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The Effects of Methamphetamine on Fine Motor Control in Rhesus Monkeys[1,2,3,4]

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JOHANSON, C. E., T. G. AIGNER, L. S. SEIDEN AND C. R. SCHUSTER. *The effects of methamphetamine on fine motor control in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 11(3) 273–278, 1979.—Six rhesus monkeys were trained to extend their arms through a tube to press a lever with between 25 and 40 g of force for 3 or 5 sec. Responding was maintained by the delivery of 1.5 cc of water. Stimulus lights indicated whether the exerted force was below 25 g, between 25 and 40 g (i.e., correct) or above 40 g. Sessions were terminated after 50 water deliveries or 30 min had elapsed. Performance was well-maintained in all monkeys. Allowing the animals access to water prior to the session had no effect on performance. Discontinuing sessions for two weeks disrupted some aspects of performance but responding improved within 5 sessions. Single injections of methamphetamine (0.06–0.5 mg/kg) were given IM 20 min prior to the session. The highest dose of 0.5 mg/kg totally eliminated responding. Lower doses decreased rate of responding somewhat and increased phasic activity (i.e., tremors) in a dose-dependent manner. The procedure seems ideally suited for investigating the effects of psychotropic drugs on fine motor control in rhesus monkeys.

Methamphetamine Fine motor control Rhesus monkeys

THE effects of psychomotor stimulant drugs on motor control systems have not been adequately investigated despite the importance of the systems for normal functioning. The studies which have been done have largely concentrated on the effects of these drugs on gross locomotor activity and stereotypy [1]. A variety of stimulant drugs such as amphetamine have been shown to increase locomotor activity and stereotyped behavior in a dose-dependent matter and these effects have been correlated with changes in catecholamines [6, 7, 8]. Since these biogenic amines have widespread influence on a variety of other motor functions, it is important to investigate them as well. Falk [2] and Samson and Falk [9] determined the effects of *d*-amphetamine, as well as other psychotropic drugs, on fine motor control in rats. In their procedure, rats were required to press a manipulandum with a specified force. They found that *d*-amphetamine increased phasic activity (i.e., tremors) while having relatively little effect on tonic activity. In addition, relatively low doses produced these effects suggesting that fine motor control was quite sensitive to disruption by *d*-amphetamine.

The present study was designed to determine whether the procedure developed by Falk and his colleagues could be modified for use with primates which compared to rats, possess fine motor skills more similar to humans. Rhesus monkeys were trained to extend their arms and press a lever with a force between 25 and 40 g for 3 or 5 sec. Methamphetamine had only small effects on performance until a dose was reached which totally suppressed responding. However, the subtle effects which were found included dose-dependent increases in phasic activity or tremoring in at least 50% of the monkeys tested. Since these intentional tremors were not grossly observable, this procedure may be ideally suited for investigating the effects of both single and repeated administrations of psychotropic drugs on fine motor control.

METHOD

Animals

The animals were four male and two female (4030 and 4091) adult rhesus monkeys weighing between 4.3 and 6.7 kg at the beginning of the study. Five of the monkeys were

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[3]Portions of the results have been published previously in: C. E. Johanson, T. G. Aigner, C. R. Schuster and L. S. Seiden, Effects of methamphetamine and haloperidol on fine motor control before and after repeated injections of methamphetamine. *Fedn Proc.* 37: no. 3, 273, 1978.

[4]The present study is part of a larger research project on the effects of repeated methamphetamine injections which will be reported in a subsequent publication.

experimentally naive. Monkey 4091 had previous lever pressing experience with responding maintained by intravenous drugs but had not received any drug nor was in any experiment for 6 months prior to the present series of experiments. Except during experimental sessions, each monkey was housed individually in a standard metal monkey cage (62×70×62 cm) in a room which housed 10 to 15 other monkeys.

Daily water intake was limited to between 150 and 250 ml. Individual fluid requirements were based upon the animal's weight as well as the minimum necessary to avoid dehydration and the maximum which still maintained consistent responding. A maximum of 75 ml was delivered during the experimental session and the remainder was available immediately after the session in the home cage. Each day monkeys received ad lib Purina Monkey Chow in the home cage and a sugar cube saturated with liquid vitamins (Vitol, Vet-A-Mix, Inc., Shenandoah, IA).

