Gaussian Random Fields for Statistical Characterization of Brain Submanifolds.

Sarang Joshi

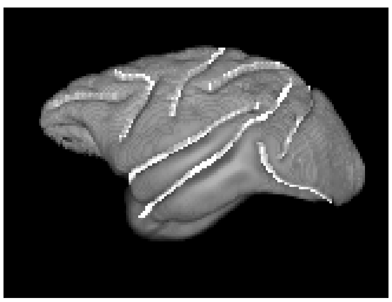
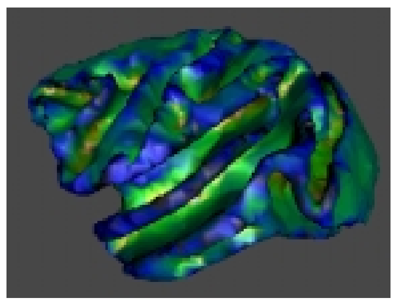
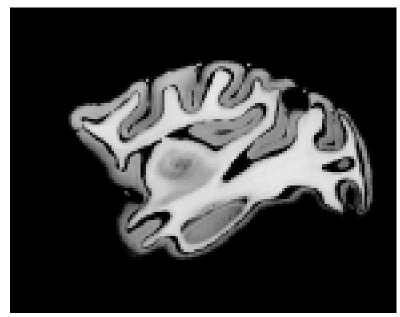
Department of Radiation Oncology and Biomedical Enginereing University of North Carolina at Chapel Hill

Global Shape Models for Computational Anatomy.

Homogeneous anatomy characterized by $(\Omega, \mathcal{H}, \mathcal{I}, P)$.

1. Ω: Collection of 0,1,2, and 3-dimensional compact sub-manifolds $\mathcal{M}_\alpha$ of $I\!R^3$,

$$\Omega = \bigcup_\alpha \mathcal{M}_\alpha \ .$$

2. $\mathcal{H}$: Family of transformations of Ω accommodating variability.

$$h \in \mathcal{H} : \Omega \leftrightarrow \Omega$$

3. $\mathcal{I}$: set of anatomical imagery {MRI, CT, PET, CRYOSECTION} .

$$I_\alpha \in \mathcal{I} : \Omega \rightarrow I\!R^N$$

4. P: probability measures on the space of transformations $\mathcal{H}$.

Global Shape Models for Computational Anatomy.

• $\mathcal{H}$ constructed from group of diffeomorphisms of coordinate system Ω.

• $h \in \mathcal{H}$ defined via vector fields of displacements.

$$x = (x_1, x_2, x_3) \in \Omega \mapsto h(x) = x - (u_1(x), u_2(x), u_3(x))$$

• $\mathcal{I}$: Homogeneous space of the group $\mathcal{H}$.

1. Two images $I_1, I_2 \in \mathcal{I}$ are topologically equivalent.
2. $\exists h \in \mathcal{H}$ such that $I_1 = I_2(h(x)), x \in \Omega$.
3. $\exists h^{-1} \in \mathcal{H}$ such that $I_2 = I_1(h^{-1}(x)), x \in \Omega$.
4. $\mathcal{I}$: orbit of a single anatomy I_0, under the group action $\mathcal{H}$:

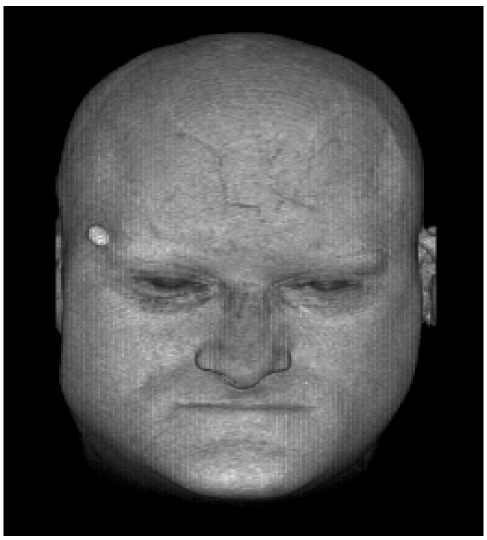
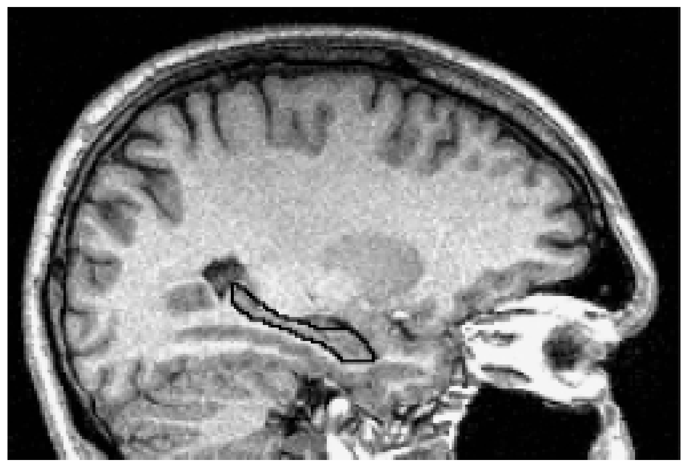
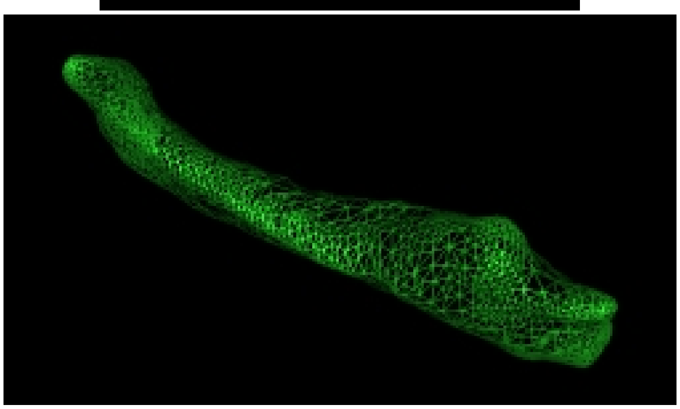
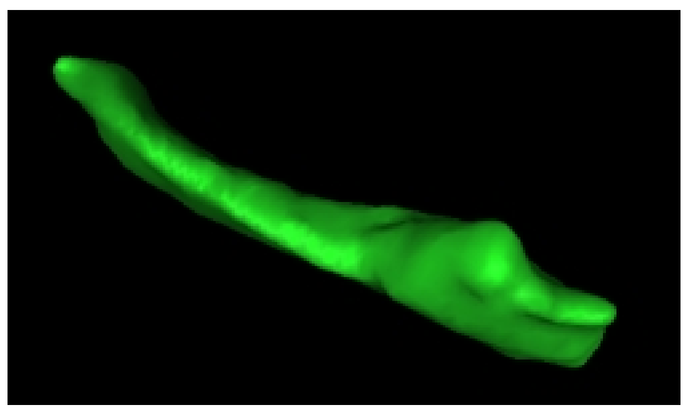
$$\mathcal{I} \equiv \mathcal{H} \circ I_0$$

• Anatomical variability understood via **empirical** construction of probability measures P on $\mathcal{H}$.

