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Multidimensional Scaling of Subjective Judgements of Drug Similarities Among Ketocyclazocine, Morphine, Cyclazocine, Naloxone and Placebo

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KUMOR, K. M., W. C. CLARK, M. N. JANAL AND C. A. HAERTZEN. *Multidimensional scaling of subjective judgements of drug similarities among ketocyclazocine, morphine, cyclazocine, naloxone and placebo.* PHARMACOL BIOCHEM BEHAV **35**(2) 397–404, 1990.—Profiles of the subjective and physiologic effects of opioid drugs in man cannot be assigned with precision to specific opioid drug-receptor interactions. We administered a set of training doses of ketocyclazocine, morphine, cyclazocine, naloxone and placebo to 10 drug-using volunteers and obtained similarity judgements between each of 2 test doses of the drugs and a training dose. These data were submitted to multidimensional scaling analysis (INDSCAL) using both neighboring cells estimates and root mean square estimates to estimate missing cells in the data matrices. The results of these analyses are convergent, appear valid and indicate that there are three drug dimensions expressed in this data set: morphine versus placebo and naloxone; cyclazocine and ketocyclazocine versus placebo and naloxone; and ketocyclazocine versus cyclazocine. We interpret this result as supporting evidence that in the set of five drugs studied, three subjective states are induced.

Multidimensional scaling Psychopharmacology Opioids Opiates Subjective effects Human

RECEPTORS are classified as opiate receptors because they share a common property of blockade by naloxone. Further subclassification of these receptors is based upon six lines of evidence: 1) differential rank order of the potency of opioid drugs in opioid reactive tissues, 2) differential dissociation constants for naloxone for the same tissue using different opioid drugs, 3) rank order differences in competitive binding that is dependent on opioid radioligand used, 4) differential tolerance among opioid drugs in animals or tissues, 5) selective alkylation of populations of receptors in binding and bioassays and, lastly, 6) opioid drugs from different chemical families have different profiles of pharmacologic activity in vivo (6).

A significant problem for the understanding of clinical data measuring physiologic and subjective responses after opioid administration is that opioid drugs are not pure agonists of any one receptor type. The problem of assigning diverse subjective and physiologic profiles of opioid drugs to specific opioid receptor subtypes is of considerable interest, especially for human data (1, 7, 13, 14, 16, 17). For heuristic purposes, the response profile of morphine is commonly accepted as the result of agonism at the mu receptor (1,13). Responses to ketocyclazocine, MR2033 and MR2034 have been used as representative of kappa agonism because the constellation of responses observed after morphine is distinct from ketocyclazocine, MR2033 or MR2034 (13,16). The pharmacologic effects of cyclazocine are thought to be mediated through sigma receptors (15,21). However, it is also clear that while these drugs bind specifically to particular opioid receptors, they may still bind to and presumably cause a pharmacologic response at other sites.

An ability to relate precisely the subjective response to opioid drug administration to an effect at a particular receptor would represent an advance in our understanding. Two simple models can be envisioned explaining the set of responses resulting from a drug interaction at an opioid receptor. Firstly, all responses can be independent, that is, the response issuing from a drug with one receptor subtype is unrelated to the response of the same drug with another receptor subtype and vice versa. Alternatively, an interaction of an opioid drug with one type of receptor may influence the response from the interaction of that opioid drug with another receptor type simultaneously. In the first case a set of profiles of responses will emerge from the set of opioid drugs. All the possible profiles may not be manifested in a particular drug response, but the responses may be classified into a set of profiles which will correspond to the set of receptor types. If, on the other hand, the drug receptor interactions are heavily dependent upon each other, that is, they modify the responses at other receptors, the dimensions emerging from data involving drugs that interact predominately with one receptor might have no common dimension with a drug which has strong interactions with that receptor and another receptor as well. Thus, there will be a set of profiles

or dimensions unique to each drug.

The use of multidimensional scaling techniques can provide information as to the number of profiles or dimensions into which the responses to opioid drugs segregate themselves (11,19). These may relate to the number of productive drug-receptor subtype interactions that influence the set of measurements. Furthermore, multidimensional scaling can provide the rank order of the drugs and doses on each dimension, thus relating the dimensions and the contribution of each drug condition to that dimension. Lastly, multidimensional scaling can be used to evaluate the relationship of individual subjects to the group result and determine the importance of each dimension for each individual. This evaluation allows the examination of dimensionality which could be related to personal drug experience and history.

We used INDSCAL, a multidimensional scaling model for individual differences (2–4), to determine the number and type of dimensions that describe a set of subjective estimations of the similarity between pairs of opioid drugs. The opioid drugs used included two that are thought to be "pure" or agonists of predominantly one receptor type, morphine for mu receptors and ketocyclazocine for kappa receptors. Cyclazocine may be an agonist of mu, kappa and possibly sigma receptors (15, 18, 20, 21). We compared our multidimensional scaling results to the scores on subjective and observer rating scales collected during the study of ketocyclazocine as compared with morphine, naloxone and cyclazocine which was previously reported (12,13). We evaluated the internal consistency between the two techniques in order to assess validity.

