Statistical Computation and Inference on the Subcortical Surface:

Search for Biomarkers in Neuropsychiatry

Lei Wang[1]

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CONTE CENTER
FOR NEUROSCIENCE RESEARCH

Washington
University in St.Louis
SCHOOL OF MEDICINE

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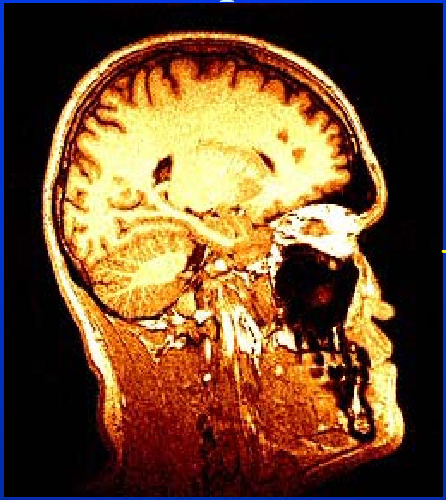
Johns Hopkins University

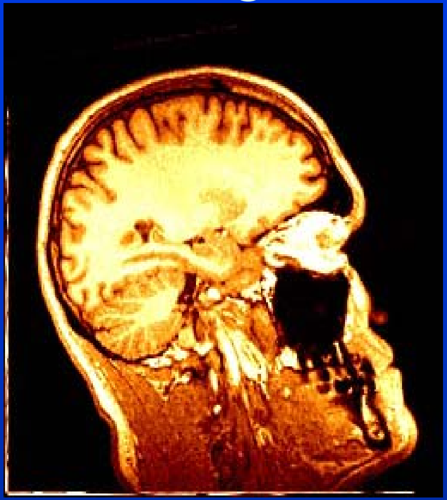
- Diffeomorphic mapping
- Computation
- Inference
- Interpretation

