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## Mathematical Description of Brain States

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Extraction of representative, reliable and physiologically relevant samples of analog waveforms and the numerical representation of the salient features of such data is a major problem in the evaluation of data from evoked potential studies, particularly in behavioral experiments in which large amounts of electrophysiological data are gathered from multiple chronically implanted electrodes. In the work here reported, it was possible to obtain remarkably similar quantitative descriptions of a set of comparable brain states in 3 different cats. The specified set of states was established in each cat by utilizing 4 different drugs. The validity of the quantitative descriptions was confirmed by administering each drug at several dose levels and showing that the resulting descriptions were fundamentally identical.

In previous work (1), we pointed out that the ongoing or evoked electrical activity recorded from a particular electrode could be represented as a "signal vector". A set of simultaneous records from different structures or sequential records from the same structure can be represented as a set of signal vectors, which exist in a multidimensional "signal space".

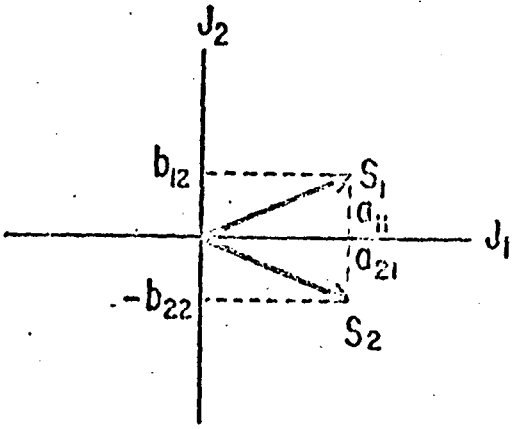
We showed further that a precise quantitative description of the signal space of the brain could be parsimoniously provided by the set of regression equations obtained by a principal component factor analysis (2) of recordings from different brain regions. The evoked activity or signal vector recorded from any brain region could be reconstructed as linear combinations of a small number of mathematical descriptors (factors) common to all brain regions. These factors were the axes of the signal space. The utility of such multivariate techniques in brain

research has subsequently been confirmed by a number of workers (3).

A major shortcoming of the principal component method arises because of the lack of specificity of the factors which it provides. Although such principal components describe the signal space in the most parsimonious way by defining successive factors in such a way as to maximize the rate of reduction of the residual variance, or unaccounted for energy, of the system, it is not yet obvious what physiological processes, if any, correspond to the set of axes for the signal space which is thus obtained. Perhaps more serious, changes in the orientation of a subset of the signal vectors in the space effectively rotates the reference axes. Principal component descriptions of two sets of data with many similarities but a few differences are often extremely different. Further, axes can make comparable contributions to many signal vectors and are not necessarily related to different signals in a differential way.

A solution to these shortcomings is provided by the Varimax procedure (4), which specifies a rotation of the principal component coordinate system in such a way as to align each axis as closely as possible to one signal vector and as far as possible from the other vectors in the space. Functionally, the utility of this method is that it maximizes differences in the description of vectors with dissimilar orientation while clustering together vectors which have common features. Hopefully, further study will elucidate the physiological processes which correspond to these new axes. The basic notions expressed in the foregoing are illustrated in Fig. 1.

In the present experiment, 3 cats were subjected to different doses of chlorpromazine (CPZ - 5, 2.5, and 1.0 mg/kilo) an experimental tranquilizer (MJ - 5, 2.5, and 1.0 mag/kilo (5), sodium phenobarbital (PHENO - 20, 10, and 5 mg/kilo, methamphetamine (METH - 1.0 and 0.5 mg/kilo, and 2 saline placebos. The injections were administered in a Lation square order, with a minimum of one week between injections, and the overall study followed a double-blind procedure, with results decoded only after final analysis was completed. All 3 cats had 34 electrodes chronically implanted into brain regions. Two of the cats had been differentially conditioned to press one lever on a work panel to obtain food when a 2 cps flicker ($V_1$) was presented and to press a second lever to avoid shock when a 5 cps flicker ($V_2$) occurred. The third cat was untrained. The flicker, delivered from an overhead source in the moderately illuminated apparatus, caused a weak fluctuation in the overall luminance of the whole visual field.

