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Assessment of Drug State Dimensionality via Drug-Drug Training and Stimulus Generalization Testing

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GOUVIER, W. D., F. R. AKINS AND M. A. TRAPOLD. *Assessment of drug state dimensionality via drug-drug training and stimulus generalization testing.* PHARMACOL BIOCHEM BEHAV 21(5) 687–693, 1984.—A procedure for determining whether different drugs share a common stimulus dimension is described. This procedure uses the presence of post-discrimination generalization gradient asymmetry as an indication that the training stimuli lay along a common stimulus dimension. Separate groups of hungry pigeons were trained to discriminate a 15 mg/kg dose of phenobarbital which was associated with frequent food reinforcement (S+) from each of 9 different drug conditions which were associated with infrequent reinforcement (S−). S− stimuli were selected to represent a drug from a completely different class (amphetamine), a drug with biphasic effects which may partially correspond with the effects of phenobarbital (Δ^9-THC), and a drug from the same class as the S+ (pentobarbital). Following discrimination training subjects were tested for generalization to five dosage levels (5, 10, 15, 20, 25 mg/kg) of phenobarbital. Steep symmetrical generalization gradients around the S+ indicated that Δ^9-THC and d-1-amphetamine were both quite discriminable from phenobarbital, and that they were perceived by subjects as representing stimulus dimensions different from phenobarbital. Shallower and asymmetrical gradients indicated that pentobarbital was less discriminable from phenobarbital, and that it was perceived as lying on a stimulus dimension common to phenobarbital. This procedure may allow better understanding of how different drug states are perceived by animals as similar or dissimilar.

Drugs Interoceptive stimuli Exteroceptive stimuli Stimulus dimensions Pigeon Keypeck Generalization Peakshift

DRUGS can serve as stimulus events to cue on animal's behavior. Overton has suggested that drug induced stimuli are organized along dimensions in a manner analogus to external sensory stimuli [16]. Many learning phenomena that have been widely studied using external sensory stimuli [13,14] can be demonstrated using drug induced stimulus cues. These phenomena include stimulus generalization [8,19], learning set [16], discrimination reversals [8], and the peak shift [1].

Following Drug-No-Drug (DND) discrimination training in which a drug stimulus signals one response, and its absence signals another, it is possible to test the animals with doses of a novel drug to determine whether drug appropriate or saline appropriate responding is elicited, thus providing a means of estimating the similarity of the novel drug to the training drug [2]. Unfortunately, the elicitation of drug appropriate responses using this test procedure merely allows one to conclude that the novel drug is perceived by the subject as more like the training drug than like the vehicle alone.

Recognizing the limitations of DND procedures, Overton has described the advantages of Drug-Drug discrimination training (DD) as a more effective means of assessing drug state similarities [17]. If a subject is unable to learn to discriminate between certain doses of two different drugs, this would provide more convincing evidence of drug state similarity than would results of DND testing procedures. Even

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so, however, one can only infer that the two drug states are similar in some way. One still cannot conclude (with any certainty) that the two drugs lie along a common stimulus dimension.

The phenomena of stimulus generalization and the peak shift can be used to determine whether two stimuli lie along the same or different stimulus dimensions. Using drug stimuli, stimulus generalization is demonstrated by a change in shape of the dose-response curve that occurs after a particular dose has been differentially associated with reinforcement. Thus, prior to differential reinforcement, one might expect to see a relatively flat dose response curve (stimulus generalization gradient) over a restricted range of doses, but following differential reinforcement to one particular dose of the drugs, as in the case in DND training, the gradient shape might be expected to be roughly symmetrical with a peak at the training dose [6,8]. The shape of the stimulus generalization gradient often changes when an animal receives training that exposes it to greater reinforcement in the presence of one stimulus (S+) than another (S−). When the two training stimuli come from different dimensions (as in DD training involving two drug classes), symmetrical gradients along the S+ dimension would be expected, but when the S+ and S− are from the same dimension, the shape of the post-discrimination stimulus generalization gradient would be expected to become asymmetrical, with the peak displaced past the S+ in a direction away from the S−. Furthermore, as the S+ and S− stimuli are moved closer along their common dimension, greater magnitudes of peak displacement are expected [7,13]. Thus, the presence or absense of a peak shift in post-discrimination stimulus generalization gradients could serve as a direct index of whether two drugs lie along the same or different stimulus dimensions.

