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# Bilateral symmetry aspects in computer-aided Alzheimer's disease diagnosis by single-photon emission-computed tomography imaging

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ABSTRACT

*Objective:* This paper explores the importance of the latent symmetry of the brain in computer-aided systems for diagnosing Alzheimer's disease (AD). Symmetry and asymmetry are studied from two points of view: (i) the development of an effective classifier within the scope of machine learning techniques, and (ii) the assessment of its relevance to the AD diagnosis in the early stages of the disease.
*Methods:* The proposed methodology is based on eigenimage decomposition of single-photon emission-computed tomography images, using an eigenspace extension to accommodate odd and even eigenvectors separately. This feature extraction technique allows for support-vector-machine classification and image analysis.
*Results:* Identification of AD patterns is improved when the latent symmetry of the brain is considered, with an estimated 92.78% accuracy (92.86% sensitivity, 92.68% specificity) using a linear kernel and a leave-one-out cross validation strategy. Also, asymmetries may be used to define a test for AD that is very specific (90.24% specificity) but not especially sensitive.
*Conclusions:* Two main conclusions are derived from the analysis of the eigenimage spectrum. Firstly, the recognition of AD patterns is improved when considering only the symmetric part of the spectrum. Secondly, asymmetries in the hypo-metabolic patterns, when present, are more pronounced in subjects with AD.



## 1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia among people over the age of 65. A considerable amount of new information has been gathered over the last 30 years concerning the factors responsible for AD, which has resulted in the development of new treatments. Although extensive clinical studies have characterized the time course of many cognitive and behavioral measures, and clinical data has been correlated with autopsy findings, a final cure remains undiscovered. In order to test and develop medical treatments and cure, early and accurate diagnosis is crucial.

The diagnosis of AD is a field of active research that includes studies of biological markers associated with the disease, and neuropsychological testing or neuroimaging techniques such as functional and structural brain imaging. Single-photon emission-computed tomography (SPECT) imaging offers the opportunity to explore functional brain behavior, as the regional cerebral blood flow. Even though the perfusion pattern and its evolution is not the same for all patients, there do seem to be some typical hypoperfusion patterns for the disease, such as the temporo-parietal region or the posterior cingulate gyri and precunei. Still, no single perfusion pattern differentiates AD patients from healthy subjects. The value of SPECT as an objective diagnostic tool for AD may depend on the degree to which abnormal metabolic patterns can be detected by quantitative classification methods.

Much of the AD literature suggests that early manifestations of AD occur in a prodromal stage, years before the symptoms of the disease appear and are clinically detectable. This makes it suitable to use non-invasive techniques such as nuclear imaging for detection. The examination of the predictive abilities of nuclear imaging with respect to AD in this early stage has been widely studied, through visual assessments performed by experts[1–4], or by means of voxel-wise statistical analysis such as SPM, NEUROSTAT & 3D-SSP, ANOVA or MANCOVA [5–12]. Recently, a new branch of emerging research has shown that machine-learning techniques may also be powerful analysis tools for brain imaging. As an example, recent works have been published that adapt state-of-the-art computer-vision techniques in magnetic-resonance imaging for

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early AD diagnosis [13,14], support-vector-machine (SVM) classification in SPECT [15–18], or positron-emission-tomography analysis [19,20]. This framework, which is geared towards decision-making, usually considers feature vectors containing a set of voxels, allowing for a regional or global brain-image analysis, which is contrary to voxel-wise statistical tools. On the other hand, the framework suffers from the small-sample-size problem. This significant problem, associated with pattern-recognition systems, occurs when the number of available features for designing the classifier is very large compared with the number of available training examples.

Symmetry has profound and important implications with regard to recognition and pattern representation, and it has also been claimed to have a privileged status in the brain response to complex stimuli, as faces when viewed as a whole [21,22]. A natural emerging question is whether symmetry has the same status in pattern-recognition systems based on machine-learning paradigms. It has been shown that the use of latent symmetries in pattern-recognition problems like face detection is beneficial [21], and that parsing techniques also perform efficiently [23,24]. This study explores the consequences of using the natural symmetry of the brain for pattern recognition of AD, and how this symmetry is connected with the disease itself.

## 2. Materials and methods

The tool for conducting the analysis is based on principal-component analysis (PCA) on an enhanced set of images. This procedure identifies the main deviations from the mean, and attempts to separate them into a set of linear independent images. This new set can be separated into symmetric and asymmetric images, as described in Section 2.1.