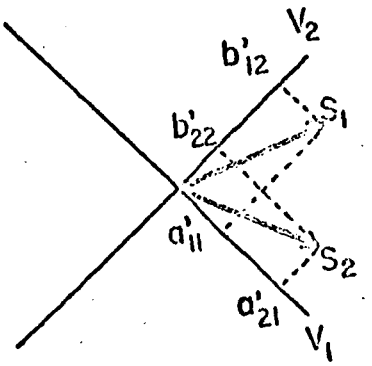



*In this description, both vectors $S_1$ and $S_2$ receive equal contributions from $J_1$, the Jacobi factor which contributes the largest amount of energy to this two-vector example. The loadings of $J_2$ upon $S_1$ and $S_2$ respectively are $b_{12}$ and $-b_{22}$, equal in magnitude but opposite in sign. Thus, $S_1$ and $S_2$ receive equal contributions from both $J_1$ and $J_2$. The factor analysis spans the space in a way which does not relate any factor selectivity to any signal vector.*

$$S_1 = a_{11} J_1 + b_{12} J_2$$

$$S_2 = a_{21} J_1 + b_{22} J_2$$

Where $a_{11} = a_{21}, b_{12} = -b_{22}$




*Varimax rotation of $J_1$ and $J_2$ is shown in B. The two Varimax factors, $V_1$ and $V_2$, are located as closely as possible to the vectors $S_1$ and $S_2$. The loadings of $V_1$ upon $S_1$ and $S_2$ are $a'_{11}$ and $a'_{21}$. Thus, $V_1$ contributes markedly more to $S_2$ than to $S_1$, since $a'_{21} > a'_{11}$. Conversely, the loadings of $V_2$ upon $S_1$ and $S_2$ are $b'_{12}$ and $b'_{22}$. $V_2$ contributes more to $S_1$ since $b'_{12} > b'_{22}$. The factor analysis now spans the space in a way which locates vector $S_1$ closest to factor $V_2$, while vector $S_2$ is closest to factor $V_1$.*

$$S_1 = a'_{11} V_1 + b'_{12} V_2$$

$$S_2 = a'_{21} V_1 + b'_{22} V_2$$

Where $a'_{21} > a'_{11}$ and $b'_{12} > b'_{22}$

Fig. 1

Each drug experiment occupied a whole day. Recording sessions were held each hour, and about 40 trials of $V_1$ and $V_2$ were presented in a random sequence. The average response latency was about 8 seconds under control conditions, and trials were separated by random intervals averaging about one minute. At the beginning of the day, two pre-drug control sessions were recorded and the experiment proceeded only if behavioral baselines were normal. The appropriate drug dose, coded so as to be unknown to the experimenter, was then administered and hourly post-drug recording sessions occupied the remainder of the day. In order to achieve the maximum sample size and simultaneity of recording of all data to be compared, the 12 recording derivations (corresponding to our 12 channel recording capability) of greatest interest were selected from the larger set of placements available in each animal. These derivations included representative examples of visual cortes, lateral geniculate body, mesencephalic reticular formation, various midline and intralaminar thalamic nuclei, and different regions of the limbic system (6).

A series of average evoked responses was computed hour by hour for each structure and each stimulus, using a sample of about 200 evoked potentials taken from 10 to 20 behavioral trials within the same session. The data were further compressed by taking the average evoked response from the 2nd pre-drug control session (CONTROL) and from the 2nd post-drug session (DRUG). All other data were disregarded for purposes of this analysis. For each cat, then, the total experiment produced a set of evoked responses consisting of 2 stimuli ($V_1$ and $V_2$) x 12 structures x 13 drug-dose conditions (3 CPZ, 3 MJ, 3 PHENO, 2 METH, 2 SALINE) x 2 samples (CONTROL and DRUG), or a total of 624 average evoked responses.