The present study examines the utility of using the peak shift as a simple behavioral means of deciding whether several different drugs share a common stimulus dimension. In particular, it examines the form of generalization gradients along the phenobarbital dosage dimension following discrimination training with S+ as 15 mg/kg phenobarbital, and S− as (1) one of several dosages of pentobarbital, or (2) one of several dosages of Δ^9-THC, or (3) one of several dosages of d-1-amphetamine. Previous research has suggested that phenobarbital and pentobarbital share at least one common dimension [15] and hence would be expected to produce a peak shift. On the other hand, generalization between phenobarbital and both d-1-amphetamine and Δ^9-THC has been shown to be minimal, suggesting that they may share no common dimensions [3, 4, 15], but given the biphasic (exitatory/sedative) action of Δ^9-THC [12], some degree of commonality between phenobarbital and Δ^9-THC might be expected.

METHOD

Subjects

The subjects were 40 experimentally naive adult White King pigeons. Each was maintained at 70 to 75% of its free feeding weight.

Apparatus

Four single-key pigeon operant conditioning chambers and automatic programming and recording equipment were used. Each ventilated and sound attenuated chamber was equipped with a houselight and a response key illuminated at a wavelength of 555 nanometers. A retractable grain hopper was located directly beneath the response key.

Drugs and Dosage Levels

Sodium phenobarbital was dissolved in isotonic saline to produce 5 dosage concentrations of 5, 10, 15, 20, and 25 mg/ml. Sodium pentobarbital in doses of 3, 5, and 7 mg/ml and d-1-amphetamine in doses of 0.25, 0.50, and 0.75 mg/kg were also prepared with this vehicle. Delta ^{9}-THC was prepared in a vehicle of 96% isotonic saline and 4% Tween-80 surfactant to yield concentrations of 0.025, 0.050, and 0.075 mg/ml. Drug doses were chosen on a basis of existing data to span a range from near-threshold to readily discriminable from the non-drugged state. Injection volume was held constant at 1 ml/kg of body weight. Intramuscular (IM) injections of THC were given 2 hours before training, all other drugs were administered IM 30 min prior to training. The site of injection varied randomly from rostral to caudal and distal to proximal along the breast bone ridge of either side.

The 15 mg/kg dosage of phenobarbital was used as the S+ for each of the 10 groups of four birds. Three groups received discrimination training between this S+ and one of three S− doses of d-1-amphetamine, 0.25, 0.50, or 0.75 mg/kg. A second set of three groups was trained to discriminate between the S+ and THC doses of 0.025, 0.050, or 0.075 mg/kg as the S−. A third set of three groups learned to discriminate between the S+ and pentobarbital doses of 3, 5, and 7 mg/kg. A tenth group received the 15 mg/kg phenobarbital dosage on both S+ and S− training days.

Procedure

Table 1 summarizes the specific tasks each group completed during each of the 6 phases of the experiment. Phase 1 (preliminary training) involved magazine training and keypeck shaping with an illuminated response key. After initial keypeck shaping, subjects were allowed to earn 50 continuous reinforcements (allowing 3 sec access to grain for each reinforcement) for 3 consecutive days, followed by a 15 min training session on a variable interval 15 sec (VI-15″) schedule on Day 4 ad a 30 min session on a VI-30″ schedule on Day 5.

Phase 2 (non-drug baseline) began on Day 6. All subjects received daily one-hour training sessions with a VI-1 minute (VI-1′) schedule in effect. Training continued until subjects had received a minimum of 20 days of training and had met the response stability criterion of at least 5 consecutive days with no more than a 5% range of variation of daily response rate.

Phase 3 (drug baseline) continued the training conditions of Phase 2, with the addition of daily 15 mg/kg injections of phenobarbital prior to each training session. This phase lasted a minimum of 20 days and until subjects met the stability criterion again.

Phase 4 (prediscrimination generalization testing) assessed each subject's generalization of keypecking to 5 doses of phenobarbital, 5, 10, 15, 20, and 25 mg/kg. The dosage sequence was randomly determined for each subject, and the VI-1′ schedule remained in effect during all tests. After each one-hour drug dosage test, subjects were retrained to a stability criterion of less than 5% deviation in response rate over 3 days. This sequence of Test-Retrain-Test continued until each subject had been tested with each dosage, and had attained the stability criterion after the last drug dosage test. The subjects were then advanced to Phase 5.