Large-Deformation Diffeomorphic Mapping

Template



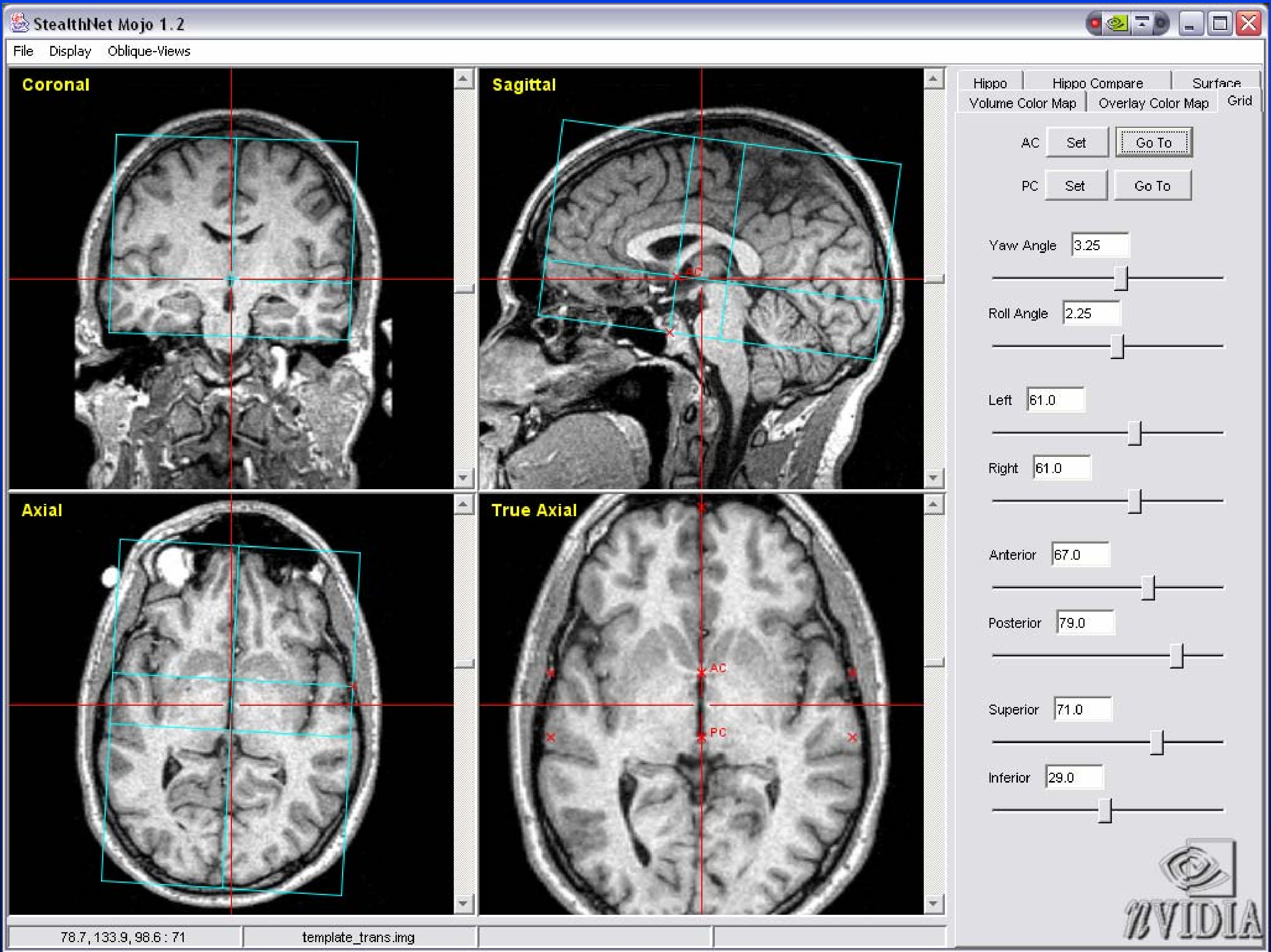
Coarse Registration



Patient

Landmark-based Low-Dimensional Transformation

Global Landmarks



Yaw Angle 3.25

Roll Angle 2.25

Left 61.0

Right 61.0

Anterior 67.0

Posterior 79.0

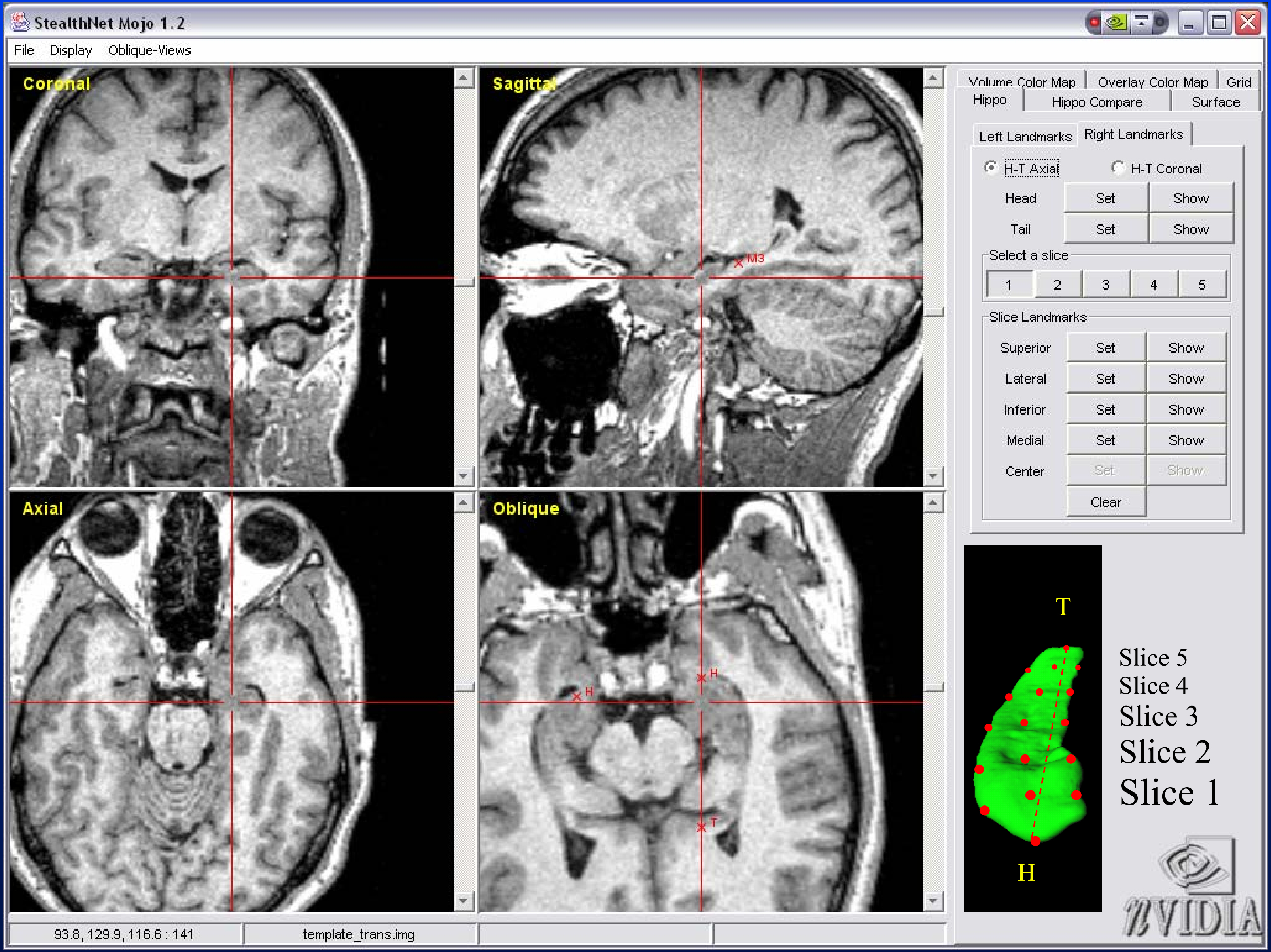
Superior 71.0

Inferior 29.0

78.7, 133.9, 98.6 : 71

template_trans.img

Local Landmarks

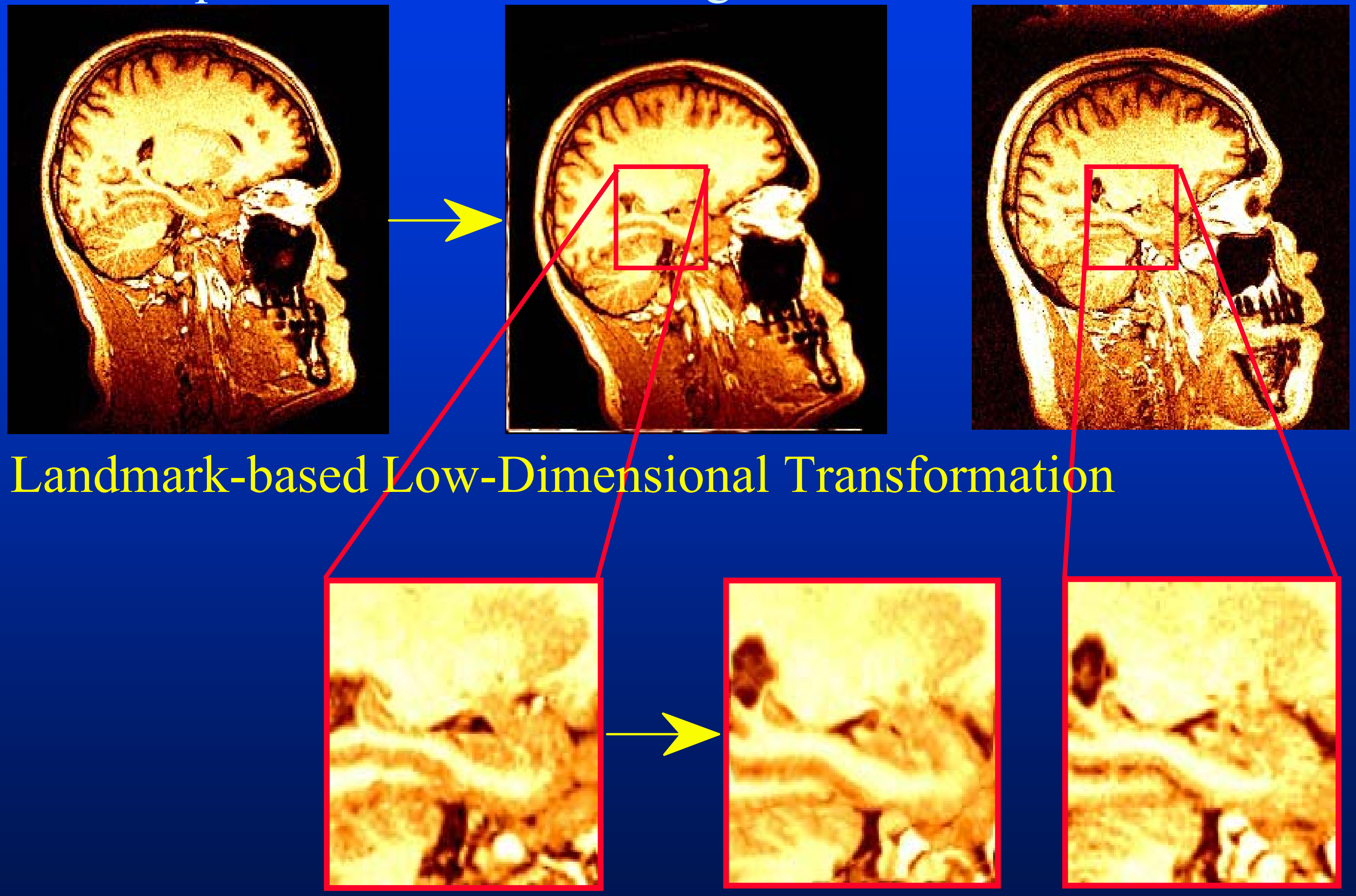


● H-T Axial ○ H-T Coronal

93.8, 129.9, 116.6 : 141

template_trans.img

Large-Deformation Diffeomorphic Mapping



Template

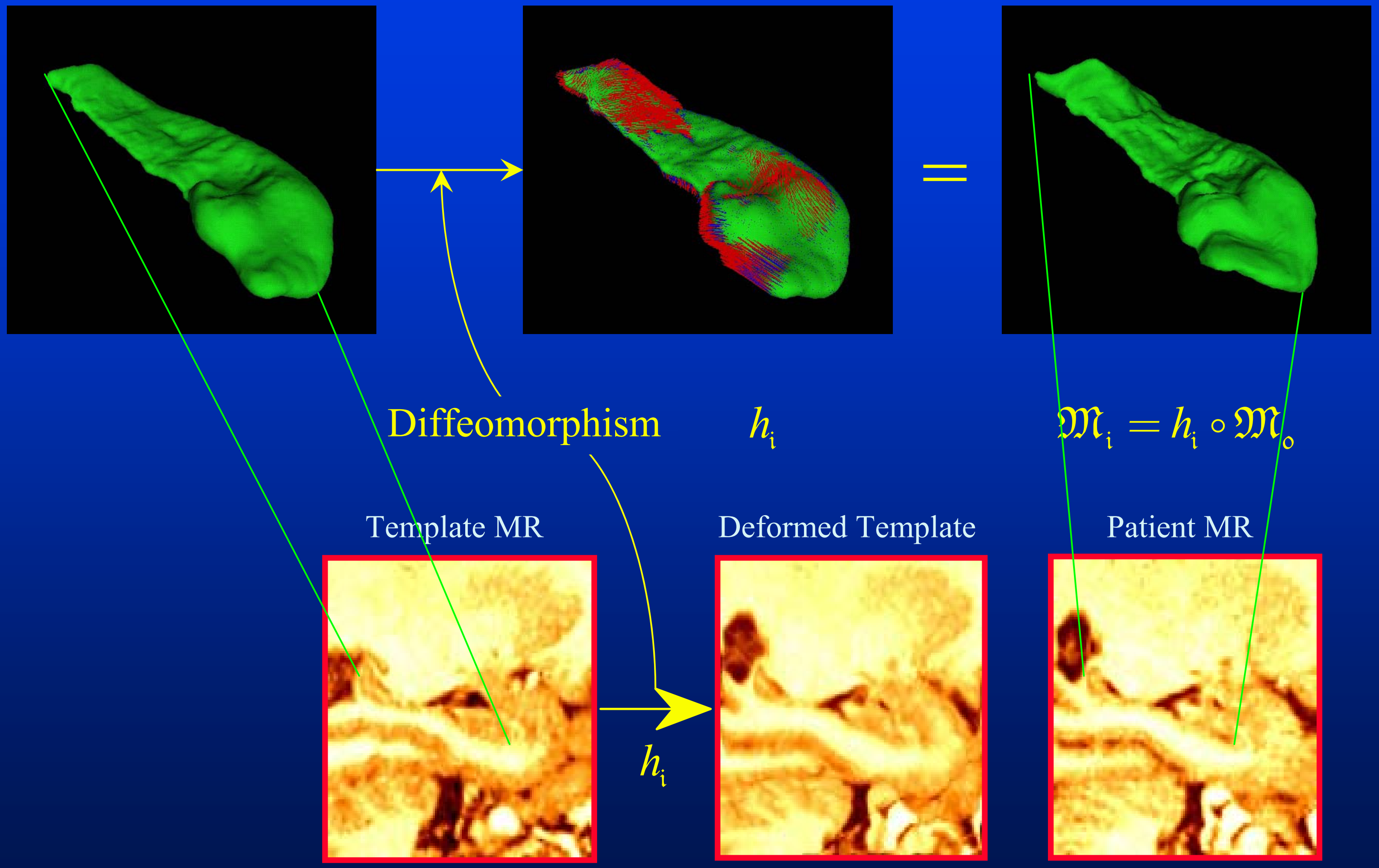
Coarse Registration

Patient

Landmark-based Low-Dimensional Transformation

Image-based Large-Deformation Diffeomorphic Mapping

Large-Deformation Diffeomorphic Mapping



Template $\mathfrak{M}_0$

Patient

=

Diffeomorphism h_i

$\mathfrak{M}_i = h_i \circ \mathfrak{M}_0$

Template MR

Deformed Template

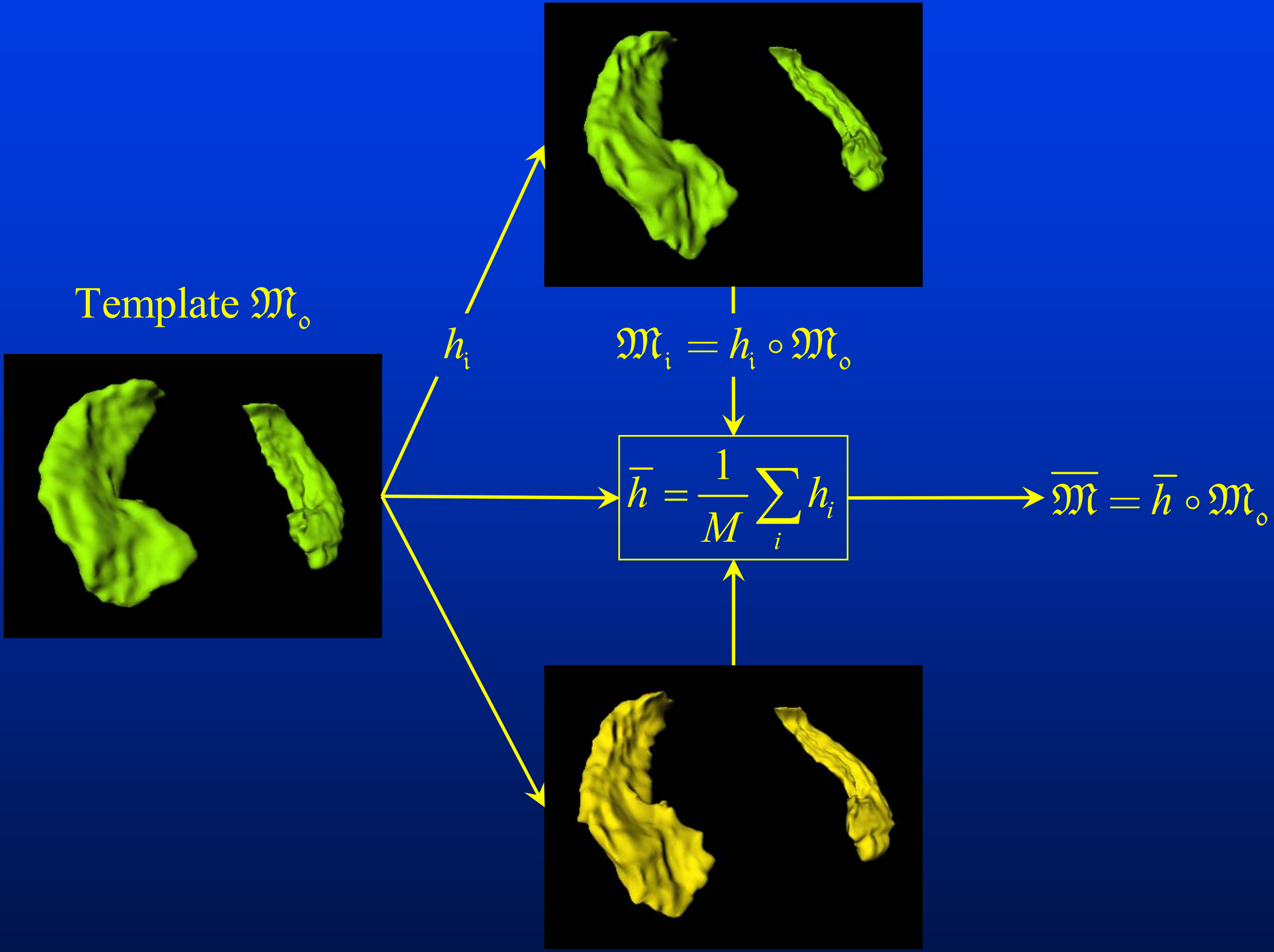
Patient MR

h_i

Image-based Large-Deformation Diffeomorphic Mapping

- Diffeomorphic mapping
- Computation
- Inference
- Interpretation

Average



Template $\mathfrak{M}_o$

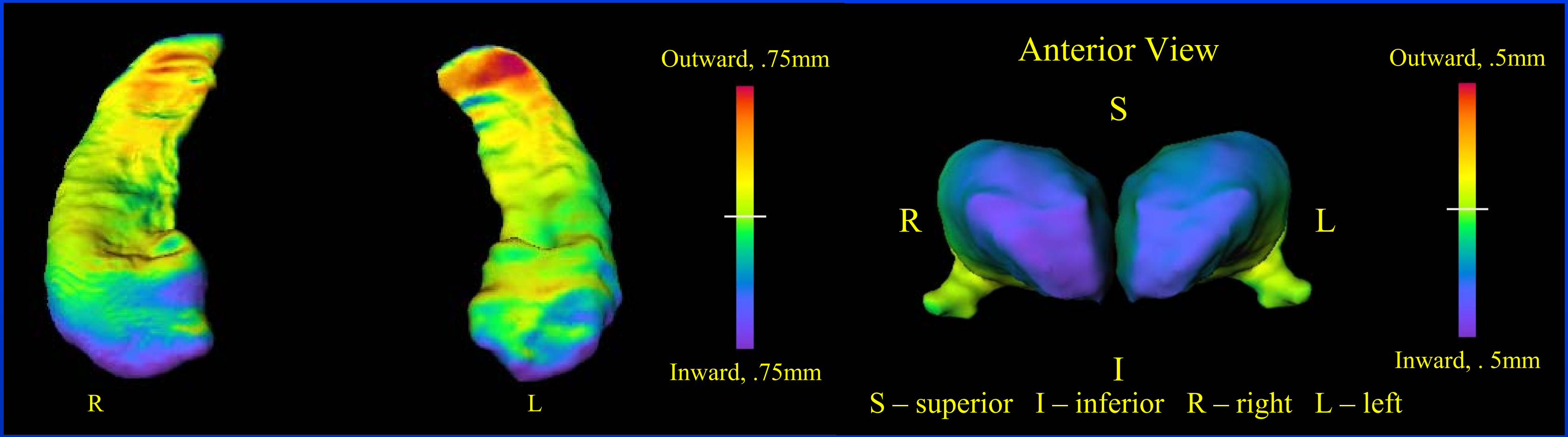
h_i

$\mathfrak{M}_i = h_i \circ \mathfrak{M}_o$

$$\bar{h} = \frac{1}{M}\sum_i h_i$$

$$\overline{\mathfrak{M}} = \bar{h} \circ \mathfrak{M}_o$$

Group Differences



Average Surface of Control Group → Average Surface of Schizophrenia Group

⇩

How to quantify the “shape” differences that are visually apparent?

Csernansky, JG et al, AJP, 2002, 2004

Singular Value Decomposition on the Cortical Surface – Joshi

$$U = \{u_i(x) = h_i(x) - x,\ x \in \overline{\mathfrak{M}}\}$$

3D Gaussian random vector fields modulo the identity map on the smooth subcortical manifold

Expand using a complete orthonormal base through the characteristic equation:

$$\lambda_k \phi_k(x) = \int_{\overline{\mathfrak{M}}} K_U(x, y) \phi_k(y) d\nu(y), x \in \overline{\mathfrak{M}}$$

$\{\lambda_k, \phi_k\}$ are the eigenvalues, eigenfunctions

$d\nu(y)$ is the surface measure around the surface point y

K_U is the covariance of U

Discretizing, we get in matrix form:

$$\lambda_k \phi_k = \hat{K} V \phi_k, \text{ where } \hat{K} = \frac{1}{M-1} U U^T, V = \text{diag}\left\{\nu(y_j)\right\}$$

Joshi S, Miller MI, Grenander U. Int J Pattern Recog Artificial Intell (Special Issue) 1997

Singular Value Decomposition on the Cortical Surface – Joshi

$$\lambda_k \phi_k = \hat{K} V \phi_k, \text{ where } \hat{K} = \frac{1}{M-1} U U^T \text{ and } \underline{V = \operatorname{diag}\left\{v(y_j)\right\}}$$

$$\lambda_k \phi_k = \frac{1}{M-1} U U^T V \phi_k$$

$$\lambda_k \underbrace{\sqrt{V}\,\phi_k} = \frac{1}{M-1} \underbrace{\sqrt{V}\,U}\, \underline{\underline{U^T \sqrt{V}}}\, \underline{\sqrt{V}\,\phi_k}$$

$$\lambda_k \tilde{\phi}_k = \tilde{U}\tilde{U}^T \tilde{\phi}_k, \text{ where } \tilde{\phi}_k = \sqrt{V}\,\phi_k \text{ and } \tilde{U} = \frac{1}{\sqrt{M-1}} \sqrt{V}\,U$$

$$\boxed{\text{SVD: } \tilde{U} = PDQ^T} \longrightarrow \tilde{U}\tilde{U}^T = PDQ^T QDP^T = PD^2P^T$$

$$\left\{\lambda_k, \tilde{\phi}_k\right\} : \left\{D^2, P\right\}$$

$$\left\{\lambda_k, \phi_k\right\} : \left\{D^2, \sqrt{V^{-1}}\,P\right\}$$

$(3 \times \text{num surface points})^2 \ (\hat{K})$

$3 \times \text{num surface points} \times \text{num subjects} \ (P)$

Joshi S, Miller MI, Grenander U. Int J Pattern Recog Artificial Intell (Special Issue) 1997

Singular Value Decomposition on the Cortical Surface – Joshi

$$\boxed{\text{SVD: } \widetilde{U} = PDQ^T}$$

where $\widetilde{U} = \dfrac{1}{\sqrt{M-1}}\sqrt{V}U$

$$U = \begin{array}{c|cccc|l}
 & u_1^{1x} & u_2^{1x} & & u_N^{1x} & \\
 & u_1^{1y} & u_2^{1y} & \cdots & u_N^{1y} & \big\} \text{ surface vertex 1} \\
 & u_1^{1z} & u_2^{1z} & & u_N^{1z} & \\
\hdashline
 & u_1^{2x} & u_2^{2x} & & u_N^{2x} & \\
 & u_1^{2y} & u_2^{2y} & \cdots & u_N^{2y} & \big\} \text{ surface vertex 2} \\
 & u_1^{2z} & u_2^{2z} & & u_N^{2z} & \\
\hdashline
 & \vdots & \vdots & & \vdots & \\
 & u_1^{jx} & u_2^{jx} & & u_N^{jx} & \\
 & u_1^{jy} & u_2^{jy} & \cdots & u_N^{jy} & \big\} \text{ surface vertex } j \\
 & u_1^{jz} & u_2^{jz} & & u_N^{jz} & \\
 & \vdots & \vdots & & \vdots & \\
\hline
 & \text{subject 1} & \text{subject 2} & & \text{subject } N &
\end{array}$$

$$\hat{K} \sim UU^T$$

$$(3 \times \text{num surface points})^2$$

$$\downarrow$$

$$P$$

$$(3 \times \text{num surface points}) \times N$$

Joshi S, Miller MI, Grenander U. Int J Pattern Recog Artificial Intell (Special Issue) 1997