Apparatus

The force lever system (Fig. 1) was a modified version of an apparatus previously described by Falk and Haas [3] designed to monitor fine motor control performance in rats. The modified apparatus consisted of a length-adjustable Plexiglas tube (Fig. 1,A) into which the monkey extended its arm to press a conical knob (Fig. 1,B) (termed "force lever") attached to a force transducer (Fig. 1,C). The experimental chamber consisted of two wooden sound-attenuating cubicles (each 76×92×78 cm) placed side by side with a 45×40 cm opening in the common wall. One cubicle contained the force lever system and transducer. The second cubicle, which was equipped with a Dayton fan that provided ventilation and a masking noise, contained a standard rhesus monkey cage with one wall removed to allow the monkey access to a Plexiglas intelligence panel built into the opening in the common wall. On the left side of the Plexiglas intelligence panel were 4 stimulus lights, (Fig. 1,D) arranged vertically, covered with amber Dialco lens caps. A cup into which water was delivered was located to the right of the bottom light (Fig. 1,E). This cup was connected by plastic tubing to a peristaltic infusion pump (7540x, Cole-Parmer Instrument Co., Chicago, IL). Operation of this pump for approximately 3 sec resulted in the delivery of 1.5 ml of water in the cup from a reservoir. The Plexiglas tube (Fig. 1), 7 cm in diameter and located to the right of the water cup was attached to the intelligence panel. The length of the tube could be adjusted from 21 to 33 cm. At the maximum extension, it was necessary for the monkeys to completely extend their arm and digits in order to press the force lever. The force lever (maximum displacement 0.1 mm) was located at the far end of the tube. Variations in the force exerted on the lever were monitored by a system composed of a Statham force transducer (Statham Instruments, Oxnard, CA, Model UC3), a Beckman Dynograph (Beckman Instruments, Inc., Lincolnwood, IL, Type R411) and BRS/LVE solid-state programming and recording equipment (BRS/LVE, Beltsville, MD). Periodically, the system was calibrated by suspending weights from the lever.

Terminal Schedule

The illumination of the top stimulus light signalled that the schedule maintaining fine motor control performance was in effect. The monkey was required to place one arm into the Plexiglas tube which was extended to its full length of 33 cm and press the lever with a force greater than 25 g and less than 40 g for either 3 (Monkeys 4030, 4091, 6083) or 5 sec (Monkeys 7034, 7035, 7036). If the force exerted was outside these limits (less than 25 g or more than 40 g) for more than 30 msec, the time requirement reset. If the time requirement was completed, the pump was activated for approximately 3 sec to deliver 1.5 ml of water. During water delivery, all lights were extinguished in the cubicle and responding had no programmed consequences. A session was terminated after 50 correct response sequences were completed or 30 min had elapsed, whichever came first.

Performance feedback was provided using the bottom 3 stimulus lights (Fig. 1,D). The light immediately below the session light was illuminated when a force between 10 g and 25 g was exerted. The next light was illuminated when responding was within the specified limits, i.e., when a force of between 25 and 40 g was exerted; the bottom light was illuminated when the exerted force was above 40 g. Four elapsed time meters were used to record the monkey's performance. One timer recorded total session time, excluding the time water was delivered. In addition, the total time a monkey responded with a force above 10 g and below 25 g (below-band responding), the total time a monkey responded within the specified limits (in-band responding) and the total time a monkey responded with a force greater than these limits (above-band responding) were recorded separately on the other three timers. Counters recorded the number of times the response force entered the required band width (from either below or above band) and the number of water deliveries obtained within the 30 min time limit.

Data Analyses

Using the above measures, the indices shown in Table 1 were calculated for each experimental session. These indices have previously been described by Falk [2] and Samson and Falk [9] and shown to be differentially sensitive to the effects of a variety of psychotropic drugs. The first 3 indices are relatively independent and can vary between 0 and 1.0 with higher values associated with well-maintained performance. Work rate measures the amount of time the monkey responds on the lever compared to the time spent engaged in other behaviors (e.g., drinking, grooming). Entrance score is the average number of band entrances per reinforcer.

