Statistics of Shape in Brain Research: Methods and Applications

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Contents

Motivation

Concept: Modeling of statistical shapes

Shape Modeling

- Surface-based 3D shape model (SPHARM)
- 3D medial models (3D skeletons/ M-rep)

Shape Analysis

Conclusions

Neuropathology of Schizophrenia

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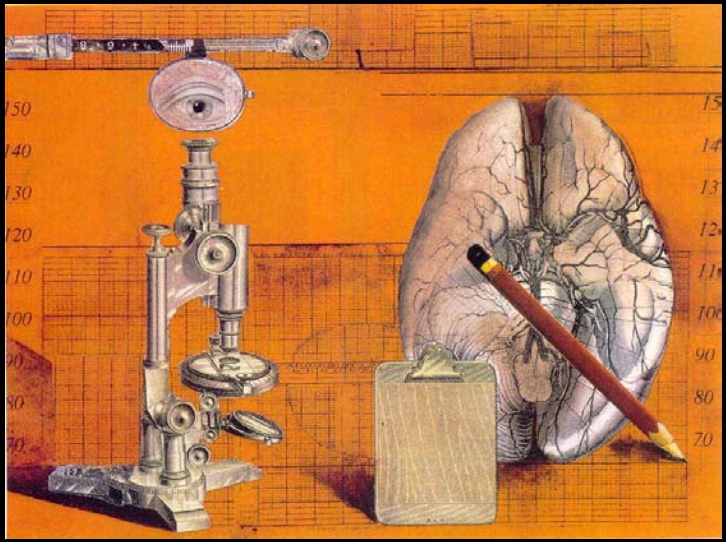
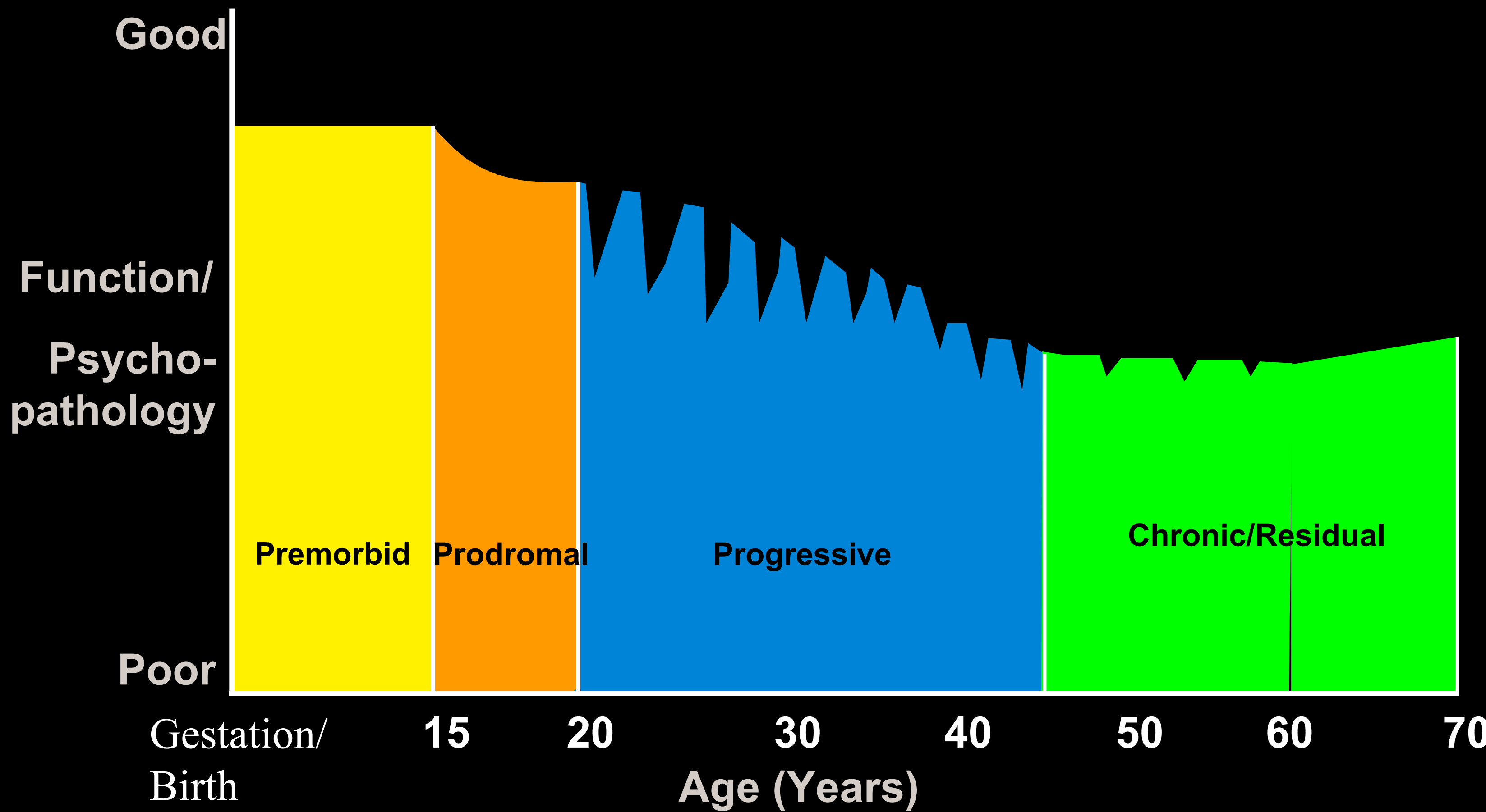
- When does it develop ?
- Fixed or Progressive ?
- Neurodevelopmental or
  Neurodegenerative ?
- Neurobiological Correlations ?
- Clinical Correlations ?
- Treatment Effects ?



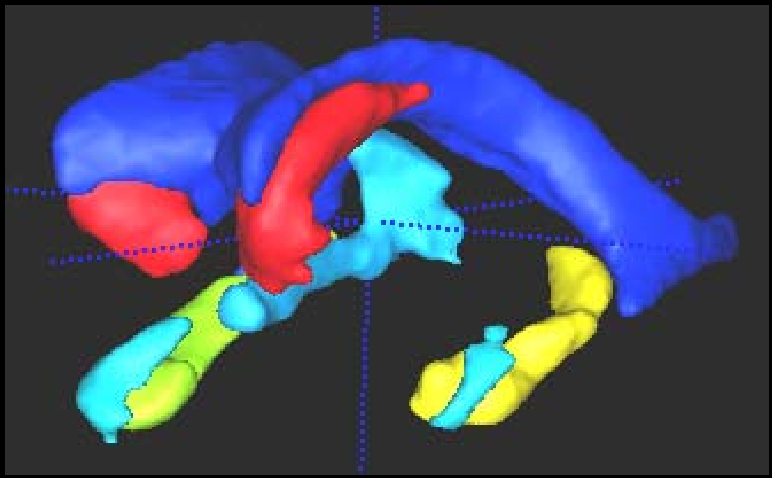
Noninvasive neuroimaging studies to study morphology and function

Natural History of Schizophrenia



Statistical Shape Models

- **Drive deformable model segmentation**
  - statistical geometric model
  - statistical image boundary model
- **Analysis of shape deformation (evolution, development, degeneration, disease)**



Segmentation and Characterization

"Good" segmentation approaches

- use domain knowledge
- generic (can be applied to new problems)
- learn from examples
- generative models
  - shape, spatial relationships, statistics about class
  - compact, parameterized
  - gray level appearance
- deformable to present any shape of class
- parametrized model deformation: includes shape description

Segmentation and Characterization

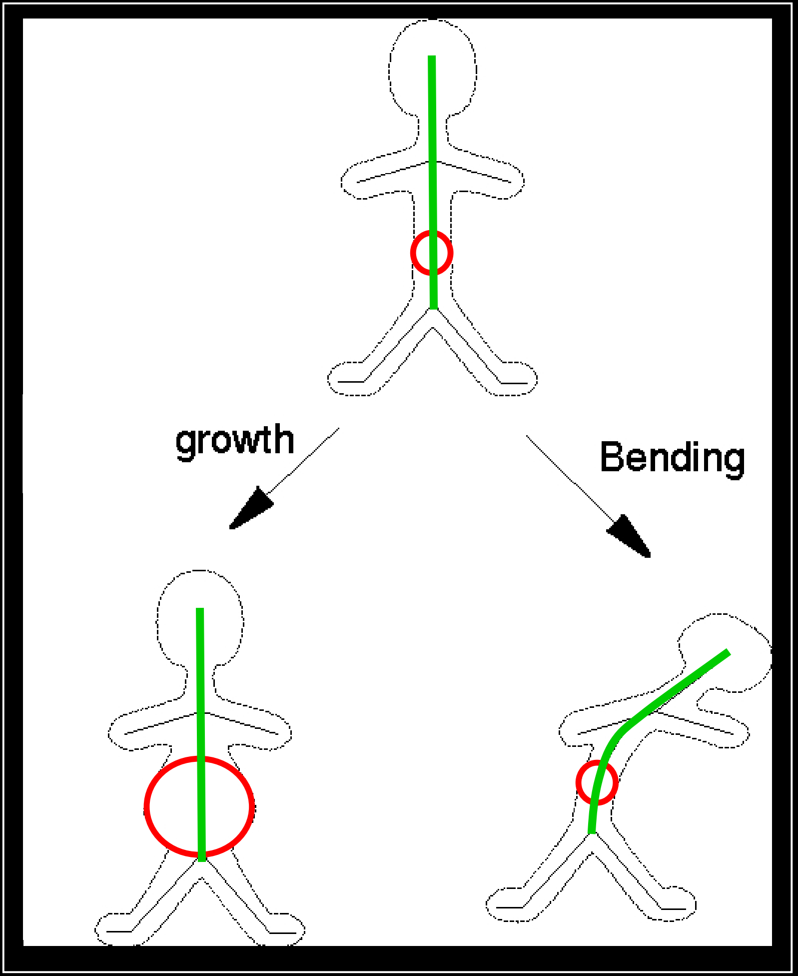
“Good” shape characterization approaches

- small (minimum) number of parameters
- CORRESPONDENCE
- generic (can be applied to new problems)
- locality (local changes only affect subset of parameters)
- intuitive description in terms of natural language description (helps interpretation)
- hierarchical description: level of details, figure to subfigure, figure in context with neighboring structures
- conversion into other shape representations (boundary ↔ medial ↔ volumetric)

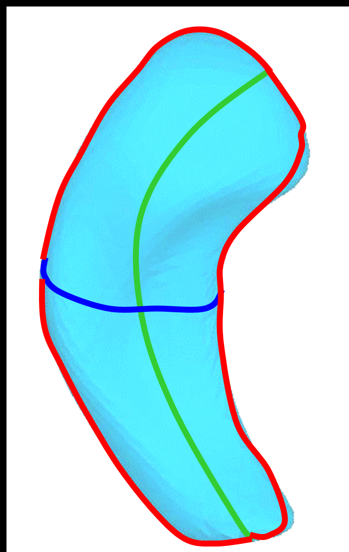
Shape Modeling

Shape Representation:

- **High dimensional warping** Miller,Christensen,Joshi / Thompson,Toga / Ayache, Thirion /Rueckert,Schnabel
- **Landmarks / Boundary / Surface** Bookstein / Cootes, Taylor / Duncan,Staib / Szekely, Gerig / Leventon, Grimson / Davatzikos
- **Skeleton / Medial model** Pizer / Goland / Bouix,Siddiqui / Kimia / Styner, Gerig



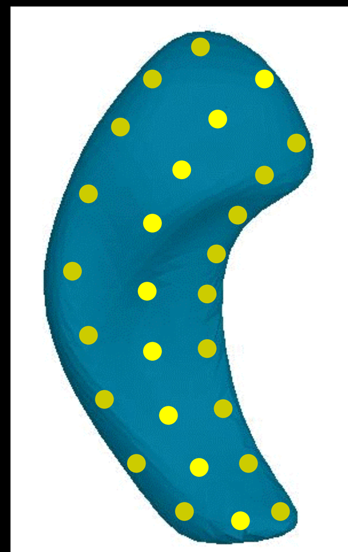
3D Shape Representations



SPHARM

Boundary, fine scale, parametric

$$r(\theta,\phi)=\sum_{k=0}^{\infty}\sum_{m=-k}^{k}\underline{c}_k^m Y_k^m(\theta,\phi)$$

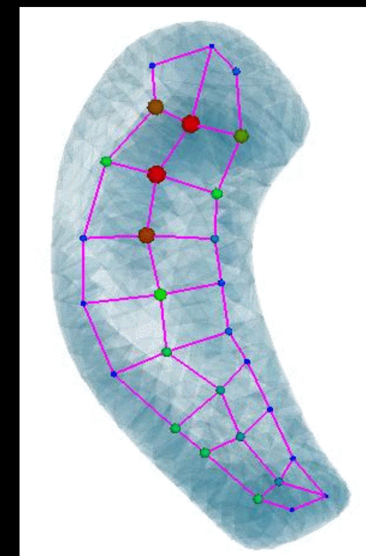


PDM

Boundary, fine scale, sampled

Skeleton

Medial, fine scale, continuous, implied surface

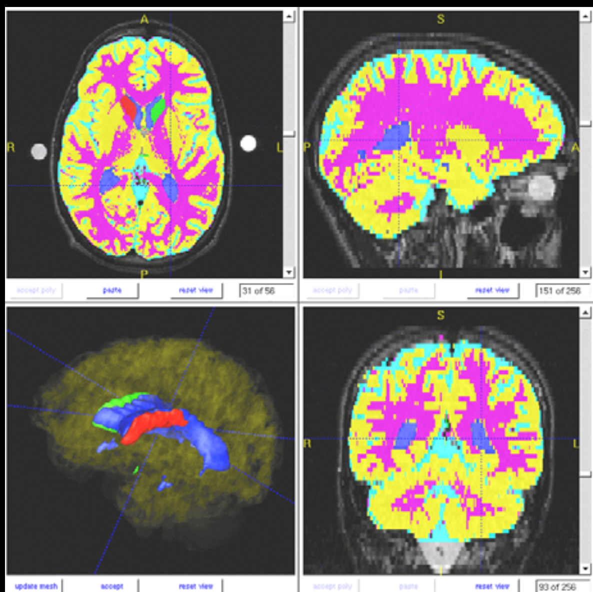


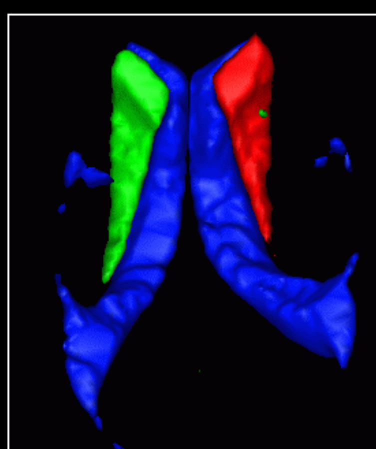
M-rep

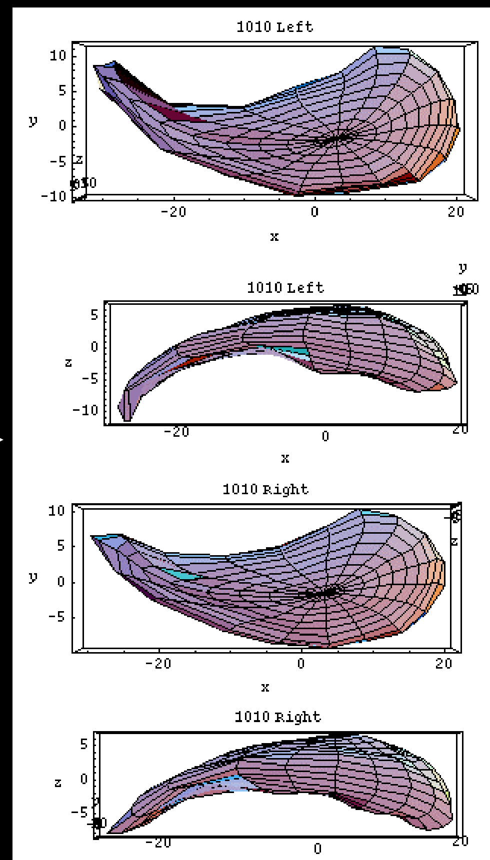
Medial, coarse scale, sampled, implied surface

$$m=\left(\underline{x},r,F,\theta\right)$$

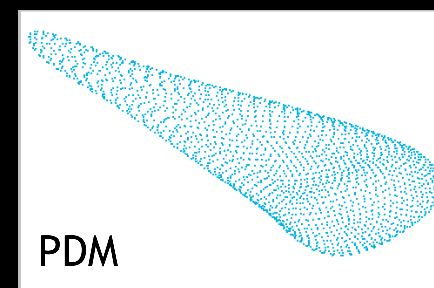
Modeling of Caudate Shape

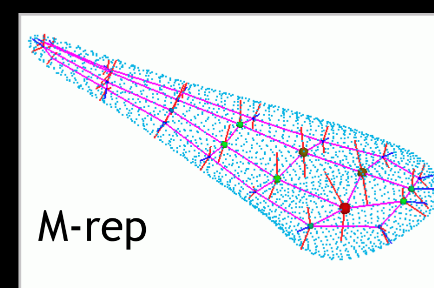






Surface Parametrization

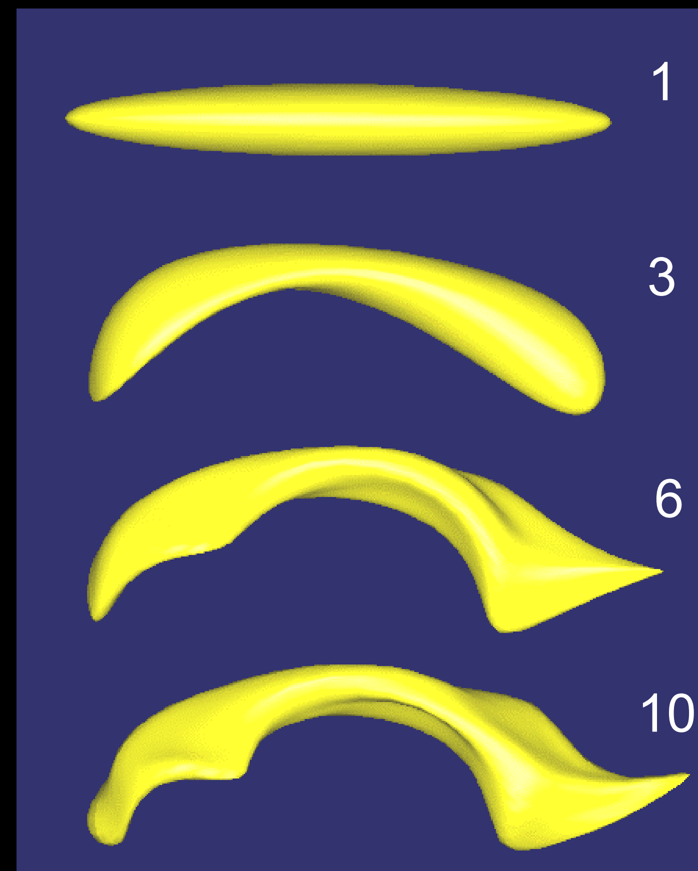




Parametrized Surface Models

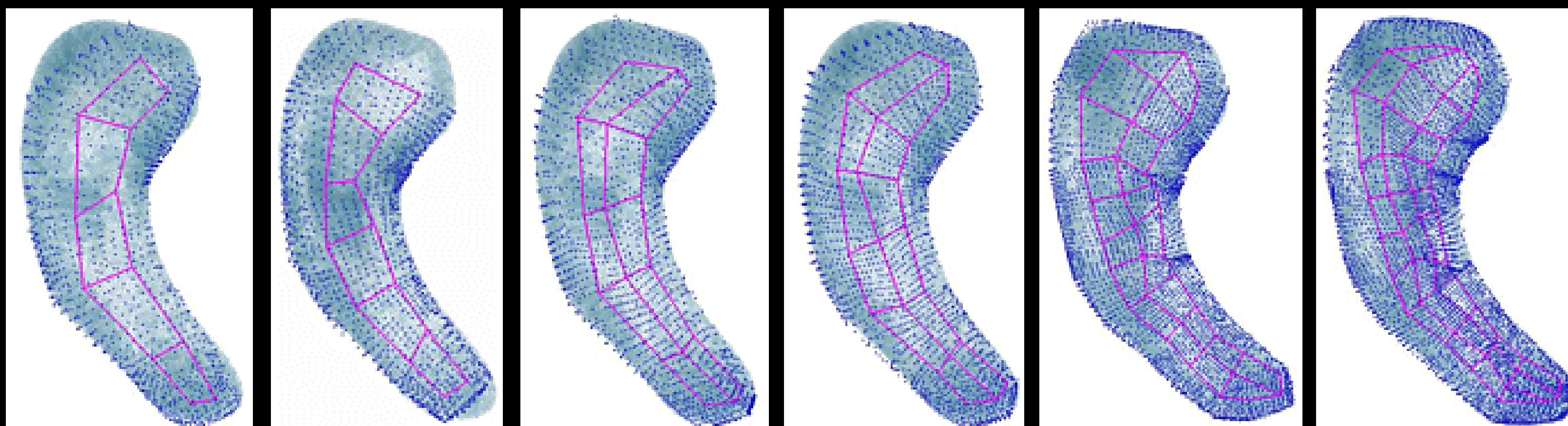
- Parametrized object surfaces expanded into spherical harmonics.
- Hierarchical shape description (coarse to fine).
- Surface correspondence.
- Sampling of parameter space -> PDM models

A. Kelemen, G. Székely, and G. Gerig, Three-dimensional Model-based Segmentation, IEEE Transactions on Medical Imaging (IEEE TMI), Oct99, 18(10):828-839

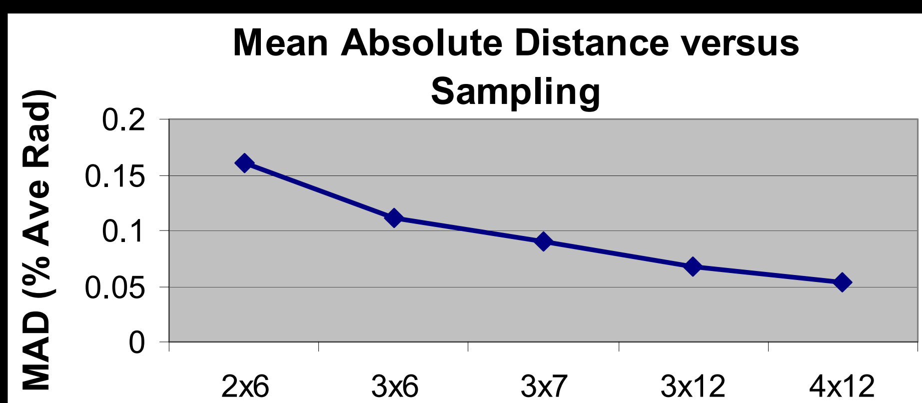


$$\boldsymbol{r}(\theta,\phi) = \sum_{k=0}^{K} \sum_{m=-k}^{k} \boldsymbol{c}_k^m \boldsymbol{Y}_k^m(\theta,\phi)$$

