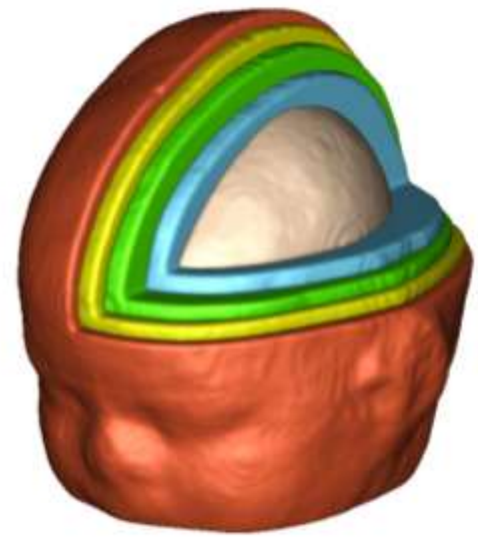
Spatiotemporal Analysis of Brain Development and Disease Progression



Guido Gerig

Scientific Computing and Imaging Institute (SCI), University of Utah

COLLÈGE DE FRANCE 1530

THE BRAIN INSTITUTE THE UNIVERSITY OF UTAH

SCI INSTITUTE

Collège de France

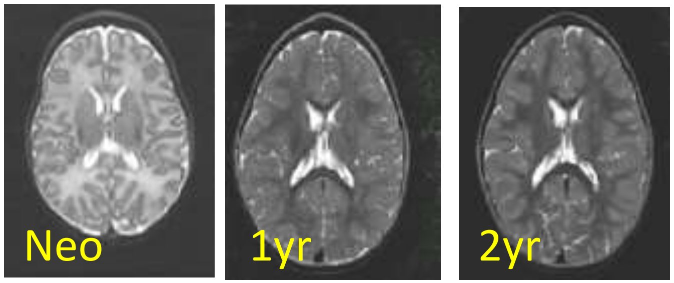
Its motto is *Docet omnia:*

"All things are taught".

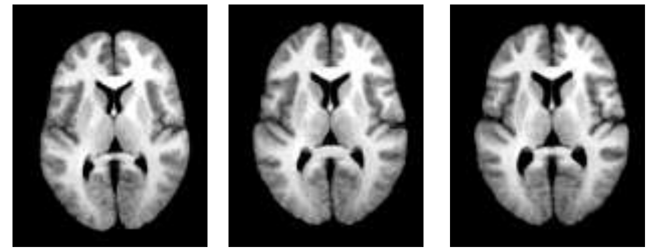
Ayache Symposium: From Medical Images to Computational Medicine

Longitudinal/Serial Image Data

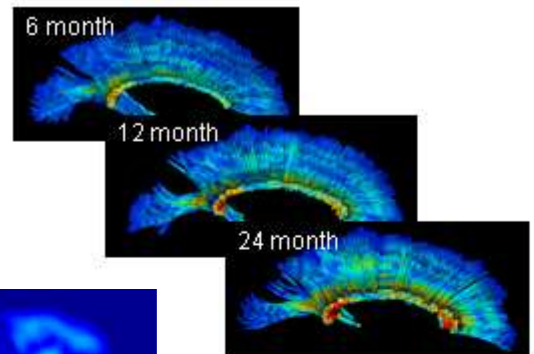
Pediatrics: Brain Growth



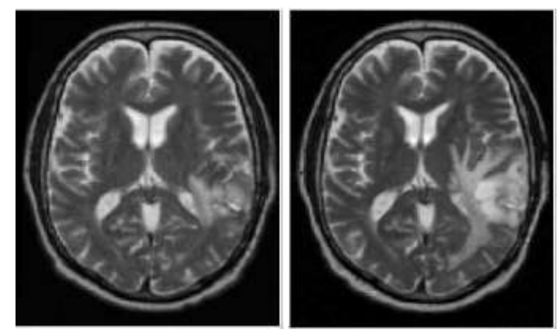
Aging / Neurodegeneration



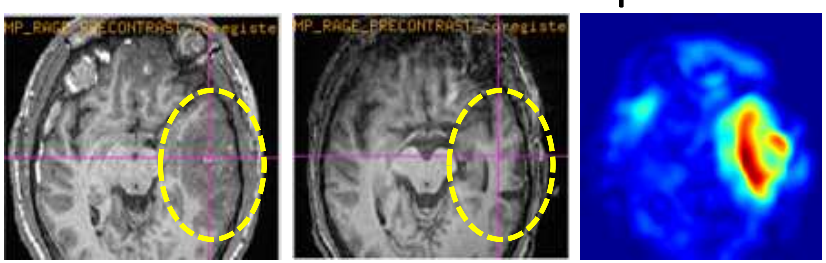
WM Maturation



Tumor Growth



Trauma: Baseline – Follow-up



- Image analysis technology for 4-D data is lagging behind acquisition
- Often: individual time-point analysis, ignores causality of repeated imaging

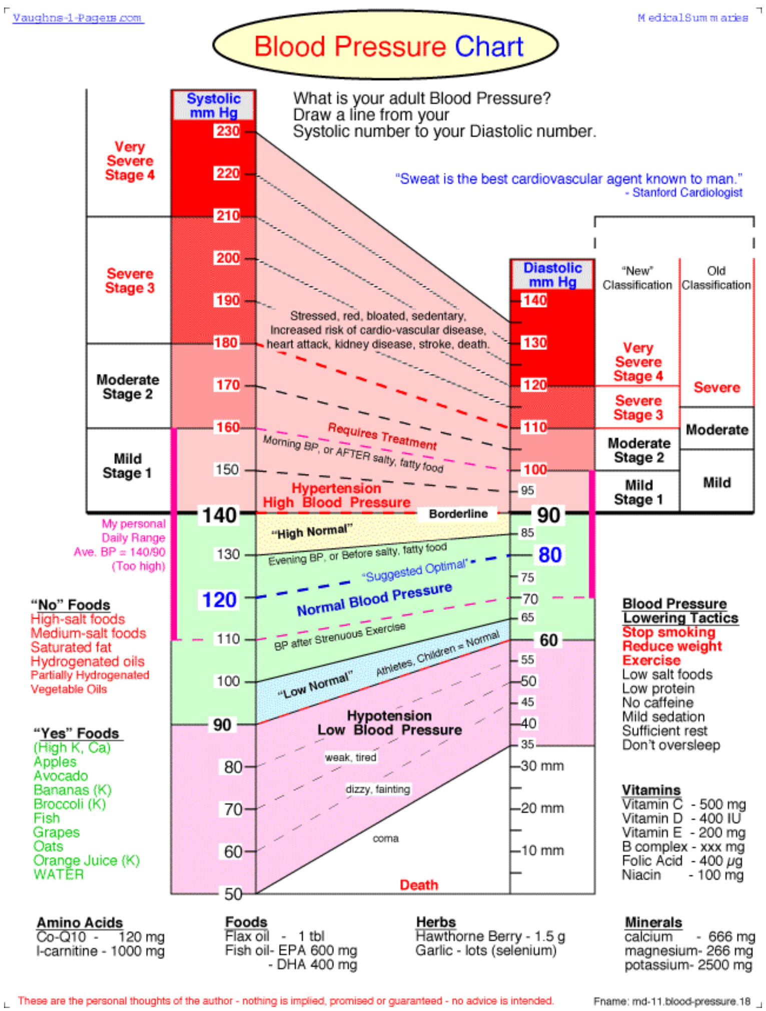
Spatiotemporal Modeling: Natural Task in Clinical Reasoning

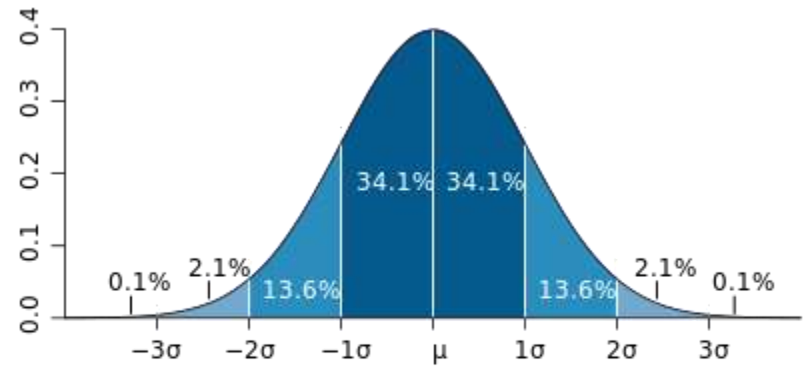
Motivation:

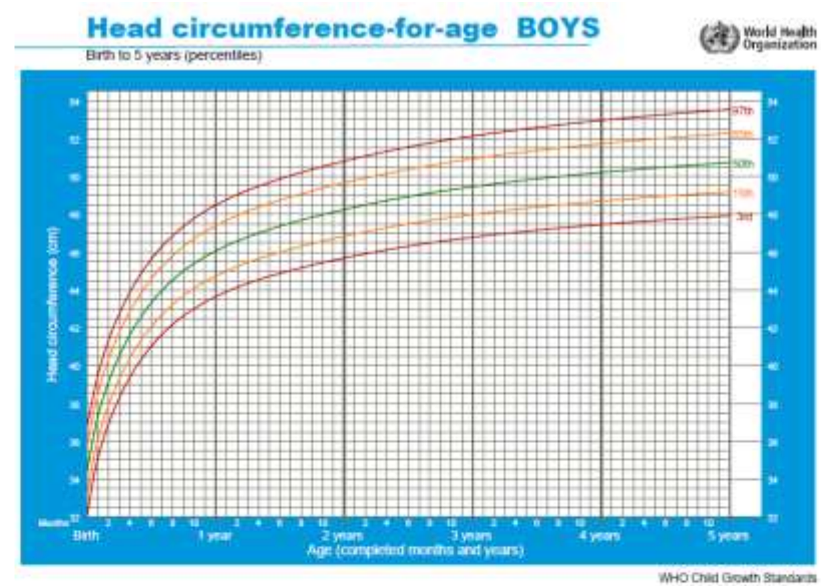
- Development, degeneration, monitoring therapeutic interventions are dynamic processes.
- Clinical terminology:
  - Departure from typical development, deviation from healthy
  - Typical but delayed growth patterns, catch-up, atypical development
  - Analysis of recovery for a patient
  - Prediction of onset of clinical symptoms
  - Monitoring of efficacy of treatment
- Personalized health care: Individual trajectories compared to expected “norm”.

→ **Focus on longitudinal design & longitudinal analysis**

Normative Data

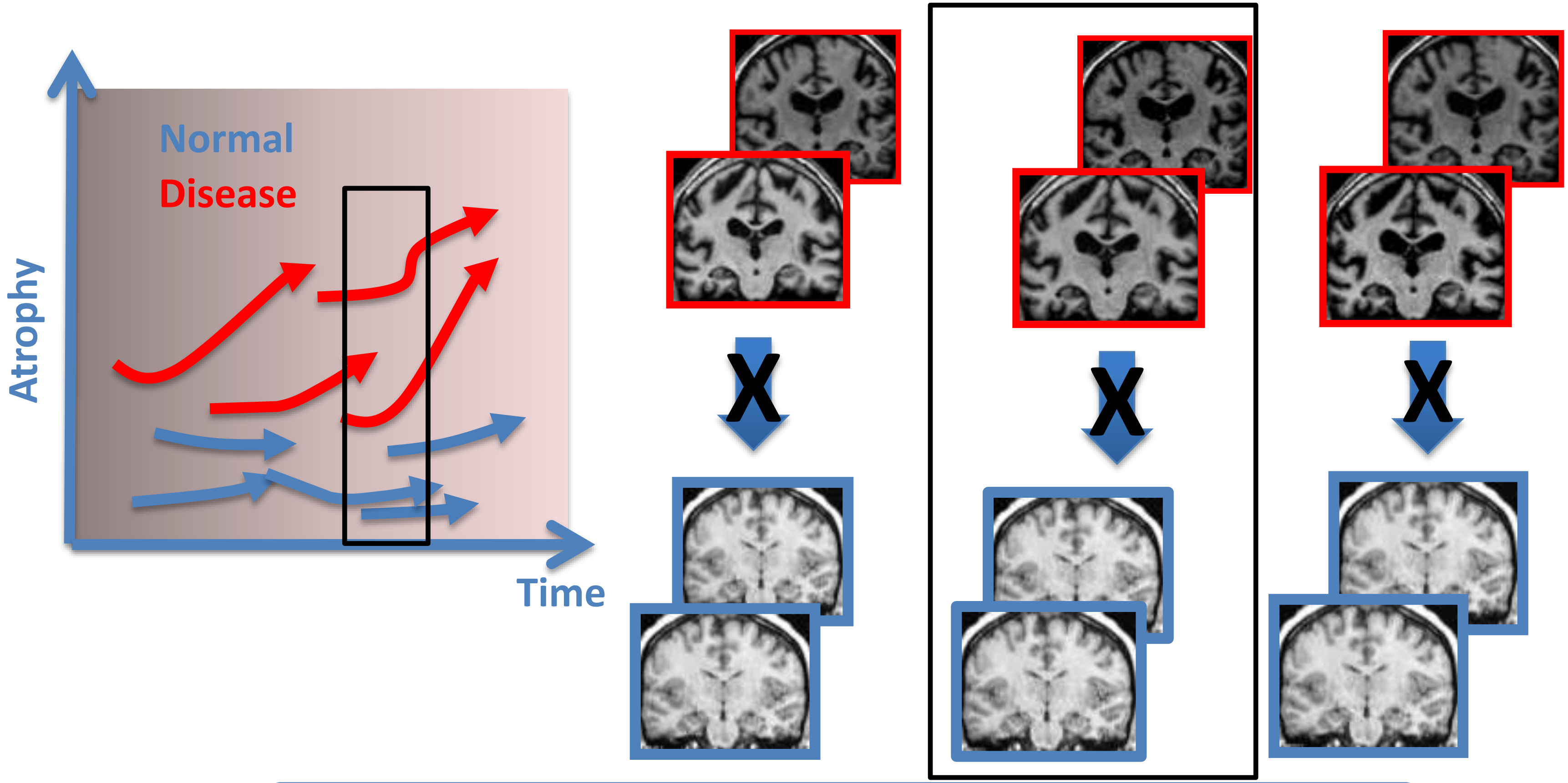






Spatiotemporal Morphometry

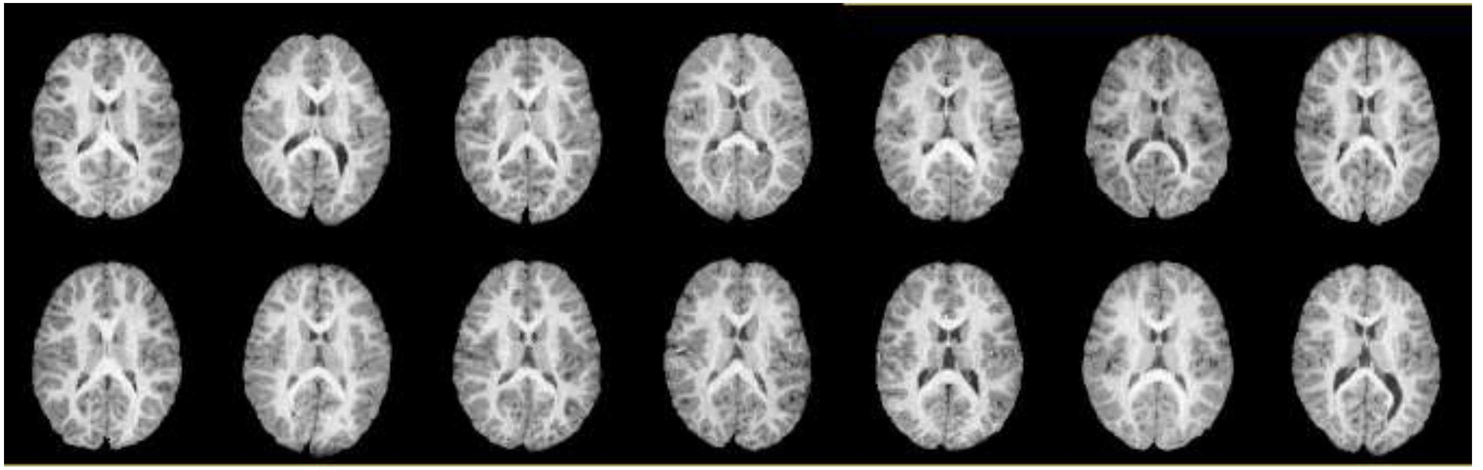
Cross-sectional paradigm

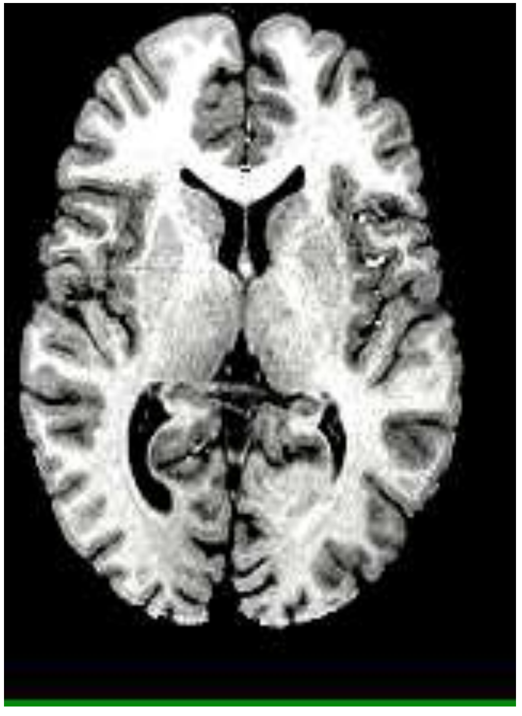


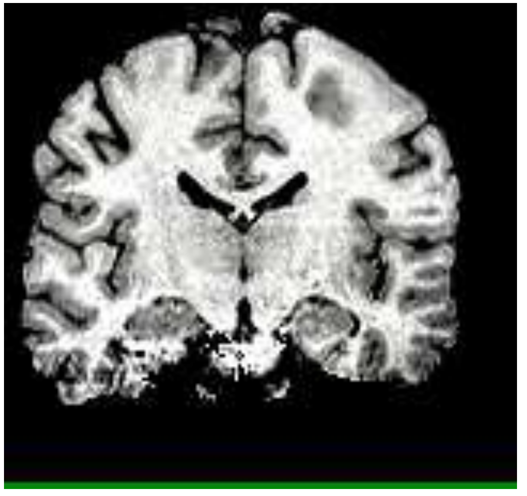
Inter-subject variability >> Intra-subject changes

Courtesy of Lorenzi & Pennec, INRIA

Population Variability





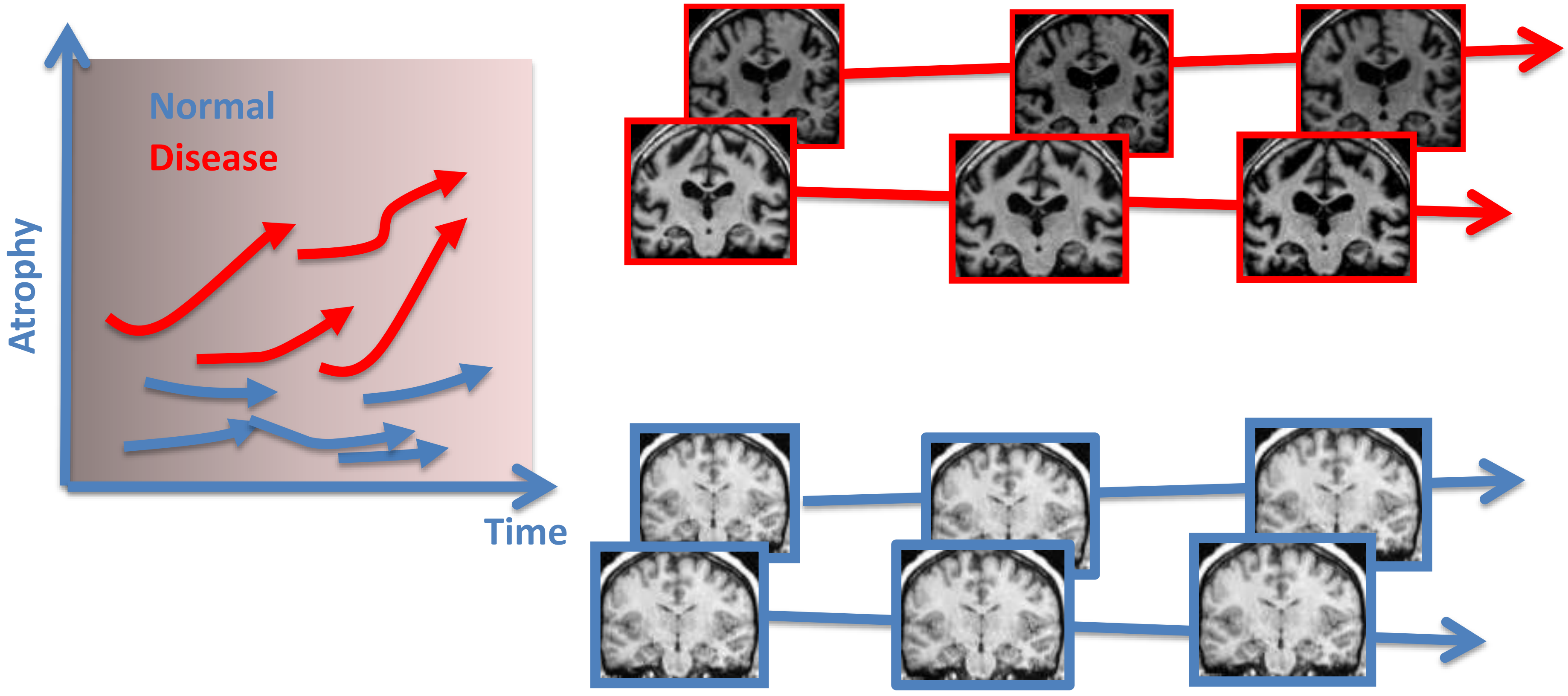


Normal Aging (50 subjects, 20 to 70 years)

Courtesy S. Joshi

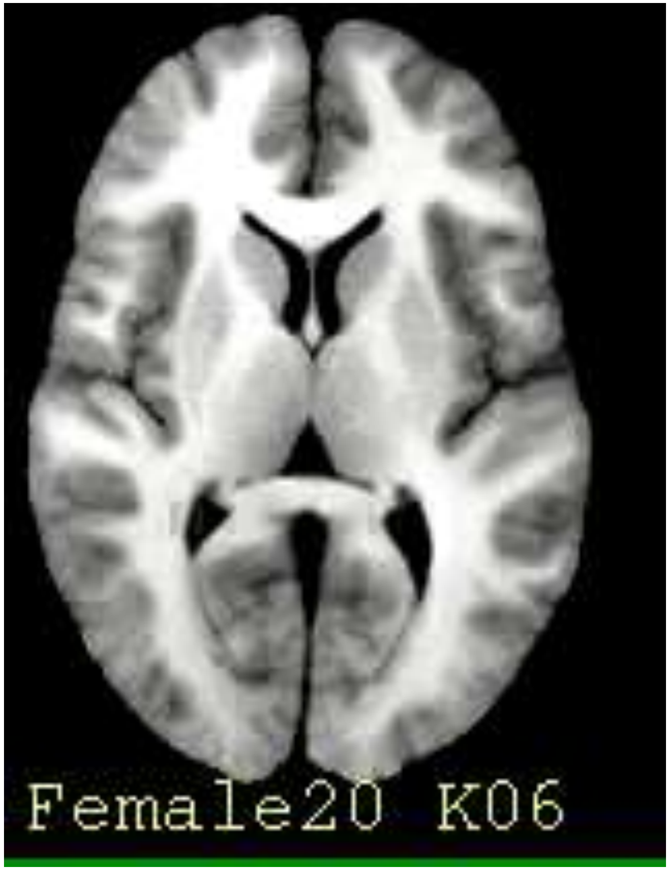
Spatiotemporal Morphometry

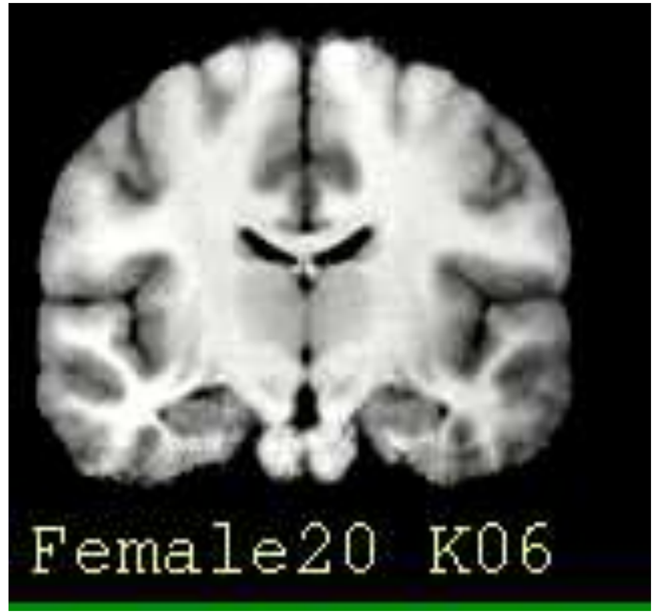
Longitudinal paradigm



courtesy of Lorenzi & Pennec, INRIA

Aging Brain via Population Shape: Manifold Kernel Regression





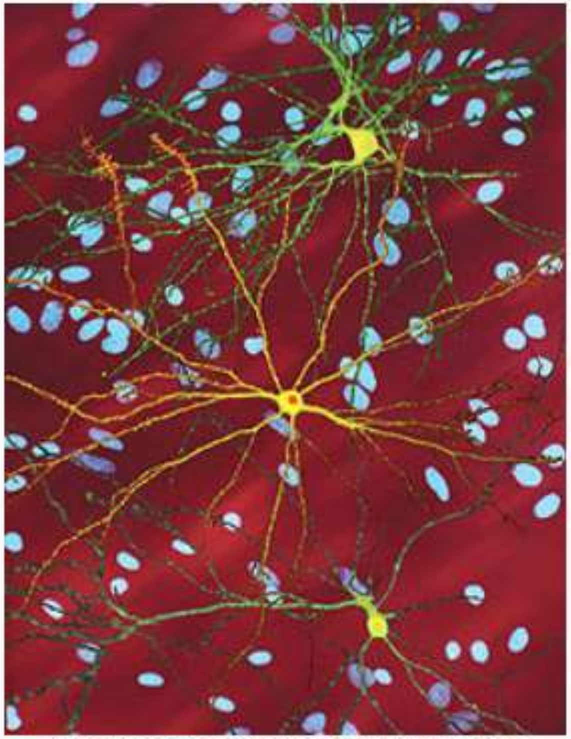
- B. Davis, S. Joshi, T. Fletcher, E. Bullitt, (UNC/Utah)
- D. Marr Prize, ICCV’07

Clinical Driving Problem: Huntington's Disease (HD)

- Neurodegenerative genetic disorder, hereditary disease.
- Causes severe debilitating symptoms by middle age.
- All affected individuals have the same root cause: Huntingtin gene.
- **NIH: PREDICT-HD Study**: Define neurobiological **progression** of HD in at-risk individuals so that therapies can be performed before symptoms reach a debilitating stage.
- Collaboration with U of Iowa via NA-MIC.

Huntington's disease

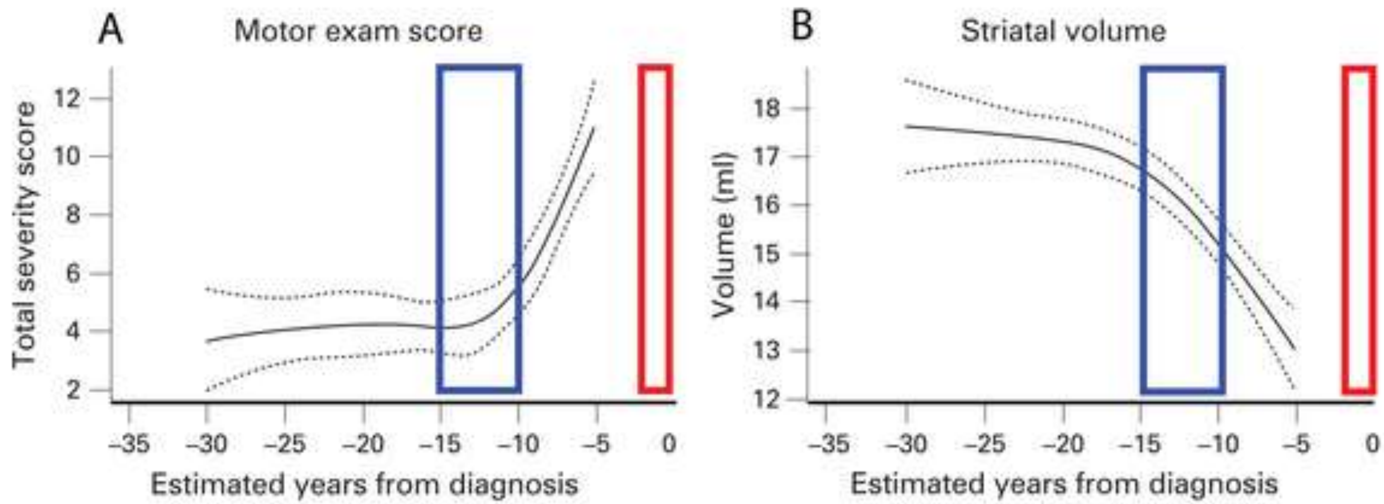
Classification and external resources



A microscope image of Medium spiny neurons (yellow) with nuclear inclusions (orange), which occur as part of the disease process, image width 360 µm

National Alliance for Medical Image Computing
A National Center for Biomedical Computing
Funded under the NIH Roadmap Initiative

PREDICT-HD



Relationship between estimated years to diagnosis of Huntington's disease and motor exam score (A) and striatal volumes (B).
Red indicates most likely time of diagnosis. Blue line is proposed time period when interventional therapies would have greatest impact.

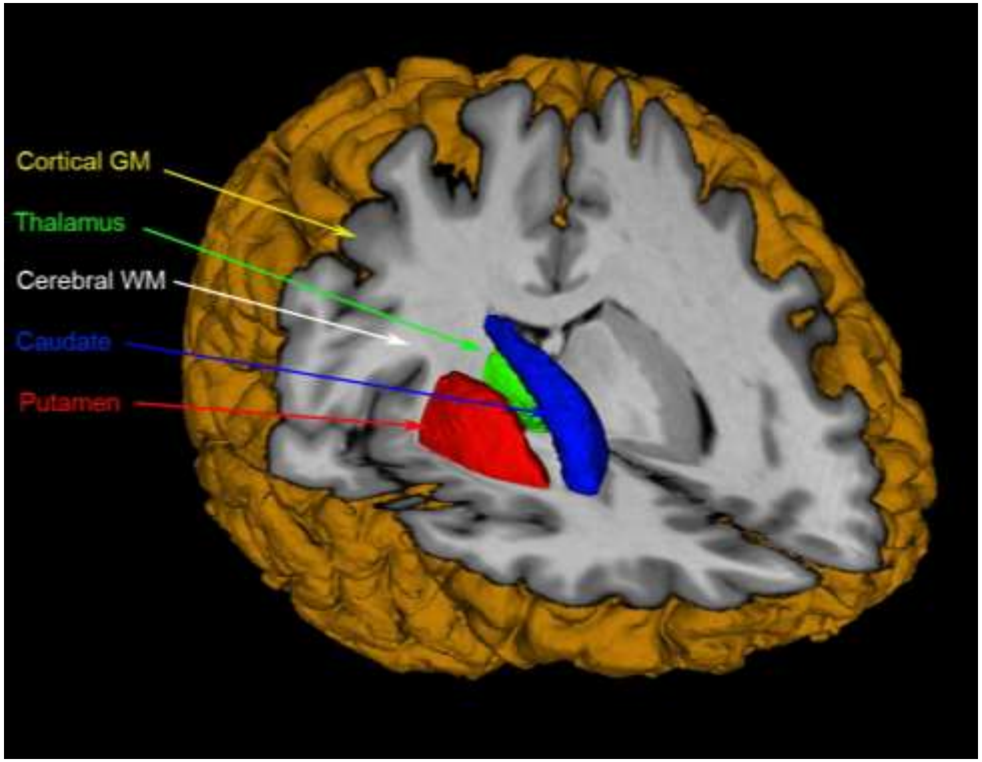
→ PREDICT Study: Longitudinal imaging study (3-5 scans 2yr intervals).