METHOD

Subject Population and Environment

The subject population was recruited using word of mouth, newspaper advertisement, and the circulation of fliers. Passage of a physical examination with blood screening tests, an interview screening for mental health problems, the Shipley Institute of Living Scale (5), the Minnesota Multiphasic Personality Inventory (8) and a basic reading test were required for all subjects participating in the study. At the time of the study subjects were not physically dependent on opioid drugs as determined by Himmelsbach rating scores for the first three days after admission to the ward (10). The selected group consisted of 10 paid male volunteers, aged 21–35 years, 3 black and 7 white. During the study period of approximately 1.5 months subjects were housed on a closed ward. Routine random urine screens measuring drugs of abuse were used to rule out the use of drugs other than those administered experimentally.

Drug History

Criteria for participation in the study also included a history of illicit use of both opioid and hallucinogenic drugs. Seven of the 10 men had extensive histories of drug use. Drug use histories were obtained in interviews with the subjects and the information gathered included the current frequency, peak frequency, route of administration and age of first use for 16 illicit drugs or drug classes. The drug histories of current and peak use were collected as quantitative data using these criteria; 0 represented no use of a drug, 1 represented experimental use (no regular use), 2 represented regular use less than 3 times per week, 3 represented regular use 3 times per week, 4 and 5 were reserved for two levels of heavier use. Only two persons were rated a 5, one for current use of marijuana, subject 433 and one for peak opioid use, subject 374.

Drug Dose and Schedule of Drug Administration

There were two sets of drug doses, training doses and test doses. The training doses were morphine 21 mg, ketocyclazocine 0.85 mg, naloxone 210 mg, cyclazocine 0.7 mg and placebo. The test doses were morphine 15 and 30 mg, ketocyclazocine 0.6 and 1.2 mg, naloxone 150 and 300 mg, cyclazocine 0.5 and 1.0 mg and placebo. The training doses represent the geometric mean dose between the two test doses of a drug and as a set were administered first in randomized order under double-blind conditions. These doses were identified only as drugs A, B, C, D, and E and were given as a primary standard drug exposure for comparison with test doses given later. After all the training doses were given, subjects received the test doses in randomized order under double-blind conditions on an every third day schedule. The first drug in the training dose series was always identified as drug A, the second as drug B and so on. Because the schedule was randomized individually, drug A for any two subjects was not the same drug except by chance assignment. All drugs were given intramuscularly in 2 ml volumes at 0900 hr on a twice weekly schedule. Water served as the placebo. On training dose days, but not on test dose days, subjects were required to fast, and had blood and urine tests in addition to the other measurements.

Measures

Twenty-four hr after each of the test drug doses, subjects were asked to make similarity judgements between the test drug received the day before and each of the five training doses, A through E. The questionnaire was administered via a computer terminal. Subjects were asked to answer a set of five questions of the form "How much like drug X?" where X was the letters A through E. The rating was a four-point interval scale with 0 identified as "not-at-all," 1 as "slightly," 2 as "moderately," 3 as "very much" and 4 as "exactly." During the training phase each subject was instructed to write notes for himself about the drug experience. These notes were kept by subjects and were used throughout the study for their reference.

Also included on the 24-hr questionnaire was a question asking subjects to identify (or match) the test drug with one of the five training drugs. Subjects were aware that the training and test drugs were drugs listed in the consent form. However, they were not aware of the doses and had no information of how many doses or drugs were included in the training or test set.

During the study we obtained periodic physiologic measurements of standing and supine blood pressures and pulses, respiratory rate, pupil diameter, and rectal temperature. Psychopharmacologic activity was assessed with subject and observer questionnaires designed to assess mood and feeling state. These questionnaires included the Single Dose Questionnaire for subjects and observers (10), the Addiction Research Center Inventory (7), the four-point "Feel the Drug" scale, the four-point "Drug Liking" scale, and the Perception Scale (12,13). The results of the drug identification and the scores of the psychopharmacologic scales from this experiment have been reported previously (12,13) and are helpful for the interpretation of the dimensions obtained in the INDSCAL group stimulus space reported here.

Construction of Similarity Half-Matrices

The original data were ten 5×9 rectangular matrices, one for each subject, containing similarity judgements between training and test stimuli. These matrices are not amenable to INDSCAL analysis, which requires a half-matrix of similarities between all 91 pairs of the 14 stimulus objects. An appropriate matrix would contain, in addition, similarities between each of the 5 training stimuli and each of the 9 test stimuli (Table 1).

Two methods were used to complete the half-matrices. For the first method, neighboring cells, estimates were calculated from

TABLE 1

5×9 RAW DATA MATRIX OF SUBJECT NO. 320

		Test Stimuli								
		P_{te}	N1	N3	M1	M3	C1	C3	K1	K3
T	P_{tr}	3	0	0	0	0	0	0	0	0
R	N2	0	3	4	0	0	0	0	0	1
A	M2	0	0	0	4	4	0	1	0	0
I	C2	0	0	1	0	0	4	4	1	1
N	K2	0	0	0	0	0	0	1	3	4

In this and the following tables, "No Similarity" is scored 0, and "High Similarity" is scored 4. Placebo is indicated by "P," morphine by "M," naloxone by "N," cyclazocine by "C," and ketocyclazocine by "K." Numbers following the letter indicate the drug dose (low to high); doses 1 and 3 were given on the test day, while dose 2 was always given as training. The placebo dose was equal on both training and test days, which are indicated by "tr" and "te," respectively.

similarities local to the missing value. In the second, root mean square (RMS), estimates were calculated from similarities both local and distant from the missing value.