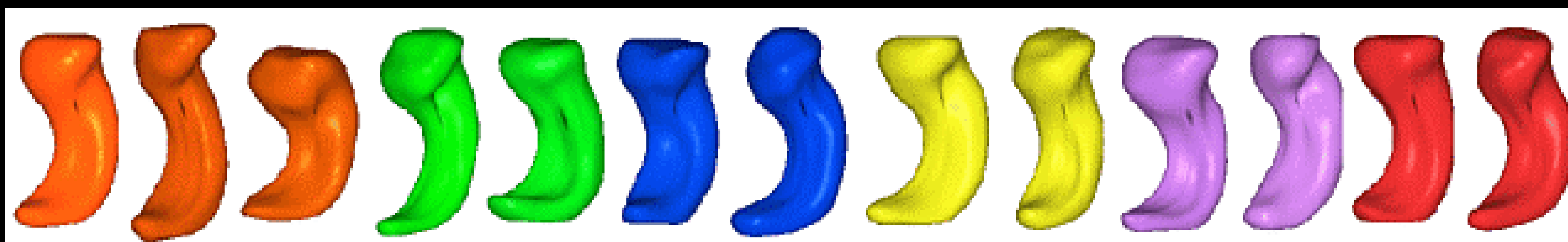
Sampling of Medial Manifold



2x6 2x7 3x6 3x7 3x12 4x12

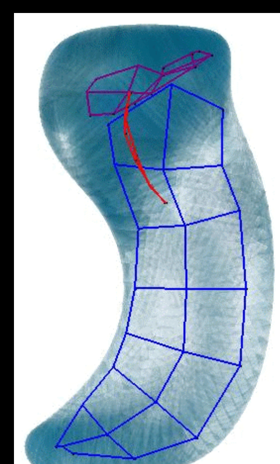


Model Building



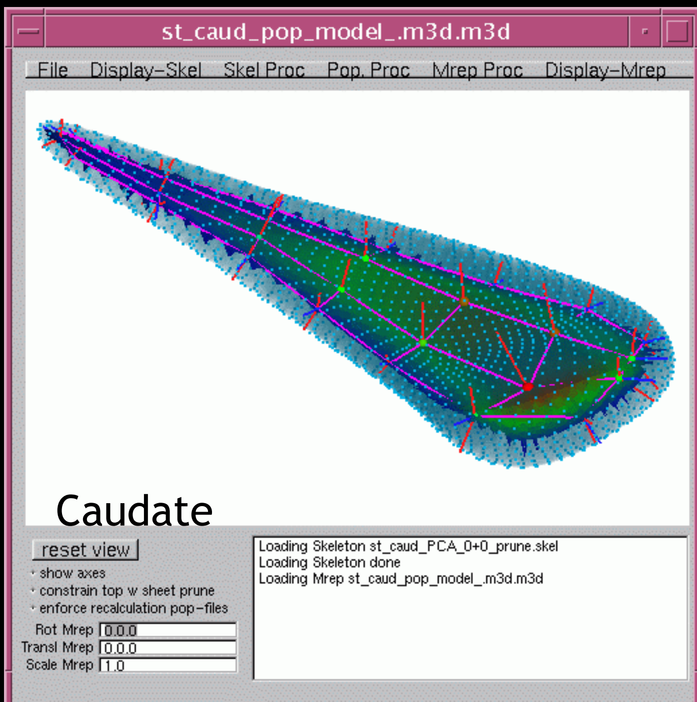
VSkelTool

Medial representation for shape population



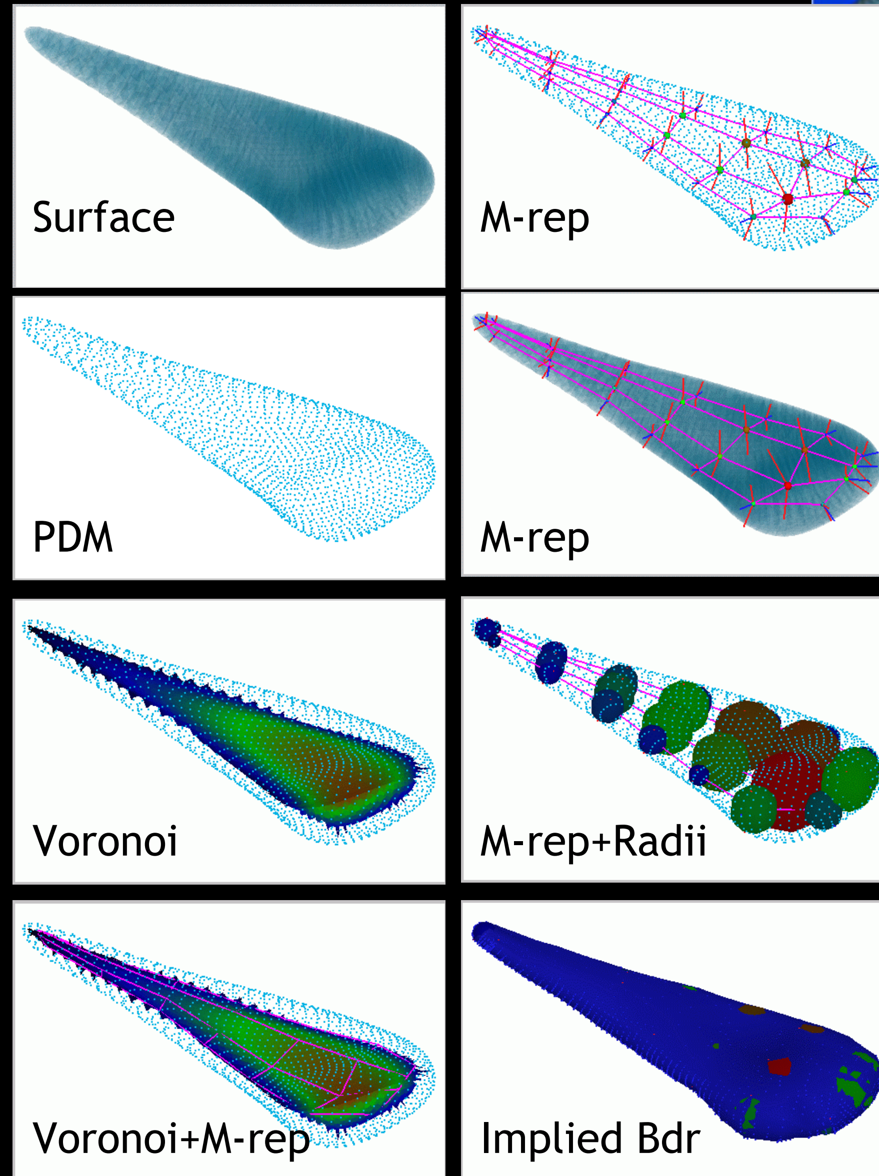
Styner, Gerig et al. , MMBIA’00 / IPMI 2001 / MICCAI 2001 / CVPR 2001/ MEDIA 2002 / IJCV 2003 /

VSkelTool
PhD Martin Styner

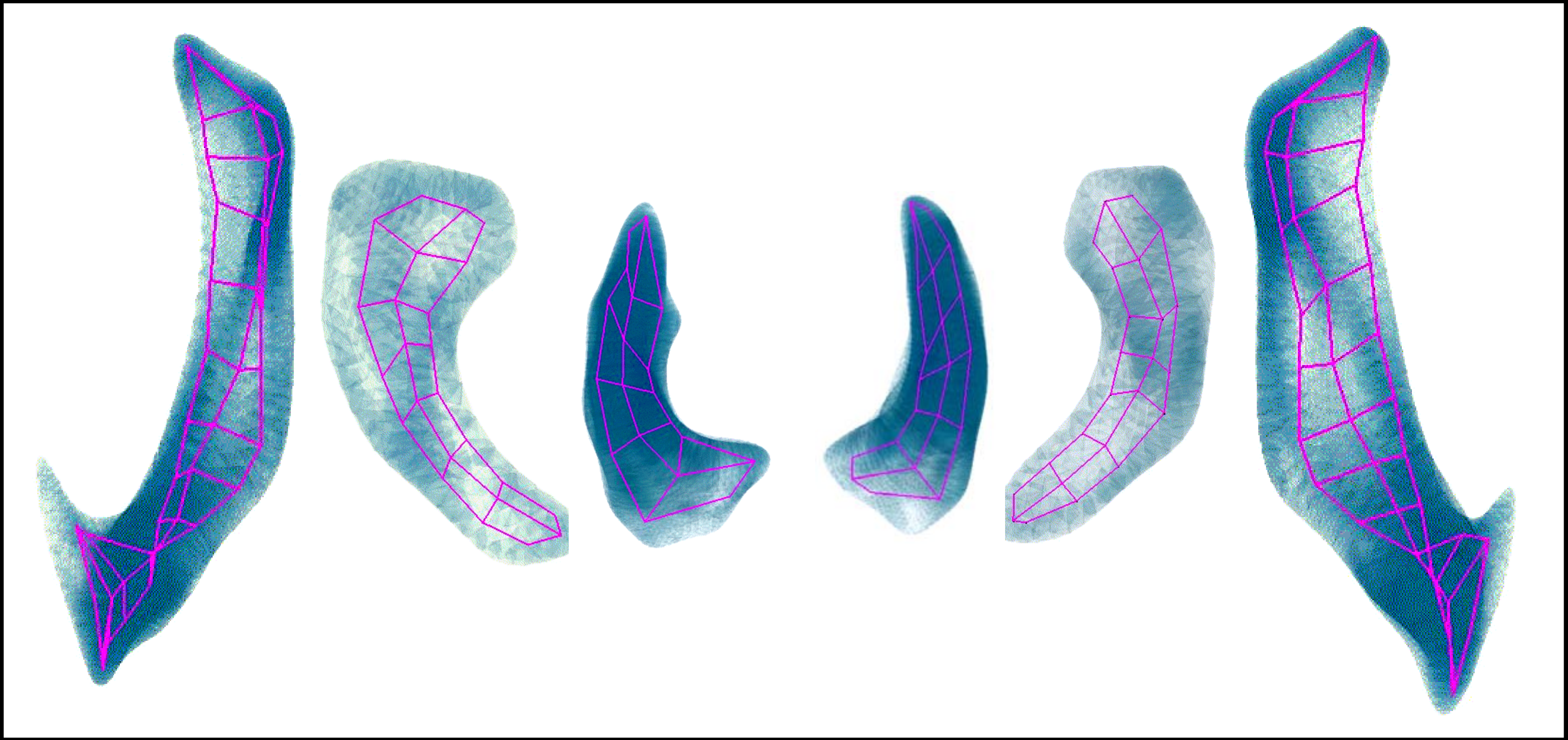


Population models:

- PDM
- M-rep



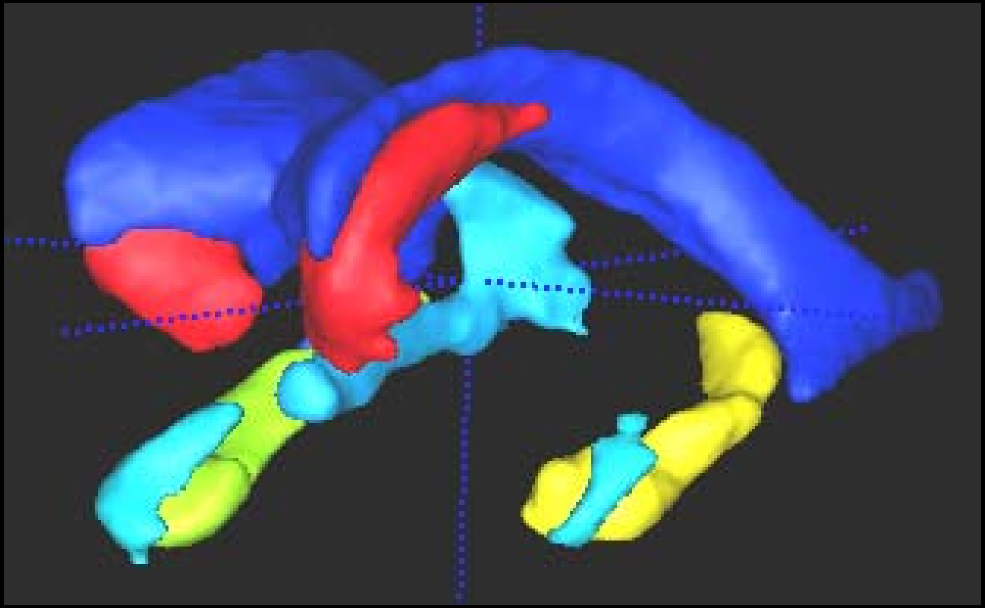
Medial models of subcortical structures



Shape Analysis

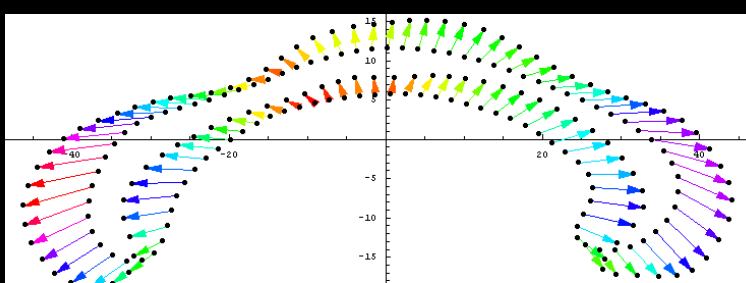
Morphometry of brain structures in:

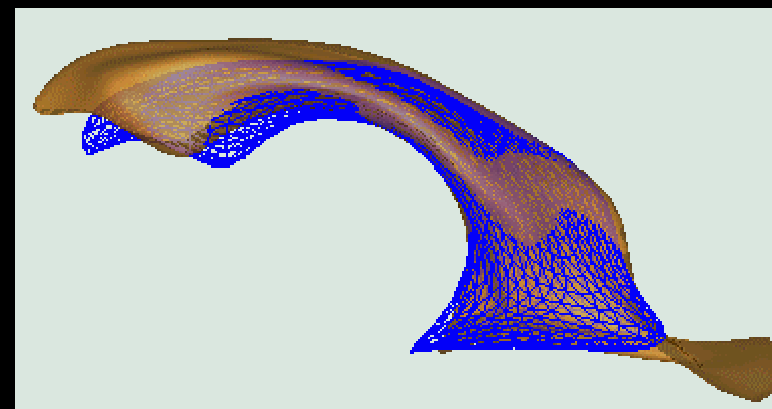
- Schizophrenia
- Twin Studies (MZ/DZ/DS)
- Autism, Fragile-X
- Alzheimer's Desease
- Depression
- Epilepsy
- …

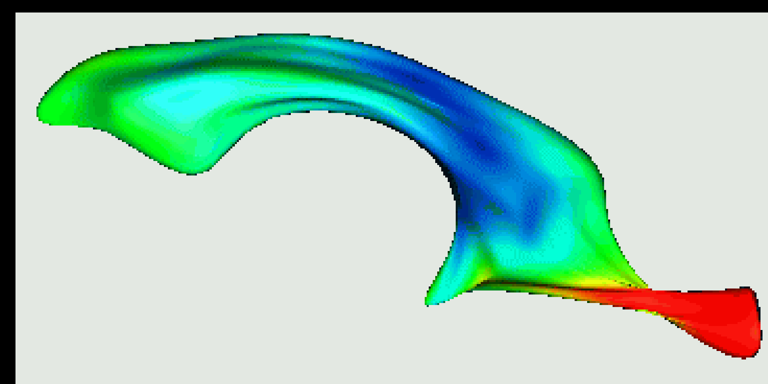


I Surface Models: Shape Distance Metrics

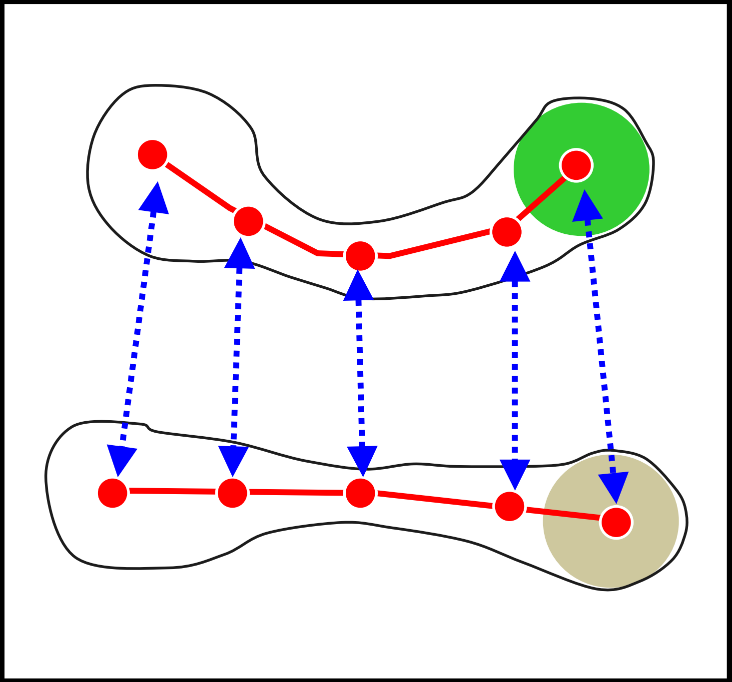
- Pairwise MSD between surfaces at corresponding points
- PDM: Signed or unsigned distance to template at corresponding points

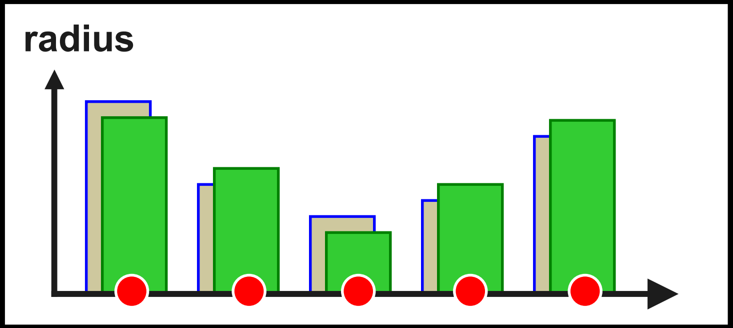


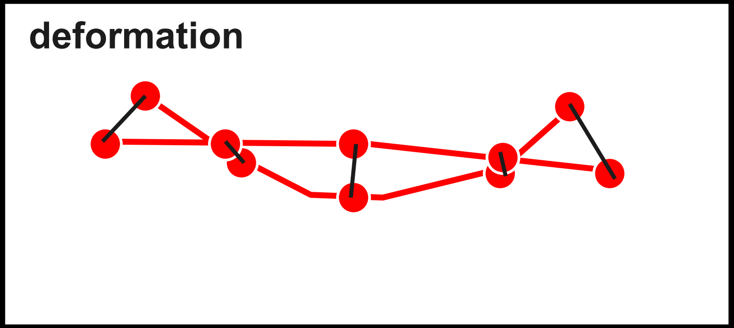




Shape Distance Metrics using Medial Representation







Local width differences (MA_rad): Growth, Dilation

Positional differences (MA_dist): Bending, Deformation

Application I: Shape Asymmetry

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Psychiatry Research Neuroimaging xx (2002) xxx–xxx

PSYCHIATRY RESEARCH NEUROIMAGING

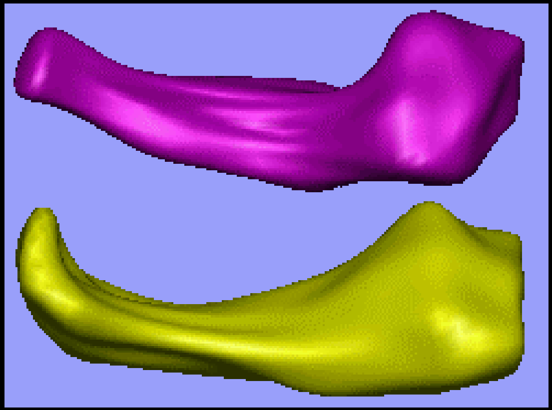
www.elsevier.com/locate/psychresns

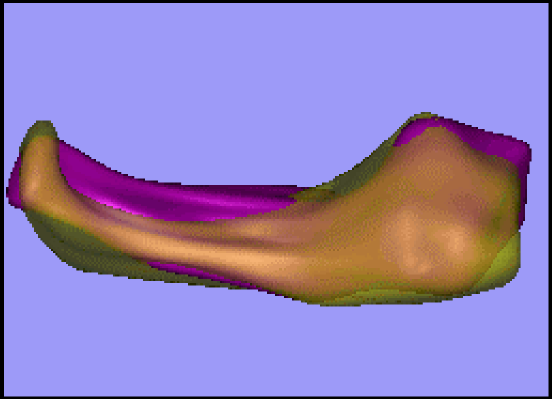
Amygdala–hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data

Martha E. Shenton[a,*], Guido Gerig[b], Robert W. McCarley[a], Gabor Szekely[c], Ron Kikinis[d]

Hippocampal Shape Asymmetry

- Mirror right hippocampus across midsagittal plane.
- Align shapes by first ellipsoid.
- Normalize shapes by individual volume.
- Calculate mean squared surface distance (MSD).
- 15 controls, 15 schizophrenics.





