TECHNICAL NOTE

*A DEVICE FOR ANALYZING DRUG-INDUCED RESPONSES
IN FREELY MOVING MICE¹*

Studies have reported correlations between the hallucinogenic activity of drugs in man and the induction of head twitches in mice (Corne and Pickering, 1967; Siegel and Poole, 1969; Siegel, 1971; Siegel and Jarvik, 1971). However, these studies have failed to quantify this response and thereby permit correlational analysis of hallucinogen-induced twitches both between and within subjects and across treatment conditions. The development of a device to record and measure head twitches might provide a suitable method for quantitatively and objectively distinguishing the hallucinogens from other psychopharmacological agents.

Previous devices originally developed for tremor analysis utilized phonograph pick-ups (Ahmed and Taylor, 1959), moving coil loudspeakers (Silverman and Jenden, 1970), kymographs (Maffi and Soncin, 1958), or pressure transducers (Holmstedt and Lundgren, 1966). Most either lacked sufficient sensitivity to detect the head twitch or failed to separate such signals from whole body tremors induced by a wide variety of psychoactive compounds. The device described here was designed to record chronically only the head twitch in freely moving animals and differs from previous tremor and activity analyzers involving considerable surgical preparation or restraints on the animal (e.g., Moore, Sigg, and Schneider, 1957; Hake, Enoch, and Kelly, 1971). The design includes low cost, simple construction, automatic recording, and reliable conversion to and interfacing with electromechanical or solid-state scheduling equipment.

A magnetized rubber strip (1 by 0.8 by 0.4 cm) was attached to a clipped and shaved area of the mouse's head with Silastic adhesive (Dow Corning Corporation, Midland, Michigan: RTV-731). The magnetic unit ("Eclipse" Magnetic Strips: James Neil and Co., Sheffield, England) was placed directly between the ears and oriented so that the North-South Pole axis was horizontal, yet perpendicular to the spinal column (Figure 1). This positioning prevented the animal from gnawing the unit and allowed for maximum disturbance of the magnetic field with the lateral head twitch.

The Silastic bonding cured in about 20 min. However, since the placement of this unit induced an initial high rate of head twitches, the preparation was allowed to dry overnight (12 hr) to permit the animal to adapt more completely. Nevertheless, the terminal rate of head twitching was higher than that observed for unprepared animals.

The prepared mouse was placed in a glass box (12 by 10 by 7 cm) equipped with woodshavings and an overhead wire loop (10.5 by 8.5 by 0.8 cm) consisting of 14 turns of #30 wire. The loop was mounted on a perforated plastic board, which formed the top of the box, and connected to the circuit shown in Figure 2. When the mouse emitted a head twitch, lateral movement of the head unit produced a change in the adjacent magnetic field. The amplitude of the voltage generated in the loop was dependent on the movement of the magnetic field. The operational amplifier (op amp) in Figure 2 provided an initial amplification gain of 10^4 and was equipped with an Offset-Null Control for optional vernier zeroing of the recorder. The Schmidt trigger was adjusted by means of a 20-turn potentiometer to register only changes greater than 5.0 microvolts. Thus, while the counter registered only voltage changes of at least 5.0 microvolts, the recorder traced all voltage changes resulting from activity of the animal. Since the head twitch was considerably faster than other behavioral responses, it always appeared as a single spike on the record as shown in Figure 3. Ear scratching or rapid grooming of the head unit itself did not trigger the counter and could be separated from head twitches on the record as well (Figure 3). Some pilot adjustment of the potentiometer is necessary here to ensure proper identification of head twitches. A Moseley 680 Autograf Recorder with pre-amplifier was used, although a variety of strip chart recorders and polygraphs are suitable. The recorder and circuitry can be located at any distance from the animal box and several units can be connected to a multi-channel recorder. The entire cost of the materials in the circuit minus the recorder, counter, and power supplies was approximately \$15.00.

To demonstrate the effectiveness of the device, 10 female Simonsen mice were prepared as described above and studied for three daily sessions of 2.5 hr each. The recorder was adjusted to record all observable head twitches as well as the 5.0 microvolt twitches registered on the counter. In addition, a human observer visually identified head twitches and recorded their occurrence. The correlation between the recorder and the observer was 0.97 while the correlation be-

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Fig. 1. Magnetic unit mounted on animal. North-South Pole axis of the magnet is perpendicular to the animal's ears.

tween the counter and the recorder was 0.81. This latter difference was due to the occurrence of "minor" head twitches (0.5 to 5.0 microvolts), which did not register on the counter. Using the recorder data the mean head twitch rate per minute was 0.50 and no significant differences were observed between or within subjects over the three sessions.

