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Methylphenidate Affects Strategic Choice Behavior in Normal Adult Humans

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SCHROEDER, S. R., K. MANN-KOEPKE, C. T. GUALTIERI, D. A. ECKERMAN AND G. R. BREESE. *Methylphenidate affects strategic choice behavior in normal adult humans.* PHARMACOL BIOCHEM BEHAV **28**(2) 213–217, 1987.—The time course of serum concentration and performance on a concurrent probability matching task were evaluated in normal adults receiving 0.15 or 0.3 mg/kg of methylphenidate. The behavioral task, an arcade-like problem-solving game, revealed that drug-treated subjects improved their performance upon repeated testings during pharmacokinetic evaluation at a lower rate than did non-treated controls over the same time span. However, drug-treated subjects failed to adopt the adaptive problem-solving strategies selected by controls.

Methylphenidate Metacognitive function Problem solving Adult Normal Humans

ASHMAN and Schroeder [4], in a recent review of methylphenidate (MPH) studies related to attention deficits and hyperactivity, found very few that related to complex human cognition. Sprague and Sleator [25] in a very influential paper, showed that the peak effective dose of MPH on short-term recognition memory was lower than that for social behavior in hyperactive children with attention deficits (ADDH). They suggested a dose-related tradeoff between the cognitive and social behaviors affected by MPH. Methylphenidate improved performance of learning disabled children in a paired associate learning task [26] and in story recall [18]. Reid and Borkowski [17] found that methylphenidate was correlated with improved performance of ADDH children on cognitive encoding tasks, such as Item Identification, Word Span, and Reaction Time, but not on decoding tasks such as Letter Matching and Category Identification. Adams [1] found an improved performance on simple reaction time (RT) but not on decision times on a choice reaction time task in ADDH. Callaway, Halliday, Peeke and Reus [7] found a similar result, in that MPH improved RT in ADDH children, but had no effect on P3 latency of the visual evoked potential. Perhaps MPH improves performance efficiency of ADDH persons by increasing selective attention [10], while having a different impact upon the environmentally determined executive system, which involves planning, problem-solving strategies, and other metacognitive functions. Such findings are consistent with the view that ADDH may reflect impairment of frontal lobe function [11].

The effects of MPH on adult cognitive and metacognitive functioning may differ from its effect on children. Aman, Vamos and Werry [3] found no effect of MPH on the Sprague and Sleator [25] recognition memory task or the Continuous Performance Test, [8,19] of younger normal adults aged 22–43 years. Wetzel, Squire and Janowsky [28] found that methylphenidate, when begun 15 minutes after infusion, impaired normal adults' performance on paired associate learning and short story recall, but not picture recognition. When the drug was infused after learning, it had no effect on retention.

Apparently, there has been little experimental study of MPH on metacognitive functions such as problem-solving and strategy formation in children or adults [9, 22, 24]. The present study represents one of the few papers in this area. It was performed within a larger context of pharmacokinetic studies which examined the clinical correlates of MPH blood levels [12].

METHOD

Subjects

The subjects were 15 normal male adult volunteers (aged 18–40 years). All of them were staff or students at the Biological Sciences Research Center. Ten were assigned randomly to two drug groups, i.e., 0.3 or 0.15 mg/kg of methylphenidate. Five no-drug control subjects were run subsequent to the drug subjects. All were in good health and were not taking medication at the time of the study. All had abstained from caffeine-containing or alcoholic beverages for 13.5 hours and had fasted for 8.5 hours. The study was begun at 8:30 a. m. At the end of the day each subject received $50 for participating in the experiment. Food was permitted 3.5 hours after dosing.

Task and Apparatus

The task was an arcade-like game called Telekinesis Star Wars, chosen to be highly engaging rather than boring, like the CPT or a rote memory task. With a monotonous task a

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subject's performance could be confounded with lack of interest rather than be an accurate reflection of ability to perform. The present study attempted to control motivation by using a highly interesting task. It involved formation of choice strategies in risky situations. A desk-like control console (151×71×61 cm) housed a 43×56 cm polacoat screen which was rear-illuminated by one or more of a green, red, yellow, or flashing white light (Fig. 1). In addition, it housed a feedback panel consisting of a 5×9 matrix of colored lamps which could be lit sequentially from either end of the matrix or from both ends simultaneously so as to display hits and misses to the subjects. Three lamps to the right of the matrix indicated when the apparatus was on, when the subject had made a response, and when the subject had missed a signal. A pushbutton switch below the lamps enabled the subject to initiate the game.

