Acta Med. Okayama, 2010
Vol. 64, No. 5, pp. 267–275

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Review

Evaluation of Motivational Effects Induced by Intracranial Self-Stimulation Behavior

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In the runway model of intracranial self-stimulation (ICSS) experimentation, the experimental animal is timed in running a fixed distance to depress a lever that releases electrical stimulation to an electrode implanted along its medial forebrain bundle. This ICSS has both a reward and a motivational component. Using the runway method and priming stimulation, we designed an experimental method for directly measuring motivation. An assessment of pharmacological agents that are known to influence motivational states was also undertaken. Using the experimental methods that we created, we observed prominent changes in running speed when animals were exposed to methamphetamine and nicotine. According to these data, the runway method employing intracranial self-stimulation behavior may be useful for the evaluation of substances that act on motivation. We review the underlying neuropharmacological and anatomical functions associated with our experimental methods. We hope that this technique will be used to scientifically evaluate the impact of drugs and/or therapeutic interventions on human motivation.

Key words: intracranial self-stimulation behavior, motivational effect, methamphetamine, nicotine

In their 2001 report the World Health Organization (WHO) described psychiatric disorders as being among the major global health issues. This report identified hypobulia (decreased motivational capacity) as a common factor underlying many psychiatric disorders [1, 2]. Humans often feel excessive stress, helplessness and hopelessness as an uncomfortable emotion or depressive feeling. When an emotion induced by helplessness is firmly fixed into the human mind, overall motivation may diminish. Long-term feelings of helplessness also raise the incidence rate of depression [3–6]. Unfortunately, there are few good treatments for alleviating this chronic decline in motivation, and preclinical studies evaluating drugs that influence motivation using experimental animal models are limited.

Intracranial self-stimulation (ICSS) behavior was discovered by Olds *et al.* [7, 8] and is believed to be an effective experimental methodology for understanding reward and motivational systems in both animals and humans [9]. According to the "constancy theory" [10], reward and motivational systems exist contiguously in the brain, and ICSS behavior occurs by both systems being activated simultaneously. However, Reid *et al.* were successful in developing a runway method employing ICSS behavior [11], which allows for discriminative investigation of the separate reward and motivational system components underlying the

Received March 2, 2010; accepted May 18, 2010.
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ICSS behavior [12]. By modifying Gallistel's runway method we have now devised an experimental methodology that can be used to evaluate drug efficacy for influencing motivational states.

Motivation is an important neural function that forms the basis for several critical undertakings in our life. The expression of motivation requires a series of affective processes that underlie reward (feelings of pleasure). It is recognized that neuronal signaling in the mesolimbic dopamine system in the brain is significantly related to the relationship between motivation and reward. This review introduces 4 types of neuronal processes involved in motivation and reward mechanisms. This review also outlines an evaluation of experimental methods [13–15] and describes the motivational properties of 2 psychoactive drugs of abuse.

Motivation and Reward Processes

The process of drive (expectancy of reward). In the case of food reward, visceral cues informing you of hunger are transferred to the hunger center of the lateral hypothalamic area. Memories of food are relayed from memory centers such as the medial temporal lobe, and a variety of information conditioned by food and affective responses associated with such information is transferred from the limbic system (including the hippocampus and amygdala) to the nucleus accumbens.

The conversion from drive to action. The nucleus accumbens plays the role of an interface converting such visceral and emotional information into the action of searching for food. In order for the nucleus accumbens to fulfill this function, orders of decision-making from the frontal lobe are required. Prior to the search action, dopamine levels decrease once, and then increase with the actual expression of the search action. Dynamic changes in dopamine nerve firing are necessary to convert drive to action.

The search action. In the search process, information from the nucleus accumbens goes through neural connections to the ventral pallidum, the mediodorsal thalamic nucleus, and the brainstem motor area; all of which are related to goal-directed motion. This generates the action of searching for food.

