pathologic abnormality or animals with motor disorder by blocking neural transmission with drugs, and investigating differences in results from control animals[1]. As to tasks for motor learning, working memory task[10] as well as prepulse inhibition (PPI)[11] are used in many cases in relation to memories. However, it has not been clarified whether these experimental animals themselves are performing motor learning or not. Therefore, it is considered that there has not been an animal model for motor learning, although research on motor learning has been made by utilizing animal models and comparing disorders.

Since motor learning[5] is supposed to turn into constant and rhythmic movement once learning is formed in repetitive motions or movements, an accelerometer is considered suitable to measure them. Accelerometers are used to monitor the status of normal operation for precision machines; however machines show constant waveforms if they are under normal operation with constant movement, and in the case of malfunction for some reasons, they will show irregular movement and change in acceleration. Movements of human bodies similar to the above include electrocardiogram. It repeats waveforms with the same amplitude under constant movement; therefore is considered to be an effective sensor to be used for animals and humans and to measure repetition of the same movements. However, it is impossible for humans to repeat completely the same movements like machines, and they are supposedly influenced by physical and mental factors such as fatigue and tiredness; therefore we assumed that they would converge within a certain level of errors. We considered it possible to understand motor learning with rats by overlapping waveforms at the part of characteristic movements. For this purpose, how to allow repeated movements and how to measure data on an accelerometer by giving less limitation to behavior is important, i.e. tasks are critical.

In regards to movements of the human body, acceleration has been used for movements in handwriting by Hollerbach (1978, according to Shmidt, et al.[6)]), and for measurement of movements by Bussmann, etc. in the past. In experiments on rats utilizing accelerometers, it seems to be utilized mainly to control the experiments, such as confirmation of startle reflex[14)], quake[15-17)], impulse[18,19)], etc.

Our animal model is characterized by facilitation of rhythmic movements with utilization of operant behavior and tasks including pressing three levers in order and within a determine timeframe. On the other hand, studies utilizing operant behavior with rats only cover accuracy of the behaviors using the behavior to reach[20,21)], and actual movements in our study are not addressed. There are also no experiments that attempt the stabilization of movements by animals so that it can be utilized as a model of motor learning. Thus, we can consider that studies addressing motor learning by stabilizing movements such as our study do not exist, i.e., there is no study on motor learning in regards tc animal modeling.

The task imposed on rats this time is a three-lever operant task designed by us. With this task, a reinforcer (food) is given by pressing three levers within the determined timeframe. Although research on learning with three levers have been reported, the tasks utilized in them are using the FR schedule foı each lever or a differentiation task for drugs (which lever is pressed more often depending on different drugs or amounts), and rats are used in most cases[21-31)]. Research that allowed learning of the order of three levers such as three-lever task like what we used this time have not been found.

Johnson[8)] expressed skills in regards to motoı learning as follows:

Skill = Speed x Accuracy x Form x Adaptability

As to these four factors, (1) most skills are performed within limitation of time, therefore speeċ is important, (2) accurate movement determines the evaluation whether the activity is successful or not, (3) form relates to economical efficiency of efforts, and (4) a proficient person can adapt and is able to effectively perform under various unpredictable conditions.

Based on the experimental method and results in this study, the following is relevant to these factors:

Speed can be understood with the change in time for one trial of a three-lever operant task. This can be calculated from the acceleration waveform, and we considered the shortening of require time as an index As a result, the required time was shortened witl repetition of experiments, and significant shortening of time was not recognized after the 10th experiment becoming plateau. Accuracy can be understood with change in efficiency. This time, efficiency wa obtained with the proportion of the enforcemen number and the total number of lever pressing, an increase in efficiency was considered as an index As a result, efficiency increased with repetition o experiments, and a significant increase in efficienc was not recognized after the 15th experiment.

Since a form is an index of efficiency, w considered it the same as performing the sam movement smoothly in the case of repetitiv movements. It means to repeat the acceleratio waveforms here in the same way, i.e. each wavefor indicates similarity. Methods to evaluate similarity of waveforms include a concept of mutual correlation. The correlation coefficient is one if the waveforms are completely identical, and approaches one if similarity is high. The results of this study showed the correlation coefficient of 0.5 or higher after the 30th experiment, after which significant change was not recognized; therefore it supposedly means that formation of motor learning was confirmed.

Adaptability should be controlled and removed in animal experiments. This is because experiments under unpredictable conditions could lead to different implication in data itself. Since breeding and experiments here were performed under control, parameters caused by the above are supposed to be small. Also, since food is a reinforcer, these experiments do not involve shaping to form behavior, which is performed for general operant behavior experiments such as diet restriction with fasting and detailed staging, although the state of hunger for experimental animals has an influence. Formation of operant behavior was reported under the experimental environment with Neuringer's[32,33] pigeons and rats, and our experimental method also considers that learning was in accordance with the search behavior of experimental animals under free-operant in the same way; therefore influence by this factor is considered to be small.