The response manipulandum was made from an automobile emergency hand-brake inserted in a central slot within comfortable reach of the seated subject. The subject could switch his scan of "green sector" or "red sector" of the "galaxy" by moving the brake forward or backward in the slot. The subject could "fire" at the stimuli by depressing the brake release button.

The entire game was programmed automatically by electromechanical apparatus which was housed in an adjoining room. The signal was a yellow light rear-projected on the lighted screen. If the subject "shot" it (pressed the button) within 1 second, it disappeared and a "hit" light illuminated on the feedback panel. If the subject failed to respond in time, an "explosion" (white flashing light) occurred and a "miss" light illuminated on the feedback panel. If the control lever was forward, a green light ("scanning green sector") trans-illuminated the screen; if the control level was moved backward, a red light ("red sector") trans-illuminated the screen. Switching to or from sectors each caused a 3-second blackout. The subject was warned by the yellow light only of a signal scheduled for the sector he was scanning. He was neither warned, nor could he respond, during blackout or to signals scheduled in the sector not being scanned. The blackout duration was a response cost for switching sectors.

Signal schedules were programmed concurrently and independently for each sector by means of two Gerbrands tape pullers which reflected a particular operant schedule. One schedule was a fixed interval where signals occurred regularly every 15 seconds (FI15″); in the other schedule signals occurred aperiodically but averaged every 15 seconds. The randomized sequences of 12 intervals, specified as averaged minimum inter-signal durations, were arithmetic, with the interval of longest duration equal to twice the average. Technically the signal schedule was a CONC VI15″ FI15″ with a limited hold of 1-second and changeover delay (COD) of 3 seconds. These schedules are likely to result in four levels of scanning strategies: (1) rapid alternation; (2) no alternation; (3) win-shift, lose-stay; (4) bias toward scanning the sector with the aperiodic schedule. Strategies (3) and (4) increased the probability of more hits than strategies (1) and (2).

Procedure

Each subject was tested individually for a whole day in a comfortable room with the Star Wars Game located in the closet. At approximately 8:30 a.m. he was taken to the room for an explanation of the game, a two-minute practice trial per game, and then a baseline trial game before receiving the drug.

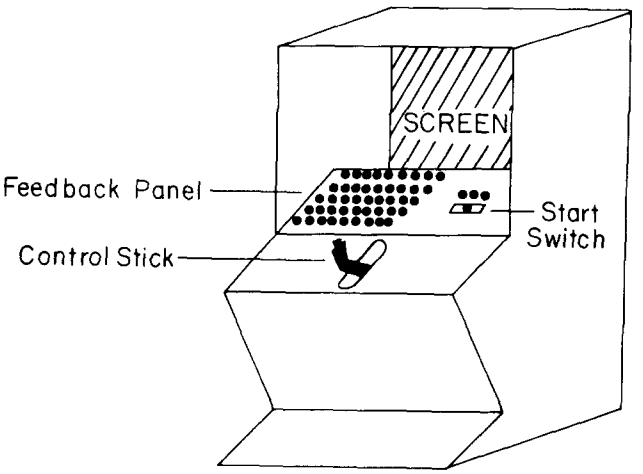

FIG. 1. Diagram of the apparatus.

After the baseline game, the subject was moved to an examining room where his height and weight were measured. A catheter equipped with a stop-cock was inserted into the antecubital vein of the non-preferred arm, fastened in place, and an initial sample was drawn. Then a standardized oral dose of methylphenidate (0.15 or 0.30 mg/kg) was administered. The control subjects received no indwelling catheter or placebo drug.

The subject was then returned to the testing room where he remained for the rest of the test day. Between testings and blood-drawings, the subjects did desk work or read or conversed with the experimenter (although not about the study). The arcade test was repeated, without instructions and practice trials, 15 minutes prior to each blood sampling. Repeated samples were then taken at 20, 40, 60, 90, 120, 180, 240, 360 and 480 minutes following drug administration. For a detailed discussion of the pharmacokinetic profiles of MPH in these subjects see Wargin, Patrick, Kilts, Gualtieri, Ellington, Mueller, Kraemer and Breese [27].