Left vs. right hippocampus

Hippocampal asymmetry in schizophrenia

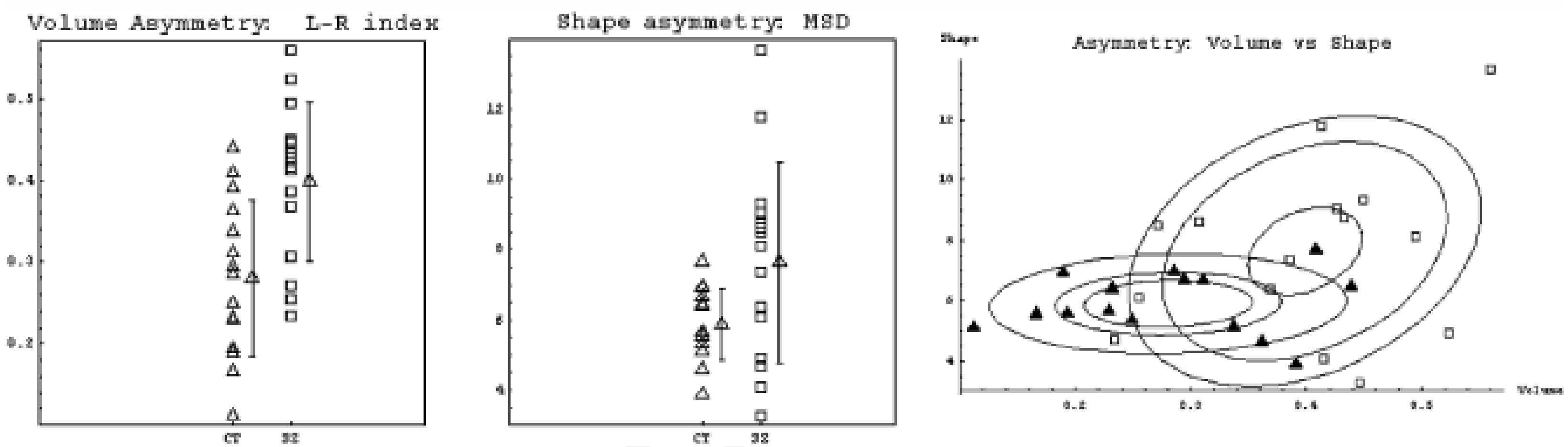
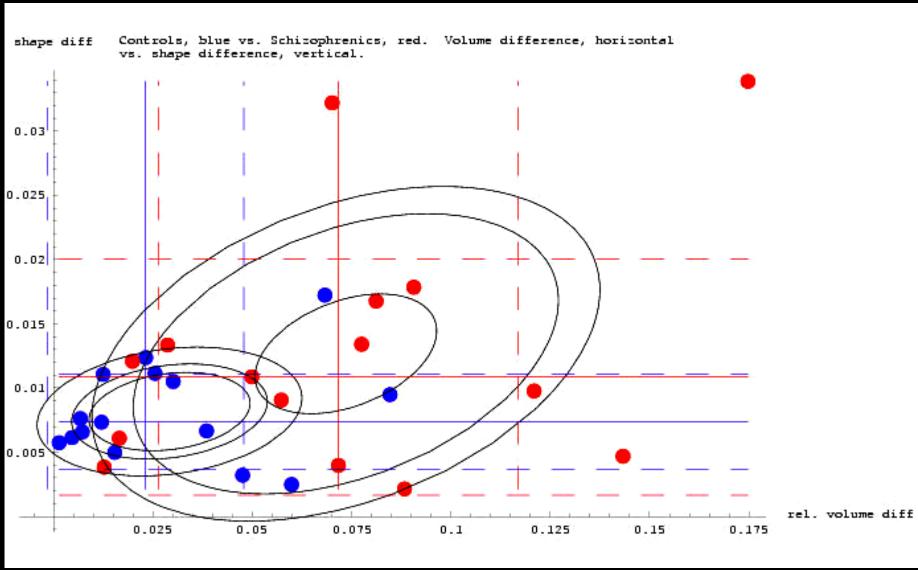


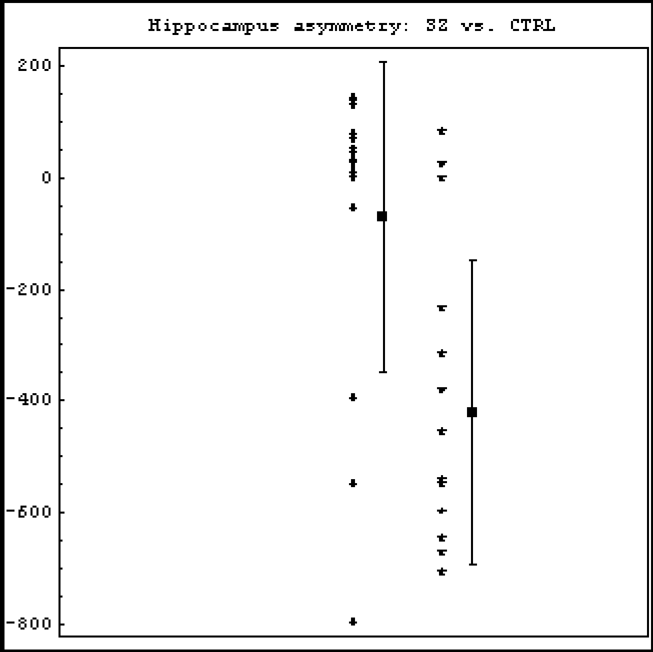
Fig. 5. Statistics of L/R volume index (left panel), L/R shape index (middle panel), and a combined two-dimensional feature space (right panel) with volume index (horizontal axis) and shape index (vertical axis). The ellipsoids represent the quantiles of the two-dimensional distributions for controls (black triangles) and for the schizophrenics (open squares). The two-dimensional plot demonstrates the improved group discrimination obtained by combining the two features.

Hippocampal asymmetry in schizophrenia



Combined analysis of relative volume difference (|L-R|/(L+R) and shape difference (MSD).

Research in collaboration with Shenton/McCarly & Kikinis, BWH Harvard



Significantly higher asymmetry in schizophrenics as compared to controls ($p < 0.0017$)

Visualization of local effects

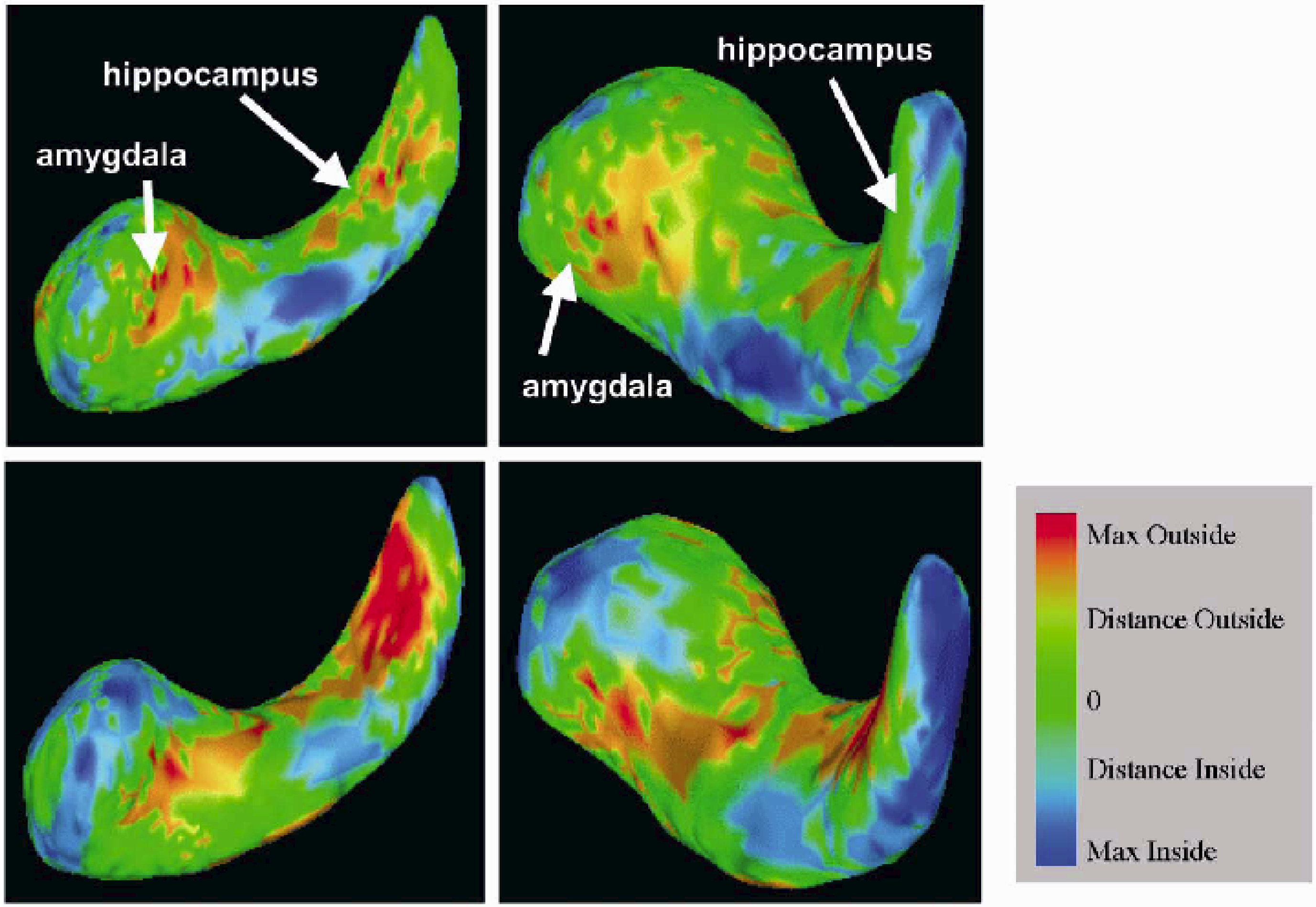


Fig. 6. A graphical visualization is presented for the left/right asymmetry of the amygdala–hippocampal complex for healthy controls (top row) and patients with schizophrenia (bottom row). The left and right columns show sagittal and posterior–anterior viewing

Application II: Study of twin pairs

Twin Study

- Monozygotic (MZ): Identical twins
- Dizygotic (DZ): Nonidentical twins
- MZ-Discordant (MZ-DS): Identical twins: one affected, co-twin at risk
- Nonrelated (NR): age/gender matched

Exploratory Analysis: Genetic difference and disease versus morphology of brain structures

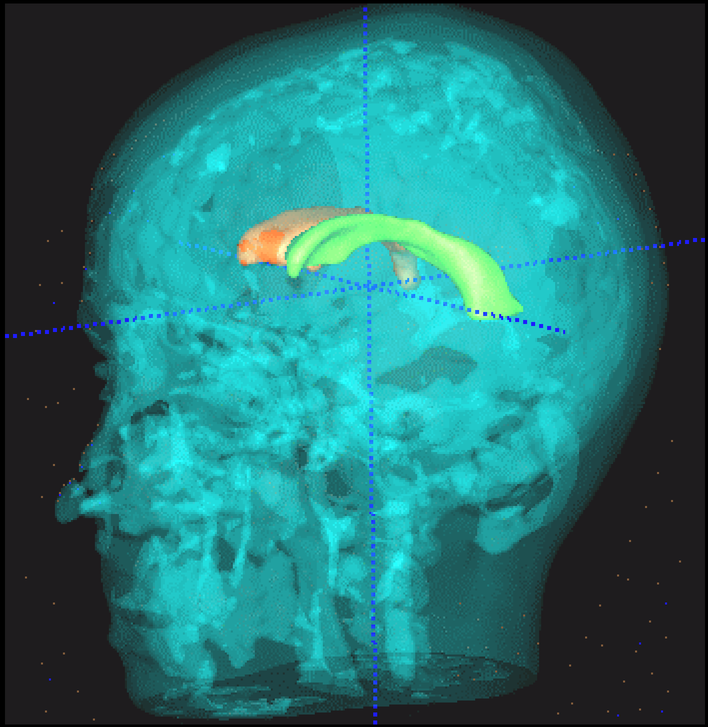
MRI MZ/DZ Twin Study

MRI dataset Daniel Weinberger, NIMH
[Bartley,Jones,Weinberger, Brain 1997 (120)]

To study size & shape similarity of ventricles in related MZ/DZ and in unrelated pairs.

Goal:

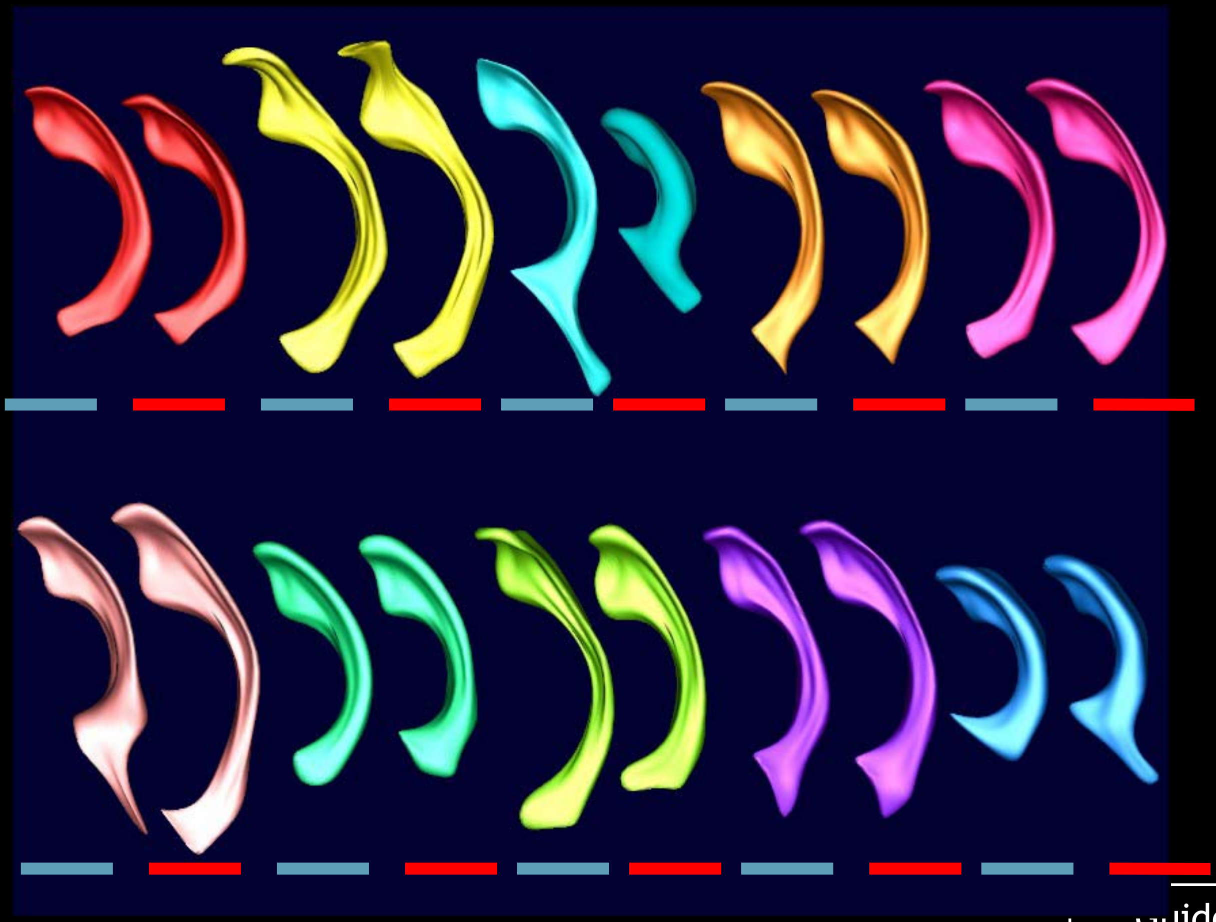
- Learn more about size and shape variability of ventricles
- Results important for studies of twins discordant to illness



Hypothesis:

- Ventricular shapes more similar in MZ
- Shape adds new information to size

Typical Clinical Study: MZ twin pairs discordant for SZ

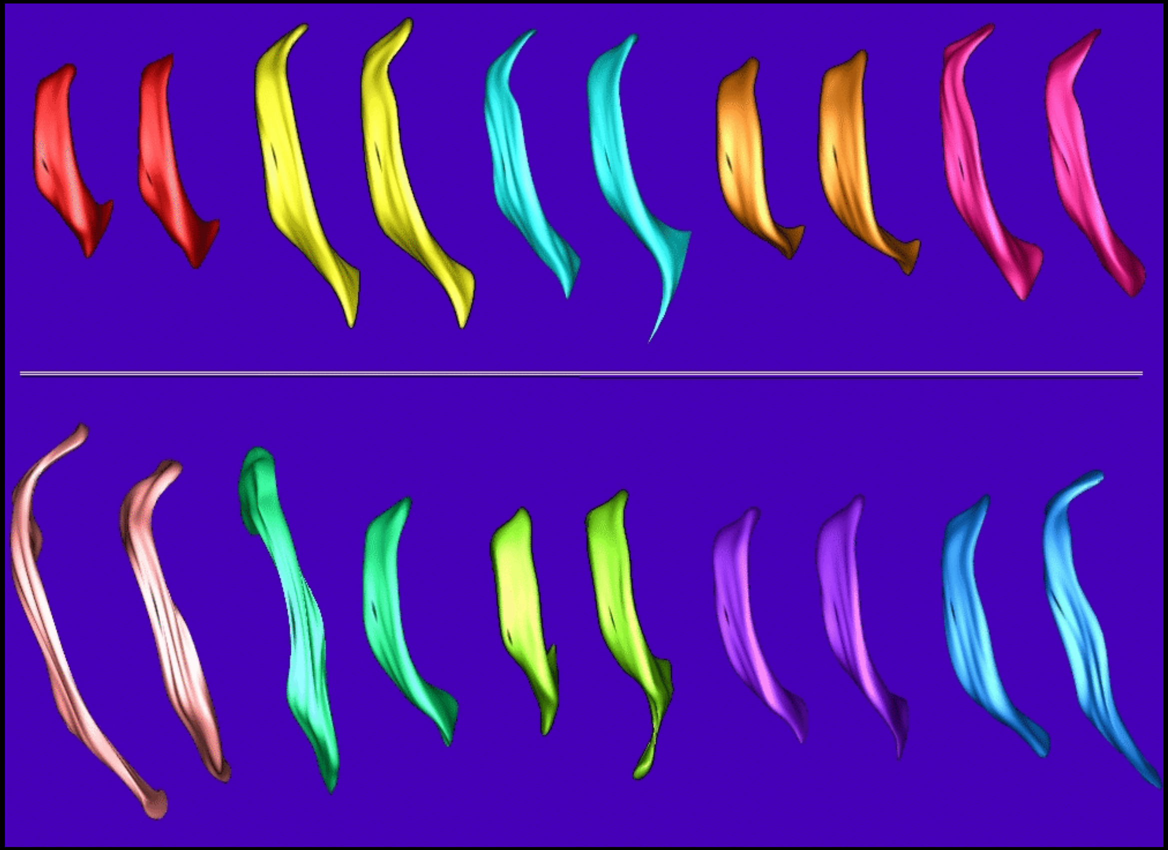


10 identical twin pairs, ventricles marker for SZ?

Left: co-twin at risk

Right: schizophrenics co-twin

Shape similarity/dissimilarity

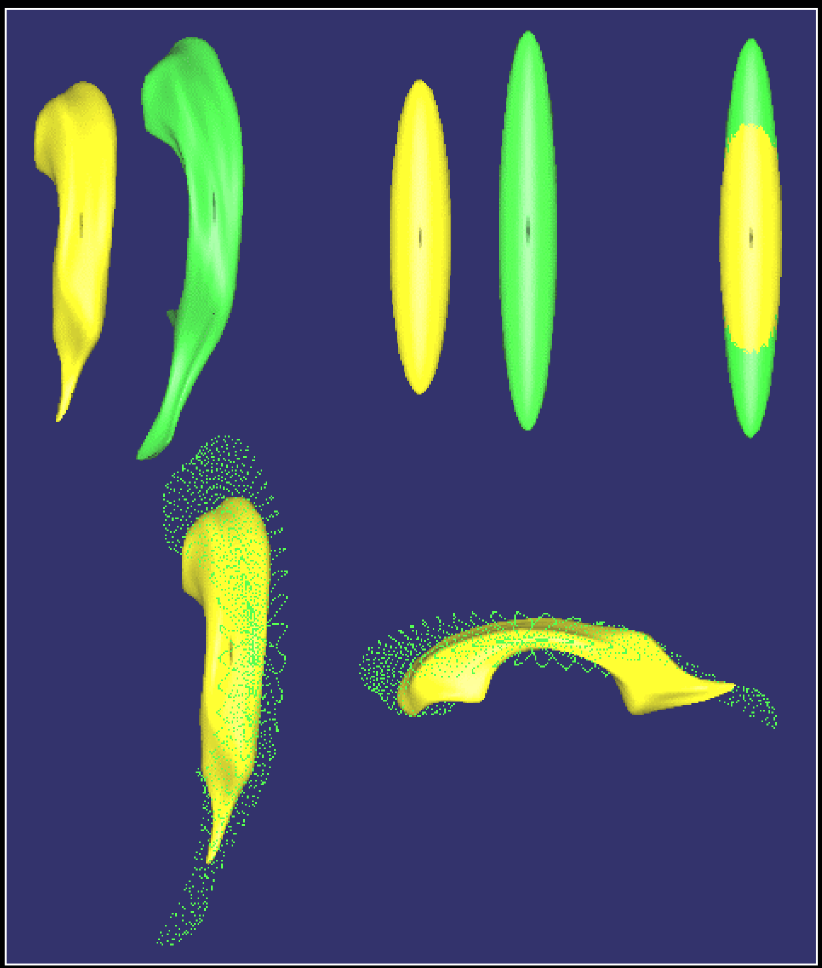


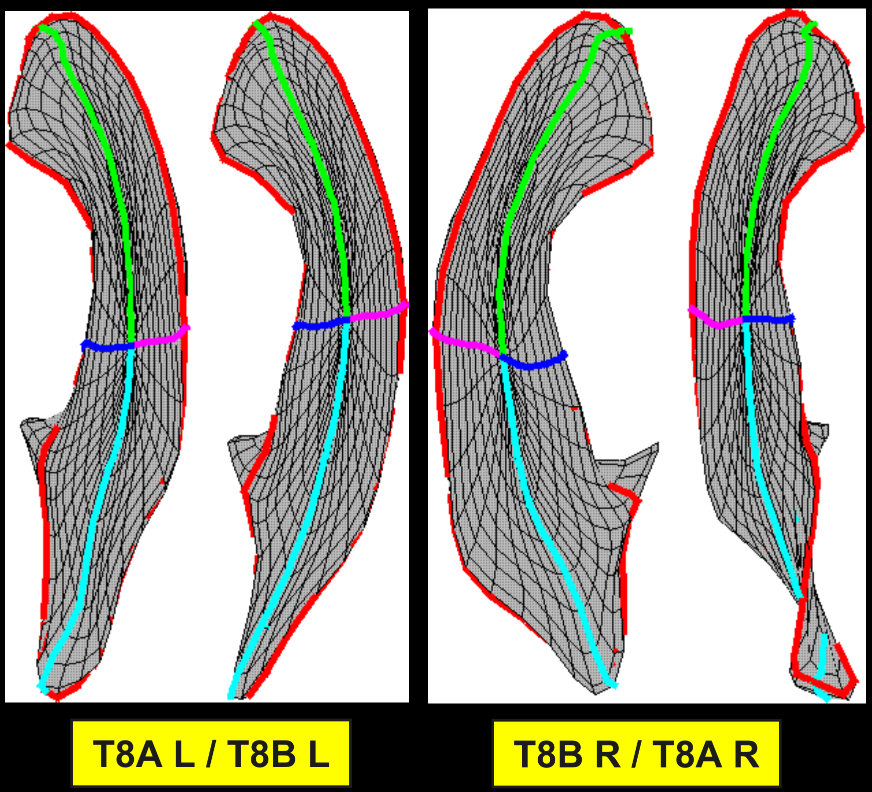
MZ

DZ

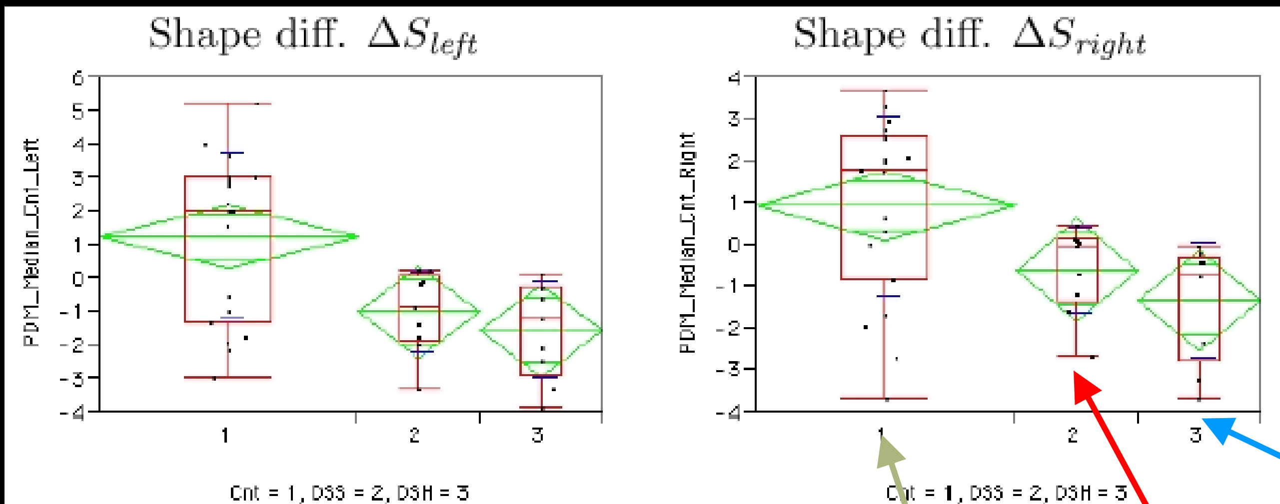
Normalized by volume

Object Alignment / Surface Homology





Group Tests: Shape Distance to Template (CNTL)



P-value	ΔS_{left}	ΔS_{right}
Cnt v. DSS	**0.039**	**0.058**
Cnt v. DSH	**0.0042**	**0.0089**
DSS v. DSH	0.39	0.22

Healthy All

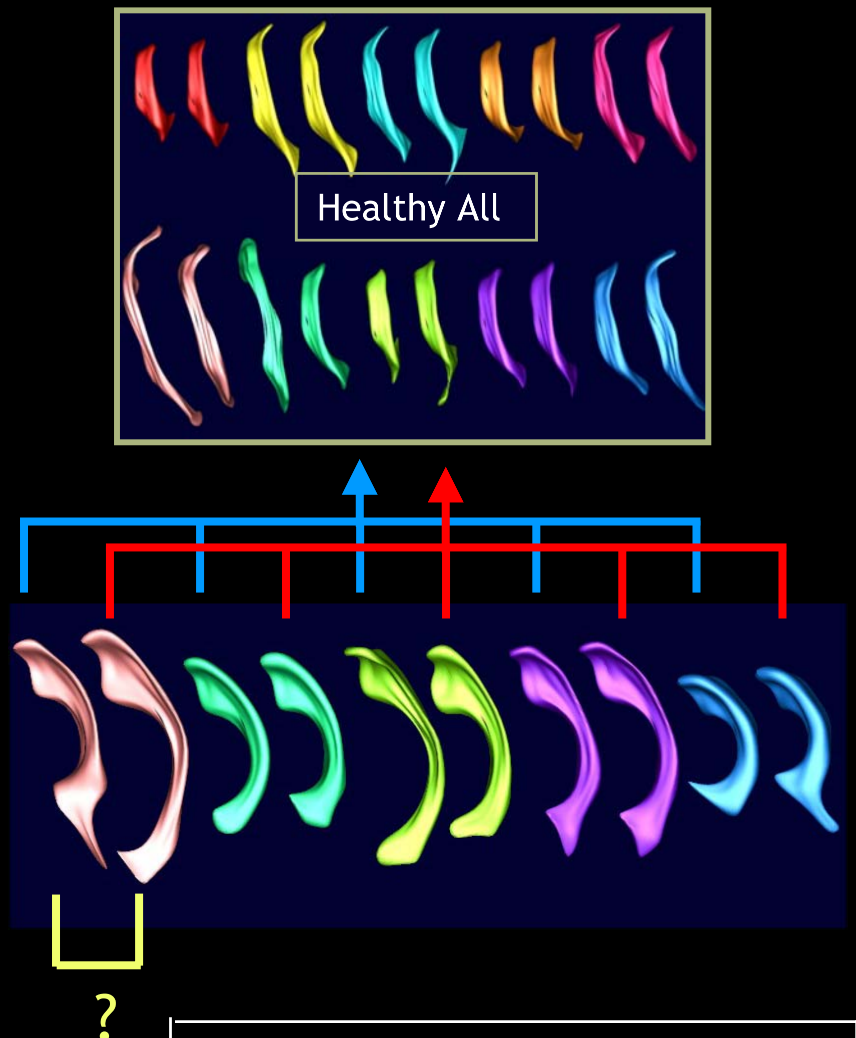
Co-twin schizophr.