During Phase 5 (drug discrimination training) the training conditions on S+ days were identical to those on the drug baseline days of Phase 3. On these days subjects received the

TABLE 1

DESIGN OF THE EXPERIMENTAL PROCEDURES

	Phase 1 Preliminary Training	Phase 2 Non-Drug Baseline	Phase 3 Drug Baseline	Phase 4 Pre-Discrimination Generalization Testing	Phase 5 Discrimination Training	Phase 6 Post-Discrimination Generalization Testing
Drugs Administered	None	None	15 mg/kg Phenobarbital	Test Days: Either 5, 10, 15, 20, or 25 mg/kg Phenobarbital Retraining Days: 15 mg/kg Phenobarbital	S+ Days: 15 mg/kg Phenobarbital S− Days: Grp Drug 1. 0.25 mg/kg THC 2. 0.50 mg/kg THC 3. 0.75 mg/kg THC 4. .25 mg/kg d-Amphetamine 5. .50 mg/kg d-Amphetamine 6. .75 mg/kg d-Amphetamine 7. 3 mg/kg Pentobarbital 8. 5 mg/kg Pentobar Pentobarbital 9. 7 mg/kg Pentobarbital 10. 15 mg/kg Phenobarbital	Test Days: Either 5, 10, 15, 20, or 25 mg/kg Phenobarbital Retraining Days: S+ and S− Training doses
Regime	Magazine and key peck training	Continuation of key peck training	Continuation of key peck training	Test Day 1 followed by retraining to 3 day responses stability criterion; test day training to 3 day response stability criterion; test day 3, etc.	Alternation of S+ S− days according to Gellerman (1933) series	Test Day 1 followed by 10 days discrimination retraining; test day 2 followed by 10 days discrimination retraining; test day 3, etc.
S^{R+} Schedule	Gradual change from CRF to VI 60 sec	VI 60 sec	VI 60 sec	VI 60 sec	VI 60 sec	Test days: VI 60 sec S+ Days: VI 60 sec S− Days: VI 10 min
Criterion for Advancement to Next Stage	Completion of 5 training sessions	Completion of a minimum of 20 Phase 2 training days and achievement of 5 day response rate stability requirement	Completion of a minimum of 20 Phase 2 training days and achievement of 5 day response rate stability requirement	Achievement of 3 day response rate stability criterion following Test Day 5	Completion of 40 total training sessions (20 S+ sessions 20 S− sessions)	Completion of Test Day 5

15 mg/kg dose of phenobarbital followed by a 1-hour training session with the VI-1′ schedule in effect. S− days involved the injection of the drug stimulus appropriate for each group (see Table 1), followed by a one-hour session in the presence of a VI-10′ schedule of grain reinforcement. S+ and S− training days occurred equally often, according to a Gellerman series [5], and continued for 40 days for all subjects.

Phase 6 (post-discrimination generalization testing) evaluated response generalization along the phenobarbital dosage dimension. This phase began following the completion of

discrimination training, and followed a Test-Retrain-Test procedure similar to that of Phase 4, except that in this case all retraining periods were 10 sessions (5 S+ and 5 S−) long. This phase continued until each subject had received a one-hour test with each of the 5 doses of phenobarbital (5, 10, 15, 20, 25 mg/kg). The order of test dosages for each subject was determined by random assignment.

RESULTS

Phase 2, 3, and 4 (Prediscrimination Training and Testing)

All subjects learned to respond on the VI-1′ schedule. All subjects met the stability criterion of Phase 2, and their response rates did not change significantly with the introduction of the drug regime in Phase 3. In generalization testing of Phase 4, there was no tendency for the subjects to respond differentially to any of the test dosages.

Phase 5 (Discrimination Training)

Discrimination performance for each group was analyzed in four-day blocks, using a discrimination ratio (mean S+ response rate/mean S+ response rate + mean S− response rate) as the measure of performance [9]. With this measure, larger ratios indicate superior differential responding with increased responding to the S+, decreased responding to the S−, or both. Thus, as the subjects learn to respond differentially to the S+ and S− stimuli, their degree of response differentiation is reflected by the magnitude of the discrimination ratio. Perfect discrimination performance would be represented by a discrimination ratio of 1.0, while a discrimination ratio of 0.5 would indicate no response differentiation between S+ and S− conditions. The discrimination ratios of all 10 groups were analyzed by a mixed design analysis of variance followed by 0.05 level Newman Keuls tests [20]. The design included drug type (4 levels), dosage level (3 levels), and training block (10 levels).