In the following, the matrix of similarities, S, contains elements s_{ij}, where i indexes training stimuli and j indexes test stimuli. *Neighboring cells'* estimates were obtained according to three rules:

1) Missing similarities, s_{ij}, between test placebo (P_{te}) and each test drug (X_j) were estimated by substituting the similarity of training placebo (P_{tr}) with each test drug, on the rationale that placebo dose was identical on both days. Through algebraic substitution, since

$$P_{tr} = P_{te}' \qquad S_{Ptr,j} = s_{i,Pte}.$$

2) Missing similarities between training drugs were estimated by averaging, for each pair of training drugs, the similarities of each training drug with the two test doses of the other drug,

$$s_{ii'} = (s_{ij} + s_{i'j} + s_{ij'} + s_{i'j'})/4.$$

For example,

$$s_{M2,N2} = (s_{M2,N1} + s_{N2,M1} + s_{M2,N3} + s_{N2,M3})/4$$

3) Missing similarities between the two doses of each test drug were estimated by averaging, for each pair of doses, the similarities of the training dose and each test dose,

$$s_{jj'} = (s_{ij} + s_{ij'})/2$$

For example,

$$s_{N1,N3} = (s_{N2,N1} + s_{N2,N3})/2.$$

After missing elements were included in the matrix, an example of which appears in Table 2 for subject No. 320, the ten 14×14 half-matrices were submitted to INDSCAL analysis.

A subset of Table 2 containing only the half-matrix of similarities between the 9 test stimuli was also analyzed. This matrix contains only estimated data points. For subject No. 320, these data are presented in Table 3.

RMS estimates of similarity among test stimuli ($s_{jj'}$) were defined as the root mean square difference between pairs of test stimuli and the 5 training stimuli (s_{ij}):

$$s_{jj'} = 4 - [\sum_{i=1}^{5}(s_{ij} - s_{ij'})^2/5]^{1/2}$$

If stimuli X_j and $X_{j'}$ are similar to one another, they should each bear a similar relationship to each X_i. When this occurs, the difference score between similarities s_{ij} and $s_{ij'}$ will approach zero (maximum similarity), while dissimilarity would produce scores approaching four. To be consistent with the initial matrix, in which similarity is indicated by large numbers, the RMS difference is subtracted from 4, the maximal rating. In a similar manner,

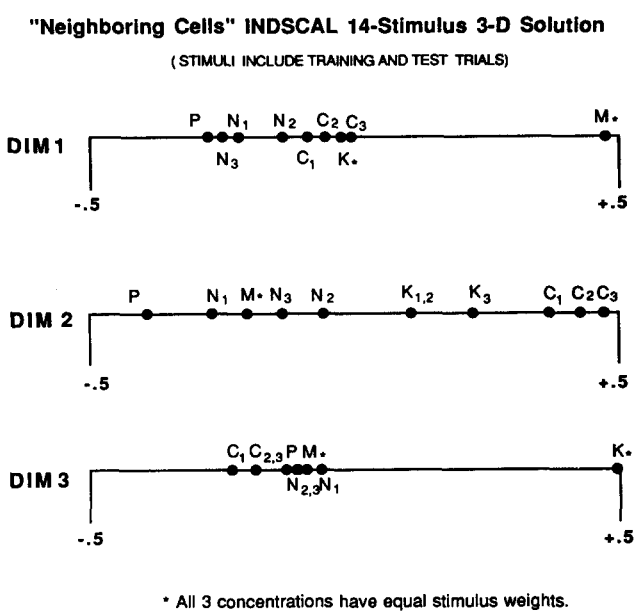

FIG. 1. Graphic representation of the stimulus weights assigned to the drug doses by the INDSCAL solution using the "neighboring cells" estimates to fill the matrix. The solution takes into account all the subjects and all the data from both training and test doses. A value of zero means that there is no contribution of the dose to this perceptual state or dimension. Large values either positive or negative mean a strong contribution to the particular dimension. The numbers 1 and 3 denote the test doses, low and high respectively, while a 2 denotes the training doses. P is placebo, N is naloxone, C is cyclazocine, M is morphine, and K is ketocyclazocine.

TABLE 2

14 × 14 HALF-MATRIX (91 CELLS) OF SUBJECT NO. 320, USING THE NEIGHBORING CELLS ESTIMATE OF 46 MISSING VALUES

	P_{tr}	P_{te}	N1	N2	N3	M1	M2	M3	C1	C2	C3	K1	K2
P_{te}	*3*												
N1	0	*0*											
N2	*0*	0	*3*										
N3	0	*0*	3.5	*4*									
M1	0	*0*	0	*0*	0								
M2	*0*	0	*0*	0	*0*	*4*							
M3	0	*0*	0	*0*	0	4	*4*						
C1	0	*0*	0	*0*	0.5	0	*0*	0					
C2	*0*	0	*0*	0.25	*1*	*0*	0.25	*0*	*4*				
C3	0	*0*	0	0	0.5	0.5	*1*	0.5	4	*4*			
K1	0	*0*	0	*0*	0	0	*0*	0	0.5	*1*	1		
K2	*0*	0	*0*	0.25	*0*	*0*	0	*0*	*0*	0.75	*1*	*3*	
K3	0	*0*	0.5	*1*	0.5	0	*0*	0	0.5	*1*	1	3.5	*4*