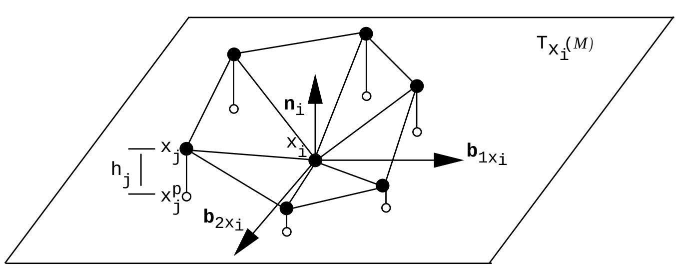
1. Given family of anatomical images $\{I_0, I_1, \cdots, I_N\}$ construct "registration" transformations $\{h_i, i = 1, \cdots, N\}, h_i \in \mathcal{H}$ mapping provisory template I_0 to the family.
2. Given maps $\{h_i, i = 1, \cdots, N\}$ estimate P.

Representation of Sub-Structures of the Brain.

The surface $\mathcal{M}$ of neuro-anatomically significant substructure is assumed to be a smooth two-dimensional C^2 sub-manifold of $\Omega \subset I\!R^3$.

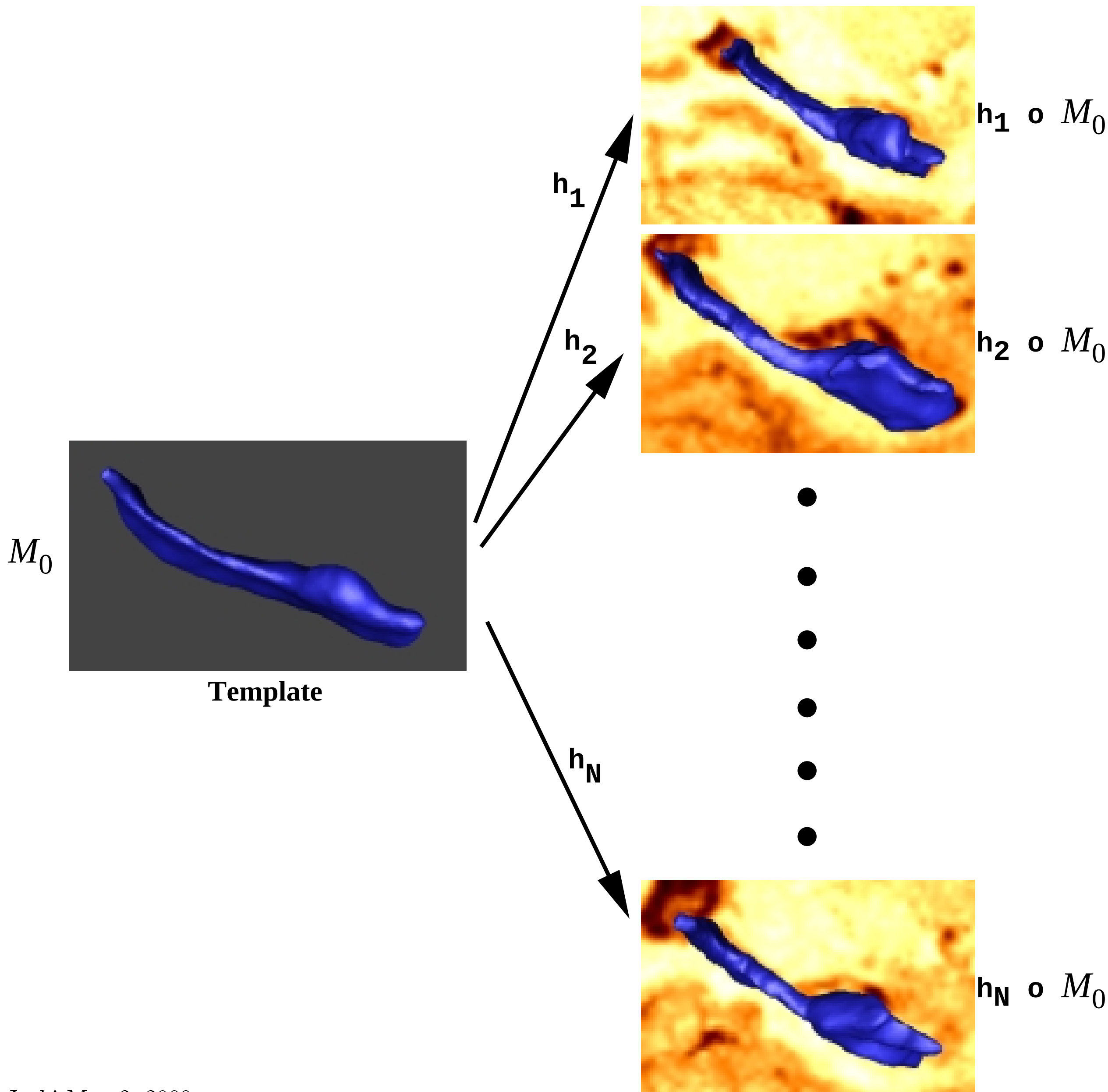
- Build local quadratic charts.



Shape of 2-D Sub-Manifolds of the Brain: Hippocampus.

The provisory template hippocampal surface $\mathcal{M}_0$ is carried onto the family of targets:

$$\mathcal{M}_0 \underset{h_1^{-1}}{\overset{h_1}{\rightleftarrows}} \mathcal{M}^1, \mathcal{M}_0 \underset{h_2^{-1}}{\overset{h_2}{\rightleftarrows}} \mathcal{M}^2, \cdots, \mathcal{M}_0 \underset{h_N^{-1}}{\overset{h_N}{\rightleftarrows}} \mathcal{M}^N \; .$$