The reward experience (feelings of pleasure). This is a process where food is consumed and satisfaction (feelings of subjective pleasure) is experienced. In this case, μ-opiate receptors that mainly exist in the ventral tegmental area, NMDA excitatory amino acid (glutamate) receptors, and D_2 dopamine receptors are involved. Dynamic changes of dopamine in the nucleus accumbens are necessary to express motivation (will), and activation of the endogenous opiate systems or dopamine systems in the ventral tegmental area are necessary to experience reward (subjective pleasure) (Fig. 1).

Experimental Techniques for ICSS Behavior and the Runway Method

Implantation of electrodes for brain stimulation. Chronic electrodes were implanted at a specific brain site along the medial forebrain bundle (MFB), and current from the electrode flowed to that brain site, causing activation of the entire MFB. Rats

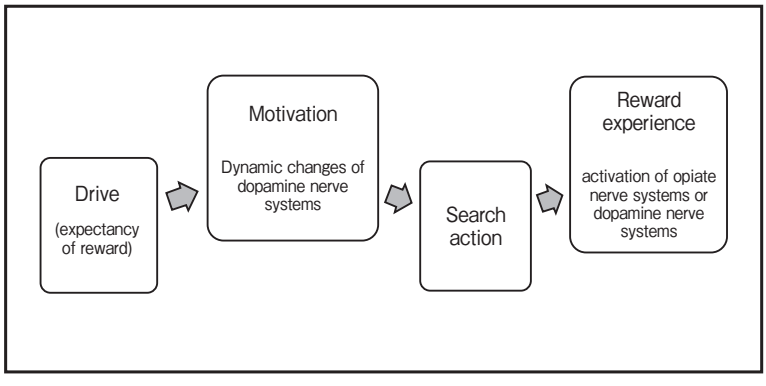

Fig. 1 Process of motivation and reward

could elicit brain stimulation by pressing a lever in a Skinner box ("self-stimulation behavior"). The MFB passes through the lateral hypothalamus, which is considered the most active brain reward site [16].

The method for implanting the chronic electrode in the brain was described previously [17]. Male Wistar rats were anesthetized by intraperitoneal injection of sodium pentobarbital (Nembutal, 50 mg/kg). Stainless steel electrodes consisting of a twisted pair of stainless steel wires (tip diameter: 0.2 mm), which were insulated except at the top 0.5 mm of the tips, were stereotaxically implanted (SR-5; Narishige Scientific Instrument Lab, Tokyo, Japan) into the medial forebrain bundle (MFB) at the level of the posterior hypothalamus (flat skull coordinates: 2.8 mm posterior to the bregma; 1.8 mm lateral to the sagittal suture; and 8.5–9.0 mm below the skull surface) [18]. After the electrodes were inserted into the MFB, they were connected to the pins of a small socket fixed to the skull using dental cement, and 2 screws were driven into the skull. At least 7 days were allowed for the rats to recover before beginning training for ICSS behavior in a Skinner box.

At the end of the experiment, all subjects were given an overdose of chloral hydrate and perfused intracardially with saline and formalin (4%). Coronal brain sections were generated and stained with crystal violet to determine the placement of electrodes.

ICSS training in the Skinner box and runway apparatus. One week after surgery the rats were trained for ICSS in the Skinner box (30.8 cm wide, 25.4 cm length, and 27.7 cm height). The rats that pressed the lever at a stable rate for 3 days in the Skinner box (50 presses per minute) were used for the runway method.