Of particular interest in the present studies were the effects of methamphetamine on in-band efficiency. Efficiency decreases if responding enters the band width for less than the specified time requirement (thus increasing in-band responding time above the minimum). This decrease could be the result of either tonic or phasic changes in performance. A tonic change in performance would be characterized by the force entering the band and staying there for a period short of the requirement because of a gradual change or drift in exerted force. In this case, efficiency would decrease and entrance score would increase slightly. Most likely tonic accuracy would also decrease if the gradual drift continued out of band. In addition, in-band efficiency could be decreased by phasic events or tremoring. However, for similar decreases to occur in this index as a result of tremoring, entrance score would increase considerably. If tremoring was relatively rapid, and occurred in intermittent bouts during a session, in-band efficiency could remain unchanged while entrance score was increased. Tonic accuracy would be relatively unchanged.

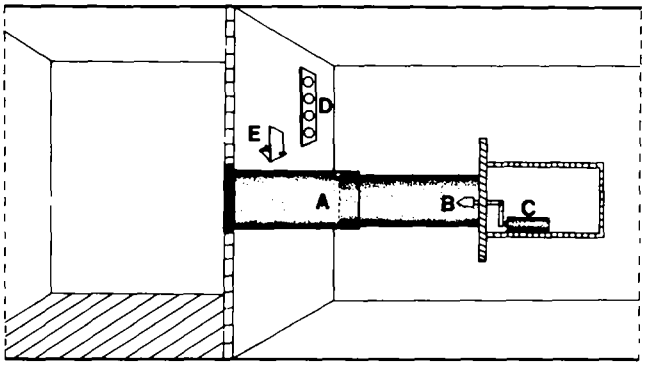

FIG. 1. Schematic diagram of the force lever apparatus. The monkey is placed in the area to the left separated from the apparatus by a Plexiglas intelligence panel. Access to the force lever (B) is *via* a Plexiglas tube (A) through which the monkey's arm can be extended. Changes in force are converted to changes in voltage by the Statham force transducer (C). These voltage changes are monitored by solid-state programming equipment located in an adjacent room. This solid-state equipment controls the behavioral contingencies, stimulus lights (D), activates the pump which delivers water at E and records the monkey's responding.

TABLE 1
PERFORMANCE INDICES

In-Band Efficiency* =	$\frac{\text{Number of Reinforcers Delivered} \times \text{Minimum Time Requirement (3 or 5 sec)}}{\text{In-Band Responding Time (Sec)}}$
Tonic Accuracy* =	$\frac{\text{In-Band Responding Time (Sec)}}{\text{Total Responding Time (Sec)}}$
Work Rate =	$\frac{\text{Total Responding Time (Sec)}}{\text{Session Time (Sec)}}$
Entrance Score* =	$\frac{\text{Total Band Entrances}}{\text{Number of Reinforcers Delivered}}$

*If responding is completely eliminated by any manipulation, this index cannot be calculated.

TABLE 2
INDEX VALUES FOR CONTROL PERFORMANCES*

Monkey	4030		4091		7034		7035		7036		6083	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
In-Band Efficiency	0.93	0.03	0.90	0.05	0.92	0.02	0.88	0.09	0.86	0.01	0.74	0.11
Tonic Accuracy	0.92	0.01	0.77	0.01	0.92	0.02	0.94	0.05	0.90	0.02	0.87	0.02
Work Rate	0.34	0.04	0.35	0.08	0.58	0.03	0.74	0.08	0.64	0.02	0.51	0.06
Entrance Score	1.7	0.2	2.6	0.2	2.4	0.4	1.3	0.3	2.5	0.3	2.9	0.7

*These values are the means of the values from the non-injection control sessions immediately preceding drug test sessions.

When responding became stable, single injections of methamphetamine were given intramuscularly 20 min prior to the experimental session in doses ranging from 0.06 to 0.5 mg/kg. These doses which were delivered in a 1 ml volume were given once in an ascending order. Drug was never given more than one time per week and only when responding had been stable for several sessions. Saline was given IM one or two sessions prior to each drug session. The other session was used as a non-injection control. Doses were calculated as the hydrochloride salt.

Two additional manipulations were made. First, prior to the experimental session, 5 of the monkeys were given 75 ml of water non-contingently. Second, for all 6 monkeys experimental sessions were not conducted for 2 weeks to determine whether responding would be disrupted when sessions were resumed. During this 2 week period, water deprivation conditions were kept the same as before.