Significant effects of drug dose, $F(3,333)=14.75$, $p<0.01$, training block, $F(9,333)=55.37$, $p<0.01$, and drug by training block interaction, $F(27,333)=5.12$, $p<0.01$, were found. Follow-up tests revealed that all groups except the control group improved in discrimination performance across training blocks and high S− dosage groups learned the discrimination more quickly than low S− dosage groups. The THC and amphetamine groups learned the discrimination more quickly than the pentobarbital groups; the discrimination ratios of the THC and amphetamine groups differed significantly from the control groups within the first training block, whereas the ratios for the pentobarbital groups did not achieve statistical significance until the third training block. The control group, who received 15 mg/kg phenobarbital injections on both S+ and S− days showed no tendency to respond differentially. This would indicate that the subjects were not using reinforcement density as a discriminative stimulus. These results are shown in Fig. 1, with the performance of the control group represented on each of the three graphs for comparison purposes.

Phase 6 (Post-Discrimination Generalization Testing)

A relative generalization gradient [10,11] for each subject was derived by expressing total responses to each test dose of phenobarbital as a percentage of that subject's total responses to all test doses of phenobarbital. These data were then subjected to an ANOVA on 3 drug types by 3 drug doses by 5 test stimuli, followed by 0.05 level Newman Keuls follow-up tests (see Table 2). Since post-discrimination gradients for the control group showed no significant tendency toward differential responding to any of the test stimuli, generalization test data from this group were not included in these analyses. Gradient symmetry was measured by subtracting the percentage of total test responses emitted to the 2 dosage levels lower than S+ from the percentage emitted to the two doses higher than S+.

Post-discrimination relative generalization gradients for all groups are presented in Fig. 2. Gradients produced by the THC and amphetamine groups were quite similar. Among these groups, the gradients were not significantly asymetrical, and the steepness of the gradients was related to the strength of the S− training dose. The high amphetamine dose

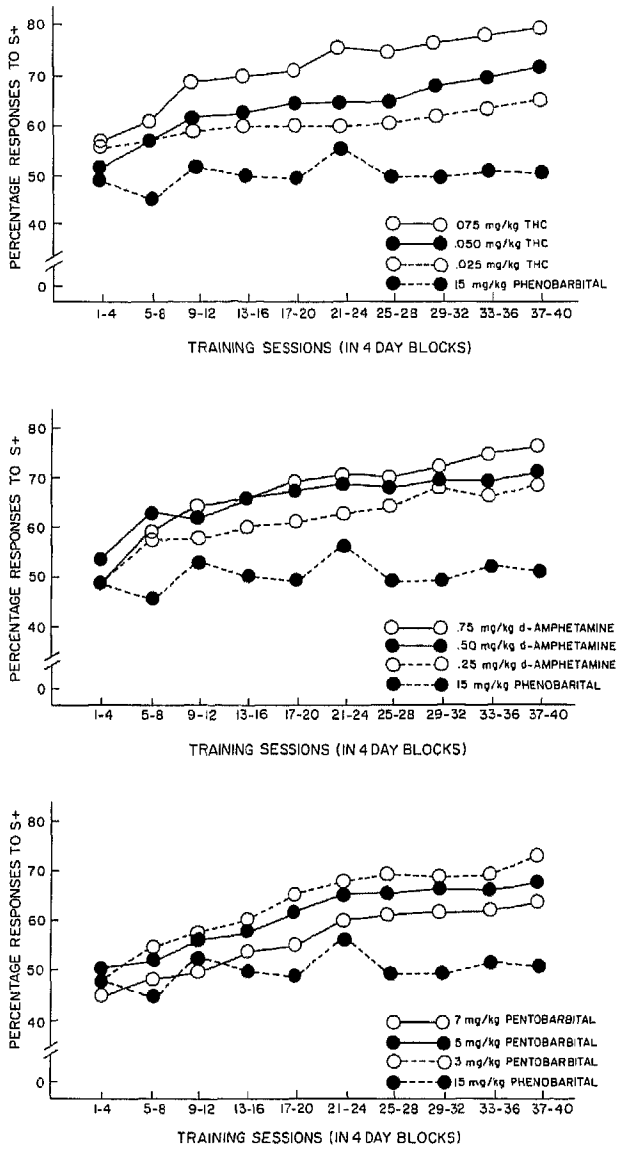

FIG. 1. Mean discrimination ratios in 4-day blocks for the experimental and control groups.

