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# ANALYSIS OF PETT IMAGES IN PSYCHIATRIC DISORDERS

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SUMMARY

A quantitative method is presented for studying the pattern of metabolic activity in a set of Positron Emission Transaxial Tomography (PETT) images. Using complex Fourier coefficients as a "feature vector" for each image, cluster, principal components, and discriminant function analyses are used to empirically describe metabolic differences between control subjects and patients with DSM III diagnosis for schizophrenia or endogenous depression. We also present data on the effects of neuroleptic treatment on the local cerebral metabolic rate of glucose utilization (LCMRGI) in a group of chronic schizophrenics using the region of interest approach.

INTRODUCTION

Although present analysis of PETT images has emphasized the distinction between grey and white matter, this distinction may be overdrawn (1) and a loss of information is perhaps incurred by imposing a priori broad anatomical distinctions to PETT images. A PETT image can also be conceptualized as a three dimensional geometric object where the metabolic activity at each point provides the third dimension. How can we obtain a set of shape descriptors that characterize the geometrical three dimensional pattern of a PETT image in a parsimonious way? This is needed for the empirical comparison of images from controls with images from psychiatric patients to evaluate different brain patterns and how they change with psychopharmacological intervention. Once a feature vector has been obtained, a set of PETT images can be described as points in multidimensional feature space. The feature vector can then be used to apply different multivariate analytical procedures to evaluate differences and similarities among images. Multivariate procedures have been used in other areas of neurobiological (2) and psychiatric research (3).

Cluster analysis (4) identifies areas in this space where points tend to conglomerate because of their quantitative similarities. It allows the visualization of natural groups in the images and to decide if these groups correspond with clinical and anatomical distinctions.

Principal components analysis (5) can also be used as a method for classifying the features of a set of PETT images. It partitions the variables into subsets that are highly correlated among themselves. This is useful not only because of the theoretical value of identifying correlated features, but also because the quantitative values of several correlated variables can be combined into a single number which describes an abstract feature of a PETT image.

Discriminant function analysis (3) is a statistical method for obtaining linear combinations of variables for the purpose of optimally separating previously defined classes of individuals. This is the most parsimonious way of representing differences between groups. If one has three groups of observations, the first discriminant function separates them along the axis of maximum differences, and the second discriminant function achieves the next highest separation, so that if true differences exist between the groups, these will be represented as three non-overlapping aggregates of points in two dimensional discriminant space.

Initial PETT studies with schizophrenic patients have reported a hypometabolic pattern of glucose utilization in the frontal cortex (6,7). The contribution of either prior or current neuroleptic treatment to this pattern is unknown. A partial answer to this problem may be provided by looking for differences in RCMGl in schizophrenic subjects before and after treatment with neuroleptics.

## MATERIALS AND METHODS

The following procedure has been applied to the complete set of 422 PETT VI (18-FDG) images obtained from twelve control subjects, thirteen schizophrenic subjects, and six depressed subjects. Five schizophrenics and three of the depressed patients had scans before and after treatment with thiothixene and doxepin, respectively.

The mean and standard deviation of the metabolic rates of each head image were obtained and these values used to standardize (z-transform) each image to a mean of zero and a standard deviation of one. This is done for the purpose of comparing patterns of metabolic activity independent of mean metabolic activity. The fast Fourier transform (8) was applied to the (128 x 128) images (pixel size: 2.78 mm). The low frequency (11 x 11) matrix of complex Fourier coefficients was selected for analysis, using the magnitude of its 61 coefficients as feature

vectors. A correlation matrix was obtained from these feature vectors and a principal component analysis was performed on this matrix. A clustering procedure used for these images is based on the furthest neighbor method (4) and the analysis was performed again using the magnitudes of the Fourier coefficients as a feature vector omitting the central coefficient. The problem common to clustering techniques of deciding on the number of clusters present in the data was addressed by selecting, on the basis of previous experience, at the level at which non- adjacent anatomical slices are differentiated. A discriminant analysis was also done on all 422 images and then repeated for those images at a given anatomical level. The levels were defined anatomically as the CS (centrum semiovale) plane, the BG (basal ganglia) plane which included the thalamic nuclei and transected the basal ganglia, the MV (midventricular) plane which is adjacent to the BG plane and transects the third ventricle and may include a portion of the thalami, and the IV (infraventricular) plane which transects cerebellum and the lower portion of the temporal lobes.