The 45 raw data values are italicized.

the similarities among training stimuli were established by calculating the RMS difference between pairs of training stimuli and the 9 test stimuli:

$$s_{ii'} = 4 - [\sum_{j=1}^{9}(s_{ij} - s_{i'j})^2/9]^{1/2}.$$

The complete 14 × 14 half-matrix derived by this method is shown in Table 4 for subject No. 320.

RESULTS

Group Stimulus Spaces

Method 1, neighboring cells. The data of the 14-stimulus matrices were subjected to 4-, 3-, 2- and 1-dimensional analyses. A replicable (from 4 different initial configurations) solution in 3 dimensions which accounted for approximately 55% of the stimulus variability in multidimensional space (R = .74) was accepted. Dimension 1 accounted for 24%, dimension 2 for 16% and dimension 3 for 15% of the total variance. The variance accounted for (VAF) is a measure of goodness-of-fit. Values of 10% or more are quite acceptable, but a dimension accounting for 3% of the variance may be acceptable if it is readily interpretable (11). The distribution of stimuli along each of the dimensions is shown in Fig. 1. The first, "morphine," dimension reflects the difference in subjective experience between the effects of three doses of morphine at one pole and the absence of this effect with placebo and naloxone at the other. The remainder of the test drugs were located near the origin (weight = 0), and, thus, are irrelevant to this dimension. The second, "cyclazocine," dimension had poles defined by the three doses of cyclazocine at one end, and placebo

TABLE 3

9 × 9 HALF-MATRIX OF SUBJECT NO. 320, USING NEIGHBORING CELLS ESTIMATES OF MISSING VALUES

	P_{te}	N1	N3	M1	M3	C1	C3	K1
N1	0							
N3	0	3.5						
M1	0	0	0					
M3	0	0	0	4.0				
C1	0	0	0.5	0	0			
C3	0	0	0.5	0.5	0.5	4.0		
K1	0	0	0	0	0	0.5	1.0	
K3	0	0.5	0.5	0	0	0.5	1.0	3.5

All 36 values are estimates.

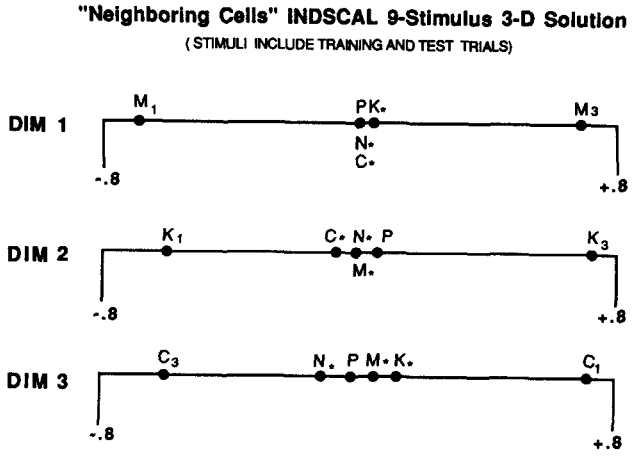

FIG. 2. Graphic representation of the stimulus weights assigned to the drug doses by the INDSCAL solution using the "neighboring cells" estimates to fill the matrix. The solution takes into account all the subjects, but only the test day data, that is, only the low and high doses of the drugs given as challenges after the completion of the training doses. All training data is excluded. A value of zero means that there is no contribution of the dose to this perceptual state or dimension. Large values either positive or negative mean a strong contribution to the particular dimension. The numbers 1 and 3 denote the test doses, low and high respectively. P is placebo, N is naloxone, C is cyclazocine, M is morphine, and K is ketocyclazocine.

TABLE 4

14 × 14 HALF-MATRIX OF SIMILARITY JUDGEMENTS FOR SUBJECT NO. 320, USING RMS ESTIMATES OF MISSING VALUES

	P_{tr}	P_{te}	N1	N2	N3	M1	M2	M3	C1	C2	C3	K1	K2
P_{te}	*3*												
N1	2.1	*0*											
N2	*0*	2.03	*3*										
N3	1.72	*0*	3.37	*4*									
M1	1.76	*0*	1.76	*0*	1.43								
M2	*0*	1.84	*0*	1.44	*0*	*4*							
M3	1.76	*0*	1.76	*0*	1.47	4	*4*						
C1	1.76	*0*	1.76	*0*	1.76	1.47	*0*	1.47					
C2	*0*	2.03	*0*	1.62	*1*	*0*	1.42	*0*	*4*				
C3	1.67	*0*	1.67	*0*	1.67	1.67	*1*	1.72	3.37	*4*			
K1	2.05	*0*	2.05	*0*	1.76	1.72	*0*	1.72	2.1	*1*	2.33		
K2	*0*	1.79	*0*	1.79	*0*	*0*	1.48	*0*	*0*	1.89	*1*	*3*	
K3	1.67	*0*	1.95	*1*	1.76	1.39	*0*	1.39	1.72	*1*	2.0	3.37	*4*

The raw data values are italicized

and low dose naloxone at the other. On this dimension, ketocyclazocine was somewhat more like the cyclazocine pole and morphine was a little closer to the placebo. The third, "ketocyclazocine-cyclazocine," dimension placed the 3 dose levels of ketocyclazocine at one pole and 3 levels of cyclazocine at the other pole. Morphine, naloxone, and placebo shared the cyclazocine pole to some extent.

