Detecting Asymmetries in Hippocampal Shape and Receptor Distribution using Statistical Appearance Models and Linear Discriminant Analysis

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Abstract

Neurological studies are often concerned with identifying abnormalities in brain structure affecting asymmetry between left and right hemispheres. This paper presents techniques which allow measurement and characterisation of differences between neuroanatomic structures due to variation in both shape and receptor distribution. This provides a potentially powerful tool for identifying subtle pathological asymmetries. We propose a combination of appearance modelling and linear discriminant analysis and present preliminary results of the technique applied to 2D hippocampal autoradiographs. We also describe experiments testing the relative performance of variants of our method to test assumptions about the nature of the analysis and the nature of the data.

1 Introduction

Despite many studies, the anatomical characteristics of the major neuropsychiatric disorders are still poorly understood. Furthermore, few rapid and sensitive techniques exist for characterising morphological variation of neural structure with which pathology can be identified. Presently, studies depend upon fairly coarse and simplistic measurements such as anatomic volume or thickness, measures which are unable to register anything other than the most gross of structural and neurochemical abnormalities. This may be particularly inappropriate for complex 3D structures such as the hippocampus, a region often associated with schizophrenic patholologies[1].A specific area of investigation is concerned with the identification of pathological asymmetries between structures located in either hemisphere of the brain. For example, studies suggest that normal asymmetries of the brain are far less in schizophrenics, some imaging studies reporting loss or reversal [2, 6], although other studies conflict with these results [7]. This paper describes a method which can be used to accurately identify subtle asymmetry of neuroanatomy.

In order to confirm theories correlating psychological disorders with types of neurological pathology, it is required that both structure and neurochemical make-up of a region can be determined. Analysing the distribution of neurotransmitters can often reveal variations which are indicative of altered neuronal development. To this end, our technique is applicable to both shape **and** receptor distributions made visible using autoradiography.

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In developing methods for identifying lateral asymmetries, a key issue is sensitivity. In structurally simple regions, such as the cortex, comparisons may be quite straightforward; methods such as the construction and averaging of depth profiles may suffice. However, more complex regions are not amenable to such simple approaches. The hippocampus, a highly concave and reentrant structure located in the temporal lobe, is an ideal test subject for any technique which seeks to identify complex or subtle asymmetry. Whilst a 3D analysis is the eventual aim of this project, we present preliminary results of our technique applied to 2D postmortem autoradiographic sections of the hippocampus.

2 Materials and Methods

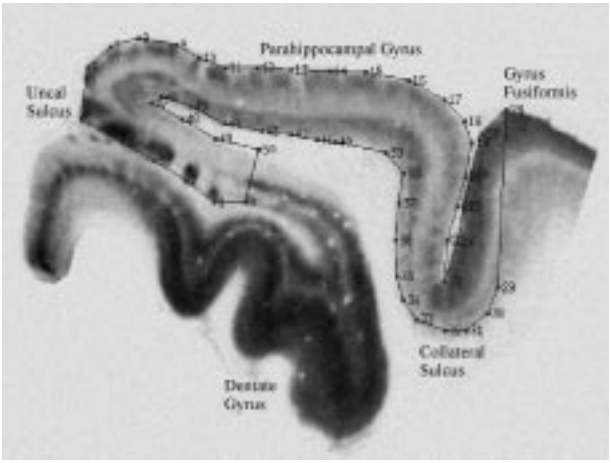

Figure 1: Hippocampal Autoradigraph

The hippocampal tissue used as test data comes from five normal brains: subjects free from a personal or family history of neurological or psychiatric disease. Both hemispheres of hippocampal tissue were cryosectioned, $20\mu m$ sections cut every $100\mu m$. Sections were stained with 8-hydroxy-2-(N,N-di-N-propyl-amino) tetralin ([3H]-8-OH-DPAT), selectively labelling 5-HT1A receptors, which are located in restricted classes of neuronal cells. The sections were then washed to remove unbound ligands, dried rapidly and exposed to high resolution tritium sensitive x-ray film for 8-12 weeks. In the resulting autoradiographs grey-level intensity represents receptor intensity. For the purpose of our 2D analysis, a single section located at a consistent anterior depth was selected from each hippocampal hemisphere. Analysis was centred on the relatively stable parahippocampal gyrus rather than the entire hippocampus, because of the intrinsic anterior-posterior variation of regions such as the dentate gyrus.