The effects of neuroleptic treatment on brain metabolism were studied in six hospitalized male chronic schizophrenic patients who met RDC criteria and were kept neuroleptic free for a period of at least two weeks. No patient had any contributing medical or neurological illness. The five age matched normal controls were screened for the absence of psychopathology by the Structured Clinical Interview (SCI). Prior to the PET run, each patient had a CT scan taken through the canthomeatal (CM) line which was used for head alignment and analysis of the PET images. All subjects were run on the PETT VI using F-18-fluorodeoxyglucose (FDG) under resting conditions in a dimly lit room with eyes open and ears plugged.

The patients then entered a treatment phase during which they received thiothixene, a standard neuroleptic, in doses up to 100 mg per day. Treatment was based solely on clinical response and tolerance of side effects and was continued until an endpoint determined by clinical judgement. At the end of the treatment period which ranged from four to ten weeks, the patients were scanned again with FDG under the conditions described above.

These PETT scans were analyzed by the region of interest (ROI) method with the appropriate CT image of each patient carefully matched to his corresponding PETT image and anatomical landmarks used to define the ROI's. Since prior studies used instruments of lower resolution such as PETT III, we attempted to reproduce at least some of the previous regions, such as the frontal region (7,8).

## RESULTS

Figure 1 shows the reconstruction of a metabolic brain image obtained with low resolution on PETT VI at the BG level using progressively larger matrixes of the low frequency Fourier coefficients. The reconstruction obtained with the central (9 x 9) matrix of the Fourier coefficient achieves good reconstruction of the original image . Only 81 numbers were needed since the matrix of numbers is symmetrical. The reduction in the number of variables achieves substantial data compression.

Table 1 presents the weights of the Fourier coefficients from the central (11 x 11) matrix for the first three principal components. The first principal component accounts for 32 % of the variance, the first and second for 48 %, and the first, second, and third for 60 %. The modulus of the first and third harmonics have high loading in the first principal component. The modulus of the fourth harmonic is largely reflected in the second principal component while the third principal component is weighted by the modulus of the second harmonic. The first principal component is related to the size of the image and separates the relatively large middle of the head (BG and MV) images from those above and below. The second principal component establishes the distinction of BG images from all the rest. The third principal component separates the infraventricular images. These results are very preliminary. We are not as yet in a position to complete the principal component analysis of a single anatomical level since a rule of multivariate analysis is to use five times as many entities as variables in the feature vector. Thus, to adequately represent the effects of treatment as trajectories in principal component space we would need 300 images in a single plane.

Table 2 presents the characteristics of the dendrogram of the cluster analyses at the level of the 20 clusters. Clusters I, O, Q and R include only images from psychiatric patients. Clusters N, B and L include twice as many images from patients as compared with control subjects, while the reverse is seen in clusters D, E and M.

Table 3 shows the results obtained from the discriminant analyses at the BG, MV, and CS levels using progressively larger matrixes of the magnitude for the Fourier coefficients. With 61 magnitudes which correspond to the (11 x 11) matrix you get 97 %, 95% and 86% discrimination between normals, schizophrenics and depressed at the BG, MVT$_3$ and CS level respectively. Some dis-

crimination is also obtained when only 13 variables are used.

Figure 2 shows the results of the ROI analyses of the brain images for the frontal region at the BG level from normals and chronic schizophrenic subjects obtained before and after neuroleptic treatment. Decreased LCMRGI in the left frontal region at the BG level was observed in the washed out schizophrenic subjects. The ratio of frontal region to whole slice remains lower in the schizophrenic group when compared with normals even after treatment (Figure 3a,b). This result is consistent with our earlier studies done on a mixed sample of medicated and unmedicated chronic schizophrenic patients (7). The lateral frontal asymmetry which is equal or greater than one in several reported studies involving normal populations (9), is slightly less than one in the schizophrenic group and significantly less than one when only the left frontal region is considered. Increasing the size of both groups to a larger sample confirms that this finding of left "hypofrontality" is statistically significant (Wolkin and Jaeger, unpublished data).

The mean LCMRGI showed a distribution of values that appear remarkably similar before and after treatment. Both the lateral asymmetry and the hypofrontality are preserved in the group after neuroleptic treatment. Thiothixene treatment resulted in a group increase of 25% in whole slice CMRGl which paralleled the group decrease of about 25% in scores on the BPRS (Brief Psychiatric Rating Scale).