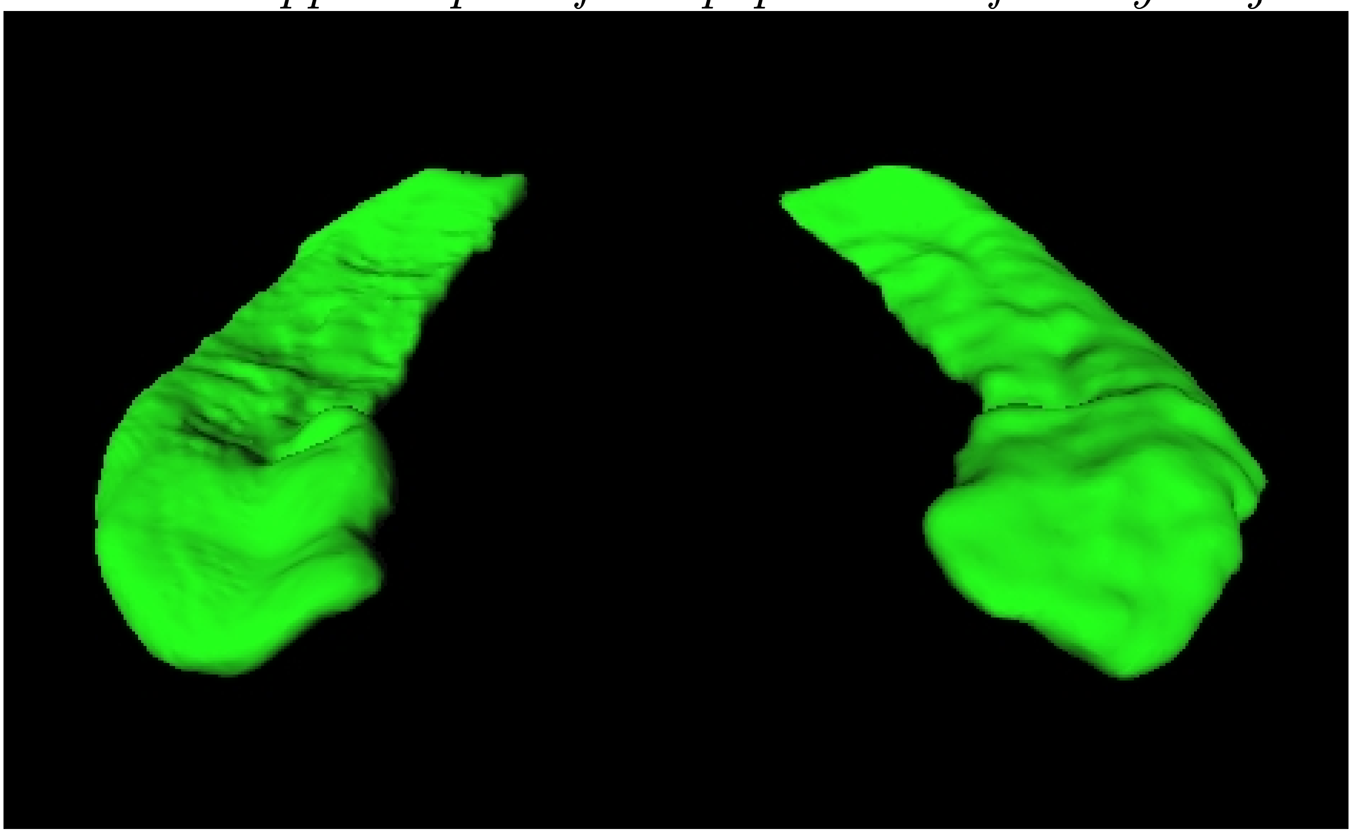


Shape of 2-D Sub-Manifolds of the Brain: Hippocampus.

- The mean transformation and the template representing the entire population:

$$\bar{h} = \frac{1}{N} \sum_{i=1}^{N} h_i \ \ , \ \ \mathcal{M}_{temp} = \bar{h} \circ \mathcal{M}_0 \ .$$

The mean hippocampus of the population of thirty subjects.



Shape of 2-D Sub-Manifolds of the Brain: Hippocampus.

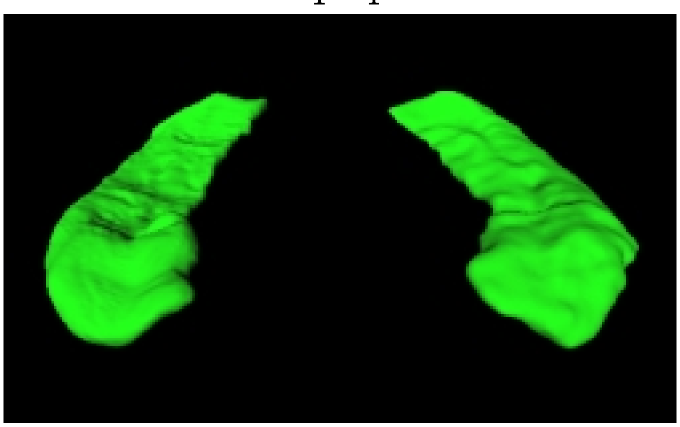
- Mean hippocampus representing the control population:

$$\bar{h}_{control} = \frac{1}{N_{control}} \sum_{i=1}^{N_{control}} h_i^{control} \ , \ \mathcal{M}_{control} = \bar{h}_{control} \circ \mathcal{M}_0 \ .$$

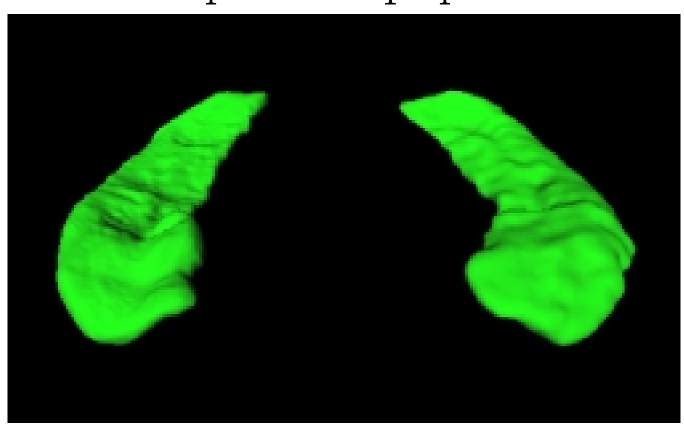
- Mean hippocampus representing the Schizophrenic population:

$$\bar{h}_{schiz} = \frac{1}{N_{schiz}} \sum_{i=1}^{N_{schiz}} h_i^{schiz} \ , \ \mathcal{M}_{schiz} = \bar{h}_{schiz} \circ \mathcal{M}_0 \ .$$

Control population



Schizophrenic population



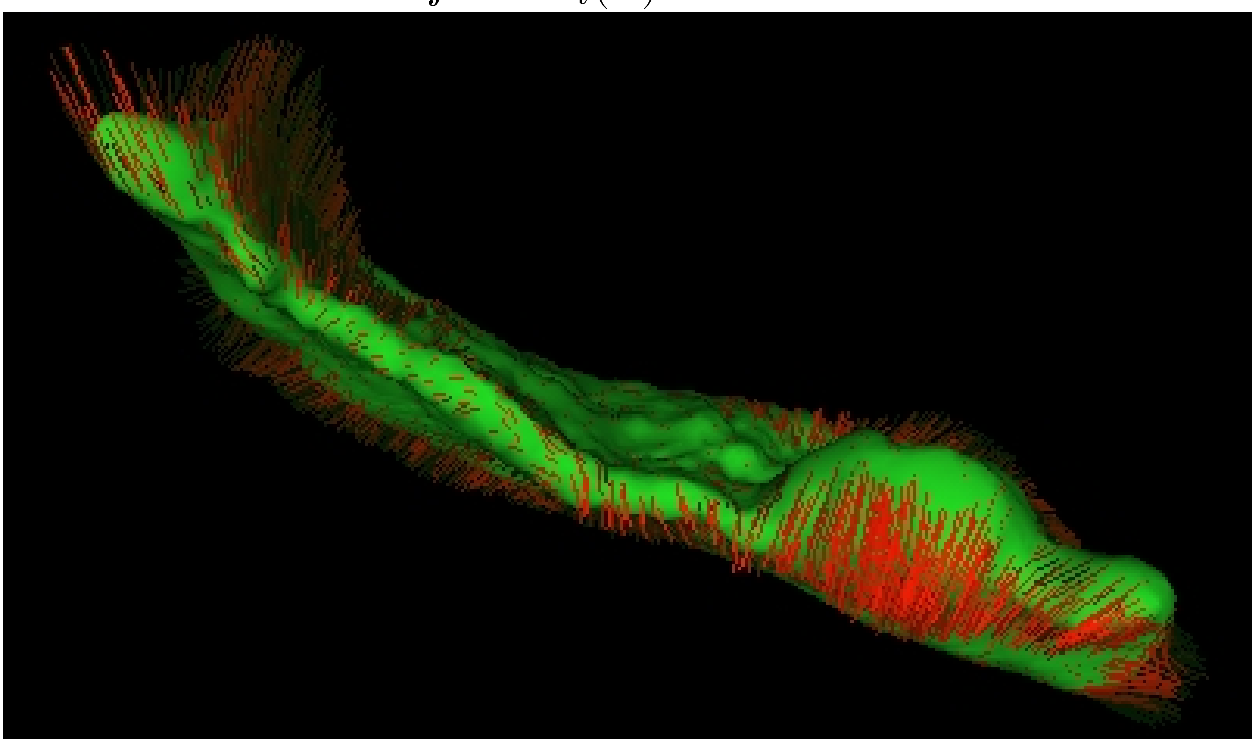
Gaussian Random Vector Fields on 2-D Sub-Manifolds.