Statistics on the Hippocampus

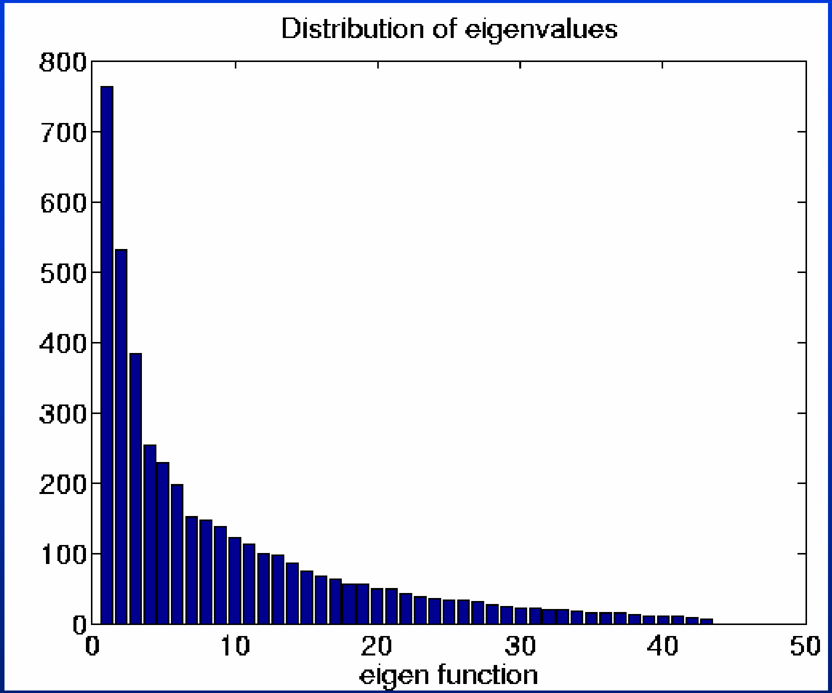
For each subject *i*, its deformation vector fields expand to:

$$u_i = \sum_k \alpha_{ik} \phi_k$$

with vector-coefficients for each subject

$$\alpha_{ik} = \langle u_i, \phi_k \rangle \doteq \int_{\mathfrak{M}} u_i^T(x) \phi_k(x) d\nu(x)$$

The coefficients α_{ik} are used in statistical analyses.



74% 87% 95%

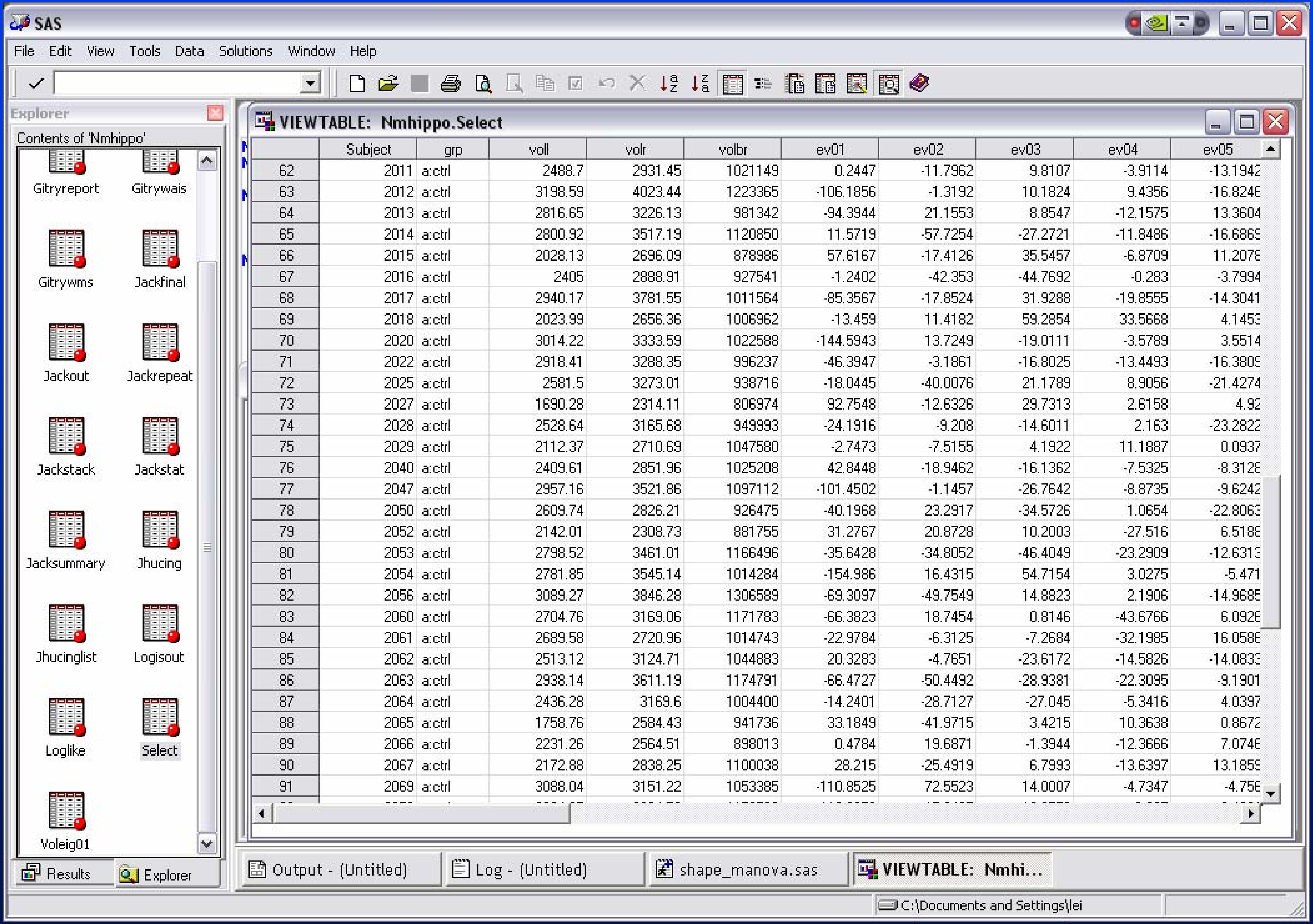
Percentage of total variance accounted for

- Diffeomorphic mapping
- Computation
- Inference
- Interpretation

Statistics on the Hippocampus

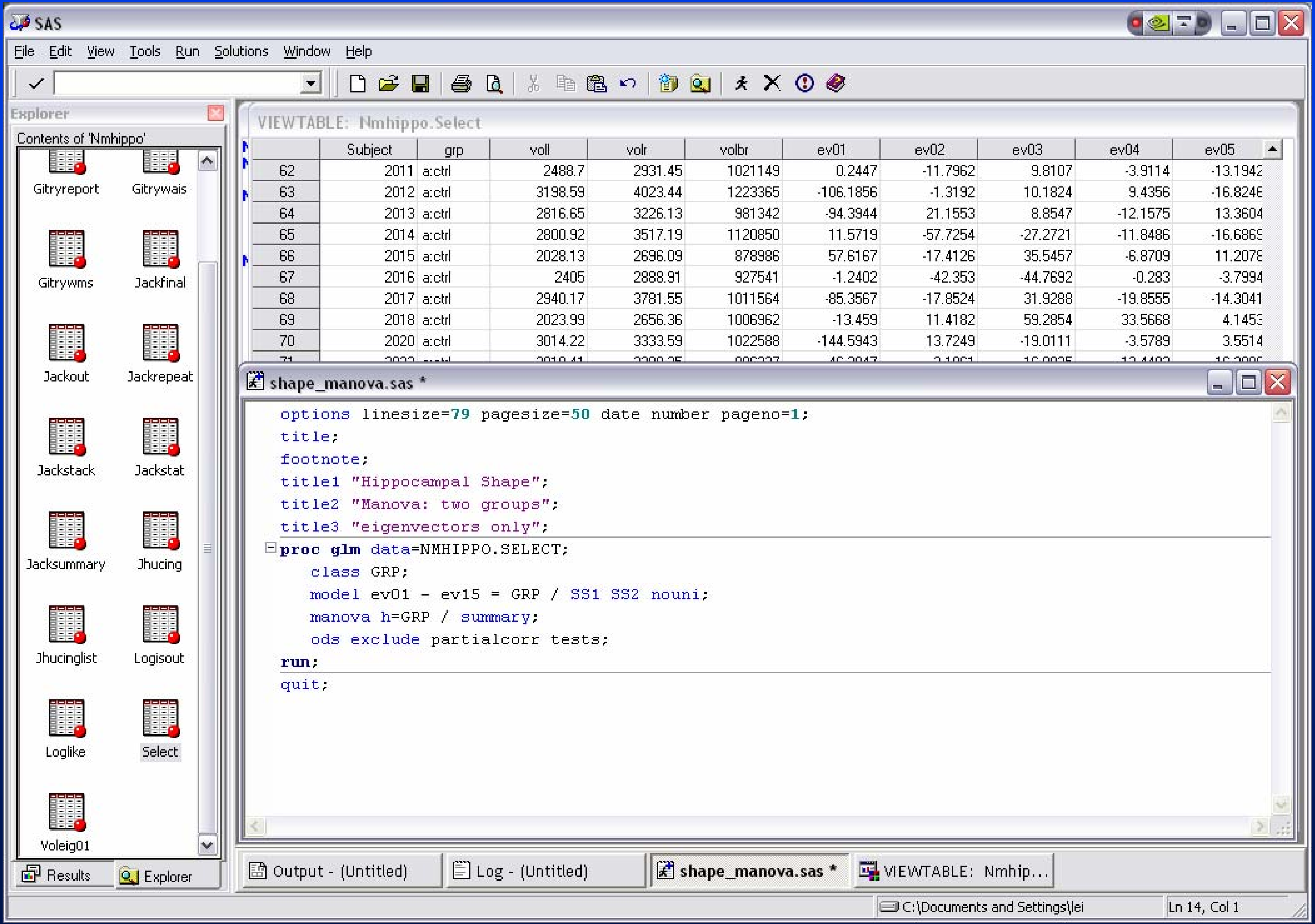
- General linear model
- Multivariate ANOVA and discrimination
- Canonical correlation for multiple-group comparisons

Statistics on the Hippocampus



	Subject	grp	voll	volr	volbr	ev01	ev02	ev03	ev04	ev05
62	2011	a:ctrl	2488.7	2931.45	1021149	0.2447	-11.7962	9.8107	-3.9114	-13.1942
63	2012	a:ctrl	3198.59	4023.44	1223365	-106.1856	-1.3192	10.1824	9.4356	-16.8246
64	2013	a:ctrl	2816.65	3226.13	981342	-94.3944	21.1553	8.8547	-12.1575	13.3604
65	2014	a:ctrl	2800.92	3517.19	1120850	11.5719	-57.7254	-27.2721	-11.8486	-16.6869
66	2015	a:ctrl	2028.13	2696.09	878986	57.6167	-17.4126	35.5457	-6.8709	11.2078
67	2016	a:ctrl	2405	2888.91	927541	-1.2402	-42.353	-44.7692	-0.283	-3.7994
68	2017	a:ctrl	2940.17	3781.55	1011564	-85.3567	-17.8524	31.9288	-19.8555	-14.3041
69	2018	a:ctrl	2023.99	2656.36	1006962	-13.459	11.4182	59.2854	33.5668	4.1453
70	2020	a:ctrl	3014.22	3333.59	1022588	-144.5943	13.7249	-19.0111	-3.5789	3.5514
71	2022	a:ctrl	2918.41	3288.35	996237	-46.3947	-3.1861	-16.8025	-13.4493	-16.3809
72	2025	a:ctrl	2581.5	3273.01	938716	-18.0445	-40.0076	21.1789	8.9056	-21.4274
73	2027	a:ctrl	1690.28	2314.11	806974	92.7548	-12.6326	29.7313	2.6158	4.92
74	2028	a:ctrl	2528.64	3165.68	949993	-24.1916	-9.208	-14.6011	2.163	-23.2822
75	2029	a:ctrl	2112.37	2710.69	1047580	-2.7473	-7.5155	4.1922	11.1887	0.0937
76	2040	a:ctrl	2409.61	2851.96	1025208	42.8448	-18.9462	-16.1362	-7.5325	-8.3128
77	2047	a:ctrl	2957.16	3521.86	1097112	-101.4502	-1.1457	-26.7642	-8.8735	-9.6242
78	2050	a:ctrl	2609.74	2826.21	926475	-40.1968	23.2917	-34.5726	1.0654	-22.8063
79	2052	a:ctrl	2142.01	2308.73	881755	31.2767	20.8728	10.2003	-27.516	6.5188
80	2053	a:ctrl	2798.52	3461.01	1166496	-35.6428	-34.8052	-46.4049	-23.2909	-12.6313
81	2054	a:ctrl	2781.85	3545.14	1014284	-154.986	16.4315	54.7154	3.0275	-5.471
82	2056	a:ctrl	3089.27	3846.28	1306589	-69.3097	-49.7549	14.8823	2.1906	-14.9685
83	2060	a:ctrl	2704.76	3169.06	1171783	-66.3823	18.7454	0.8146	-43.6766	6.0926
84	2061	a:ctrl	2689.58	2720.96	1014743	-22.9784	-6.3125	-7.2684	-32.1985	16.0586
85	2062	a:ctrl	2513.12	3124.71	1044883	20.3283	-4.7651	-23.6172	-14.5826	-14.0833
86	2063	a:ctrl	2938.14	3611.19	1174791	-66.4727	-50.4492	-28.9381	-22.3095	-9.1901
87	2064	a:ctrl	2436.28	3169.6	1004400	-14.2401	-28.7127	-27.045	-5.3416	4.0397
88	2065	a:ctrl	1758.76	2584.43	941736	33.1849	-41.9715	3.4215	10.3638	0.8672
89	2066	a:ctrl	2231.26	2564.51	898013	0.4784	19.6871	-1.3944	-12.3666	7.0746
90	2067	a:ctrl	2172.88	2838.25	1100038	28.215	-25.4919	6.7993	-13.6397	13.1859
91	2069	a:ctrl	3088.04	3151.22	1053385	-110.8525	72.5523	14.0007	-4.7347	-4.756