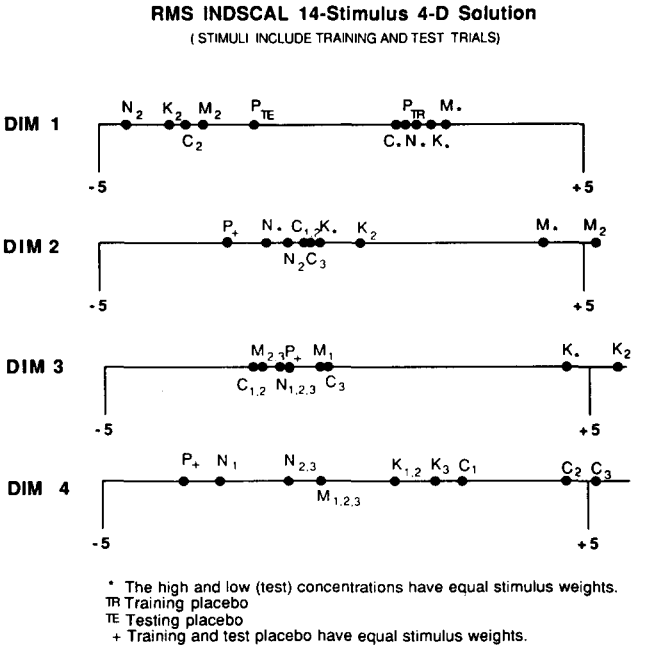

FIG. 3. Graphic representation of the stimulus weights assigned to the drug doses by the INDSCAL solution using the RMS (root mean square) estimates to fill the matrix. The solution takes into account all the subjects and all the data from both training and test doses. A value of zero means that there is no contribution of the dose to this perceptual state or dimension. Large values either positive or negative mean a strong contribution to the particular dimension. The numbers 1 and 3 denote the test doses, low and high respectively, while a 2 denotes the training doses. P is placebo, N is naloxone, C is cyclazocine, M is morphine, and K is ketocyclazocine.

The three independent dimensions which were found suggest that the subjective effects of these drugs produced three distinct stimulus profiles or stated another way, perceptual-emotional (mood) states. One was associated with the effects produced by morphine and opposite to a no-drug state. A second was associated with the effects of cyclazocine relative to a no-drug state. The third dimension reflects some type of stimulus continuum which is common to the cyclazocine and ketocyclazocine drugs.

The neighboring cells estimate applied to 9 stimulus conditions (training trials omitted) produced a replicable 3-dimensional solution accounting for 49% of stimulus variation (see Fig. 2). Each of these dimensions reflected the effect of drug dose for morphine (VAF = 21%), cyclazocine (14%), and ketocyclazocine (14%). Naloxone and placebo had stimulus weights close to zero.

Method 2, RMS. Data obtained by estimating missing matrix elements for the 14-stimulus squared difference (RMS) matrix were subjected to 5-, 4-, 3-, 2- and 1-dimensional INDSCAL analyses. A replicable solution in 4 dimensions which accounted for approximately 68% of the variance was accepted (see Fig. 3). This total was partitioned as 36% for the first dimension, 13% for the second, 10% for the third and 9% for the fourth. The first dimension represents the type of test experience; it positions the training stimuli [dose level 2, and placebo on training day (P_{tr})] at one pole and the test stimuli [dose levels 1 and 3, and placebo on test day (P_{te})] at the other. Thus, training days differ intrinsically from test days, regardless of drug. The second, "morphine," dimension places morphine at one pole and innocuous stimuli (placebo and naloxone) at the other pole. This dimension means that morphine produced a unique stimulus or subjective experience not shared by the other drugs. The third dimension had cyclazocine at one end and ketocyclazocine at the other. This dimension represents a subjective stimulus experience of some sort (perceptual, emotional, physiological) which is common to the cyclazocine-ketocyclazocine class of drugs and is shared somewhat by morphine, naloxone and placebo. The fourth dimension, "cyclazocine," had cyclazocine at one pole and placebo and naloxone at the other. It is worth noting that the last three dimensions are the same as those found by Method 1 above. High correlations (>.90) were found between dimensions 2–4 of the RMS solution and dimensions 1–3 of the neighboring cells analysis, providing further evidence of the similarity between these analyses based on different estimation strategies. Thus, the RMS solution substantiates the results of the neighboring cells method, and provides, in

TABLE 5

FOUR DIMENSIONAL, 14-STIMULUS RMS INDSCAL SOLUTION

Subject	R	Dim 1	Dim 2	Dim 3	Dim 4
320	.88	.56	.43	.35	.36
309	.86	.54	.48	.32	.33
365	.73	.52	.14	.49	0
355	.77	.44	.45	.43	.10
370	.92	.44	.46	.43	.48
374	.91	.74	.43	.08	.30
426	.82	.72	.30	0	.25
433	.72	.48	.29	.22	.39
435	.83	.74	.30	.20	.08
445	.77	.70	.19	.11	.24

Subject weights space and correlation of multidimensional fit to the group stimulus space by subject.

addition, a fourth dimension which distinguishes training from test trials.