- Hippocampi $\mathcal{M}^i, i = 1, \cdots, N$ deformation of the mean $\mathcal{M}_{temp}$:

$$\mathcal{M}^i : \{y | y = x + u_i(x)\ , x \in \mathcal{M}_{temp}\}$$

$$u_i(x) = h_i(x) - x, x \in \mathcal{M}_{temp}\ .$$

Vector field $u_i(x)$ shown in red.



- Construct Gaussian random vector fields over sub-manifolds.

Gaussian Random Vector Fields on 2-D Sub-Manifolds.

• Let $\mathcal{H}(\mathcal{M})$ be the Hilbert space of square integrable vector fields on $\mathcal{M}$. Inner product on the Hilbert space $\mathcal{H}(\mathcal{M})$:

$$\langle f, g\rangle = \sum_{i=1}^{3} \int_{\mathcal{M}} f^i(x) g^i(x) d\nu(x)$$

where $d\nu$ is a measure on the oriented manifold $\mathcal{M}$.

Definition 1 *The random field* $\{U(x), x \in \mathcal{M}\}$ *is a* **Gaussian random field** *on a manifold* $\mathcal{M}$ *with mean* $\mu_u \in \mathcal{H}(\mathcal{M})$ *and covariance operator* $K_u(x, y)$ *if* $\forall f \in \mathcal{H}(\mathcal{M})$, $\langle f, \cdot\rangle$ *is normally distributed with mean* $m_f = \langle \mu_u, f\rangle$ *and variance* $\sigma_f^2 = \langle K_u f, f\rangle$

• Gaussian field is completely specified by it's mean μ_u and the covariance operator $K_u(x, y)$.

• Construct Gaussian random fields as a quadratic mean limit using a complete $\mathbb{R}^3$-valued orthonormal basis

$$\{\phi_k, k = 1, 2, \cdots\}\ ,\ \langle \phi_i, \phi_j\rangle = 0\ , i \neq j$$

Isotropic Stochastic Process on The Sphere: Oboukhov expansion

• Let $\mathcal{H}(\mathcal{S})$ be the Hilbert space of square integrable functions on the sphere $\mathcal{S}$. Inner product on the Hilbert space $\mathcal{H}(\mathcal{S})$:

$$\langle f, g \rangle = \int_{\mathcal{S}} f(\theta,\phi) g(\theta,\phi) sin(\theta) d\theta d\phi$$

where $sin(\theta)d\theta d\phi$ is the measure on the sphere $\mathcal{S}$.

• The Spherical Harmonics Y_n^m are a complete orthonormal basis of $\mathcal{H}(\mathcal{S})$

Define process $\{u(p), p \in \mathcal{S}\}$

$$u(p) = \lim_{N\to\infty} \ in\ q.m. \ \sum_{n=0}^{N} \sum_{m=-n}^{n} Z_{nm} Y_n^m(p) \ ,$$

where • Z_{nm} are zero mean independent Gaussian random variables with variance λ_n with $\Sigma \lambda_n < \infty$.

Theorem: The stochastic process $\{u(p), p \in \mathcal{S}\}$ constructed above is an isotropic zero mean q.m. continuous Gaussian process with covariance

$$K(x,y) = \sum_{n=0}^{\infty} \lambda_n P_n(\cos d(x,y))$$

Gaussian Random Vector Fields on 2-D Sub-Manifolds.

Theorem 1 *Let* $\{U(x), x \in \mathcal{M}\}$ *be a Gaussian random vector field with mean* $m_U \in \mathcal{H}$ *and covariance* K_U *of finite trace. There exists a sequence of finite dimensional Gaussian random vector fields* $\{U_n(x)\}$ *such that*

$$U(x) \stackrel{\text{q.m.}}{=} \lim_{n \to \infty} U_n(x)$$

where

$$U_n(x) = \sum_{k=1}^{n} Z_k(\omega)\phi_k(x) \ ,$$

$\{Z_k(\omega), k = 1, \cdots\}$ *are independent Gaussian random variables with fixed means* $E\{Z_k\} = \mu_k$ *and covariances* $E\{|Z_i|^2\} - E\{Z_i\}^2 = \sigma_i^2 = \lambda_i, \sum_i \lambda_i < \infty$ *and* (hk, λ_k) *are the eigen functions and the eigen values of the covariance operator* K_U*:*

$$\lambda_i \phi_i(x) = \int_{\mathcal{M}} K_U(x,y)\phi_i(y) d\nu(y) \ ,$$

where $d\nu$ *is the measure on the manifold* $\mathcal{M}$*.*

If $d\nu$*, the surface measure on* $\bar{\mathcal{M}}_{temp}$ *is atomic around the points* x_k *then* $\{\phi_i\}$ *satisfy the system of linear equations*

$$\lambda_i \phi_i(x_k) = \sum_{j=1}^{M} \hat{K}_U(x_k, y_j)\phi_i(y_j)\nu(y_j) \quad , i = 1, \cdots, N \ ,$$

where $\nu(y_j)$ *is the surface measure around point* y_j*.*

Eigen Shapes of the Hippocampus.

• Assume that deformation fields $\{u_i(x), i = 1, \cdots, N\}$ are realizations from a Gaussian field on the surface of the mean hippocampus $\mathcal{M}_{temp}$.

• Empirical estimate of the covariance operator given by

$$\hat{K}_U(x, y) = \frac{1}{N-1} \sum_{i=1}^{N} u_i(x) u_i(y)^T \ .$$

• Numerically compute the eigenfunctions and eigenvalues of using Singular Value Decomposition:

1. Let $\{\boldsymbol{\phi}^{(i)}, i = 1, \cdots, N\}$ be vectors of length $3M$ with

$$\boldsymbol{\phi}_k^{(i)} = \phi_i(x_k)$$

2. Λ be a diagonal matrix of size $3M \times 3M$ with

$$\Lambda_{3j,3j} = \Lambda_{3j+1,3j+1} = \Lambda_{3j+2,3j+2} = \nu(y_j),$$

3. $\hat{\mathbf{K}}_{\mathbf{U}}$ be a $3M \times 3M$ symmetric matrix with

$$\hat{\mathbf{K}}_{i,j} = \hat{K}_U(x_i, x_j).$$

The system of linear equations in the above theorem becomes

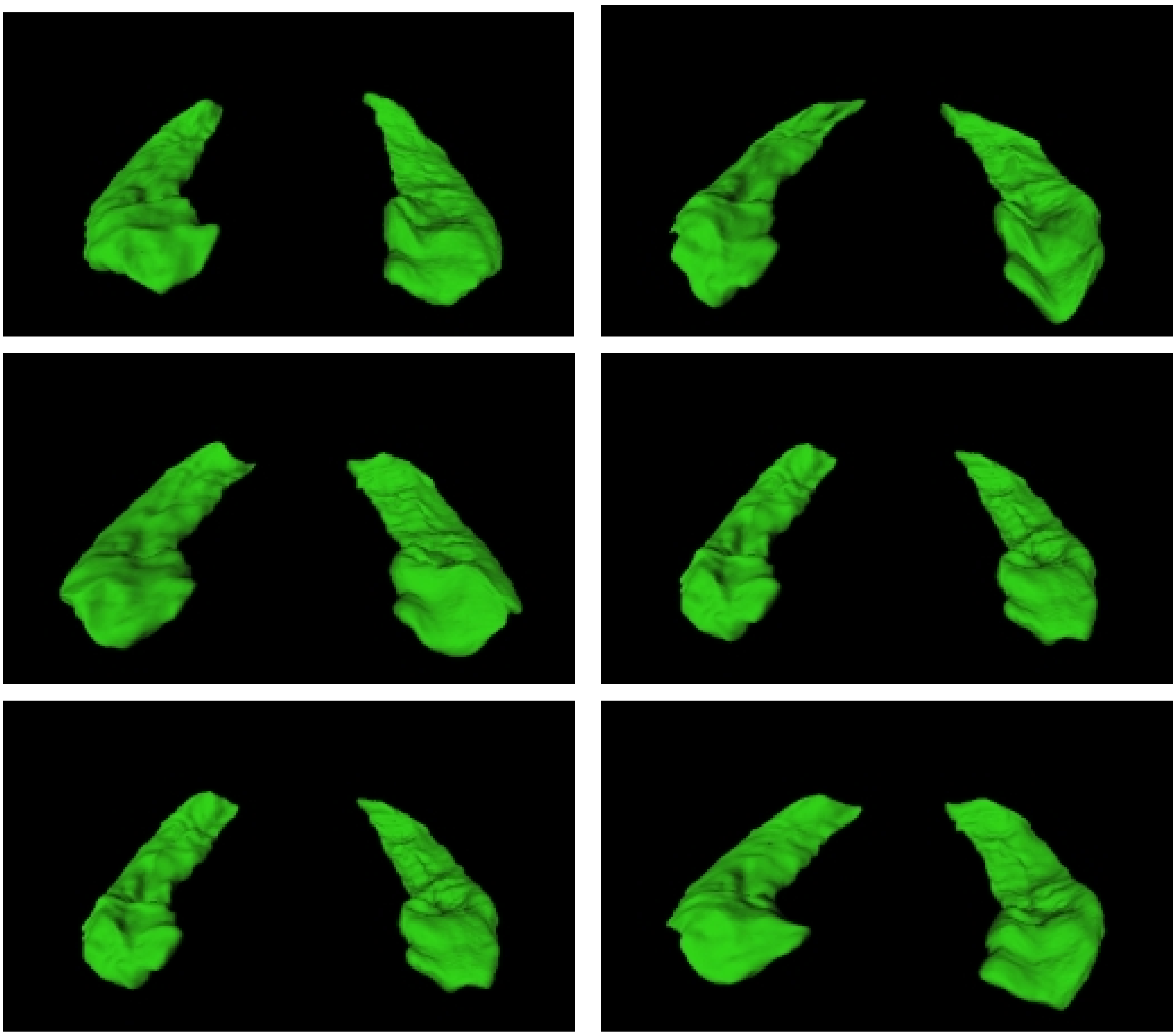
$$\lambda_i \boldsymbol{\phi}^{(i)} = \hat{\mathbf{K}} \Lambda \boldsymbol{\phi}^{(i)}, i = 1, \cdots, N.$$

The basis vectors $\{\boldsymbol{\phi}^{(i)}, i = 1, \cdots, N\}$ are generated by diagonalizing the matrix $\hat{\mathbf{K}}\Lambda$.

Eigen Shapes of the Hippocampus.

- Eigen shapes $\mathcal{E}^i, i = 1, \cdots, N$ defined as:

$$\mathcal{E}^i = \{x + (\lambda_i)\phi_i(x) : x \in \bar{\mathcal{M}}_{temp}\} \ .$$



- Eigen shapes completely characterize the variation of the submanifold in the population.

Statistical Significance of Shape Difference Between Populations.

- Assume that $\{u_j^{schiz}, u_j^{control}\}, j = 1, \cdots, 15$ are realizations from a Gaussian process with mean $\bar{u}_{schiz}$ and $\bar{u}_{control}$ and common covariance K_U.

Statistical hypothesis test on shape difference:

$$\begin{aligned} H_0 : \bar{u}_{norm} &= \bar{u}_{schiz} \\ H_1 : \bar{u}_{norm} &\neq \bar{u}_{schiz} \end{aligned}$$

- Expand the deformation fields in the eigen functions ϕ_i:

$$\begin{aligned} u_N^{schiz(j)}(x) &= \sum_{i=1}^{N} Z_i^{schiz(j)} \phi_i(x) \\ u_N^{control(j)}(x) &= \sum_{i=1}^{N} Z_i^{control(j)} \phi_i(x) \end{aligned}$$

- $\{Z_j^{schiz}, Z_j^{control}, j = 1, \cdots, 15\}$ Gaussian random vectors with means $\bar{Z}_{schiz}$ and $\bar{Z}_{control}$ and covariance Σ.

Hotelling's T^2 test:

$$T_N^2 = \frac{M}{2}(\hat{\bar{Z}}_{norm} - \hat{\bar{Z}}_{schiz})^T \hat{\Sigma}^{-1} (\hat{\bar{Z}}_{norm} - \hat{\bar{Z}}_{schiz}) \ .$$

N	T_N^2	p-value : $P_N(H_0)$
3	9.8042	0.0471
4	14.3086	0.0300
5	14.4012	0.0612
6	19.6038	0.0401

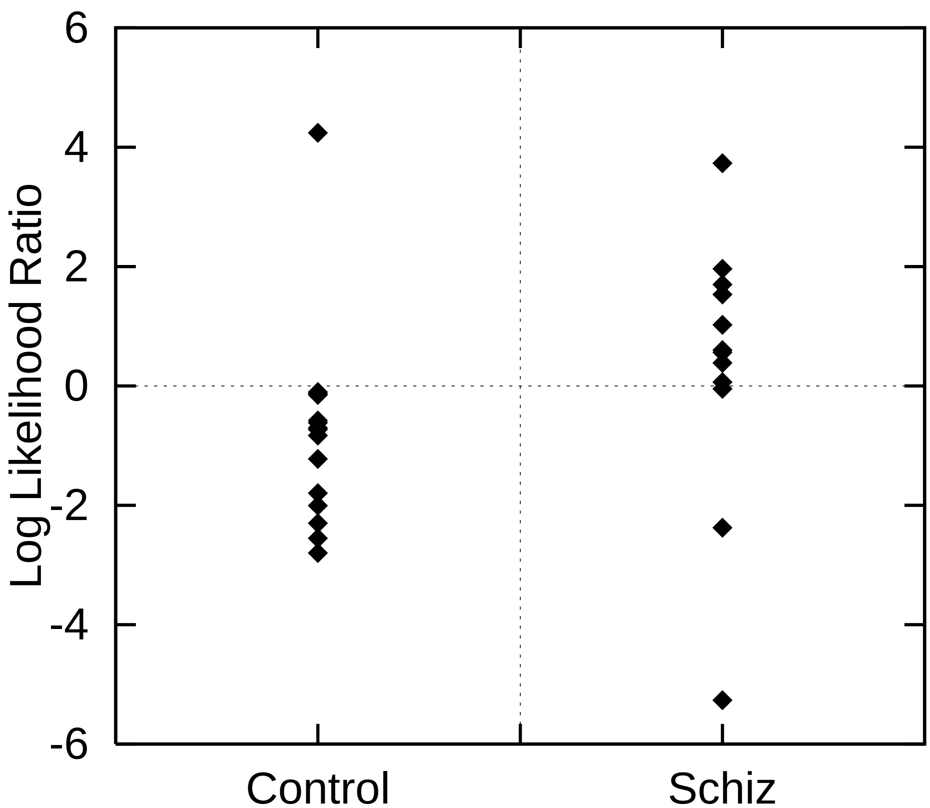
N: number of eigen functions.