An additional group of mice was then prepared and studied for 30-min baseline periods. Immediately following this baseline period, animals were randomly divided into groups of eight and each group received one of the following drug treatments: water; mescaline, 1 mg/kg; mescaline, 10 mg/kg; mescaline, 25 mg/kg; mescaline, 50 mg/kg; mescaline, 100 mg/kg; d-amphetamine, 1 mg/kg; d-amphetamine, 2 mg/kg; d-amphetamine, 5 mg/kg; d-amphetamine, 10 mg/kg; d-amphetamine, 15 mg/kg. Each drug was administered in a distilled water vehicle with a constant volume of 20 ml/kg, i.p. The animal was then replaced in the box for a 2 hr session. Table 1 shows the mean head twitch rates for mescaline and d-amphetamine for each group of animals in blocks of 30 min. These rates were calculated from the recorder data using all twitches of at least 0.5 microvolt amplitude. In these initial studies, the counter was not set to register "minor" twitches. However, the adjustable Schmidt trigger en-

Table 1

Mean head twitch rates per minute for each group of mice in mescaline and d-amphetamine experiment. Pre-Drug rates were calculated from the 30-min baseline recording before drug treatment while Post-Drug rates were calculated in consecutive blocks of 30-min from the 2-hr recording following treatment ($n=8$).

Treatment	Pre-Drug Rate	Post-Drug Rate			
		1	2	3	4
Vehicle (water)	0.48	0.51	0.51	0.57	0.40
Mescaline					
1 mg/kg	0.61	0.56	0.60	0.38	0.50
10 mg/kg	0.59	0.62	0.68	0.54	0.48
25 mg/kg	0.58	1.10	1.12	0.42	0.40
50 mg/kg	0.50	1.37	0.66	0.50	0.55
100 mg/kg	0.61	0.49	0.70	0.25	0.28
d-Amphetamine					
1 mg/kg	0.55	0.50	0.51	0.48	0.46
2 mg/kg	0.36	0.48	0.44	0.53	0.52
5 mg/kg	0.51	0.61	0.57	0.55	0.52
10 mg/kg	0.48	0.59	0.51	0.43	0.56
15 mg/kg	0.58	0.50	0.61	0.62	0.54

Fig. 2. Block and schematic diagrams of amplifier circuit. All resistors are in ohms.

ables a more exact setting of the counter than was used here. Most head twitches occurred in the first hour following mescaline administration (73% with 25 mg/kg, 66% with 50 mg/kg) with peak activity occurring 25 min after injection. These data correspond to states of mescaline-induced behavioral excitation and inhibition previously observed for mice in learning situations (Siegel and Jarvik, 1971). Treatment with d-amphetamine produced tremors and spasms in the mice with no significant changes in head twitch rate. Thus, the present device has the unique advantage of measuring hallucinogen-induced responses that

are independent of the general activity changes such as those following amphetamine administration (*cf.* Corne and Pickering, 1967). In addition, we are currently using the chronic preparation for the study of repeated administrations, dose-time parameters, as well as drug interaction with on-going operant and respondent behaviors.

When prepared in the above manner, the head unit did not impair normal operant or respondent behaviors and the animals wore the unit for over 30 days with little problem from regrowing hair. If ceramic or alnico magnets are used, care must be taken not to

Fig. 3. Sample record showing large single spikes of head twitches and smaller tracings of grooming movements.

restrict the animal's movements with these heavier materials and a smaller unit should be used. In general, the magnetized rubber strips have been found to be lighter, more flexible, easier to cut, and considerably less expensive than their metal or ceramic counterparts. However, when rubber strips are used, mice must be housed individually to prevent other animals from gnawing the preparation.

Several other experiments are suggested by the utility of this device. Studies may be conducted on other distinct behavioral responses of animals that are characterized by activity in localized anatomical regions. For example, it is well known that tail-rattling is an index of agonistic behavior in mice (Scott, 1966). Preliminary studies with mice equipped with magnetic units on their tails indicated that this response could be analyzed without conventional visual monitoring by the experimenter. Such units should be completely encased in Epoxy resin to prevent removal by the animal's grooming movements. For studies involving monitoring of such responses in groups, the use of subcutaneously implanted ceramic magnets is suggested. Pilot studies indicate that this technique allows for recording from an individual member of a group without providing "overt" physical targets for spurious grooming or exploratory behaviors by other animals.

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