Subject Weight Spaces

The subject space for the 14-stimulus RMS 4D solution is presented in Table 5. Subject weights specify how salient or important each of the dimensions (in the group stimulus space) was to a subject in making similarity judgements. These tables show not only how well a particular subject's data fit the multidimensional solution for the group stimulus space (multiple R), but also the importance of each dimension in determining the goodness-of-fit. These values may be interpreted as indicative of the relevance of a particular dimension to a particular subject. In Table 5, for subjects No. 320, 309, 370, all 4 dimensions were important (R>.85). Subject 374, on the other hand, also had a high multiple R, but D1 was very important and D3 unimportant. Subject 365 had a weight of 0 on dimension 4 (no relevance), whereas dimension 3 accounted for a large proportion of this subject's judgement.

We also computed correlations between the individual subjects' weights space from the 4-dimensional, 14-stimulus RMS INDSCAL solution and six aspects of the subject's drug experience history: current opioid use, peak opioid use, current hallucinogen use, peak hallucinogen use, peak marijuana use, and peak PCP use. Thus, 10 subject weights for Dimension 1 were correlated with each of the six aspects of the subject's history. Then Dimensions 2 through 4 were done similarly. Generally, the correlations were unrevealing and none were statistically significant, despite the fact that multiple correlations were made without adjusting the p value for the multiple comparisons. Dimension 4, which strongly reflected the influence of cyclazocine, correlated .35 with both the current and past history of hallucinogen use and though the result is not significant ($p=0.15$ for both correlations), it is pertinent since cyclazocine is hallucinogenic (13). However, a similar phenomenon, but opposite in direction was observed for Dimension 3, which is strongly influenced by ketocyclazocine, another hallucinogenic drug (13). Dimension 3 correlated with current hallucinogenic use ($-.35$; $p=0.2$) as well as PCP use [$-.29$; $p=0.15$].

DISCUSSION

Stimulus objects in this experiment were the subjective states induced by powerful psychoactive drugs with a duration of action lasting more than 12 hours. An inter-test interval of 3 days

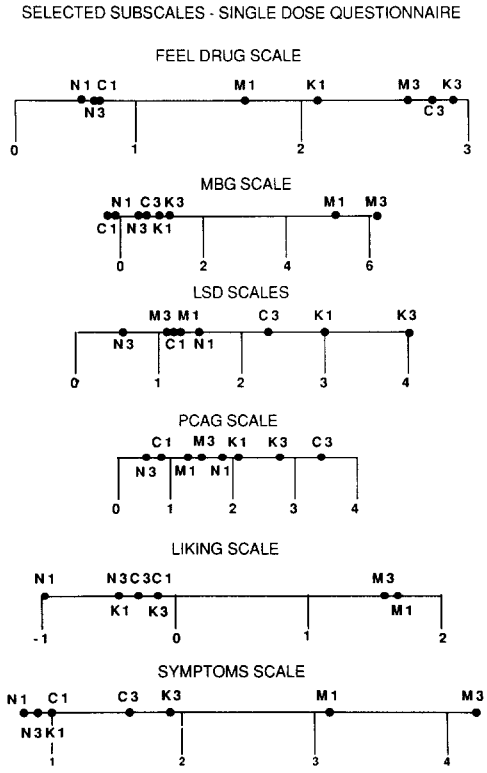

FIG. 4. Graphic representation of results of Single Dose Questionnaire Scales for the same subjects and doses studied here (9,10). The baseline scores were subtracted from the maximum scores of the scale for all the study days. The maximum difference scores for placebo were then subtracted from the maximum difference scores for each drug dose and the value plotted on a line. This renders a relative intensity on the scale for each drug normalized against placebo. The numbers 1 and 3 denote the test doses, low and high respectively, while a 2 denotes the training doses. P is placebo, N is naloxone, C is cyclazocine, M is morphine, and K is ketocyclazocine.

was needed to permit drug elimination prior to the next test. Judgements of similarity between all pairwise objects were not obtained because of these constraints. These missing values were determined in Method 1 (Neighboring Cells) by interpolation from values in the immediately surrounding cells, and in Method 2 by estimates based on RMS as described by Schiffman *et al.* (19). Both methods were used to examine individual 14-stimulus matrices (one for each subject) which included actual similarity judgements between training and test days, as well as constructed values within training and test days. The cells of the 9-stimulus triangular matrices, with the exception of a placebo comparison, contained only constructed values (for test day) since the test day-training day comparisons were omitted from the matrix to yield pure test-day half-matrices. Although 4 to 6 stimuli are generally required per derived dimension (11,19), we waive that guideline here because solutions of higher dimensionality were replicable, accounted for substantial variance, and were interpretable. In addition, at this early stage in the application of the INDSCAL model, more hypotheses can be generated through use of higher dimensionality.