## *DISCUSSION*

Research psychiatry and psychometrics have developed quantitative classification models of patients based on their symptoms (10). Strategies for sequentially performing different types of multivariate analysis on large data sets and for validating the taxonomic models when additional subjects are studied have also been developed, as well as the relationship between these models and response to treatment (3). This logic of analysis can be applied to the quantitative study of feature vectors of PETT images.

Studies of the spectral characteristics of the EEG in large samples of patients has also used multivariate analytical strategies. Using cluster analysis, subgroups of control subjects with distinct electroencephalographic wave patterns have been identified (11). Since the variance among control subjects is large, it is important to take this into consideration and not only compare patients with controls.

Although multivariate analysis can be performed on feature vectors derived from a set of metabolic rates obtained from anatomical "regions of interest", we are also using the magnitudes from the complex Fourier coefficients as feature vectors for the following reasons:

1. The brain can be conceptualized as a system whose functions are distributed through widespread anatomical regions (12). Because of this, the study of the global pattern of metabolic activity is complementary to the study of localized anatomical "regions of interest" metabolic rates.

2. The Fourier transform can be automatically obtained from a set of PETT images in a rapid fashion which allows the analyses of large matrices of data.

3. Fourier coefficients represent global geometric shape properties of an image. Their use enables data compression and the number to be included in the multivariate models can be increased in an orderly fashion as the classification model grows with the additon of new subjects.

Cluster analysis is a systems tool for managing complexity (13,14). It has been used to classify patients empirically into homogeneous subgroups on the basis of clinical symptoms (10). The same multivariate strategy can used for grouping their brain metabolic patterns. For diagnostically meaningful psychiatric results, a larger sample of subjects and a replication study will be needed. This work is in progress. Cluster analysis can be used to study other feature vectors derived from PETT images (such as mean metabolic values for a set of anatomical regions).

The fact that adequate three group discrimination can be achieved using such broad 7 cms/cycle feature characteristics points to the spatially widespread abnormal patterns perhaps present in both schizophrenic and depressed patients. Future work will have to determine if this discrimination persists as well as the neuroanatomical and neurophysiological significance of the discriminant function dimensions. Control subjects show more dispersion in some of these normal / abnormal and schizophrenic / depressed discriminant dimensions than the two patient groups. We plan to continue efforts in subtyping normal subjects. In order to validate these PETT subgroups, extensive personality testing will be mandatory.

We did not anticipate finding such clear differences between control and patient images by discriminant function analysis. Some of the issues that need to be investigated before any psychiatric or neurobiologic conclusions can be drawn using this strategy of analysis are: how do we assign spectral features that

discriminate among subjects to spatial characteristics? Which PETT parameters should be correlated with the clinical domain? What is the effect of z-transforming or of normalizing all images to the same size on the multivariate spectral models?

Although the results of this study of the effect on LCMRGl of neuroleptic treatment of a group of chronic schizophrenics on LCMRGl are preliminary, the left hypofrontal derangement appear to be a consistent finding seen in chronic schizophrenics. The failure to alter the hypofrontal pattern of LCMRGl with treatment and clinical improvement when each subject served as his own control helps to explain our earlier findings with a mixed group of medicated and unmedicated chronic schizophrenics (7).

Two basic strategies have been used in the analysis of the data obtained from the studies done on psychiatric patients using PETT, the regional approach (7) and the integrative approach (15). Both approaches have been presented. The regional approach is based on neuroanatomical knowledge of relations between anatomy and function. The integrative approach is based on an interactive model of brain functioning (12). Combination of both approaches offers a way of mapping the brain by means of its anatomical structures as well as by functional landmarks.

ACKNOWLEDGEMENTS

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## Legends to Tables

Table 1: Loadings of {11x11} magnitudes of low frequency for Fourier coefficients on first three principal components (adjusted for magnutide of eigenvalues).

Table 2: Cluster analysis of 422 PETT VI ($^{18}$FDG) images using 60 magnitudes of low frequency Fourier coefficients as feature vector. The first row gives a consecutive label to each of 20 clusters. The second row presents the number of images in each cluster. The third row gives the percent of the images in each cluster that are from control subjects. The last row gives the percent of the images in each cluster that are from either schizophrenic or depressed subjects.

