

EFFECTS OF METHYLPHENIDATE (RITALIN) ON PAIRED-ASSOCIATE LEARNING AND PORTEUS MAZE PERFORMANCE IN EMOTIONALLY DISTURBED CHILDREN^{1, 2}

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The stimulant drug methylphenidate was administered in a double-blind, placebo controlled study over a 10-day period to 81 children in 2 institutions. The children were deprived or emotionally disturbed, but none was known to be psychotic, brain damaged, or mentally retarded. Following tests, it was found that 2 children's anxiety scales and an impulsivity scale were unrelated to learning, and individual differences on these scales did not appear to be related to improvement on the drug. There was some indication that the greatest improvement on the mazes occurred for the children with lowest IQ. The results were interpreted as reflecting increased delay of impulsive discharge. Further research on the role of attention mechanisms in response to this drug is suggested.

Central nervous system stimulating drugs have been shown to have a beneficial clinical effect on children with behavior disorders (Bradley, 1950; Bradley & Bowen, 1941; Eisenberg, Lachman, Molling, Lockner, Mizelle, & Conners, 1963; Pasamanick, 1951). Recent clinical reports of uncontrolled studies of one such drug, methylphenidate, have indicated promising benefits for similar problems (Knobel, Wolman, & Mason, 1959; Knobel & Lytton, 1958). An unpublished study from our clinic indicates that methylphenidate may also diminish the overactivity of brain damaged children of low intelligence (Whitehouse, Conners, Molling, & Eisenberg, unpublished manuscript). Relatively little seems to be known about the specific behavioral effects of this drug, however, and a careful examination of existing positive

reports in the literature shows a lack of adequate controls, small numbers of cases, and a lack of objective measures of improvement.

In one of the few controlled studies that uses objective indices of clinical improvement, Robin and Wiseberg (1958) found that methylphenidate had no effects on depressed adult patients compared with matched controls who received placebo. Tedeschi and Vella (1957) reported improved attention in adult neurotics compared with normal controls. A carefully designed study with adults by Froelich and Heckel (1962) led to the conclusion that the drug had few noticeable effects on learning, though it produced a slight delay of initial learning and a slight facilitation of recall.

It is known that methylphenidate facilitates reconditioning, decreases simple reaction time (Schneider & Costiloe, 1957; Schneider, 1960), and increases verbal facility (Gottschalk, 1960). Physiological studies on animals indicate that methylphenidate has antihypertensive effects (unlike amphetamine), which are probably centrally mediated (Maxwell, Plummer, Ross, & Daniel, 1958), and it may have some depressive action on limbic structures similar to that of the barbiturates (Sigg & Schneider, 1957). Davis (1957) found that hyperkinesia in monkeys resulting from pre-

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frontal lesions is appreciably reduced by methylphenidate or amphetamine. In general, this drug is thought to be primarily a central stimulating agent intermediate in effect between caffeine and amphetamine, somewhat lacking the adrenergic effects of the latter.

In some respects children with behavior disorders share important common features with the brain damaged child. Not only do such children have a high incidence of EEG abnormality (Pasamanick, 1951), but they also frequently have the labile emotional characteristics and hyperkinetic behavior of the organic child. These children function as though they lacked central cortical inhibitory capacity over their internal drives and the external stimuli impinging upon them. It seems plausible to assume that the clinical improvement in such children when given central stimulants results from some form of heightened cortical activity. Such an increase in central functioning should result in a greater ability to attend to relevant task dimensions, to inhibit irrelevant stimuli, and to inhibit impulsive responding. In the present study learning tasks and the Porteus mazes are employed, since learning should be improved under conditions which heighten attention and because the mazes demand careful planning and inhibiting of impulsive responding. Whereas the rapid serial learning tasks are experimenter-paced and place a demand on the subject's ability to respond quickly and accurately, the mazes are paced only by the subject who is penalized mainly for poor planning and impulsive response. Conceivably, a drug which simply energized the total organism might aid a subject on tasks requiring quick, accurate response, but not on a task which requires inhibition of response.