RESULTS

Table 2 shows the non-injection control values of the 4 calculated indices. Although the monkeys differed somewhat in their performances, in general responding was well-maintained. In-band efficiency and tonic accuracy averaged 0.87 and 0.89, respectively. These high values indicate that most time spent responding in-band continued uninterrupted until the time requirement was satisfied (efficiency) and that relatively little time was spent responding out of band (accuracy). Although work rate varied considerably and was as low as 0.34 (Monkey 4030), all monkeys were easily able to earn 50 reinforcers within the 30 min time limit. However, the low values do indicate that for most monkeys, responding did not occur during more than 50% of the session. Entrance scores varied between 1.3 and 2.9 indicating little tremoring.

Figure 2 shows representative Beckman analog recordings from several monkeys. The topography of the responding differed somewhat between animals. Monkey 7036 immediately entered the band requirement. Although small tremors were evident, they rarely exceeded the band width and therefore had little effect on the measures of performance (Table 2). A similar topography was shown by Monkey 4030. Monkey 7035 also immediately entered the band requirement, but evidenced no small tremors. Monkey 4091, however, exceeded the 40 g upper limit and slowly drifted down into the band. As a result, tonic accuracy was relatively low (0.77) and entrance score was twice that of Monkey 7035, even though neither animal exhibited small trem-

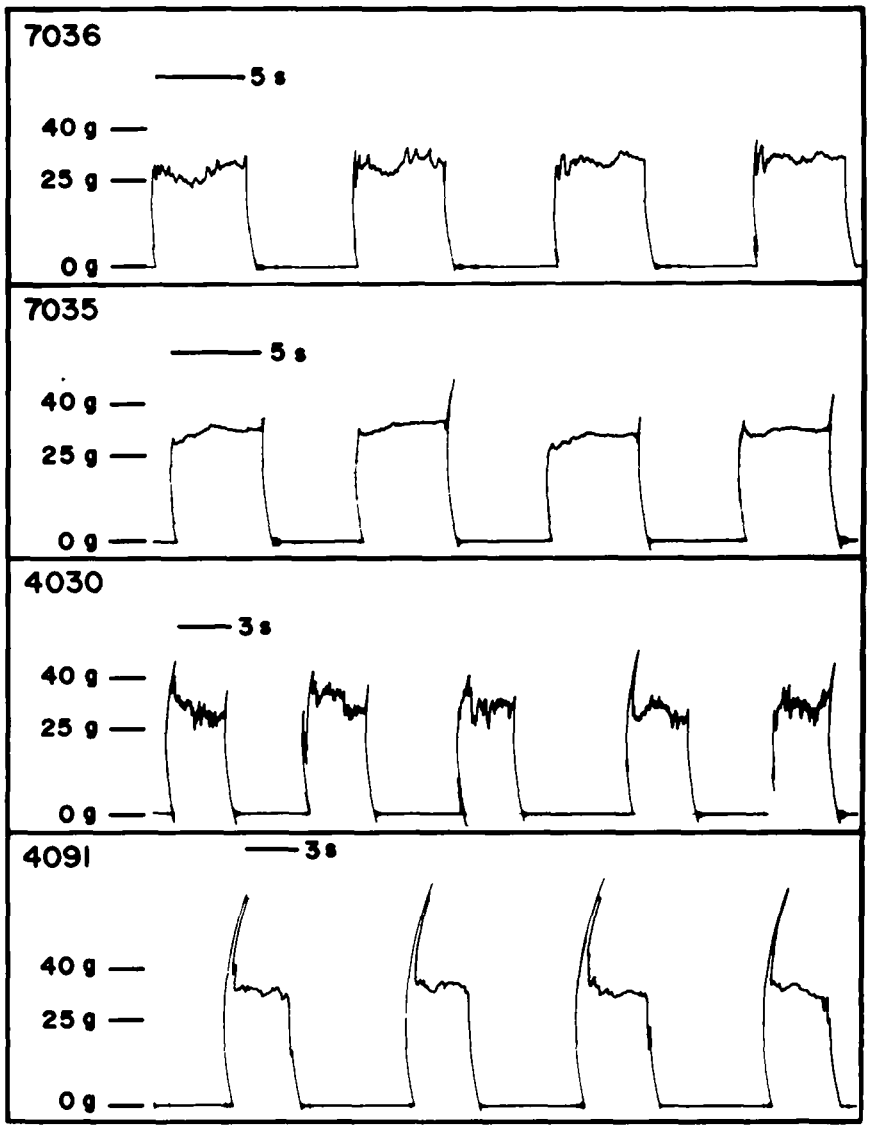

FIG. 2. Representative analog records of control responding of 4 monkeys. The tracing moves horizontally with time and vertically with changes in force exerted on the lever.