Statistics on the Hippocampus



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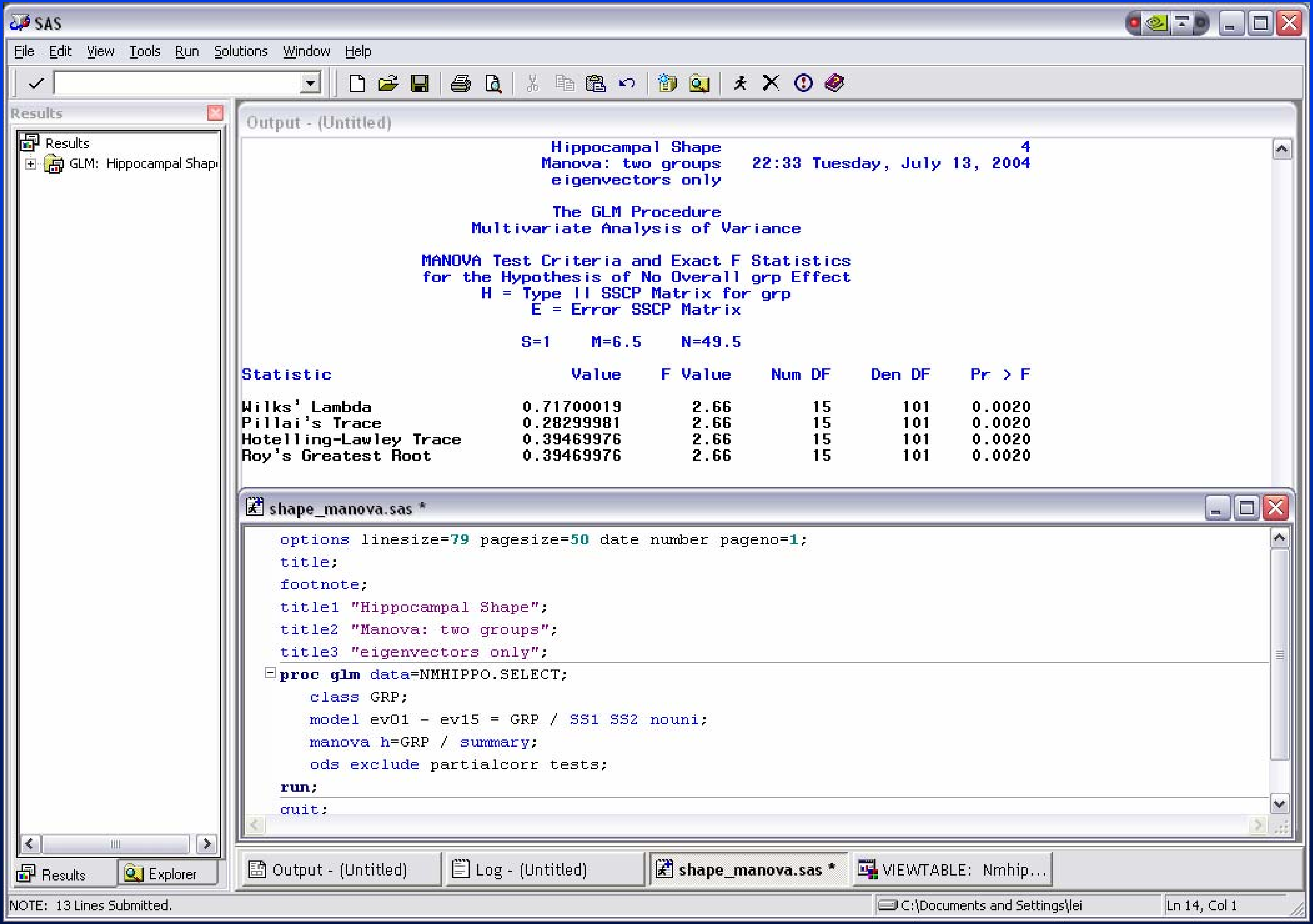
69	2018	a:ctrl	2023.99	2656.36	1006962	-13.459	11.4182	59.2854	33.5668	4.145
70	2020	a:ctrl	3014.22	3333.59	1022588	-144.5943	13.7249	-19.0111	-3.5789	3.5514

```
options linesize=79 pagesize=50 date number pageno=1;
title;
footnote;
title1 "Hippocampal Shape";
title2 "Manova: two groups";
title3 "eigenvectors only";
proc glm data=NMHIPPO.SELECT;
   class GRP;
   model ev01 - ev15 = GRP / SS1 SS2 nouni;
   manova h=GRP / summary;
   ods exclude partialcorr tests;
run;
quit;
```

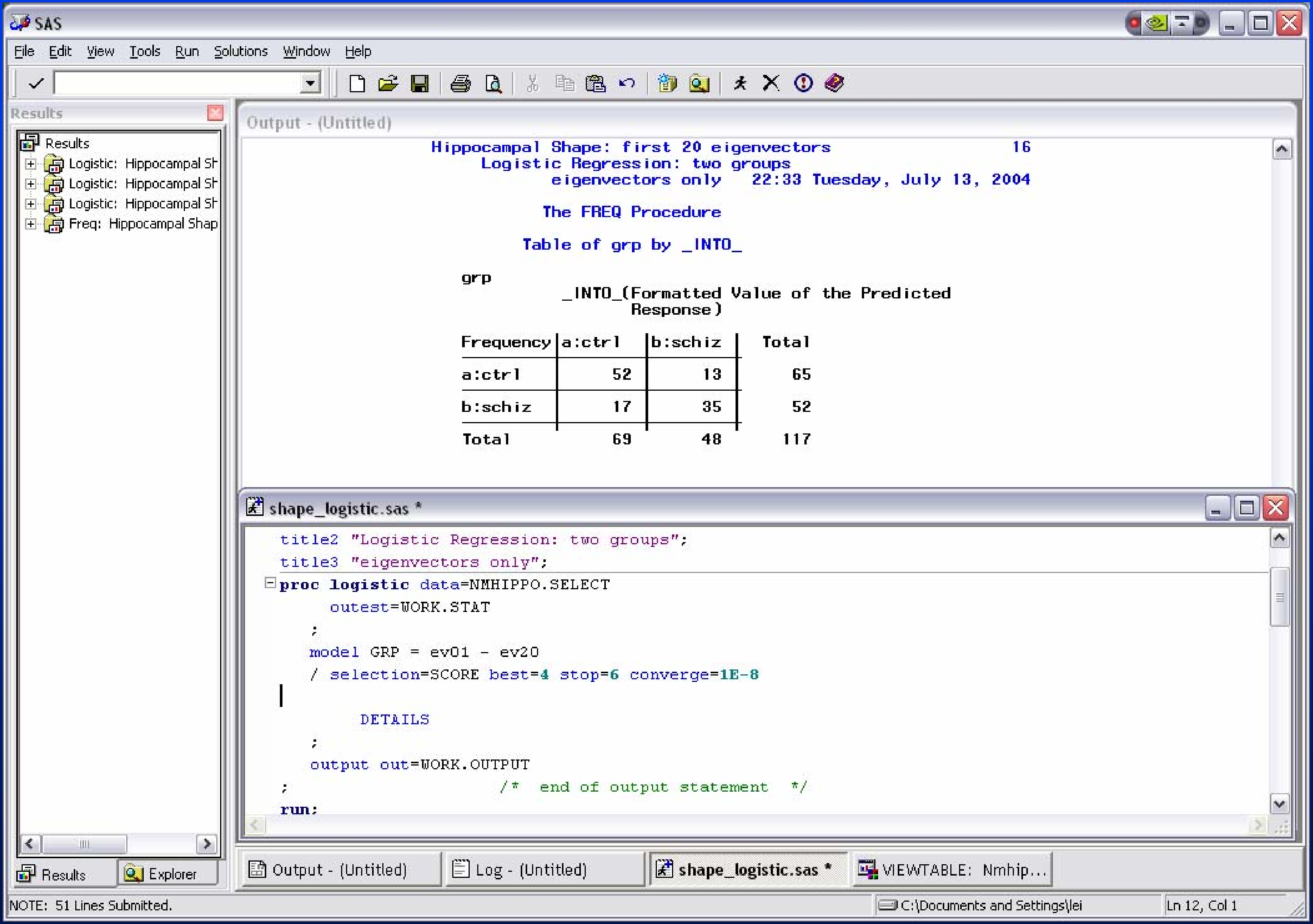
Statistics on the Hippocampus



```
                         Hippocampal Shape                                4
                       Manova: two groups    22:33 Tuesday, July 13, 2004
                         eigenvectors only

                          The GLM Procedure
                  Multivariate Analysis of Variance

             MANOVA Test Criteria and Exact F Statistics
             for the Hypothesis of No Overall grp Effect
                   H = Type II SSCP Matrix for grp
                        E = Error SSCP Matrix

                       S=1     M=6.5     N=49.5

Statistic                      Value    F Value    Num DF    Den DF    Pr > F

Wilks' Lambda             0.71700019       2.66        15       101    0.0020
Pillai's Trace            0.28299981       2.66        15       101    0.0020
Hotelling-Lawley Trace    0.39469976       2.66        15       101    0.0020
Roy's Greatest Root       0.39469976       2.66        15       101    0.0020
```

```
options linesize=79 pagesize=50 date number pageno=1;
title;
footnote;
title1 "Hippocampal Shape";
title2 "Manova: two groups";
title3 "eigenvectors only";
proc glm data=NMHIPPO.SELECT;
   class GRP;
   model ev01 - ev15 = GRP / SS1 SS2 nouni;
   manova h=GRP / summary;
   ods exclude partialcorr tests;
run;
quit;
```

Statistics on the Hippocampus



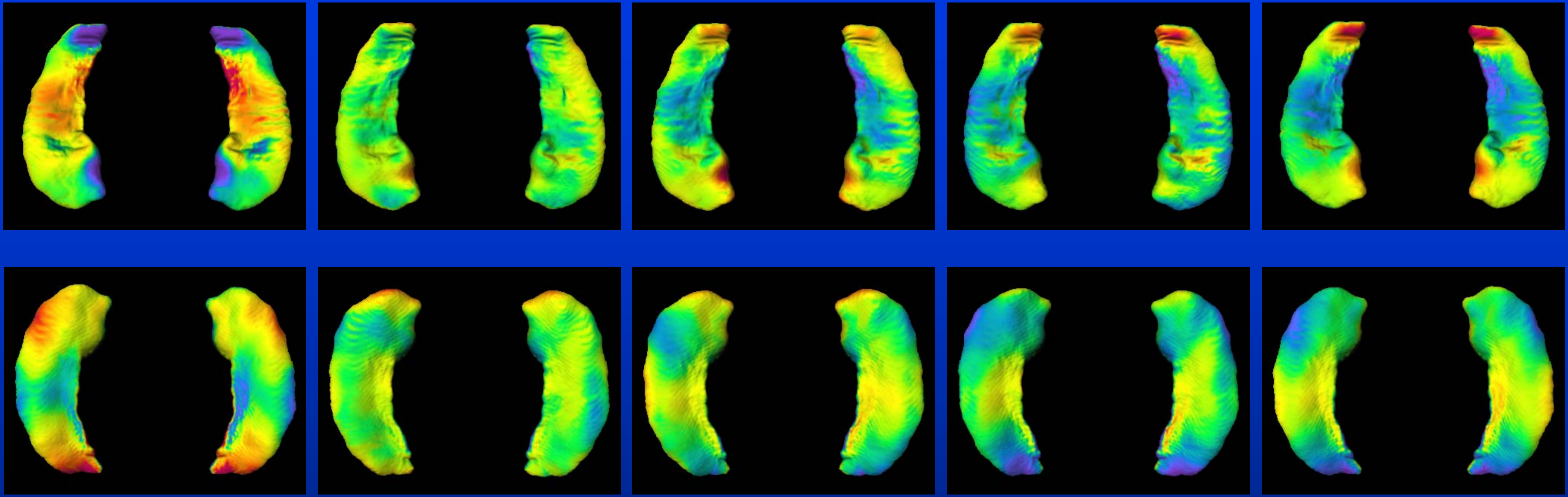
```
                 Hippocampal Shape: first 20 eigenvectors                    16
                      Logistic Regression: two groups
                             eigenvectors only   22:33 Tuesday, July 13, 2004

                            The FREQ Procedure

                          Table of grp by _INTO_

               grp
                         _INTO_(Formatted Value of the Predicted
                                 Response)

               Frequency|a:ctrl  |b:schiz  |  Total
               ---------+--------+--------+
               a:ctrl   |     52 |     13 |     65
               ---------+--------+--------+
               b:schiz  |     17 |     35 |     52
               ---------+--------+--------+
               Total          69       48      117
```

```
 title2 "Logistic Regression: two groups";
 title3 "eigenvectors only";
proc logistic data=NMHIPPO.SELECT
      outest=WORK.STAT
    ;
    model GRP = ev01 - ev20
    / selection=SCORE best=4 stop=6 converge=1E-8

        DETAILS
    ;
    output out=WORK.OUTPUT
;                    /*  end of output statement  */
run;
```

NOTE: 51 Lines Submitted.