The runway method of Gallistel *et al.* was used in this experiment [19, 20]. The runway apparatus (Neuroscience, Tokyo, Japan) was made from 5-mm acrylic sections and consisted of a start box (26.5 cm wide, 26 cm long, and 30 cm high), a controlled start door (26.5 cm wide, 30 cm high) that opened by dropping down, a runway (18 cm wide, 180 cm long, 30 cm high), and a priming box (30 cm wide, 30 cm long, and 30 cm high) (Fig. 2). A retractable lever was set at the end of the runway 7 cm above the floor (the goal lever). Each rat was trained in the runway until its running speed stabilized. Upon reaching the goal end and pressing the lever, they received a reward stimulation of 0.2-msec pulses of 60 Hz alternating current. The current was set at 50–200 μA to produce a maximal priming stimulation effect (PSE, the maximal difference between the running speeds on primed versus unprimed trials). The stimulation current was individually adjusted for each rat. In a trial, the rat was removed from the runway as soon as it received reward stimulation and placed in the priming box that stood beside the runway, where 25 sec later it received 10 priming stimulations (1 stimulation per second, the same parameters as the reward). When the priming stimulation ceased, the rat was transferred from the priming box to the start box of the runway. Five sec after cessation of the priming stimulation, the start box door opened. If the rat ran to the goal lever and pushed it, the rat received reward stimulation. The running time from the opening of the door to the pressing of the goal lever was recorded by

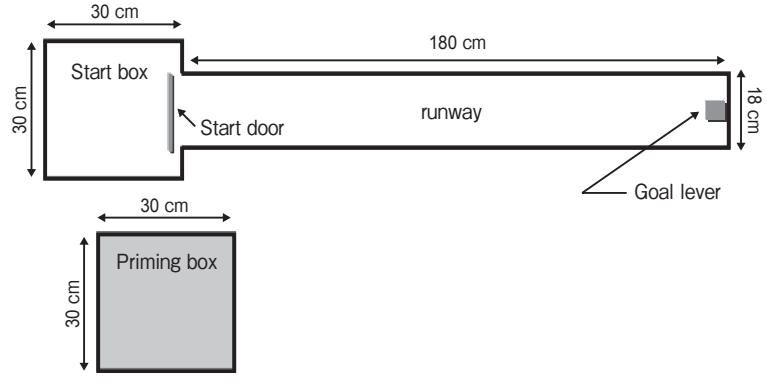

Fig. 2 The experimental apparatus used for the runway method of ICSS behavior. Cited from Acta Med Okayama (2008) 62(4): 227–233.

microcomputer.

Characteristics of priming stimulation in the runway method.

1. Correlation of priming stimulation frequency and running speed

Each rat was trained on the runway until its running speed was stabilized without priming stimulation. Studies of the effect of priming stimulation frequency on running speed consisted of 50 consecutive trials, with 5 stages of 10 trials each. The rat received 0, 1, 3, 5, and 10 priming stimulations (1 per sec, the same parameters as for the reward) in stages, and one reward stimulation upon pushing the goal lever. The running time from the door opening to the pressing of the goal lever was recorded using a microcomputer.

The priming stimulation frequency was significantly and positively correlated with running speed ($r = 0.897$, $p < 0.05$) (Fig. 3). Running speed also increased with the current strength of the priming stimulation [20, 21]. These results indicate that in the runway method employing ICSS, priming stimulation enhances running speed to obtain the reward stimulation by pressing the goal lever. In addition, Reid *et al.* hypothesized that the change in running speed with respect to the priming stimulation indicates a motivational effect in the runway method [11]. Thus, priming stimulation may have enhanced the motivation to obtain the reward stimulation.

2. Effect of priming stimulation on running speed in the runway method

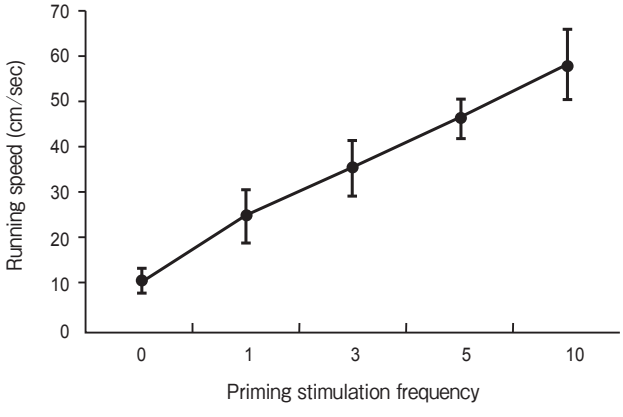

Fig. 3 Correlation of priming stimulation frequency and running speed of rats. Running speed increased with priming stimulation frequency. Each point represents the mean ± S.E.M. of running speed in 10 trials (n = 4). Cited from Biol Pharm Bull (2008) 31(4): 541–545.