TABLE 3

EFFECTS OF ADMINISTERING 75 ml OF WATER PRIOR TO SESSION*

N=5	$\bar{X}$	SD
In-Band Efficiency	99.2	4.0
Tonic Accuracy	107.8	11.0
Work Rate	80.2	23.2
Entrance Score	97.0	6.0

*Expressed as percent of two preceding sessions

ors. In spite of these differences in performance patterning, the records clearly demonstrate that the monkeys were extremely capable of performing the task efficiently and accurately. Although attempts to determine whether the discriminative stimuli controlling responding were external (stimulus lights) or internal (proprioception) were not done systematically, preliminary findings plus casual observations indicate that the stimulus lights exerted little control over responding.

Table 3 shows the effects of delivering 75 ml of water 20 min prior to the session in 5 monkeys expressed as a percent of the mean of the 2 preceding control sessions. In general, this manipulation had little effect on performance. The percent decrease in work rate was largely due to one monkey (7035) whose rate decreased to 44% of control. The work rates for the other 4 monkeys varied from 74% to 106% with a mean of 89.3%.

Table 4 shows performance indices expressed as a percent of control on the first and fifth sessions following a 2 week period when sessions were not conducted. Although performance was affected in 5 of the 6 monkeys, the effects were variable as reflected by the large standard deviations. By the fifth session, those indices which had shown evidence

TABLE 4

PERFORMANCE FOLLOWING 2 WEEKS WITHOUT SESSIONS: PERCENT CONTROL

	4030	4091	6083	7034	7035	7036	$\bar{X}$	SD
Session 1								
In-Band Efficiency	60	97	99	99	92	96	90.5	15.2
Tonic Accuracy	74	96	94	99	101	98	93.7	9.9
Work Rate	108	32	100	97	102	102	90.2	28.7
Entrance Score	421	116	107	120	42	130	156.0	133.6
Session 5								
In-Band Efficiency	87	98	98	95	92	90	93.3	4.5
Tonic Accuracy	91	92	90	101	95	104	95.5	5.8
Work Rate	98	76	100	95	101	103	95.5	9.9
Entrance Score	158	100	80	107	223	149	136.2	52.0

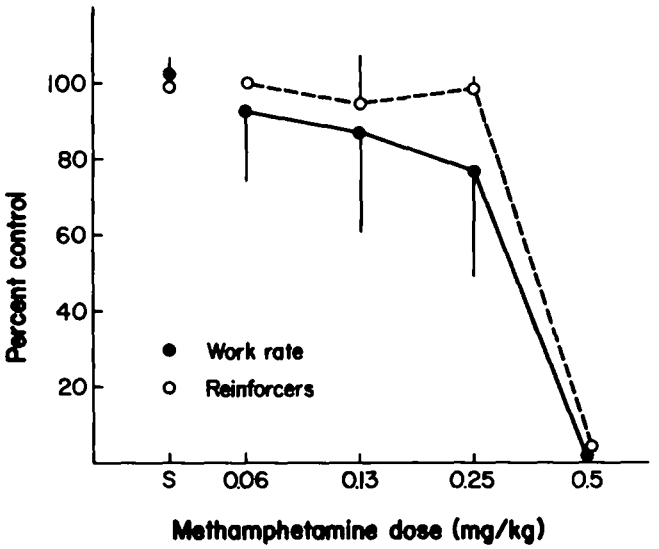

FIG. 3. The effects of single injections of methamphetamine on work rate (solid line) and number of reinforcers earned (dashed line) expressed as a percent of control. The vertical lines indicate one (1) standard deviation. See Table 1 for description of work rate.

of disruption approximated baseline values and variability was decreased.