- Diffeomorphic mapping
- Computation
- Inference
- Interpretation

Interpreting Eigenvectors



Max ev02 coefficient

Case Group I vs. Control

Case Group II vs. Control

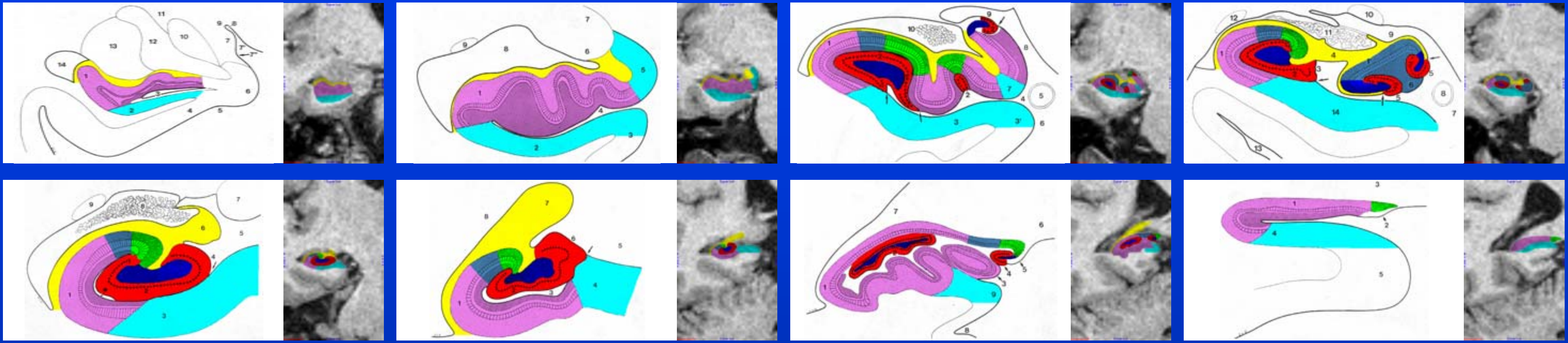
Case Group III vs. Control

Min ev02 coefficient

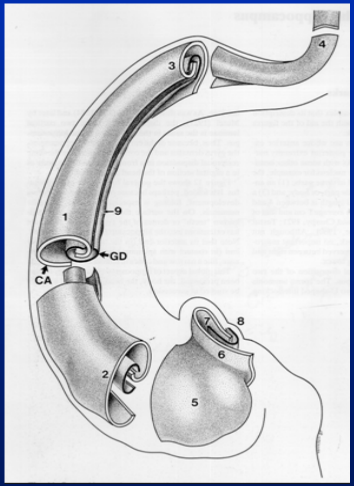
$$\hat{u}_i = \alpha_{i2}\phi_2$$

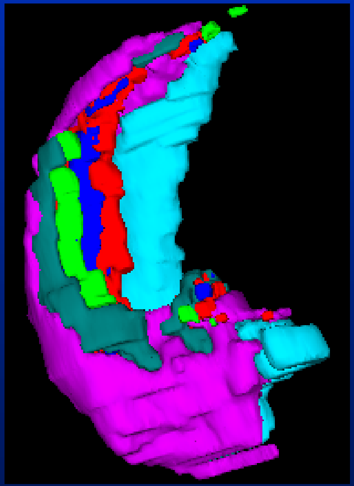
Autism, Wang, L, Dager, S, Constantino, J, Csernansky J, 2004, unpublished

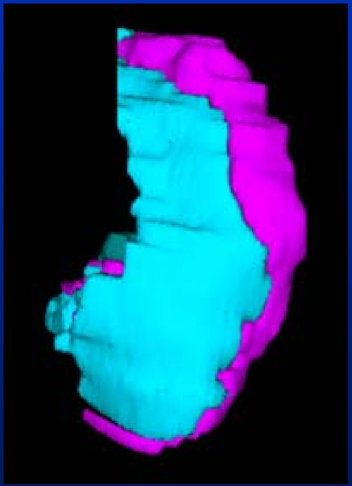
Subfield Zones of the Hippocampus in AD

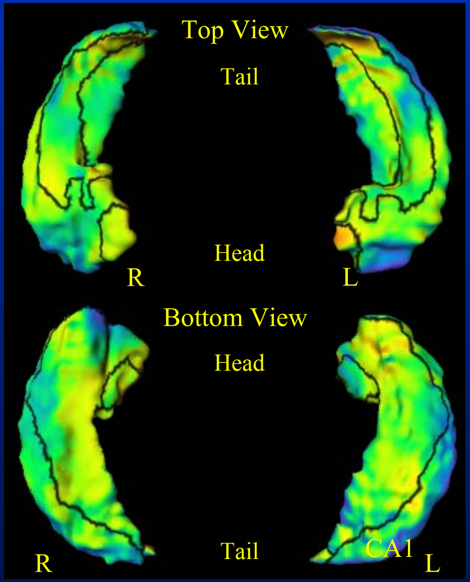


🟪 CA1 🟦 CA2 🟩 CA3 🟦 CA4 🟥 Gyrus Dentaus 🟦 Subiculum









Alzheimer’s disease, Csernansky J, Wang L, Miller M, Morris J 2004

Duvernoy, Henri M. *The Human Hippocampus: An Atlas of Applied Anatomy.* New York: Springer-Verlag, 1988.
Glick, I. *Senior Honors Thesis*, Washington University in St. Louis, 2002.
Wang, L etl al, NeuroImage, 2003.

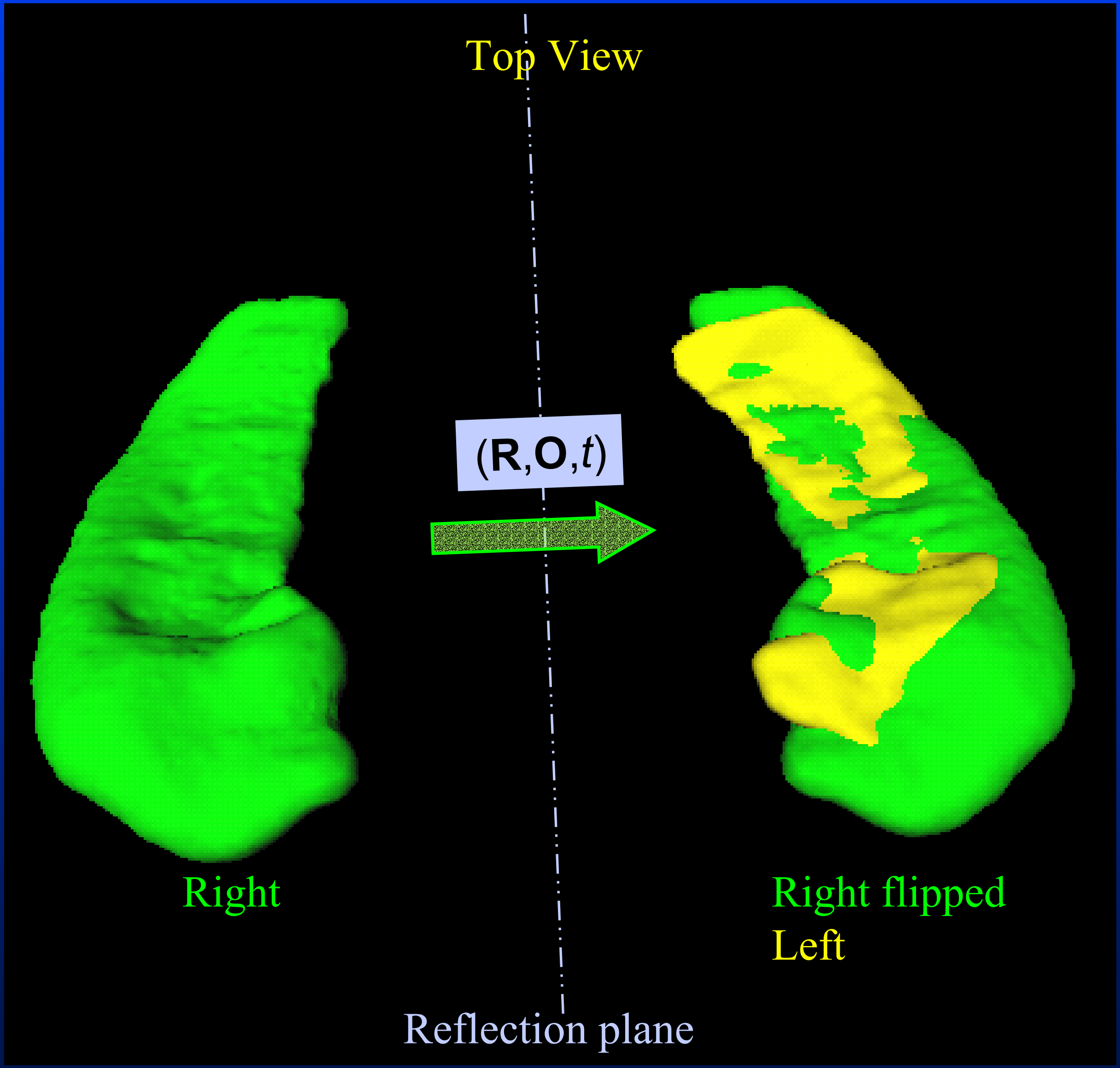
Extension to Other Vector Fields Analyses

- Asymmetry in schizophrenia
  - Formulation: L-R flip across mathematical sagittal plane
  - Asymmetry = residual
  - *Measure of shape asymmetry*
- Time-dependent change in AD
  - Formulation: rigid-motion registration of follow-up and baseline
  - Change = residual
  - *Measure of shape change*

Asymmetry

Reflection plane:

$$\left\{ x \;\middle|\; x = \mathbf{OR}\, x + \vec{t} \right\}$$

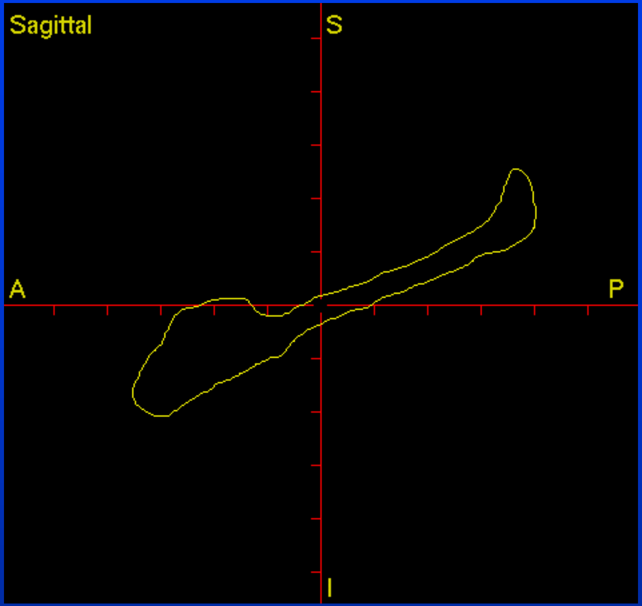


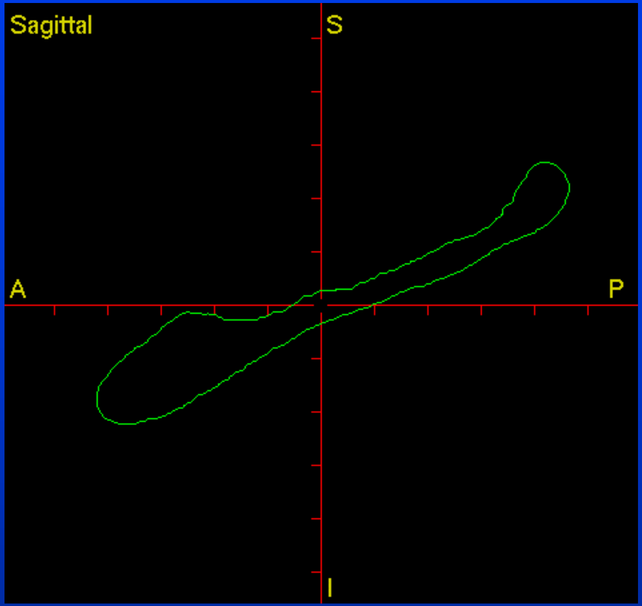
Right flipped

$\mathbf{OR}\ \text{right} + \vec{t}$

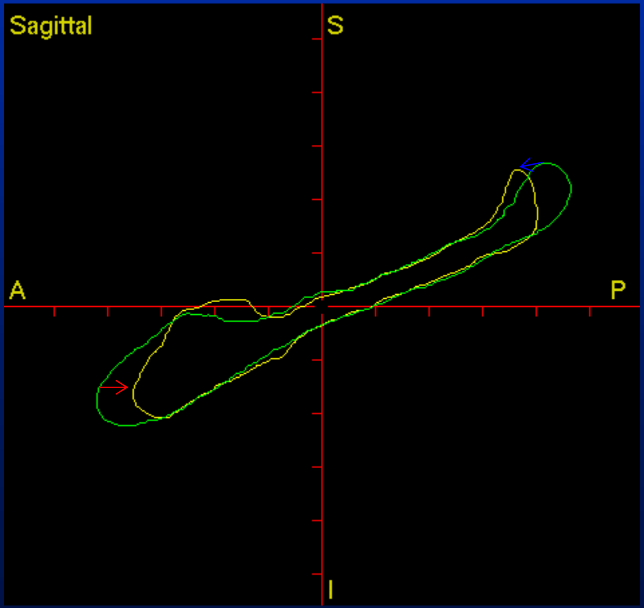
Asymmetry

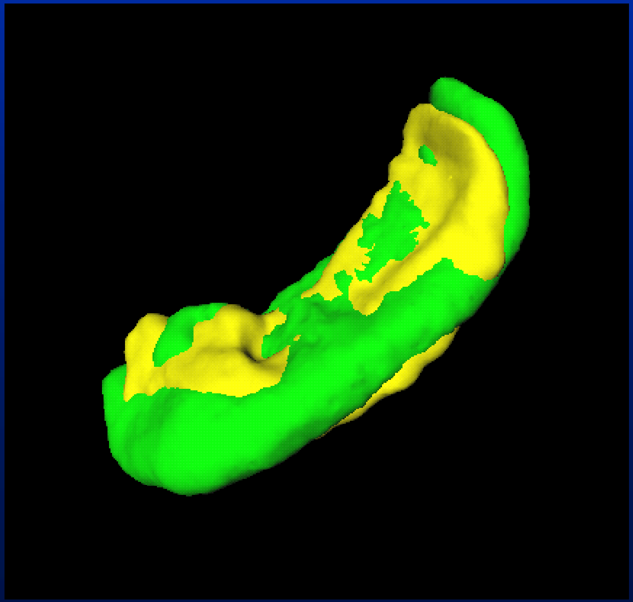
Left





Right,
flipped





u

asymmetry
vector
field

Asymmetry

Singular Value Decomposition

Empirical estimate of covariance:

$$K = \frac{1}{N-1}\sum_{i=1}^{N}(u_i - \overline{u})(u_i - \overline{u})^T \Rightarrow \left(\lambda_k, \phi_k\right)$$

$$u \sim N(\overline{u}, K), \qquad u_i = \sum_{k=1}^{N} Z_i \phi_k, \qquad Z_i = \left\langle u_i, \phi_k \right\rangle$$

Pooled sample covariance:

$$\Sigma = \frac{1}{N_1 + N_2 - 1}\left\{\sum_{i=1}^{N_1}(Z_i - \overline{Z}^1)(Z_i - \overline{Z}^1)^T + \sum_{i=1}^{N_2}(Z_i - \overline{Z}^2)(Z_i - \overline{Z}^2)^T\right\}$$