Each rat was trained on the runway until its running speed was stabilized with 10 trains of priming stimulation. Studies of the effect of priming stimulation on running speed consisted of 45 consecutive trials. After 10 trials in which a reward stimulation was applied, the rat was subjected to 20 trials in which there was no reward stimulation even when the goal lever was pressed. In 15 further trials, the rat received 1 reward stimulation after pushing the goal lever. Under the reward and priming stimulation condition, the rats maintained a steady running speed toward the goal lever. However, under the condition of priming stimulation without reward, the running speed toward the goal lever gradually decreased. Thereafter, returning to the first condition of priming and reward stimulation, the running speed toward the goal lever rapidly returned to a level similar to the original speed under this condition (Fig. 4).

The decrease in running speed indicates an extinction of the effect of the priming stimulations for obtaining the reward stimulation. When the rats were subsequently given the reward stimulation again, the running speed toward the goal lever rapidly increased and returned to a level similar to that in the previous condition of reward and priming stimulation. Thus, the electrical brain stimulation is a reinforcer. The electrical reward and priming stimulations both stimulated the MFB at the same site of the brain. Theoretically, both the electrical reward and priming stimulations are potential reinforcers. However, the observation of the gradual decrease in running speed toward the goal lever in the absence of reward stimulation suggests that the electrical reward stimulation, and not the priming stimulation, is the reinforcer in this experimental setup. Instead, the effects of priming stimulation are considered to influence the motivational effects of obtaining the electrical reward stimulation.

Technique for measuring the motivational effects of reward drugs on ICSS using the runway method. This experimental procedure involved 30 trials and consisted of pre-sessions, baseline sessions, and test sessions (Fig. 5). Each session comprised 10 trials. In the pre-session, the rat received 10 priming stimulations and a reward stimulation for pushing the goal lever. In the baseline session, the rats received 5 priming stimulations and a reward stimulation for pushing the goal lever. In the

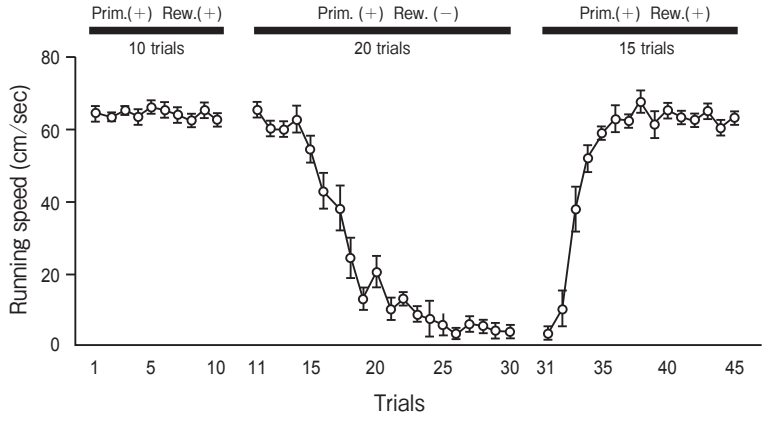

Fig. 4 Effect of reinforcing stimulation on running speed in the runway test. Experiments consisted of 45 consecutive trials. Contingent rewarding (reinforcing) stimulation was not available during trials 11–30, but was available in trials 31–45. [Remark 3] The assigned values are the mean ± S.E.M. for 4 rats. Prim., priming stimulation; Rew., reward stimulation. Cited from Biol Pharm Bull (2008) 31(4): 541–545.