Figure 3 shows the effects of single injections of methamphetamine on both the mean number of reinforcers earned and the mean work rate averaged for the 6 monkeys. Responding was well maintained at doses between 0.06 and 0.25 mg/kg and nearly all possible reinforcers were obtained. The dose of 0.5 mg/kg totally eliminated responding in all monkeys except 4091 who earned 4 reinforcers at the beginning of the session before responding ceased. There were small dose-dependent decreases in work rate for 4 of the monkeys. The other 2 monkeys showed no effect (7035) or small increases (7036) at the lower doses.

Table 5 shows the effects of the three lower doses of methamphetamine on the other 3 indices of performance. In-band efficiency and tonic accuracy were relatively unaffected. The most striking changes in performance were increases in band entrances. Since in-band efficiency did not change concurrently, these increases are indicative of changes in phasic activity, i.e., tremoring. Although the effect is variable, Table 6 shows that substantial increases occurred in all monkeys.

DISCUSSION

Although motor functioning is complex and its mechanisms are not clearly understood, changes in the dopaminergic nigrostriatal pathway are generally believed to be involved in some motor function deficits and disease states [4,5]. Drugs such as methamphetamine which are known to cause dopamine release in the central nervous system have been shown to have specific effects on motor functioning such as increased locomotion and, at higher doses, stereotypy. However, the effects of these drugs on fine motor control have not been extensively investigated. To accomplish this, it is necessary to develop methods which generate a stable behavioral performance based upon fine motor control. Falk [2] developed a procedure for studying the effects of drugs on a task requiring rats to depress a lever with a specified amount of force and to hold it within a force

TABLE 5

EFFECTS OF METHAMPHETAMINE ON 3 INDICES OF PERFORMANCE

Dose (mg/kg)	Saline		0.06		0.12		0.25	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Efficiency In-Band	99.5	2.4	94.3	10.0	92.2	9.8	88.3	13.2
Tonic Accuracy	100.5	2.1	90.8	9.1	91.0	10.3	90.3	15.2
Entrance Score	102.3	7.1	113.3	13.0	127.2	37.8	171.0	62.2

TABLE 6

BAND ENTRANCE SCORE FOR INDIVIDUAL MONKEYS EXPRESSED AS PERCENT CONTROL

	Monkey					
	4030	4091	6083	7034	7035	7036
Control SD	±12	±8	±23	±19	±11	±12
Saline	100	96	104	115	96	103
0.06 MA(mg/kg)*	88	119	112	124	118	119
0.13 MA(mg/kg)*	194	119	82	102	142	124
0.25 MA(mg/kg)*	176	88	270	204	150	138

*MA = Methamphetamine

band for a period of time. Not only was the procedure unique but the analyses he developed allowed a differentiation of subtle tonic and phasic changes in responding. As a result, he could conclude that although a variety of psychotropic drugs disrupt this type of fine motor control, *d*-amphetamine specifically increases phasic activity, i.e., tremoring, at relatively low doses [2,9]. These changes were not obvious either from observation of the animal or from the analog records (Falk, personal communication).

The present study was designed to determine whether Falk's system could be modified for use with primates. Rhesus monkeys were trained to perform a task which required them to depress a lever with a force of between 25 and 40 g for a 3 or 5 sec interval. Although the patterning of the fine motor control differed between monkeys, they all performed efficiently and accurately and were able to earn the maximum number of 50 reinforcers within a 30 min session over a 6 month period. In addition, stable performance was maintained. Neither administering water prior to the session or discontinuing sessions for a 2 week period disrupted performance to any marked degree.

Single injections of methamphetamine in doses ranging from 0.06 to 0.25 mg/kg produced small dose-dependent decreases in work rate which did not affect frequency of reinforcement. Although other measures of performance were relatively unaffected across this dose range, entrance scores increased in most monkeys. This increase indicated that methamphetamine was producing an increase in phasic activity or tremoring at low doses. Additional studies, hopefully, will indicate whether or not this effect is related to changes in the dopaminergic system.

In summary, the present study confirms the previous work of Falk regarding the effects of amphetamines on fine motor control [2,9] and extends it to a species of primate. The adaptation of this method for use with primates allows the investigation of drug effect on fine motor performance in a species whose neural systems are very similar to those of human. Such a method which allows for the study of fine motor control performance for long periods of time may be especially useful for determining the effects of repeated drug administrations on motor functioning.

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