Co-twin at risk, healthy

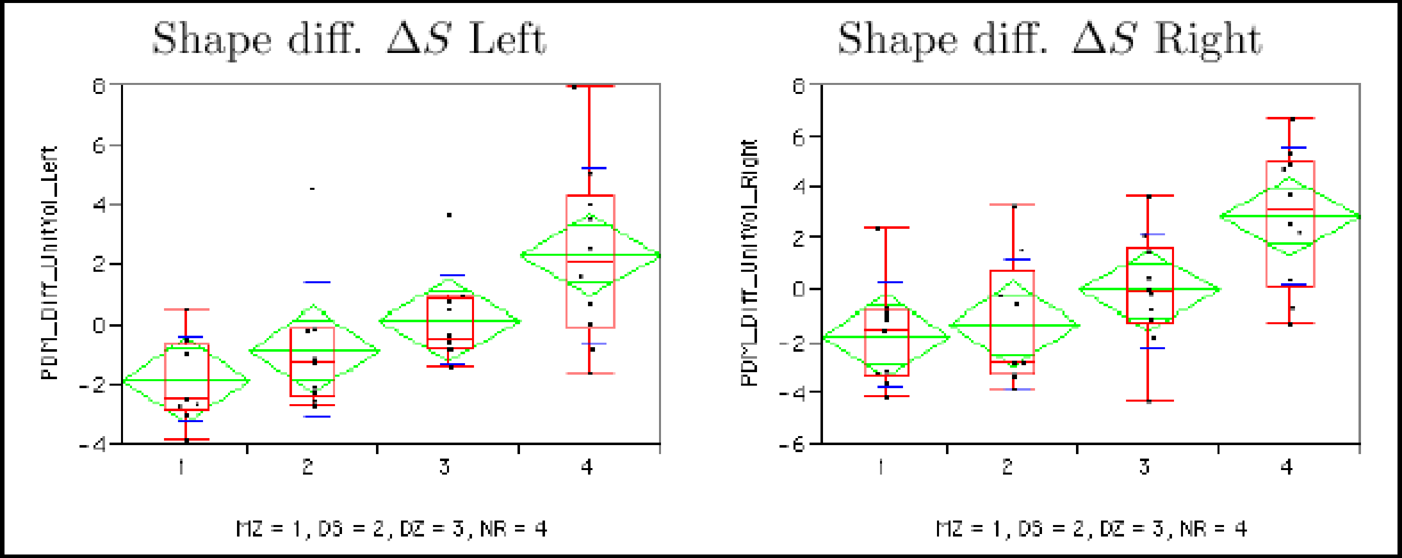
Global shape difference S (residuals after correction for gender and age) to the average healthy objects. Table of P-values for testing group mean difference between the groups. Value significant at 5% level are printed in bold typeface.

Result Group Tests

- Both subgroups of the MZ discordant twins (affected and at risk) show significant shape difference
- Ventricular shape seems to be marker for disease and possibly for vulnerability
- But: Same global deviation from template does not imply co-twin shape similarity



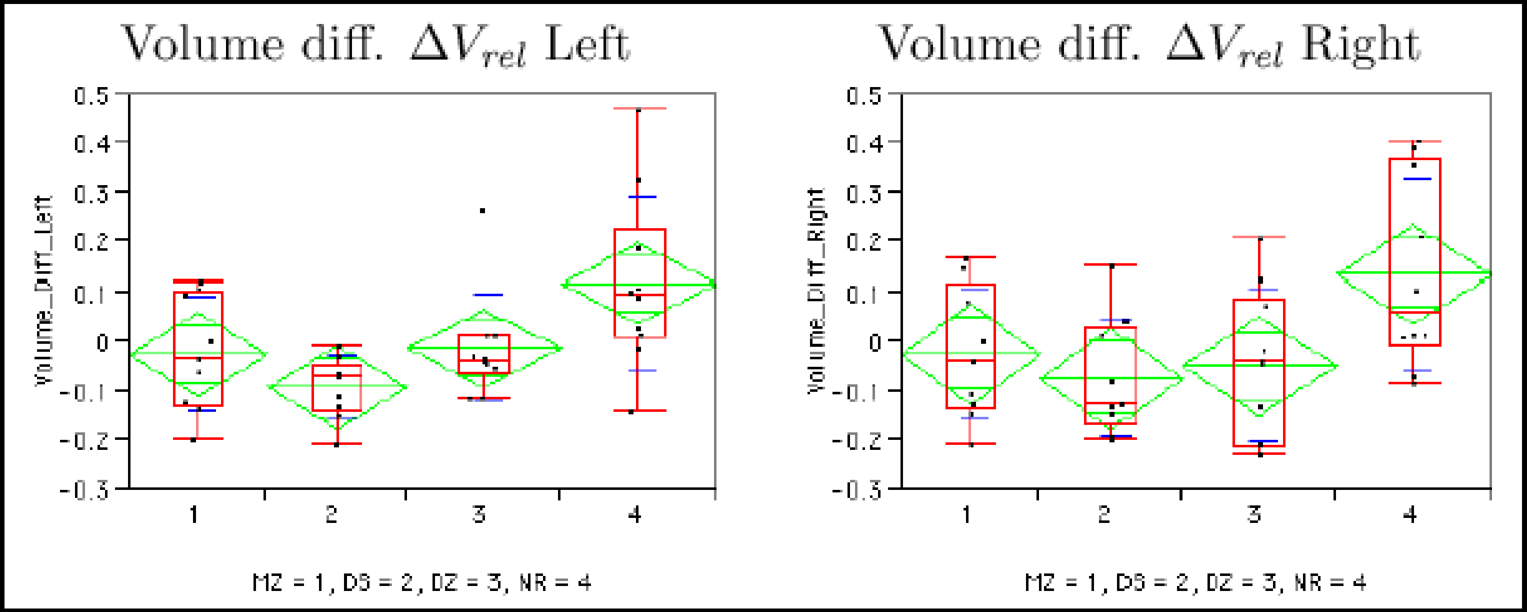
Pairwise MSD shape differences between co-twin ventricles



P-value	ΔS L	ΔS R
MZ vs. NR	**0.0013**	**0.0006**
MZ vs. DZ	**0.0082**	**0.0399**
MZ vs. DS	0.28	0.68
DS vs. NR	**0.018**	**0.0026**
DS vs. DZ	0.25	0.24
DZ vs. NR	**0.050**	**0.016**

MZ healthy and MZ discordant show same pairwise shape similarity

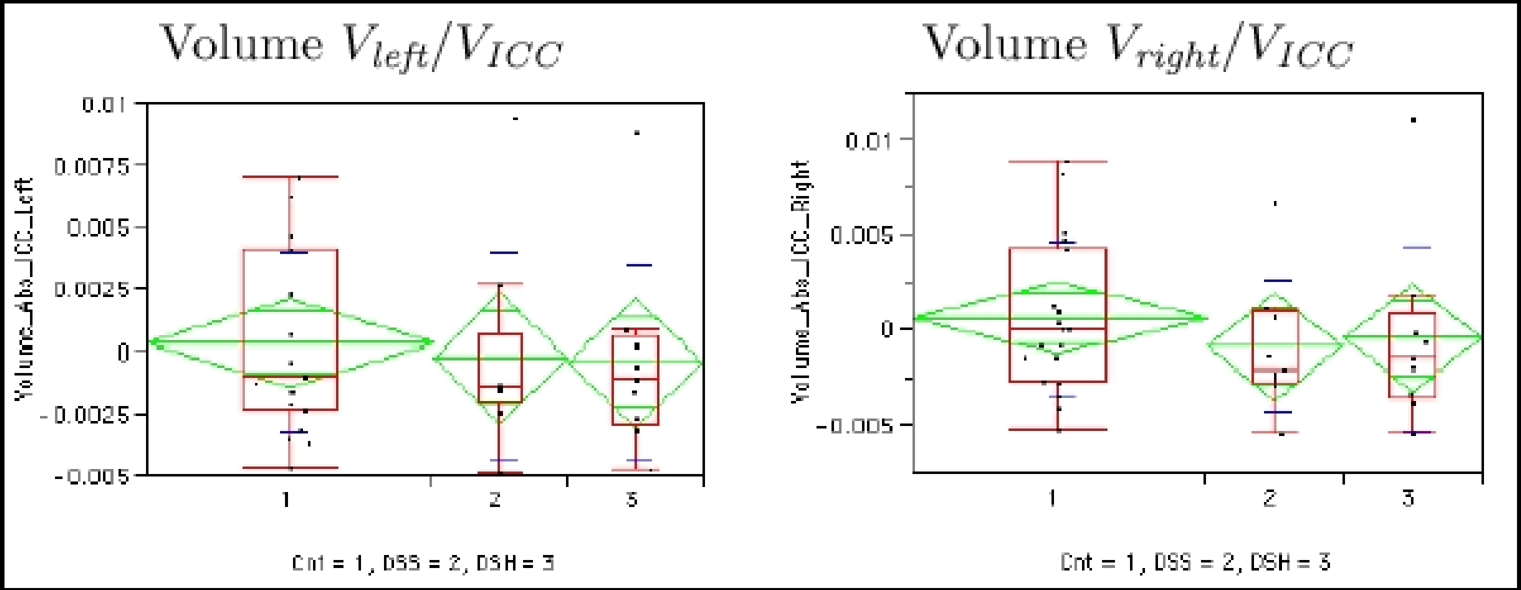
Pairwise tests among co-twins



P-value	ΔV_{rel} L	ΔV_{rel} R
MZ vs. NR	0.0537	0.0513
MZ vs. DZ	0.82	0.71
MZ vs. DS	0.18	0.42
DS vs. NR	**0.0033**	**0.011**
DS vs. DZ	0.069	0.70
DZ vs. NR	0.057	**0.027**

Trend MZ < DZ < NR: Volume similarity correlates with genetic difference

Group Tests of Ventricular Volumes



P-value	$\frac{V_{left}}{V_{ICC}}$	$\frac{V_{right}}{V_{ICC}}$
Cnt v. DSS	0.71	0.35
Cnt v. DSH	0.60	0.56
DSS v. DSH	0.91	0.82

All tests nonsignificant

Average distance maps of co-twin ventricles

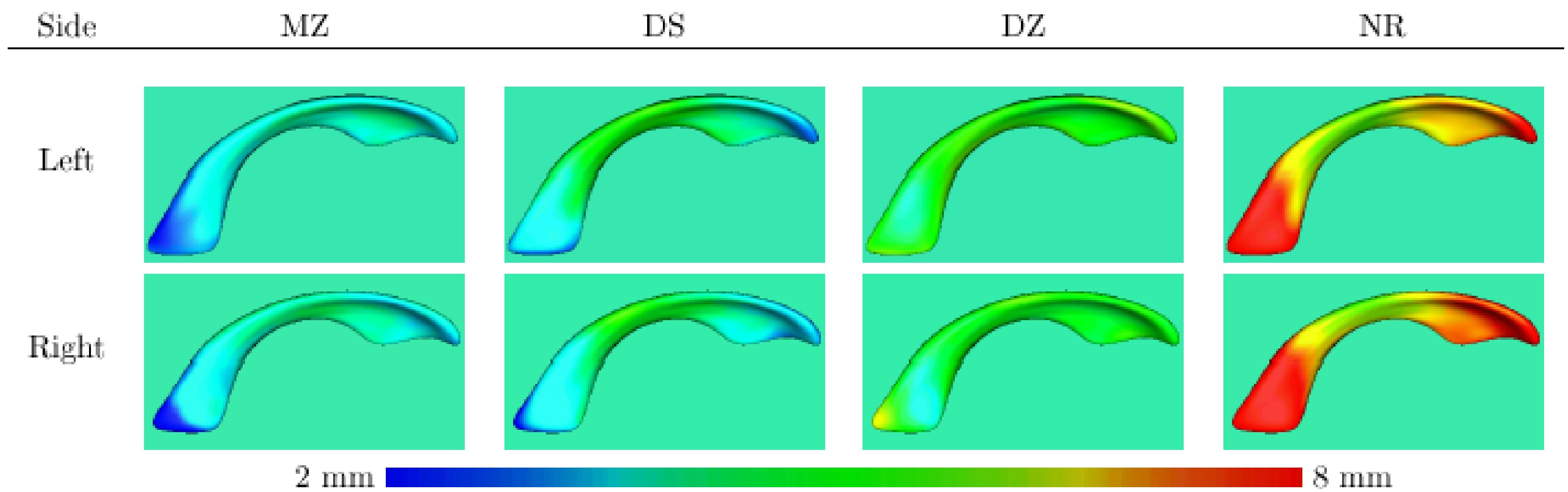


Figure 5: Average distance maps visualize the pointwise averaged pair-individual distance maps (see Fig. 2) for each group (residuals after correction for gender and age). The distances are color-coded according to the provided colormap.

Pairwise co-twin ventricle shape distance (SnPM statistics)

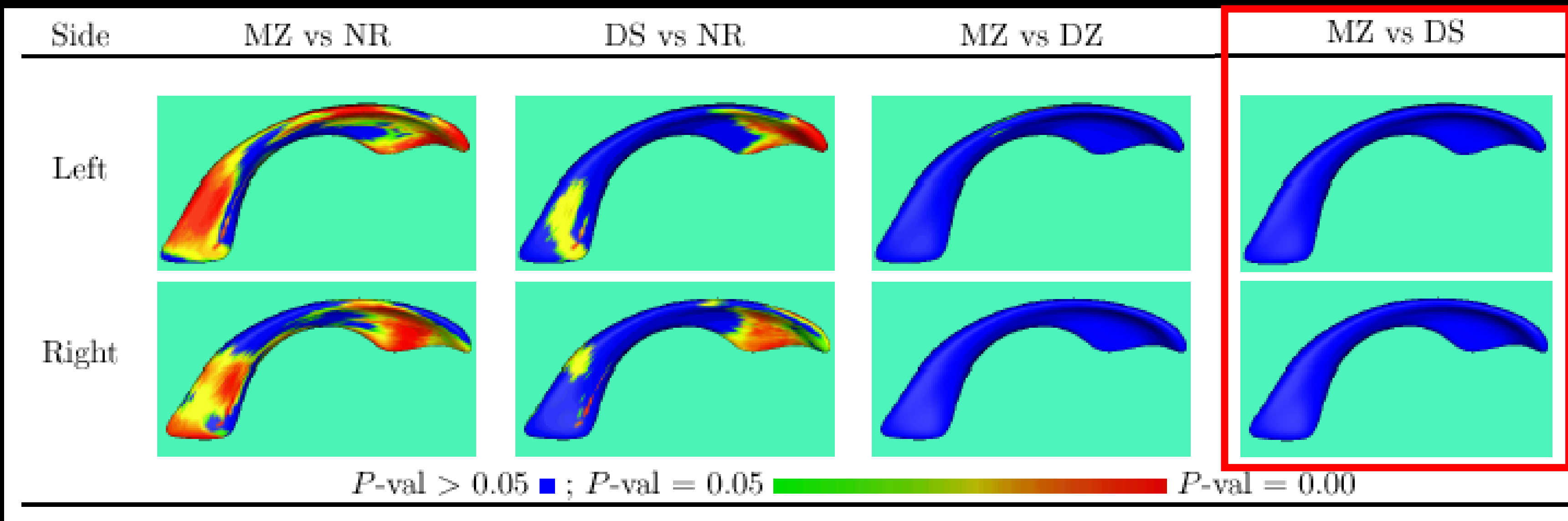
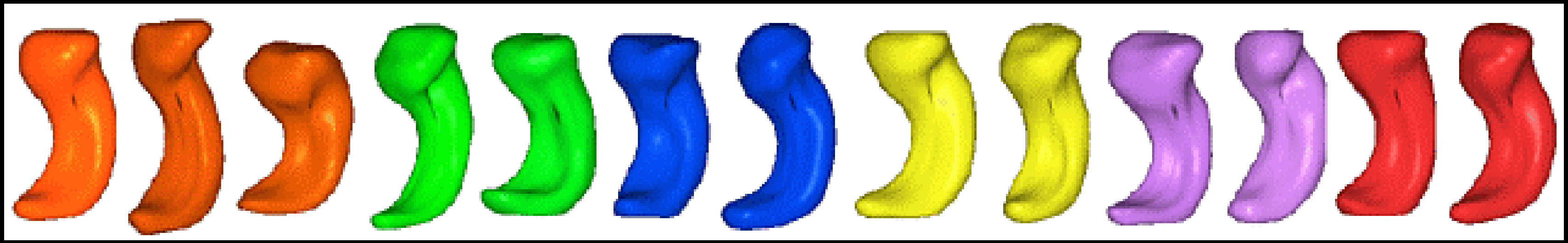
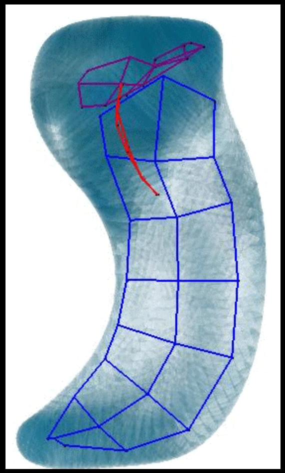


Figure 6: Statistical maps visualize the locations of significant difference between groups using pair-individual distance maps (residuals after correction for gender and age, also corrected for multiple comparisons). The distances are color-coded according to the provided colormap.