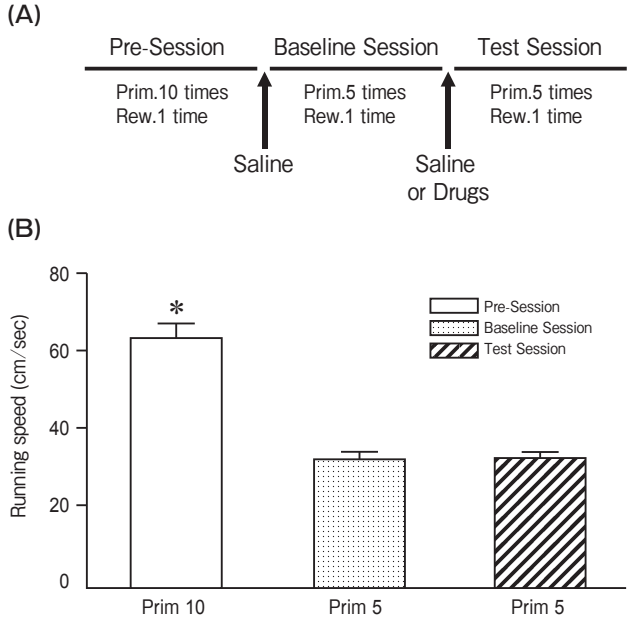

Fig. 5 Experimental design for the measurement of motivation and running speed. (A) Each session consisted of 10 trials. The value assigned for each rat was the mean value of 10 trials in each session. When the value for the test session was significantly higher than the value for the baseline session, the test drug was considered to have a motivational effect. (B) Running speed in the pre-session, baseline session, and test session. Saline was administered in the baseline and test sessions. Each column represents the mean ± S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Sheffé test. $^{*}p < 0.05$, significantly different from baseline session. Prim., priming stimulation; Rew., reward stimulation. Cited from Biol Pharm Bull (2008) 31(4): 541–545.

test session, after the administration of vehicle or drugs, rats received 5 priming stimulations and a reward stimulation for pushing the goal lever. Vehicle and drugs were administered before the baseline or test session. The motivational effect of the drugs was determined as the ratio of the baseline running time to the test-session running time. When the running time for the test session was significantly lower than the running time of the baseline session, it was determined that the motivational effect of the tested drug was positive.

Assessment of the Motivational Effects of Methamphetamine

We first measured the motivational effects of methamphetamine, a psychostimulant drug that is well known to enhance motivation clinically. At 1 and 3 mg/kg, methamphetamine produced an increase in running speed ($F(3, 20) = 16.257$, $p < 0.01$), suggesting that methamphetamine facilitates priming stimulation with respect to ICSS behavior in the runway test (Fig. 6). Methamphetamine-induced hyperactivity is insufficient to explain the observed enhancement of target-oriented behavior. Motivational and rewarding effects are indispensable for completion of the target-oriented behavior, and such complex behavior is not simply regulated by locomotor activity. In the end, the influence of methamphetamine-induced hyperactivity on goal-directed behavior should be much

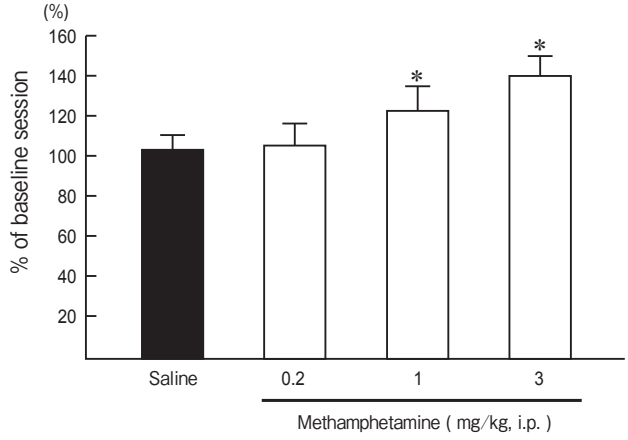

Fig. 6 Motivational effect of methamphetamine on ICSS behavior in the runway test using priming stimulation. Each column shows the percentage by which running speed in the test session differed from that in the baseline session. Saline (0.9% sodium chloride) and methamphetamine (0.2, 1, and 3 mg/kg) were administered by i.p. injection 30 min before the measurement. Each result represents the mean ± S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Sheffé test. $^*p < 0.05$, significantly different from saline. Cited from Biol Pharm Bull (2008) 31(4): 541–545.