Courtesy Hans Johnsen, Jane Paulsen, IOWA

PREDICT-HD

Search for noninvasive biomarker with imaging…

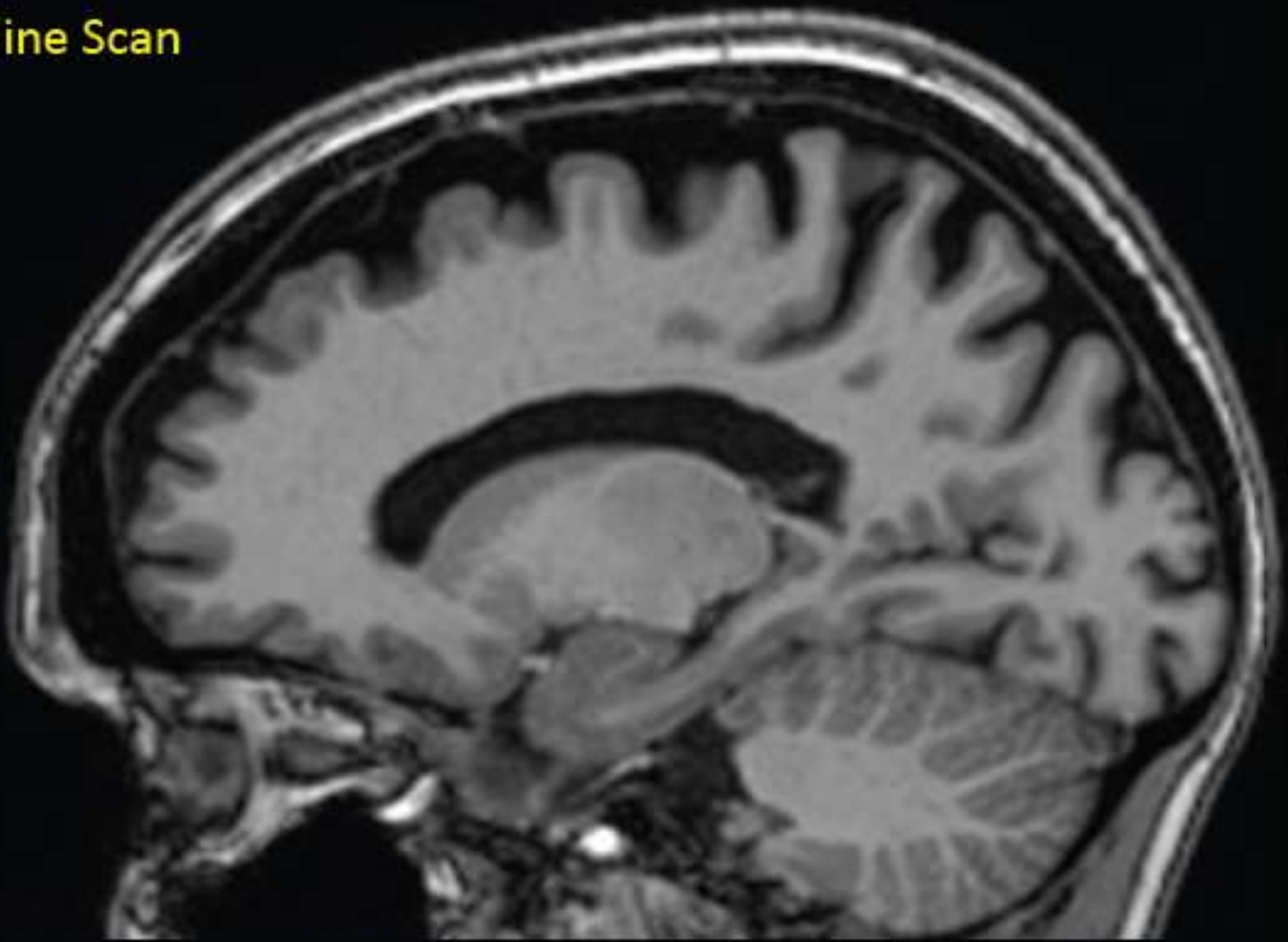
- Symptomatic HD imaging findings
  - Atrophied caudate and putamen
  - Disproportionate loss of white matter
- Prodromal HD imaging findings
  - Striatal atrophy correlates with:
    - Neurological impairment
    - Poorer performance on cognitive assessments
    - Years to motor symptom onset



Courtesy Jane Paulsen, Hans Johnson, U-Iowa

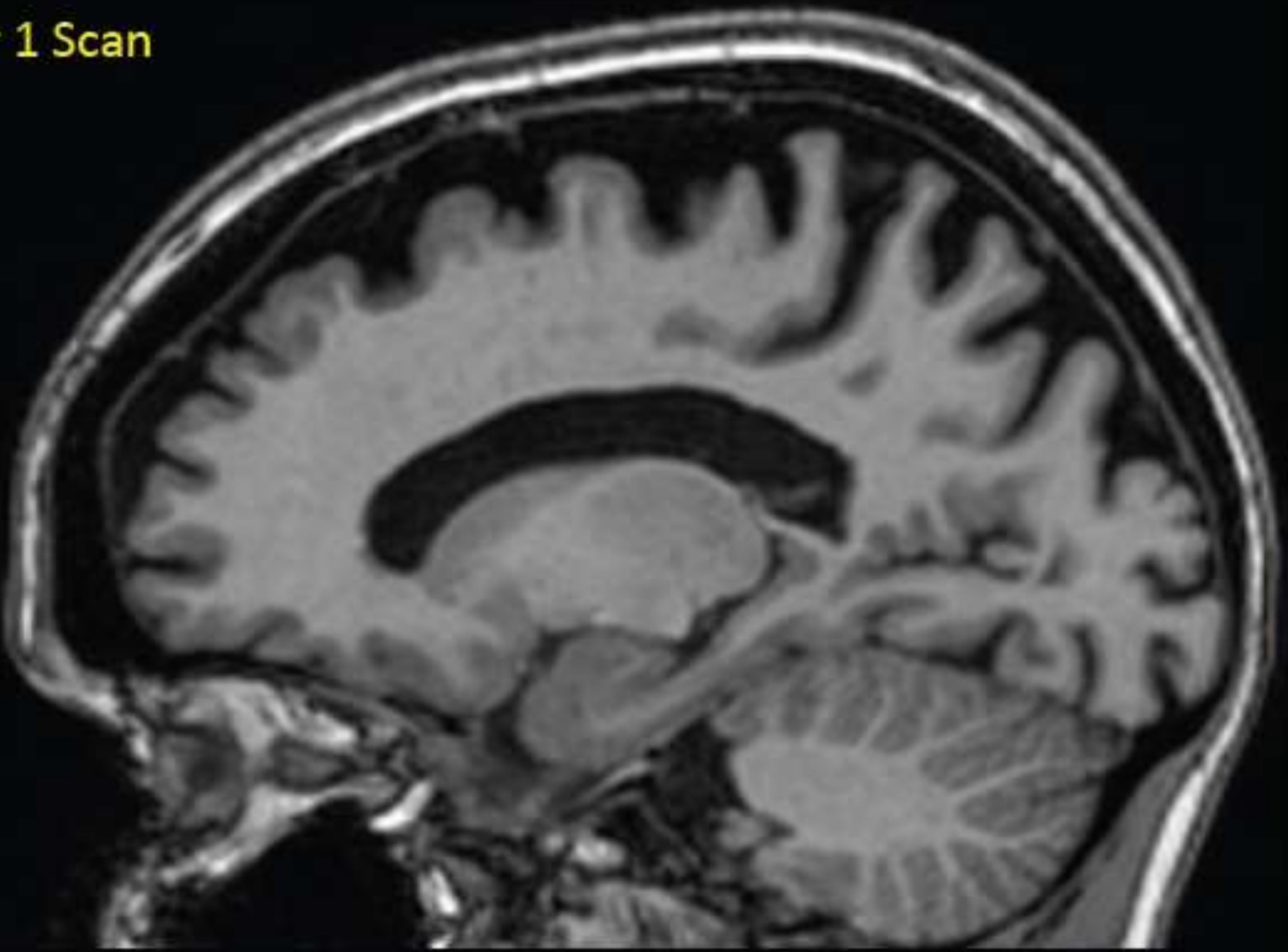
TRACK-HD Stage 1 HD Subject

Baseline Scan

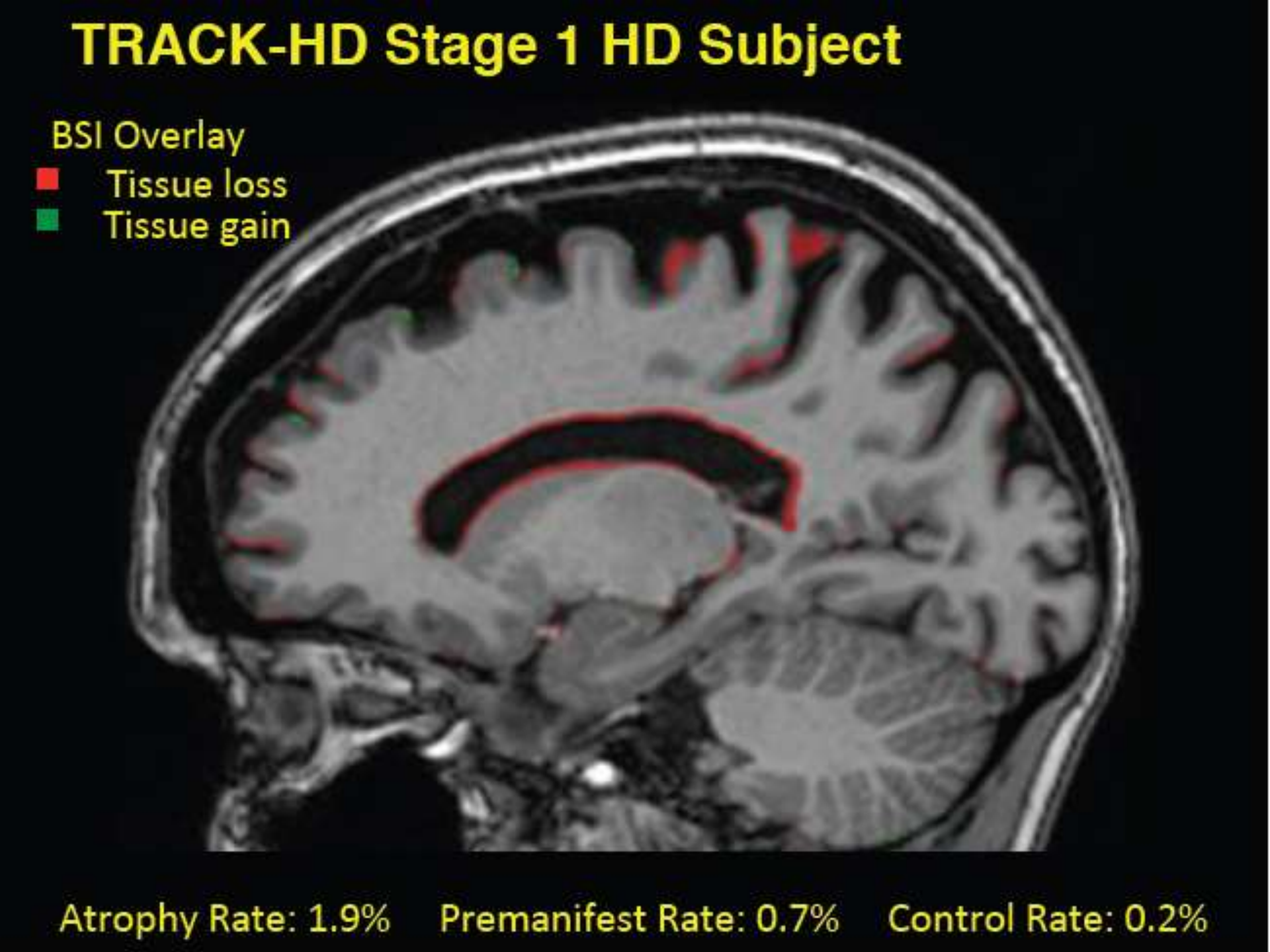


Courtesy Hans Johnsen, Jane Paulsen, IOWA

TRACK-HD Stage 1 HD Subject



Courtesy Hans Johnsen, Jane Paulsen, IOWA


TRACK-HD Stage 1 HD Subject
BSI Overlay
Tissue loss
Tissue gain
Atrophy Rate: 1.9%
Premanifest Rate: 0.7%
Control Rate: 0.2%

Clinical Driving Problem: Understanding Early Development

Brain Development in High Risk Children

- Understanding rate and variability of normal development
- Detect differences from typical development (autism, drug addiction, alcohol)
- Early diagnosis → early therapy → better life quality and future for infants and families

Early Brain Development Studies

- John Gilmore, M.D.
  Principal Investigator
- Studies
- Investigators
- Image Analysis
- Progress/Publications
- Training Opportunities
- Links
- Contact Us

EDBS HOME

Early Brain Development Studies

Normal Controls

Twins

Mild Ventriculomegaly (MVM) (Brain)

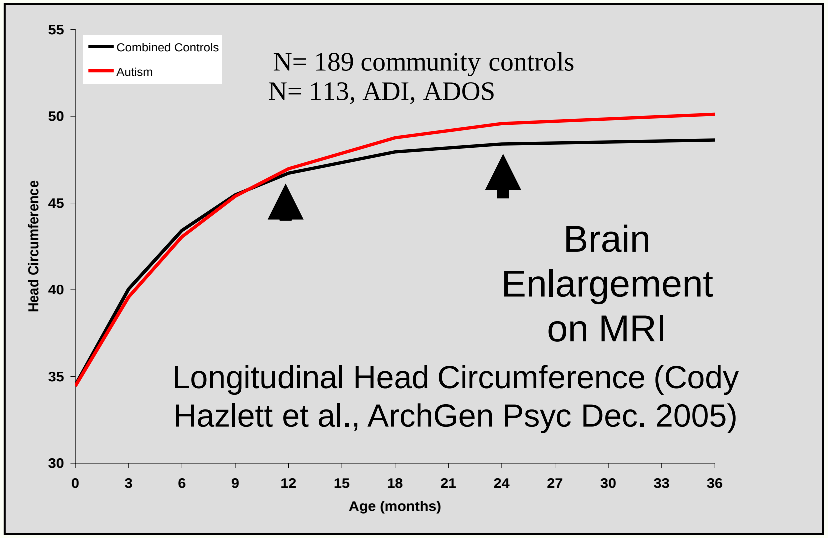
Babies of Mothers with Schizophrenia

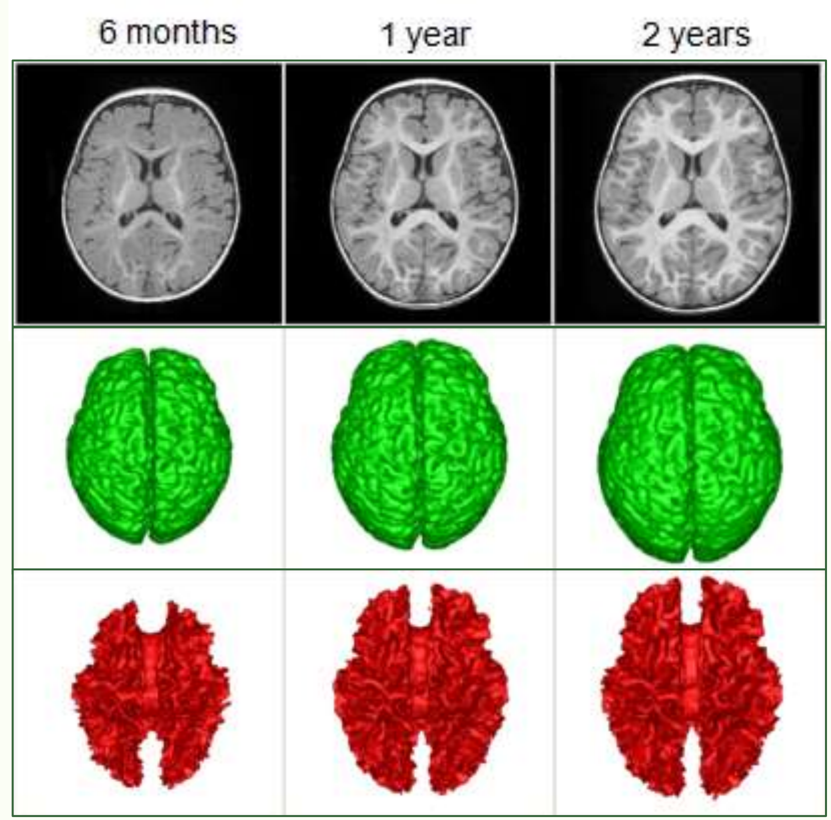
Offsprings of cocaine-addicted mothers

Neonatal Brain Development in High Risk Children (J. H. Gilmore, MD)

- Understanding rate and variability of normal development
- Detect differences from typical development
- Early diagnosis → early therapy → help families

Autism: Longitudinal Infant Neuroimaging Study





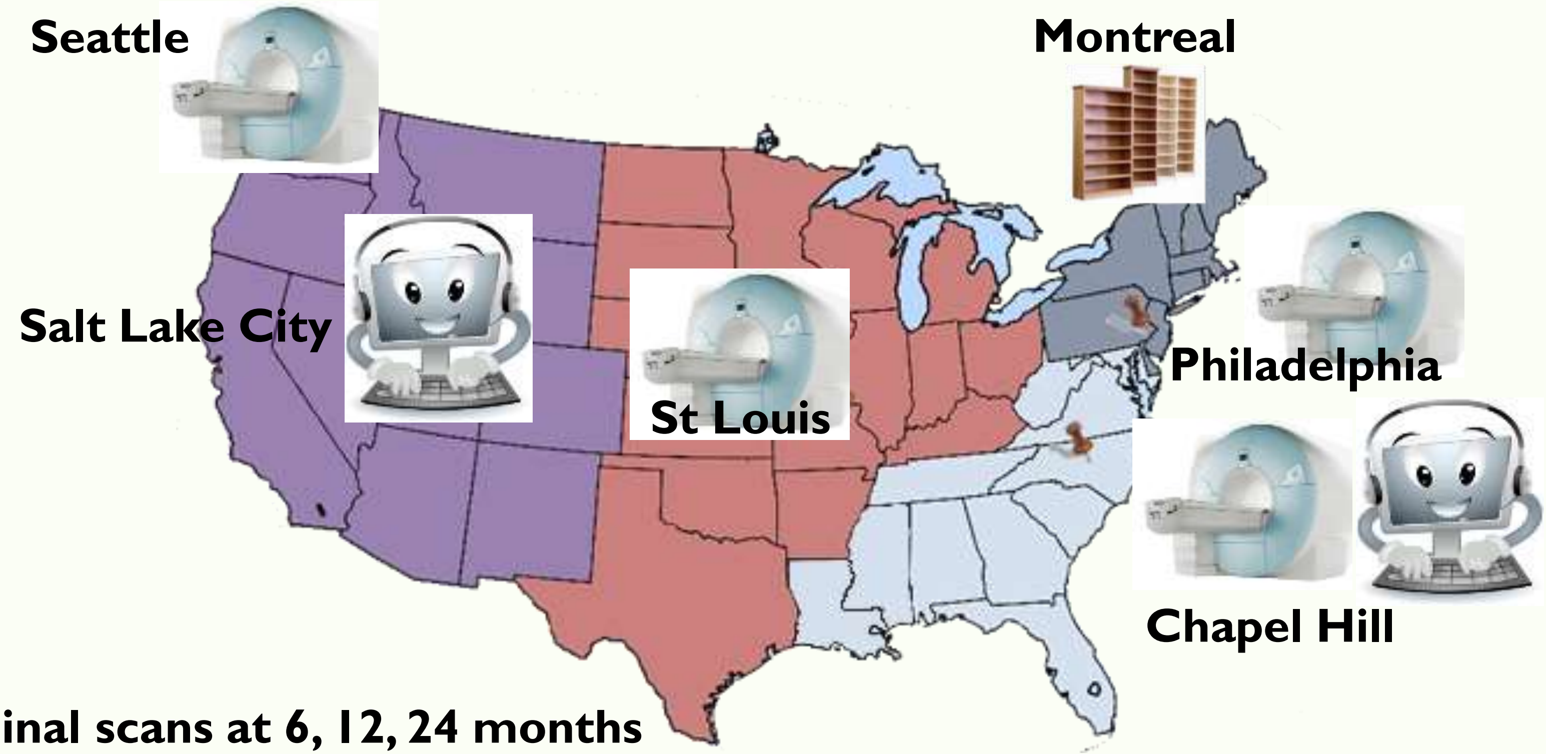
Brain enlargement in autism starts at year 1.

Why? What? Effect?

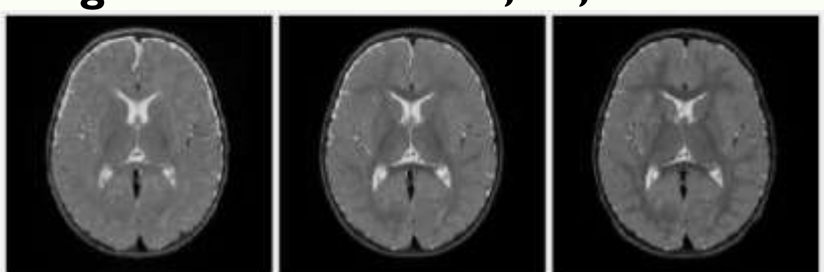
Autism-Centers-Excell.-IBIS NIH Study:

- UNC, McGill, Seattle, WU, CHOP, Utah
- Longitudinal MRI/DTI study, >1500 MRI/DTI

Better understanding → Early intervention to improve outcome



Longitudinal scans at 6, 12, 24 months

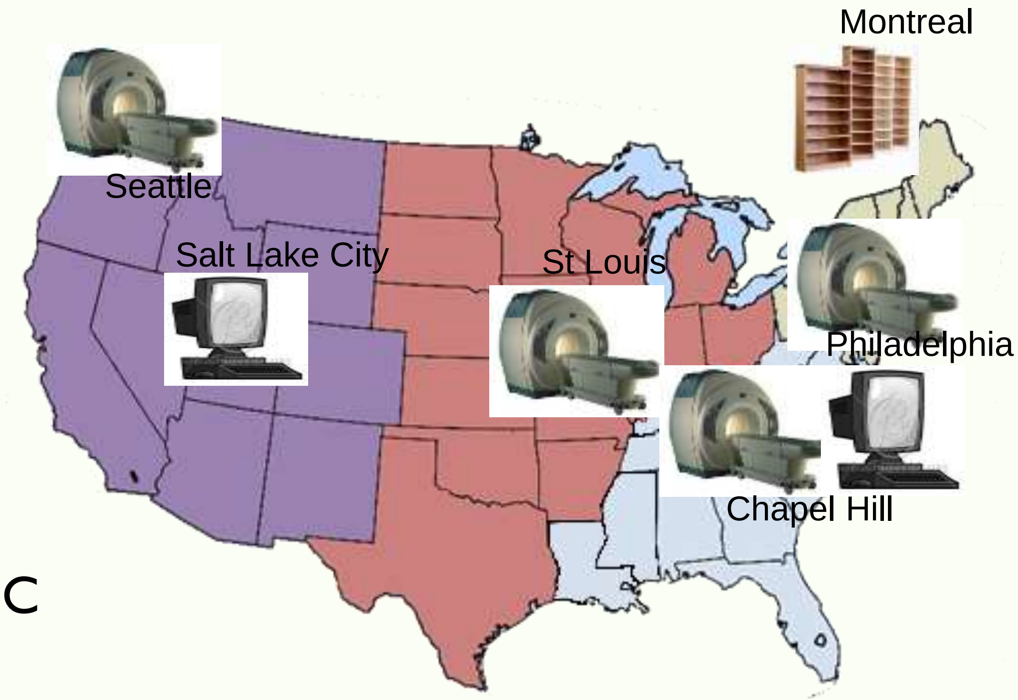


Goal: Pre-diagnostic imaging biomarkers

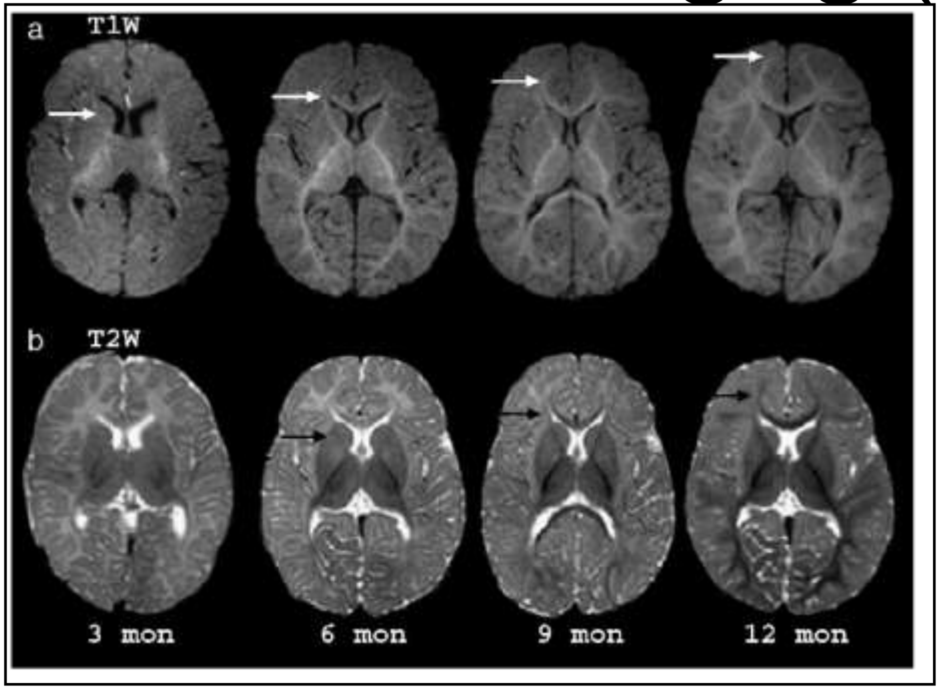
PI: Dr. Joseph Piven, UNC

ACE: Autism Network of Excellence
Infant Brain Imaging Study IBIS

- P.I. Joseph Piven, UNC
- ACE grant: Autism Center of Excellence.
- Longitudinal study of infant siblings at risk for Autism scanned at 6mo, 1y and 2yr (total >1500 MRI/DTI)
- 4 scanning sites:
  - Seattle
  - St Louis
  - Philadelphia
  - Chapel Hill
- DCC: MNI Montreal
- Image analysis: Utah & UNC

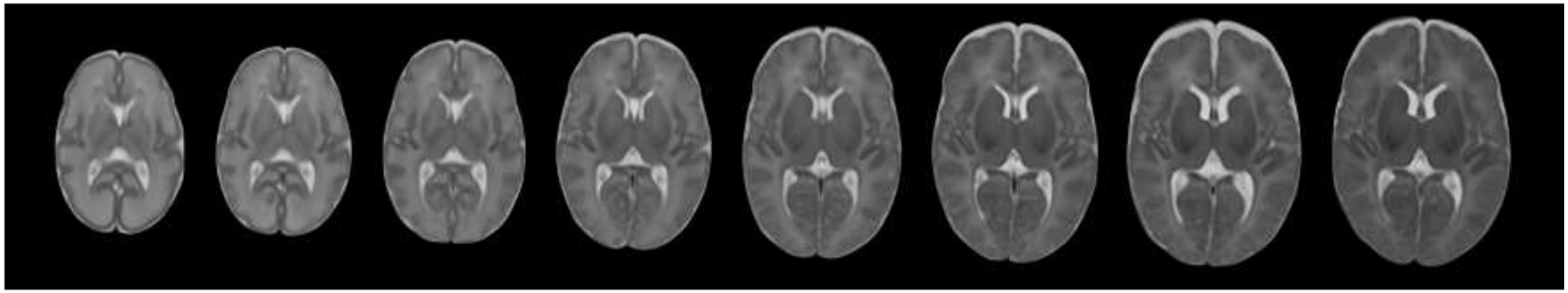


Longitudinal Magnetic Resonance Imaging (MRI)