These total set of averages could be organized into a matrix with N rows and M columns, in which N equals 26 (CONTROL and DRUG samples obtained from one structure in response to one stimulus in 13 different drug experiments) and M equals 24 (12 different structures and 2 different stimuli). The 24 columns of this matrix were then separately subjected to principal component factor analysis and the results were rotated according to the Varimax procedure. The 24 resulting analyses were then combined to obtain on overall description of the effect of the set of conditions on the whole signal space.

Since Varimax factors from different analyses are not uniquely identified, it was necessary to define a numbering convention. The convention adopted defined factor 1 as the factor which accounted for most energy (largest weighting coefficient) of the CONTROL waveshapes, factor 2 as the factor other than factor 1 on which CPZ waveshapes showed the highest loading, factor 3 as the factor other than factors 1 and 2 on which MJ

waveshapes had the highest loading, factor 4 as the factor other than factors 1-3 on which PHENO waveshapes had the highest loading, factor 5 as the factor other than factors 1-4 on which METH waveshapes had the highest loading. Factors 6 and above were undefined.

It must be made clear that this convention in no way prejudices the outcome. The definitions adopted relate to the identification of similar axes in different analyses and do not affect the loading of a particular waveshape upon a specific vector in any way.

Each column in the matrix contained 26 waveshapes, representing the different states or modes displayed by the corresponding brain region while responding to the same exteroceptive stimulus delivered under a variety of conditions. From this viewpoint, the exteroceptive stimulus can be regarded as a test probe or perturbation which reflects the state of the system upon which it impinges by the nature of the elicited response. One might reasonably expect the 13 control waveshapes to be markedly similar, reflecting the normal or baseline state of the brain. Ideally, the waveshapes obtained after different doses of the same drug would be fundamentally similar, indicating that a basic similarity existed among the states produced in the brain by those different dose levels and reflected the characteristic action of that particular drug. Further, one might hope that although differences in mode within different doses of the same drug were small, differences in mode between the effects of different drugs would be relatively large, insofar as the different drugs caused characteristically different states and modes of response in the relevant brain region.

To the extent that the control data from a structure were basically stable and the effects of the 13 drug conditions on the activity of that structure exactly corresponded to the ideal case described above, and to the extent that a Varimax analysis of that body of data ("column analysis") successfully reflected those facts in an accurate and reliable way, the characteristics of the resulting analysis can be predicted.

The CONTROL and SALINE signal vectors should load predominantly upon factor 1 only, CPZ signal vectors predominantly upon factor 2, MJ signal vectors predominantly upon factor 3, PHENO signal vectors predominantly upon factor 4, and METH signal vectors predominantly upon factor 5. The results which were obtained in this experiment corresponded strikingly with this ideal outcome.

A representative column analysis, from the visual cortex (bipolar) of cat 2, is illustrated in Fig. 2. Along the left side of the figure are arranged the average response waveshapes obtained under 11 control and 13 drug conditions (7). To the right of each waveshape is the regression equation which reconstructs that waveshape with 97 % accuracy, as a linear combination of the Varimax factors, with the percentage contribution of each factor indicated by the size of the corresponding loading coefficient. Note that the CONTROL and SALINE waveshapes load almost exclusively on factor 1, the CPZ waveshapes predominantly on factor 2, the MJ waveshapes predominantly on factor 3 and the METH waveshapes predominantly on factor 5. Note that PHENO does not load on a separate factor in this analysis. All 3 doses diplay a highest loading on factor 2, suggesting that on the visual cortex, the effect of this drug resembles that CPZ. In particular, the 20 mg/k dose of PHENO shows a 91 loading on factor 2, the "CPZ-like" dimension defined earlier. Examination of Fig. 2 shows that the 20 mg/k PHENO waveshape was in fact very similar to the 5 mg/K CPZ waveshape. In other brain regions of this cat, that similarity was not observed, but PHENO showed heaviest loadings on the fourth factor. These results correspond fairly well to the ideal outcome. Different doses of the same drug load primarily upon the same factors, while different drugs tend to load on different factors.