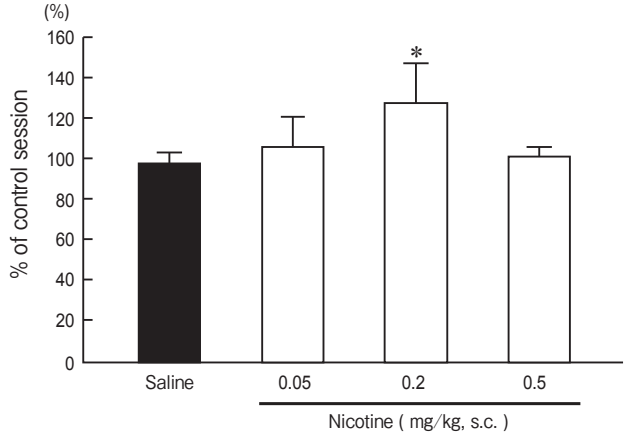

Fig. 7 The motivational effect of nicotine on the runway method using priming stimulation. Each column shows the ratio of baseline running speed to test session running speed. Saline and nicotine (0.05, 0.2, 0.5 mg/kg) were administered by subcutaneous injection (s.c.) 30 min prior to the measurement. Data represent the mean ± S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Scheffé test. Change in running speed following administration of 0.2 mg/kg nicotine was significantly different from that observed after saline injection. $^*p < 0.05$. Cited from Acta Med Okayama (2008) 62(4): 227–233.

less than its motivational effect.

Psychostimulants such as methamphetamine affect the mesoaccumbens dopaminergic system [22, 23]. This system is closely connected with the motivational nervous system [24–27], and might be one of the neural substrates influenced by methamphetamine. In the current study, the electrodes for ICSS were implanted in the MFB. At the level of the posterior hypothalamus, the MFB intersects with the mesoaccumbens dopaminergic pathway. Thus, it is conceivable that methamphetamine activates the mesoaccumbens dopaminergic system and facilitates priming stimulation due to stimulation of the MFB.

It was also demonstrated that running speed was significantly enhanced with a moderate dose of nicotine (0.2 mg/kg) [$F(3, 20) = 4.756$, $p < 0.05$]. With both a smaller dose (0.05 mg/kg) and a higher dose (0.5 mg/kg), the running speed remained unchanged, similar to the effects of saline. The effect of nicotine on ICSS behavior in the runway method thus displayed an inverted U-shaped dose-response curve (Fig. 7). This inverted U-shaped dose response is consistent with results of other nicotine self-administration studies, where an intravenous injection dose of 0.03 mg/kg has been shown to reliably support operant responding in animals [28–35]. Furthermore, modifications of the nicotine U-shaped dose-response curve in forced swimming tests have been used as a screening method for antidepressants. Nicotine, at a subcutaneous injection dose of 0.2 mg/kg, has been shown to significantly decrease the duration of immobility in forced swimming tests after examining an experimental dose range of 0.01–1.0 mg/kg [35]. In addition, subcutaneous injection of nicotine at a dose of 0.2 mg/kg significantly inhibited the effect of naloxone-induced place aversion [36–38]. These findings indicated that the subcutaneous injection dose of 0.2 mg/kg nicotine was suitable for alleviating both depression-like behavior and aversive motivational states. These results may explain why subcutaneous injection of 0.2 mg/kg nicotine was the optimal dose for enhancing running speed and motivation.