Paus et al. 2001

Courtesy LeBihan 2005

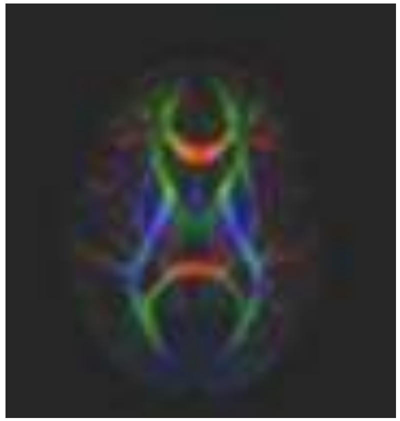


A. Serag et al., Neuroimage, 2012

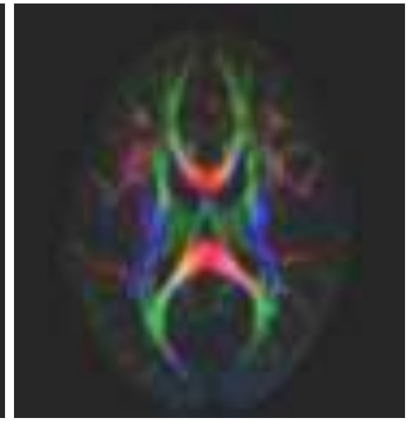
Longitudinal MR Diffusion Imaging

Neonate

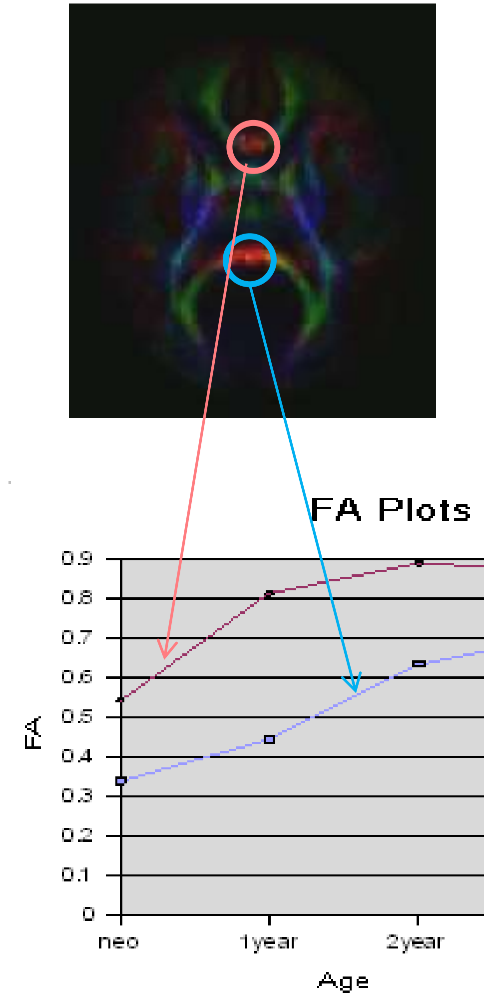
1 year

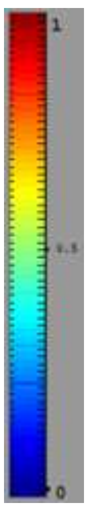


2 years

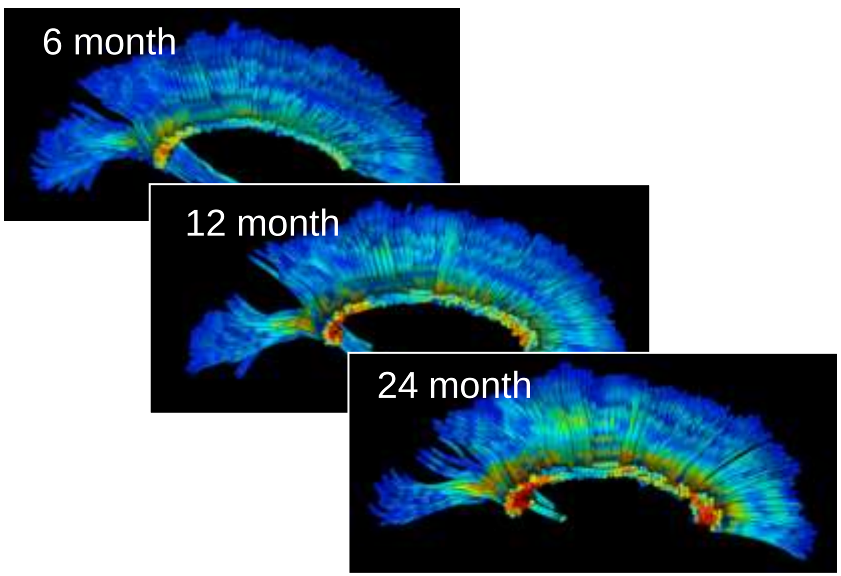


Cine





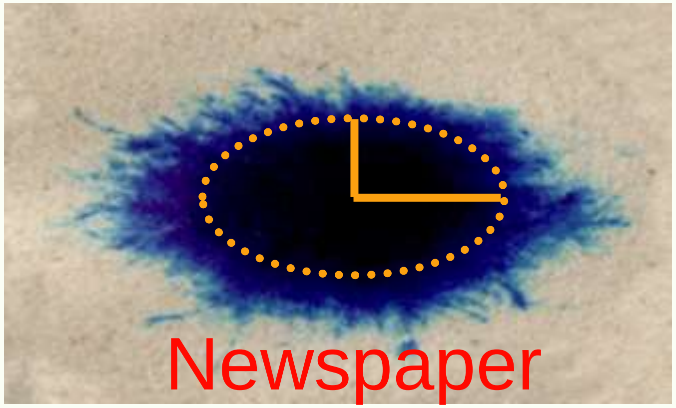
FA



Autism infant study: ACE-IBIS, J. Piven PI

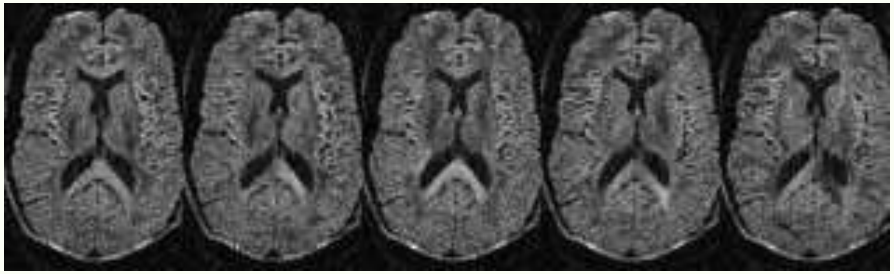
Diffusion in Biological Tissue

- Brownian motion of water through tissue



G. Kindlmann

- Anisotropy: diffusion rate depends on direction
- Le Bihan 1984 (C R Acad Sci): Diffusion MRI



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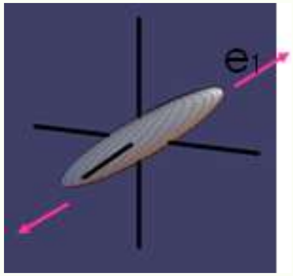

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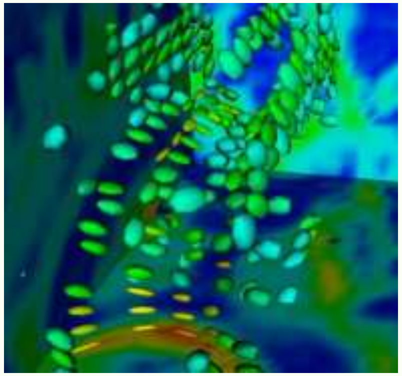
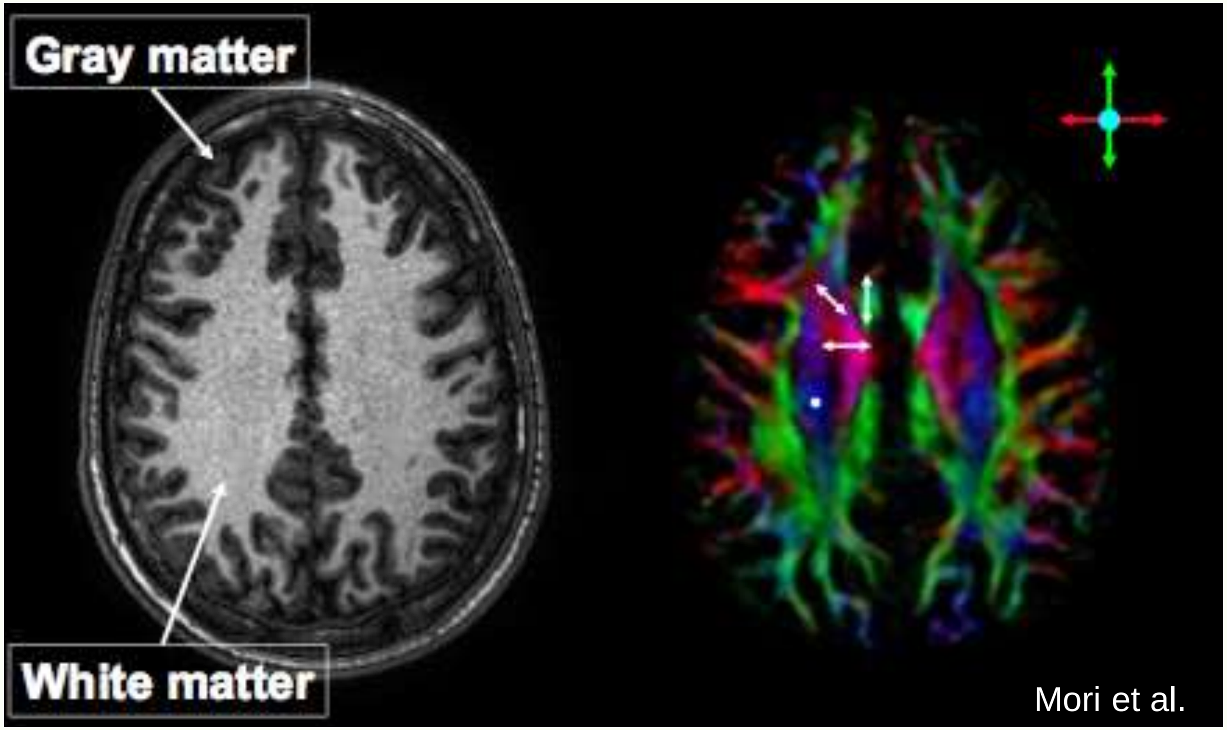
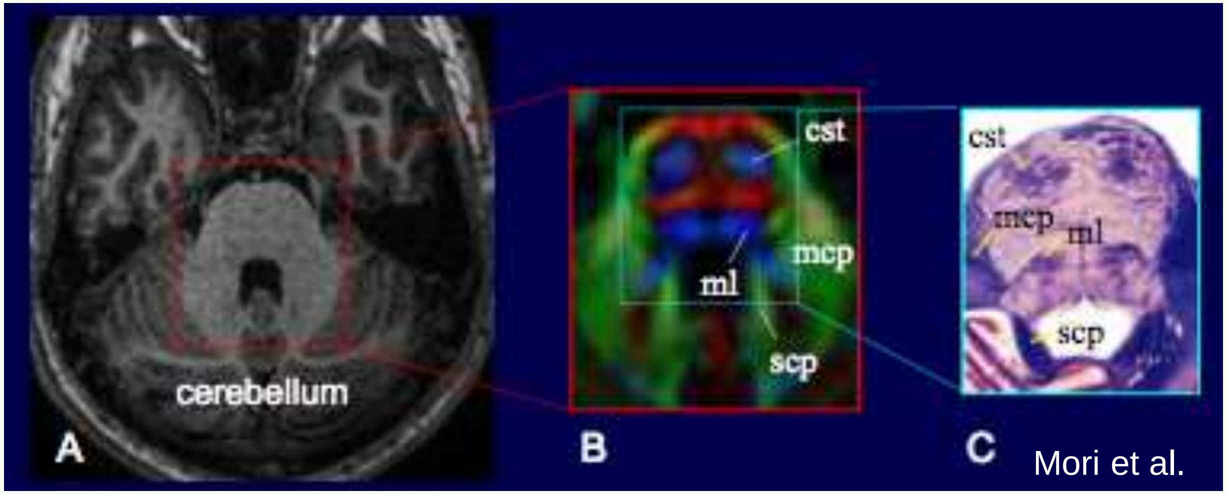
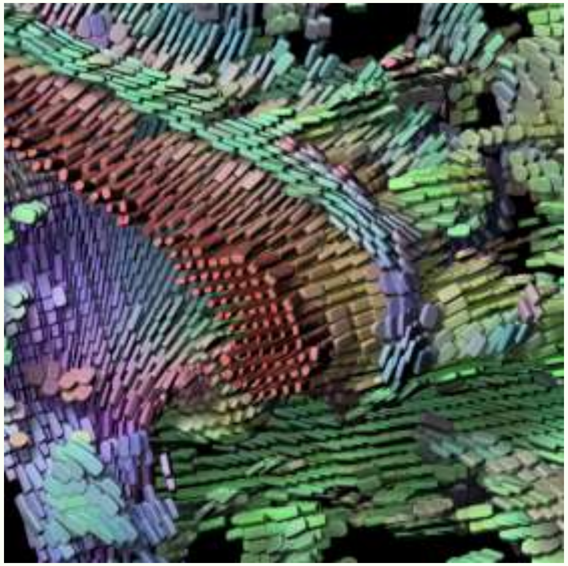


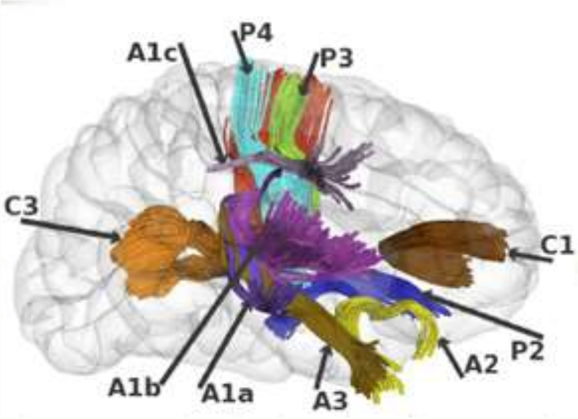
Diffusion tensor imaging reveals white matter anatomy







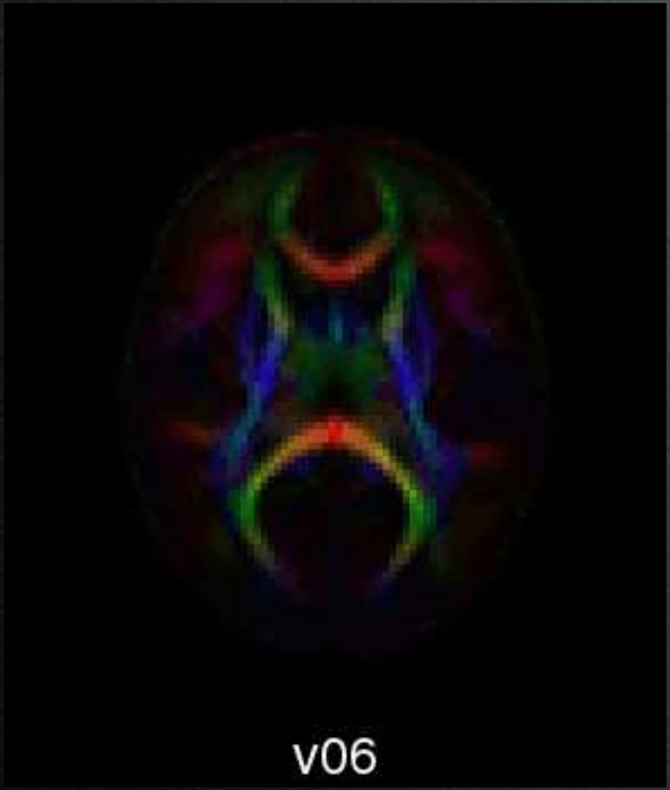
Kindlman et al.



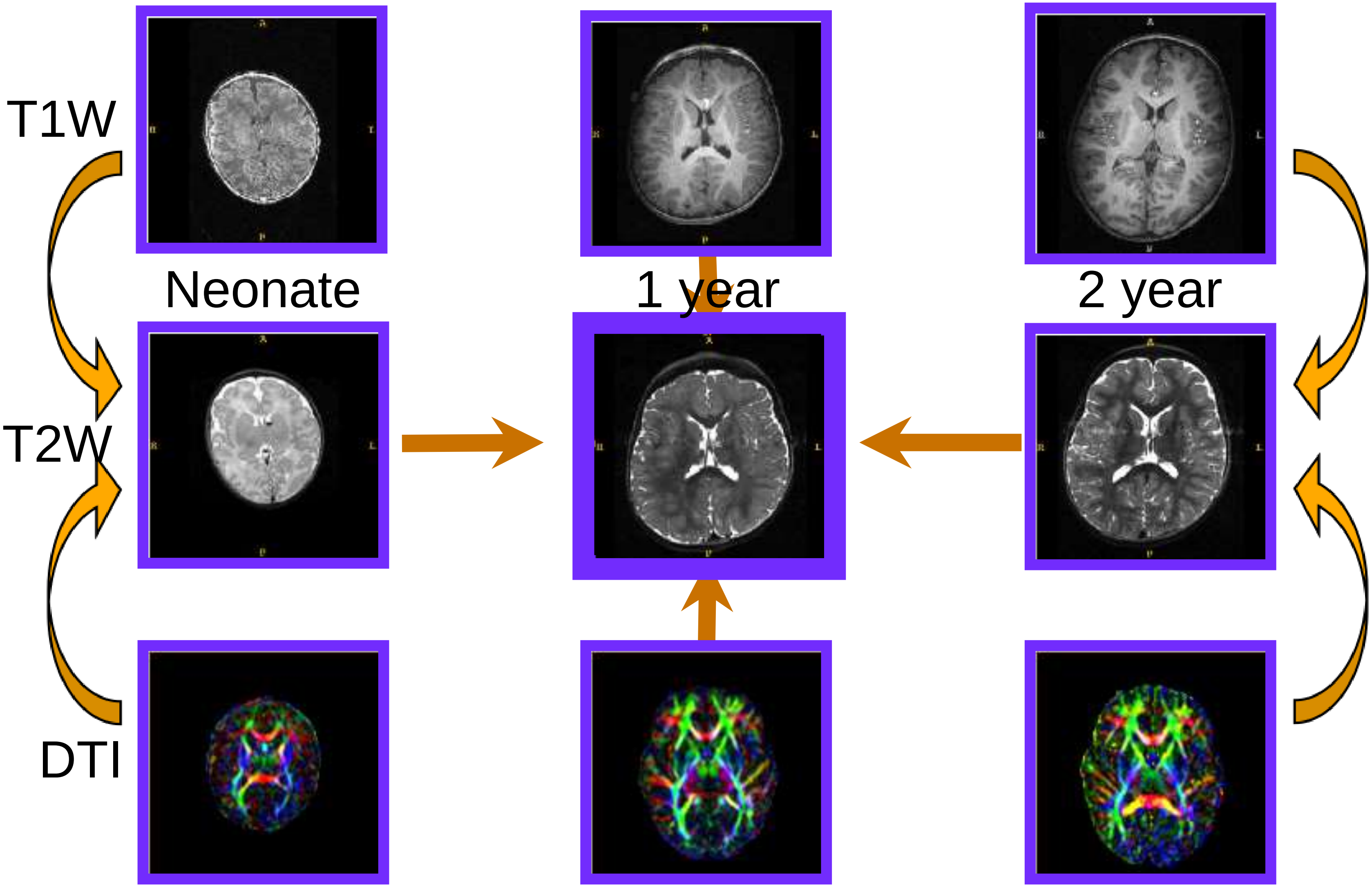
Geng et al., 2012

Longitudinal Model

Generated with 978 Diffusion MRI (481 subjects)

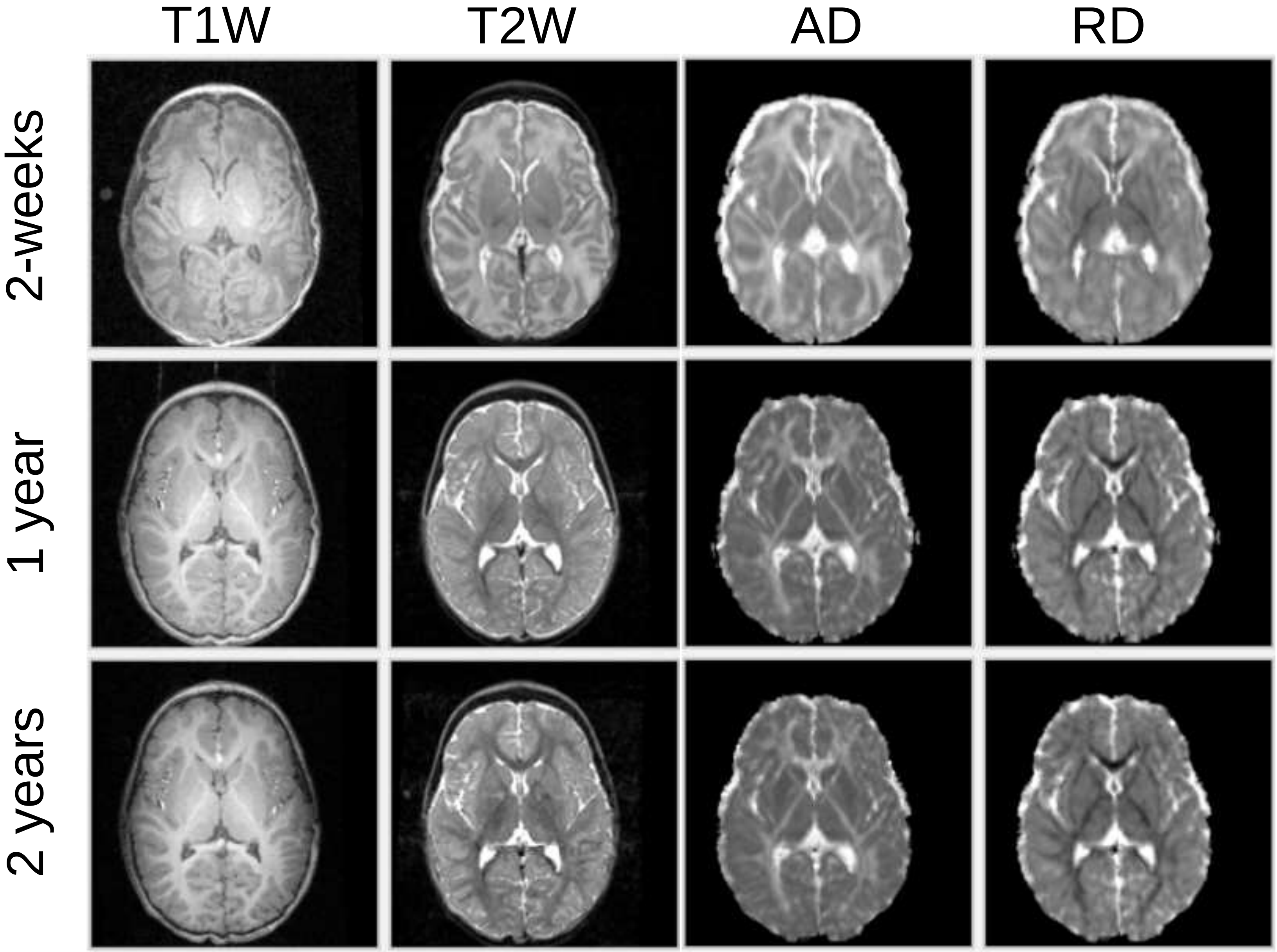


Co-Registration (Age, Modalities)

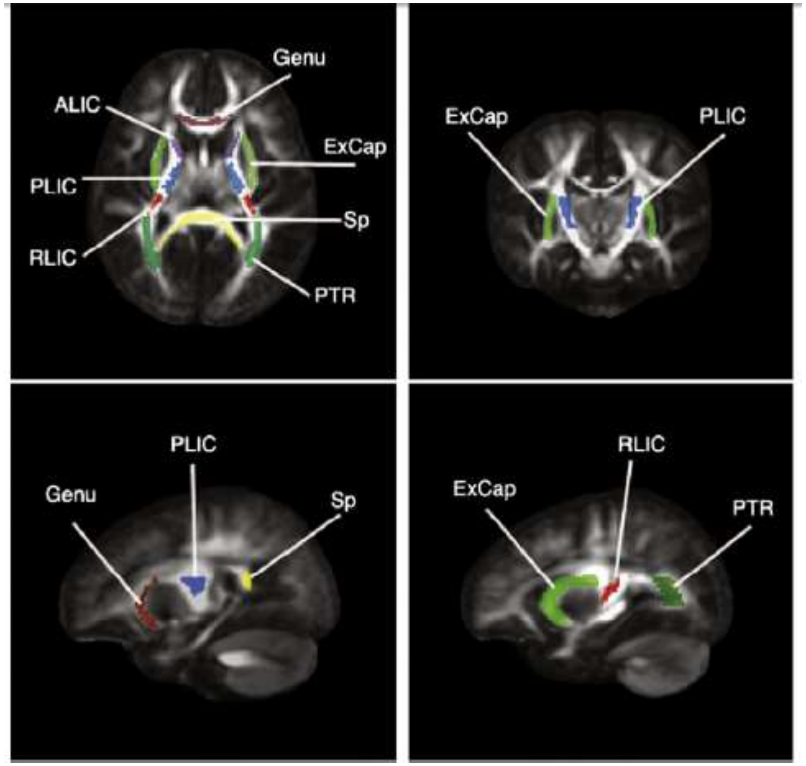


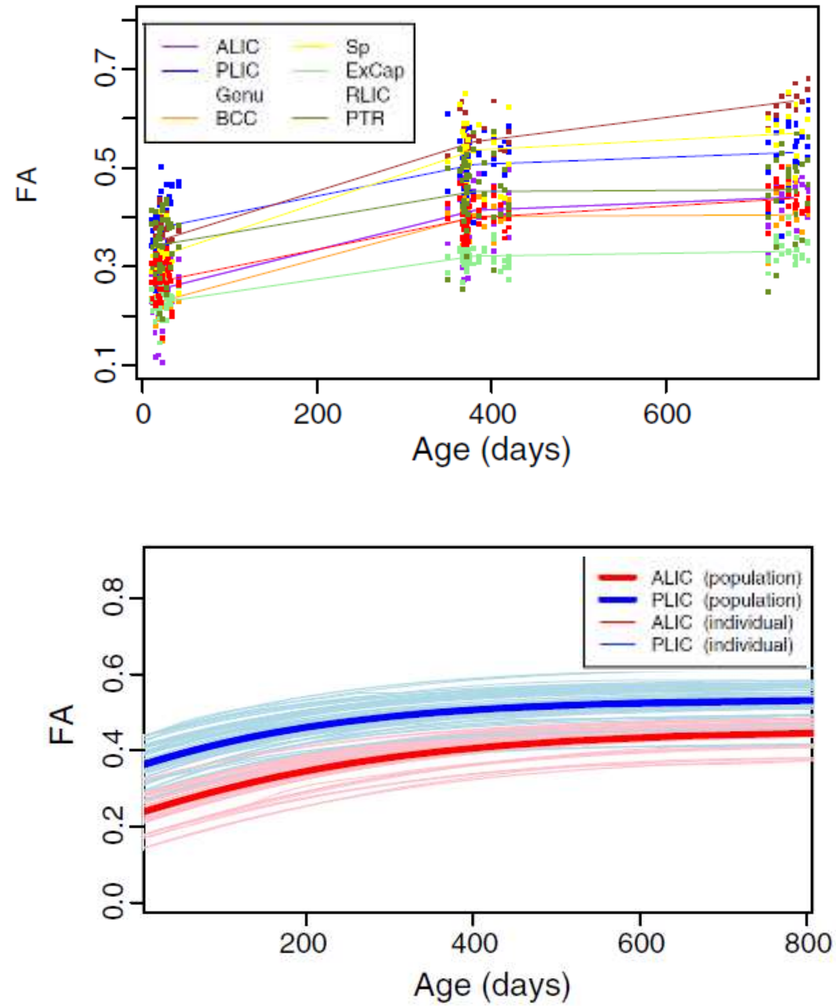
Sadeghi et al., Neuroimage 2013

Co-Registration (Age, Modalities)



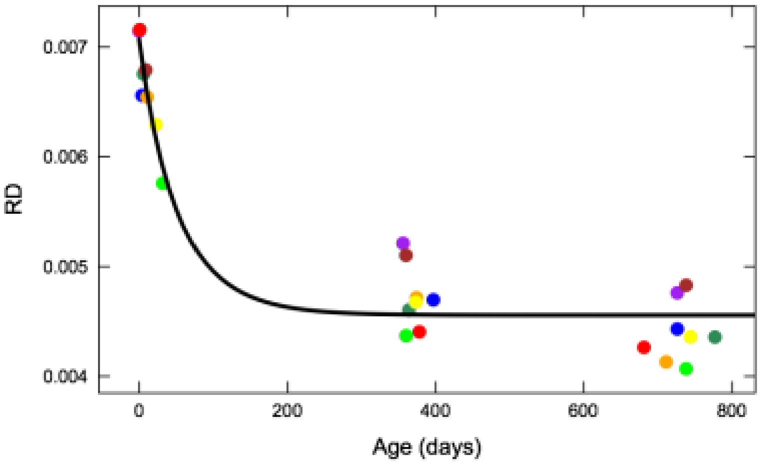
Longitudinal analysis of DTI: Nonlinear mixed-effect modeling





Sadeghi et al., Neuroimage 2013

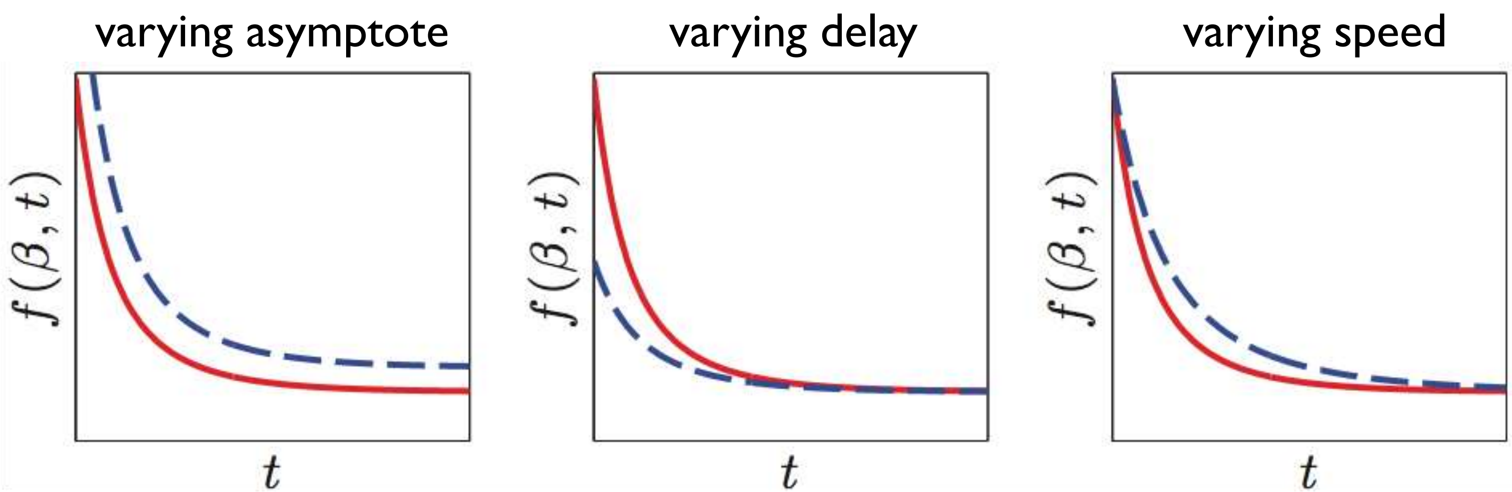
Modeling nonlinear change via Gompertz function



$$y = \textbf{asymptote}\ \exp(-\textbf{delay}\ \exp(-\textbf{speed}\ t))$$

$$y = f(\beta, t) = \beta_1 \exp\{-\beta_2 {\beta_3}^t\}$$

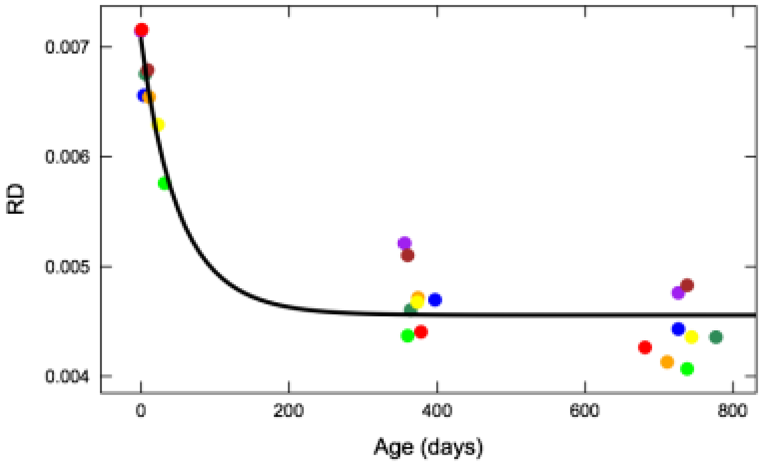
$$\beta_3 = exp(-speed)$$



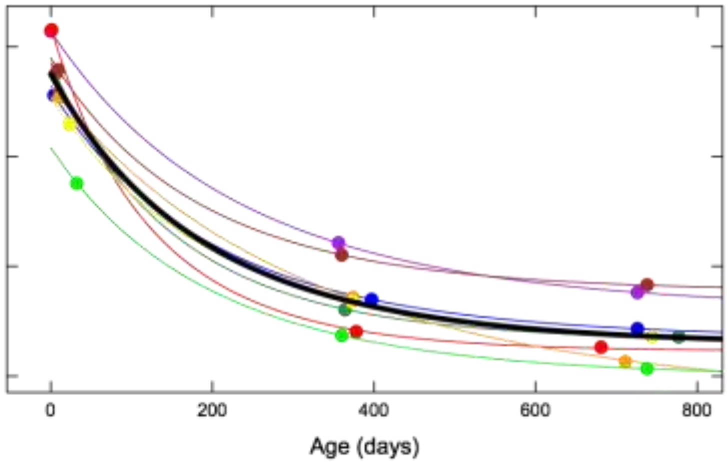
Sadeghi et al., Neuroimage 2013

"True" Longitudinal Analysis: Data and Model

Regression of Longitudinal Data: Disregard repeated measures



Longitudinal Modeling of Longitudinal Data: Explicit modeling of repeated measures.