Intelligence is an important factor in both learning and maze performance. Although little is known about the relation between intelligence and drug response, it is of interest to determine if intellectual level interacts in some way with drug treatment. Although no specific predictions were made in this study regarding intelligence, it seemed plausible to assume that the drug would be of greatest benefit to those most impaired on

TABLE 1
CHARACTERISTICS OF THE SAMPLE

	Group A Foster children	Group B Emotionally disturbed
<i>N</i>	43	38
Age		
<i>M</i>	12.4	11.3
<i>SD</i>	1.74	1.74
Range	7-15	8-14
IQ		
<i>M</i>	84.8	88.6
<i>SD</i>	12.3	13.3
Range	65-123	65-135
Males	23	30
Females	20	8

the tasks studied here, namely, among those of low IQ. Other individual difference factors such as degree of impulsivity and anxiety are also explored in this study, as both factors seem likely to affect learning and maze performance.

METHOD

Subjects

The total population of two institutions for residential treatment ($N = 81$) was included in the study. One institution (A) is a center for children awaiting foster placement in permanent homes. These children are wards of the city who are awaiting their first foster home or who have failed to adjust in previous foster homes. In general they are a deprived group who come from disrupted and broken homes where parents have frequently died, deserted, or failed to provide minimal care. Other studies suggest that a high proportion of these children have serious problems of emotional adjustment (Eisenberg, 1962). The other institution (B) is a residential psychiatric treatment center for emotionally disturbed children. None of these children is diagnosed as psychotic, mentally retarded or brain damaged, but they are likely to be somewhat more disturbed than those from Institution A (Group A). Most are diagnosed as aggressive behavior disorders or adjustment reactions of childhood. The characteristics of the total sample are given in Table 1.

Structuring the Study

Previous experience with drug administration in an institutional setting has shown the importance of the expectations and attitudes of subjects for the

outcome of drug treatment (Molling, Lockner, Sauls, & Eisenberg, 1962). Despite careful attempts to keep the expectations of the subjects in this study as neutral as possible, it soon became apparent that specific effects were anticipated by many of the subjects. The children referred to the pills as "smart pills" and assumed the pills would also make them calmer and happier. Postexperimental questions confirmed that a large proportion of the children held such expectations. Enthusiasm for the drug was high throughout both institutions, and the motivation of the children was enhanced by the promise of a small gift at the end of the two testing periods. (After completing the various tests, both before and at the end of the drug period, the children received a choice from an array of prizes such as wallets, flashlights, purses, etc.). However, it was made clear that receiving a prize was not contingent upon quality of performance.

Predrug Measures

After a brief introduction to the purpose of the study and the proposed schedule, each child individually was administered two anxiety scales, an impulsivity scale, and the verbal part of the Wechsler Intelligence Scale for Children, in which the vocabulary subtest was omitted and replaced by the digit-span subtest. (The latter subtest was given in place of vocabulary for convenience and because the digit-span test could easily be repeated after drug treatment.) The two anxiety scales were the Children's Manifest Anxiety Scale (CMAS) and the General Anxiety Scale for Children (GASC). These were read to the children by the experimenter and, except for occasional rephrasing, were the same as in the original publications (Castaneda, McCandless, & Palermo, 1956; Sarason, Davidson, Lighthall, Waite, & Ruebush, 1960). The impulsivity scale has been validated by Sutton-Smith and Rosenberg (1959) and in most cases was also rephrased and read to the children where necessary because of the child's reading difficulties.

The learning task consisted of pairs of digits and symbols to be learned by the anticipation method. The items were taken from the WISC digit-symbol subtest and were presented automatically by a slide projector for 4 seconds each, with an interitem time of 1 second. The symbol was presented first and subjects had to learn to anticipate the correct number before the number appeared together with the symbol. In the practice period the subjects were instructed to watch the items closely, without responding for one complete trial (i.e., until eight pairs of items had been presented), and then on the first experimental trial to call out the number that belonged to the symbol. The procedure was continued until one perfect trial was attained or for a maximum of 15 trials. There was approximately a 3-second interval following the fourth trial while the projector was reset to the beginning of the sequence. There were four different random

orders of item pairs to minimize serial position effects.

After all the children had completed preliminary testing, the IQ distribution was divided into three groups, with half of each of these groups randomly assigned to receive the active drug or the matched placebo. The mean age for the drug and placebo groups thus formed was 11.92 and 11.88, respectively; the mean IQ for the groups was 87.51 and 85.86, respectively. Both differences were nonsignificant. The two sexes, age, race, and two residences were approximately evenly distributed at all three levels of IQ for the drug and placebo groups.

The medication code was not broken by the experimenters until the end of the experiment. The cottage parents and nurses were instructed to give each child his medication immediately after breakfast and after lunch for 10 days. The dosage started at 20 milligrams per day, and was gradually increased to 60 milligrams per day; this level was maintained for the last 5 days. The placebo group received matched capsules which were increased at the same rate as in the drug group.