Pairwise co-twin differences of MZ and MZ-DS are not significantly different (global and local stats)

II: Medial Models for Shape Analysis

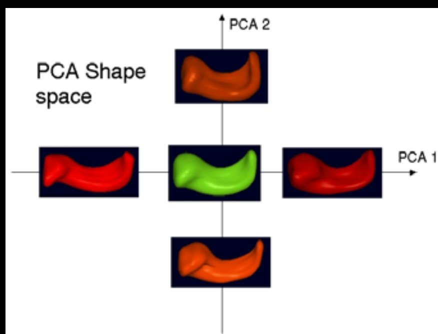




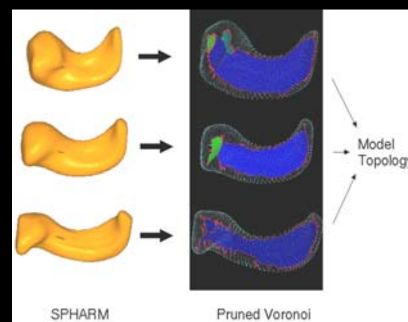
Medial representation for shape population

Styner and Gerig, MMBIA'00 / IPMI 2001 / MICCAI 2001 / CVPR 2001/ ICPR 2002

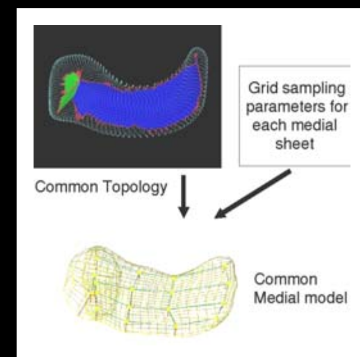
Medial model generation scheme



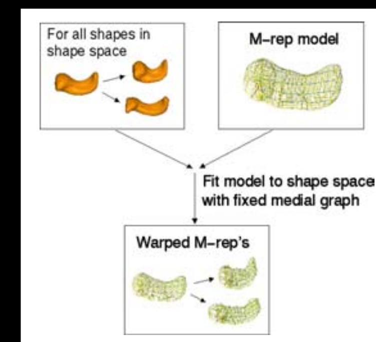
Step 1: Define shape space



Step 2: Extract common topology



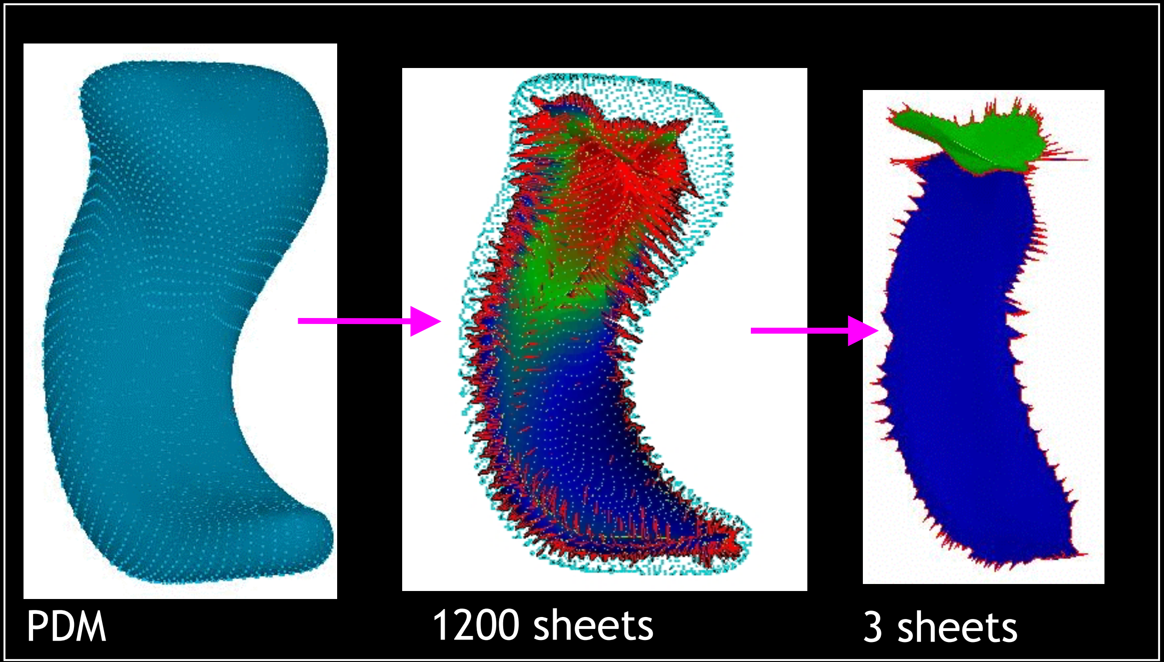
Step 3: Compute minimal sampling



Step 4: Determine model statistics

Goal: To build 3D medial model which represents shape population

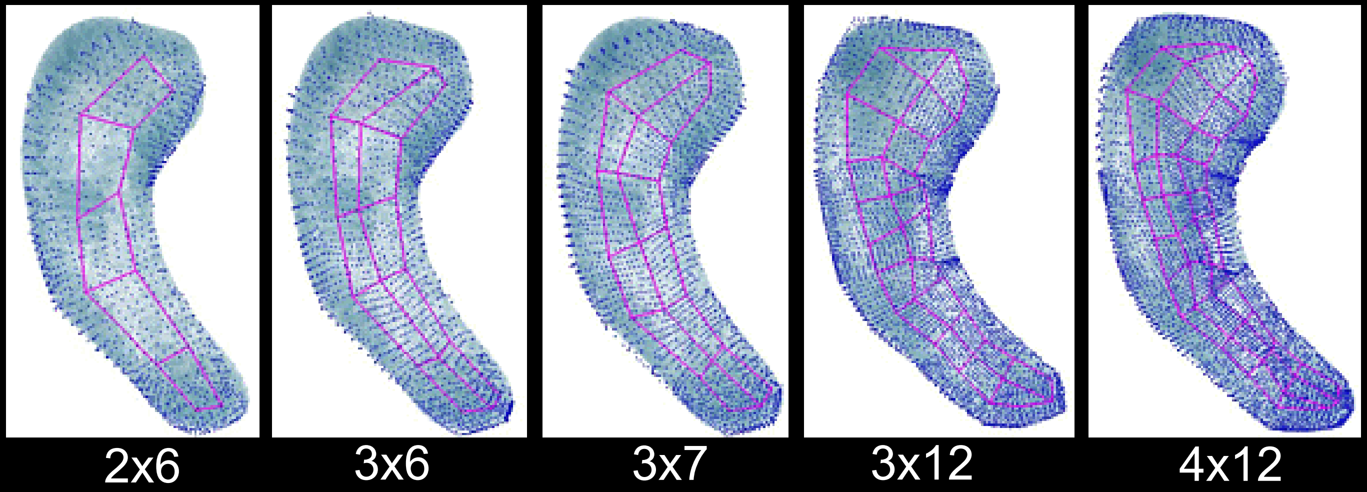
Simplification VD single figure

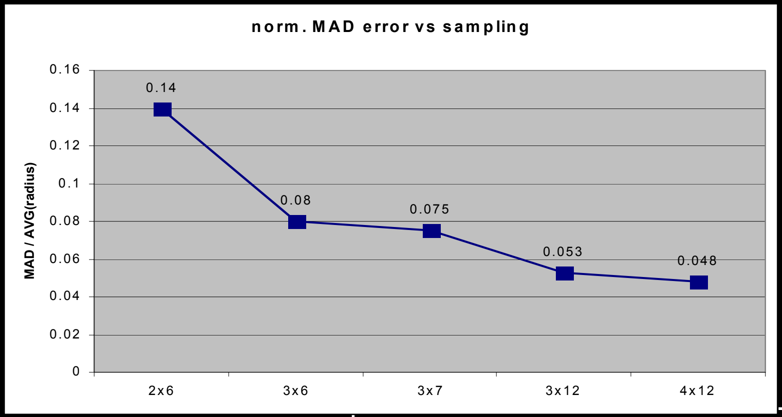


- Compute inner VD of fine sampled boundary
- Group vertices into medial sheets (Naef)
- Remove nonsalient medial sheets (Pruning)
- Accuracy: 98% volume overlap original vs. reconstruction

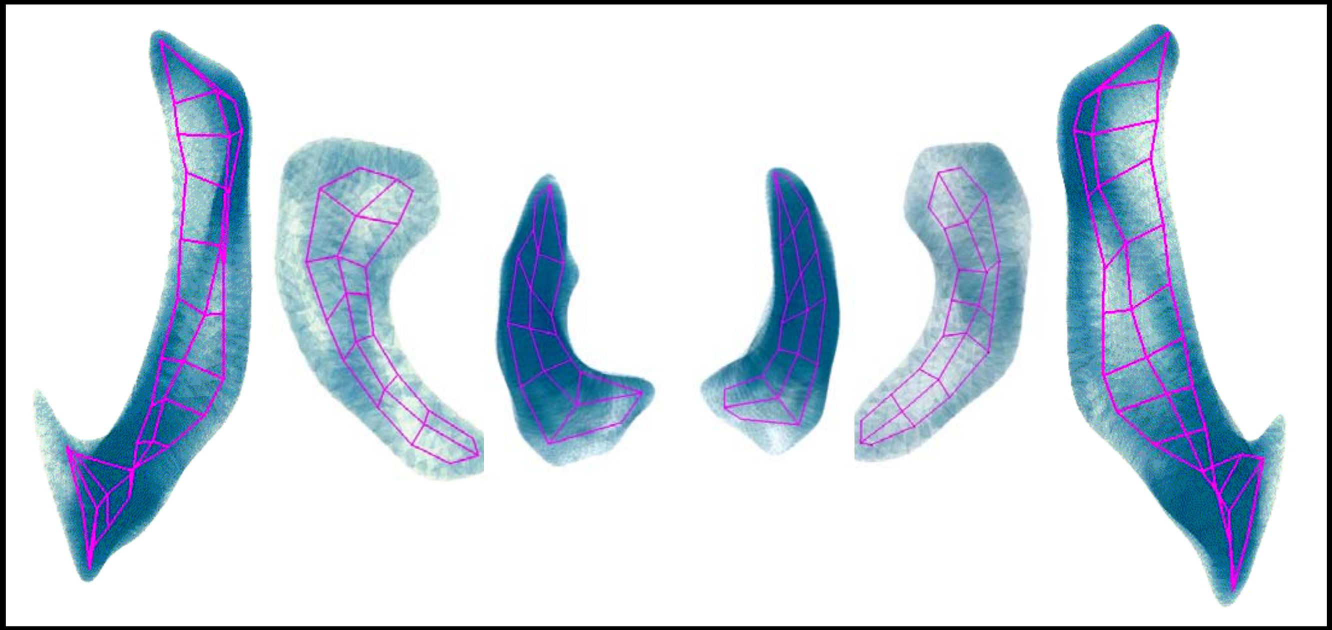
Optimal (minimal) sampling

Find minimal sampling given a predefined approximation error





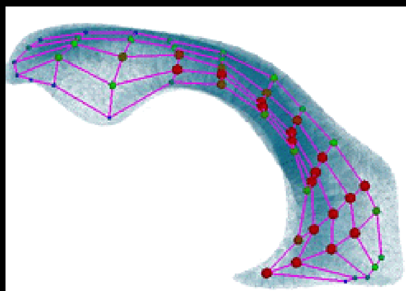
Medial models of subcortical structures



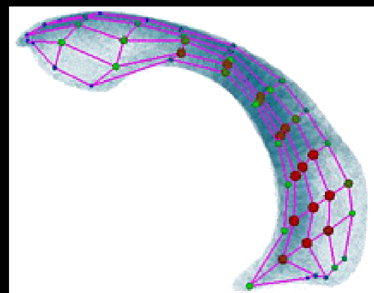
Shapes with common topology: M-rep and implied boundaries of putamen, hippocampus, and lateral ventricles.

Medial representations calculated automatically (goodness of fit criterion).

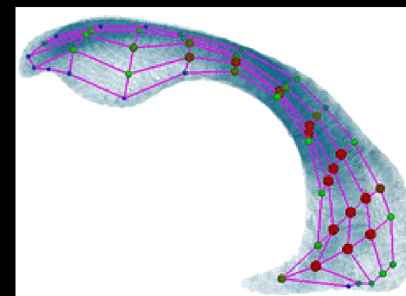
Twin Study: Medial Representation



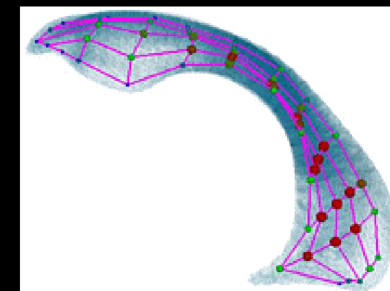
A



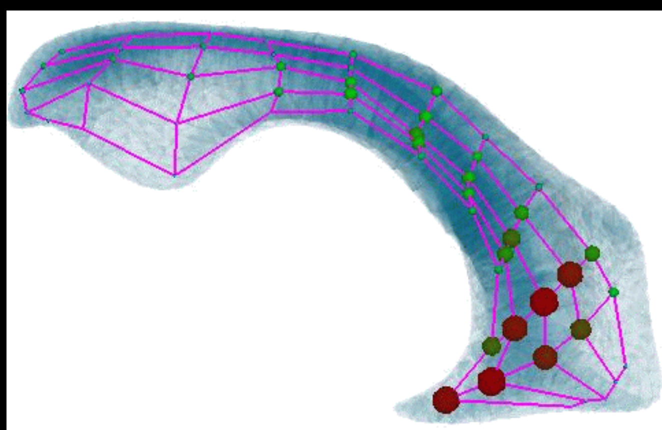
B



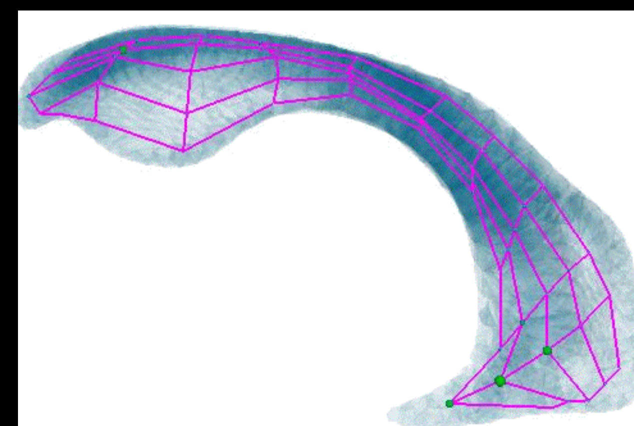
A



B



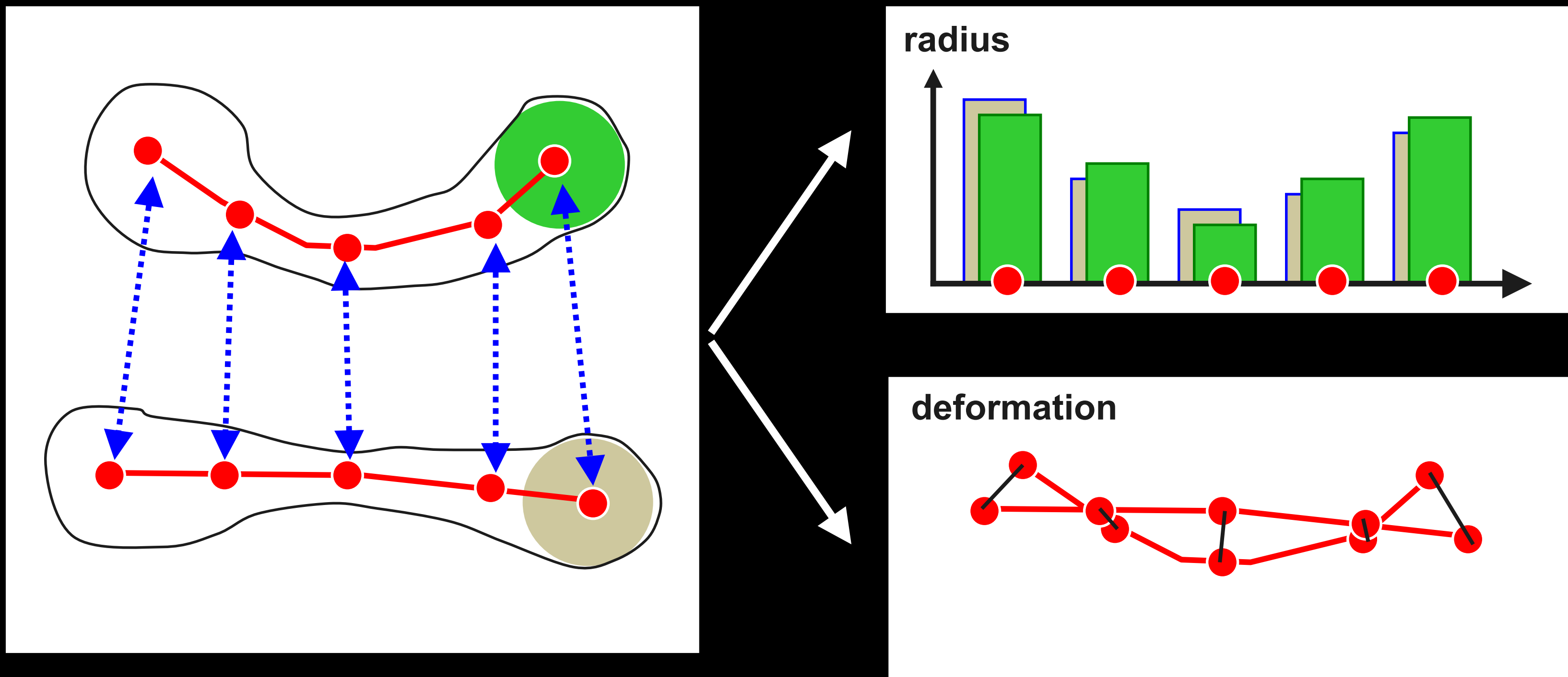
A minus B: Left Ventricles



A minus B: Right Ventricles

-0.3  +1.5

Shape Analysis using Medial Representation



Local width differences (MA_rad): Growth, Dilation

Positional differences (MA_dist): Bending, Deformation

Similarity of ventricles in MZ/DZ: Radius Difference

10 twin pairs (20 MRI)

Groups:

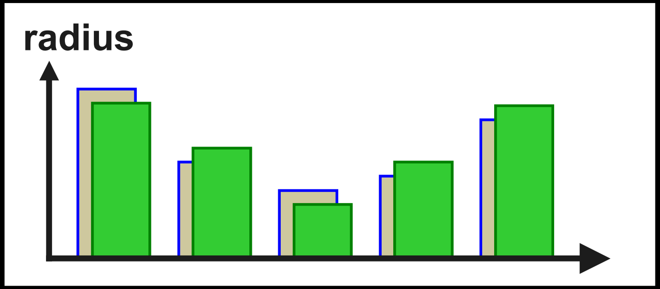
- 5 MZ (identical)
- 5 DZ (non-identical)
- 180 nonrelated pairs

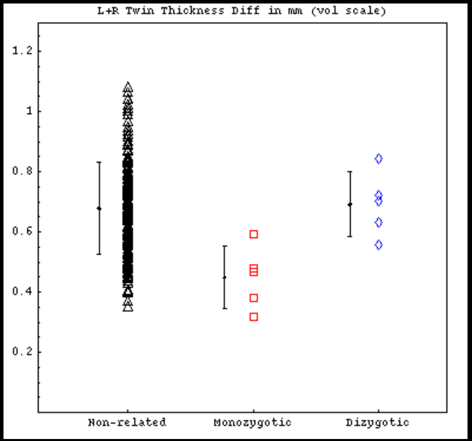
Medial representations

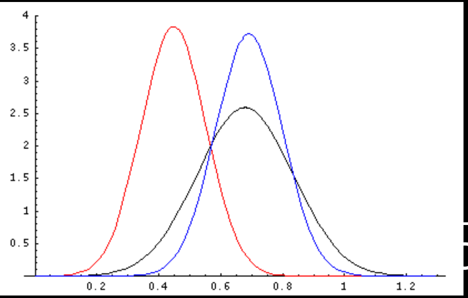
- mean abs. radius diff.

Results:

- MZ vs. DZ: $p<0.0065$
- MZ vs. unrel: $p<0.0009$
- DZ vs. unrel: $p<0.86$







Similarity of ventricles in MZ/DZ: Positional Difference

10 twin pairs (20 MRI)

Groups:

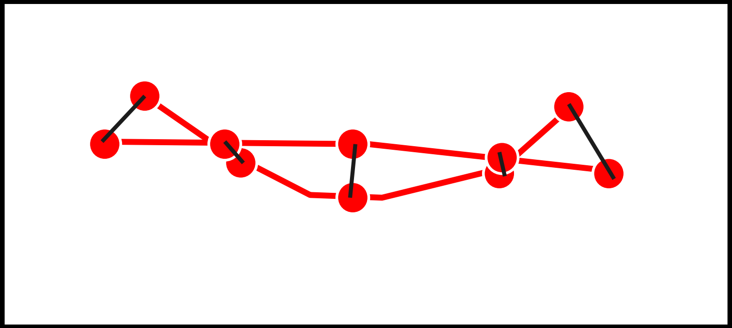
- 5 MZ (identical)
- 5 DZ (non-identical)
- 180 nonrelated pairs

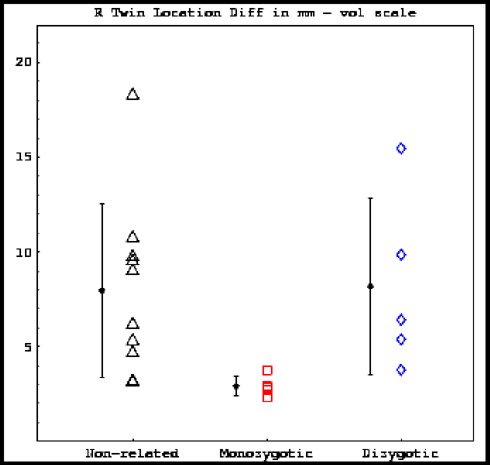
Medial representations

- mean abs. positional diff.

Results:

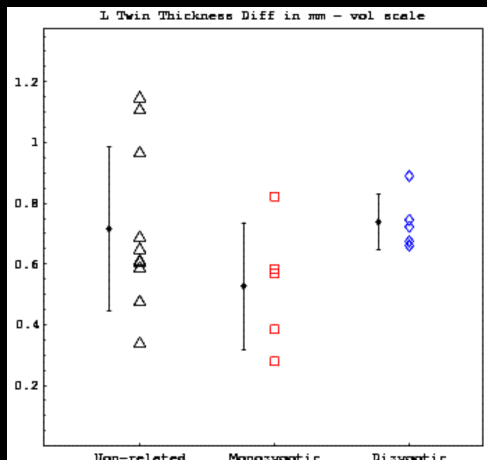
- MZ vs. DZ: p<0.0355
- MZ vs. unrel: p<0.0110
- DZ vs. unrel: p<0.6698



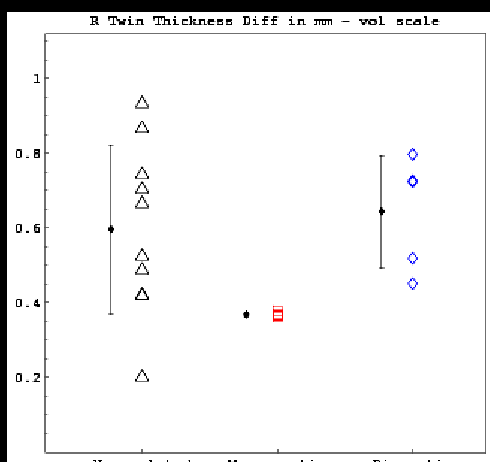


M-rep thickness

L



R



- Shapes volume normalized
- Integrated difference in width (radius)

Group Statistics:

	MZ/DZ	MZ/unr	DZ/unr
L,A	$p<0.072$	$p<0.195$	$p<0.858$
R,A	$p<0.014$	$p<0.011$	$p<0.681$

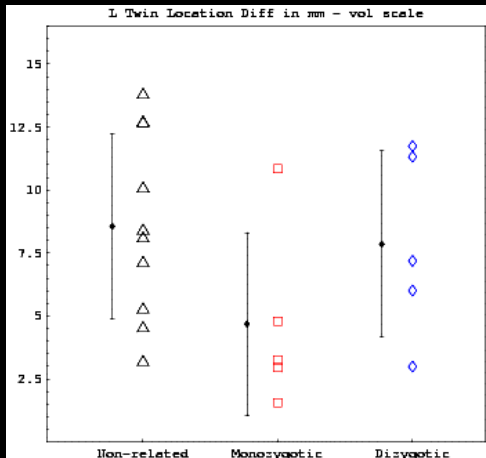
Right: MZ vs unrel. significantly different

Right: MZ vs DZ significantly different

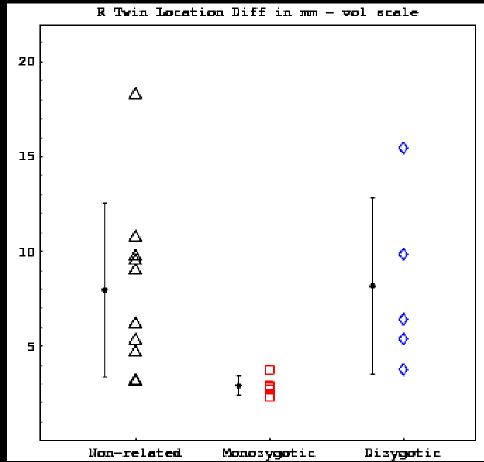
Left: no significant differences

M-rep analysis: Deformation

L



R



- Shapes volume normalized
- Integrated absolute difference in deformation

Group Statistics:

	MZ/DZ	MZ/unr	DZ/unr
L,B	$p<0.209$	$p<0.075$	$p<0.730$
R,B	$p<0.035$	$p<0.006$	$p<0.932$