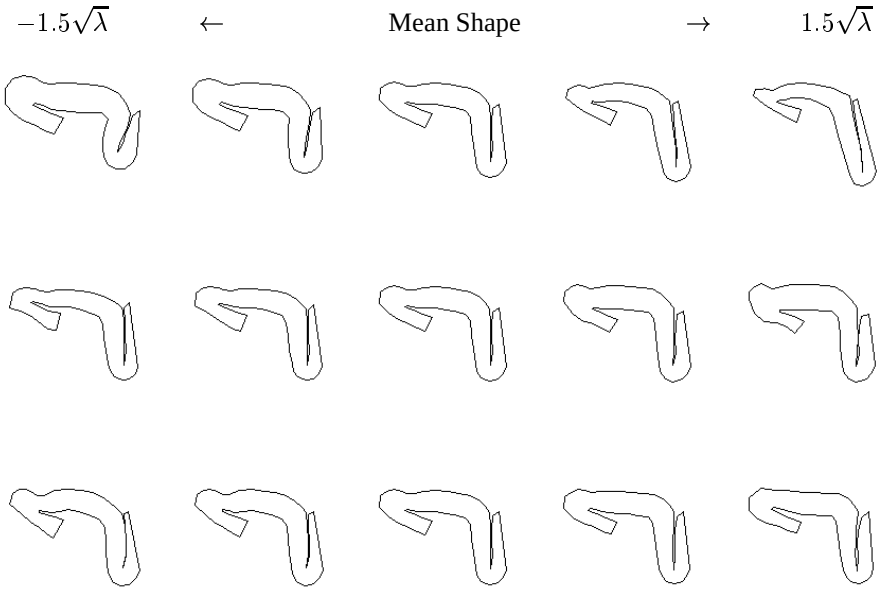

Figure 2: Shape Modes : Combined hemisphere model

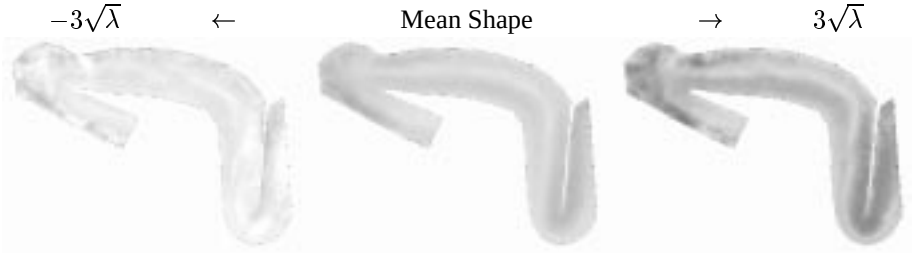

Figure 3: Grey-level Mode : Combined hemisphere model

2.1 Point Distribution Models

Our method of identifying shape and grey-level asymmetries employs the point distribution model and appearance modelling techniques presented by Cootes et al[3]. The shape information is captured by labelling the training images with consistent landmark points (See Figure 1). Our training set was labelled under the guidance of a neurologist and with the aid of a semi-automatic point planting software. Landmarks were typically curvature extrema or distinctive regions of receptor intensity, supplemented by uniformly spaced points between.

Each training image x_i labelled with p point coordinates can be described by its $2p$ shape vector $(x_{i0}, y_{i0}, x_{i1}, y_{i1} \ldots x_{ip-1}, y_{ip-1})^T$. It will be shown how the training set of shape vectors can be used to identify shape differences between left and right hemisphere hippocampi.

Grey-level information can also be expressed as a vector composed of the grey-level

intensity of pixels making up the hippocampus. However, before these can be constructed, variation due to shape must be eliminated. This is achieved by warping all training images to the mean shape calculated from the training shape vectors. For each training image we now have a grey-level vector $(x_{i0}, x_{i1}, \ldots x_{im-1},)^T$ where m is the number of pixels contained within the boundary of the mean shape. See related work by Lanitis et al[5].

Normal variation in the training set can be specified by performing principal components analysis on the shape and grey-level vectors. This generates a set of *modes of variation* : eigenvectors of the covariance matrix which span a shape or grey-level space of dimension considerably smaller than $2p$ (or m).

In addition to the data compaction, the modes *characterise* the principal ways in which the training set varies. Figure 2 shows the first three shape modes of a model built from hemispheres of *both* left and right hemisphere hippocampi. The most significant mode shows a lengthening of the collateral sulcus with an associated thinning of the parahippocampal gyrus. The second most significant mode shows some vertical movement of the right had side of the collateral sulcus. The third mode shows some bending and bowing of both the parahippocampal gyrus and the collateral sulcus.

Figure 3 shows the most significant grey-level mode superimposed onto a mean hippocampus shape. The variation described seems mainly to do with global increases in receptor intensity.