Postdrug Measures

After 10 days of drug treatment, an alternate form of the digit-symbol paired-associate learning test was administered in the same manner as the pretest. Following this, another paired-associate task was given in which the pairs were two digits and a letter of the alphabet. This latter test was presented on a standard Gerbrands memory drum, with the presentation time of 3 seconds and interitem time of 1 second. Unlike the digit symbol, the eight items of the letter digits were presented in the same serial order for each trial. The criterion was one perfect trial or a maximum of 15 trials. The tape of the memory drum was long enough to accommodate only 4 trials so that following every fourth trial there was a 10-second rest interval. At the same time that a subject was learning the letter digits his hands were resting on a Luria-type tremorograph apparatus and he was instructed to press with the right hand when he gave his oral response. (This procedure, which will be detailed elsewhere, probably had the effect of making the learning task somewhat more difficult than it would otherwise have been.)

The Vineland Revision of the Porteus mazes was given according to the method described in the Stoelting and Company manual. Following this test the digit-span subtest from the WISC was readministered and a brief interview was given regarding the side effects of the drug. The children then received another prize and were excused from the study.³

³ Behavior ratings were made by cottage parents and staff members before and at the end of the study. The results of the clinical measures, side effects, and tremorograph responses will be reported in detail elsewhere.

RESULTS

Learning Tasks

Digit Symbol. For purposes of analysis, the learning trials are divided into five blocks of three trials each. The three levels of IQ, two drug treatments (active or placebo), and five blocks of trials are analyzed in a Lindquist Type III design (Lindquist, 1953, p. 281) in which the treatments, IQ, and treatments \times IQ interaction are between-subjects effects, and the trials and other interactions are within-subjects effects. In addition, in order to equate the groups for any initial differences in learning, the pretest error scores are used as a control measure in an analysis of covariance design. The analysis is limited to subjects who completed both a pretest and a posttest digit-symbol task, with 24 subjects at each of the three levels of IQ. Three subjects from the original drug group and four from the placebo group were randomly excluded in order to keep equal numbers in the six cells of the 3×2 blocks. Inspection of various criteria showed both sets of excluded subjects to be representative of the group from which they came and to be identical on the pretest measures. The results of the analysis are shown in Table 2. It is apparent that there is little drug effect on error scores, though there is a trend for the

TABLE 2
ANALYSIS OF COVARIANCE FOR DIGIT-SYMBOL
PAIRED-ASSOCIATE LEARNING TASK

Source	Adjusted <i>MS</i>	<i>df</i>	<i>F</i>
Between subjects		(70)	
Drugs (D)	4.16	1	<1
IQ	19.69	2	<1
Drugs \times IQ	96.44	2	2.24*
Error (between)	42.96	65	
Within subjects		(287)	
Trials (T)	340.72	4	56.07***
Drugs \times Trials	.59	4	<1
IQ \times Trials	4.67	8	<1
D \times IQ \times T	6.69	8	1.10
Error (within)	6.08	263	
Total		357	

* $p < .20$.*** $p < .001$.

TABLE 3

ANALYSIS OF COVARIANCE ON DIGIT-SYMBOL ERROR
SCORES WHEN INSTITUTIONS A AND B ARE COMPARED

Source	Adjusted <i>MS</i>	<i>df</i>	<i>F</i>
Between subjects		(66)	
Drugs (D)	19.81	1	<1
Residence (A or B)	56.33	1	1.08
Drug \times Residence	51.14	1	<1
Error (between)	52.20	63	
Within subjects		(271)	
Trials (T)	318.47	4	
T \times D	2.22	4	<1
T \times R	6.75	4	1.15
T \times D \times R	14.22	4	2.43**
Error (within)	5.86	255	
Total		337	

** $p < .05$.

drug to interact with levels of IQ ($p < .20$). The plot of the learning curves showed that the mean errors for the drug group are lower at every trial.

Because the two groups of subjects, A and B, might be reacting somewhat differently to the drug and obscuring an overall drug effect, and because it was thought that the more disturbed children from Institution B (Group B) might be likely to profit most from the drug, a separate analysis of covariance was performed using Groups A and B as separate between-subjects effects, ignoring levels of IQ. The results are shown in Table 3 and Figure 1. Apart from the highly significant trials effect (which merely indicates that learning took place for all groups), the triple interaction effect is significant ($p < .05$). Examination of the means in Figure 1 shows that the effect is largely determined by the better performance of the drug treated children of Group B, especially in the last block of trials. The drug has apparently reduced the errors of the more disturbed children near the end of the period of learning.