Using 14 stimuli, the two methods yielded similar solutions describing three dimensions (Figs. 1 and 3). The neighboring cells INDSCAL dimensions 1, 2, 3 correspond respectively with RMS INDSCAL dimensions 2, 4 and 3. These produce: 1) a morphine

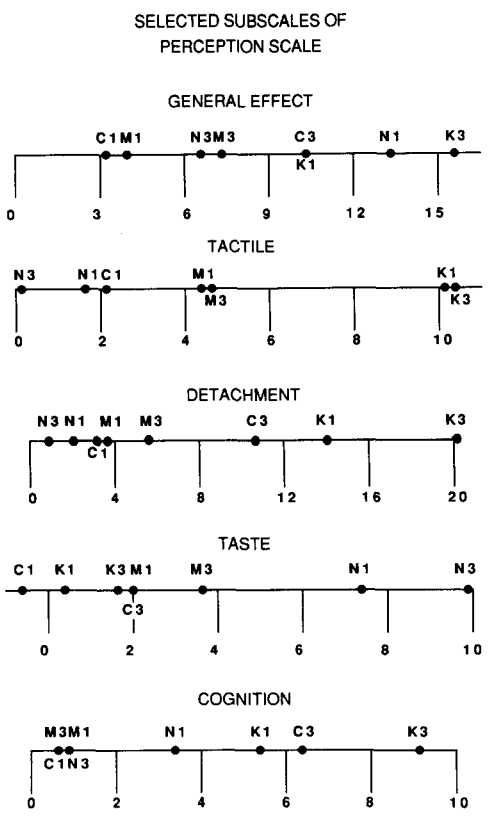

FIG. 5. Graphic representation of results of selected subscales of the Perception Scale for the same subjects and doses studied here (9,10). The baseline scores were subtracted from the maximum scores of the scale for all the study days. The maximum difference scores for placebo were then subtracted from the maximum difference scores for each drug dose and the value plotted on a line. This renders a relative intensity on the scale for each drug normalized against placebo. The numbers 1 and 3 denote the test doses, low and high respectively, while a 2 denotes the training doses. P is placebo, N is naloxone, C is cyclazocine, M is morphine, and K is ketocyclazocine.

subjective effect dimension with placebo and naloxone at its weaker end; 2) a cyclazocine subjective effect dimension with placebo and naloxone at its weaker end; and 3) a dimension defined by the difference in effect between ketocyclazocine and cyclazocine (where morphine, placebo, and naloxone share the latter trait). In addition, RMS estimates produced a fourth dimension that reflects the difference between test and training conditions, irrespective of drug.

The 9 stimulus INDSCAL matrices are based on the concept that all paired comparisons were among test stimuli (no training stimuli). Thus, except for the within-test comparison with placebos, the cells are constructed according to either the neighboring cells rule or the RMS rule. The 9 stimulus neighboring cells rule yielded (Fig. 2) dimensions that reflected the subjective effects of high and low doses of each drug. This result demonstrates that different subjective effects were produced by each substance, and that the strength of the effect varied with concentration in a very direct manner. These results are an extremely clear demonstration of independent drug-induced subjective effects. These results are compatible with dimensions 2 and 4 of the 14 stimulus RMS analysis although the latter failed to isolate a dimension for concentration. The cause of difference between the 14 and 9 stimulus group stimulus spaces remains unknown, but eliminating training drug information from the matrix seems to enhance dose-related information. It is possible that the dose responsiveness was a hidden dimension on the 14 stimulus analysis and would have emerged with a larger number of subjects.

Methods 1 and 2 differed in the way missing elements were estimated. A large number of zero elements were estimated in the neighboring cells matrices, while these elements in the square difference matrices were rarely zero, because the latter produced estimates from all elements in the row or column. Thus, neighboring cells estimates maximized differences between levels of each test drug and minimized inter-drug effects. RMS estimates, by averaging the similarity scores of each test drug over all the training drugs, may reflect more of the subjective differences in drug action. In the case of neighboring cells, estimates of the missing elements are defined by known elements near (surrounding) the missing element in the matrix. In the case of the square differences, estimates of the missing element are calculated by taking all known row or column estimates in the matrix. Because RMS estimates produced a training-test drug difference, we may conclude this method was the more robust.

The data from the Single Dose Questionnaire Symptoms Scale (9,10) aid in the interpretation of the dimensions found in the INDSCAL group stimulus space. The value of the maximum difference from baseline of each drug versus placebo was plotted along an attribute scale (Fig. 4). The continuum constructed from the subjects' ratings of the number and intensity of symptoms by the various drugs was closely related to the morphine-placebo dimension order profile (D-1, Fig. 1, D-2, Fig. 3). This result suggests that the dimensional ordering for morphine results from the large number of symptoms produced, rather than any particular subjective effects of morphine, such as euphoria. The liking (euphoria), drug seeking scale, with morphine at one pole and the cyclazocine and placebo at the other, agrees with D-1 (Fig. 1) and D-2 (Fig. 3), suggesting the subject's perception here of euphoriant qualities. The Feel Drug (psychoactive intensity) scale demonstrates a strong concentration gradient over the three substances. It appears to represent a combination over drugs of the 3 dimensions representing concentration gradients in Fig. 2.