Asymmetry Measure: $eff = \sqrt{Z^T \Sigma^{-1} Z}$

Wang, L, et. al, *NeuroImage* 2001

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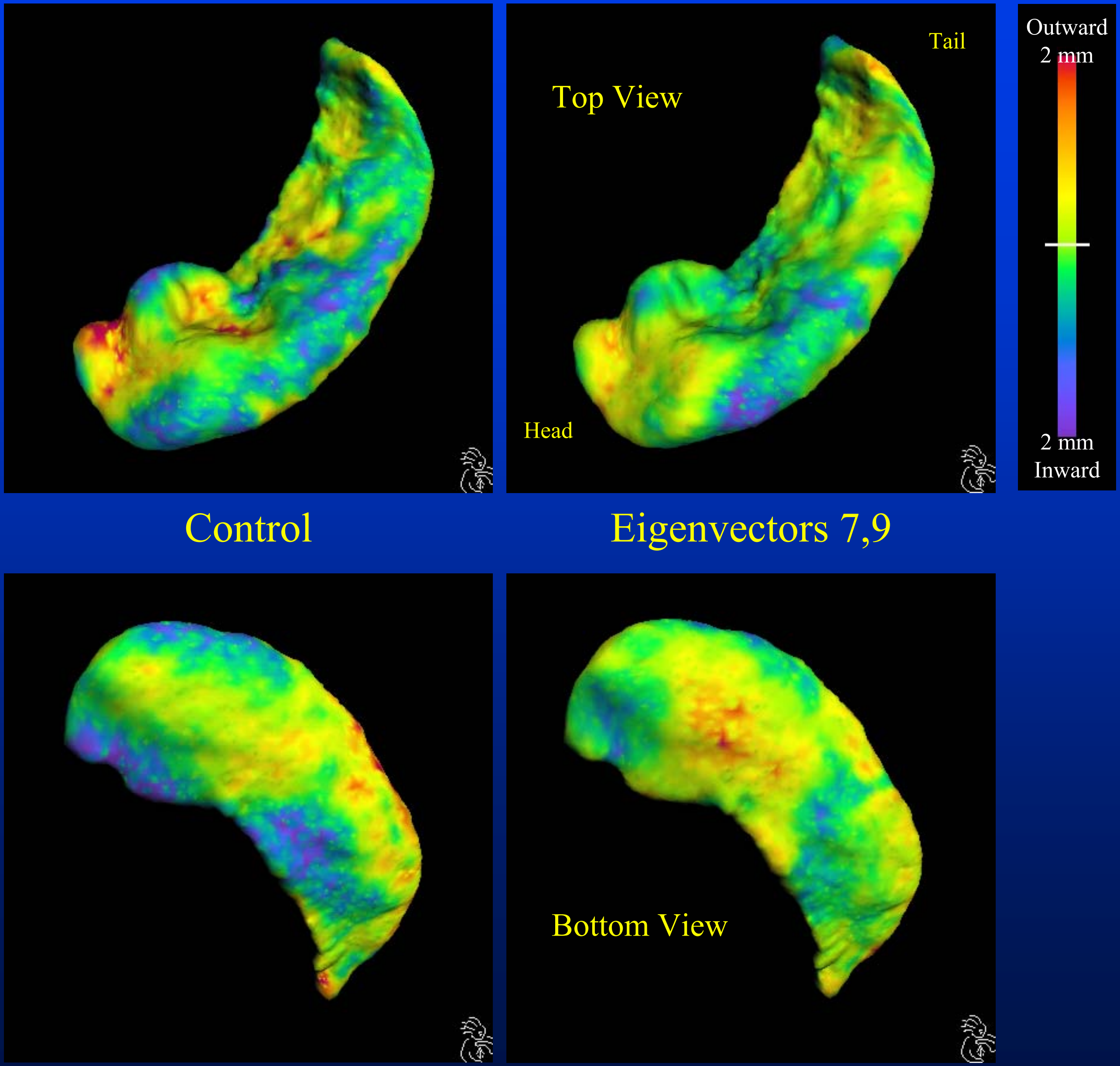
Asymmetry: Normative



Control

Eigenvectors 7,9

$$\bar{u}^{\text{ctrl}} = \sum_{k=1}^{K} \bar{Z}^{\text{ctrl}} \phi_k$$

$$Z^{\text{ctrl}} \sim N(\bar{Z}^{\text{ctrl}}, \Sigma)$$

$$e\overline{ff} = 1.58$$

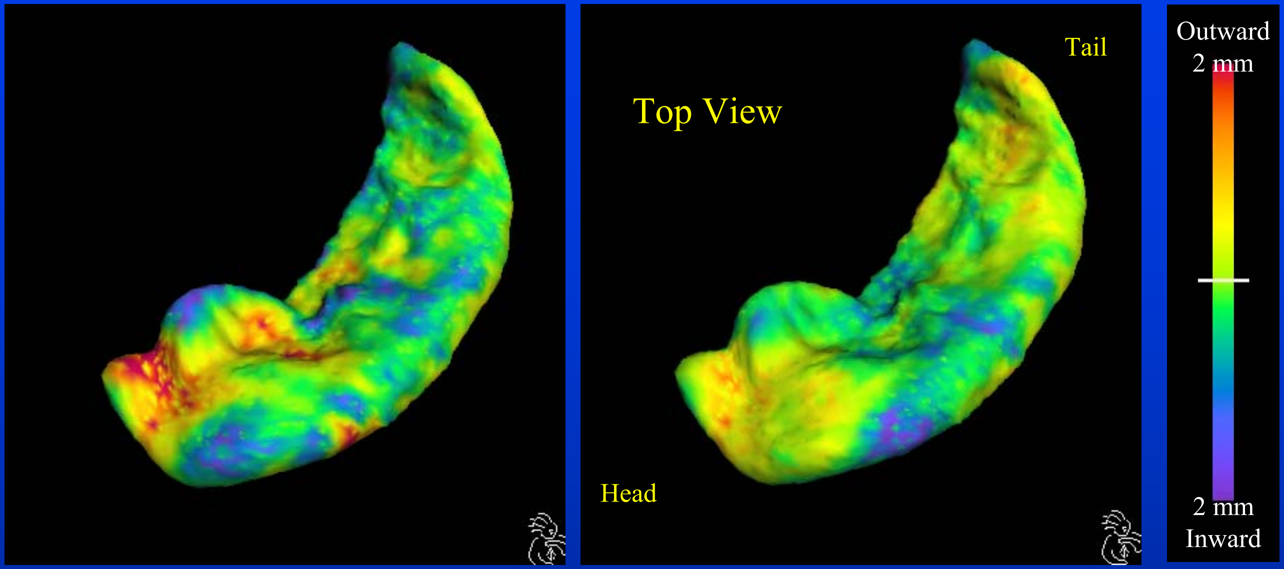
$$F = 17.42$$

$$df = 2,13$$

$$p = .0002$$

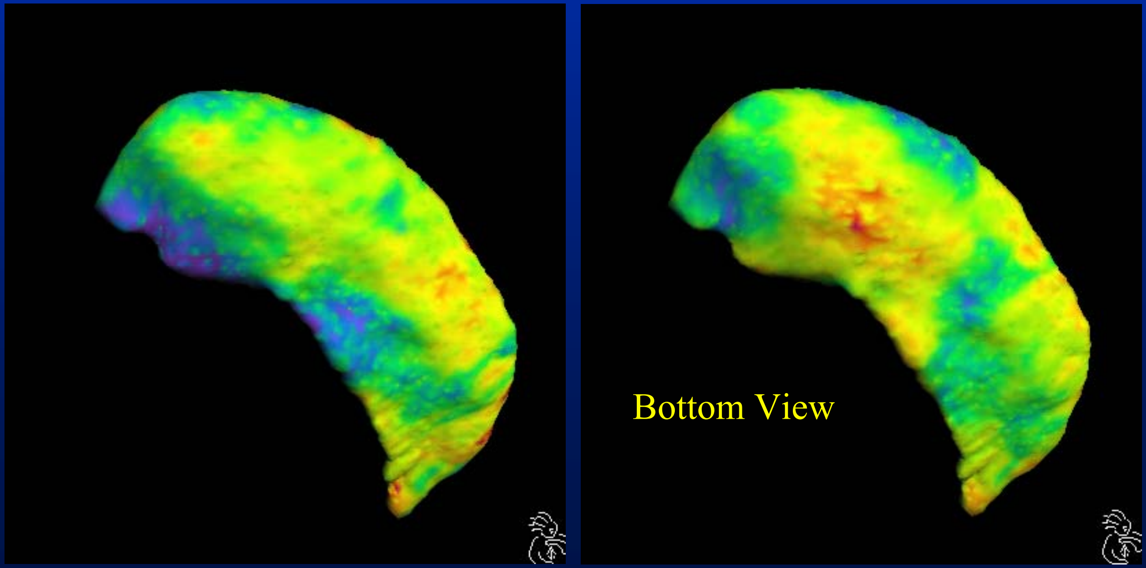
Wang, L, et. al, *NeuroImage* 2001

Asymmetry: Schizophrenia



Schizophrenia

Eigenvectors 7,9



$$\overline{u}^{\text{schiz}} = \sum_{l=1}^{L} \overline{Z}^{\text{schiz}} \phi_l$$

$$Z^{\text{schiz}} \sim N\left(\overline{Z}^{\text{schiz}}, \Sigma\right)$$

$$\overline{eff} = 1.53$$

$$F = 16.24$$

$$df = 2,13$$

$$p = .0003$$

Wang, L, et. al, *NeuroImage* 2001

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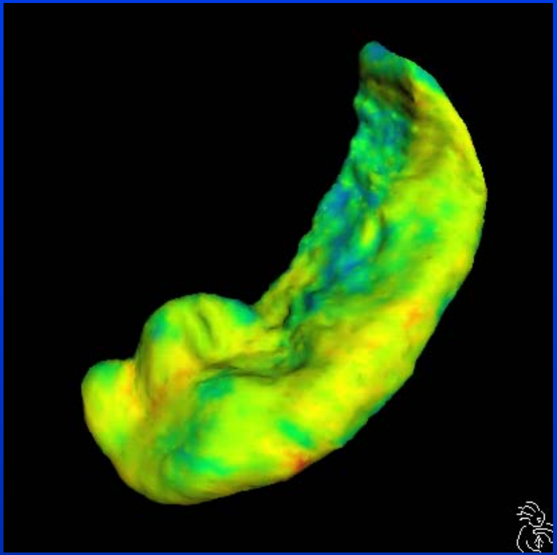
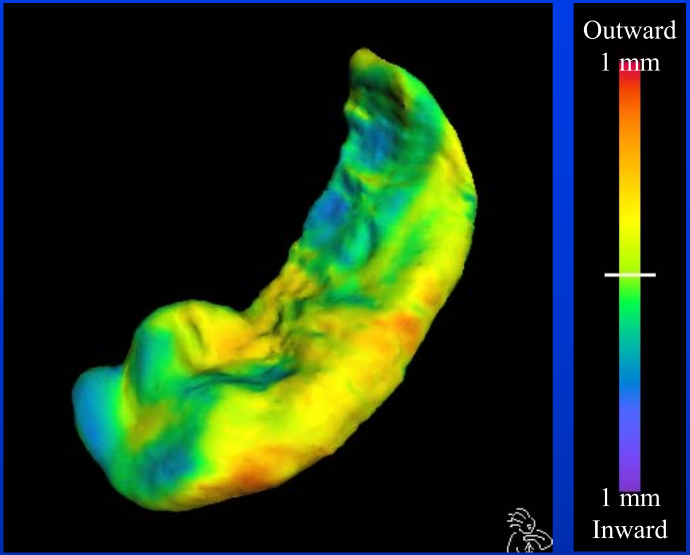
Asymmetry: Control vs. Schizophrenia





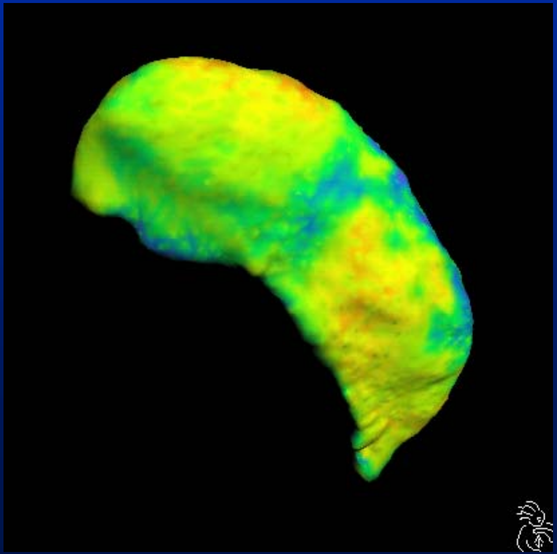
$$\overline{u}^{\text{ctrl}} = \sum_{k=1}^{K} \overline{Z}^{\text{ctrl}} \phi_k$$

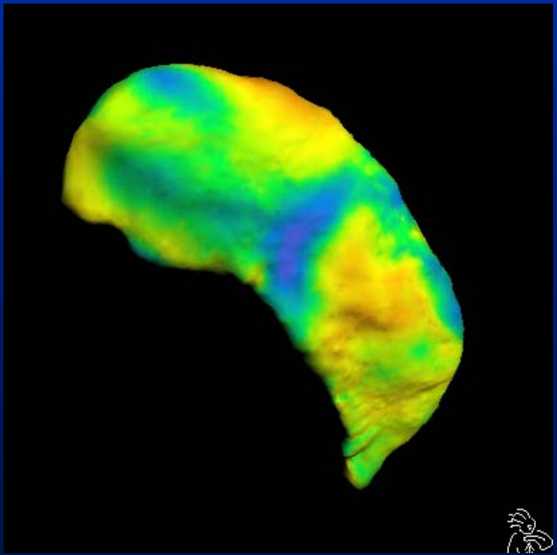
$$\overline{u}^{\text{schiz}} = \sum_{l=1}^{L} \overline{Z}^{\text{schiz}} \phi_l$$