TABLE 2

ANALYSIS OF VARIANCE OF THE DIFFERENCES IN S+ CONTROL AND DIFFERENCES IN RELATIVE GRADIENT SYMMETRY

Source	SS	df	MS	F
Between Subjects	1116.00	35		
Drug	156.25	2	78.13	7.35*
Dose Level	118.08	2	59.04	5.56*
Drug × Dose Level	554.67	4	138.67	13.04*
Error	287.00	27	10.63	
Within Subjects	4940.00	45		
Response Distribution	3094.22	1	3094.22	478.20*
Drug × Response Distribution	697.53	2	348.77	53.91*
Dose Level × Response Distribution	494.37	2	247.19	38.20*
Drug × Dose Level × Response Distribution	420.88	4	105.22	16.26*
Error	233.00	36	6.47	

*$p<0.01$.

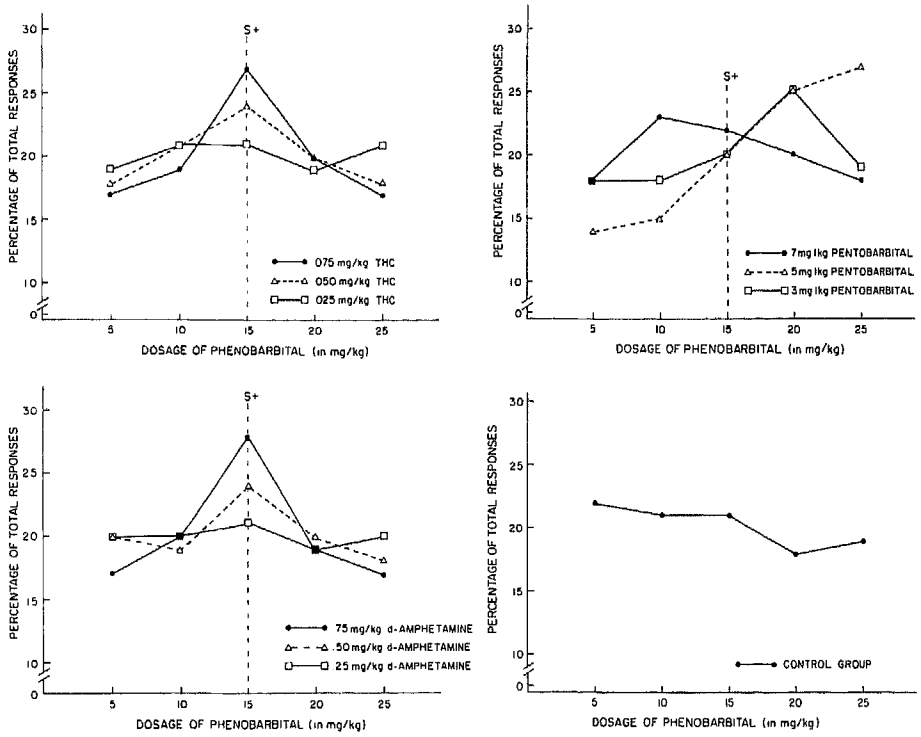

FIG. 2. Mean post-discrimination generalization gradients along the phenobarbital dosage dimension for the experimental and control groups.

group had significantly steeper gradients than the low and medium dose groups, and all the THC groups differed significantly from each other.

The three pentobarbital groups produced quite different gradients from those of the THC and amphetamine groups. No gradients (for pentobarbital groups or individual subjects) peaked at the S+. Rather, the gradient for each pentobarbital group peaked at a different point (low dose group, 20 mg/kg; medium dose group, 25 mg/kg; high dose group, 10 mg/kg.

Additionally, the three pentobarbital groups all showed significant gradient asymmetry, and they each differed from one another in the form of that asymmetry (Newman Keuls follow-up testing $p<0.05$).