RESULTS

Data Analysis of the Behavioral Response to Methylphenidate

There were three main measures of interest. One was a performance measure, i.e., the *percentage correct hits*, (the total number of hits divided by hits plus misses × 100). The second was the *number of changeovers* between the two schedules, which reflected the win-shift, lose-stay strategy. The third was the *matching relation*, [13] i.e., the proportion of hits in a given sector as a function of the relative proportion of time allocated to scanning that sector. This measure reflected a high-level strategy of biasing one's monitoring toward the unpredictable (VI15″) vs. the predictable (FI15″) schedule. An efficiency-type of measure, called the Matching Index, was derived for each game by dividing the number of hits in green sector by the number of hits in red sector (H_G/H_R) and then dividing that into the amount of time spent in green divided by the time spent in red (T_G/T_R). The results for each measure are summarized below. Missing data points were estimated using Yates' procedure as described by Kirk [14]. The data were analyzed using repeated measure analysis of variance for the effect of Drug Group (three levels) and Time (ten levels).

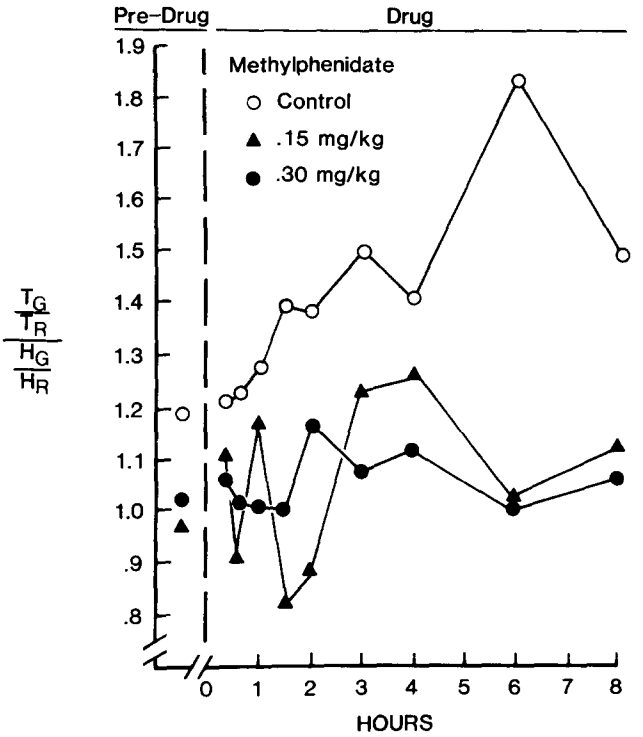

FIG. 2. Changes in the Matching Index as a function of time since drug administration for three drug dosages (0.3, 0.15, 0 mg/kg) of methylphenidate.

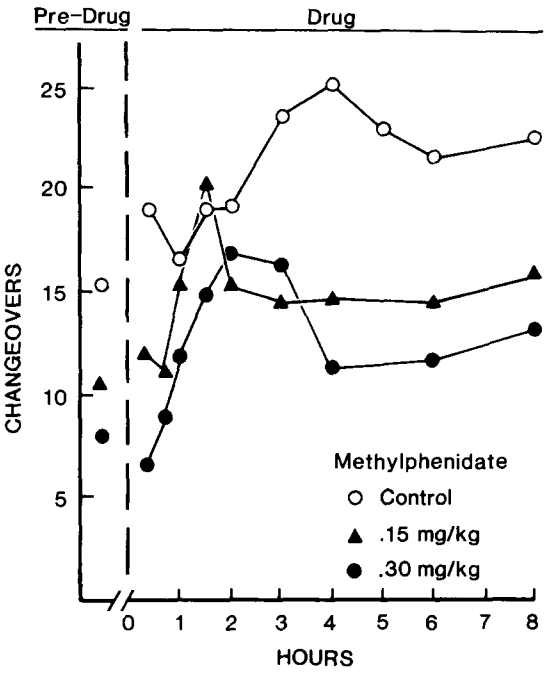

FIG. 3. Mean number of changeovers between signal schedules as a function of time since administration for three drug dosages (0.3, 0.15, 0.0 mg/kg) of methylphenidate.

Effect of Methylphenidate on Matching Strategy

One of the most thorough analyses of animal or human operant behavior is the analysis of choice between two or more alternative schedules of reinforcement. In vigilance experiments like the present one it has been found that subjects allocate their time and detection rates to the signal rates of the different schedules used [20,21] just as animals match their relative response rates to the relative reinforcement rates for different choices [13]. In both types of experiments the Matching Law that emerges is:

$$\frac{B_1}{B_1 + B_2} = \frac{r_1}{r_1 + r_2}$$

where B_1 and B_2 are the response frequencies or amount of time allocated to Alternatives 1 and 2, and r_1 and r_2 are the frequencies of reinforcement (or detection) produced by responding to Alternatives 1 and 2.