Since it was generally the case that different doses of the same drug loaded predominantly upon the same factor, the Varimax descriptions of different dose effects of each drug were averaged. The 24 column analyses quantifying the results obtained from 12 structures in response to $V_1$ and $V_2$ were then combined into an overall description of the effects of these various substances upon the signal space representing the brain of each cat. It is possible to depict the relative orientation of signal vectors in the hyper-dimensional space using conventional Cartesian coordinates, if one restricts oneself to presenting only 3 dimensions at a time.

Figure 3 shows the effects of these different drugs upon cats 1, 2 and 3, as reflected in the "factor 2-3-5" space, that is, factor 2, factor 3 and factor 5 were represented as the 3 axes of the coordinate system. The dose-averaged and structure-average signal vectors are shown in this coordinate system, with relative orientations determinde by their loading upon factors 2, 3 and 5. Since the control vectors loaded almost completely upon factor 1 in all 3 animals, the origin of the space depicted in Fig. 3 corresponds to the state of the brain under normal conditions. The various drug vectors can be conceptualized as the trajectory through signal space describing the alteration in brain state caused by that drug.

Average Response Waveshapes and Corresponding Regression Equations -- Column Factor Analysis, VISUAL CORTEX, $V_1$, Cat 2

| Pre Drug | DOSE mg/kg | | Post Drug | DOSE mg/kg | |
|---|---|---|---|---|---|
| CPZ | 5 | $= .72F_1+.14F_2+.03F_3+.00F_4+.09F_5$ | CPZ | 5 | $=.06F_1+.91F_2+.00F_3+.00F_4+.01F_5$ |
| | 2.5 | $= .71F_1+.07F_2+.19F_3+.00F_4+.01F_5$ | | 2.5 | $=.23F_1+.69F_2+.03F_3+.00F_4+.03F_5$ |
| | 1 | $=.79F_1+.09F_2+.08F_3+.00F_4+.02F_5$ | | 1 | $=.13F_1+.68F_2+.15F_3+.00F_4+.03F_5$ |
| MJ | 5 | $= .73F_1+.16F_2+.08F_3+.00F_4+.01F_5$ | MJ | 5 | $=.15F_1+.18F_2+.57F_3+.00F_4+.08F_5$ |
| | 2.5 | $= .64F_1+.09F_2+.07F_3+.00F_4+.18F_5$ | | 2.5 | $=.08F_1+.22F_2+.65F_3+.00F_4+.04F_5$ |
| | 1 | $=.67F_1+.16F_2+.11F_3+.00F_4+.04F_5$ | | 1 | $=.16F_1+.01F_2+.77F_3+.00F_4+.03F_5$ |
| PHENO | 20 | $=.70F_1+.15F_2+.07F_3+.00F_4+.06F_5$ | PHENO | 20 | $=.03F_1+.91F_2+.03F_3+.00F_4+.02F_5$ |
| | 10 | $=.66F_1+.10F_2+.19F_3+.00F_4+.02F_5$ | | 10 | $=.25F_1+.48F_2+.25F_3+.00F_4+.00F_5$ |
| | 5 | $= .65F_1+.11F_2+.18F_3+.00F_4+.05F_5$ | | 5 | $=.23F_1+.60F_2+.15F_3+.00F_4+.00F_5$ |
| METH | 0.75 | $= .67F_1+.10F_2+.01F_3+.00F_4+.20F_5$ | METH | 0.75 | $=.13F_1+.00F_2+.06F_3+.00F_4+.78F_5$ |
| | 050 | $= .82F_1+.01F_2+.07F_3+.00F_4+.08F_5$ | | 050 | $=.33F_1+.09F_2+.06F_3+.00F_4+.50F_5$ |
| | | | SALINE | | $=.80F_1+.10F_2+.03F_3+.00F_4+.05F_5$ |
| | | | | | $=.57F_1+.06F_2+.03F_3+.00F_4+.32F_5$ |