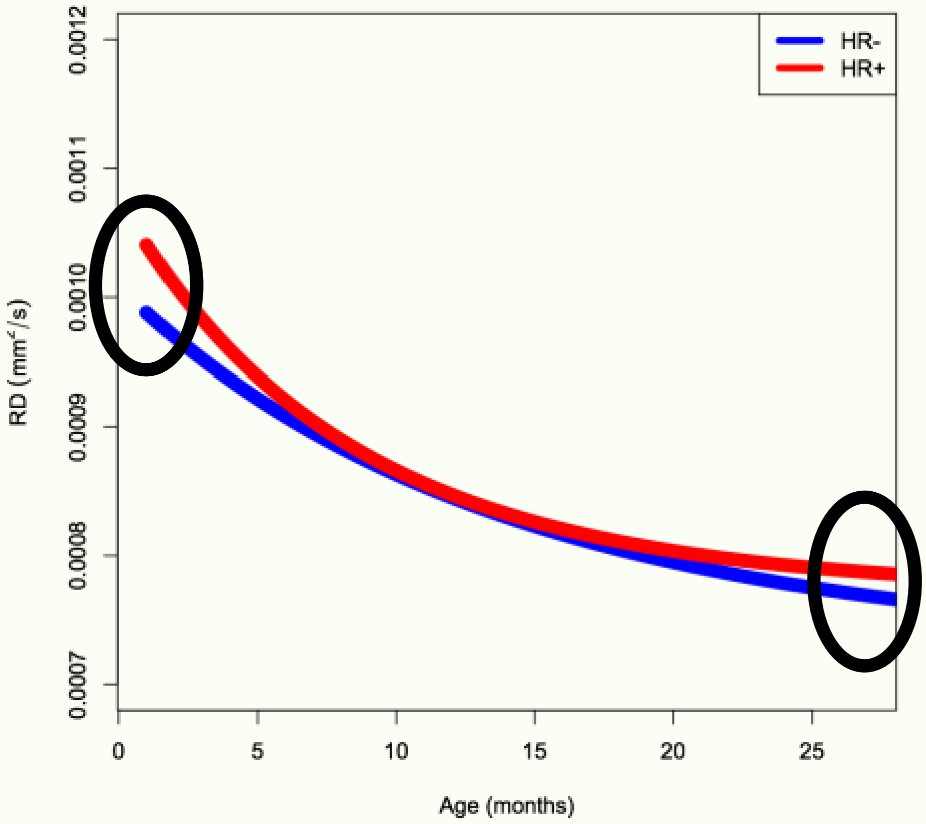


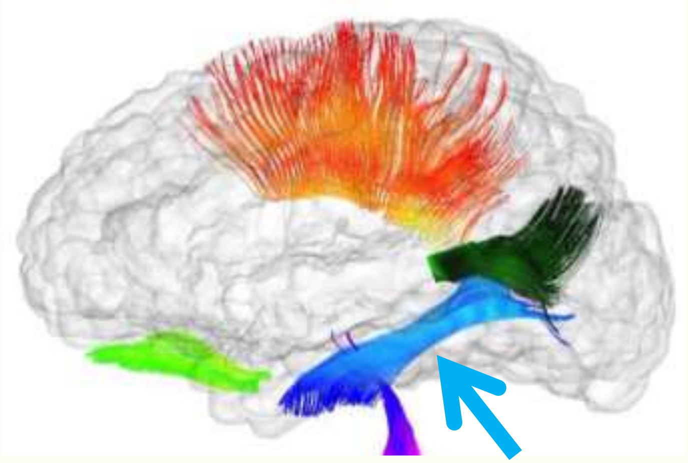
Regression is not an appropriate model of longitudinal data, the growth trajectory is not representative of individual trajectories

→ Mixed Effect Models

Population Trajectory Differences

HR+: High risk for autism, positive diagnosis
HR-: High risk for autism, negative diagnosis





Hypothesis testing on DTI:
ILF: Speed & Asymptote ($p < 0.05$)

Longitudinal DTI in Autism

THE AMERICAN JOURNAL OF PSYCHIATRY

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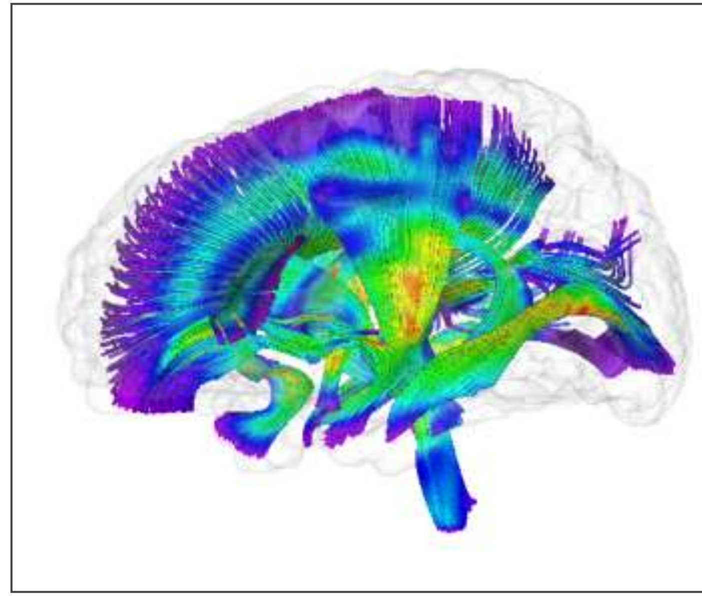
The American Journal of Psychiatry, VOL. 169, No. 6

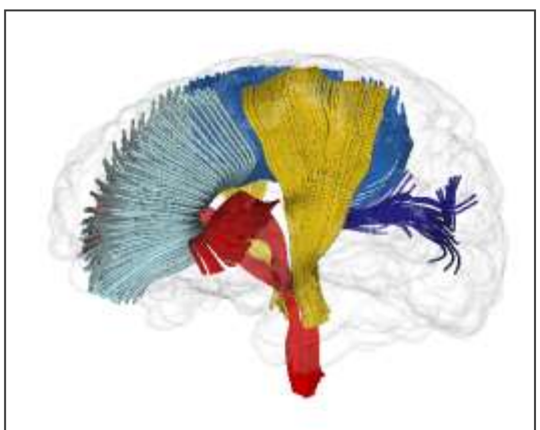
ARTICLES | June 01, 2012

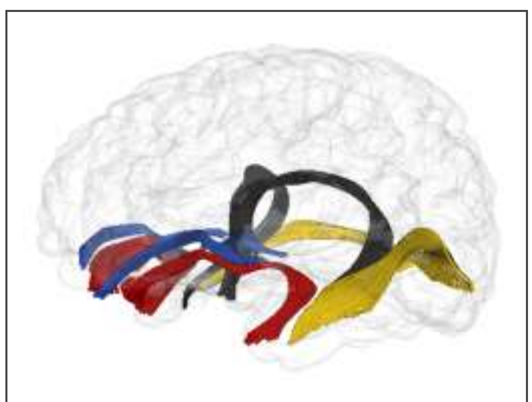
Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism

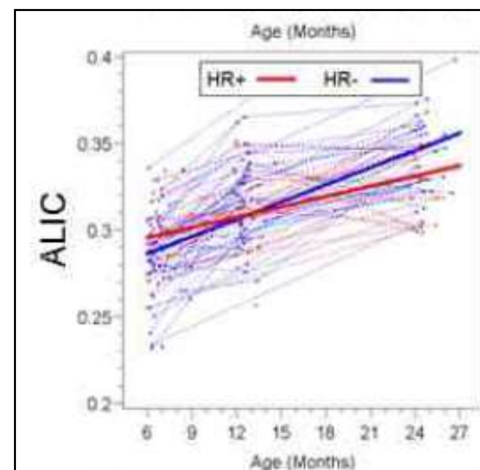
Jason J. Wolff, Ph.D.; Hongbin Gu, Ph.D.; Guido Gerig, Ph.D.; Jed T. Elison, Ph.D.; Martin Styner, Ph.D.; Sylvain Gouttard, M.S.; Kelly N. Botteron, M.D.; Stephen R. Dager, M.D.; Geraldine Dawson, Ph.D.; Annette M. Estes, Ph.D.; Alan C. Evans, Ph.D.; Heather C. Hazlett, Ph.D.; Penelope Kostopoulos, Ph.D.; Robert C. McKinstry, M.D., Ph.D.; Sarah J. Paterson, Ph.D.; Robert T. Schultz, Ph.D.; Lonnie Zwaigenbaum, M.D.; Joseph Piven, M.D.; the IBIS Network

RESULTS: FA trajectories differed significantly between infants who did versus did not develop ASDs for 12 of 15 fiber tracts. Development for most fiber tracts in infants with ASDs was characterized by elevated FA at 6 months followed by slower change over-time relative to infants without ASDs. Thus, by 24 months of age, lower FA values were evident for those with ASDs.









Study: Brain scans detect early signs of autism

Link to CBS News

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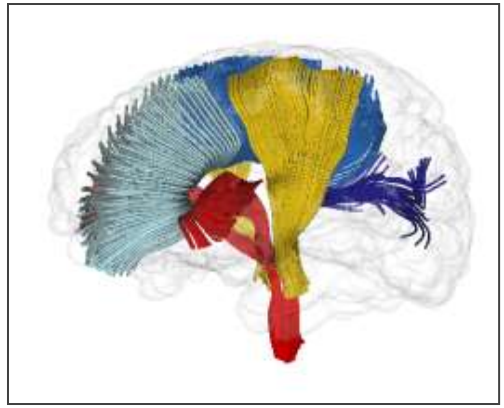
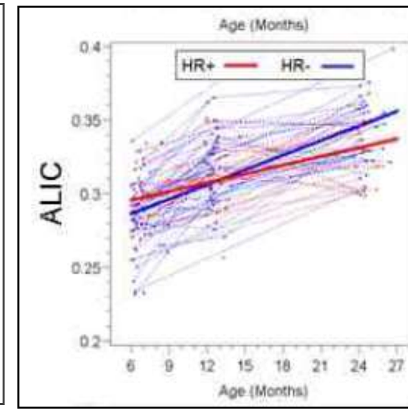
The American Journal of Psychiatry, VOL. 169, No. 6

ARTICLES | June 01, 2012

Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism

Jason J. Wolff, Ph.D.; Hongbin Gu, Ph.D.; Guido Gerig, Ph.D.; Jed T. Elison, Ph.D.; Martin Styner, Ph.D.; Sylvain Gouttard, M.S.; Kelly N. Botteron, M.D.; Stephen R. Dager, M.D.; Geraldine Dawson, Ph.D.; Annette M. Estes, Ph.D.; Alan C. Evans, Ph.D.; Heather C. Hazlett, Ph.D.; Penelope Kostopoulos, Ph.D.; Robert C. McKinstry, M.D., Ph.D.; Sarah J. Paterson, Ph.D.; Robert T. Schultz, Ph.D.; Lonnie Zwaigenbaum, M.D.; Joseph Piven, M.D.; the IBIS Network





Researchers See Differences in Autism Brain Development as Early as 6 Months

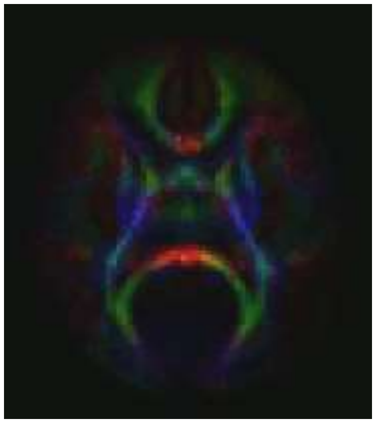
Scientists created 3D images of major brain pathways in infants at high risk for developing autism. [Credit: UNC]

The defining features of autism—hampered communication, social challenges and repetitive actions—may not become obvious until after a baby's first birthday. But the changes in brain development that underlie these behaviors may be detectable much earlier. In a new study, researchers found clear differences in brain communication pathways starting as early as 6 months and continuing through 2 years of age in children who were later diagnosed with autism spectrum disorder (ASD). The findings appear online today in the *American Journal of Psychiatry*.

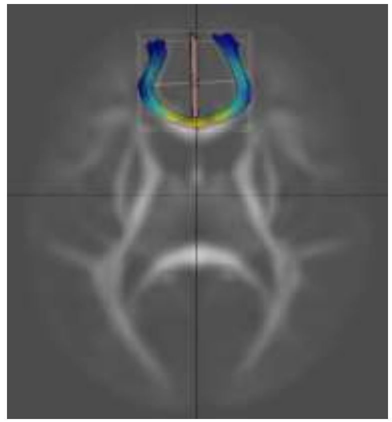
Study Suggests Pre-Autism Brain Differences In Six Month Olds

Longitudinal Tract-Based Modeling

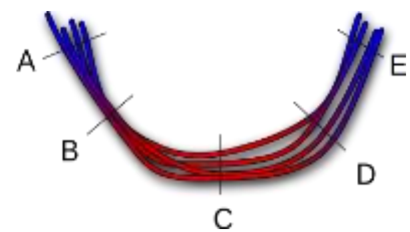
Cine

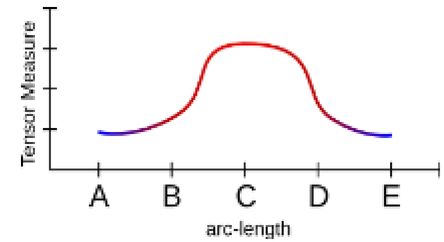


Genu Tract

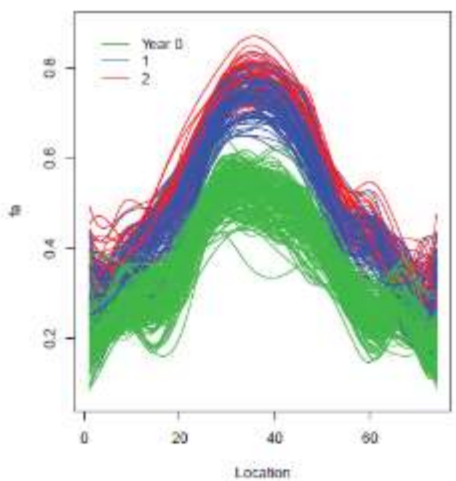


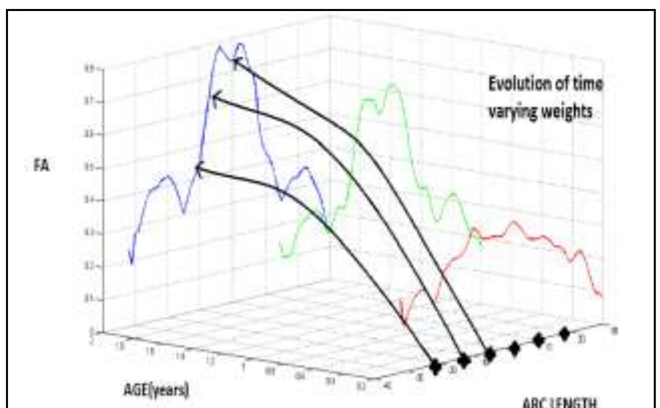
Parametrization by arc-length

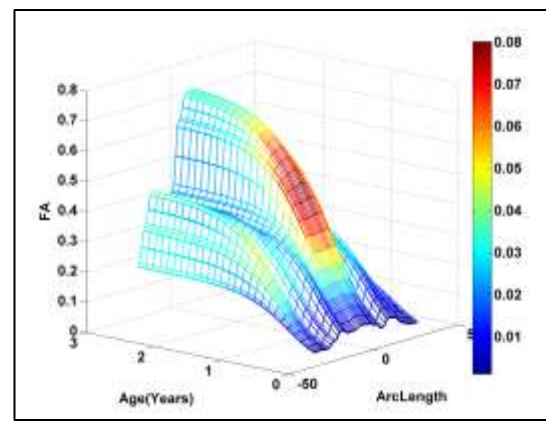




Spatio-temporal statistical tract model



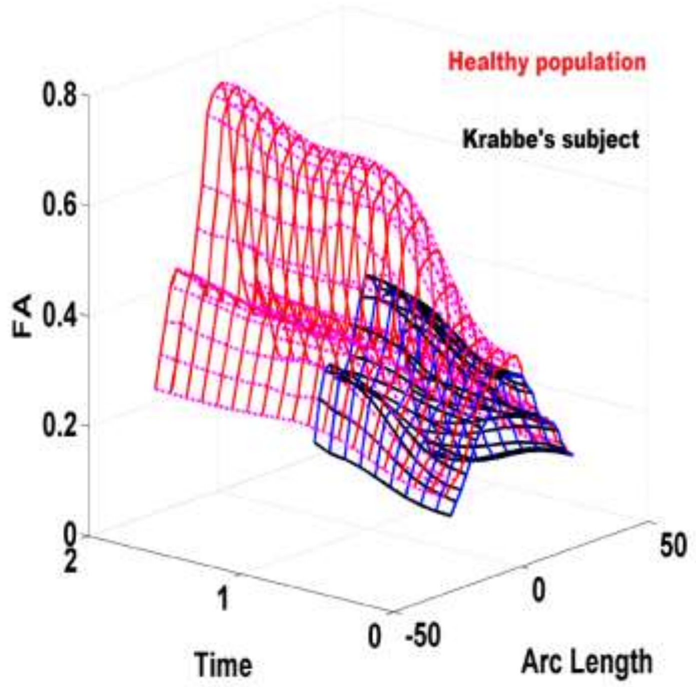




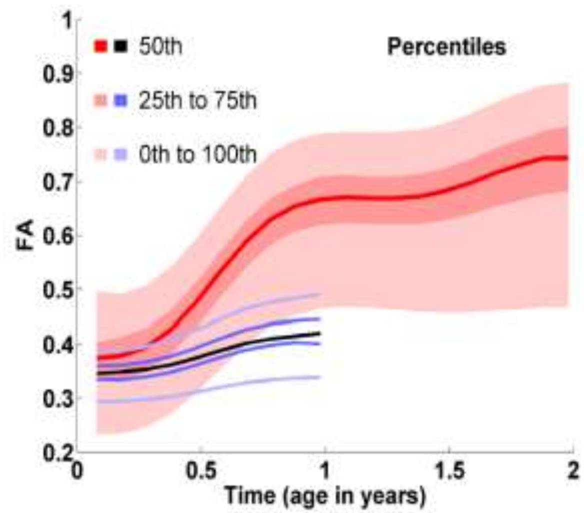
Corouge et al., ‘06, Goodlett et al, ‘09, Sharma et al., ISBI ‘12, ‘13

Subject-specific Analysis: Krabbe's Disease

- Krabbe's disease affects myelin of the nervous system.
- Degenerative in nature, often fatal without early therapy.

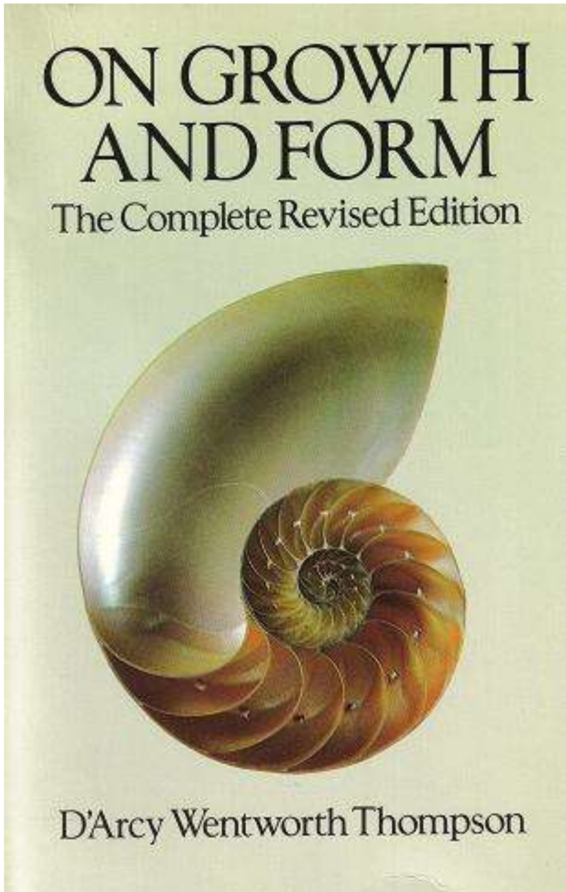


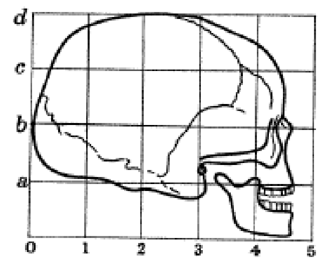
Normative FA trajectory wrt a single Krabbe's subject.

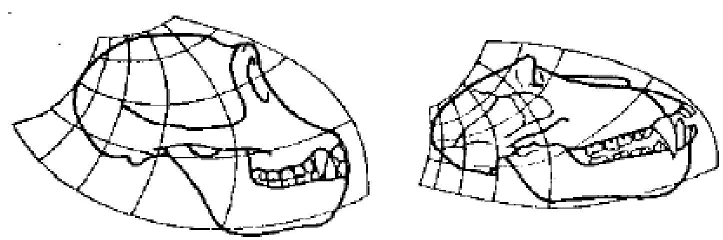


FA quartiles for a single tract location along time.

Spatiotemporal Shape Analysis

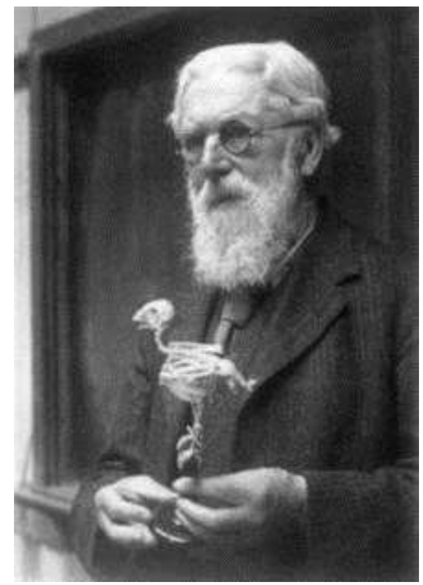






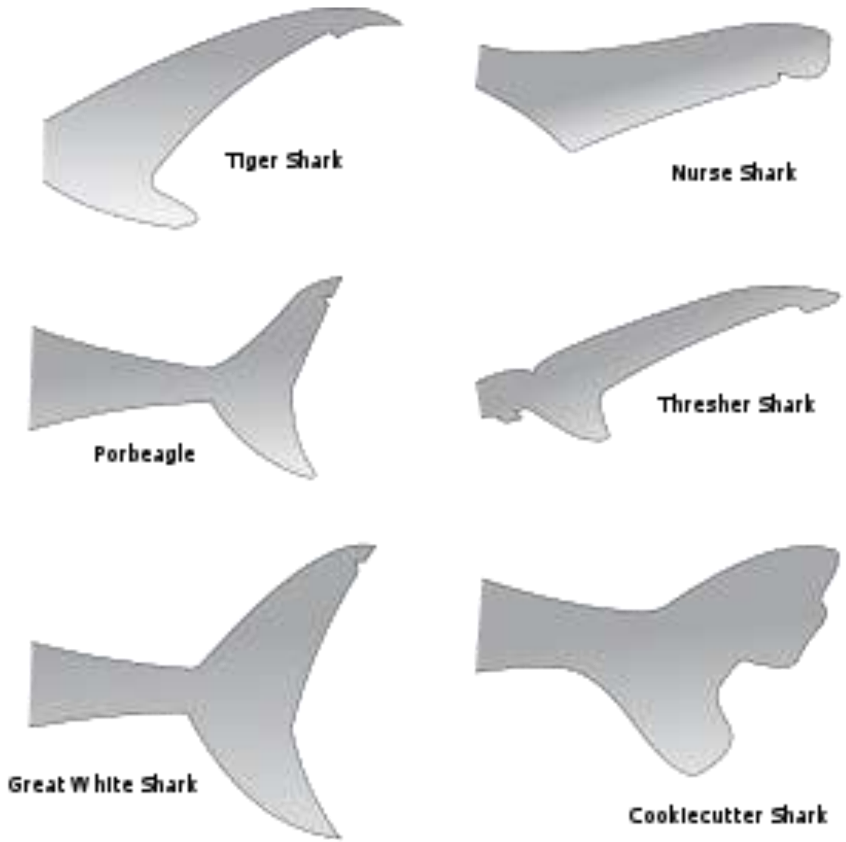
(a)

(b)



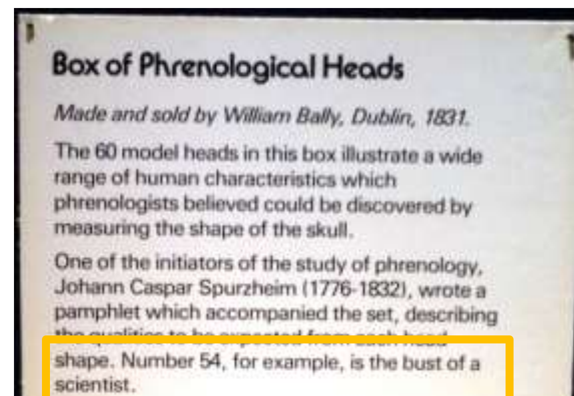
D'Arcy Wentworth Thompson, On Growth and Form (1917, mathematics and biology)

Why Shape?



Shark Tails
The Diversity of Form and Function

Shape Variability



Box of Phrenological Heads

Made and sold by William Bally, Dublin, 1831.

The 60 model heads in this box illustrate a wide range of human characteristics which phrenologists believed could be discovered by measuring the shape of the skull.

One of the initiators of the study of phrenology, Johann Caspar Spurzheim (1776-1832), wrote a pamphlet which accompanied the set, describing

shape. Number 54, for example, is the bust of a scientist.

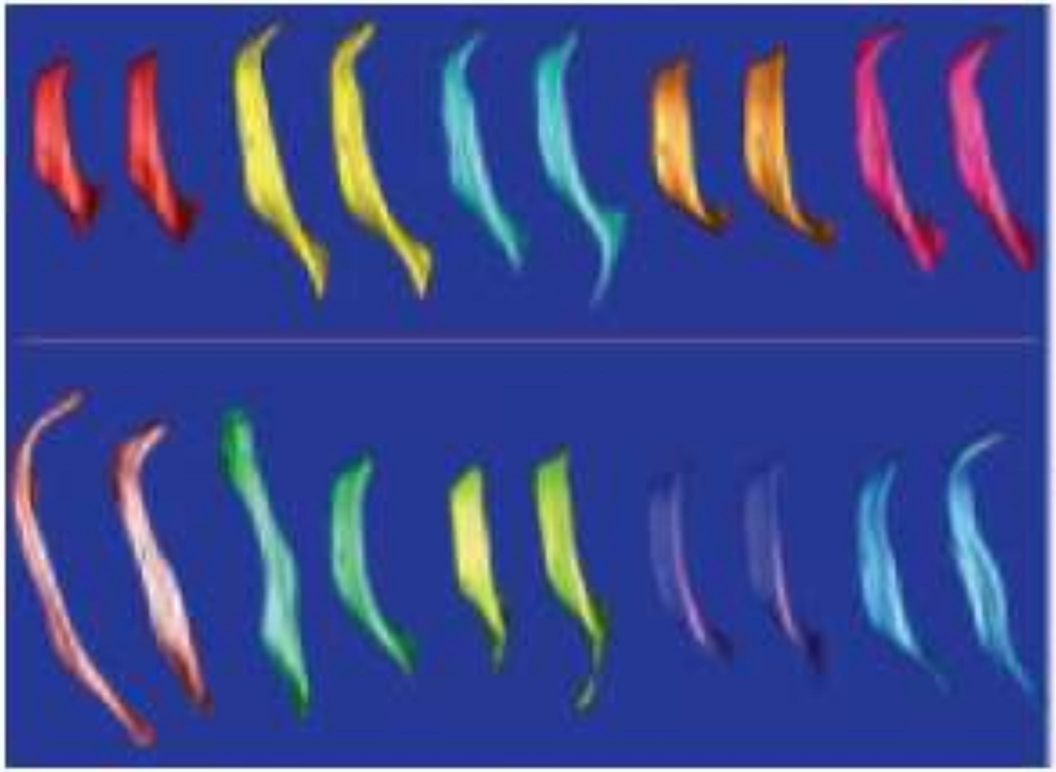
science museum

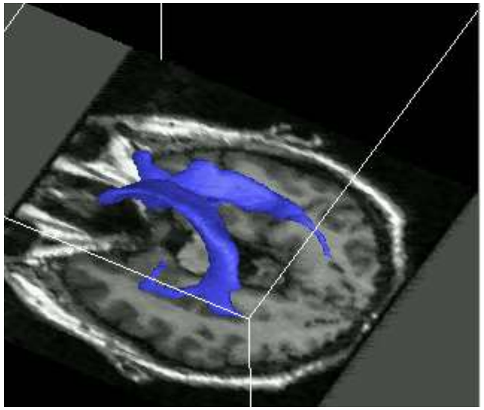
Brought to Life

Exploring the History of Medicine

[link]

Shape Similarity in Twins

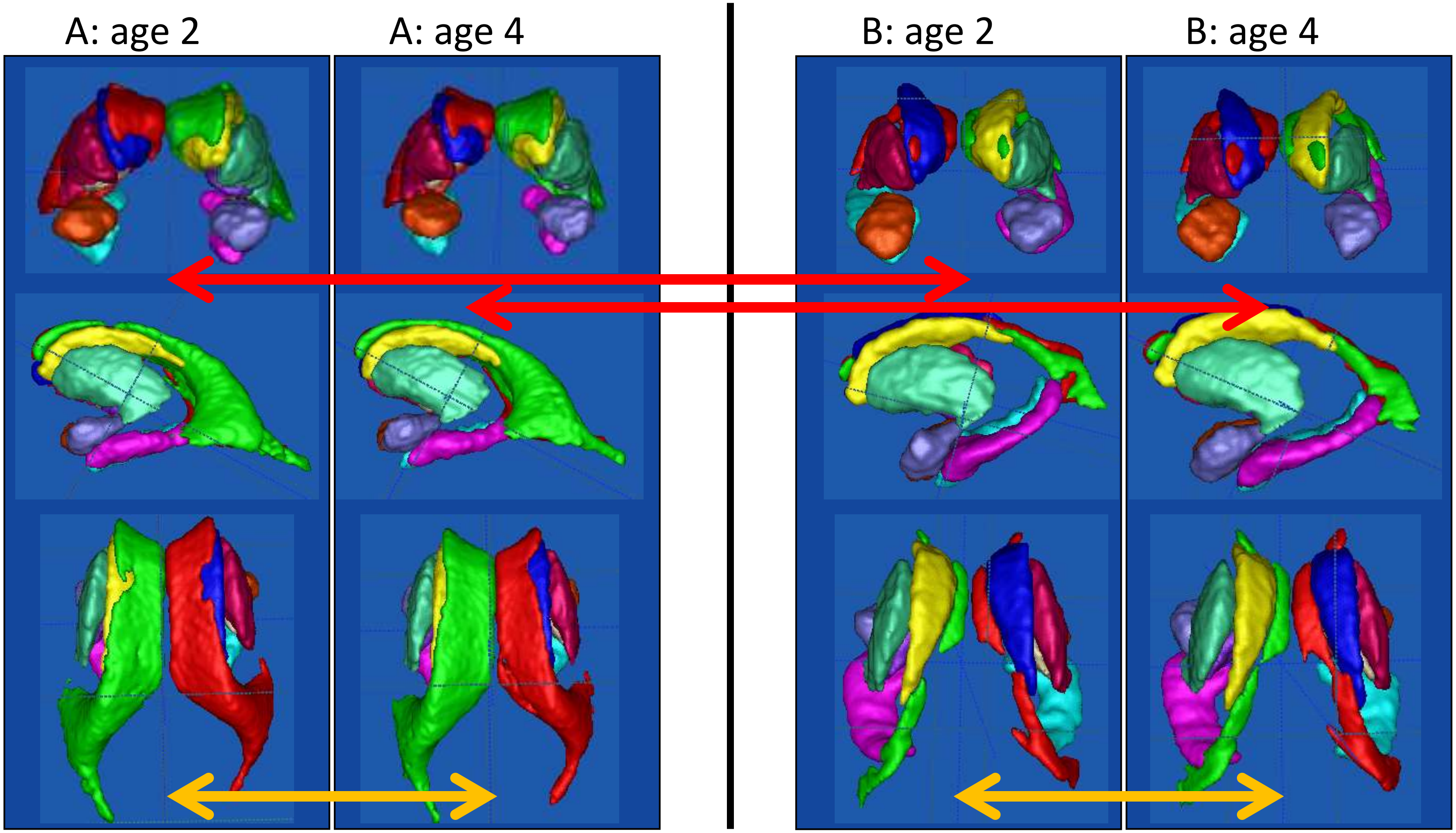




Upper row: identical twin pairs
Lower row: non-identical twin pairs

Styner/Gerig PNAS 2005

Example Infant Study: Cross-sectional vs. Longitudinal



Cross-sectional: Huge changes between sets of shapes

Longitudinal: Subtle changes of sets of shapes with time

Shape >> Volume

Morphometric analysis of lateral ventricles in schizophrenia and healthy controls regarding genetic and disease-specific factors

Martin Styner*†‡§, Jeffrey A. Lieberman†¶, Robert K. McClure†‖, Daniel R. Weinberger, Douglas W. Jones**, and Guido Gerig*†**

*Department of Computer Science, University of North Carolina, Chapel Hill, NC 27599-3175; †Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC 27599-3175; **Clinical Brain Disorder Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892; and §M. E. Müller Research Center for Orthopaedic Surgery, Institute for Surgical Technology and Biomechanics, University of Bern, CH-3014 Bern, Switzerland

Communicated by Frederick P. Brooks, Jr., University of North Carolina, Chapel Hill, NC, February 9, 2005 (received for review October 21, 2004)

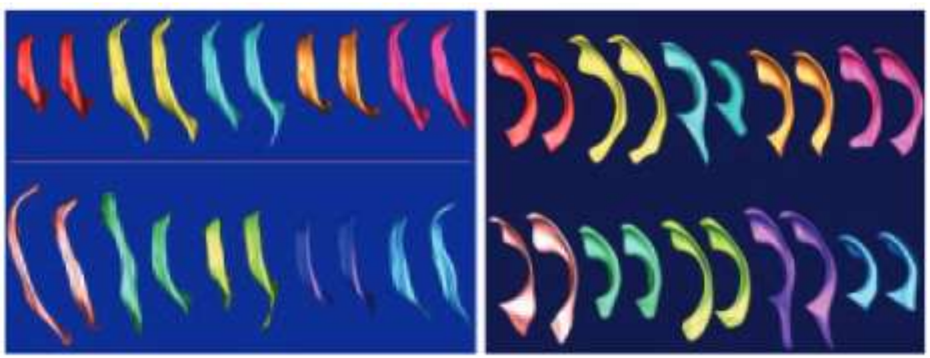


Fig. 1. Graphical view of aligned and size-normalized ventricles. (*Left*) Superior view of left ventricles of five MZ twin pairs (*Upper*) and five DZ twin pairs (*Lower*) displayed from the top. Ventricles of co-twins are shown by using the same color. (*Right*) Sagittal view of right ventricles of 10 DS pairs, with affected and unaffected shown side by side. The third pair (*Upper Right*) was excluded because of hydrocephaly in the unaffected twin.