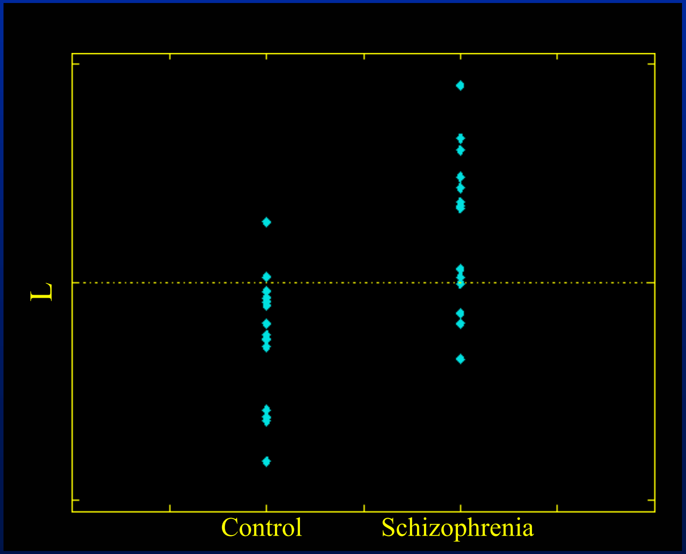
Control → Schizophrenia

Eigenvectors 2,12,17

Eigenvectors 2,12,17

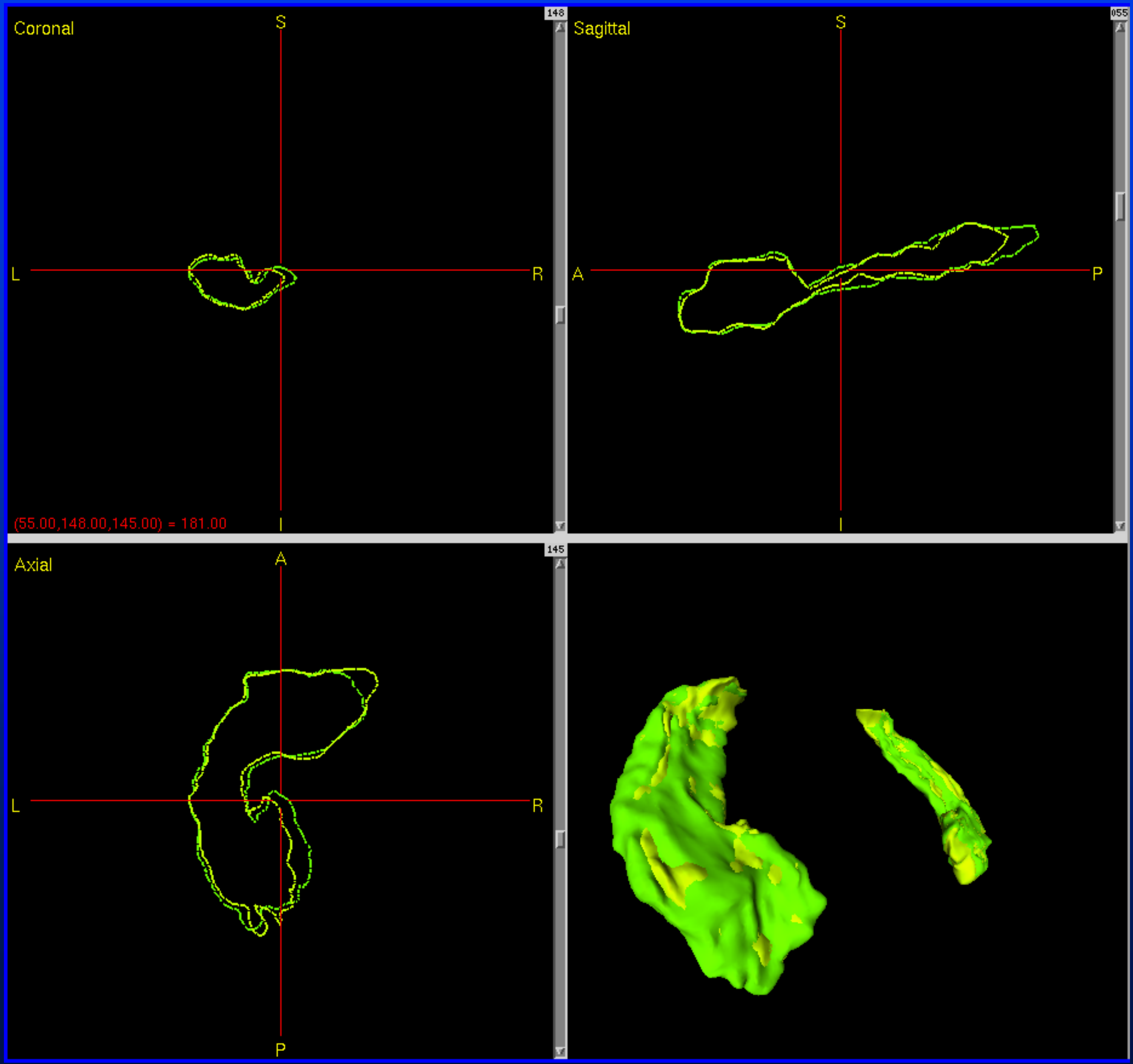






Wang, L, et. al, *NeuroImage* 2001

Progression



Baseline

↓

Follow-up

u

change
vector
field

Progression

Singular Value Decomposition

Empirical estimate of covariance:

$$K = \frac{1}{N-1}\sum_{i=1}^{N}(u_i - \overline{u})(u_i - \overline{u})^T \Rightarrow \left(\lambda_k, \phi_k\right)$$

SVD:

$$u \sim N(\overline{u}, K), \qquad u_i = \sum_{k=1}^{N} Z_i \phi_k, \qquad Z_i = \left\langle u_i, \phi_k \right\rangle$$

Pooled sample covariance:

$$\Sigma = \frac{1}{N_1 + N_2 - 1}\left\{\sum_{i=1}^{N_1}(Z_i - \overline{Z}^1)(Z_i - \overline{Z}^1)^T + \sum_{i=1}^{N_2}(Z_i - \overline{Z}^2)(Z_i - \overline{Z}^2)^T\right\}$$

Change Metric: $eff = \sqrt{Z^T \Sigma^{-1} Z}$

Wang, L, et. al, *NeuroImage* 2003

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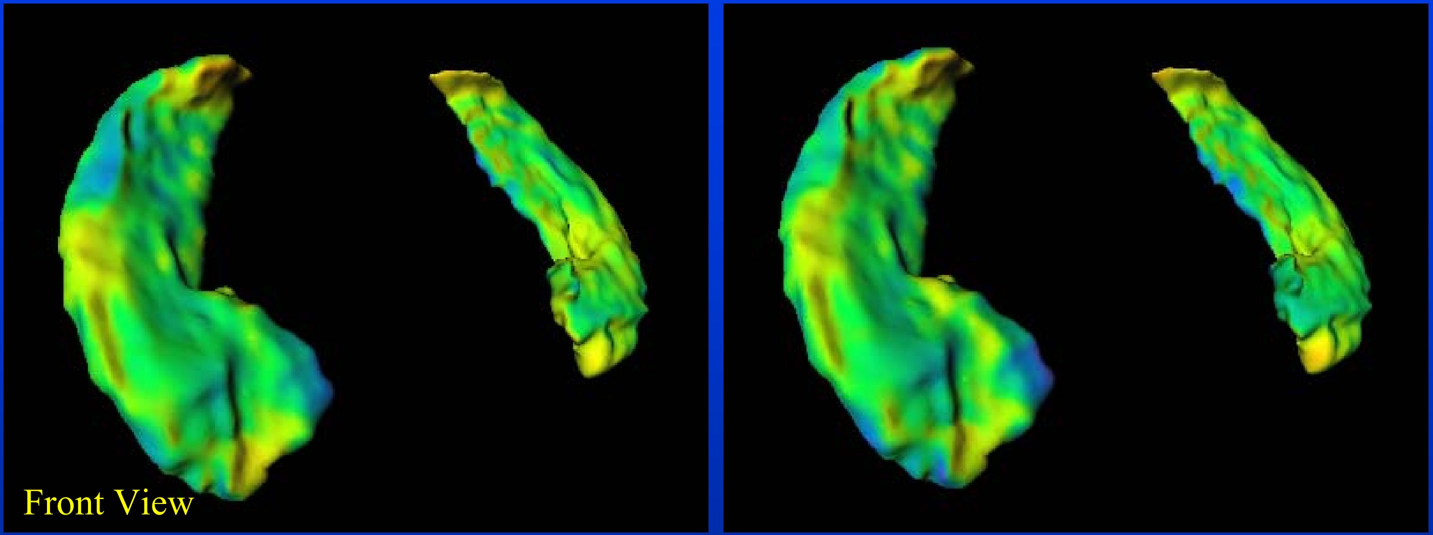
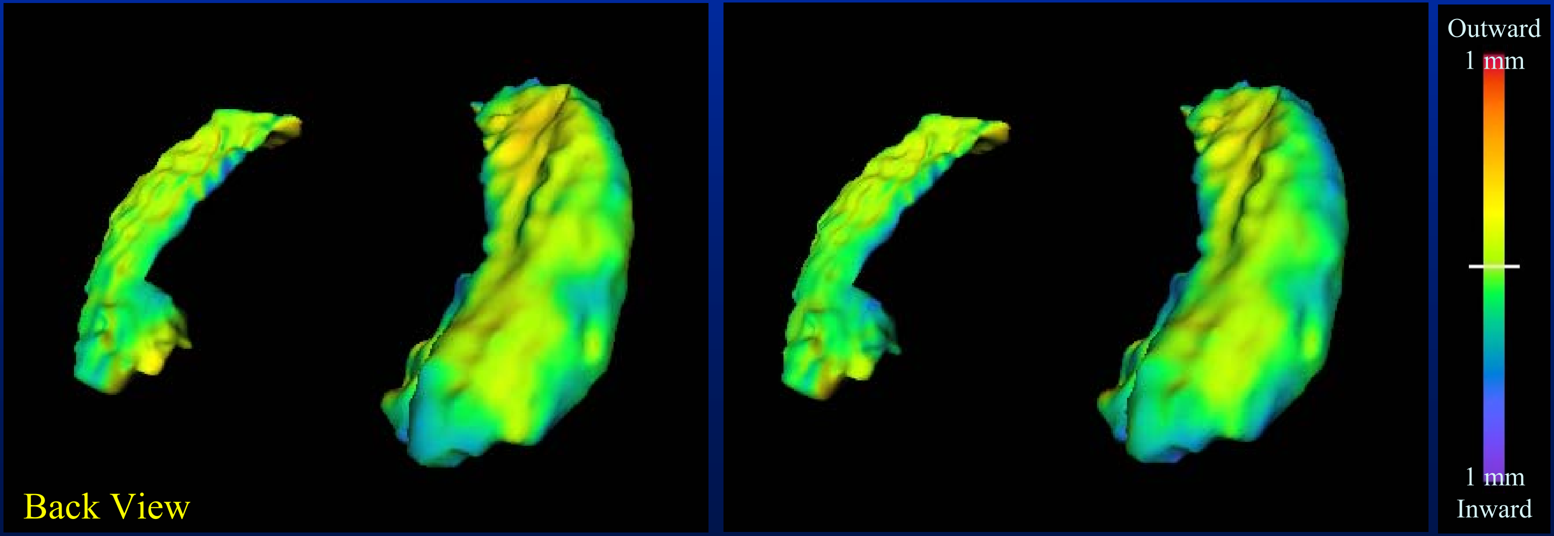
Change: Normal Aging



Eigen functions 8,11



$$\overline{u}^{\text{ctrl}} = \sum_{k=1}^{K} \overline{Z}^{\text{ctrl}} \phi_k$$