Right: MZ vs unrel. significantly different

Right: MZ vs DZ significantly different

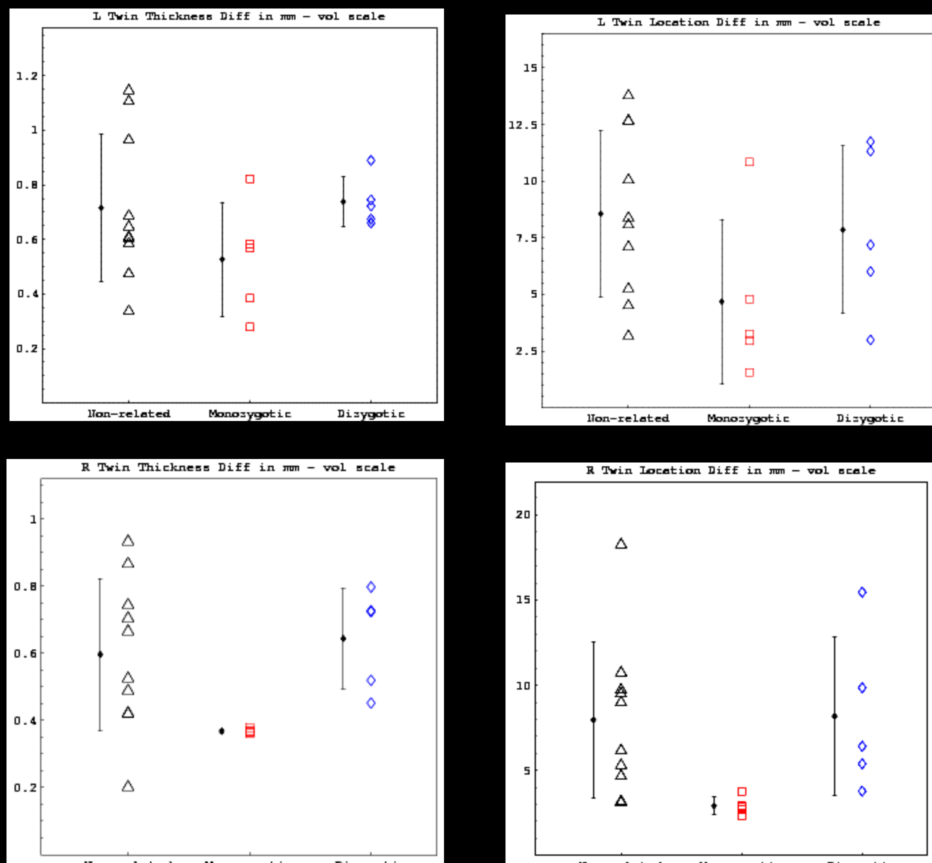
Left: no significant differences

Medial Representation: Statistics

Width Deformation

L

R



Left Ventricle:
No significant differences MZ/DZ

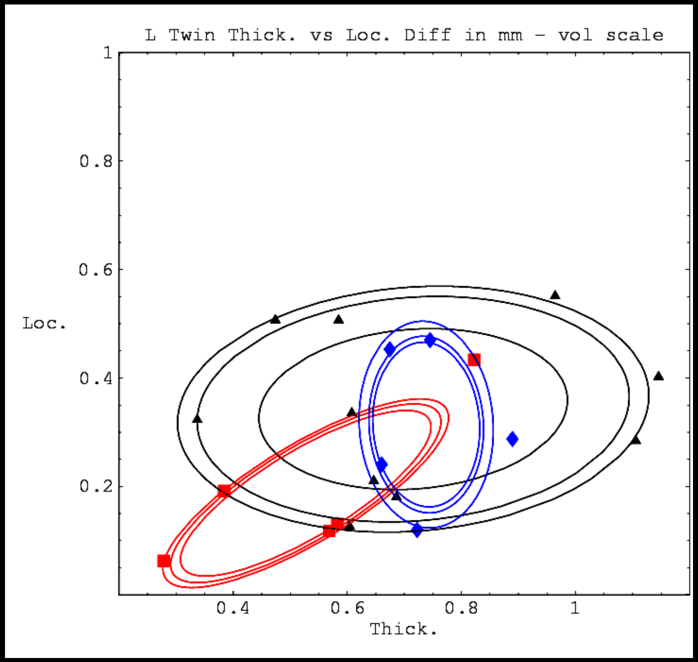
Right Ventricle:
Significant Differences MZ/DZ

Width ($p < 0.014$)
Deform ($p < 0.035$)

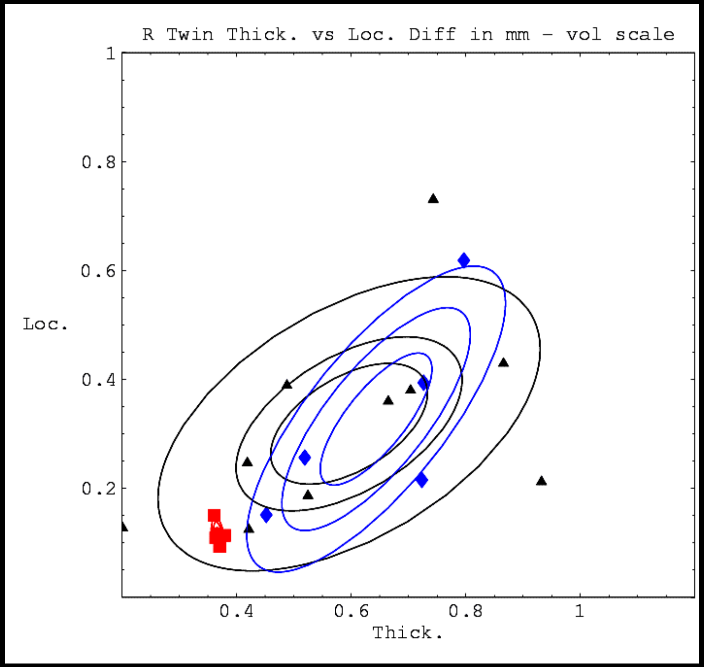
M-rep: Composite shape statistics

- Shapes volume normalized
- Integrated difference in thickness (x-axis) and position (y-axis)

Left



Right



MZ: red

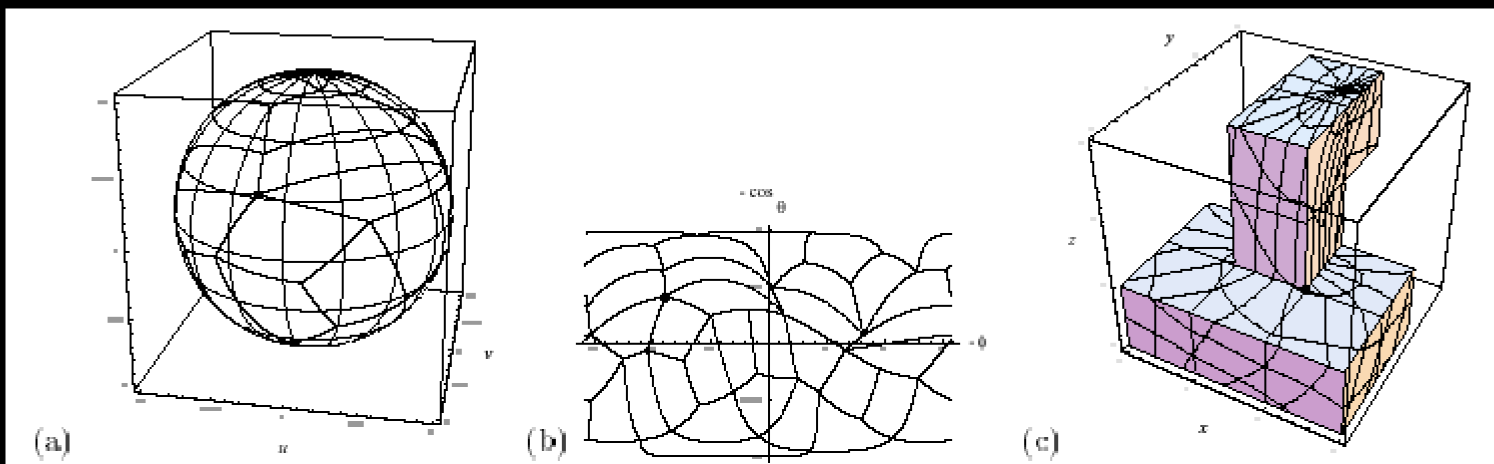
DZ: blue

NR: black

Towards local analysis

- Integrated shape measures do not reflect locality
- Clinical questions: Where and what is different
- Intuitive description of change

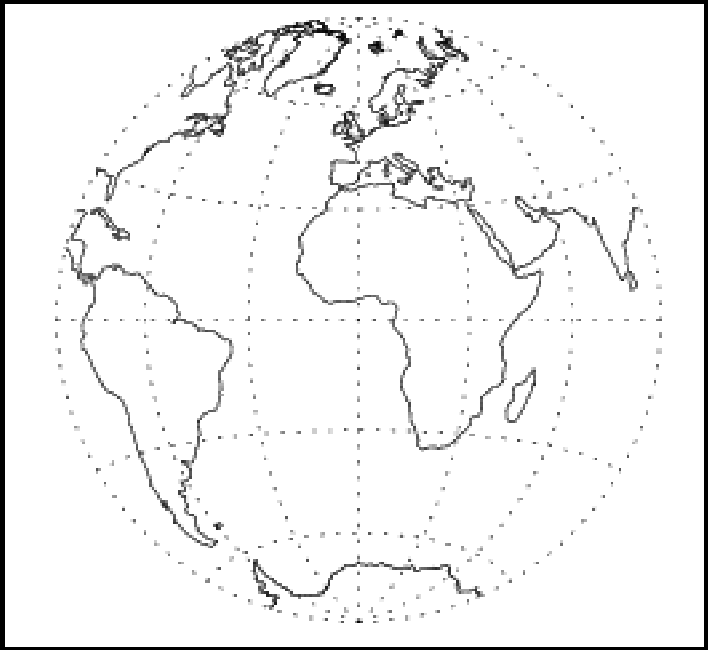
Mapping surfaces to 2D maps ctd.



a) Spherical parameter space with surface net, b) cylindrical projection, c) object with coordinate grid.

After optimization: Equal parameter area of elementary surface facets, minimal distortion.

Mapping surfaces to 2D maps



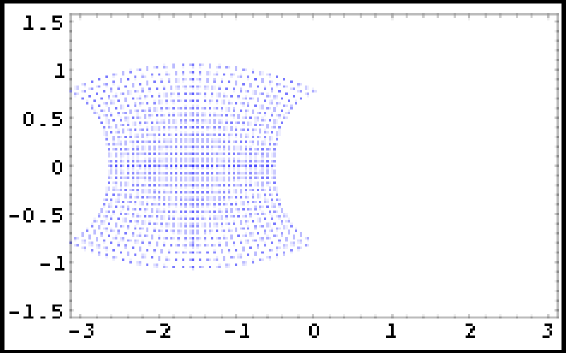
Lambert Azimuthal Equal–Area Projection

A special case of a cylindrical equal–area projection with standard parallel of $\phi_s = 0°$.

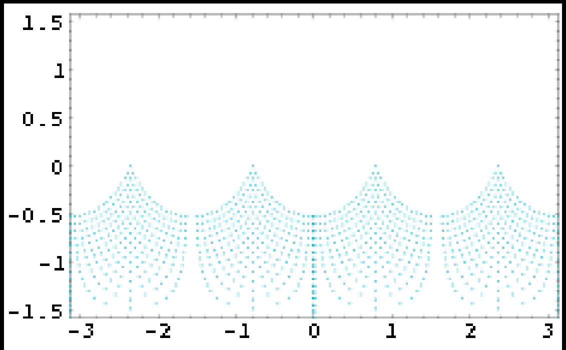
$$x = k' \cos\phi \sin(\lambda - \lambda_0)$$

$$y = k'[\cos\phi_1 \sin\phi - \sin\phi_1 \cos\phi \cos(\lambda - \lambda_0)],$$

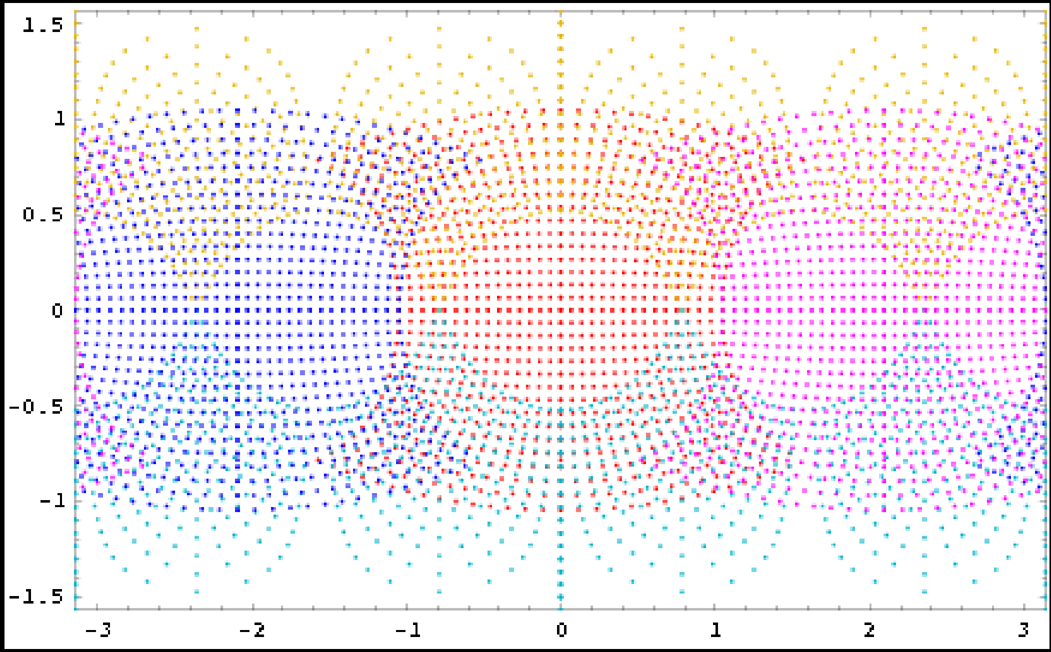
Mapping



1.5
1
0.5
0
-0.5
-1
-1.5
-3 -2 -1 0 1 2 3

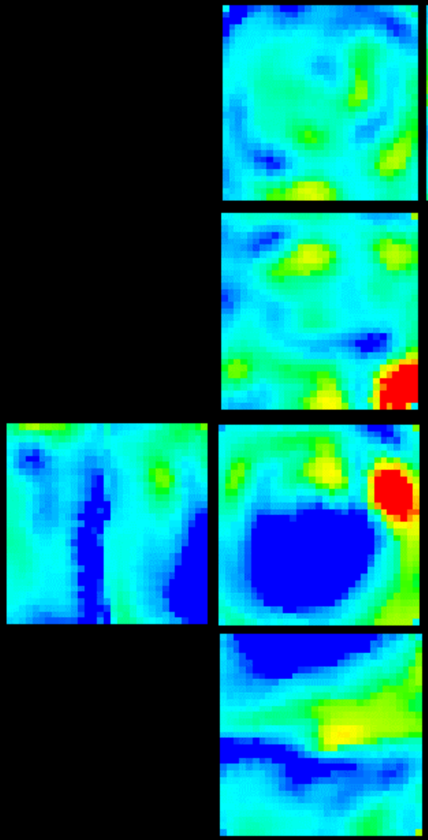


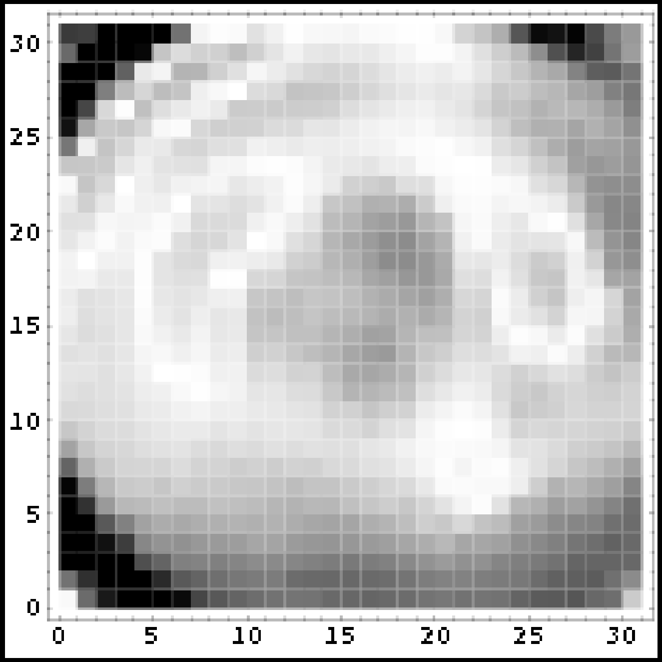
1.5
1
0.5
0
-0.5
-1
-1.5
-3 -2 -1 0 1 2 3



1.5
1
0.5
0
-0.5
-1
-1.5
-3 -2 -1 0 1 2 3

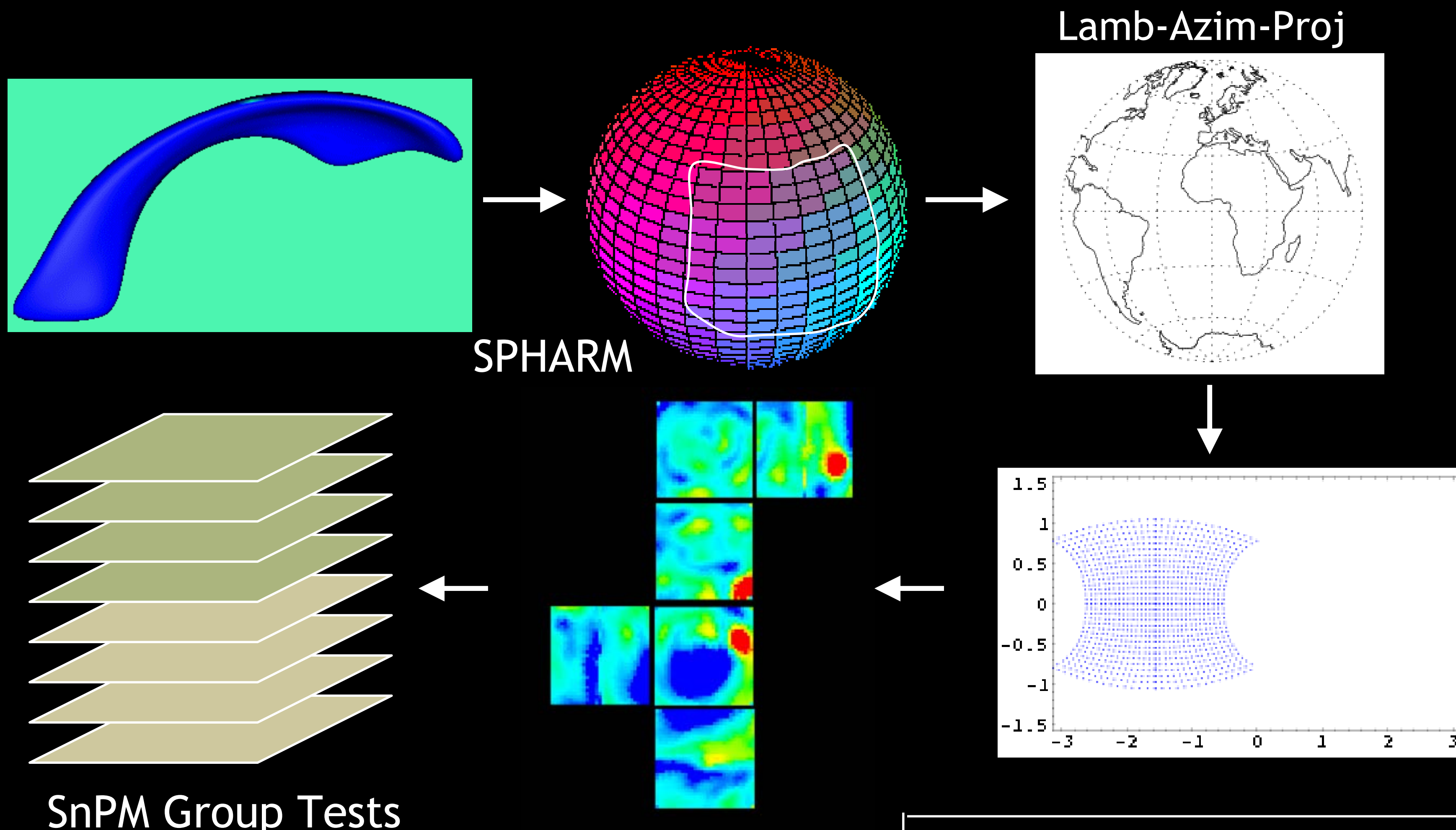
Mapping





Shape distance properties of individual shape,

Mapping surfaces to 2D patches



Pairwise co-twin ventricle shape distance (SnPM statistics)