Table 3: Tabulation of results of 15 three group discriminant function analyses between images from control subjects and from patients with diagnosis of schizophrenia or endogenous depression using the magnitudes of the Fourier coefficients as feature vectors. The first column identifies the anatomical level (centrum semiovale, basal ganglia and midventricular). The second column indicates the number of variables used for discrimination. The third column gives the percent of images that were correctly classified into one of three groups. The fourth column gives the percent of misclassification due to control images being identified as patient images or vice versa. The fifth column gives the percent of misclassifications due to images from one diagnostic group being identified as the other.

TABLE I

LOADINGS OF FOURIER COEFFICIENTS ON FIRST THREE PRINCIPAL COMPONENTS (PC) (n=422)

First PC

| | 0 | +1 | +2 | +3 | +4 | +5 |
|---|---|---|---|---|---|---|
| +5 | .42 | .33 | .04 | -.24 | -.21 | .18 |
| +4 | -.28 | -.23 | -.02 | .36 | .43 | -.24 |
| +3 | -.55 | -.67 | -.83 | -.76 | -.12 | -.01 |
| +2 | -.10 | .17 | .66 | -.78 | -.92 | -.22 |
| +1 | -.87 | -.85 | -.63 | .66 | -.89 | -.66 |
| 0 | -.71 | -.90 | -.82 | .33 | -.81 | -.74 |
| -1 | | -.85 | -.62 | .59 | -.91 | -.78 |
| -2 | | .17 | .66 | -.80 | -.93 | -.44 |
| -3 | | -.68 | -.84 | -.80 | -.26 | .11 |
| -4 | | -.23 | -.04 | .31 | .43 | -.15 |
| -5 | | .35 | .08 | -.28 | -.36 | .10 |

Second PC

| | 0 | +1 | +2 | +3 | +4 | +5 |
|---|---|---|---|---|---|---|
| +5 | .33 | .46 | .70 | .67 | .15 | -.35 |
| +4 | -.83 | -.87 | -.90 | -.74 | .01 | .13 |
| +3 | -.11 | -.16 | -.30 | -.50 | -.59 | .28 |
| +2 | .08 | .05 | .05 | .22 | -.02 | -.17 |
| +1 | .12 | .10 | -.05 | -.21 | .30 | .09 |
| 0 | .03 | .12 | .02 | -.37 | .41 | .18 |
| -1 | | .10 | -.03 | -.16 | .26 | .09 |
| -2 | | .05 | .09 | .17 | -.05 | -.15 |
| -3 | | -.16 | -.30 | -.49 | -.66 | .11 |
| -4 | | -.86 | -.90 | -.75 | -.10 | .12 |
| -5 | | .44 | .70 | .70 | .27 | -.35 |

Third PC

| | 0 | +1 | +2 | +3 | +4 | +5 |
|---|---|---|---|---|---|---|
| +5 | .15 | .12 | .11 | .31 | .57 | .29 |
| +4 | .10 | .07 | .02 | .09 | .49 | .43 |
| +3 | .26 | .30 | .28 | .17 | .12 | .49 |
| +2 | -.80 | -.80 | -.37 | .22 | .01 | .06 |
| +1 | -.36 | -.40 | -.57 | -.19 | -.02 | -.09 |
| 0 | -.40 | -.28 | -.36 | -.29 | .00 | -.11 |
| -1 | | -.40 | -.58 | -.22 | .02 | -.08 |
| -2 | | -.82 | -.44 | .23 | .02 | .04 |
| -3 | | .30 | .27 | .13 | .05 | .43 |
| -4 | | .06 | -.02 | .03 | .44 | .55 |
| -5 | | .11 | .07 | .27 | .57 | .40 |

TABLE 2

CLUSTER ANALYSIS OF MAGNITUDES OF FOURIER COEFFICIENTS (n=422 $^{18}$FOG) PETT VI IMAGES

| Label | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Images | 48 | 39 | 34 | 12 | 19 | 16 | 39 | 48 | 9 | 33 | 22 | 8 | 13 | 16 | 13 | 19 | 5 | 2 | 18 | 9 |
| % Control | 53 | 29 | 33 | 89 | 88 | 48 | 37 | 68 | 0 | 37 | 56 | 30 | 70 | 17 | 0 | 50 | 0 | 0 | 63 | 42 |
| % Psychiatric | 47 | 71 | 67 | 11 | 12 | 52 | 63 | 32 | 100 | 63 | 44 | 70 | 30 | 83 | 100 | 50 | 100 | 100 | 37 | 58 |