$$Z^{\text{ctrl}} \sim N\left(\overline{Z}^{\text{ctrl}}, \Sigma\right)$$

$$\overline{eff} = 1.00$$

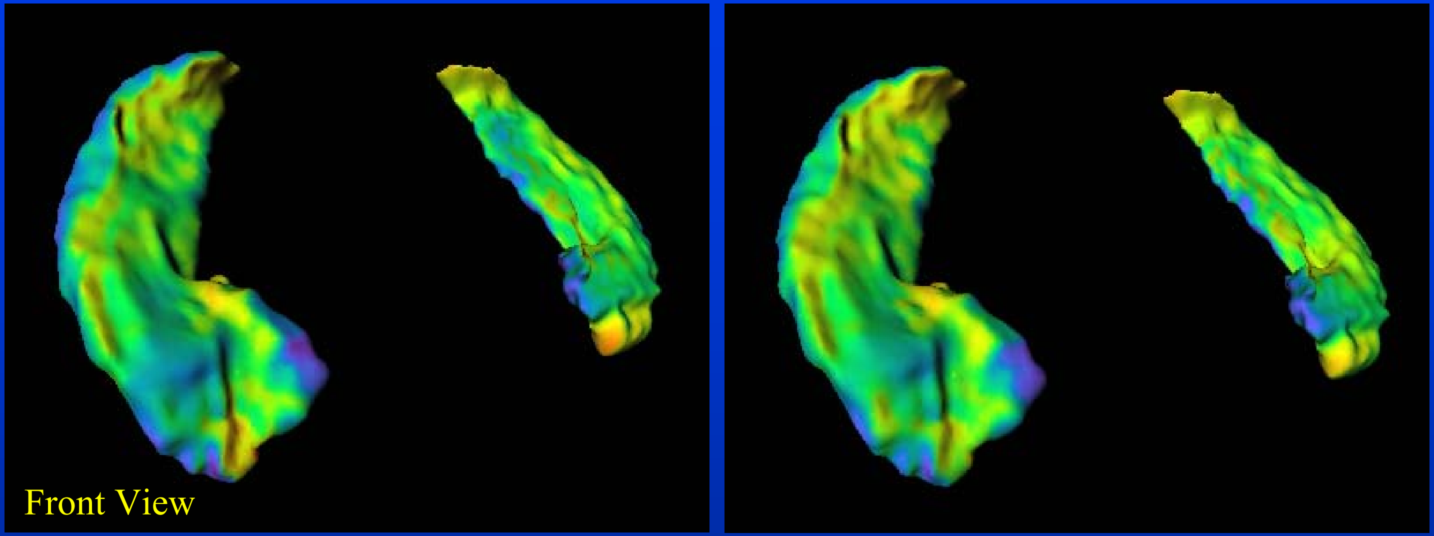
$$F = 12.41$$

$$df = 2,24$$

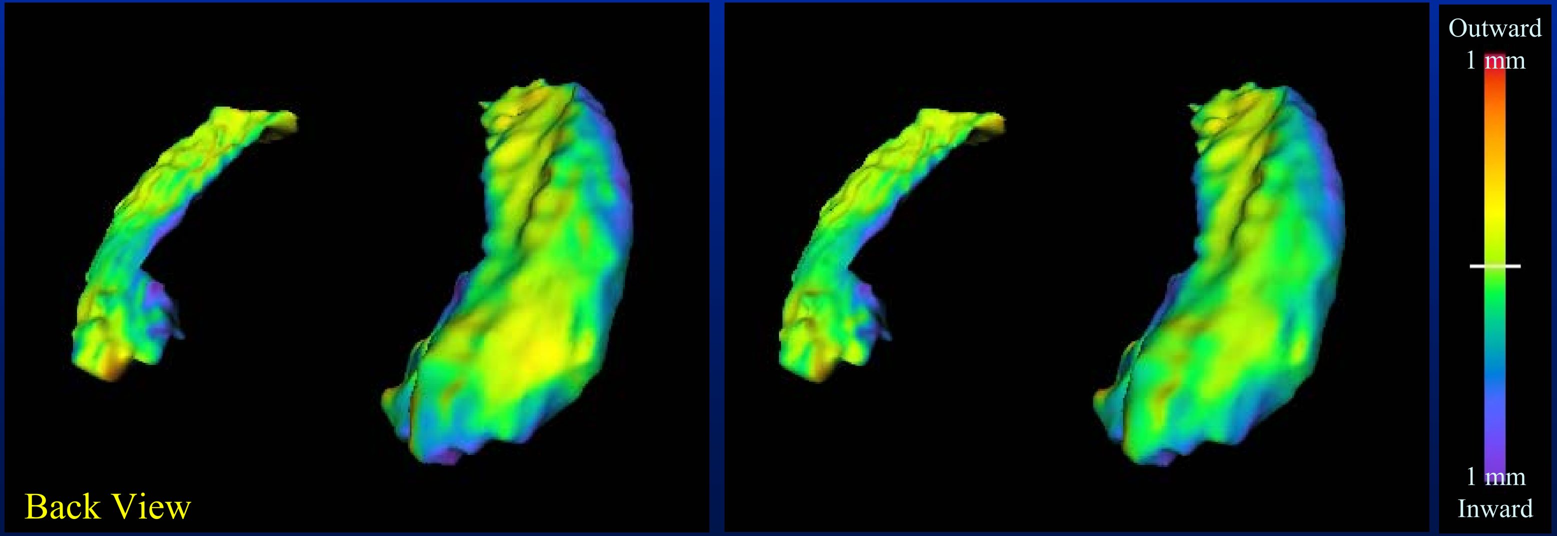
$$p = .0002$$

Wang, L, et. al, *NeuroImage* 2001

Change: Mild AD



Eigen functions 1,4,8



$$\overline{u}^{\text{dat}} = \sum_{l=1}^{L} \overline{Z}^{\text{dat}} \phi_l$$

$$Z^{\text{dat}} \sim N\left(\overline{Z}^{\text{dat}}, \Sigma\right)$$

$$\overline{eff} = 1.70$$

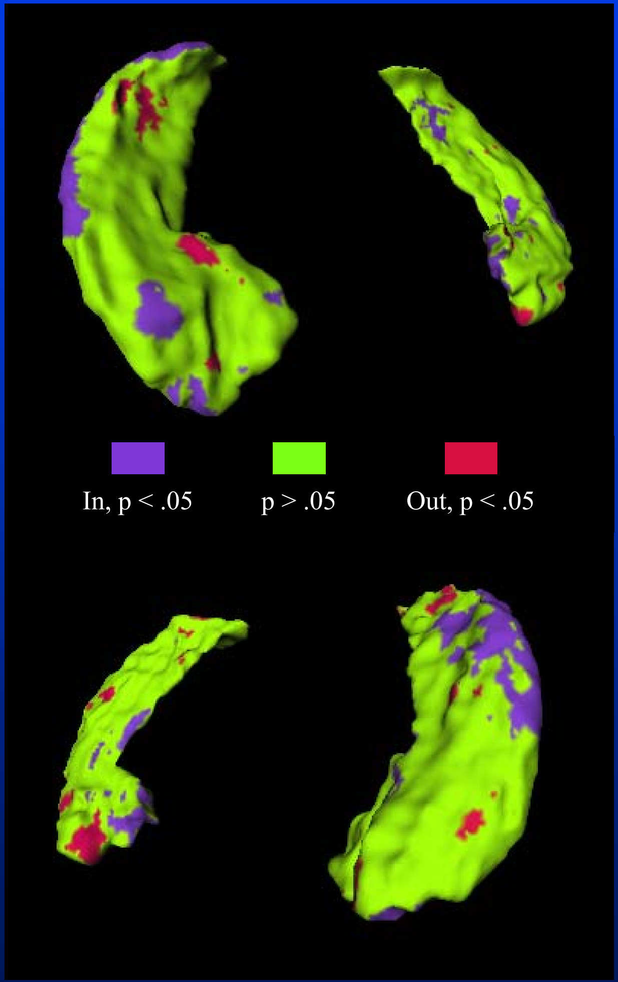
$$F = 13.35$$

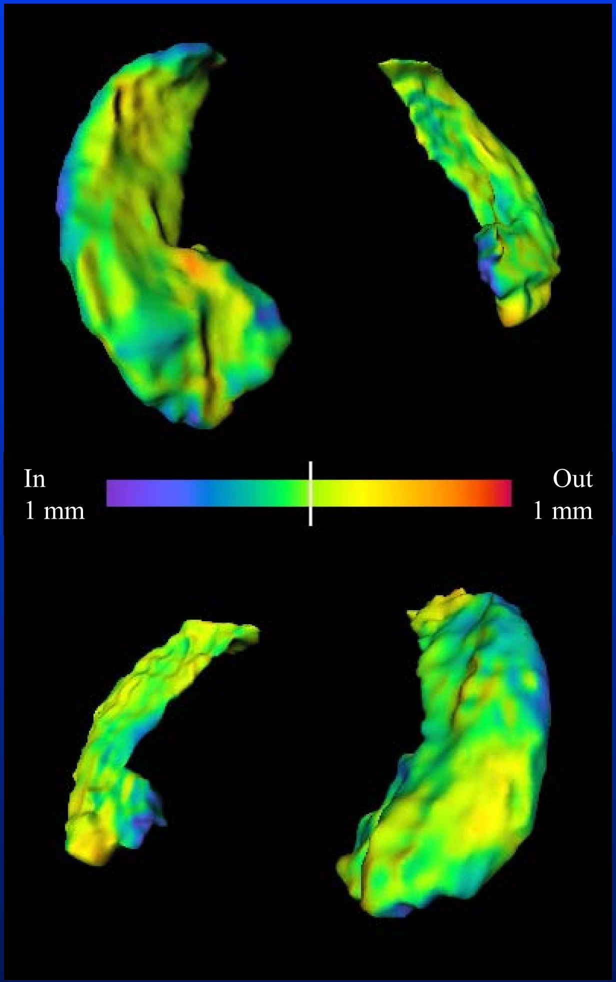
$$df = 3{,}15$$

$$p = .0001$$

Wang, L, et. al, *NeuroImage* 2001

Progression: Normal Aging vs. Mild AD

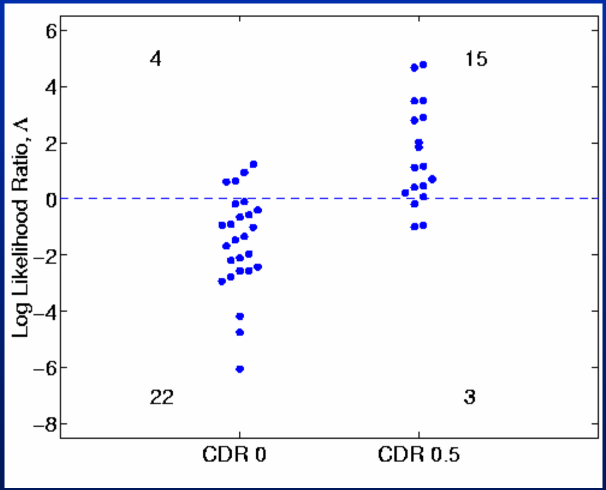




CDR 0.5 vs. CDR 0

$$\overline{u}^{\text{ctrl}} = \sum_{k=1}^{K} \overline{Z}^{\text{ctrl}} \phi_k$$

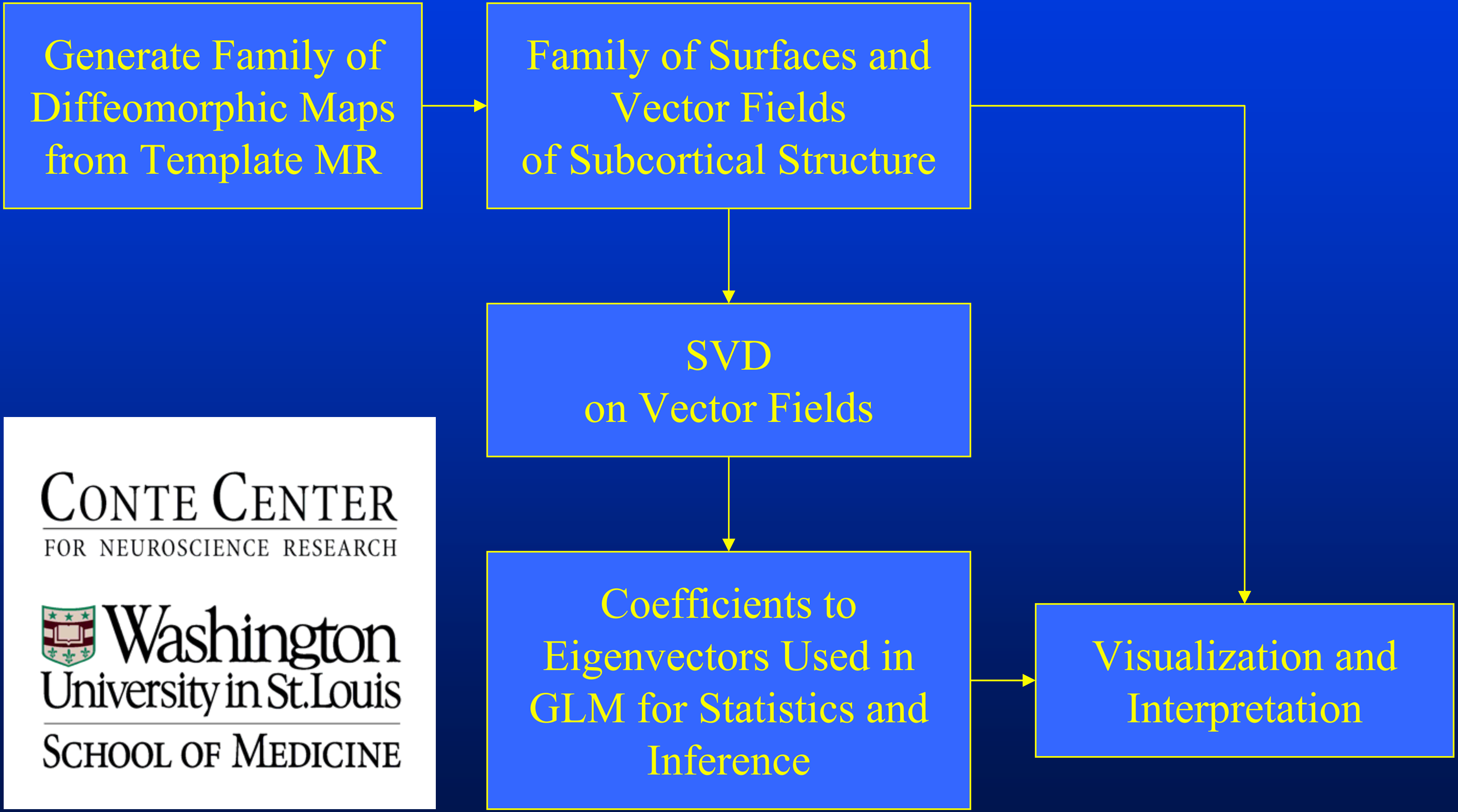
$$\overline{u}^{\text{schiz}} = \sum_{l=1}^{L} \overline{Z}^{\text{dat}} \phi_l$$



Eigenvectors 1,2,4,11

Wang, L, et. al, *NeuroImage* 2001

Statistical Computation and Inference on the Subcortical Surface



Generate Family of Diffeomorphic Maps from Template MR

Family of Surfaces and Vector Fields of Subcortical Structure

SVD on Vector Fields

Coefficients to Eigenvectors Used in GLM for Statistics and Inference

Visualization and Interpretation

CONTE CENTER
FOR NEUROSCIENCE RESEARCH

Washington University in St. Louis
SCHOOL OF MEDICINE

References

1. Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, Miller JP, Grenander U, Miller MI: Hippocampal morphometry in schizophrenia by high dimensional brain mapping. Proc Natl Acad Sci U S A 1998; 95(19):11406-11
2. Csernansky JG, Wang L, Joshi S, Miller JP, Gado M, Kido D, McKeel D, Morris JC, Miller MI: Early DAT is distinguished from aging by high-dimensional mapping of the hippocampus. Neurology 2000; 55(11):1636-43
3. Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, Heydebrand G, Miller JP, Miller MI: Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. American Journal of Psychiatry 2002; 159(12):2000-6
4. Csernansky JG, Schlinder MK, Splinter NR, Wang L, Gado M, Selemon LD, Rastogi-Cruz D, Posener JA, Thompson P, Miller MI: Abnormalities of thalamic volume and shape in schizophrenia. Am J Psychiatry 2004; 161(5):896-902
5. Csernansky JG, Wang L, Joshi SC, Ratnanather JT, Miller MI: Computational Anatomy and Neuropsychiatric Disease: Probabilistic Assessment of Variation and Statistical Inference of Group Difference, Hemispheric Asymmetry, and Time-Dependent Change. NeuroImage, Special Issue on "Mathematics in Brain Imaging", Thompson PM, Miller MI, Poldrack R, Nichols TN (eds) 2004; accepted
6. Grenander U, Miller MI: Computational Anatomy: An Emerging Discipline. Quarterly of Applied Mathematics 1998; LVI(4):617-694
7. Joshi S, Miller MI, Grenander U: On the geometry and shape of brain sub-manifolds. Int J Pattern Recog Artificial Intell (Special Issue) 1997
8. Wang L, Joshi SC, Miller MI, Csernansky JG: Statistical analysis of hippocampal asymmetry in schizophrenia. Neuroimage 2001; 14(3):531-45.
9. Wang L, Swank JS, Glick IE, Gado MH, Miller MI, Morris JC, Csernansky JG: Changes in hippocampal volume and shape across time distinguish dementia of the Alzheimer type from healthy aging. Neuroimage 2003; 20(2):667-82.