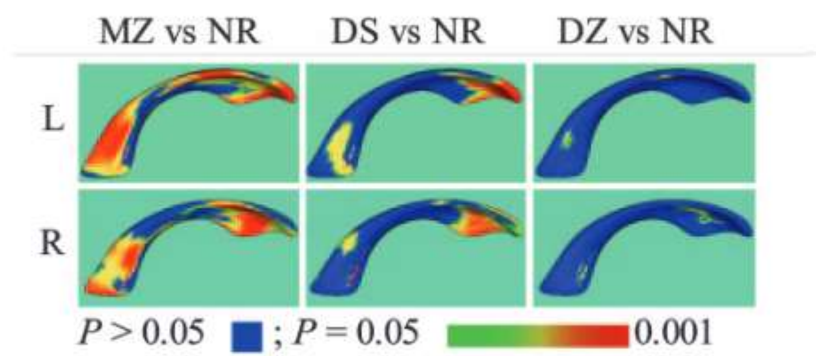
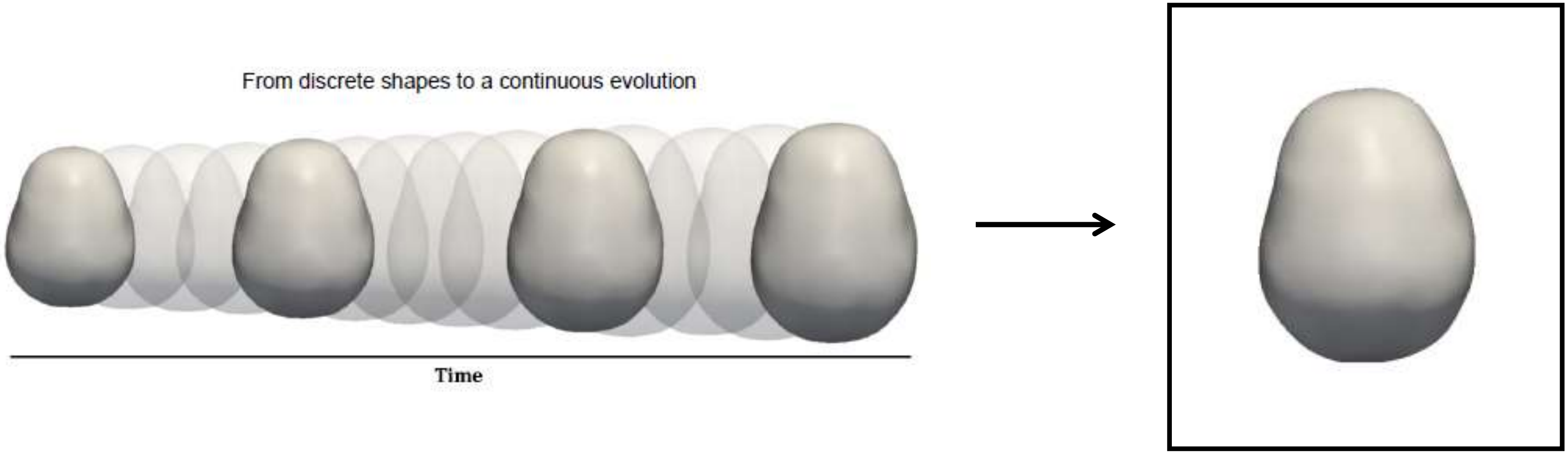


Fig. 6. Statistical maps displaying the locations of significant differences between groups for the co-twin analysis. The colors indicate the level of significance as shown in the color map. Results for group comparisons not shown in this figure did not have significant regions

4D Shape Modeling from Time-Discrete Data



- **Concept**: Given a set of discrete shapes, interpolate a continuous 4D growth model via shape regression.
- **Assumption**: Growth/degeneration of biological tissue is inherently smooth in space and time & nonlinear, locally varying process.
- **Method**: Continuous flow of diffeomorphisms via correspondence-free "currents". *Cost function = Data Matching + Regularity*.

Durrleman, Pennec, Ayache, Trouve, Gerig, MICCAI '09
Fishbaugh, Durrleman, Gerig, MICCAI '11, SPIE'12, MICCAI'12, IPMI'13

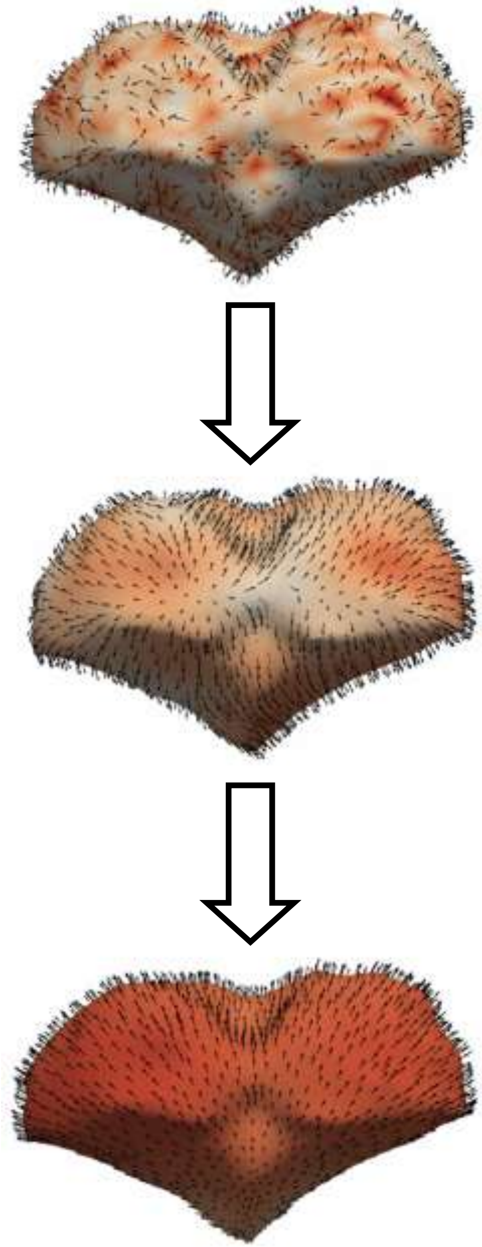
Acceleration Controlled Shape Regression

We define the acceleration field a(x(t)) as a vector field of the form

$$a(x(t)) = \sum_{i=1}^{N} K^V(x(t), x_i(t))\alpha_i(t)$$

x_i: the shape points carrying a point force vector α_i

$K^V(x, y) = exp(-\|x - y\|^2 / \lambda_V^2)$: a Gaussian kernel with standard deviation λ_V



Time varying deformation $\phi_t(x_i)$ given by:

$$\ddot{\phi}_t(x_i) = a(x_i(t))$$

$x_i(0)$: initial position

$\dot{x}_i(0)$: initial velocity

Regression Criterion

Let $\mathbf{x}(t)$, $\mathbf{a}(t)$, and $\boldsymbol{\alpha}(t)$ be the concatenation of the $x_i(t)$'s, $a_i(t)$'s, and the $\alpha_i(t)$'s.

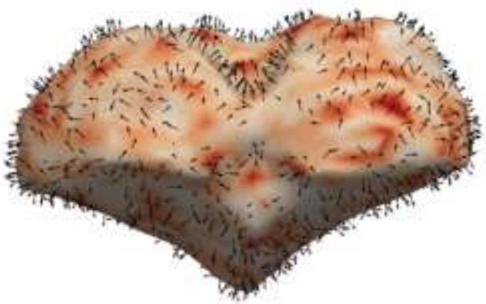
$$E(\dot{\mathbf{x}}(0), \boldsymbol{\alpha}(t)) = \sum_{t_i} \|\phi_{t_i}(\mathbf{x}(0)) - \mathbf{x}(t_i)\|^2_{W^*} + \gamma \int_0^T \|\mathbf{a}(t)\|^2_V \, dt$$

$\|\cdot\|_{W^*}$ is the norm on currents

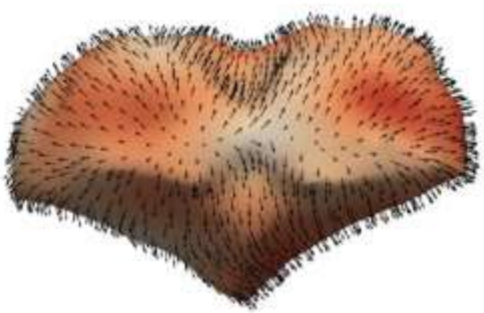
$\|\mathbf{a}(t)\|^2_V = \boldsymbol{\alpha}(t) K^V(\mathbf{x}(t), \mathbf{x}(t)) \boldsymbol{\alpha}(t)$

Acceleration Controlled Shape Regression

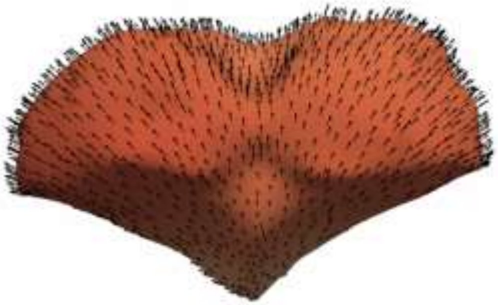
Evolution of cerebellum from 6 to 24 months



Point forces α



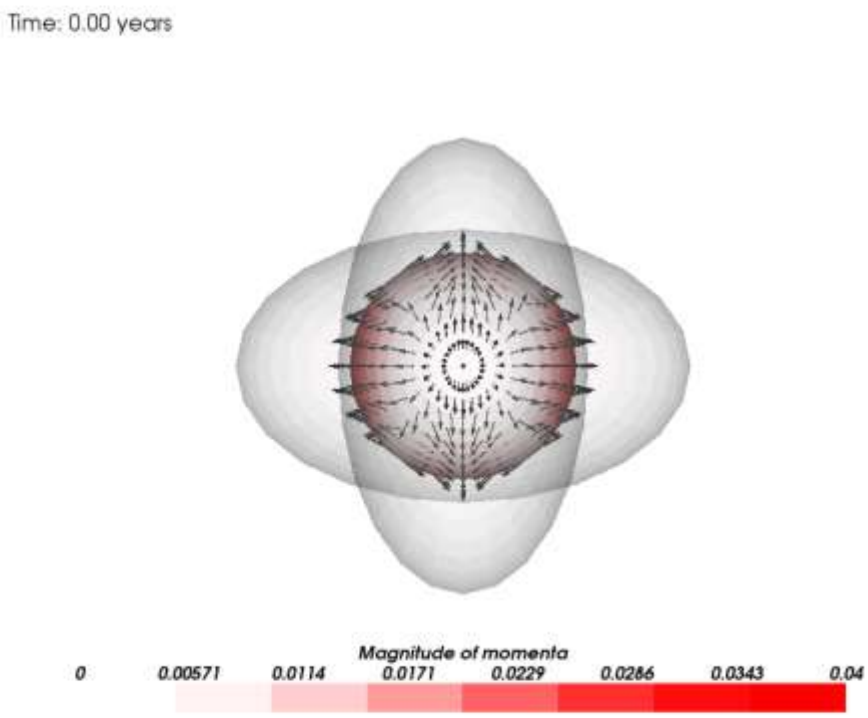
Acceleration



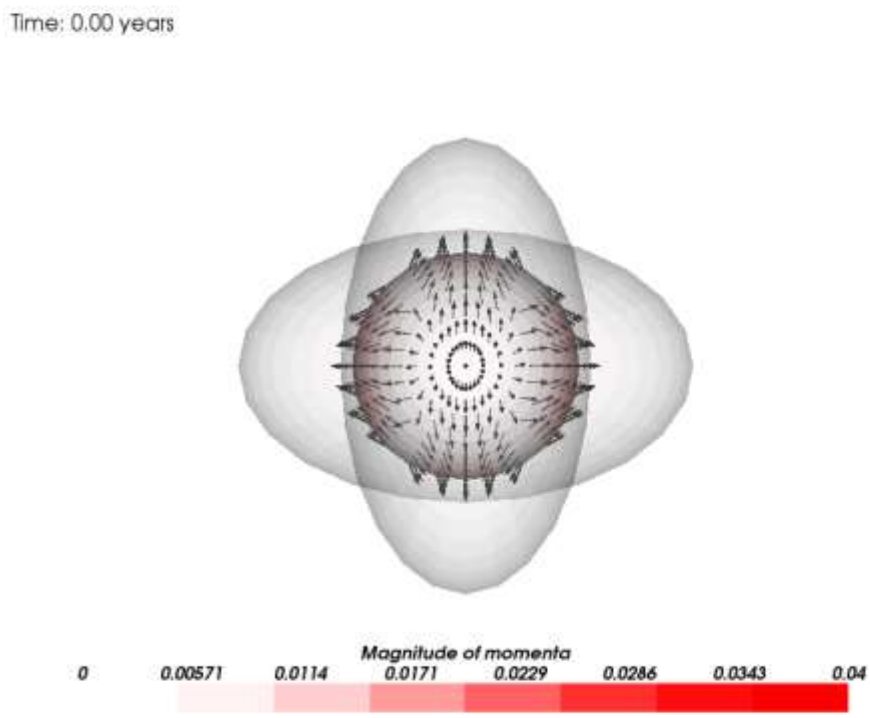
Velocity

Piecewise Geodesic vs Acceleration Controlled

Synthetic experiment comparing piecewise geodesic and acceleration controlled shape regression

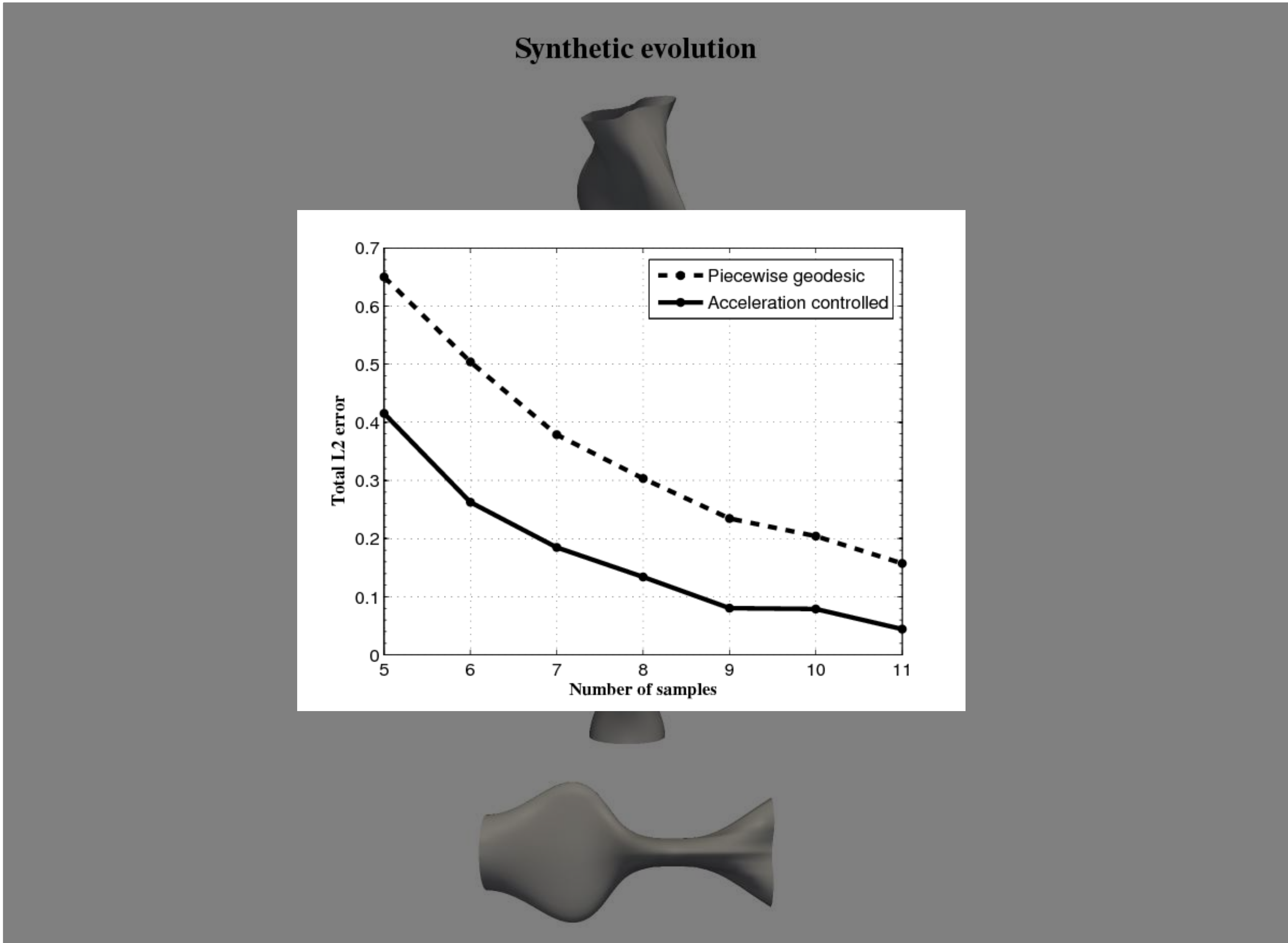


Piecewise geodesic



Acceleration controlled

Interpolation Properties



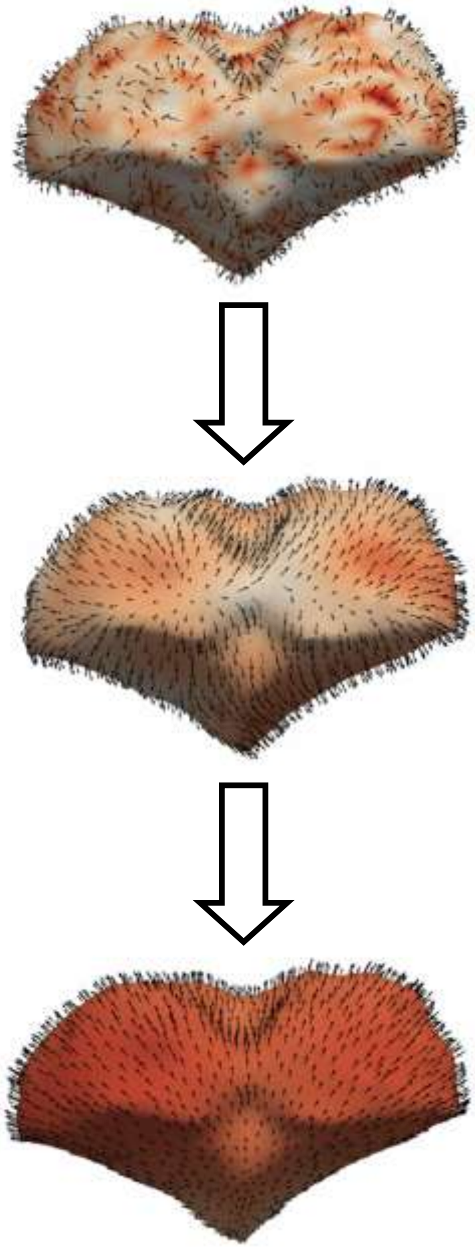
Summary

Benefits:

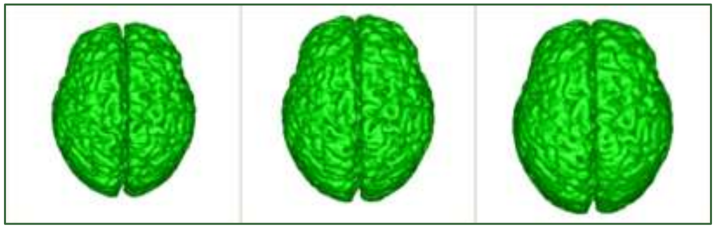
- More biologically realistic trajectories
- Nice interpolation properties

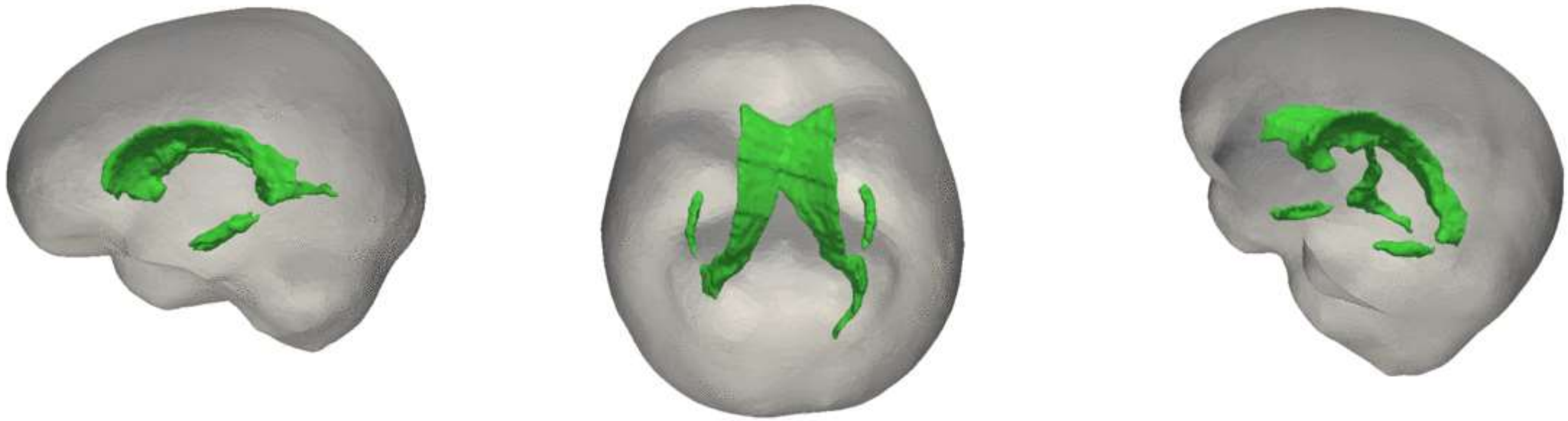
Drawbacks:

- Not compact or generative



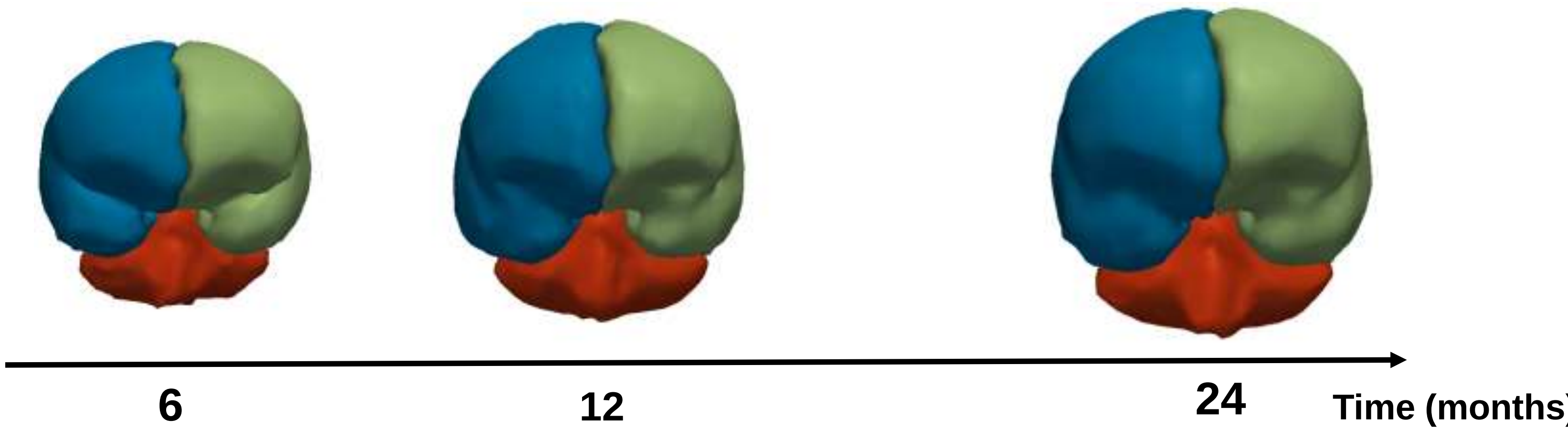
Longitudinal Shape Regression



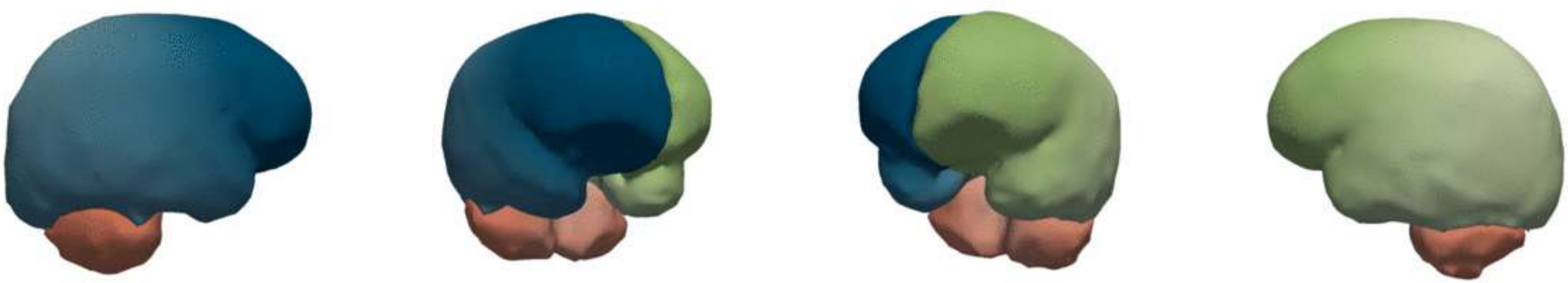


Durrleman, Fishbaugh, Gerig,
MICCAI 2011, MICCAI 2012

4D Shape Regression

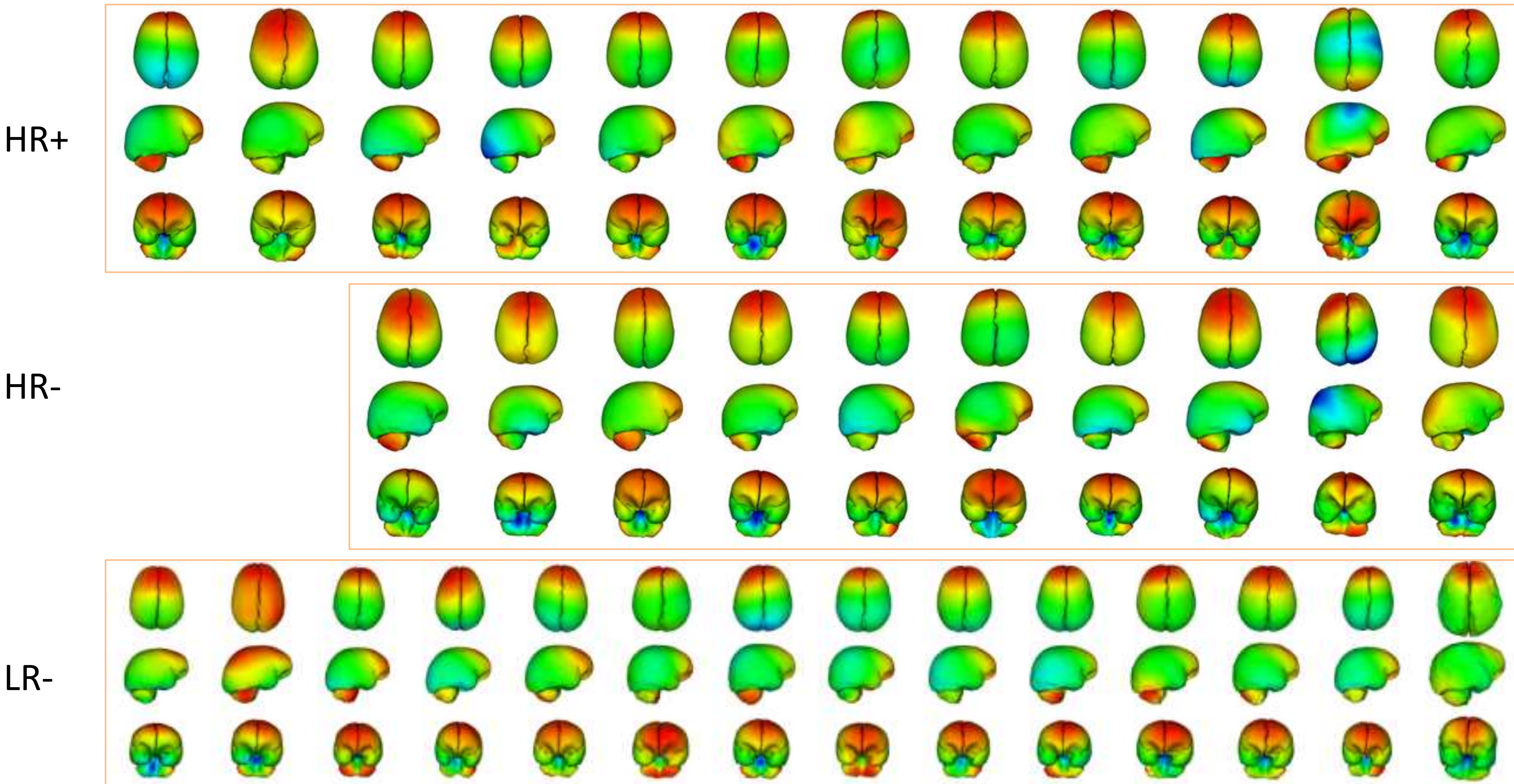


From discrete 3D shapes (6m,12m,24m) to continuous 4D shape model

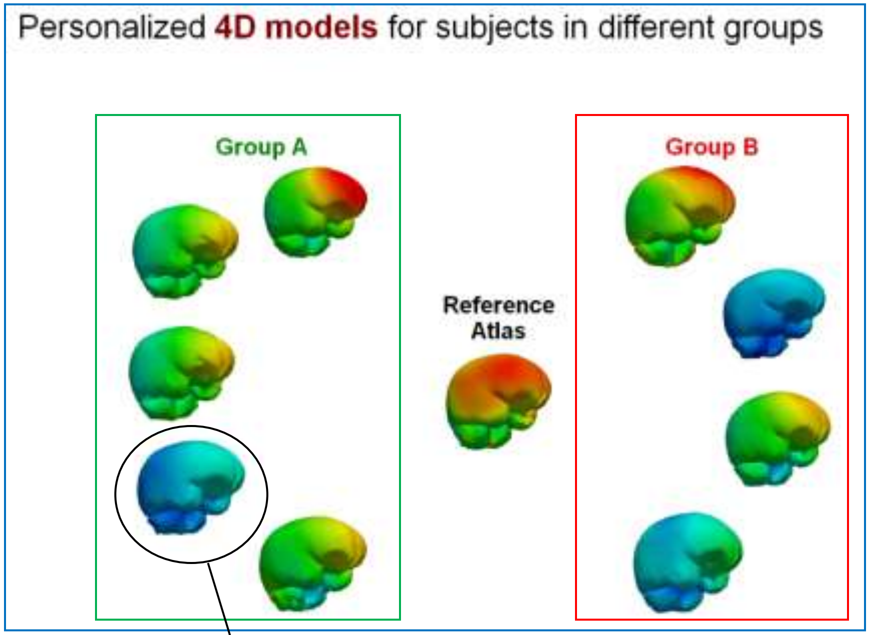


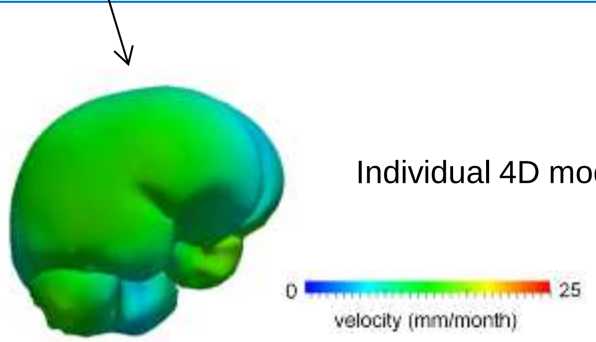
Fishbaugh, Durrleman, Prastawa, Gerig, MICCAI 2011, 2012