Fig. 2

AVERAGE VARIMAX LOADINGS

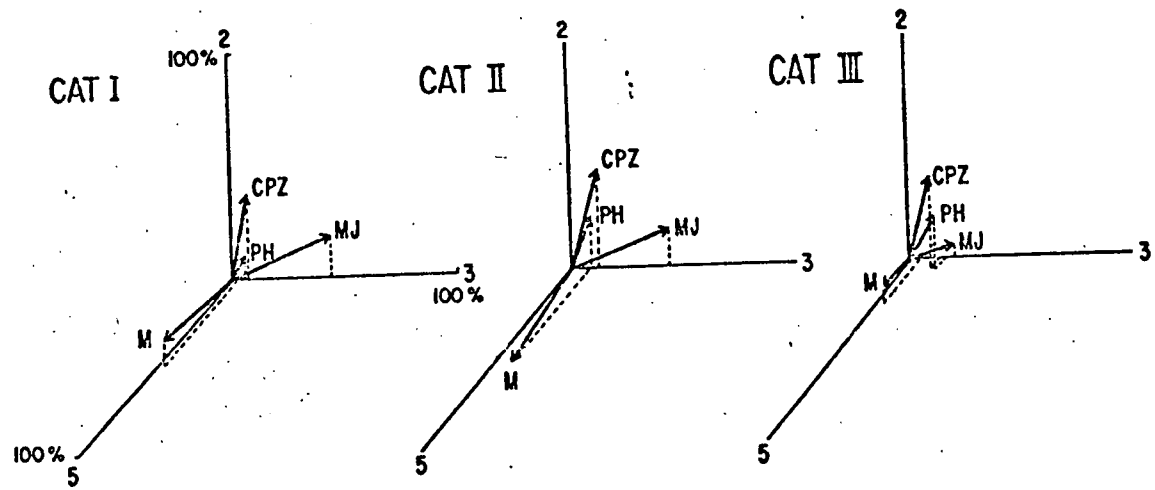



Fig. 3

Although the results do not achieve the theoretically ideal outcome, they come remarkably close. No drug effect loads exclusively upon only a single factor, but each drug effect consistently loads heaviest upon one particular factor. In fact, what is required for practical utility of this method is not so much exclusive loading of a state upon a single factor as consistent and unique orientation of that state in the signal space. These results show that this has been acheived in the case of these experiments.

The findings which have been reported here show that factor analytic techniques may provide a meaningful quantitative description of drug action upon the brain. Such a quantitative drug nomenclature may have utility for screening and evaluating new drugs, as well as in elucidating the functional basis for certain aspects of the drug effects. It should be pointed out, however, that drugs were employed in this study because they provided a convenient way to establish definable brain states which could reasonably be expected to have similar features in different animals. The method which has been described has generality, since it will provide a reliable quantitative description of any set of brain states which an investigator chooses to define (8).

## REFERENCES AND NOTES

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5) These animals are still alive and under study for other purposes. Therefore, histological confirmation of these placements is not yet available. However, since the signal vectors are treated as samples of the

signal space of the brain, with no anatomical reference or interpretation offered in this paper, the actual electrode location is not relevant to our present concerns.

6) Because our PDP-12 computer has a limited memory capacity, our column factor analysis could only accommodate 24 signal vectors. The 2 pre-SALINE control waveshapes were therefore excluded from the analysis.

7) A full description of the results of these experiments has been prepared and submitted for publication elsewhere.

8) Supported by PHS grant No. MH08579 and grants from Mead Johnson, Abbott Laboratories, Ciba-Geigy Pharmaceuticals. We wish to acknowledge the programming skill of Dr. Paul Baston.