Based on the above findings, we were able to confirm in this experiment for motor learning the learning speed in the order of required time, efficiency, and similarity of acceleration waveforms. Therefore, it was indicated that learning was formed in the order of speed, accuracy and form. As it was described in regards to learning speed for general operant tasks that "it is difficult to find a study that openly compared the effect of various procedures to the learning speed upon controlling conditions,"[34] the learning process with operant response is considered to be natural and detailed reports were not found. Our animal model might be the first case.

From the change in acceleration waveforms that captured rats' movement this time, the animal model was presented as a sufficient fundamental in that "standard biology and behavior pattern can be studied." [35] Therefore, as a next step, it is necessary to verify that an animal model is "an organism that enables to study the pathologic process induced spontaneously or artificially and that indicates similarity with biological phenomenon observed in humans or other kinds of animals in one or more ways."

Regarding similarity with humans, Seki et al.[9] reported motor learning for humans by applying the change in acceleration waveforms at the time of cotton rug work operation for humans performed by Seki, et al.[36] as well as the three-lever operant task for rats performed this time, and similar findings are reported in acceleration waveforms in this rat study.

By applying current animal models for various diseases to this motor learning model, we can expect the possibility of utilizing it to clarify causes of diseases as well as development of future medical cures. As to motor learning, cerebral cortex, basal ganglia and cerebella might also be involved in motor learning.

Doya, et al.[37] , and Kawato et al.[38] mentioned that the each of cerebral cortex, basal ganglia and cerebella is involved in various cognitive functions when learning is perceived from the three frameworks of "learning with a teacher," "reinforcement learning," and "learning without a teacher." Based on this, it is described as follows: "Cerebella provides an internal model obtained through 'learning with a teacher' and 'predicts' results of behavior. Basal ganglia predicts 'reward' by 'reinforcement learning' and provides evaluation to the result of certain behavior. Cerebral cortex provides an internal expression necessary and enough for outside situations and behavioral output through 'learning without a teacher'." We consider how these are integrated into behavioral change and are functioning will lead to clarification of motor learning mechanism. When this connection is reconsidered with neurotransmitter systems in the brain, dopamine has a strong relationship with movement disorders; however there is supposedly almost no route for dopamine in the cerebellum, which is considered to be important for motor control. Therefore, we consider that various neurotransmitter systems and localized parts of the brain have a correlation for motor learning. What becomes important here includes serotonin and norepinephrine, which are addressed in relation to movement and learning. It is possible to control neural transmission within the brain by administering drugs, which will also enable research on their general influence. It will be necessary to expand into various areas for investigation such as analysis of brain composition, brain destruction, and drug influence in the future.

Conclusion

A three-lever operant behavior was measured with an accelerometer for 16 male Wistar rats at the age of nine weeks.

1. The reinforcement number remained at 150 or more after the fifth experiment.
2. Convergence was observed in efficiency after the 15th experiment, in required time after the 10th experiment, and in the mutual correlation coefficient of acceleration waveforms after the 50th experiment.

By understanding the motor learning process by three-lever operant behavior from acceleration waveforms as well as by confirming retention of motor learning, it is considered that motor learning is formed in animal models, which can be utilized for fundamental research on motor learning for humans in the future.

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加速度計で計測したラットの３レバー・オペラント行動と運動学習の動物モデル

米田　貢，関　規寛，関　昌家

要　旨

本研究では、運動学習の動物モデルを確立するために、ラットの3レバーのオペラント行動を加速度計で計測し、加速度波形の類似性を標準化により定量化することで評価し、その有効性を検討した。週齢9週のウイスター系雄ラットに3つのレバーを順番にかつ設定時間内に押すオペラント課題を行わせ、その際のラットの身体の動きを加速度計で計測した。１実験は１日60分、週5回の頻度で、計80回行った。課題の成功（強化）数、強化数に対する効率、所用時間、波形の類似性について検討した。強化数は実験5回目以降に150回以上を維持した。効率は実験15回目以降に50%以上を維持した。所要時間は実験の繰り返しにより短縮し、実験10回目以降におおよそ一定となった。加速度波形は1実験ごとに50個の波形を重ね合わせたところ、視覚的に重なり波形の類似性が確認された。さらに加速度波形を標準化しその波形の類似性を相関係数で検討したところ、実験の繰り返しで相関係数は高くなり、30回目以降に0.5以上の値で収束した。今回、3レバーのオペラント行動における運動学習過程を加速度波形で定量的に捉えたことから、動物モデルとしての有用性が示唆された。本研究のモデルにおける運動学習は、成功数の増加、功率の増加、時間短縮、加速度波形の相関係数の増加の順で収束することが示唆された。これまでに行動を用いた運動学習の動物モデルはなかったが、このオペラント行動を利用した運動学習モデルは、新しい動物モデルとして基礎研究への応用が期待できる。