The ordering of the drugs on the ARCI Morphine, Benzedrine Group (MBG) (Fig. 4) subscale falls between the Symptoms and "Drug Liking" scales and is related to D-1 (Fig. 1) and D-2 (Fig. 3). Note that morphine is further from placebo (here noted as 0) on the MBG scale than cyclazocine and ketocyclazocine are on the phenobarbital, chlorpromazine and alcohol (PCAG) scale or LSD scales (13); this pattern is related to the INDSCAL finding that morphine accounts for more of the variance (yields a better fit to the group stimulus space) than do the other drugs. The ordering of the drugs on the PCAG scale, from placebo to high doses of cyclazocine and ketocyclazocine, is not well reflected in any of the INDSCAL dimensions. However, if the placebo standard comparison and the low doses of cyclazocine are omitted, then the scale from morphine to cyclazocine approximates the ordering of (Fig. 1) D-2, and (Fig. 3) D-4. The LSD dysphoria scale appears closest to the D-3 (Fig. 1) and D-3 (Fig. 3) dimensions separating ketocyclazocine from morphine and cyclazocine.

Several of the Perception Scale subscales are interpretable as related to derived dimensions (Fig. 5). The General Effect Scale, the Detachment Scale and the Tactile Scale with the approximate order C_1, M_1, M_3 to K_1, C_3, K_3 appear somewhat similar to the order of stimuli (drugs) on D-3 (Figs. 1 and 3). The Cognition scale appears closely related to D-3 (Fig. 3). Other subscales, smell, visual, auditory, dizziness and paranoia were not responsive to the drug conditions.

It is important to define the constellation of symptoms or physiologic data that result for specific drug-receptor interactions in man. However, this is not directly observable. We have sought

to develop new ways of analyzing and defining psychopharmacologic responses in order to make inferences about these interactions, to form testable hypotheses, and to confirm informal clinical impressions (1). We administered a set of training doses of ketocyclazocine, morphine, cyclazocine, naloxone and placebo and obtained similarity judgements between these doses and a set of test doses. These data were submitted to multidimensional scaling analysis using 2 methods to estimate the missing cells in the data matrices. The results indicate that there are three drug dimensions expressed in this data set: morphine versus placebo and naloxone, cyclazocine and ketocyclazocine versus placebo and naloxone, and ketocyclazocine versus cyclazocine. These dimensions appear to have validity for four reasons. 1) They can be related to scores from subjective rating scales from the same subjects. 2) Multidimensional analyses found dimensions expressing differences among drug doses. 3) Multidimensional analyses found a dimension expressing differences between training and test conditions, a finding having face validity because in the design of the experiment training and test days were conducted differently. 4) Lastly, the results were convergent, i.e., the drug dimensions were reproducible despite differences in matrix construction and initial configuration.

We interpret the finding of three main drug psychopharmacologic dimensions as supporting evidence that in the set of four drugs and placebo three profiles of subjective states can be induced. These three may be fundamental response profiles representing drug-receptor interactions. Although high doses of naloxone have weak psychopharmacologic activity in man (9,12), the multidimensional analyses did not find evidence for a separate dimension of activity for naloxone. The lack of separate dimension for naloxone suggests that the weak psychopharmacologic activity of naloxone in man is too indistinct to characterize or that the action is mediated through the same mechanisms which operate for the actions of morphine, ketocyclazocine or cyclazocine.

Furthermore, the multidimensional scaling results for cyclazocine are compatible with the idea that the acute action of one receptor with a drug does not strongly influence the action of that drug at another drug receptor. Cyclazocine, an agonist at several receptor types, can be placed on the "morphine" dimension (D-2; Fig. 3) and on "ketocyclazocine and cyclazocine" dimension (D-3; Fig. 1). Thus, the activity of cyclazocine may be conceived as the sum of activities of the receptor types. If opioid responses were strongly influenced by one another, the expectation would be that cyclazocine would require more dimensions than the number of drugs or a failure to accomplish an acceptable fit. However, this interpretation does not rule out the possibility that the responses are interdependent since we have studied only a small subset of drugs active at opioid receptors.

Lastly, the multidimensional scaling results aid in the interpretation and validation of the subjective questionnaires. Typically, drug studies undertaken for nontherapeutic research do not involve large numbers of subjects. Validation of scale results cannot be readily accomplished because of this limitation. Multidimensional scaling is helpful because it uncovers dimensions of differences between drugs, places the drugs at a location along the dimensions, and a comparison of the relative placement of drugs along a dimension with the relative scale scores on questionnaires. Since the similarity judgements and the questionnaire scores are methodologically different data, the convergence of the results suggests that both kinds of data are reflecting fundamental subjective states.

We believe that this first study of multidimensional scaling of subjective judgements concerning drugs is promising. The results are in general agreement with extant theories concerning opiate receptors and may be helpful in maximizing the information we can obtain in the study of human subjects. It is necessary that these data be confirmed to assess the confidence we may invest in it. Additionally, the questions we have posed concerning the number of receptor-drug interactions require new studies of different opioid drugs to determine if the same dimensions or new dimensions emerge with the new drug set.

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