General Discussion of Motivational Effects Induced by the Opportunity for Intracranial Self-Stimulation

"Motivation" is a process that moves behavior continuously along one direction towards a goal, and can be conceptualized as a series of steps relating to that

process. Thus, motivation can be defined as either a factor that regulates goal-oriented behavior or the entire interaction of a variety of factors involved in such an aim.

Motivation in psychology is divided into physiological motivation and other motivations. Physiological motivation relates to drinking behavior, eating behavior, thermoregulatory behavior, sexual behavior, and emotional behavior. On the other hand, other motivations include intrinsic motivations, such as personal interests and curiosity, and social motivation, which relates to interpersonal behavior. For humans, it is mainly dysfunctions in intrinsic and social motivations that can lead to social problems. Thus, animal models targeting intrinsic motivation, not physiological motivation, may be more suitable to evaluate medicines that act on human motivation. We used ICSS behavior in animals to evaluate the efficacy of medicines that act on motivation since this animal model is thought to have high face and predictive validity in modeling psychiatric disorders of intrinsic motivation.

Traditional operant intracranial self-stimulation (ICSS) behavior is comprised of both a reward and a motivational effect. Priming stimulation is known to promote the motivational effects of ICSS behavior [39]. Using the runway method and priming stimulation, the reward and motivational effects of ICSS behavior can be distinguished [39]. The operant runway procedure has been successfully used to study the motivating properties of a wide variety of reinforcers, including food [40], water [41], and sex [42], as well as intravenous heroin [43, 44], amphetamine [45], nicotine [46], and cocaine [47]. These reports indicate that the operant running speed reflects the animal's motivation [43–47].

Using a runway method of experimentation and the opportunity for ICSS as reward, we showed that running speed substantially increased as the number of priming stimulations increased. We believe that the priming stimulation given before the animals were put in the start box increased the drive of seeking the goal lever, which in turn increased running speed. Waraczynski *et al.* reported similar results [48], and also reported that under priming stimulation conditions the running speed also increased with increases in simulation frequency (without changing the current of the reward stimulation). Our study results complement the results of Waraczynski *et al.* in that motivation was increased when we changed the number of stimulations; they changed the frequency. The impact of priming stimulations in the runway method can be interpreted as behavioral changes resulting from activation of neuronal substrates in the brain subserving motivation. The experimental results shown in Fig. 3 strongly support this interpretation. Our results demonstrate that the priming stimulation cannot act as a reinforcing stimulation. If the priming stimulation was reinforcing, the rats would have continued to run at the same pace even under extinction conditions with respect to the runway-lever pairing. Considering the behavioral characteristics of rats, they might eventually alter their behavior by recognizing the priming stimulation that is given 10 times as a new rewarding stimulation, more so than the stimulation of a goal lever that is only received once. Rats that are not rewarded by a goal lever might gradually start running to obtain stimulation that is given in the priming box. In this case, the priming stimulation can become reinforcing. In our experiment, when only priming stimulation was given, the running speed toward the goal lever decreased in each trial. When the rats were again allowed to run while the reinforcing stimulation by the goal lever was available, the running speed gradually increased and by the 10th trial the running speed returned to that observed during the pre-session. Instead of a reinforcer, the priming stimulation in the runway method can best be interpreted as a stimulation that inactivates the drive mechanism that compels the rats to run toward a goal lever to obtain rewards. Medicines that impact the priming stimulation effect in the runway method may represent drugs that influence the neural mechanisms of motivation.

Using the experimental methods that we created, we observed prominent changes in running speed after exposure to methamphetamine and nicotine, corresponding to their well known effects on motivation. As these substances serve as positive controls, our results indicate that the runway method of ICSS behavior may be used to evaluate drugs that act on motivation. In addition, it is of note that certain anxiolytic agents [49], anti-depression drugs [50], and drugs to treat Parkinson's disease also modify the effects of priming stimulation in this method. We hope the experimental method that we created will be used in the future to scientifically evaluate the impact of

drugs and therapeutic medicines on human motivation.

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