Individual 4D Growth Profiles

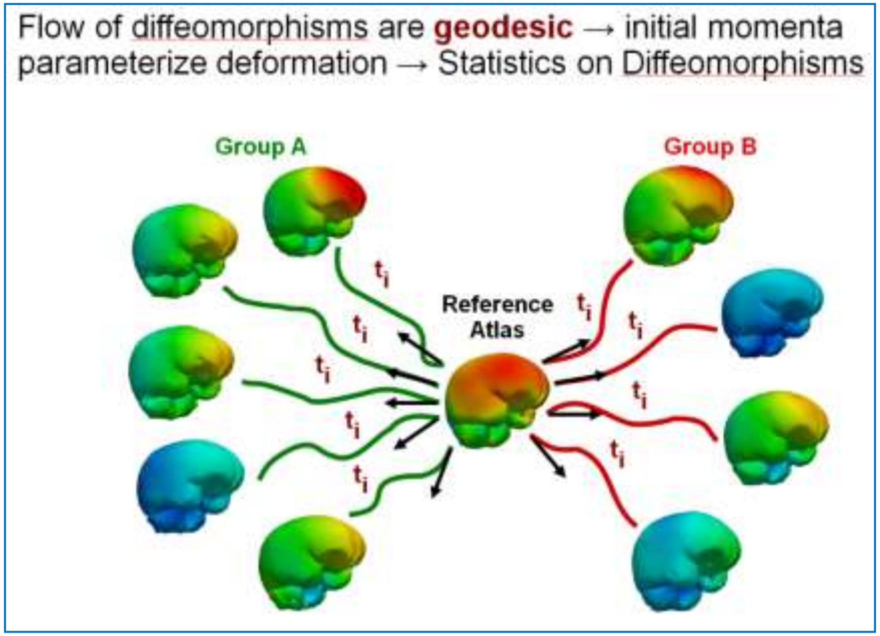


Statistics of 4-D Shape Trajectories

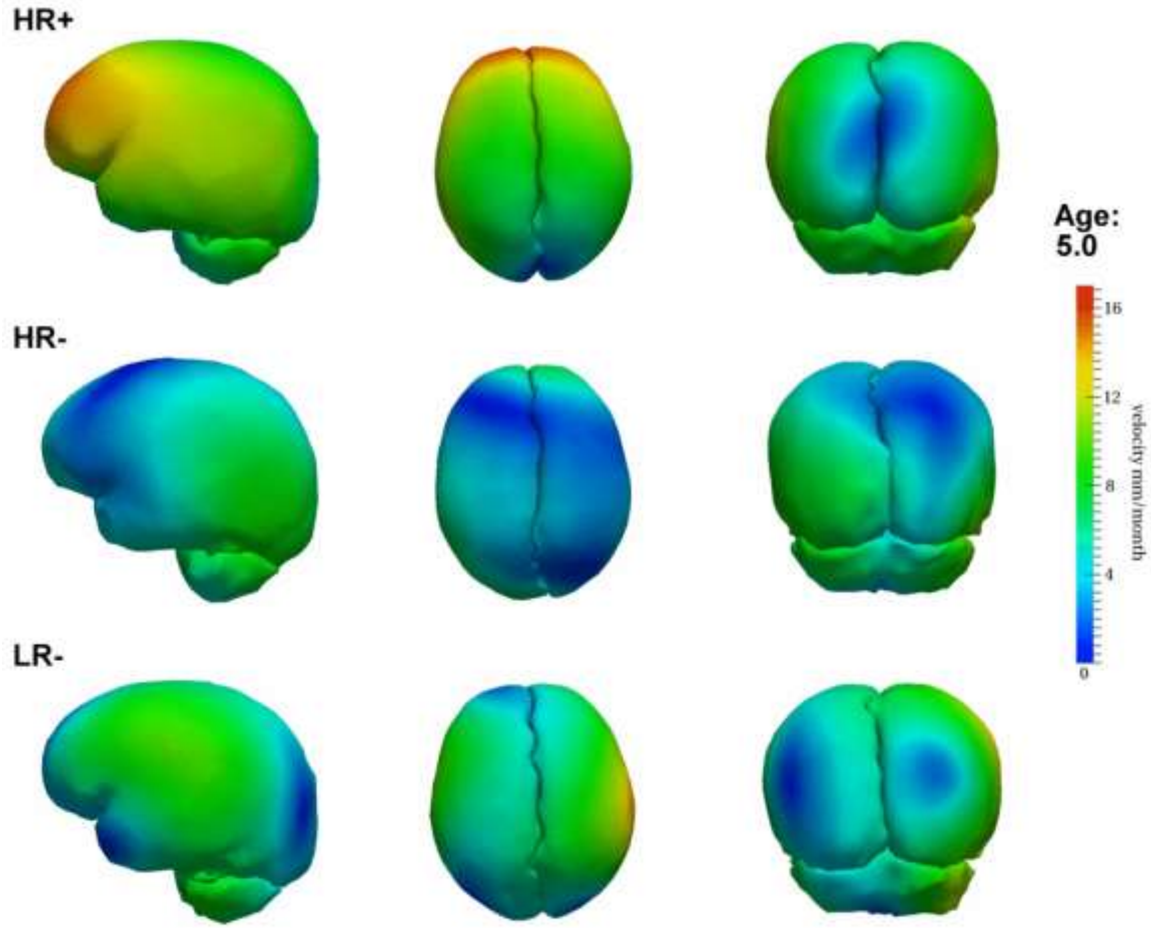




Individual 4D model



Work in progress: Statistics of 4D growth profiles



Autism Research Collaboration UNC (Piven, Hazlett)

HR+: High risk infant ADOS pos.

HR-: High risk infants ADOS neg.

LR-: Low risk healthy infants

Autism Research Collaboration ACE-IBIS (PI J. Piven, UNC)

Quantification of spatio-temporal population differences

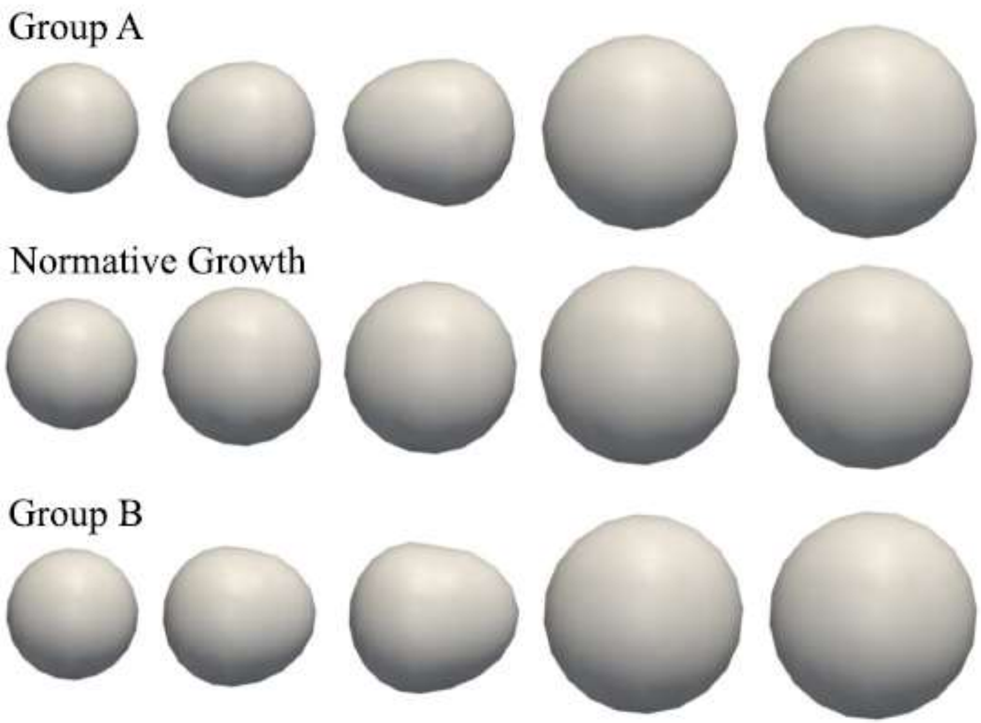


Fig. 2. The synthetic shape database with observations at 6, 10, 12, 18, and 24 months. **Top**: Typical shape observations for a subject from group A. **Middle**: The normative growth scenario. **Bottom**: Typical shape observations for a subject from group B.

Fishbaugh et al., MICCAI'12

New: Quantification of spatio-temporal population differences

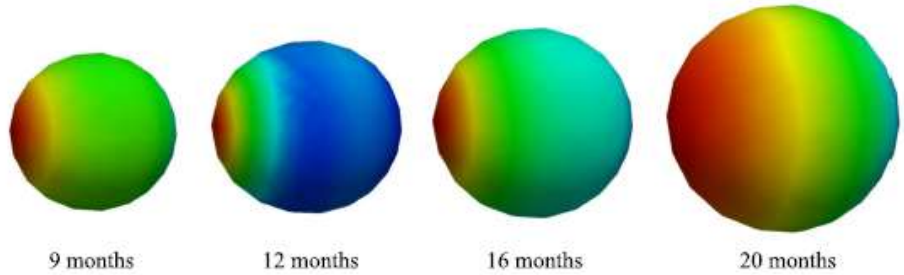


Fig. 3. The first major mode of deformation from PCA (mean plus one standard deviation) at selected time points for group A. Color indicates the displacement from the mean shape. The variability in the protuberance is clearly captured.

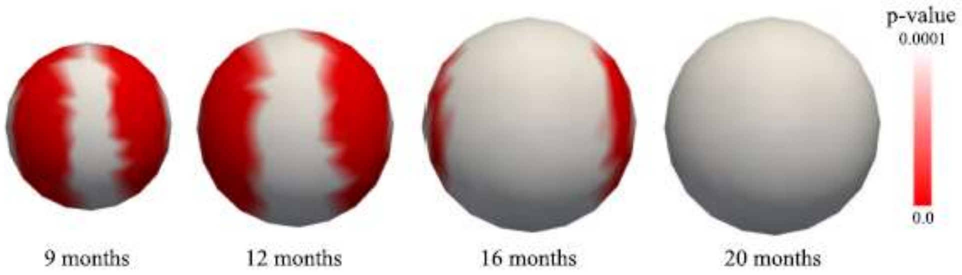
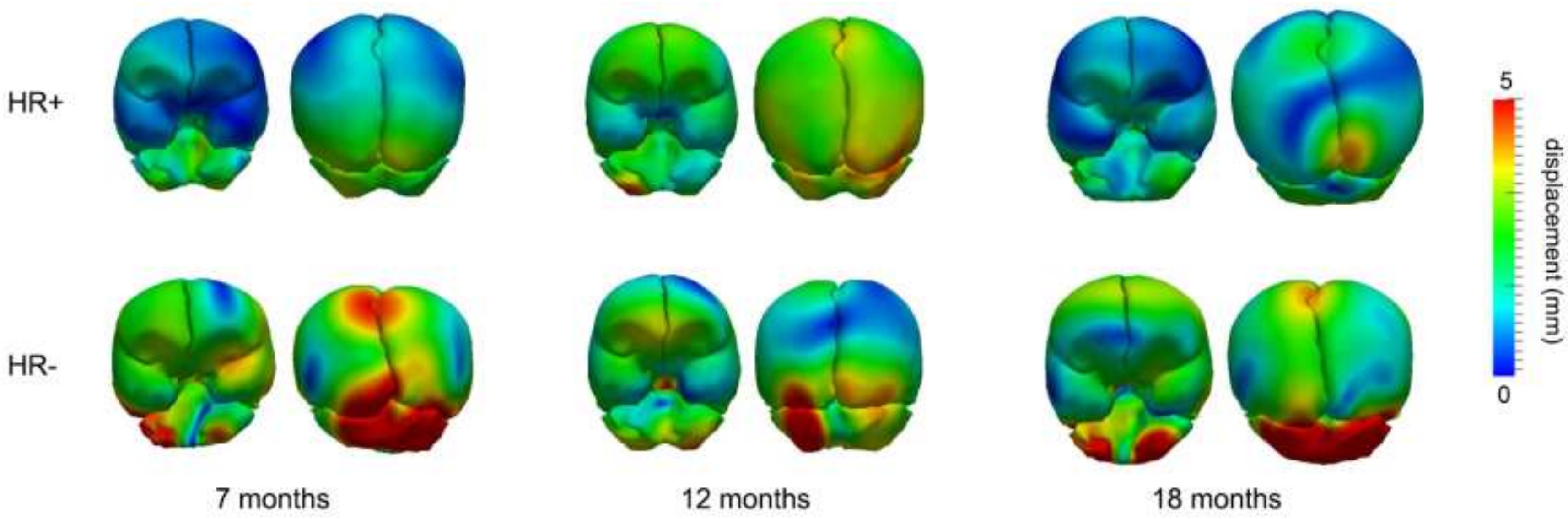


Fig. 4. Significant differences in magnitude of momenta between group A and B at several time points, with p-values displayed on the surface of the reference atlas.

Fishbaugh et al., MICCAI'12

First mode of deformation from **PCA** per age group

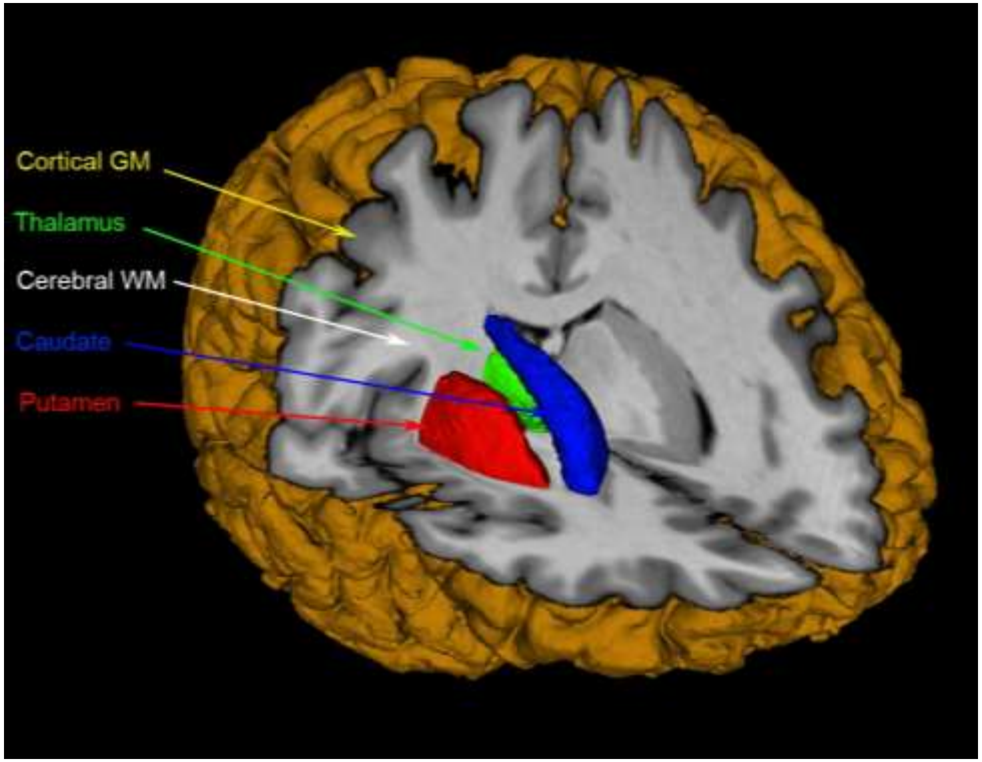


Hypothesis testing → **no significant** differences in magnitude of initial momenta

PREDICT-HD

Search for noninvasive biomarker with imaging…

- Symptomatic HD imaging findings
  - Atrophied caudate and putamen
  - Disproportionate loss of white matter
- Prodromal HD imaging findings
  - Striatal atrophy correlates with:
    - Neurological impairment
    - Poorer performance on cognitive assessments
    - Years to motor symptom onset

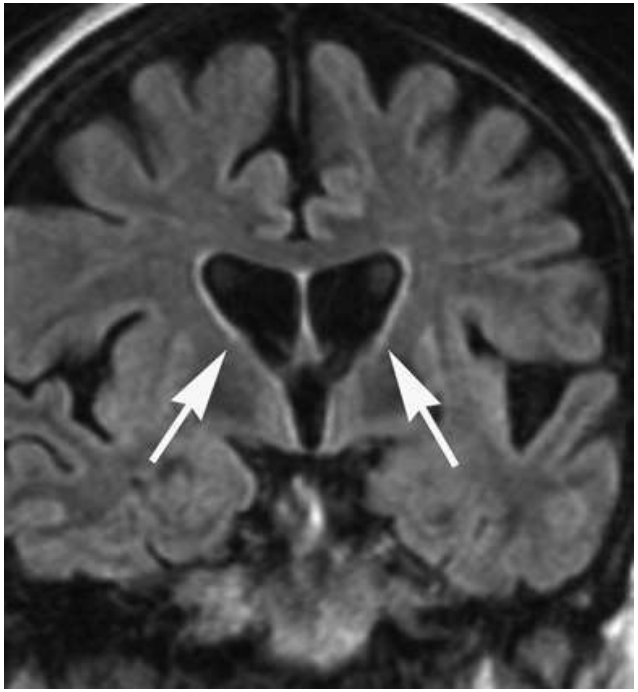


Courtesy Jane Paulsen, Hans Johnson, U-Iowa

Purpose: Huntington’s Disease

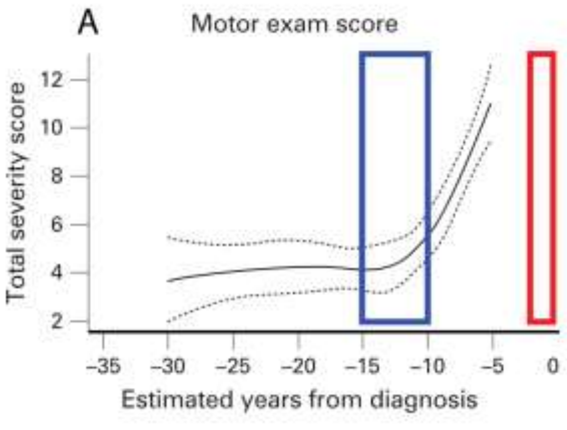
What is Huntington’s disease (HD)?

- Etiology
  - Progressive autosomal-dominant, polyglutamine disease
  - Mutation: Expanded trinucleotide CAG-repeat in huntingtin gene [77]
- Signs and symptoms: Motor, cognitive, and psychiatric disturbances
- Diagnosis
  - Usually made in mid-life (35-42)
  - Onset of motor symptoms with positive family history [76]
  - Confirmed with genetic testing (expanded CAG-repeat)
  - Radiographic feature: Prominently decreased striatum (caudate and putamen) at mid-stage
- Treatment: Symptomatic only
- Prognosis: Duration of disease is 17-30 years after diagnosis, depending on CAG-repeat length

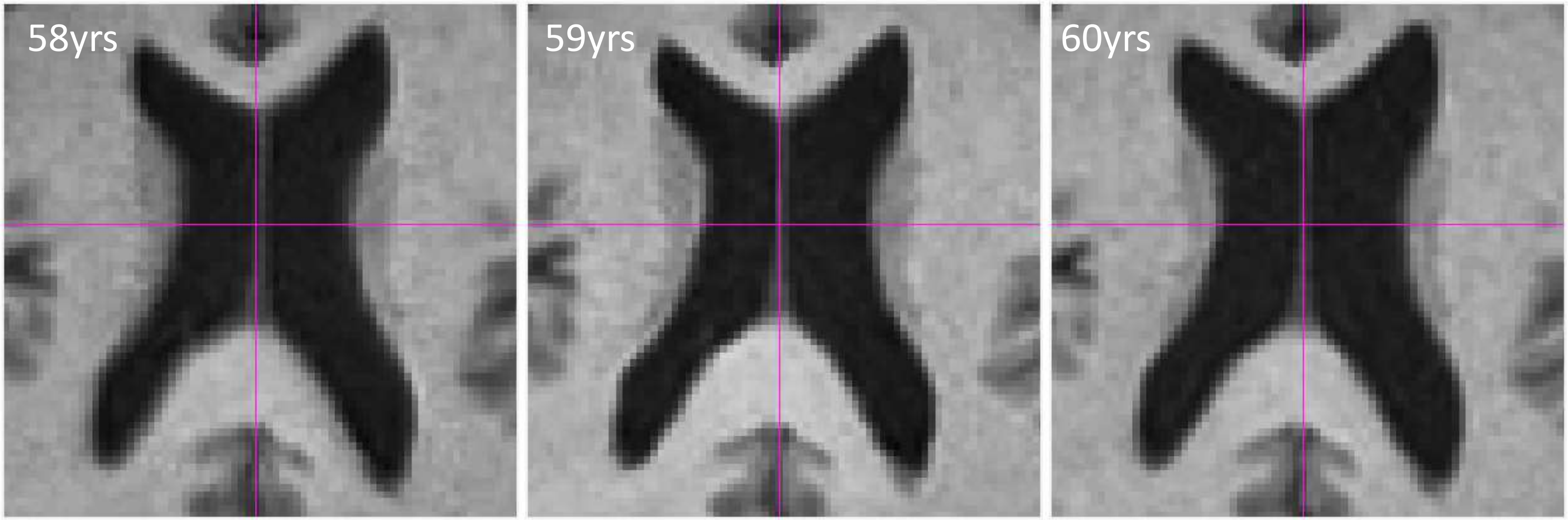


Purpose: HD treatment

- How can we help HD patients?
  - Present: Symptomatic treatment (no cure)
  - Future: Treatment for pre-symptomatic or **prodromal HD patients** that slow or stop progression **before** debilitating symptoms start
- What do prodromal treatment studies need?
  - Method to **monitor treatment efficacy** when visible symptoms are not present
  - **Solution: Use noninvasive biomarker**
    - Representable on a continuous scale
    - Distinguishes individuals by disease state

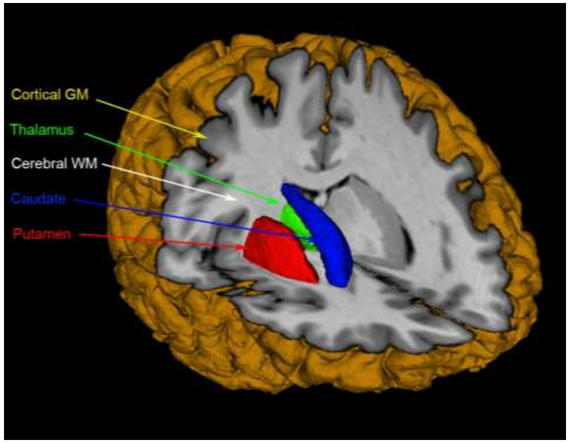


PREDICT-HD

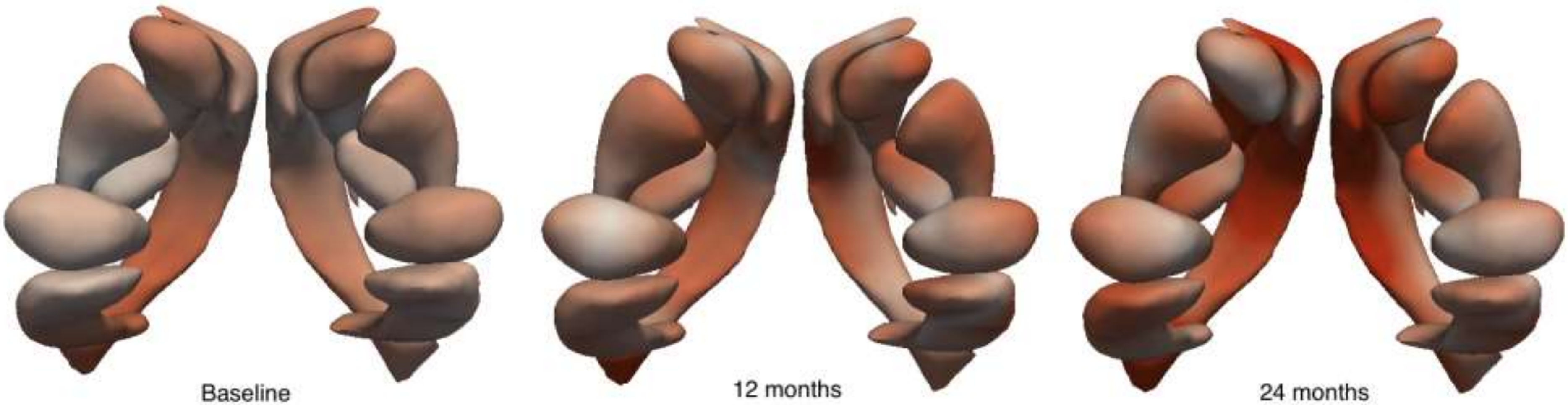


Huntington’s Disease Imaging Study:

- Neurodegenerative, progressive disease
- Longitudinal imaging (MRI)
- Subtle changes over time
- <u>Atrophied</u> caudate and putamen
- Processing: Longitudinal shape regression

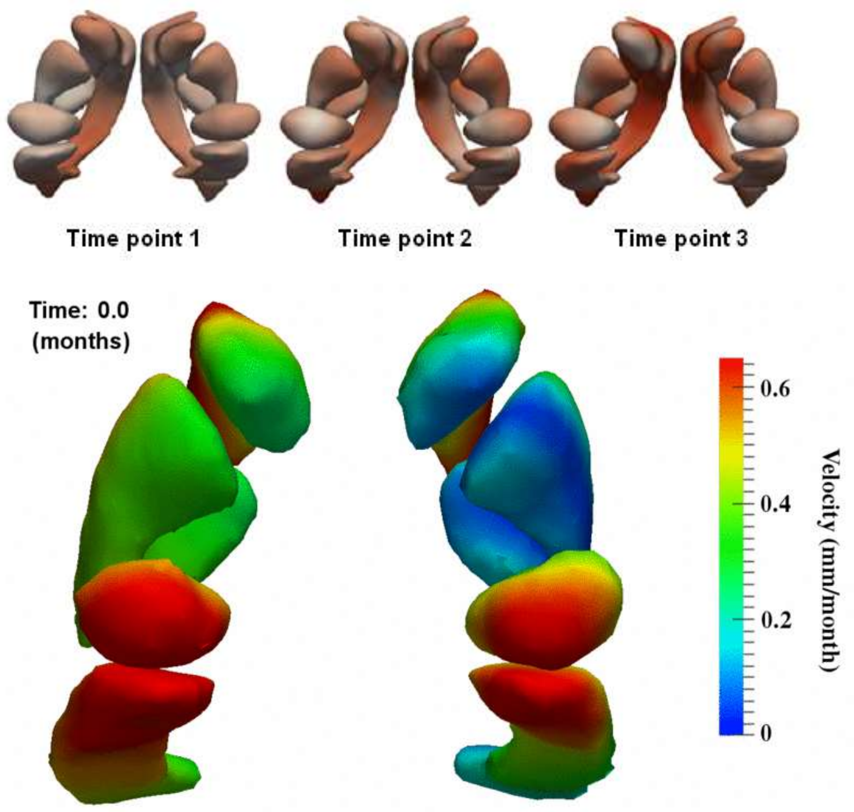


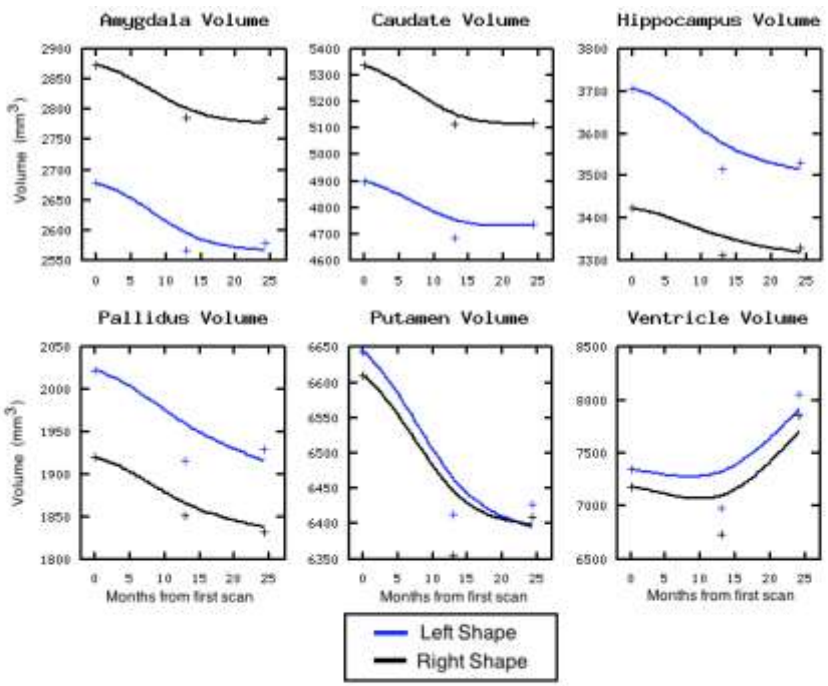
Huntington's Disease: Joint analysis of sets of anatomical structures