TABLE 3

CLASSIFICATION OF PETT IMAGES USING DISCRIMINANT ANALYSIS (n=422)

FOR DIFFERENT ANATOMICAL LEVELS

| | No. of Variables | % Correct | C/A Misclassification | S/D Misclassification |
|---|---|---|---|---|
| CS | 5 | 61 | 26% | 28% |
| (n=139) | 13 | 73 | 12% | 15% |
| | 25 | 73 | 12% | 15% |
| | 41 | 76 | 9% | 15% |
| | 61 | 86 | 4% | 10% |
| BG | 5 | 61 | 24% | 15% |
| (n=96) | 13 | 72 | 16% | 12% |
| | 25 | 86 | 5% | 9% |
| | 41 | 93 | 1% | 6% |
| | 61 | 97 | 0% | 3% |
| MV | 5 | 61 | 23% | 16% |
| (n=94) | 13 | 64 | 18% | 18% |
| | 25 | 79 | 8% | 13% |
| | 41 | 88 | 2% | 10% |
| | 61 | 95 | 2% | 3% |

## Legends to Figures

Figure 1: Reconstruction of a brain image at the basal ganglia level using the progressively larger matrixes of the low frequency Fourier coefficient (the central {3x3}, {9x9} and {11x11} matrixes).

Figure 2: Histogram of the mean rGMRgl in left and right frontal gray regions at the basal ganglia levels from normal subjects and from schizophrenics before and after treatment.

Figure 3a: Schematic representation of LCMRGl in normal subjects and drug-free schizophrenics. Data are expressed as region/whole slice ratios in the BG plane. Cortical regions are depicted with frontal region at the top, temporal and occipital at the bottom with left on the left.

Figure 3b: Comparison of LCMRGl in normal subjects and schizophrenics after neuroleptic treatment. Data are expressed as in Figure 3.

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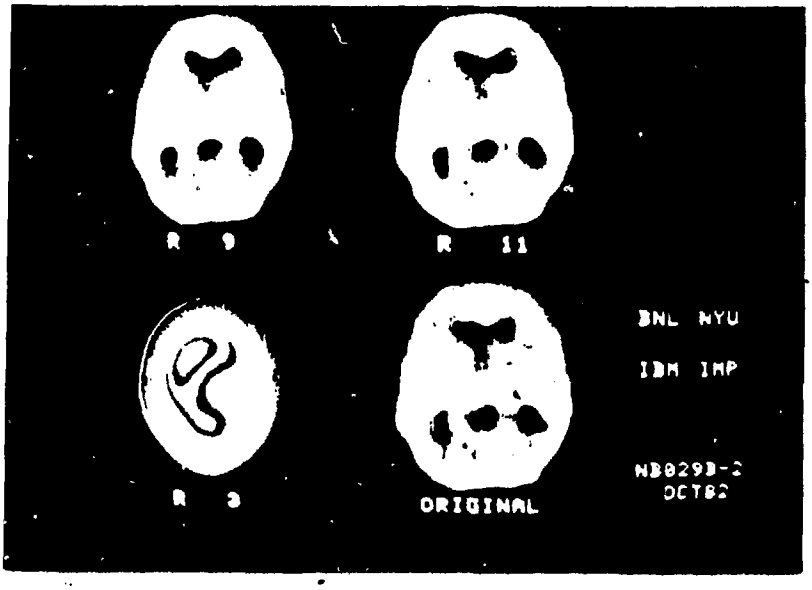
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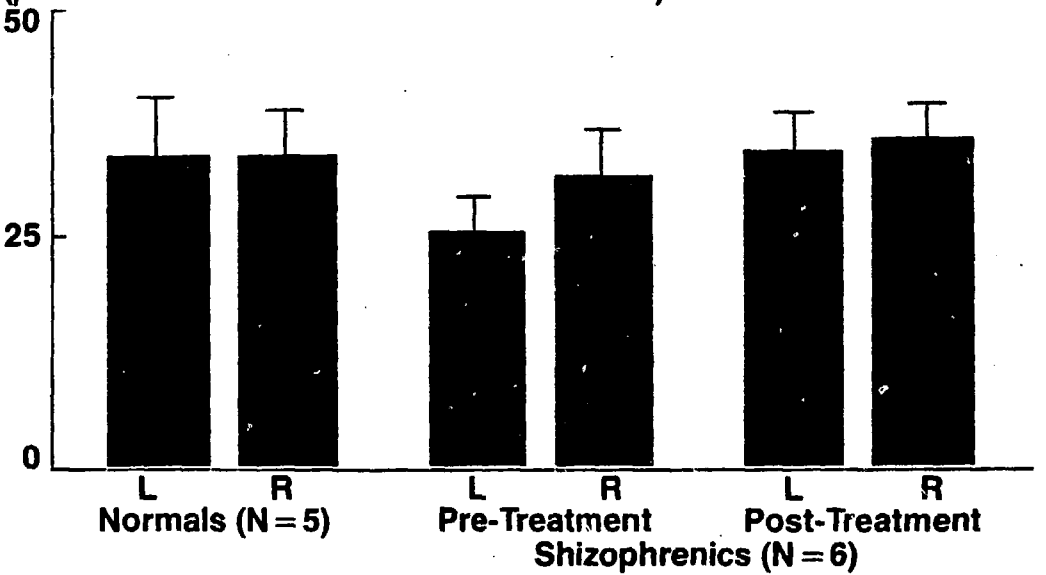
figure 1