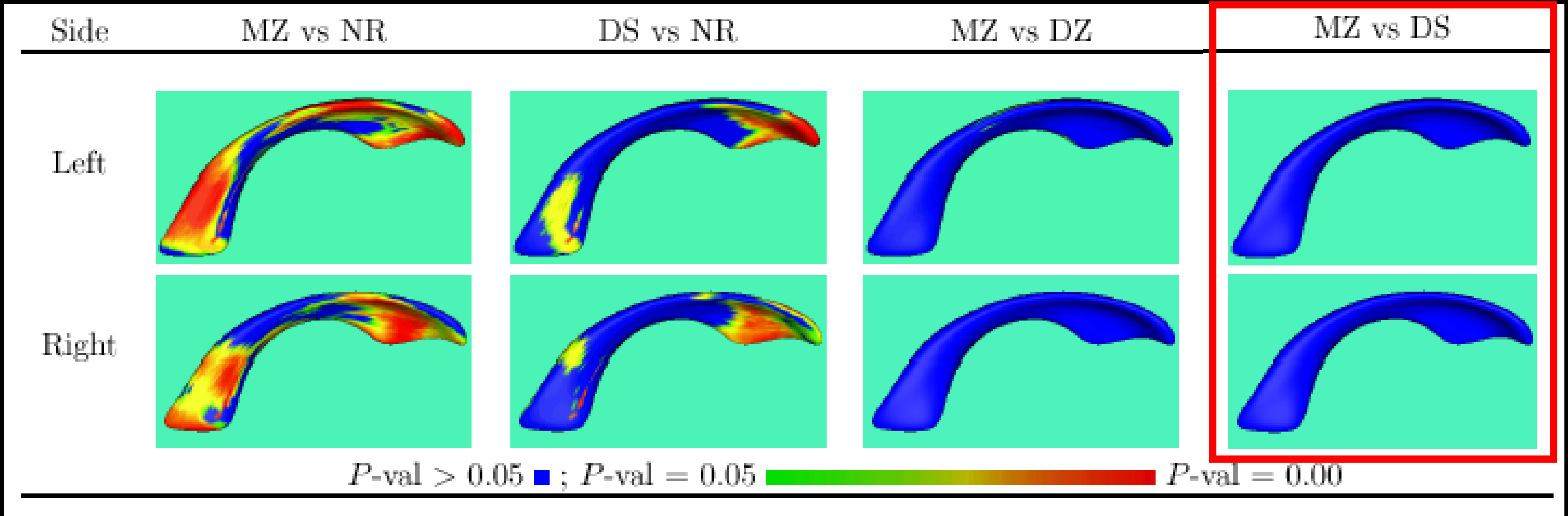
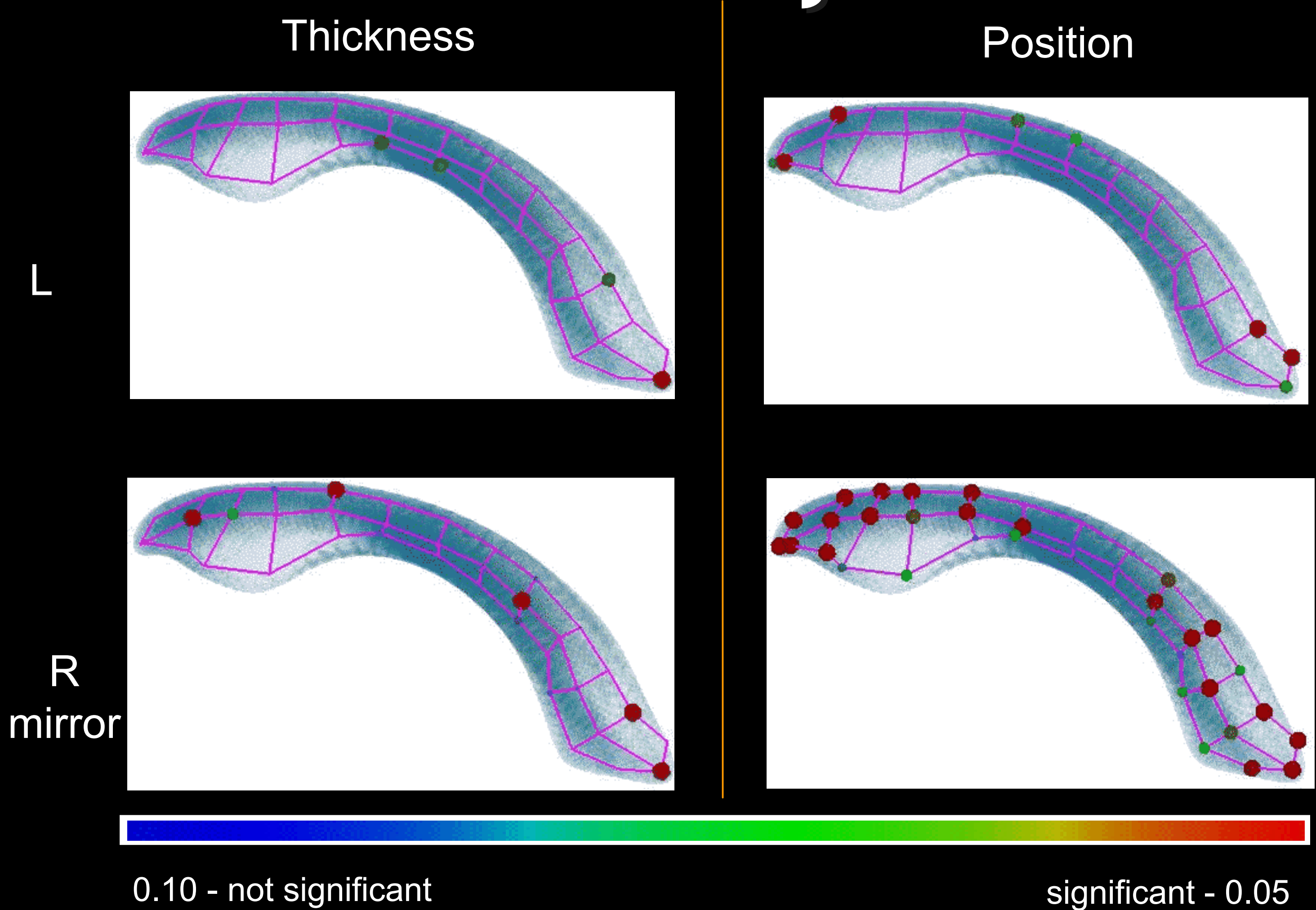


Figure 6: Statistical maps visualize the locations of significant difference between groups using pair-individual distance maps (residuals after correction for gender and age, also corrected for multiple comparisons). The distances are color-coded according to the provided colormap.

Pairwise co-twin differences of MZ and MZ-DS are not significantly different (global and local stats)

Towards local analysis



- Locations of significant local difference between MZ/DZ
- Display in average object
- Individual atoms considered independent (needs work)

Application III: Stanley Schizophrenia Study

Datasets

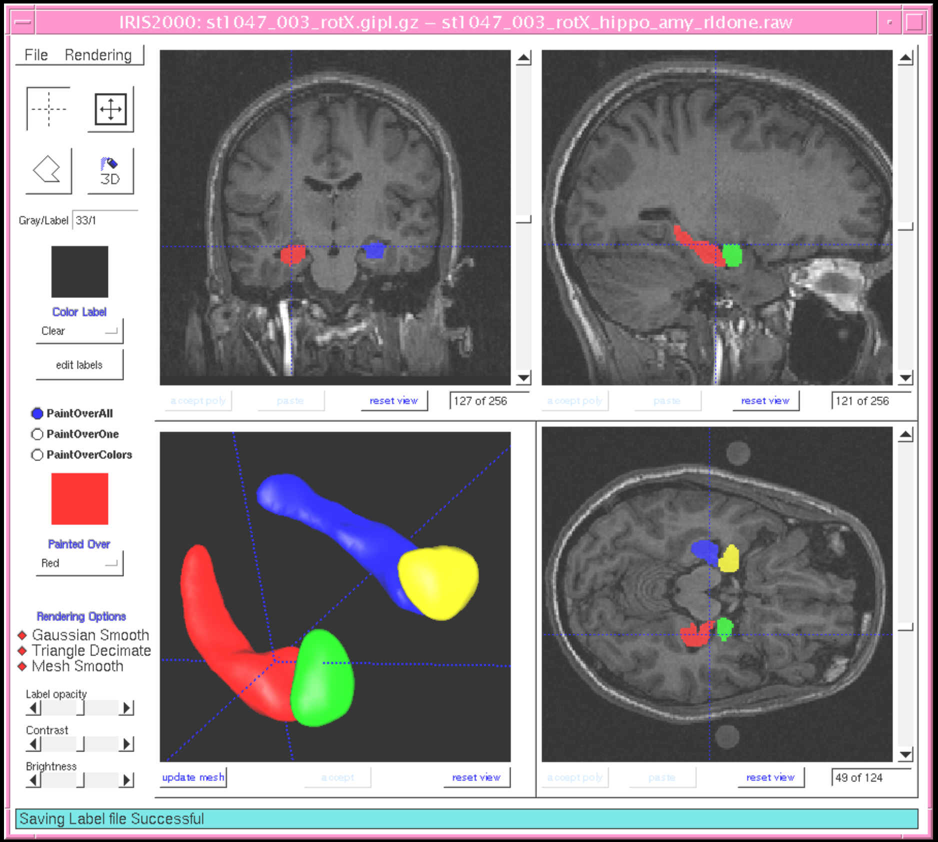
- 26 controls (age, gender matched)
- 56 schizophrenics
  - 28 treatment responsive
  - 28 treatment non-responsive

Hypothesis:

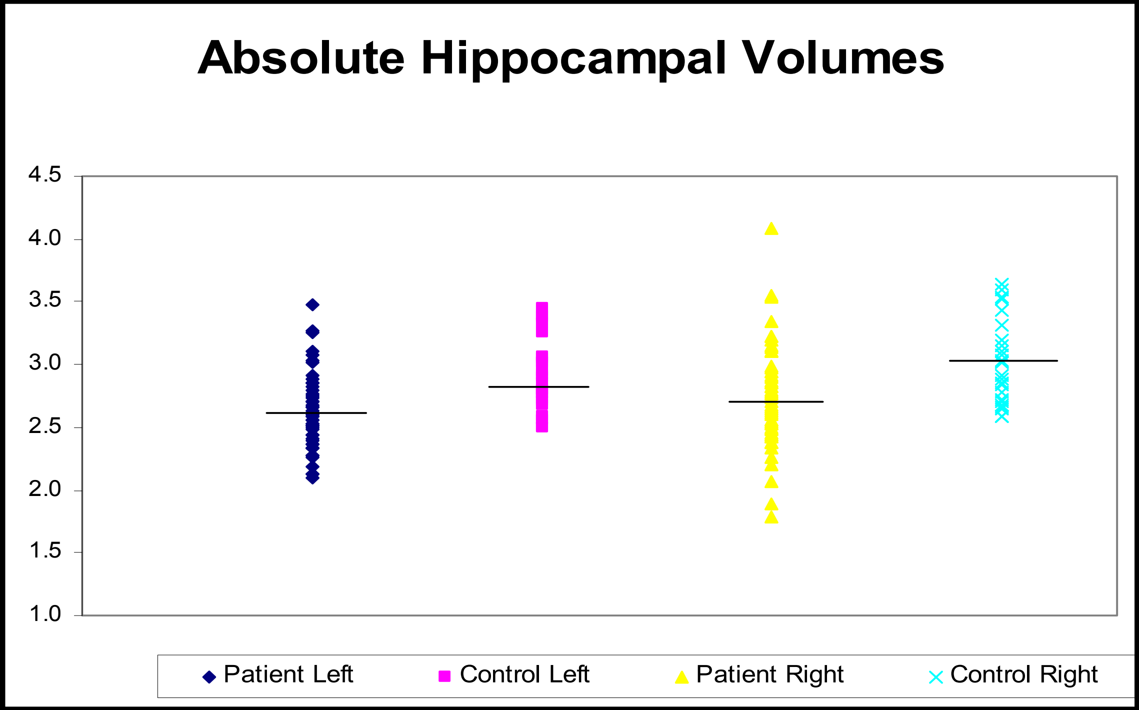
- Hippocampal morphology (size/shape) differs in SZ as compared to NCL.
- Shape more sensitive than size.
- Severity of disease (patient outcome) reflected by hippocampal morphology.

Manual Expert’s Segmentation

- IRIS: Tool for interactive image segmentation.
- Manual painting in orthogonal sections.
- 2D graphical overlay and 3D reconstruction.
- 2D/3D cursor interaction between cut-planes and 3D display.
- Hippocampus: reliability > 0.95 (intraclass corr.)

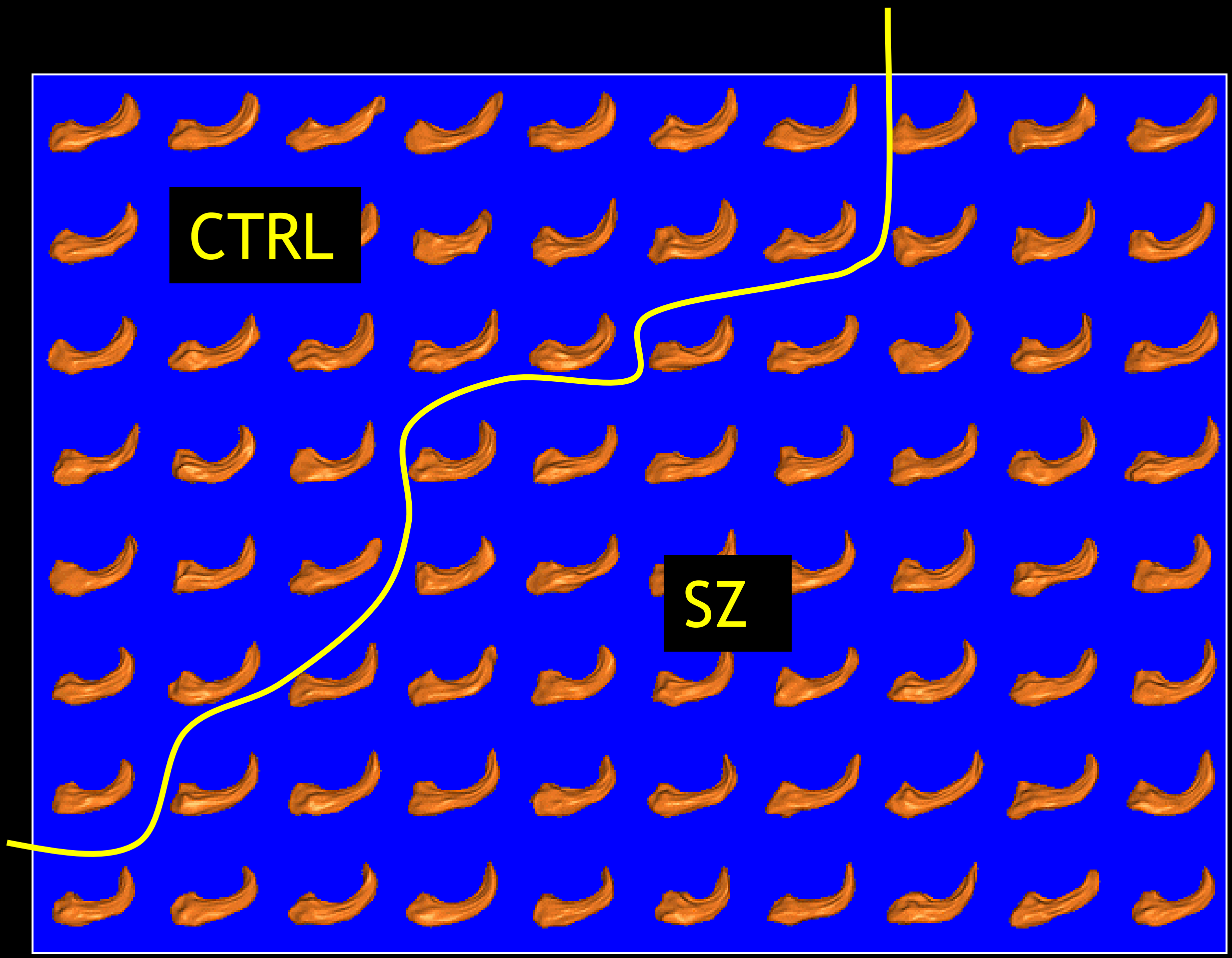


Hippocampal Volume Analysis



- Statistical Analysis (Schobel/Chakos)
  - Left smaller than right
  - SZ smaller than CTRL, both left and right
  - Variability SZ larger than CTRL

Shape Analysis Problem

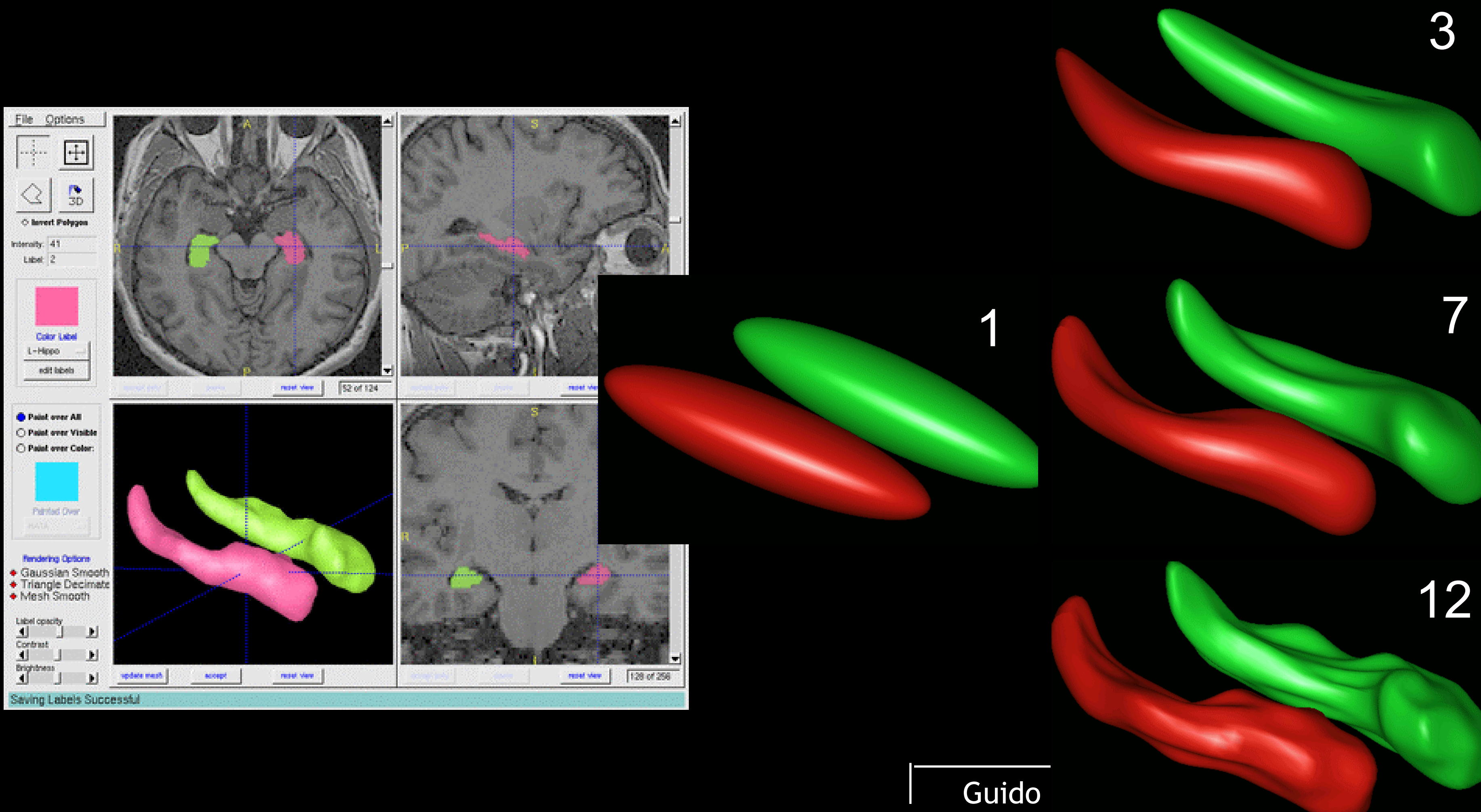


- Left hippocampus of 90 subjects
- 30 Controls
- 60 Schizophr.

? Biological variability

? Metric for measuring subtle differences

Parametrization with spherical harmonics



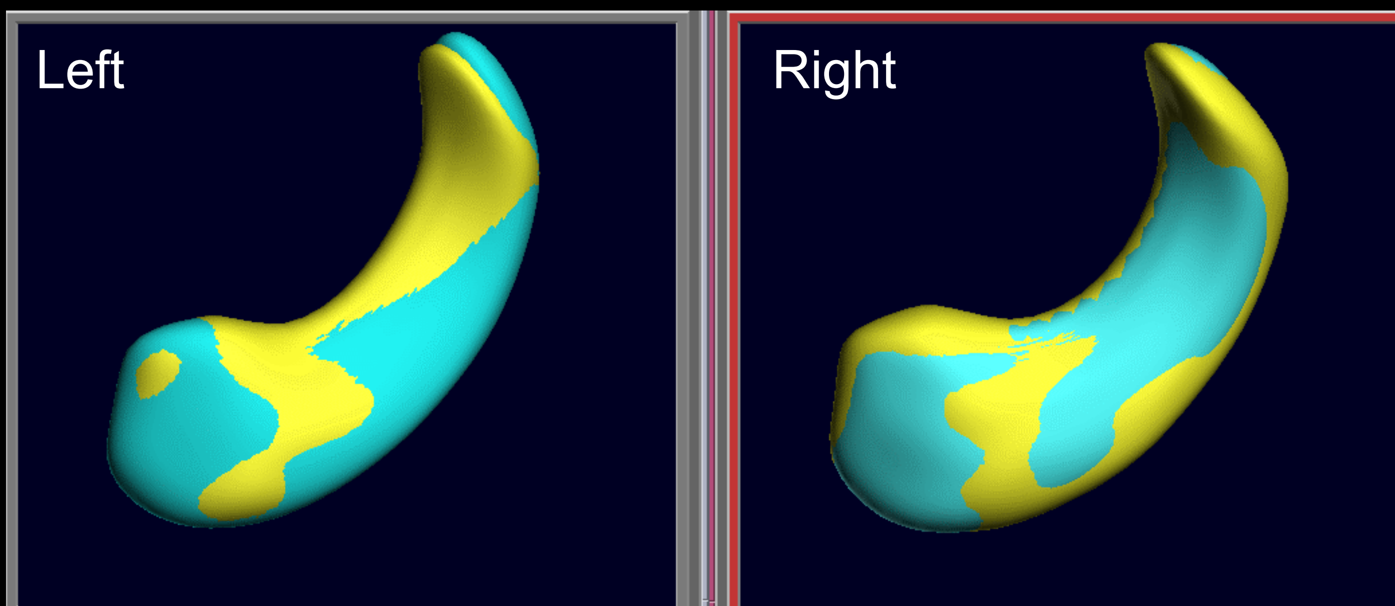
Guido

Shape Difference between CTRL and SZ shapes

Left and right hippocampus: Overlay mean shapes

cyan: SZ

yellow: CTRL



Shape Difference CTRL vs. SZ shapes

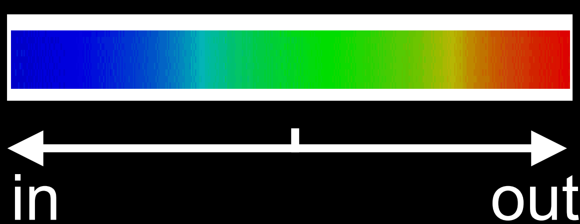
Left and right hippocampus: Surface distances between SZ and CTRL mean shapes:

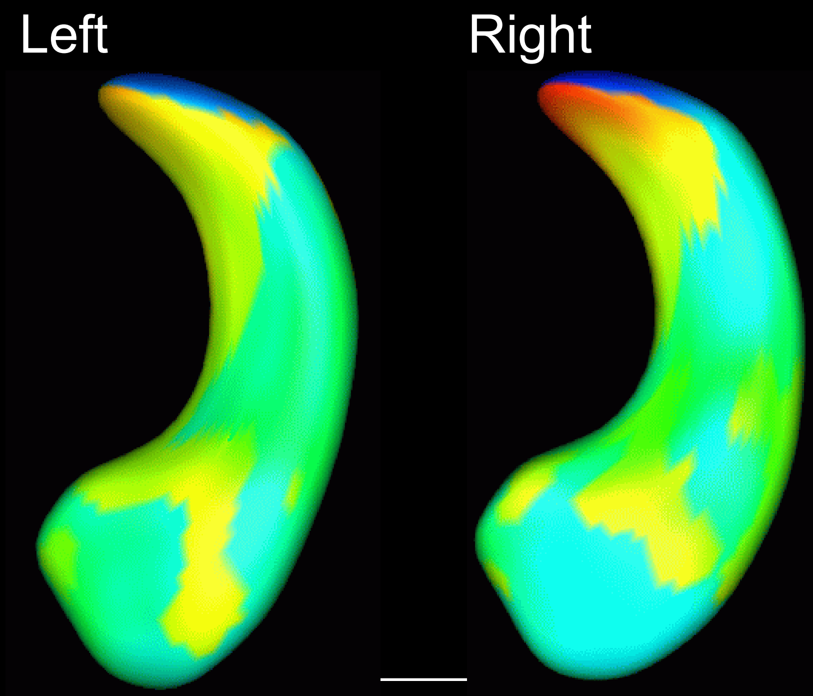
Reference shape: SZ

red/yellow: out

green: match

blue/cyan: in



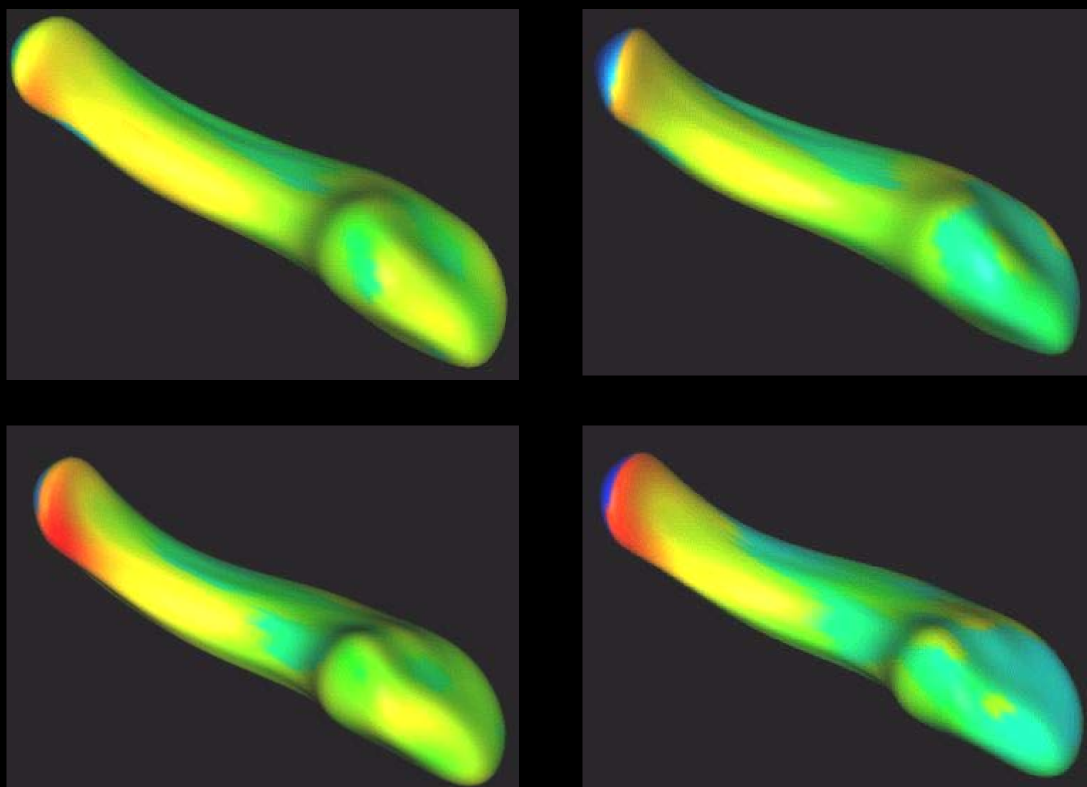


Boundary Analysis: PDM

no scaling | scaling to unit volume

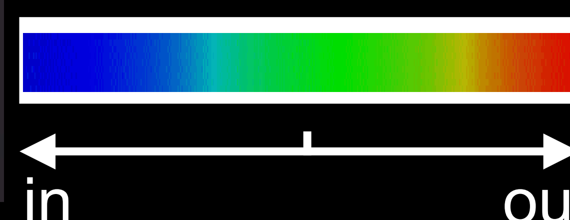
left

right



Left and right hippocampus: Comparison of mean shapes Controls-SZ

(signed distance magnitude)

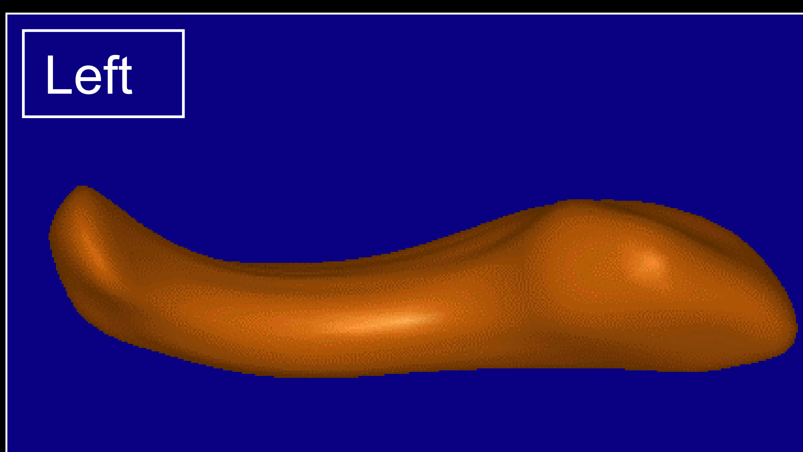


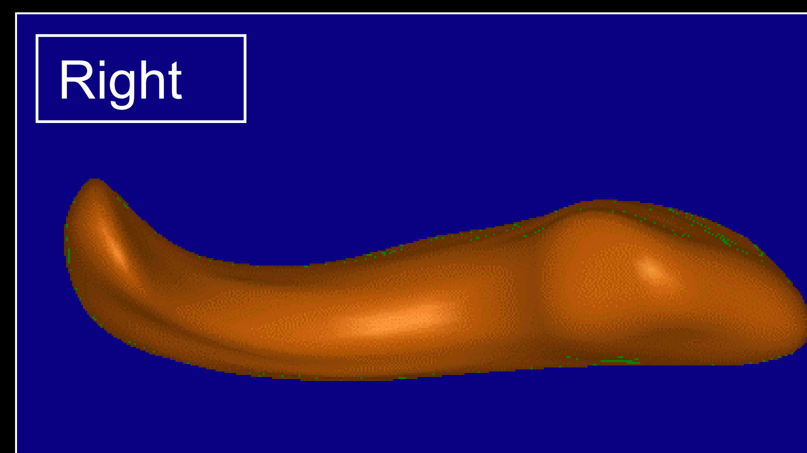
Shape change between aligned CTRL and SZ average shapes

Left and right Hippocampus, not volume normalized

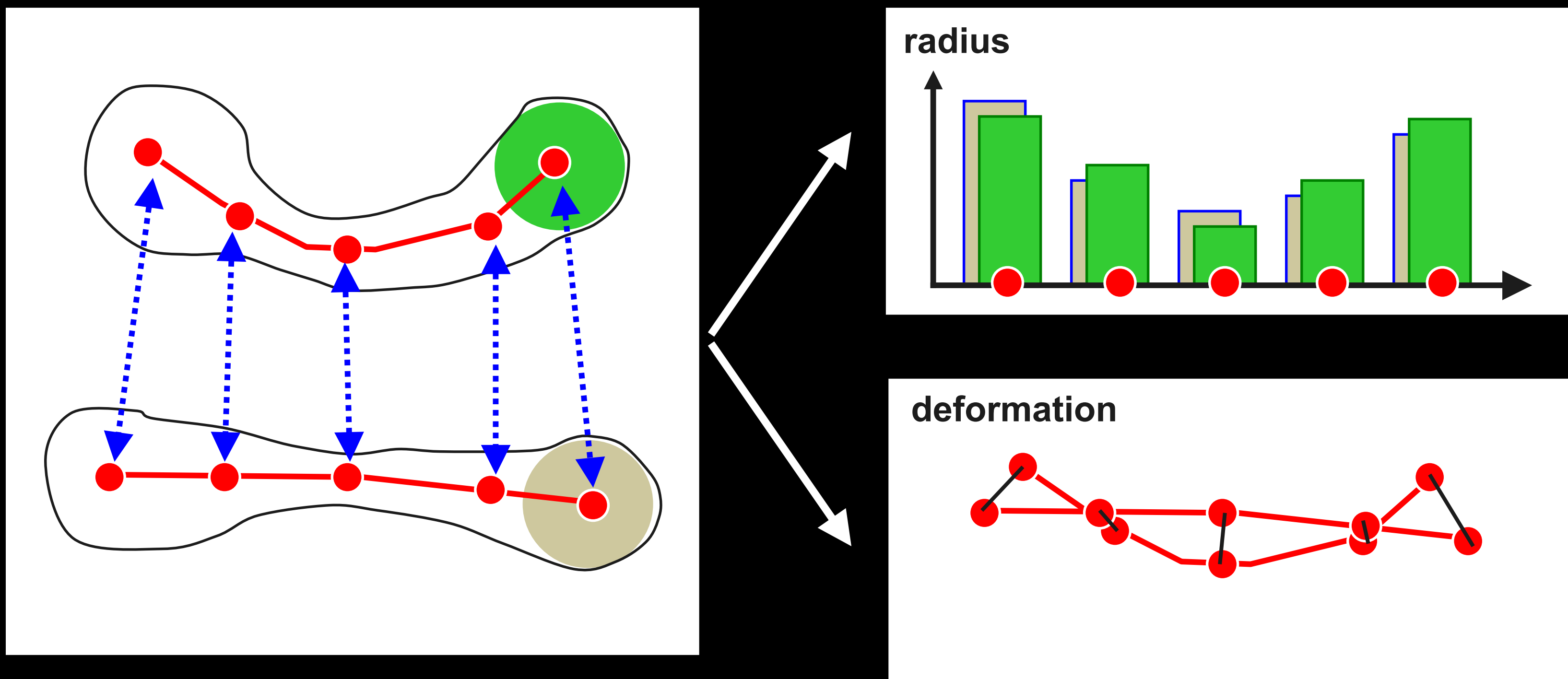
Flat tail: SZ

Curved tail: CTRL





Shape Analysis using Medial Representation



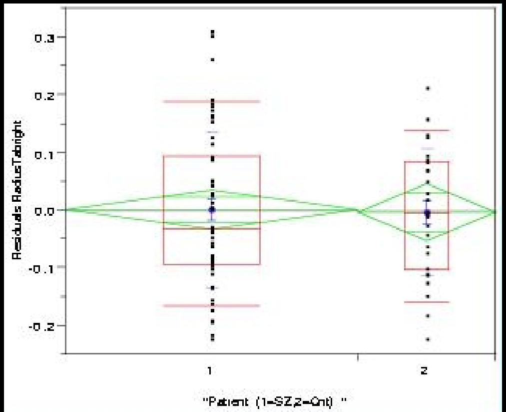
Local width differences (MA_rad): Growth, Dilation

Positional differences (MA_dist): Bending, Deformation

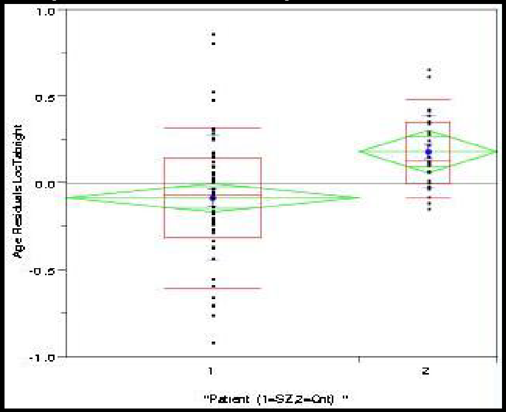
Hippocampus M-rep: Global Statistical Analysis

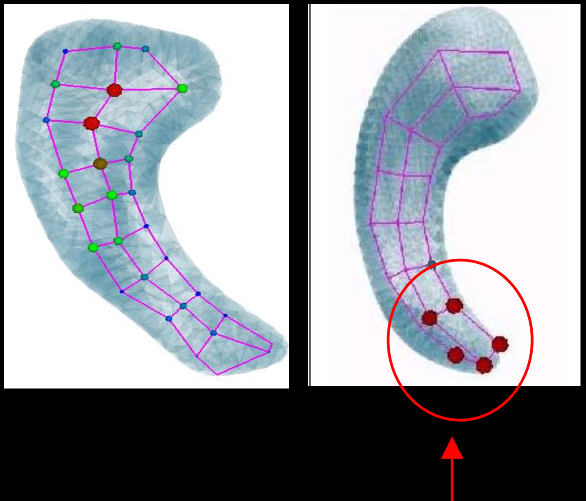
Right Hippocampus: Integrated difference to reference shape (mean template), volume normalization.

Width ($p<0.75$)



Deformation ($p<0.0001$)

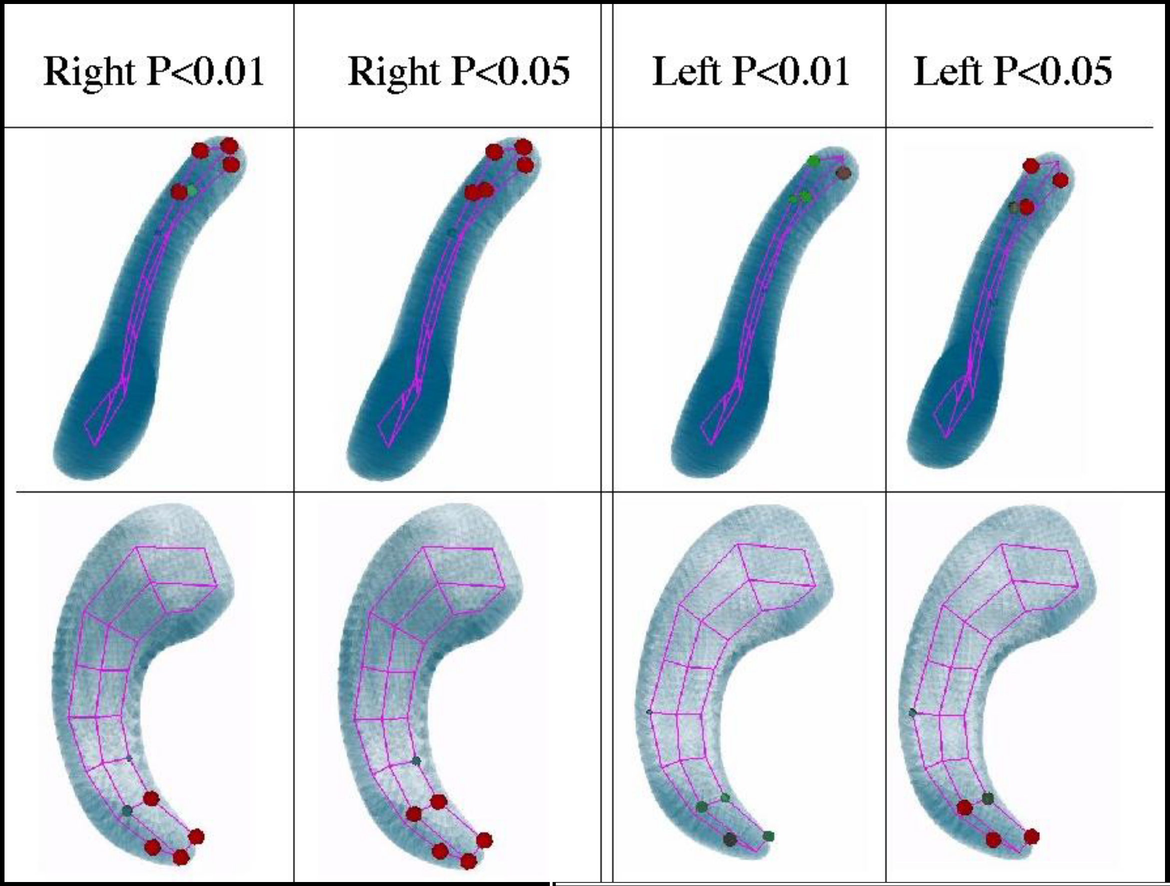




$p<0.01$

Local Statistical Tests

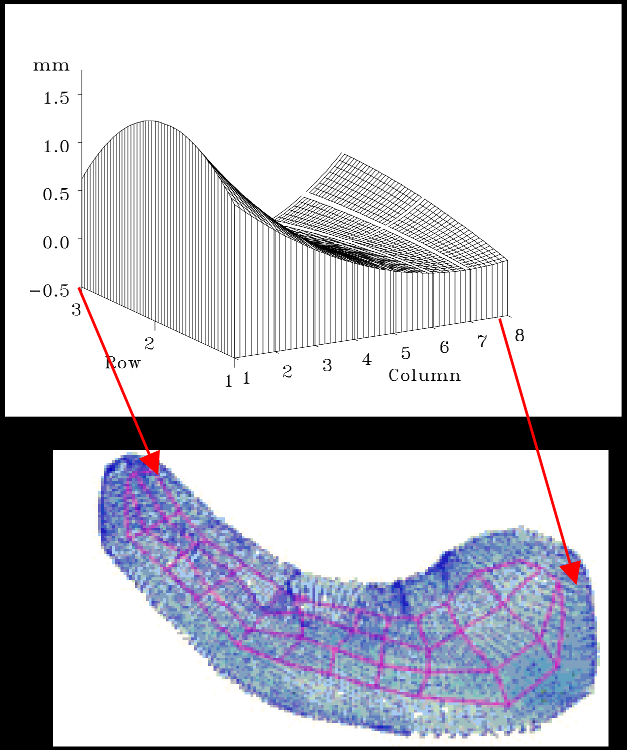
Medial representation study confirms: Hippocampal <u>tail</u> is region with significant deformation.



Statistical Analysis of M-rep representations

- *Work in progress Keith Muller, UNC Chapel Hill
- systematic embedding of interaction of age, duration of illness and drug type into local statistical analysis
- correction for multiple tests
- encouraging results on Schizophrenia hippocamal study

Difference in hippocampus shape between SZ and CNTRL as measured by M-rep distance



*Repeated measures ANOVA, cast as a General Linear Multivariate Model, as in Muller, LaVange, Ramey, and Ramey (1992, JASA). Exploratory analysis included considering both the "UNIREP" Geisser-Greenhouse test and the "MULTIREP" Wilks test.

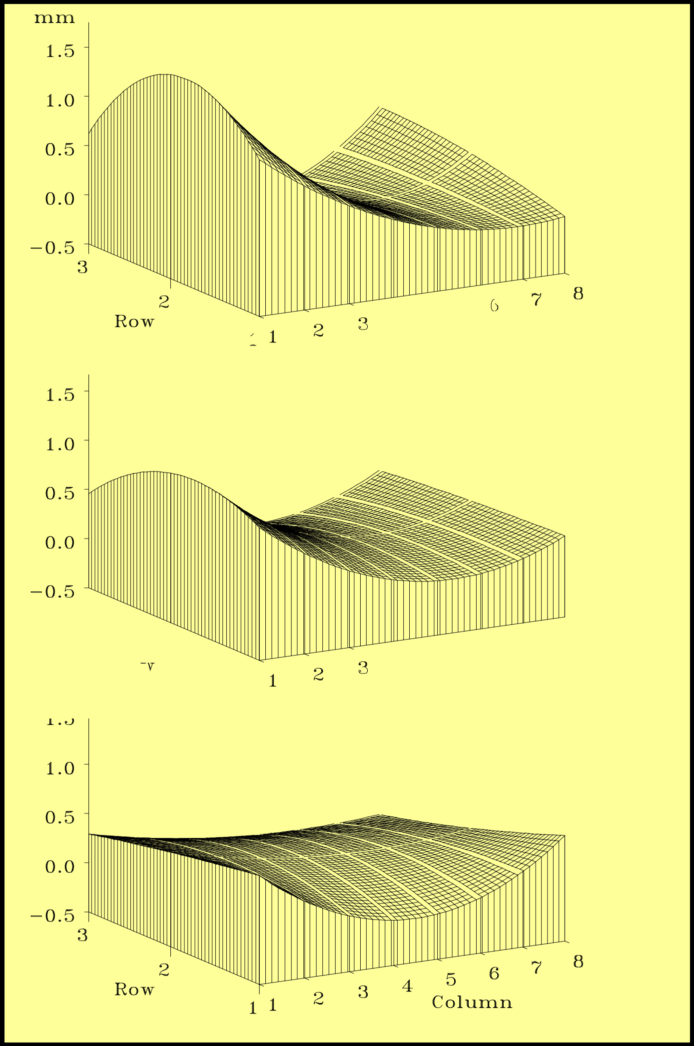
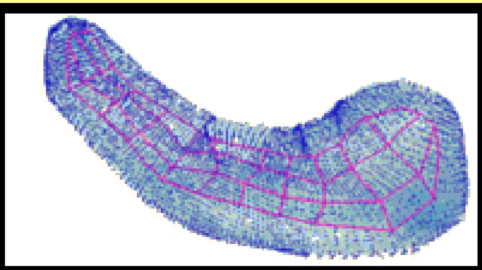


Figure C : Pt-Control Distance Difference at Age 40

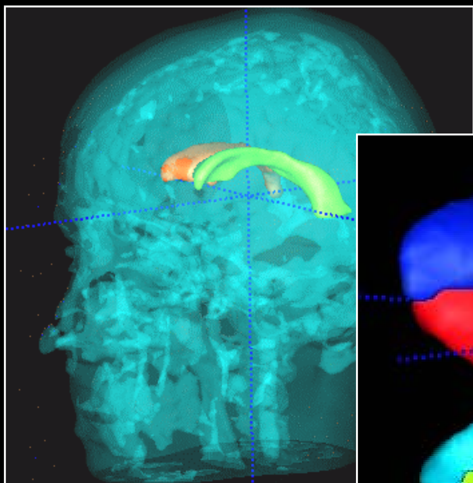
Figure B : Pt-Control Distance Difference at Age 30

Figure A : Pt-Control Distance Difference at Age 20

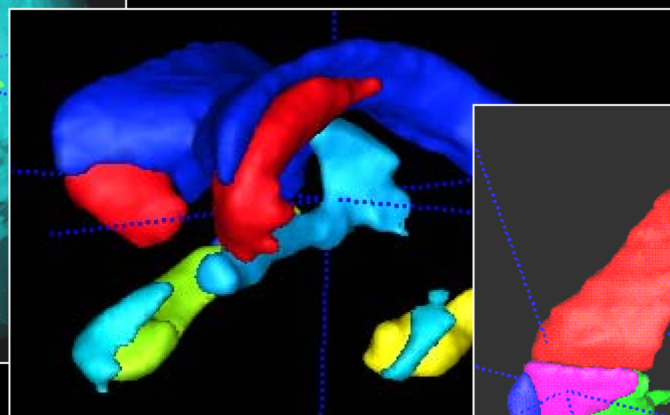


M-rep 3x8 mesh

Goal: Multi-Scale Representation: Figurally relevant spatial scale levels

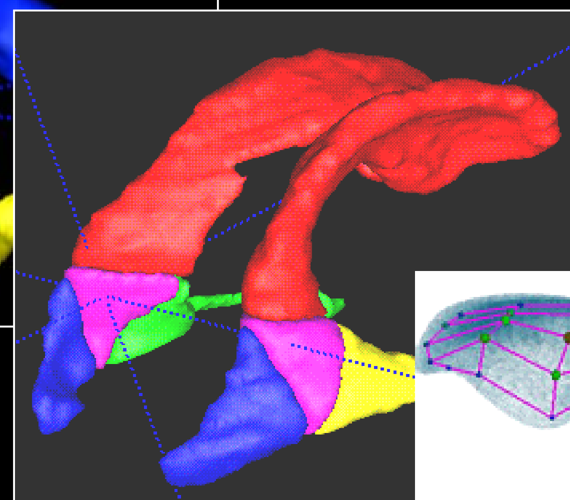


Whole Body/Head



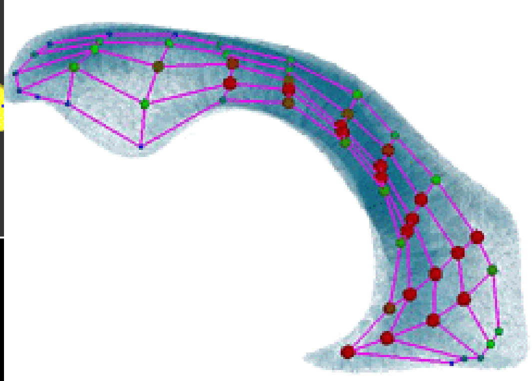
Multiple Objects

(lateral ventricles, 3rd ventricle, caudates, hippocampi, temporal horns)



Individual Object: Multipe Figures:

ventricles: lateral, occipital, temporal, atrium



Individual Figure: Medial Primitives, coarse to fine sampling