- Data: Iowa Huntington Disease (HD) study (NAMIC)
- Goal: Prediction of onset of HD from longitudinal preclinical imaging

Clinical Application: Neurodegeneration in Huntington's Disease



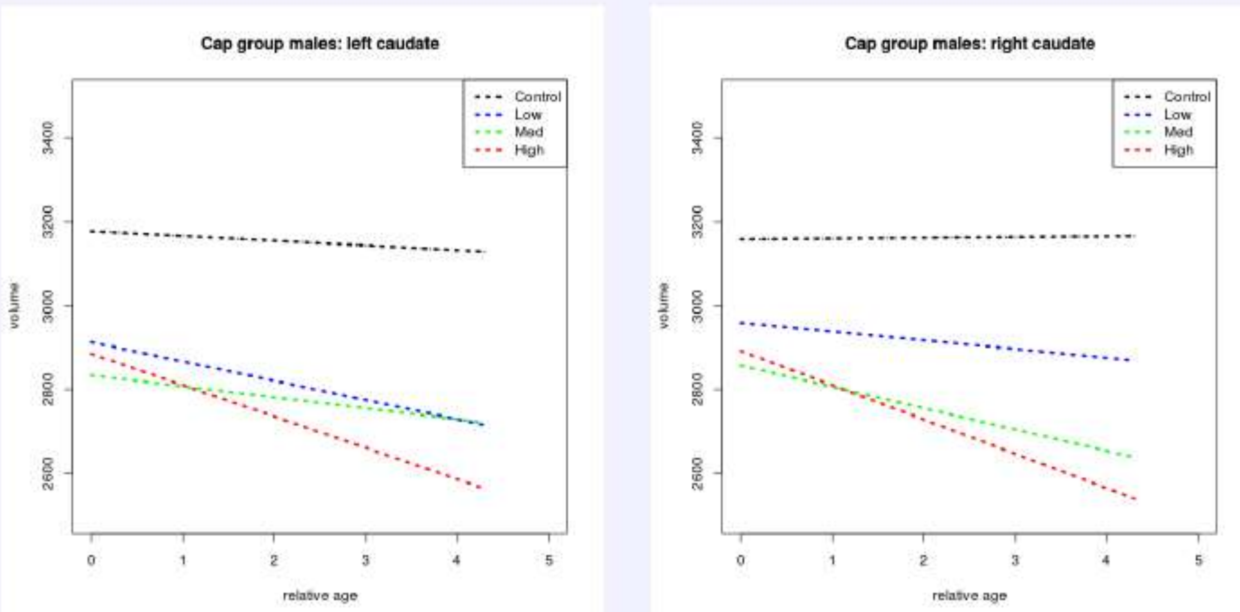


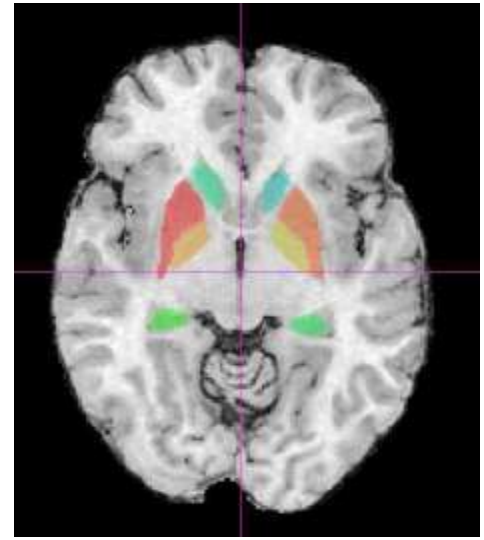
Continuous individual subjects' growth models

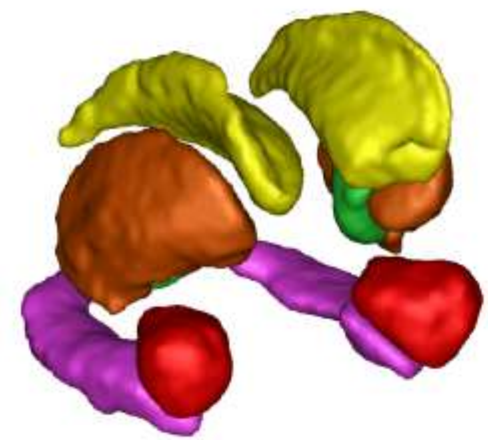
Quantitative information derived from 4-D shapes

James Fishbaugh et al., Utah

Degeneration of Caudate Volume by Clinical Risk Groups





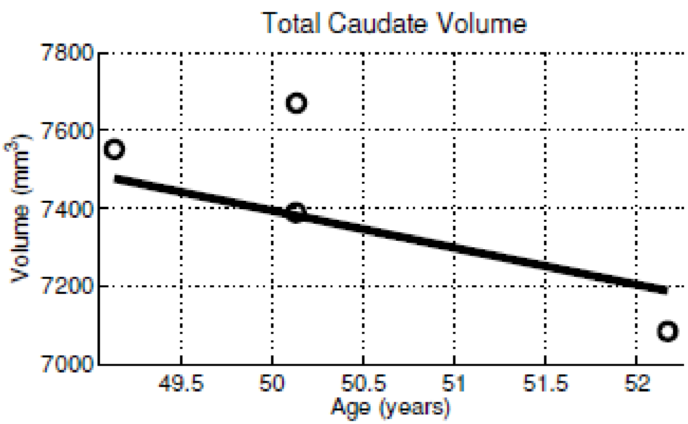


Model:

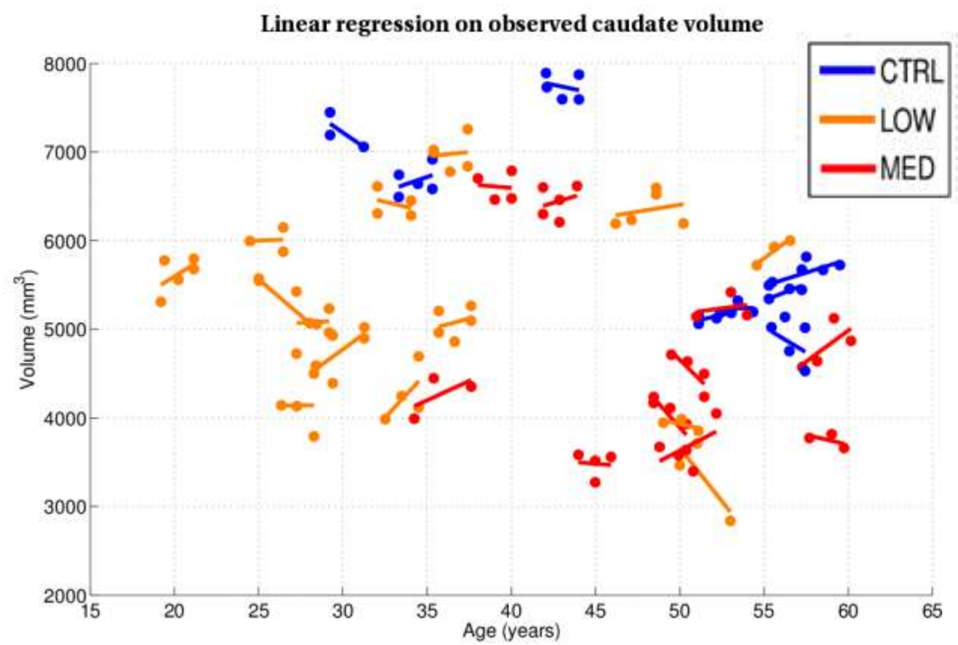
$$\text{volume} = \beta_0 + \beta_1\,(\text{relAge})$$
$$+\beta_2\,(\text{cap group}) + \beta_3\,(\text{relAge} * \text{cap group})$$

Muralidharan, Fletcher, Fishbaugh, Gerig, 2013

Personalized/Individual Profiles: Problem of Variability in 3D Segmentation

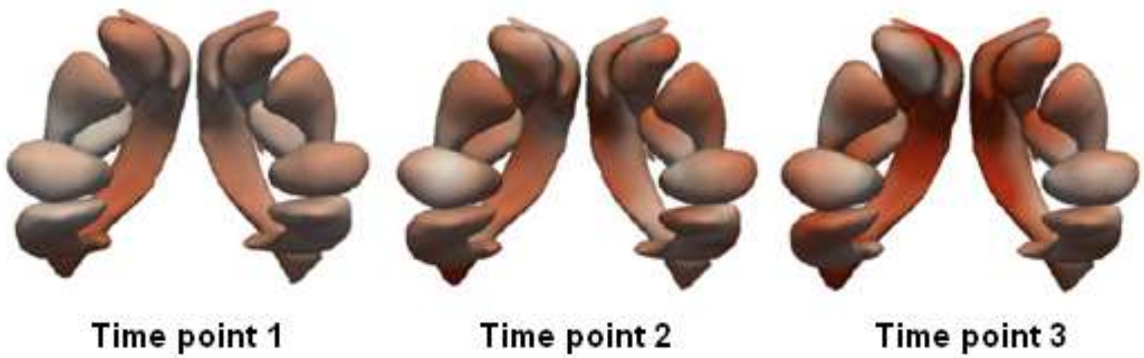


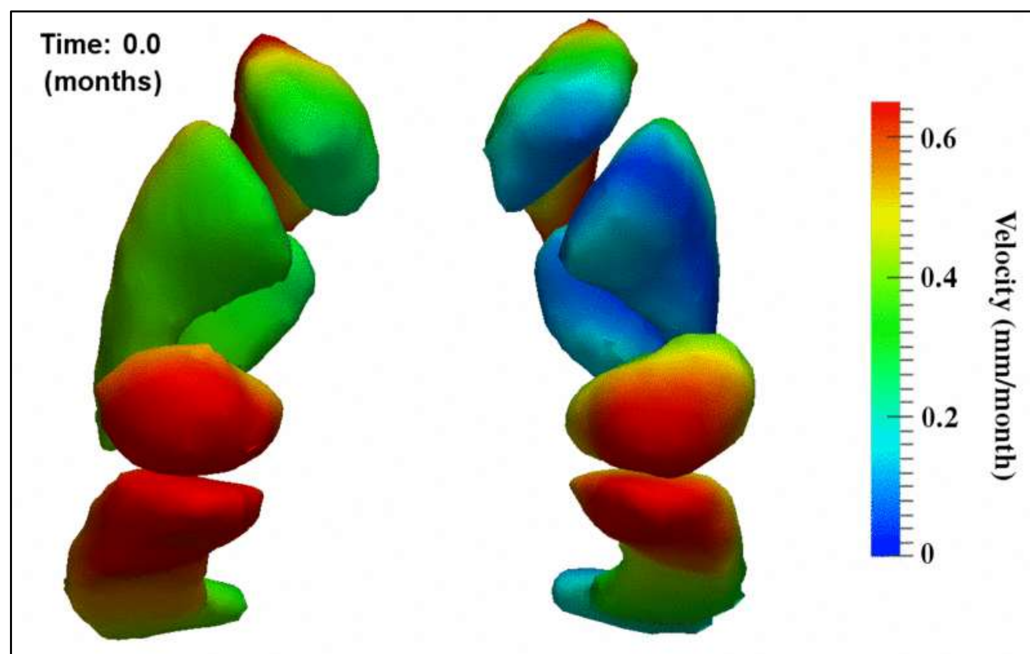
Volumes from one subject



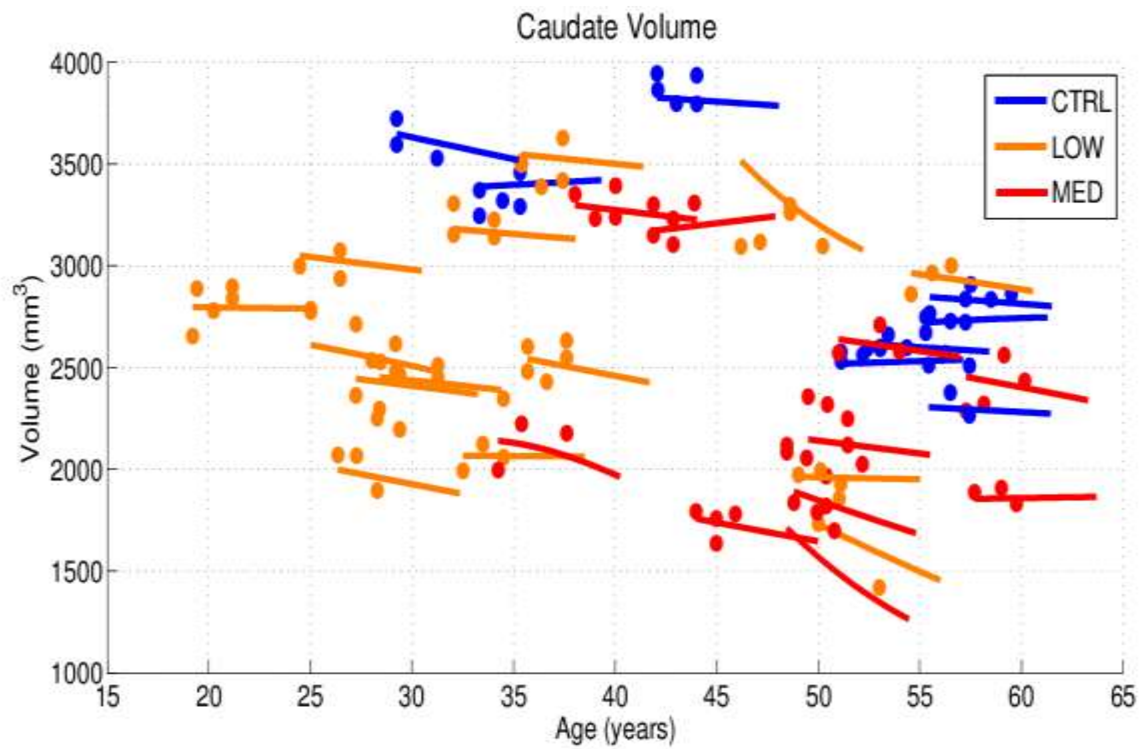
Volumes from multiple subjects with varying disease burden

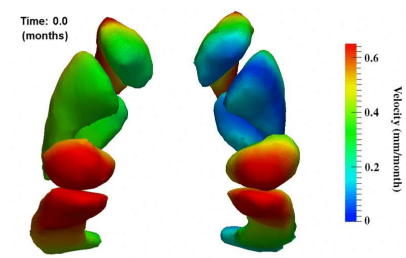
HD: Joint 4D Modeling of subcortical structures





Subject-Specific Shape Modeling





	CTRL	LOW	MED
Caudate	0.78%	4.22%	6.25%
Hippocampus	0.65%	1.09%	2.18%
Acumben	0.11%	2.13%	3.09%

Table 1: Average percentage volume decrease for caudate, hippocampus, and acumben.

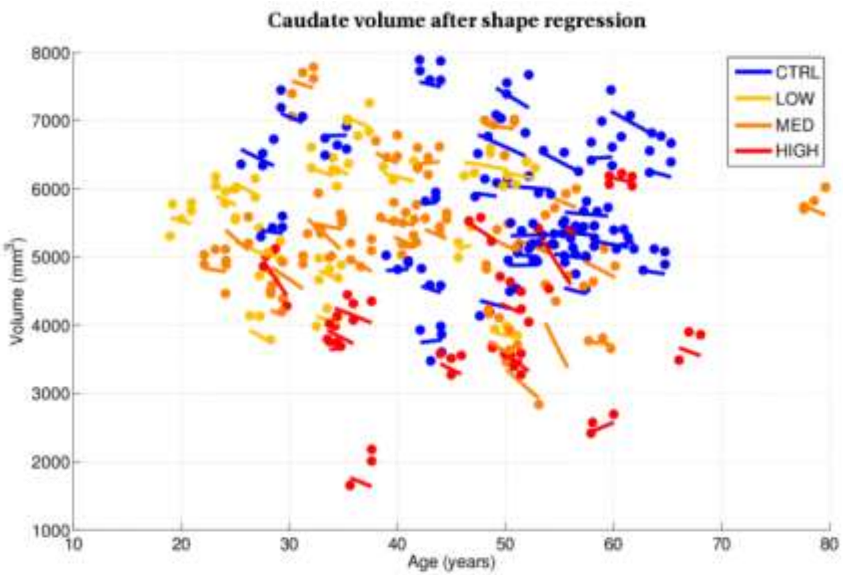
- Caudate volume for 32 subjects (3 time pts) extracted after shape regression.
- Observed volumes shown as circles, highlighting the noise in segmentation.
- Our shape regression estimates consistent shape trajectories by considering all shapes simultaneously.
- **Result: Improved subject-specific modeling of neurodegeneration.**

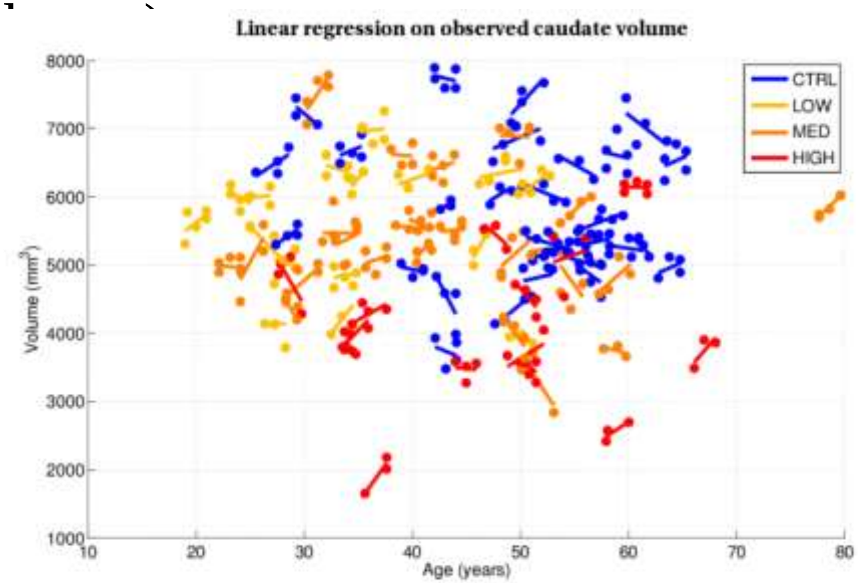
Muralidharan, Fishbaugh et al, MICCAI 2014

Longitudinal Segmentation

Huntington's Disease study (30 CTRL, 16 LOW, 24 MED, 14 HIGH)

- Models estimated with subcortical shape complexes (12

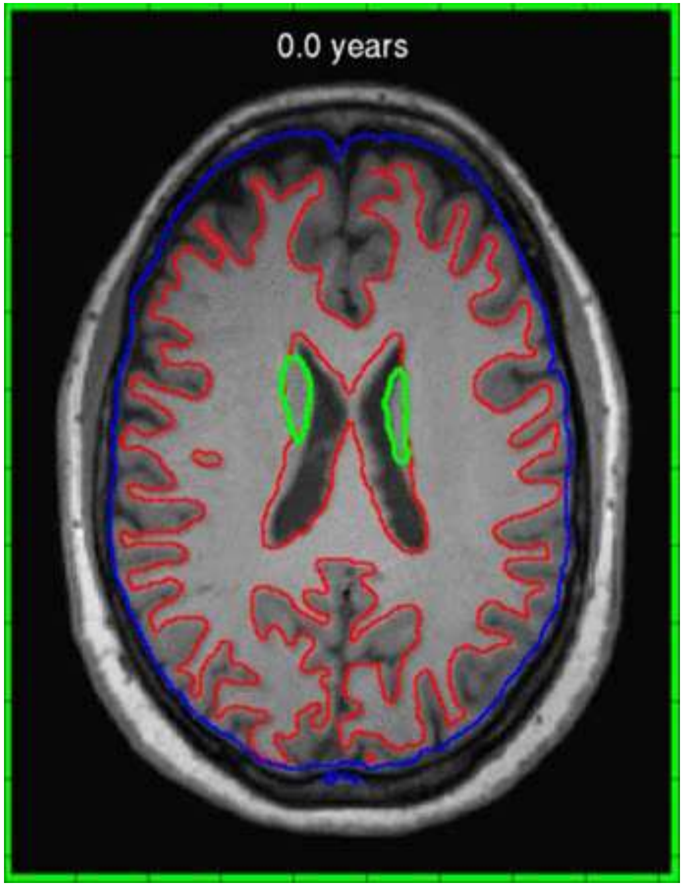




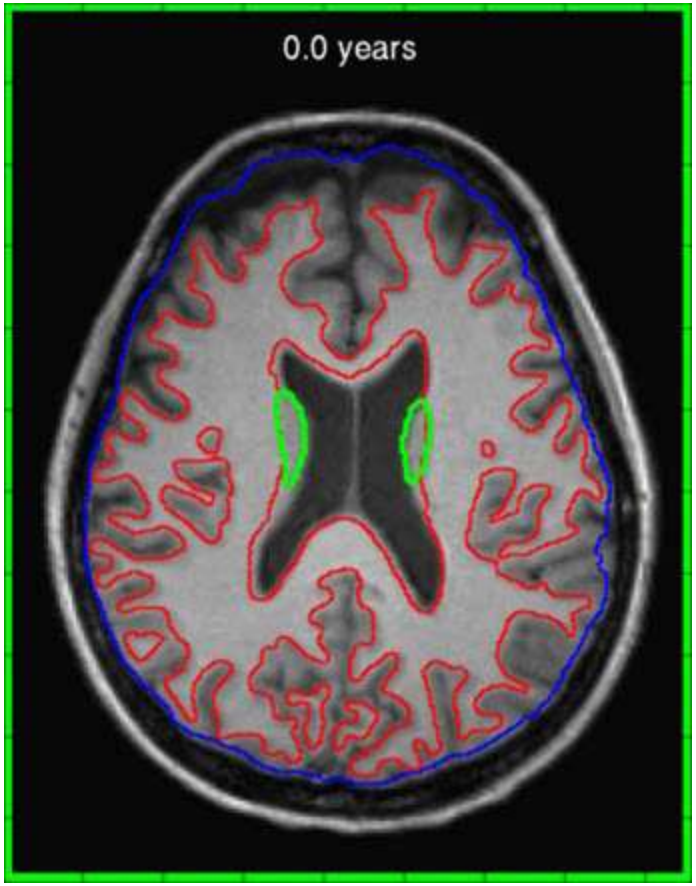
	PERCENT VOLUME CHANGE FROM SHAPE REGRESSION				PERCENT VOLUME CHANGE FROM LINEAR REGRESSION			
	CTRL	LOW	MED	HIGH	CTRL	LOW	MID	HIGH
CAUDATE	-1.41	-2.11	-3.39	-4.84	0.01	1.31	1.00	1.05
PUTAMEN	-3.11	-5.01	-5.42	-6.74	0.29	-0.09	0.06	0.01
HIPPOCAMPUS	-1.55	-1.38	-1.34	-1.55	0.32	0.93	1.23	0.96
THALAMUS	-1.68	-2.47	-1.19	-1.93	0.66	0.49	-0.06	0.40
ACUMBEN	-0.58	-1.52	-1.39	-2.67	-0.04	-2.81	-0.01	1.36
PALLIDUS	-3.82	-5.49	-5.51	-6.76	0.29	-0.25	-0.52	-2.43

Subject-specific 4-D shape & image regression

Control 2yrs Interval

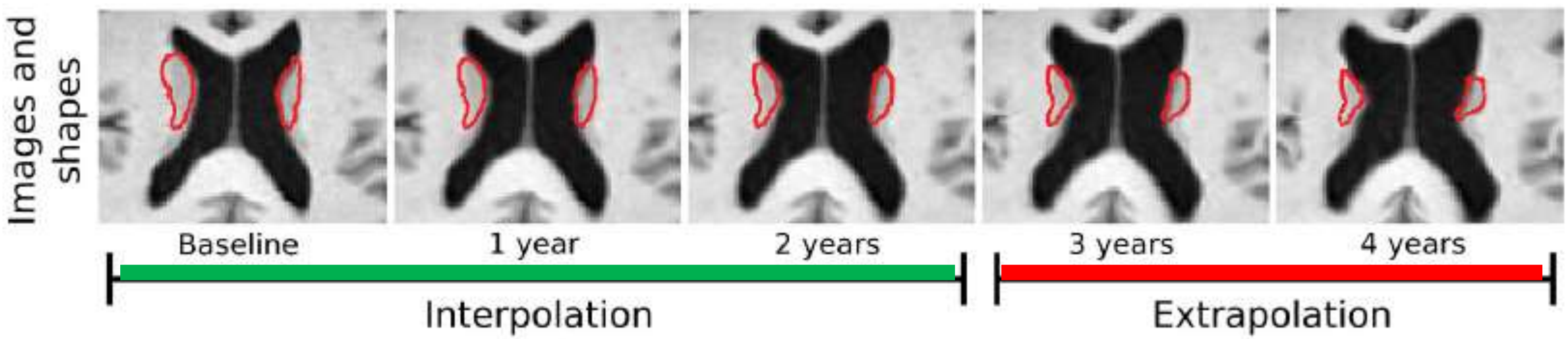


Huntington's D. 2yrs Interval



Fishbaugh et al., IPMI 2013

Huntington's Disease: Joint 4-D Modeling of Shapes and Images



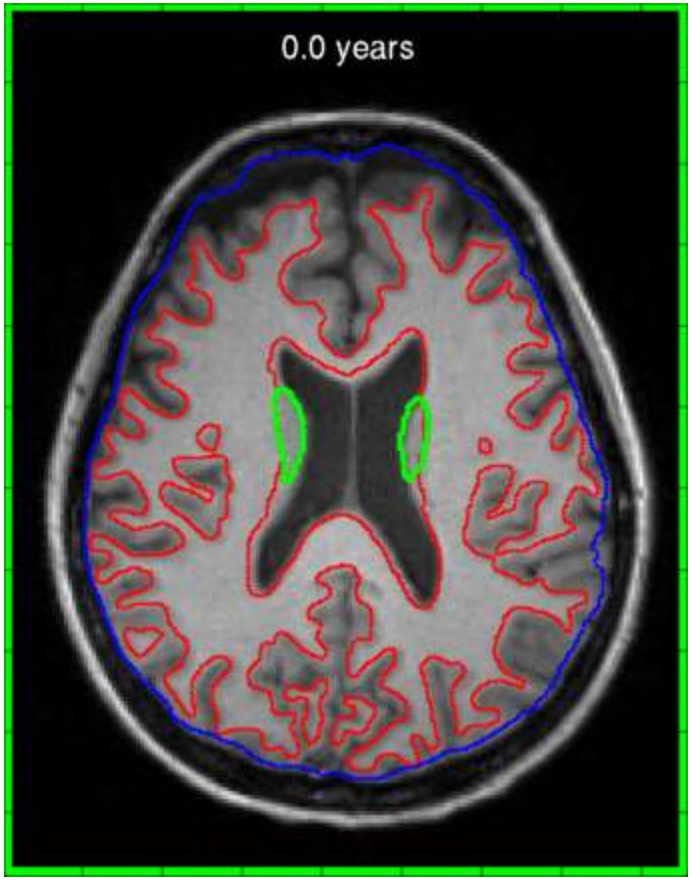
Single subject diagnosed with HD scanned at 58, 59, and 60 years of age.

- T1W images.
- Left/right caudate segmented and manually cleaned.
- Geodesic model can be used to *extrapolate* into the future.