An elaborate network of equations and constants has been developed to account for the various reinforcement schedule effects and response biases that affect the generalized matching relation. In the present experiment the appropriate equation is that of Baum [5]:

$$\frac{T_G}{T_R} = W \frac{H_G}{H_R}$$

where T_G, T_R are time spent in red or green sector, H_G, H_R are the number of hits (detections of yellow lights) when scanning red or green sector and w is bias programmed into the signal schedules (VI15'' in green sector and FI15'' in red sector).

Matching is shown in Fig. 2, where a Matching Index was constructed dividing the ratio of green to red hits into the ratio of time spent in green vs. red sector by each group across the pharmacokinetic curve for methylphenidate. Factorial analysis of variance was used to examine the Matching Index Scores, which showed a significant interaction between time and drug level groups, $F(18,108)=2.01$, $p<0.05$. Since the interest was on different strategies used by the groups, the most logical breakdowns for further analyses were comparisons of the groups at each time interval. Although several comparisons approached significance, at only two time points, 90 minutes and 360 minutes, were significant differences between the groups found, $F(2,12)=9.97$ and $F(2,12)=16.74$, $p<0.05$, respectively. In both cases, post hoc comparisons revealed that the mean Matching Index scores for the control group were significantly higher than mean scores for both treated groups, and, in addition, there was no significant difference between the two treated groups. These results would suggest that, while the control subjects learned to spend more time monitoring green sector, the treated subjects failed to develop such a strategy.

Effect of Methylphenidate on Number of Changeovers

Changeover in the present experiment referred to switching back and forth between red and green sectors. Rapid alternation resulted in a constant blackout and missing all targets. No shifting resulted in missing 50 percent of available targets. A win-shift, lose-stay strategy resulted in a higher hit rate.

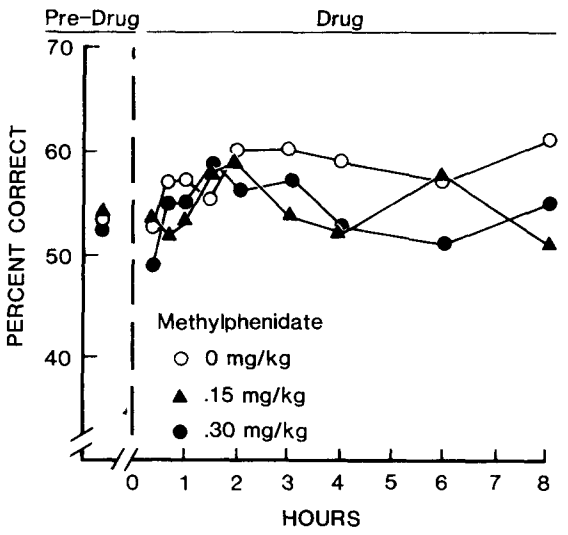

FIG. 4. Mean percentage correct detections as a function of time since drug administration for three drug dosages (0.3, 0.15, 0 mg/kg).

Figure 3 displays a significantly negative effect of methylphenidate on changeover rate on treated subjects vs. controls, $F(2,12)=5.829$, $p<0.025$. There was also a significant effect across trials, $F(9,108)=6.479$, $p<0.001$, but no significant interaction effects, although changeover rates of the 0.30 mg/kg appear to be higher in the early games. The failure of the interaction effects to be statistically significant may have been due to intersubject variability and the small N per group used for analysis. As in Fig. 2, it appears that subjects experimented with different strategies in early games and then settled on a strategy on the last four trials.

Effect of Methylphenidate on Percentage Correct Hits

As can be seen in Fig. 4, there were significant differences for percentage correct detections across time, $F(9,108)=2.02$, $p<0.05$. A Newman-Keuls post hoc comparison of mean differences across the different time points indicated that the mean number of correct detections at 90 minutes and 120 minutes were both significantly higher than at 20 minutes. There was no significant interaction found for correct detections between drug level groups (0.3 mg/kg, 0.15 mg/kg, or none) and time (repeated measurements from baseline to 480 minutes after drug administration), $F(18,108)=1.04$. Nor was there a significant main effect for the drug level groups, $F(9,108)=0.67$ although the no-drug group score was consistently higher than the other two. Rank order correlation between mean changeover rate and percentage correct hits was 0.68 ($p<0.01$), and mean changeover rate and matching index was 0.50 ($p<0.05$). Between mean matching index and percentage correct hits it was 0.11 (N.S.).