### 2.1. Enhanced dataset: parity study

The three-dimensional volume of a brain image is represented by a scalar function $t(\mathbf{x})$ of position $\mathbf{x} = (x, y, z)$ (in the following, an image), with the image centered on the dividing plane of both hemispheres $x = 0$. We consider the possibility of extending the database to an ensemble of images:

$$t_n(x, y, z) \cup t_n(-x, y, z) \tag{1}$$

with $n = 1, 2, \ldots, N$, where $N$ is the number of images. The symmetrized and averaged brain image of the dataset is defined as:

$$t(x, y, z) = \frac{1}{2N} \sum_{n=1}^{N} (t_n(x, y, z) + t_n(-x, y, z)) \tag{2}$$

Following the approach in [17], each brain image is represented by its eigenbrain expansion. Firstly, PCA requires that the average of the image set is subtracted from each brain image, producing a new set $\hat{t}_n = t_n - t$. Here, an image $\hat{t}$ is even (in the mid-plane) if:

$$\hat{t}_n(x, y, z) = \hat{t}_n(-x, y, z) \tag{3}$$

and odd if

$$\hat{t}_n(x, y, z) = -\hat{t}_n(-x, y, z) \tag{4}$$

In practice, the function $\hat{t}_n$ takes only discrete values at voxels. The intensity values of $\hat{t}_n(x, y, z)$ are concatenated to form the $M$-dimensional column vector $\mathbf{t}_n$, and the mirrored counterpart $\hat{t}_n(-x, y, z)$ forms the column vector $\bar{\mathbf{t}}_n$, where $M$ is the total number of voxels in the image.[1] On the set $\{\mathbf{t}_n \cup \bar{\mathbf{t}}_n\}$, a PCA transformation is composed of $M$-dimensional orthogonal vectors $\mathbf{u}_i$, such that

$$\lambda_i = \frac{1}{2N} \sum_{n=1}^{N} (\mathbf{u}_i^T (\mathbf{t}_n + \bar{\mathbf{t}}_n))^2 \tag{5}$$

is maximum, subject to the constraint:

$$\mathbf{u}_i^T \mathbf{u}_j = \delta_{ij} \tag{6}$$

where $\delta_{ij}$ is the Kronecker delta. The resulting $\mathbf{u}_i$ and $\lambda_i$ are the eigenvectors and eigenvalues respectively of the covariance matrix:

$$\mathbf{C} = \frac{1}{2N} \sum_{n=1}^{N} [\mathbf{t}_n \mathbf{t}_n^T + \bar{\mathbf{t}}_n \bar{\mathbf{t}}_n^T] \tag{7}$$

The orthogonal eigenvector basis $\{\mathbf{u}_i\}$, $i = 1, \ldots, 2N$ forms the so-called eigenbrains. Within this framework, the coefficients in the eigenbrain expansion are uncorrelated, and each eigenvalue represents the statistical variance of the corresponding coefficient in the expansion. As is directly verified, we can rewrite $\mathbf{C}$ as the sum of an even part $\mathbf{C}^s$ and an odd one $\mathbf{C}^a$:

$$\mathbf{C}^s = \frac{1}{4N} \sum_{n=1}^{N} [\mathbf{t}_n + \bar{\mathbf{t}}_n][\mathbf{t}_n + \bar{\mathbf{t}}_n]^T \tag{8}$$

$$\mathbf{C}^a = \frac{1}{4N} \sum_{n=1}^{N} [\mathbf{t}_n - \bar{\mathbf{t}}_n][\mathbf{t}_n - \bar{\mathbf{t}}_n]^T \tag{9}$$

that which are orthogonal and have eigenvectors that are even and odd, respectively. In other words, the eigenspace of $\mathbf{C}$, $E(\mathbf{C})$ can be expressed as the direct sum of $E(\mathbf{C}^s)$ and $E(\mathbf{C}^a)$ (see [25]), that is:

$$E(\mathbf{C}) = E(\mathbf{C}^s) \oplus E(\mathbf{C}^a) \tag{10}$$

If we define the *symmetric* image $\mathbf{t}_n^s$ as:

$$\mathbf{t}_n^s = \mathbf{t}_n + \bar{\mathbf{t}}_n \tag{11}$$

and the *asymmetric* image $\mathbf{t}_n^a$ as:

$$\mathbf{t}_n^a = \mathbf{t}_n - \bar{\mathbf{t}}_n \tag{12}$$

it follows that we should consider the following two decoupled problems:

$$\mathbf{C}^s \mathbf{u}_i^s = \lambda_i \mathbf{u}_i^s \tag{13}$$

$$\mathbf{C}^a \mathbf{u}_j^a = \lambda_j \mathbf{u}_j^a \tag{14}$$

where:

$$\mathbf{C}^s = \frac{1}{4N} \sum_{n=1}^{N} \mathbf{t}_n^s (\mathbf{t}_n^s)^T \tag{15}$$

$$\mathbf{C}^a = \frac{1}{4N} \sum_{n=1}^{N} \mathbf{t}_n^a (\mathbf{t}_n^a)^T \tag{16}$$

These two problems can be viewed as equivalent to starting out with two separated ensembles $\mathbf{t}_n^s$ and $\mathbf{t}_n^a$, $n = 1, 2, \ldots, N$ consisting of even and odd images, and then proceed with the two cases independently. To solve them, it is necessary to diagonalize two $M \times M$ covariance matrices, which for brain images would be approximately a $5 \cdot 10^5 \times 5 \cdot 10^5$ matrix. There are alternatives to deal with these problems, for instance based on the diagonalization of the

[1] It is to be understood that the vectors $\mathbf{t}_n$ and $\bar{\mathbf{t}}_n$ are centered as $\hat{t}_n$, but explicit reference has been removed in order to simplify the notation.