Another learning measure of interest concerns the extent of "oscillation" or variability of learning from item to item in successive trials. A subject will frequently make a correct anticipation of a pair in one trial, only to fail in the next. Difference scores were

obtained for each subject by subtracting his pretest from his posttest oscillation score. The difference between drug and placebo groups for these scores approaches significance, with the drug group tending to show an *increase* in oscillations ($t = 1.70$, $p < .10$, $df = 74$). Since the drug group shows a decrease in errors, and since errors are positively correlated with oscillations ($r = +.67$), the results suggest that the drug may be causing a subject to be more variable on his way to more efficient final performance.

Digit-Letter. An analysis of covariance was performed on the error scores using the pretest of the digit symbol as a control variable to reduce any initial differences between drug and placebo groups (as well as to reduce individual variation). Levels of IQ are not included in the analysis since several subjects were lost due to equipment failure and balancing such a design would lose several more subjects. For this reason only 64 subjects are included in the analysis of Table 4, with 32 subjects in the drug and 32 in the placebo group. It is apparent that there is no difference between the drug and placebo groups, though the means are again in the

TABLE 4
ANALYSIS OF COVARIANCE FOR DIGIT-LETTER PAIRED-ASSOCIATE LEARNING USING DIGIT-SYMBOL ERROR SCORES AS A CONTROL VARIABLE

Source	Adjusted <i>MS</i>	<i>df</i>	<i>F</i>
Between subjects		(62)	
Drugs	195.07	1	1.90*
Error (between)	102.69	61	
Within subjects		(255)	
Trials	380.02	4	53.76***
Drugs \times Trials	5.26	4	<1
Error (within)	7.07	247	
Total		317	

* $p < .20$.
*** $p < .0001$.

predicted direction (Figure 2). There is some indication that the drug group has learned slightly more by the final trial, though the difference does not reach statistical significance ($t = 1.95$, $p < .10$, $df = 62$). Figure 2 also indicates that the relative superiority of the more disturbed of the drug treated children (Group B) that occurred in the final block of trials for the digit-symbol learning

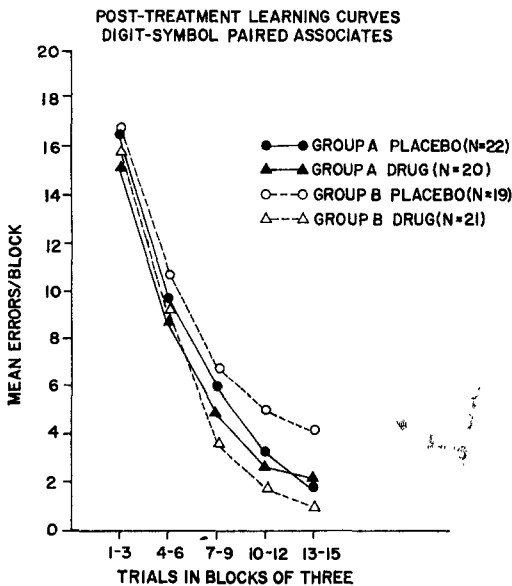


FIG. 1. Post treatment learning curves for digit-symbol paired associates for Institutions A and B on drug or placebo.

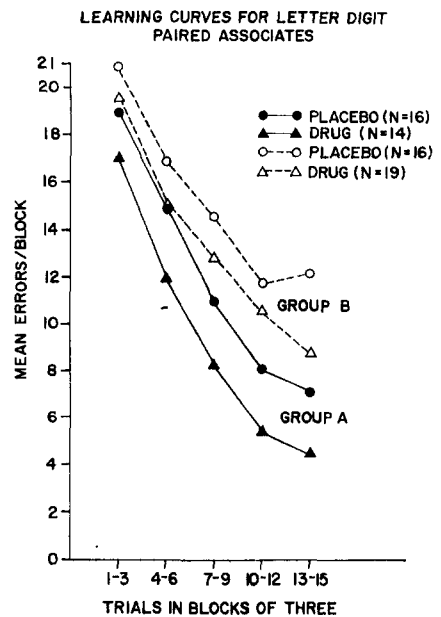


FIG. 2. Learning curves for letter-digit paired associates for Institutions A and B on drug or placebo.

test does not hold up for the digit-letter test. Analysis of variance confirmed the fact that Group A and Group B do not differ for the drug effect, though Group A appeared to have an overall superiority of learning in both drug and placebo groups on the digit-letter task. This latter effect may be due to the faster rate of presentation and the apparently greater difficulty of this test as compared with the digit-symbol learning test, which would presumably make it relatively more difficult for the more disturbed children.