Relation Between the Peak Matching Performance and Peak Concentration Time of the Drug

Visual comparison of individual curves revealed that the Matching Index and pharmacokinetic curves for each subject were not closely related. The slopes of the behavioral curves were not as unimodal and bitonic as were the pharmacokinetic curves. The latencies to maximal effect were also not significantly related, a result similar to that found by Brown *et al.* [6] studying amphetamine effects on behavior. The statistical approach chosen for analyzing this result was the "growth curve model approach" [15,16] which is a special case of repeated measurements design. (We are grateful to Dr. Dana Quade of the Department of Biostatistics, the University of North Carolina for suggesting this analysis.) The basic plan is to reduce the data of each subject to a minimum number of summary statistics and then perform a statistical test. Therefore, the current analysis compared only the latency until peak level for behavioral performance and plasma concentration. For 7 of the subjects the matching index peak was at or before the maximal serum concentration and for 3 subjects the opposite was the case. Using a simple sign test [23], the ratio was 7 to 3 and one-sided $p=0.16$, which is not significant.

DISCUSSION

Methylphenidate may have a dissociative effect on criterion performance versus performance efficiency. In the present experiment, MPH had a significant negative effect on changeover rate and matching proportion of hits to the proportion to time allocated to the signal schedule chosen by the subject (green or red sector). The drug failed to achieve a significant effect on percent correct hits, although the dose effects were in a direction consistent with the matching and changeover rate data. The reason for this result is reflected by the fact that changeover rates correlated significantly with both matching and percentage correct hits, but matching did not correlate highly with percentage correct hits. In the present study, the parameters of the task were set deliberately at a very high difficulty level, so that the percentage correct data probably reflect a ceiling effect. Consequently, the changeover rate and matching were the response measures most affected by MPH. The present task is particularly interesting because it simultaneously involves at least three levels of cognitive function: (1) vigilance involving signal detection under time pressure, (2) simple decision making, i.e., changeover from red to green sector, and (3) a matching strategy, i.e., biased scanning to maximize signals detected. Each of these functions is separable by parametrically manipulating key variables related to each level. Vigilance can be manipulated by changing signal frequency, regularity, duration of the limited hold upon signal presentation, etc; changeover rate can be manipulated by varying the duration of the changeover delay; and matching can be manipulated by changing disparity and schedule of signal presentation of the two concurrent signal schedules. There is a wealth of human and animal operant literature [5, 13, 21] which we intend to exploit in future research with this task.

Sprague and Sleator [25] also noted a dissociative effect as a function of dosage of methylphenidate on quite different measures. At 0.3 mg/kg of methylphenidate, children's performance on a complex memory task, i.e., a delayed matching-to-sample test, was significantly better than with placebo or 1.0 mg/kg. Conversely, their Conners Teachers' Questionnaire scores were significantly lower at 1.0 mg/kg than at 0.3 mg/kg or placebo. The deterioration in matching performance of the adults at 0.3 mg/kg in the present experiment may have been comparable to Sprague and Sleator's [25] children given 1.0 mg/kg. Most of the subjects, when questioned after the present experiment, reported a generally negative subjective effect of the drug. Typical comments included: "felt as if I were getting drunk," "had to work harder to concentrate on the task," "had difficulty remem-

bering," "felt less concerned about doing well." Some slurred their words and showed a mild difficulty in completing a sentence to convey a point they wanted to make.

Most of the laboratory tasks which have yielded a favorable response to methylphenidate involve sustained attention to a boring task, e.g., paired associate learning or delayed matching to sample. The Telekinesis Star Wars task is not primarily a memory task or a sustained attention task like the CPT, but a problem-solving task where the subject tries to find the best strategy to optimize his performance. Methylphenidate had a negative effect on this type of behavior. This raises the possibility that different cognitive tasks, which may be mediated by different CNS substrates, may show a systematically different response to methylphenidate. Until recently, most of the available research in this area failed to capitalize on the voluminous behavioral research on these tasks which could yield a finer-grained analysis of their responsiveness to drugs and the inferred neuropharmacological or CNS processes. Parametric manipulation of the variables that affect these different processes may provide clues as to which of them is affected more with a drug-like methylphenidate [2]. For instance, in the delayed matching-to-sample task, examining the parametric effects of stimulus complexity, response delay, task difficulty, or information redundancy, would tell us more about the nature of the cognitive effects of methylphenidate than would comparison of the dose response on two different measures whose correlation is unknown.

The presently measured cognitive behavioral response to methylphenidate was, at best, poorly correlated to pharmacokinetic response. Even the maximal concentration was not significantly related to the maximal behavioral response. Therefore, it appears that a great deal more research on the variables which affect the pharmacokinetic curve of methylphenidate will be required before peak concentration time of different serum levels or half-lives can be extrapolated to predict a behavioral response to the drug reliably [12].

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