## MEAN rCMRgl (±SD) IN LEFT AND RIGHT FRONTAL GRAY REGIONS AT THE BASAL GANGLIA LEVEL

($\mu$ Moles Glucose/100 Gram Tissue/Minute)

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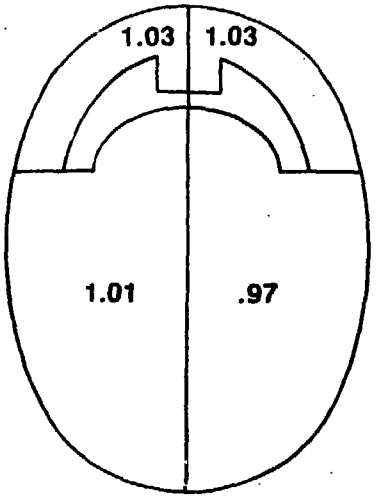
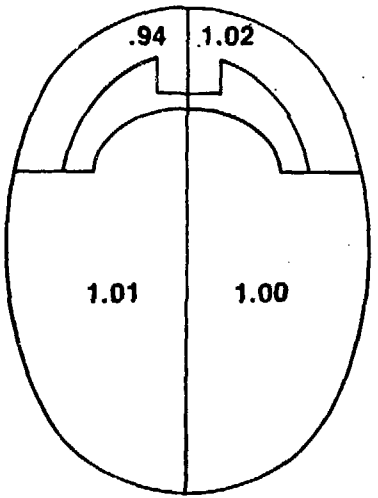
# REGION/WHOLE SLICE RATIO




Normals
(N = 5)




Schizophrenics
Pre-Treatment (N = 6)

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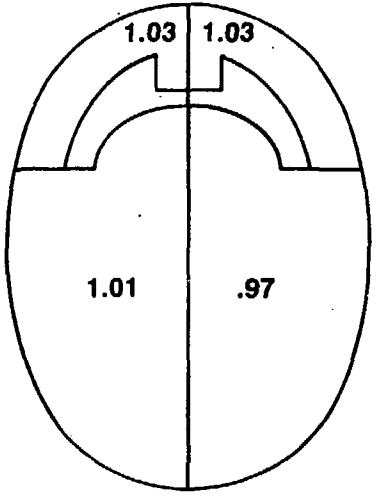
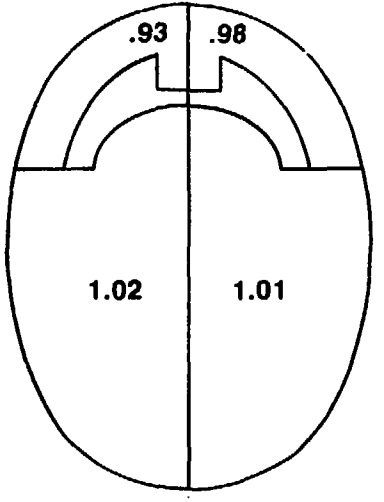
# REGION/WHOLE SLICE RATIO




Normals
(N = 5)




Schizophrenics
Post-Treatment (N = 6)

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