Since the digit-letter task contained items presented in the same serial order from trial, it is possible to examine the shape of the serial learning curves for drug effects. However, an analysis of the number of errors at each serial position showed no differences between groups and there were no significant differences in the number of oscillations at different positions.

In summary, there appears to be little support for the prediction that methylphenidate improves paired-associate learning. On the digit symbol version, it is true that significantly greater learning occurs in the drug treated group among the more disturbed children, as evidenced by the significant triple interaction between trials, groups, and treatments. However, the failure of this result to appear in the digit-letter task weakens the force of such a finding. The hint in the digit-letter task that the drug group shows some superiority by the final trial of learning suggests that future studies might profit by using a more extended period of learning than was used here, as well as a greater range of drug dosage—both of which might sharpen the differences between drug and placebo groups.

Porteus Mazes

The test quotients on the mazes were analyzed by analysis of variance, which gave an overall F of 5.34 ($p < .025$) for drug treatments, and a significant IQ effect ($F = 6.33$, $p < .01$). The drug group therefore appears to be superior to the placebo group, but since no pretest maze scores were available, the results cannot be considered unequivocal. However, examination of initial

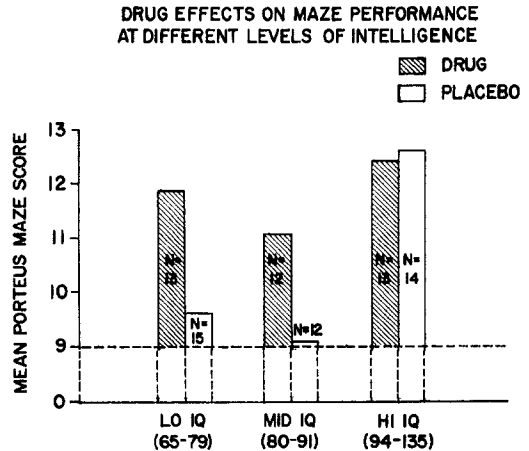


Fig. 3. Drug effects on Porteus maze performance at different levels of intelligence.

symptoms, error scores on learning, and other variables measured in the pretest showed no other differences between the two groups which might account for the obtained effects.

The effects of the drug on maze performance for the three levels of IQ are shown graphically in Figure 3, which indicates a trend for the lower IQ subjects to obtain the most benefit from the drug. The lowest IQ group shows the largest difference ($t = 2.13$, $p < .05$), while the middle IQ group is slightly less significant ($t = 1.70$, $p < .10$). These differences between IQ levels warrant further investigation, although the present findings must be interpreted with caution inasmuch as the overall IQ \times Treatments interaction effect is not significant in the analysis of variance. Comparisons between the two institutions revealed that both showed approximately the same degree of differences between treatments on the mazes.

Anxiety and Impulsivity Measures

In a preliminary attempt to examine individual difference factors which might be important in drug response, subjects above and below the median on the anxiety and impulsivity measures were compared with the various criteria of improvement described above. None of the scales showed any relationship with improvement. Interestingly, the scales bore no relationship to ease of learning,

despite the fact that such anxiety scales are known to be related to paired-associate learning among normal children (Sarason et al., 1960). It is possible that the high level of anxiety in the present population makes it difficult to discover such effects.

According to McCandless, the verbal administration of the anxiety scales may also decrease their validity, as indicated by higher lie scores (personal communication). The correlations of the combined anxiety scales with digit-symbol and digit-letter error scores were only .17 and $-.06$, respectively. The two scales showed a moderate inter-correlation with each other ($r = .65$, $N = 81$), indicating that approximately 40% of the variance of the two scales is held in common. Considering the separate reliabilities of these scales, this would appear to be satisfactory evidence that they are measuring similar anxiety factors. Interestingly, however, the CMAS is also significantly correlated with the Impulsivity scale ($r = .31$, $N = 81$), while the GASC shows a nonsignificant negative relationship ($r = -.10$).

Digit Span. An analysis of the difference scores for the pre- and posttest digit span scores showed no differences between drug and placebo groups. The fact that IQ was unrelated to digit span scores suggests that these scores may have been too unreliable to reflect any drug effects, since the test normally correlates moderately well with other Wechsler subtests. The unreliability may be due to the highly variable performance of the emotionally disturbed sample of this study.