Bayesian Classification on Hippocampus Shape Between Population.

- Bayesian log-likelihood ratio test: H_0: normal hippocampus, H_1: schizophrenic hippocampus.

$$\Lambda_N = -(Z - \hat{\bar{Z}}_{schiz})^\dagger \hat{\Sigma}^{-1} (Z - \hat{\bar{Z}}_{schiz}) + (Z - \hat{\bar{Z}}_{norm})^\dagger \hat{\Sigma}^{-1} (Z - \hat{\bar{Z}}_{norm}) \underset{H_1}{\overset{H_0}{\lessgtr}} 0$$

- Use Jack Knife for estimating probability of classification:



DISTRIBUTION FREE STATISTICAL TESTING.

- Use Fisher's method of randomization to empirically estimate the distribution of the test statistics with out the Gaussian assumption.

- Under the null hypothesis H_0 the expansion coefficients $(Z_i^N)_{schiz}, Z_i^N)_{control})$ for $i = 1, \cdots, M$ are independent random samples from a single population.

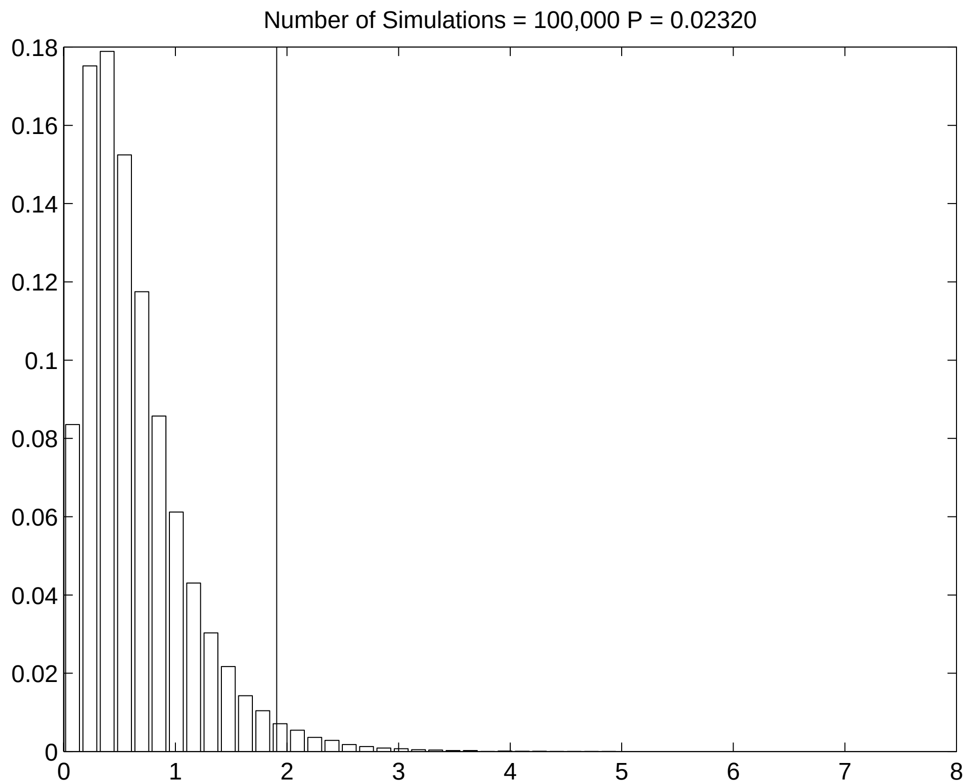
- Each of the $\binom{2N}{N}$ possible permutations of the data are equally likely and can be used for estimating the distribution of the test statistics under the hypothesis H_0.

- For $N = 15$, $1.551175e+08$ different combinations.

- Use monte carlo simulations for estimating the probability distribution by generating uniformly distributed random combinations.

DISTRIBUTION FREE STATISTICAL TESTING.

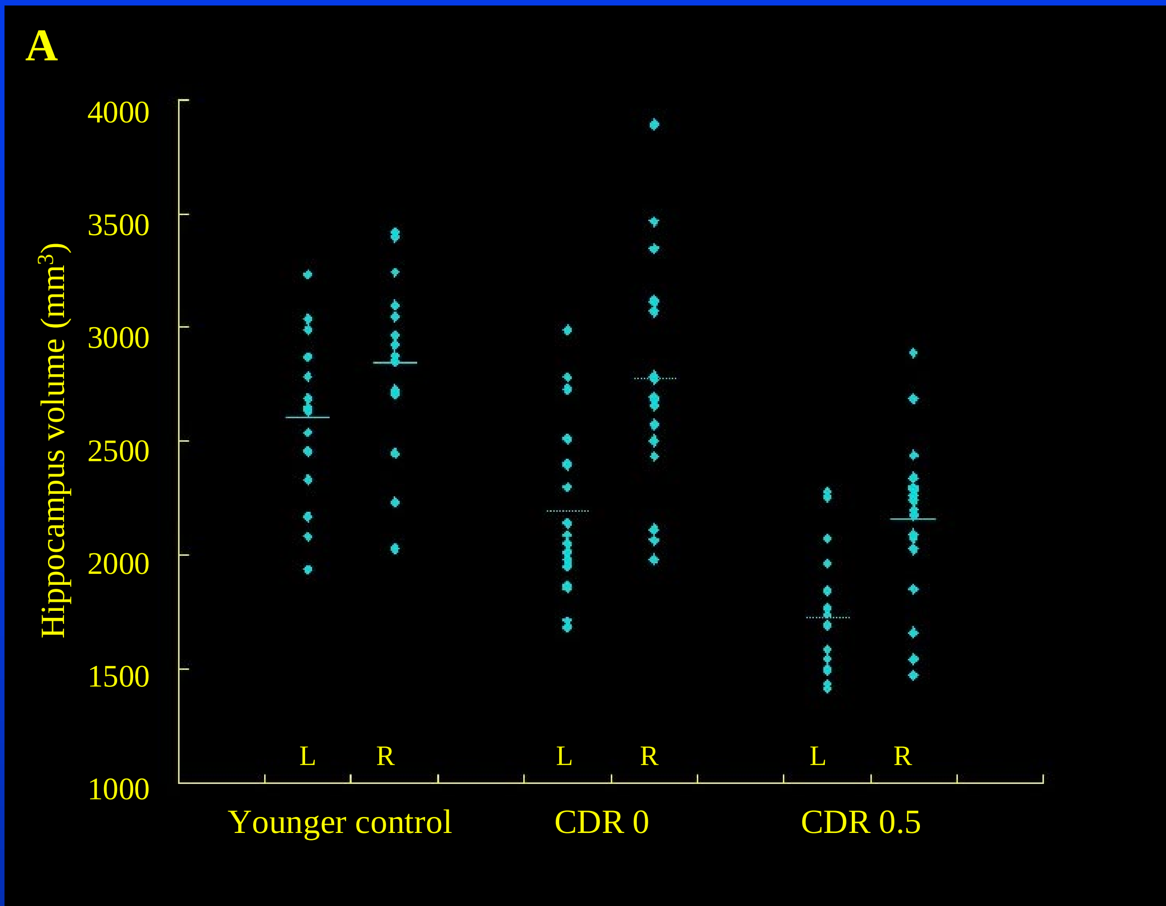
- Estimate probability distribution of the T^2 statistics under the hypothesis H_0 computed using 100000 monte carlo simulations.