Whilst these modes may contain some of the variation between left and right hemisphere hippocampi, we cannot guarantee that they do so specifically and at the exclusion of other variations. Principal component analysis identifies the variation *within* a single training set. We require a technique which identifies variation *between* two training sets.

2.2 Linear Discriminant Analysis

We can think of each training example as a point in a space of high dimensionality. The task of identifying shape and grey-level differences between left and right hemisphere hippocampi can be viewed as the the task of separating two groups of points in this space. Linear discriminant analysis is a statistical technique which seeks to maximise the difference between the two groups.

In figure 6, we see how the discriminant vector, represented by the dashed line a provides an axis onto which the point distribution can be projected, maximally seperating the two groups. On this axis we can perform scalar measurements of separation between the groups. Furthermore, the discriminant vector characterises the group separation. Imagine a point resting on the vector at t: moving one way along the vector makes the point more like the first group, moving it the other way makes the point more like the other group.

Given a training set of points divided into two groups, how do we calculate the coefficients which ensure the discriminant function maximally separates the two groups?

A metric which describes the separation between two groups x_1 and x_2, subject to an arbitrary discriminant coefficient vector a, is :

$$V = \frac{a^T \overline{x_1} - a^T \overline{x_2}}{a^T W a} \tag{1}$$

where $\overline{x_1}$ and $\overline{x_2}$ are vectors of dimension $2p$, representing the means of groups 1 and 2 respectively, and W the *pooled within-class covariance matrix* given by

$$W = \frac{1}{n_{x_1} + n_{x_2} - 2} \sum_{i=1}^{2} \sum_{j=1}^{n} (x_{ij} - \overline{x_i})(x_{ij} - \overline{x_i})^T \quad (2)$$

nx_1 and n_{x_2} denote the number of members in groups 1 and 2 respectively.) W is simply the sum of the covariance matrices for groups 1 and 2.

So what does the metric described by equation 1 mean ? The term $a^T\overline{x_1} - a^T\overline{x_2}$ simply projects the means of both groups onto the discriminant vector formed by the coefficients a, and calculates their difference. This is intuitive : as the distance between the groups increases, so must the separation of their means, and so equation 1 is maximised. The term $a^T W a$ projects the pooled covariance matrix into a pooled variance value in the 1-D discriminant space. The smaller the variance of both groups (and hence the pooled variance value), the less likely they will be to overlap and hence their separation will increase. So as the variance decreases, so equation 1 is maximised.

Differentiating equation 1 with respect to a yields *Fishers Linear Discriminant Function* :

$$a = cW^{-1}(\overline{x_1} - \overline{x_2}) \quad (3)$$

where c is a scaling factor.

The discriminant coefficient vector a is a linear combination which maximally separates group x_1 from group x_2.(See ref[4]).

2.3 Paired Linear Discriminant Analysis

The definition of discriminant analysis provided above is phrased in terms of a separation between two groups. However, in the case of our hippocampal asymmetries we cannot be sure that such global distinctions between left and right hemispheres exist. In order to gain some feeling for how asymmetries may be expressed in the training set, the data was inspected in the following manner. Left and right hemisphere hippocampi were projected into the parameter space provided by the modes of a principal component analysis. With a reduced parameter space, it becomes possible to visualize the training set.

Figure 4 shows the hemispheres of the five brains projected onto the three most significant modes of shape variation (covering 85 per cent of all training set variation).The annotation of a point with the prefix *r* indicates a hippocampus from the right hemisphere, whilst *l* indicates a hippocampus from the left hemisphere. Points sharing the same symbol type indicate hippocampi from the same brain. As can be seen from Figure 4 the training set does not separate readily into distinct left and right hemisphere groups.

However, if we examine the training set purely on the basis of the most significant mode (representing 55 per cent of total variation) we can see that although the groups do not separate cleanly, the right hemisphere hippocampi have a *consistently* higher value than their left hemisphere partners (See Figure 5). So although there is no significant difference between the *group* of left hippocampi and the *group* of right hippocampi, there may be consistent differences between *pairs* of hippocampi from the same brain.