DISCUSSION

The results of this study support the assumption that methylphenidate has a mild beneficial effect on maze performance in emotionally disturbed children, but do not indicate any significant effects on rote learning. The findings are thus partially consistent with clinical reports of the ability of this drug to increase calmness in disturbed children (Knobel et al., 1959), and give further objective support to several clinical and behavioral studies which indicate that the drug has a positive effect on certain kinds

of performance. Tedeschi and Vella (1957) have reported more direct evidence on the heightening of attention with this drug among adult neurotics, and proposed that a general inhibiting ability over disturbed ego functions may result from its use. Similarly, Knobel et al. (1957) have suggested that methylphenidate acts by providing greater behavioral control for children with "immature central nervous system development." In previous studies from our clinic (Eisenberg et al., 1963; Whitehouse et al., unpublished manuscript), stimulant drugs have been useful for children specifically characterized by their inability to delay impulsive discharge, namely, for delinquents and brain damaged children.

The mechanism of action of methylphenidate is still not known. However, except for the absence of strong adrenergic effects, it appears to function at a behavioral level in the same way as the amphetamines, to which it is chemically related. It is of interest that Helper, Wilcott, and Garfield (1963) found that both serial learning tasks and Porteus maze performance were worsened by chlorpromazine. They noted that the Porteus test quotients appeared to have some common factor with paired-associate learning, and concluded that the deficit on these tasks obtained with chlorpromazine treatment of children was possibly because "... chlorpromazine impairs the maintenance of active attention to novel and significant details." The findings of some *improvement* on these tasks in the present study suggests the possibility that the same functions being depressed by chlorpromazine are being activated by methylphenidate. These behavioral findings are in keeping with the fact that the amphetamines and chlorpromazine have reciprocally antagonistic effects on EEG and behavior, possibly because of opposite effects on the reticular system (Elkes, 1958). However, inferences about locus of drug action from behavioral studies alone are generally precluded by multiplicity of sites of action within the nervous system (Dews, 1962).

The rote learning tasks used in the present study do not give unequivocal support to the notion that sustained attention in an

experimenter-paced task has been improved. Only for the more disturbed group of children, and only on the digit-symbol task, was there some evidence that the treatment had an effect on learning. The possible effects of drug dosage, rate of presentation of the items to be learned, and differences between institutions in this study precludes any final judgment as to the efficacy of methylphenidate to affect sustained attention. One of the problems in the present study is that a rather heterogeneous group of disturbed children (of necessity) was included in the design. It is possible that, if the drug reduces distractibility, it would appear primarily in those subjects whose learning ability is grossly affected by this factor, but not necessarily in subjects for whom distractibility is not a major problem.

Further studies in which attention factors are specifically studied with methylphenidate would seem to be useful, particularly in the brain damaged child or the child of low IQ who is a behavior problem as well. In this connection, the filter theory of Broadbent (1958) provides a model that could prove useful in the design of further experiments to test the functions being affected in the sequence of information processing, especially since it appears to be precisely at the level of filtering that this drug is operating. It should be feasible to employ some of the experiments described by Broadbent and others (e.g., Bahrick & Shelley, 1958), in which amounts of distracting information are varied while the subject performs another, simultaneous task. Increased selectivity of a filter mechanism due to drug effects might be expected to appear as a greater ability to process information when irrelevant information is simultaneously presented. The ability of the filter mechanism to shift rapidly from one task to another could also be studied by the simultaneous task method. In this manner a more unequivocal test of the notions suggested by our present findings could be made.

It should be noted that other than strictly pharmacological effects might be operating in this and similar studies of performance. Schachter and Singer (1962) have shown that

motivational and cognitive factors are highly important in some drug response. Applying the logic of Schachter's experiments in this study, one might argue that the known initial positive expectations of our subjects, plus their strong desire to reward the experimenters with a good performance, can entirely account for the kinds of improvement shown by the drug treated subjects. If the drug subjects perceive a physiological arousal effect, and conclude that something *is* happening to them, then they may be more motivated to perform well on the various tasks (since expectations of improved learning were clearly salient during the experiment). Perhaps the subjects most motivated to improve their learning because of past trouble in that area, namely the subjects of low IQ, would also be those most eager to perform well on the tests. While such an explanation is speculative and entirely post hoc, it should not be ruled out without further study. Drug enthusiasts are likely to be only too willing to attribute obtained effects to pharmacology when the effects might be due to basic demand properties of the experiment.

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