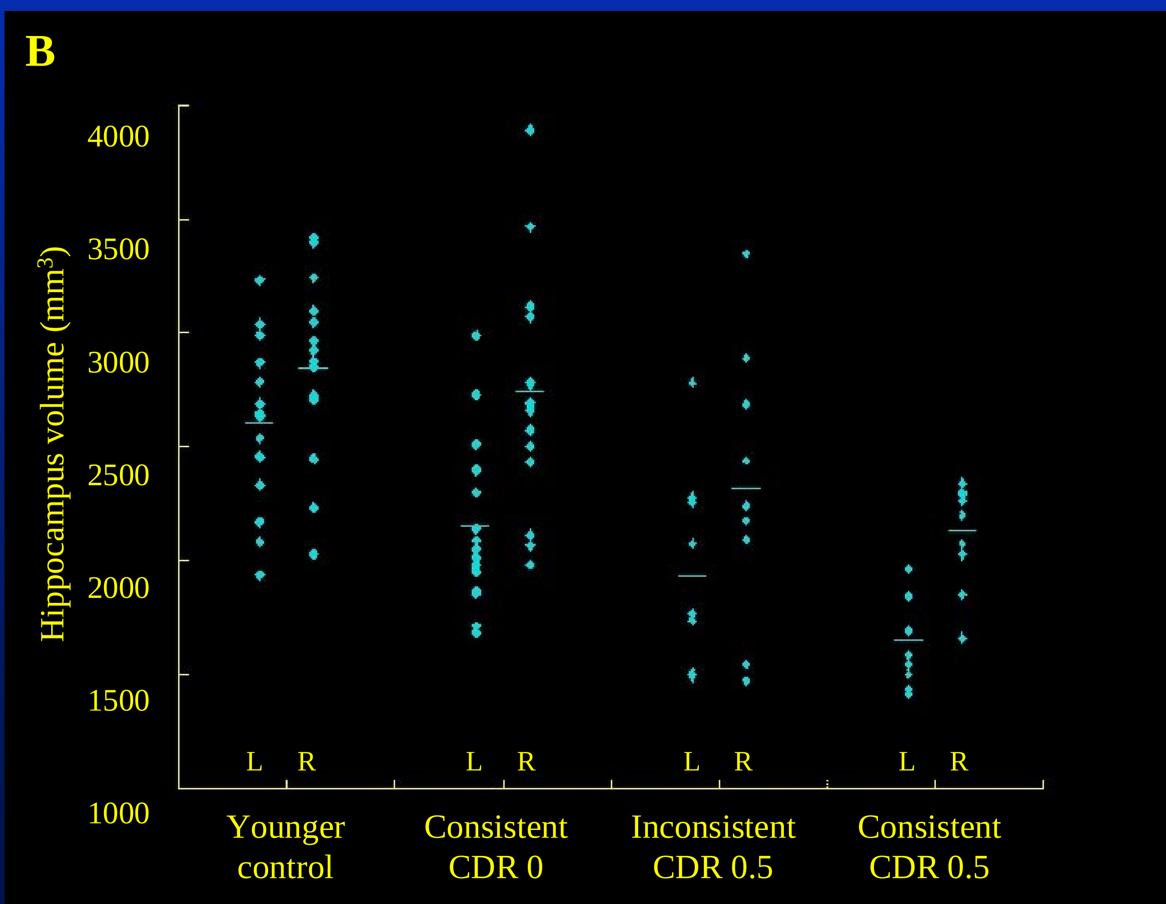


- The significance level or the p-value becomes:

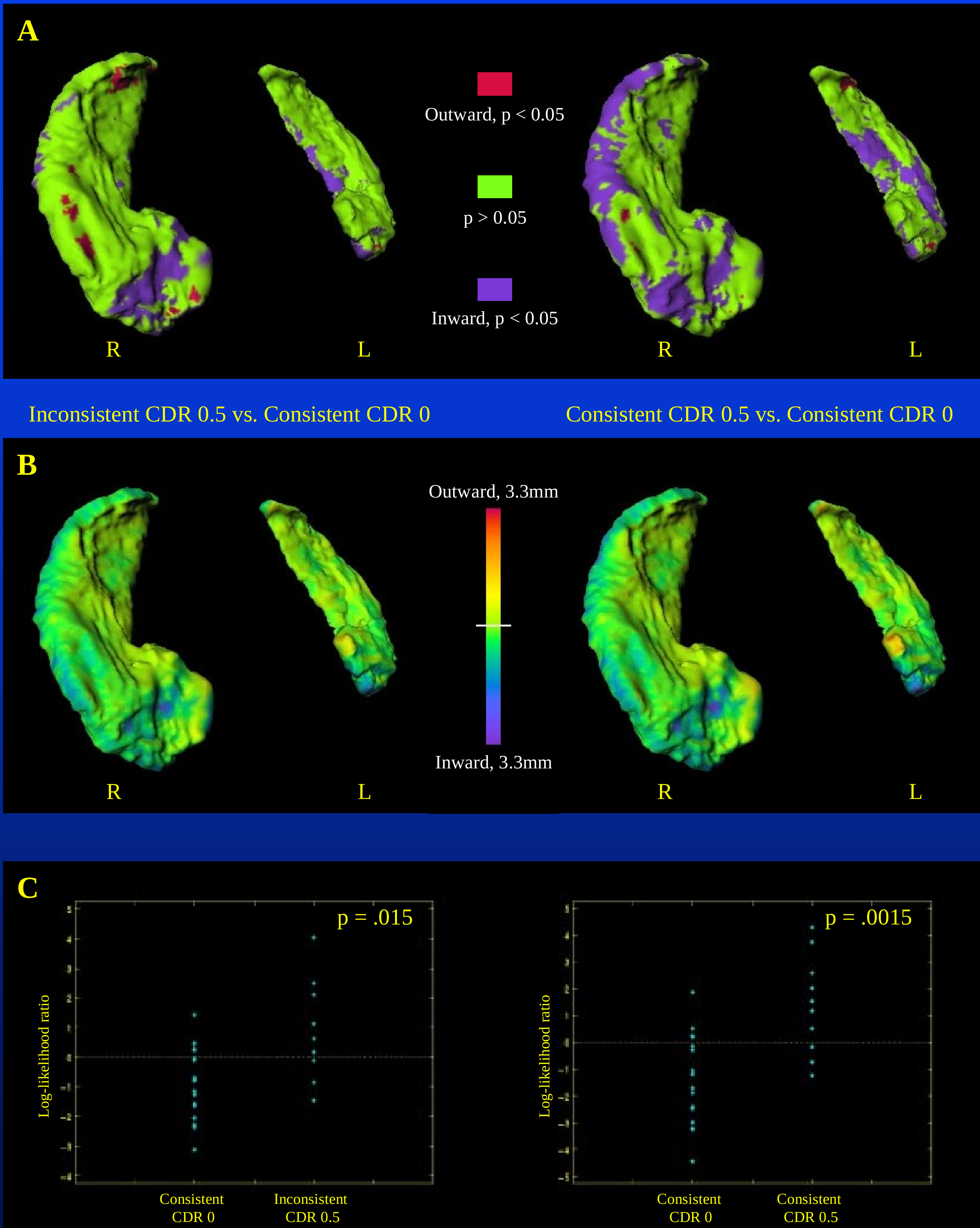
$$P = \int_{T^2}^{\infty} \hat{F}(f)df \ .$$