Work in Progress: Patient-specific 4-D shape & image regression

Control Extrapolated

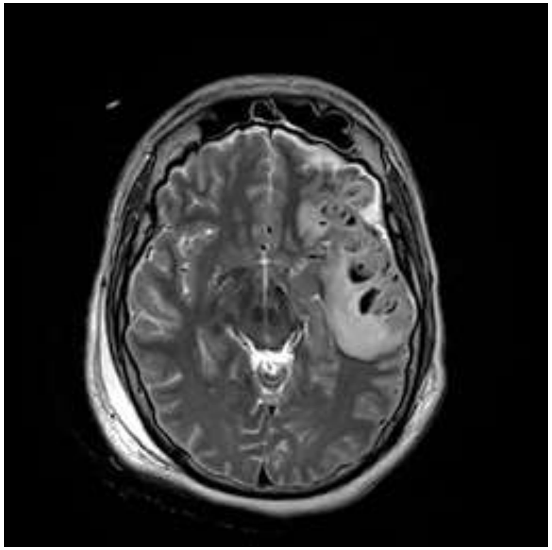
HD Extrapolated

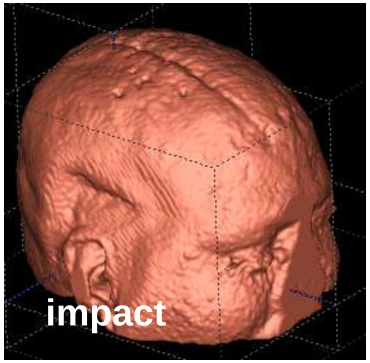


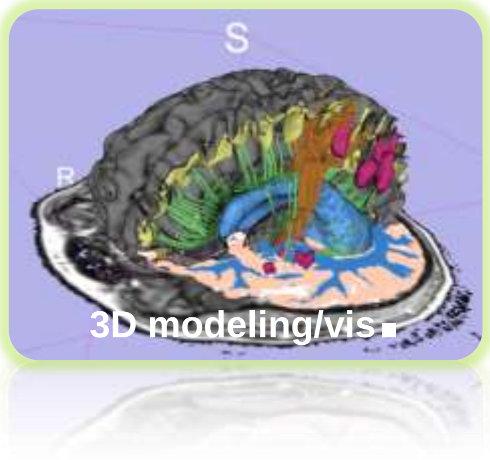
Fishbaugh et al., ISBI '13, IPMI '13

Traumatic Brain Injury: Patient-specific Modeling of Brain Damage and Recovery

- US: 1.5 Million TBI cases per year, sports, car acc., workplace, veterans, ..
- 650,000 hospitalizations for long-term brain injury: "silent death".
- Few treatment options, no proven rehabilitation, only management.
- **Goal**: Towards rehabilitation experiences that change brain neuroanatomy & function with a reduction/cessation of symptoms.
- Collaboration UCLA TBI, UCLA Neurosurgery, USC LONI, Utah

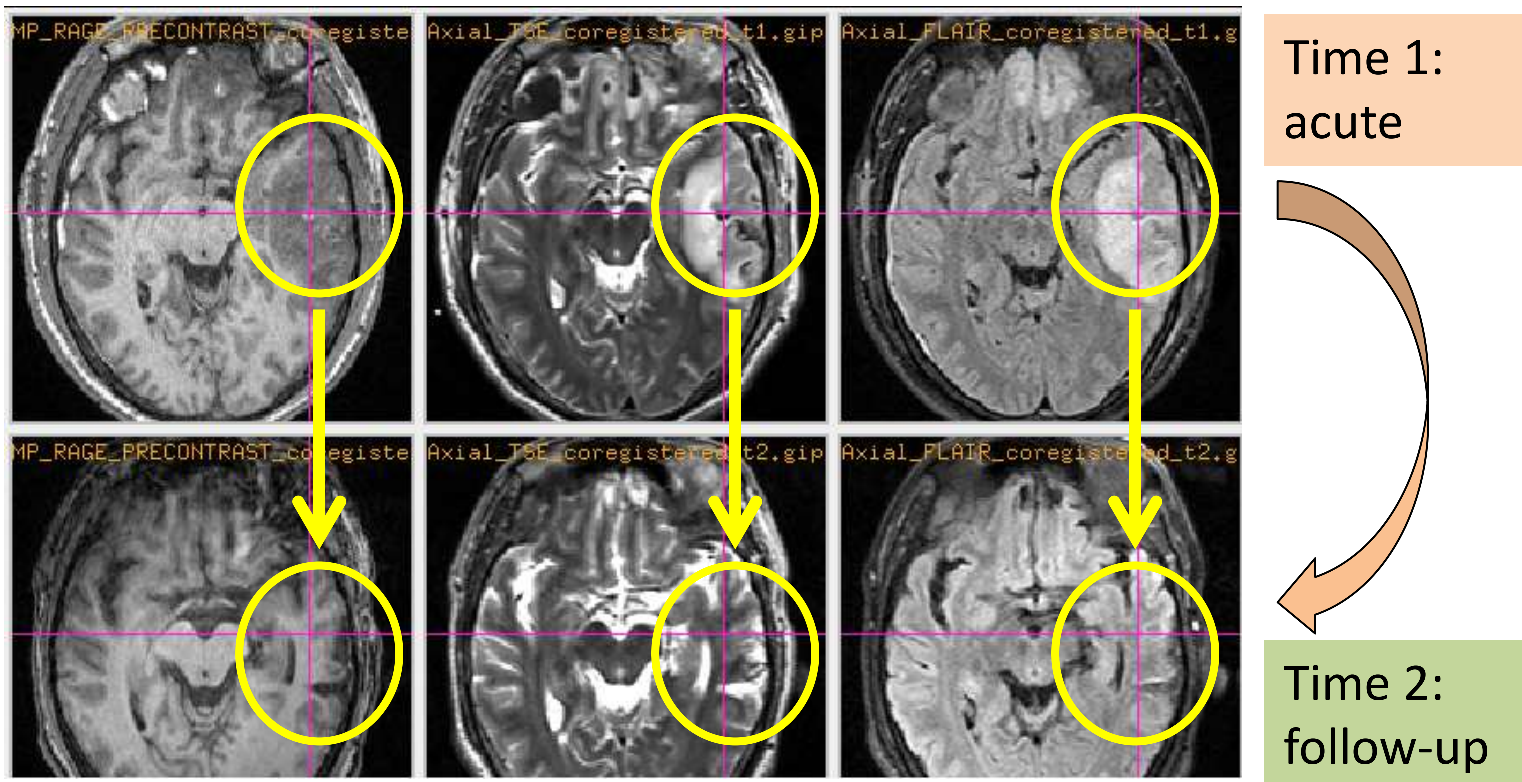






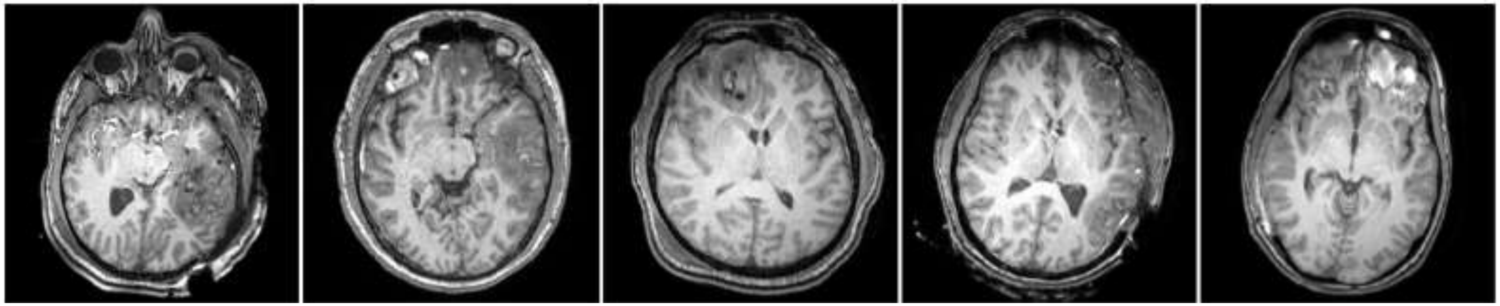
Multi-contrast & multi-time point image analysis in presence of complex pathology

Change of normal anatomy & lesions over time



TBI subject, collaboration UCLA TBI clinic & LONI

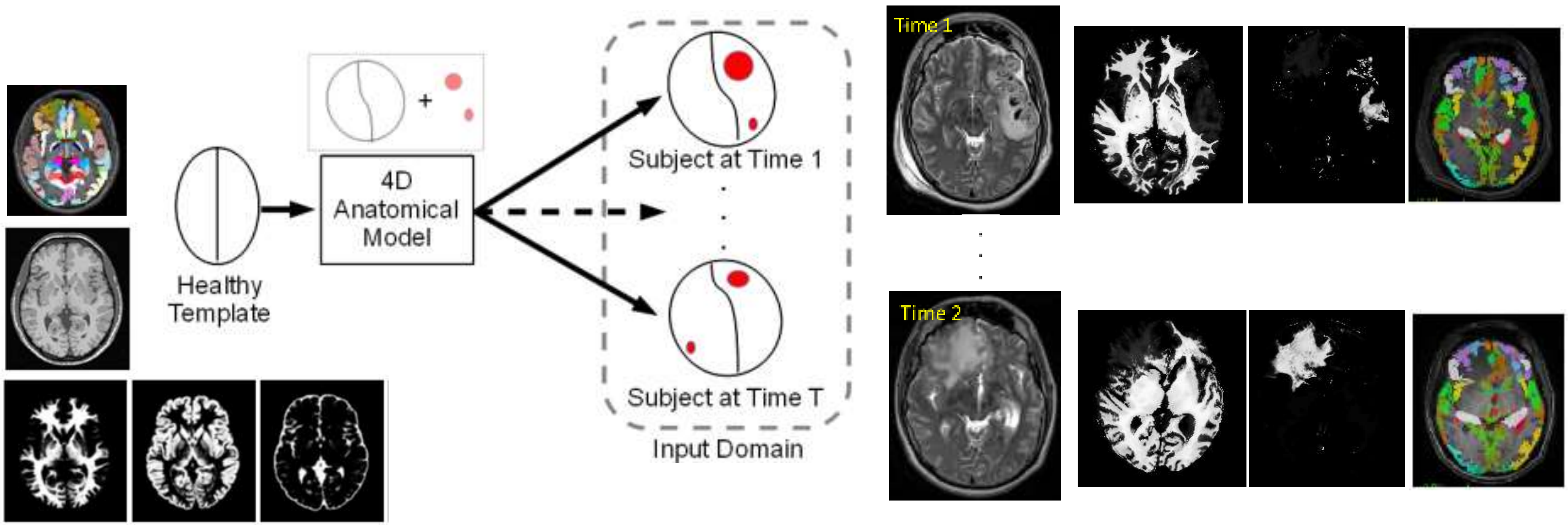
The “Pathological Anatomy”



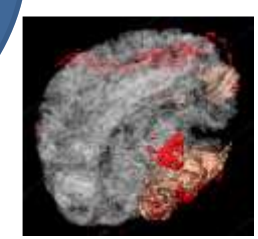
Axial views of acute T1 images of five TBI subjects

Irimia et al., Frontiers in Neurotrauma, 2012
Irimia et al., NeuroImage: Clinical, (1),1, 2012
Wang, Prastawa, Gerig et al., ISBI 2012

The “Pathological Anatomy”

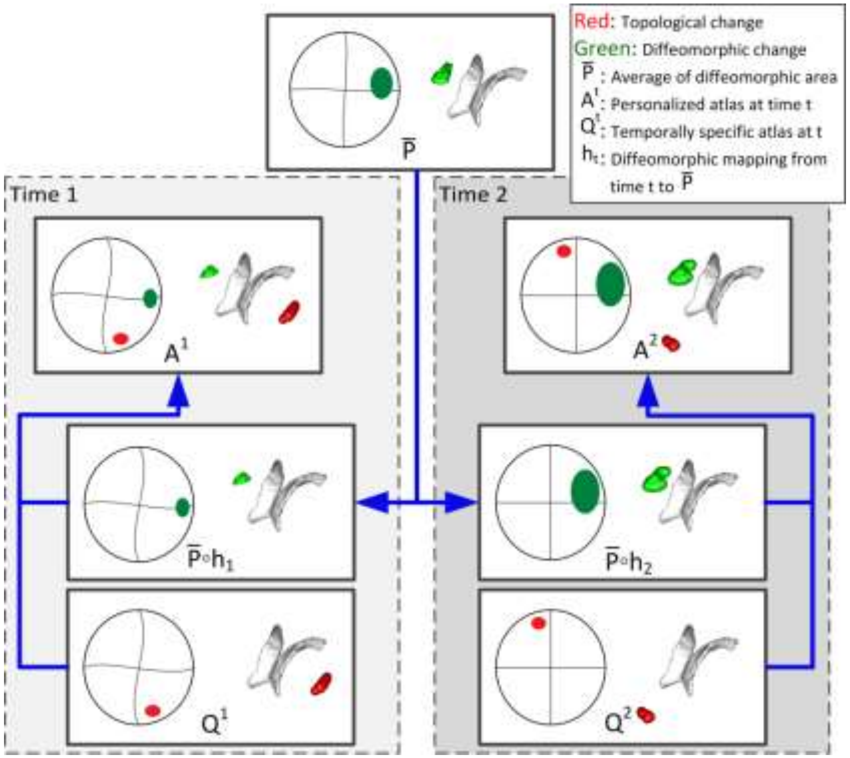


**Map “pathological images”
into reference frame of “normals”**



Irimia et al., Frontiers in Neurotrauma, 2012
Irimia et al., NeuroImage: Clinical, (1),1, 2012
Wang, Prastawa, Gerig et al., ISBI 2012

4D Registration/Segmentation



- Personalized atlas: Smooth subdivision of posteriors into diffeomorphic and non-diffeomorphic regions using the probability of topological change.
- Diffeomorphic component: Temporally global atlas.
- Non-diffeomorphic com-ponents: Temporally local pdfs.
- IEEE ISBI 2012: Wang et al.

The personalized atlas at time point t is defined as:

$$A^t = (1 - \Gamma^t)\bar{P} \circ h_t + \Gamma^t Q^t.$$

where Γ^t is the probability of topological change.

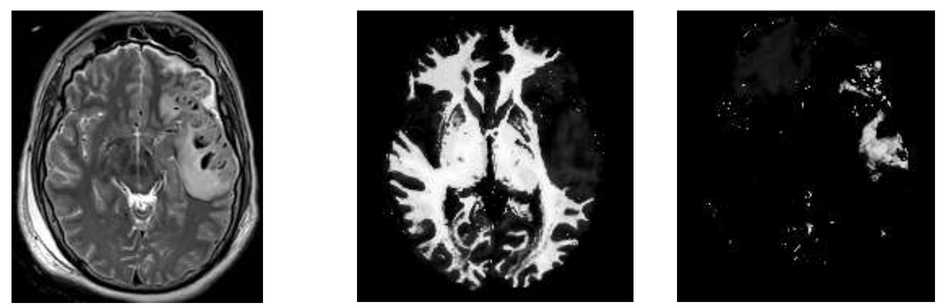
The personalized atlas construction is formulated as a minimization of the energy function Ψ :

$$\Psi = \sum_t \| (1-\Gamma^t)(P^t - \bar{P} \circ h_t) \|^2 + \| \Gamma^t (P^t - Q^t) \|^2 + w \| \Gamma^t \|^2 + R(h_t).$$

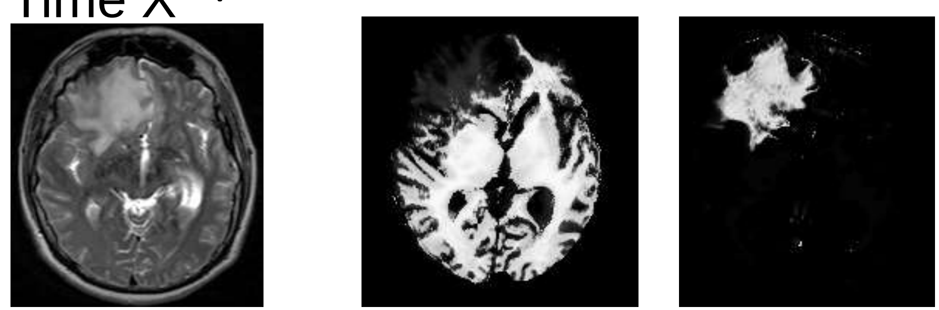
4D-PARSeR (Pathological Anatomy Regression via Segmentation and Registration

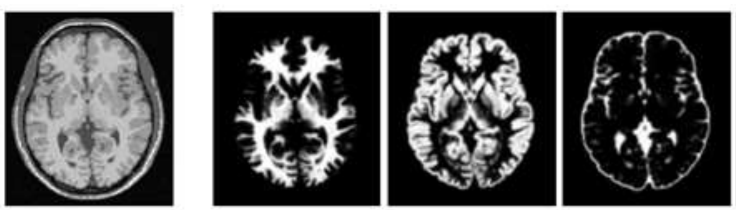
- Split diffeomorphic from non-diffeomorphic changes
- Spatial prior ${P^c}_t$ for class c at time point t: $P_t^c = A^c \circ \phi_t + Q_t^c$
  - *A* is the tissue class probability
  - Q_t: non-diffeomorphic probabilistic change at time t
  - Subject-specific atlas

Time 1



Time X





Normative brain template

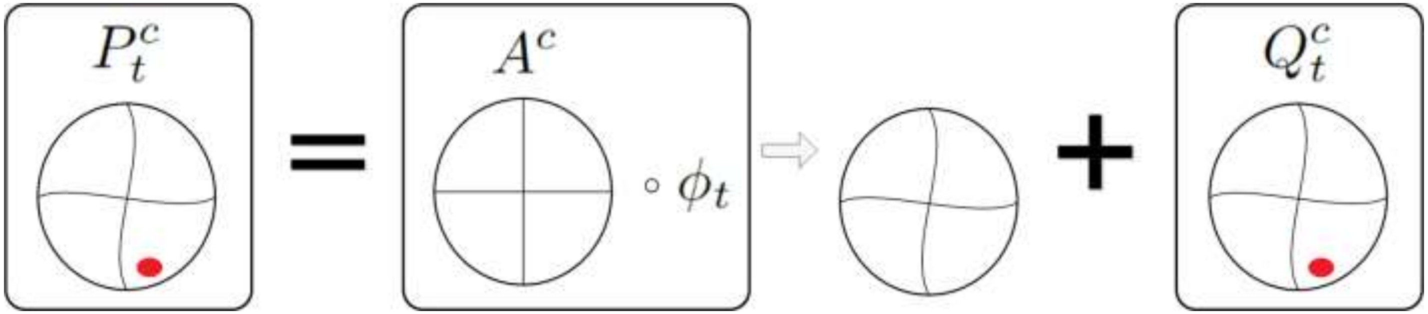
Spatial Prior

The spatial prior P_t^c is modeled as:

$$P_t^c = A^c \circ \phi_t + Q_t^c$$

where A^c is the tissue class probability that is initially associated with the healthy template, ϕ_t is the diffeomorphic deformation from time *t* to the atlas, and Q_t^c is the non-diffeomorphic probabilistic change for time *t* (e.g. lesions).

Concept:



Modeling Pathological Anatomy

Given the model and 4D multimodal images I_t at timepoints t , we estimate model parameters that minimizes the following functional:

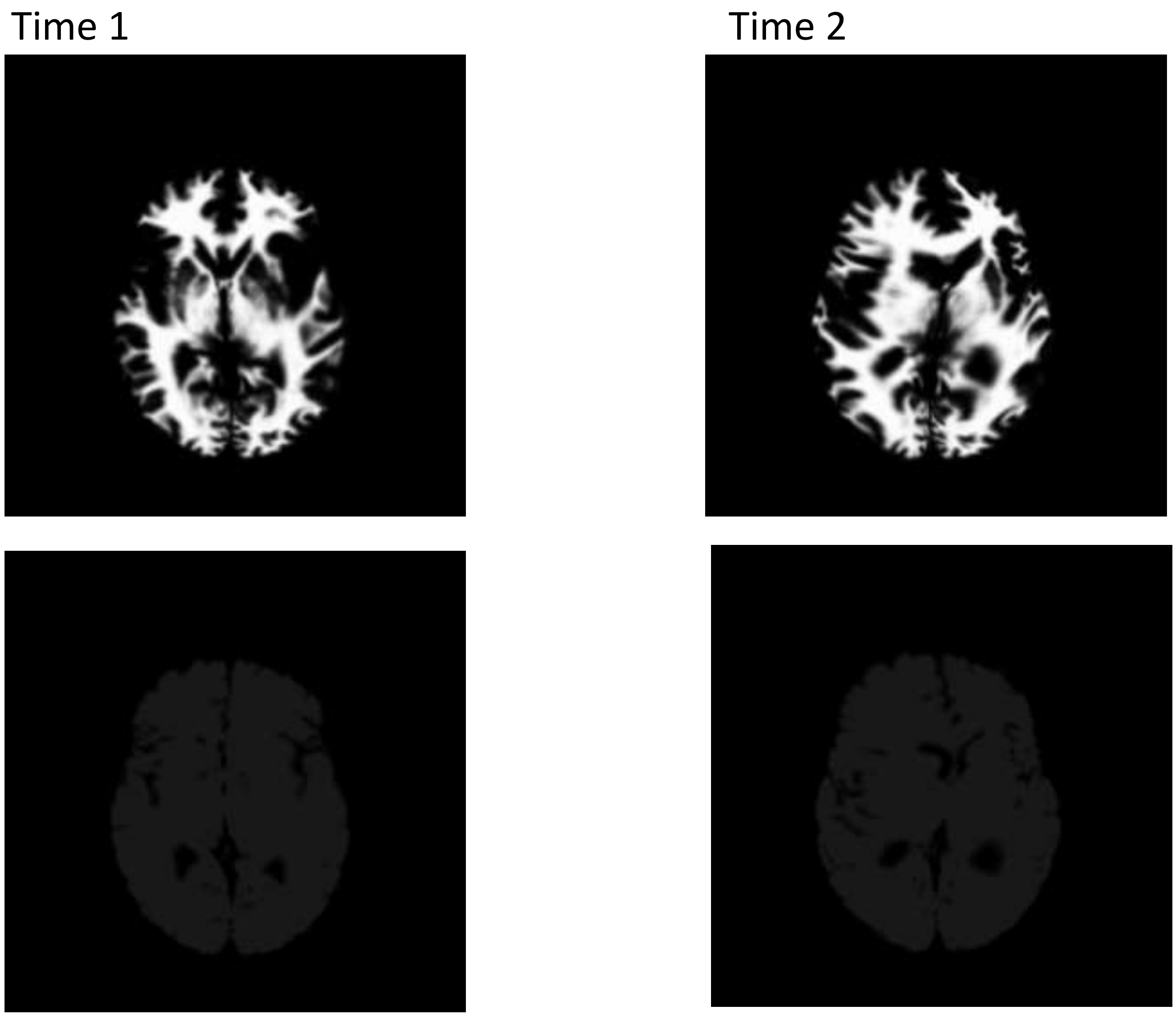
$$\operatorname{argmin}_{A,\phi_t,Q_t,\theta_t} \mathcal{F}(A,\phi_t,Q_t,\theta_t) + \mathcal{R}_1(Q) + \mathcal{R}_2(A) + \mathcal{R}_3(\phi)$$

where $\mathcal{F}$ is data functional (negative total log-likelihood):

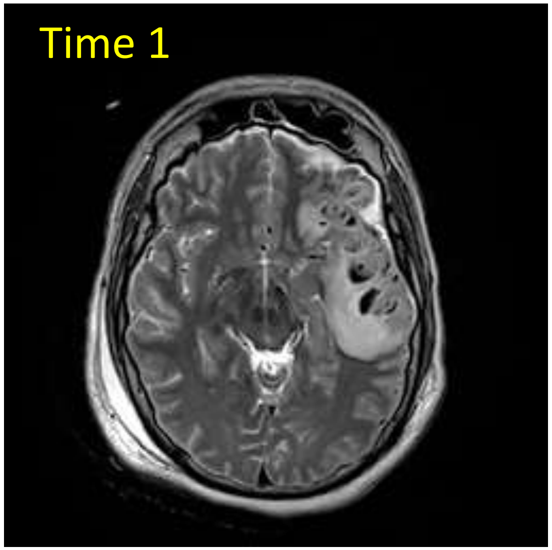
$$\mathcal{F}(A,\phi_t,Q_t) = -\sum_{t=1}^{T}\sum_{x=1}^{N}\log\left(\sum_{c=1}^{C} P_t^c(x)\, p(I_t(x)|c,\theta_t^c)\right)$$

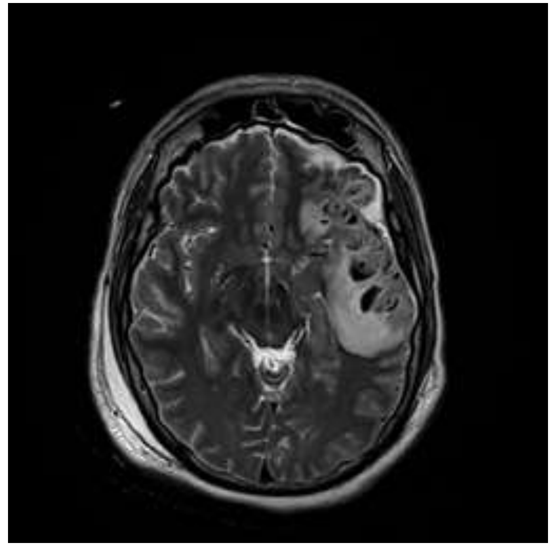
where P_t^c is spatial prior, $\mathcal{R}$ represents the regularity terms. User input or **domain adaptation** can be used to initialize data likelihood.

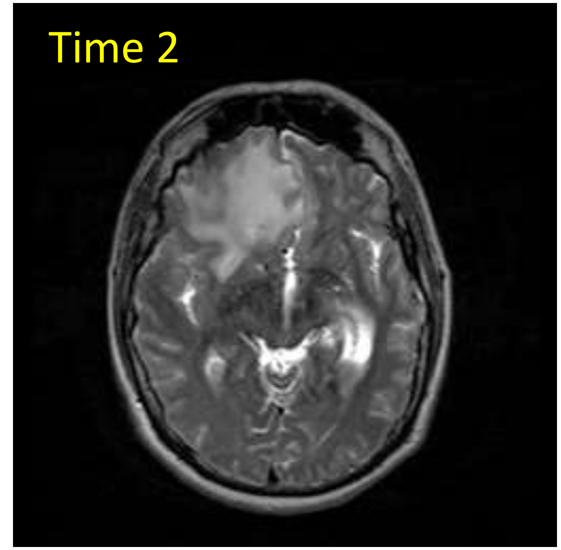
Pathological Anatomy Regression

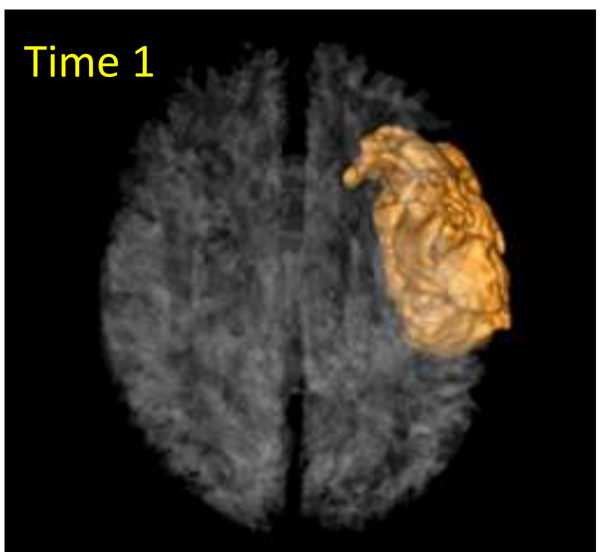


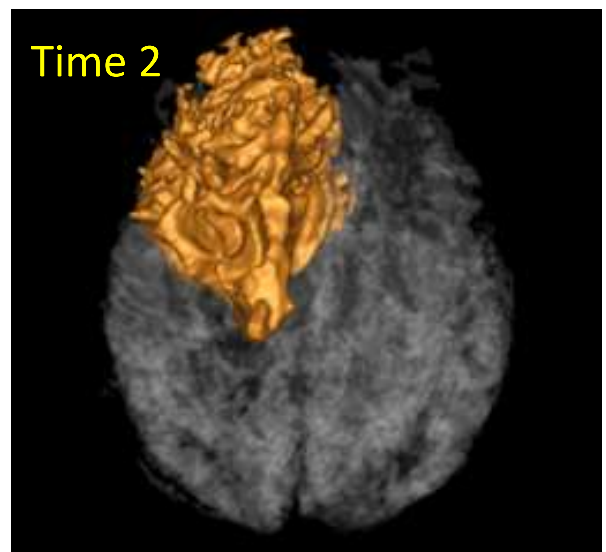
TBI Case (UCLA)



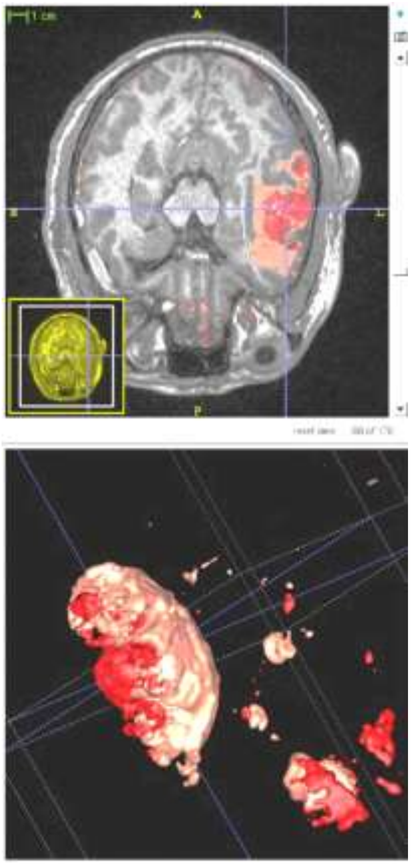




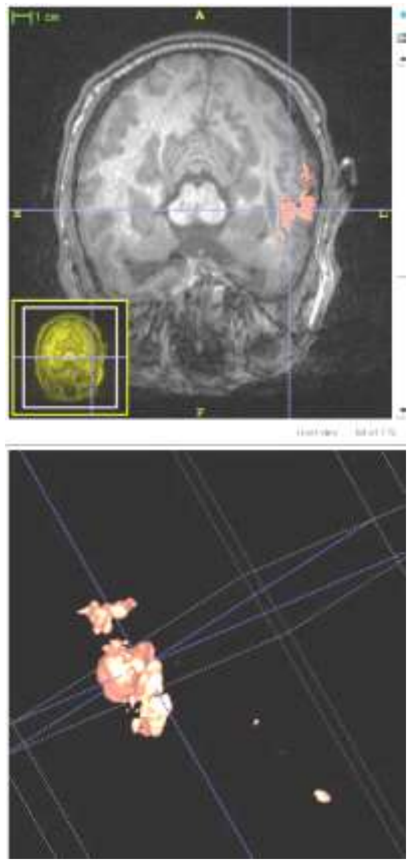




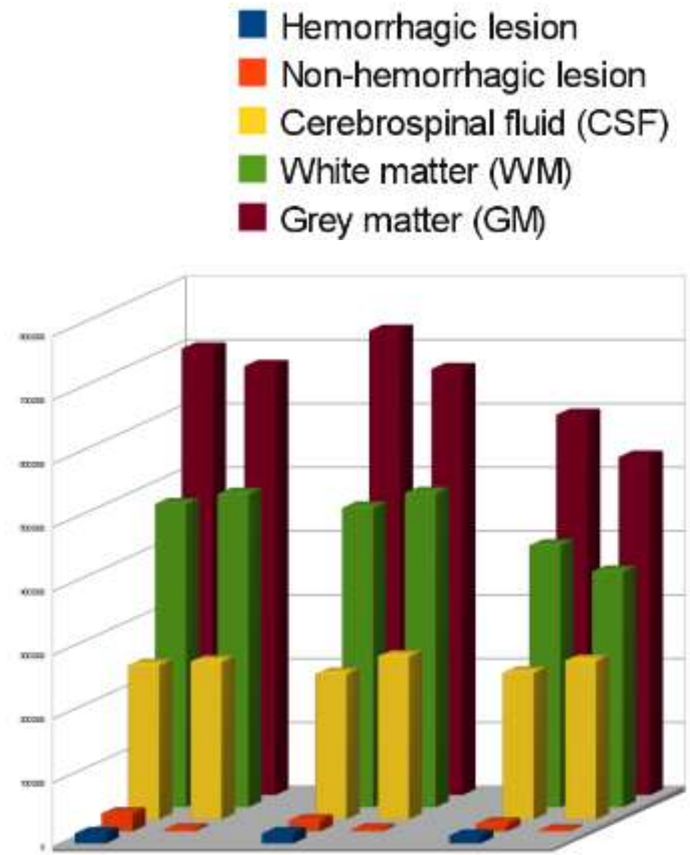
Quantitative Results 4-D TBI Imaging



Acute



Chronic



3 cases, acute-chronic

Conclusions

- Spatio-temporal Image & Shape Analysis: Emerging field:
  - Multidisciplinary by definition.
  - Actively developing field driven by new imaging technologies and novel biomedical driving problems.
  - Challenging fundamental, algorithmic and statistical problems.
  - Research progress enables new scientific discoveries.
- Clinically highly relevant for quantitative analysis of subject-specific, personalized changes due to disease or therapy.
- **Main take home message**: Longitudinal image data significantly benefits from 4-D processing and modeling.
- **Todo**: Integrate geometrical with physiological & functional modeling (N. Ayache et al., P. Hunter et al.).

Acknowledgements

- **NIH-NINDS**: 1 U01 NS082086-01: 4D Shape Analysis
- **NIH-NIBIB**: 2U54EB005149-06 , NA-MIC: National Alliance for MIC
- **NIH (NICHD) 2 R01 HD055741-06**: ACE-IBIS (Autism Center)
- **NIH NIBIB 1R01EB014346-01**: ITK-SNAP
- **NIH NINDS R01 HD067731-01A1**: Down’s Syndrome
- **NIH P01 DA022446-011:** Neurobiological Consequences of Cocaine Use

- **USTAR**: The Utah Science Technology and Research initiative at the Univ. of Utah
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- Martin Styner, UNC

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- Joseph Piven, UNC Psychiatry
- Jane Paulsen and Hans Johnson, U of Iowa
- Paul Vespa and Dave Hovda, UCLA TBI Clinic
- Maria Escolar, Chrildren's, Pittsburgh

Freely available Software

ExoshapeAccel: C/C++ NAMIC toolkit SW for estimating continuous evolution from a discrete collection of shapes,
James Fishbaugh Public download

Deformetrica

Stanley Durrleman
http://www.deformetrica.org/