DISCUSSION

The fact that all experimental subjects readily learned to discriminate between S+ and their respective S− reaffirms the fact that the drugs and dosages employed here can function as stimuli. The fact that flat gradients were obtained in Phase 4, prior to discrimination training, suggests that drugs can function in a manner analogus to many exteroceptive stimuli dimensions which, in the absence of differential reinforcement, exert little control over responding [14,18]. In Phase 5, significantly more rapid acquisition of the discrimination by the higher dosage THC and amphetamine groups indicates that as more distinctive (intense) cues are used in discrimination training, the discrimination becomes easier to learn. The failure to observe this relationship in the discrimination acquisition for the pentobarbital groups suggests that in this study, pentobarbital S− stimuli act in a manner qualitatively different from the THC and amphetamine S− stimuli. With pentobarbital, the most rapid and best discrimination was seen with the 3 mg/kg dosage. This would indicate that the 3 mg/kg pentobarbital was easier to discriminate from 15 mg/kg of phenobarbital than were the higher 5 mg/kg and 7 mg/kg pentobarbital doses. The failure of the control group to respond differentially on S+ and S− days rules out extra-drug sources of cues (e.g., differential reinforcement density) as the basis for the discrimination in the other groups.

The results from post-discrimination generalization testing along the phenobarbital dose dimension were quite different when the S− of discrimination training had been pentobarbital than when it had been THC or amphetamine. For THC and amphetamine, the higher S− training doses resulted in clear-cut symmetrical gradients that peaked at the S+ value of phenobarbital dosage. For the lower doses of THC and amphetamine S−'s, generalization gradients were not clearly evident. This suggests that unlike the rat [2], DND discrimination training with phenobarbital is not sufficient to imbue the phenobarbital dose dimension with differential response controlling capabilities in the pigeon. In this regard, the phenobarbital dimension appears to operate like relatively non-salient exteroceptive stimulus dimensions such as the auditory tone dimension in pigeons [10], rather than like salient localizable dimensions such as the visual wavelength dimension in pigeons [6]. Salient dimensions can acquire response controlling stimulus properties without the benefit of explicit differential reinforcement along the dimension, while non-salient stimulus dimensions require such training.

The degree of control the S+ (phenobarbital) dimension exerts over responding increased with the distinctiveness of the S− stimuli used in training as is the case with exteroceptive discrimination learning [14]. This is reflected in the drug by dose level interaction in which the relationship between gradient steepness and S− dosage was observed with THC and amphetamine, but not the pentobarbital groups. This suggests that it is not the absolute intensity of the S− stimuli that determines S+ stimulus control, but the relative amount of drug state change between the S+ and S−. This suggestion is also supported from the discrimination data of Phase 5.

When the S− in discrimination training had been pentobarbital, none of the generalization gradients along the phenobarbital dose dimension were symmetrical, and none peaked at S+. Rather, the gradients for both the 3 and the 5 mg/kg groups peaked on the high side of S+, which implies that both 3 and 5 mg/kg pentobarbital lie below 15 mg/kg phenobarbital on the common dimension. The fact that the gradient for the 5 mg/kg pentobarbital group was steeper than that of the 3 mg/kg group implies that 5 mg/kg pentobarbital is the closer to 15 mg/kg phenobarbital on the common dimension. The fact that the gradient for the 7 mg/kg group peaked on the low side of S+, implies that 7 mg/kg pentobarbital lies above 15 mg/kg phenobarbital. Thus, between 5 mg/kg and 7 mg/kg there presumably lies a dosage of pentobarbital that is indistinguishable from 15 mg/kg phenobarbital on the phenobarbital dose dimension. Other research has pointed to this same conclusion [16].

In conclusion, it appears that the peak-shift/no peak-shift procedure may be a promising approach to deciding whether one drug shares a dimension with another drug. The particular drugs chosen for this study were chosen because it is well established that phenobarbital and pentobarbital are closely related, whereas there is no evidence of such a close relationship between phenobarbital and d-1-amphetamine or THC. The similarity of results between the THC and amphetamine groups suggests that the sedative effects of THC are not perceived by the subjects as sharing a common strength of sedation dimension with phenobarbital. The fact that the peak-shift criterion correctly sorted the several drugs and dosages suggests that this procedure might be more generally useful as a means of identifying drugs which share stimulus dimensions.

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