- Using 4 eigen shapes the p-value is estimated at 0.0232
- Statistically significant difference in the populations.

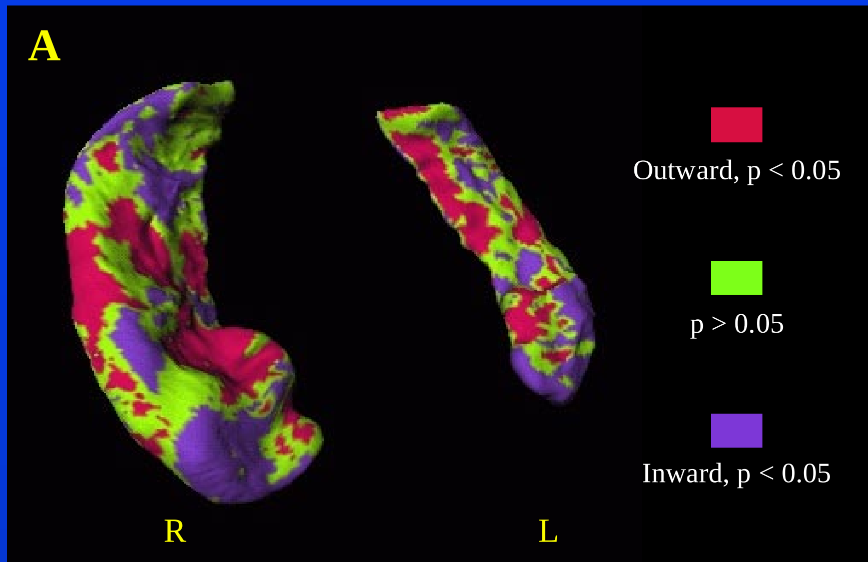




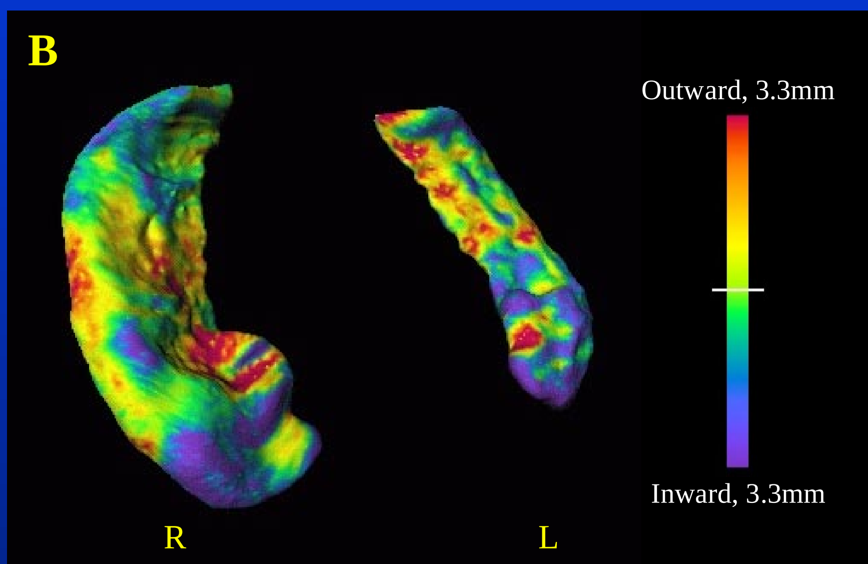
John G. Csernansky, Lei Wang, Sarang Joshi, J. Philip Miller, Mohktar Gado, Daniel Kido, Daniel McKeel, John C. Morris, Michael I. Miller, "Hippocampal Deformities Distinguish Dementia of the Alzheimer Type from Healthy Aging," submitted to Science, 1999.

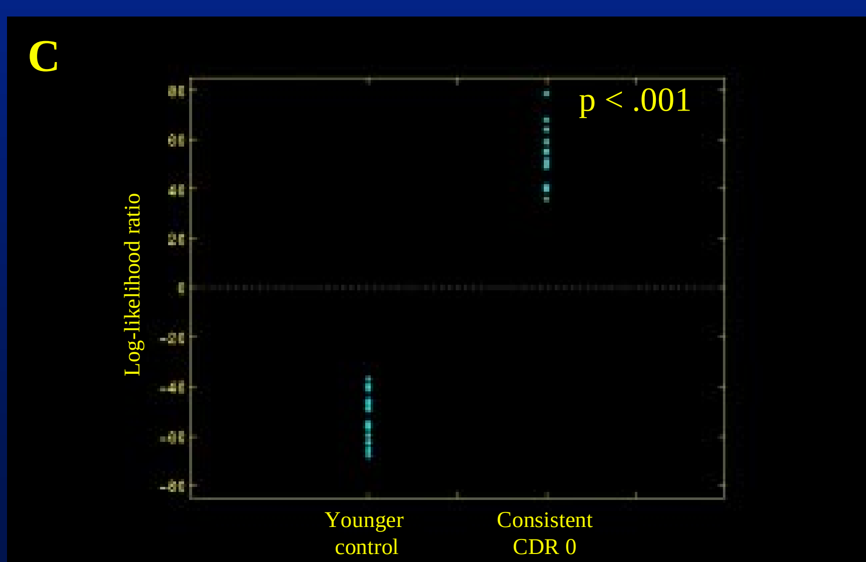


John G. Csernansky, Lei Wang, Sarang Joshi, J. Philip Miller, Mohktar Gado, Daniel Kido, Daniel McKeel, John C. Morris, Michael I. Miller, “Hippocampal Deformities Distinguish Dementia of the Alzheimer Type from Healthy Aging,” submitted to Science, 1999.



Consistent CDR 0 vs. Younger control





John G. Csernansky, Lei Wang, Sarang Joshi, J. Philip Miller, Mohktar Gado, Daniel Kido, Daniel McKeel, John C. Morris, Michael I. Miller, "Hippocampal Deformities Distinguish Dementia of the Alzheimer Type from Healthy Aging," submitted to Science, 1999.