We propose a form of discriminant analysis which seeks to maximise separation between a *group of pairs* rather than a *pair of groups.* Figure 7 shows a distribution where a

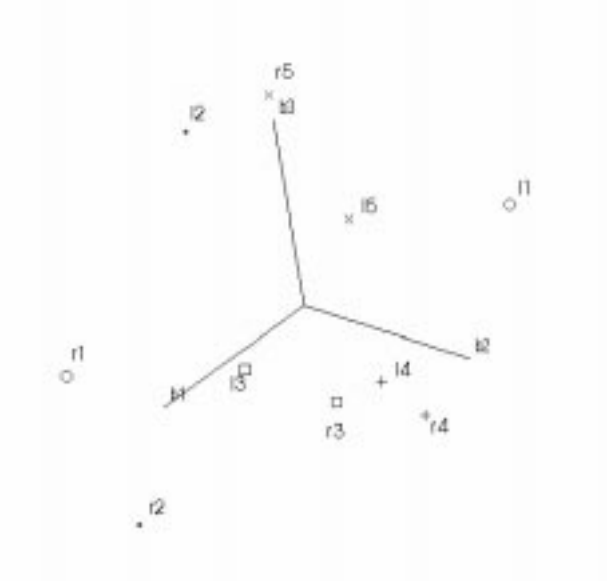

Figure 4: Training set projected into PCA space

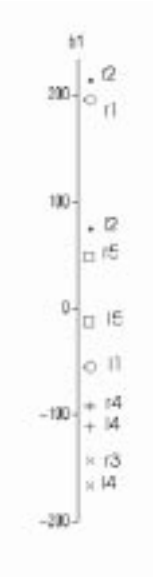

Figure 5: Training set projected onto most significant mode

set of pairs are maximised in their separation by a discriminant vector a. We modify the standard discriminant analysis scheme thus :

Let the ith pair of points in the distribution of n pairs be given by the m dimensional vectors:

$$x_{i1} = (x_1, x_2, ..., x_m) \qquad x_{i2} = (x_1, x_2, ..., x_m) \tag{4}$$

The difference between the ith pair is

$$d_i = x_{i1} - x_{i2} \tag{5}$$

and the mean difference is therefore

$$\overline{d} = \frac{1}{n} \sum_{i=1}^{n} d_i \tag{6}$$

We can define our *paired covariance matrix* as

$$P = \frac{1}{n-1} \sum_{i=1}^{n} (d_i - \overline{d})(d_i - \overline{d})^T \tag{7}$$

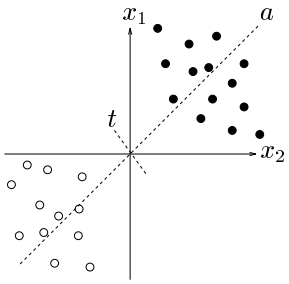

Figure 6: Discriminant mode for two populations

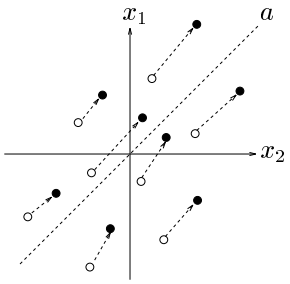

Figure 7: Discriminant mode for a paired population

where the variances are expressed in terms of differences between pairs. Using the same steps as in section 2.2, the set of coefficients which maximise paired separation are given as :

$$a = cP^{-1}\overline{d} \tag{8}$$

3 Experiment : Applying Discriminant Analysis to 2D Hippocampal Data

Although the theory behind standard and paired discriminant analysis is well founded, the assumption that hippocampal asymmetries are a paired rather than global phenomena is untested. The first task then, is to assess to what extent paired linear discriminant analysis produces better separations in hippocampal sections than standard discriminant analysis.

A second issue is what parameter space to perform the analysis on. Using principal component analysis, the dimensionality of the training vectors can be drastically reduced. With this in mind, comparisons need to be made to make clear whether the computational savings achieved by performing discriminant analysis on the reduced space are outweighed by any effects this may have on the detection of separations.

3.1 Experimental Procedure

The 10 hippocampal sections (5 left hemisphere and 5 right) were subject to discriminant analysis of shape and grey-level under the following conditions:

- **Paired Discriminant Analysis** : maximisation of separation between paired observations of data, *or* **Standard Discriminant Analysis** : maximisation of separation between two groups of data.
- **Reduced b-space Vectors** : training data composed of b-space vectors formed in construction of shape and grey-level models of combined hemisphere hippocampi (see section 2.1) *or* **Sample Space Vectors** : training data composed of vectors containing the coordinates of landmark points describing the hippocampal structure, or vectors of pixel grey-level values describing receptor distribution.

Each experiment will yield a set of discriminant coefficients, each of which allow the training set to be projected onto a one dimensional discriminant mode. Comparison of the separations provided by the different modes can then be performed. The metric proposed to allow quantitative comparison of separations is the t-test statistic. Although this test requires normality, which is certainly not guaranteed using our small data set, we only require a measure which gives an indication of the *relative* significance of separations over the different conditions.

4 Results

The t-test statistics and corresponding significance levels for the four different experimental conditions are presented in tables 1 and 2 . It is clear that paired discriminant analysis is providing a better description of the separation between the groups, particularly in the case of grey-level differences. Figures 8 and 9 provide visualisations of the shape and grey-level changes which occur along the axis of greatest separation between left and right hemispheres. In these visualisations the centre hippocampal section can be regarded as a section which is neutral of laterality, being an average of left and right hemispheres. Moving one way along the mode, makes the section more ”leftish” and the other way more “rightish”. The limit set for the variation in these visualisations is $l/2$, where l is the average separation between paired hemispheres.

$-\frac{l}{2}$ (left hemisphere) $\leftarrow$ Mean Shape $\rightarrow$ $+\frac{l}{2}$ (right hemisphere)

Figure 8: Paired discriminant mode for shape

$-\frac{l}{2}$ (left hemisphere) $\leftarrow$ Mean Grey-level $\rightarrow$ $+\frac{l}{2}$ (right hemisphere)

Figure 9: Paired discriminant mode for grey-level intensity

The visualisations demonstrate the the form of left-right hippocampal asymmetry. Left hemisphere hippocampi have longer and more vertically aligned collateral sulci than

Condition	Num. samples	Dimensions	t-value	Sig. level
Normal LDA (unpaired)				
Reduced b-space	10	9	1.22	74.3%
Full sample space	10	102	2.99	98.3%
Paired LDA				
Reduced b-space	5	9	2.35	92.2%
Full sample space	5	102	35.46	$> 99.9\%$

Table 1: Shape asymmetry significance levels over four experimental conditions

Condition	Num. samples	Dimensions	t-value	Sig. level
Normal LDA (unpaired)				
Reduced b-space	10	9	0.03	2.2%
Full sample space	10	40186	0.19	14.9%
Paired LDA				
Reduced b-space	5	9	3.56	97.6%
Full sample space	5	40186	4.39	98.8%

Table 2: Grey-level asymmetry significance sevels over four experimental conditions

right hemisphere hippocampi, whose collateral sulci are stumpy and often slanted in orientation. In addition, left hemisphere hippocampi have slightly straighter parahippocampal gyri than right hemisphere hippocampi, whose gyri are more bowed. (See Fig 1 for anatomical terms).

The grey-level discriminant mode is more difficult to interpret, although it can be said that most of the left/right asymmetry takes place in the top left hand corner, where the parahippocampal gyrus bends into the uncal sulcus. Although it is difficult to discern from these diagrams, animations show that right hemisphere hippocampi have a greater profusion of striations in the parahippocampal gyrus.

5 Discussion

The difference between left and right hemisphere populations is small in the context of natural variability amongst individuals. The paired discriminant analysis seeks to find a *consistent* mode of separation. The fact that a better separation is found by the paired analysis indicates that while the left and right populations might overlap in their shape and grey-level, the shifts between them are consistent. The paired discriminant analysis is clearly a better way of identifying a discriminant vector for groups which are paired.

The second issue is the performance of both discriminant techniques when applied to the model-space representation of the data set. The significance of the separations is not as great as that gained when using the full sample space. There are two points regarding this result. Firstly, the significance values for full parameter space seem suspiciously high. This is due to the fact that we are trying to locate a vector which separates only 10 pieces of data in a space of very high dimensionality: it is possible for many such vectors to be

located. Results must therefore be regarded cautiously. Secondly, the use of a reduced parameter space results in lower separations, possibly truncating some of the asymmetry we are hoping to identify. It is possible, and indeed even quite likely, that some of the asymmetries are quite small, and so are subsequently removed by the dimensional reduction taking place in the principal component analysis. However, the fact that significant separations are still detectable under such a reduction offers encouragement.

6 Summary

We have demonstrated that linear discriminant analysis, coupled with accurate landmarking of structure, provides a potentially powerful way of generating quantitative and specific descriptions of lateral asymmetries in hippocampal sections, both in shape and receptor distribution. We have presented a modified discriminant analysis scheme which detects paired asymmetries. The results suggest that whilst left-right shape asymmetries exist, and may be detected by considering the two hemispheres as groups; *paired* asymmetries due to shape *and* receptor distribution seem to be more pronounced on examining the *paired* differences.

At a particular level of the parahippocampal gyrus, we have identified specific lateral asymmetries. The significance of the measurements needs to be regarded with caution given the small data set available, but the initial result allows us to form the hypothesis that similar differences will be detected by a 3D study using the more substantial data set which is currently being collected for this project.

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