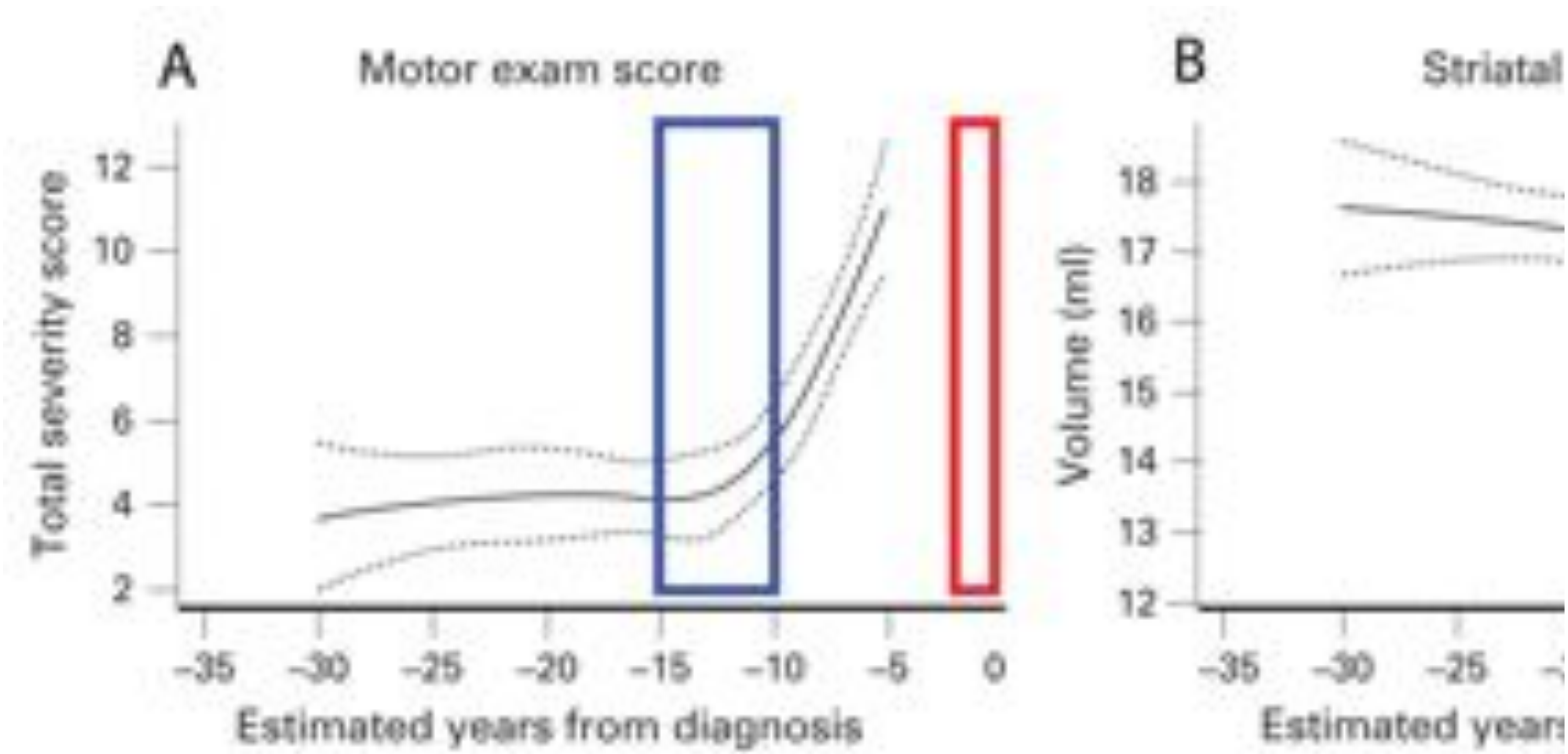
# Driving Biological Problem
# Huntington's Disease

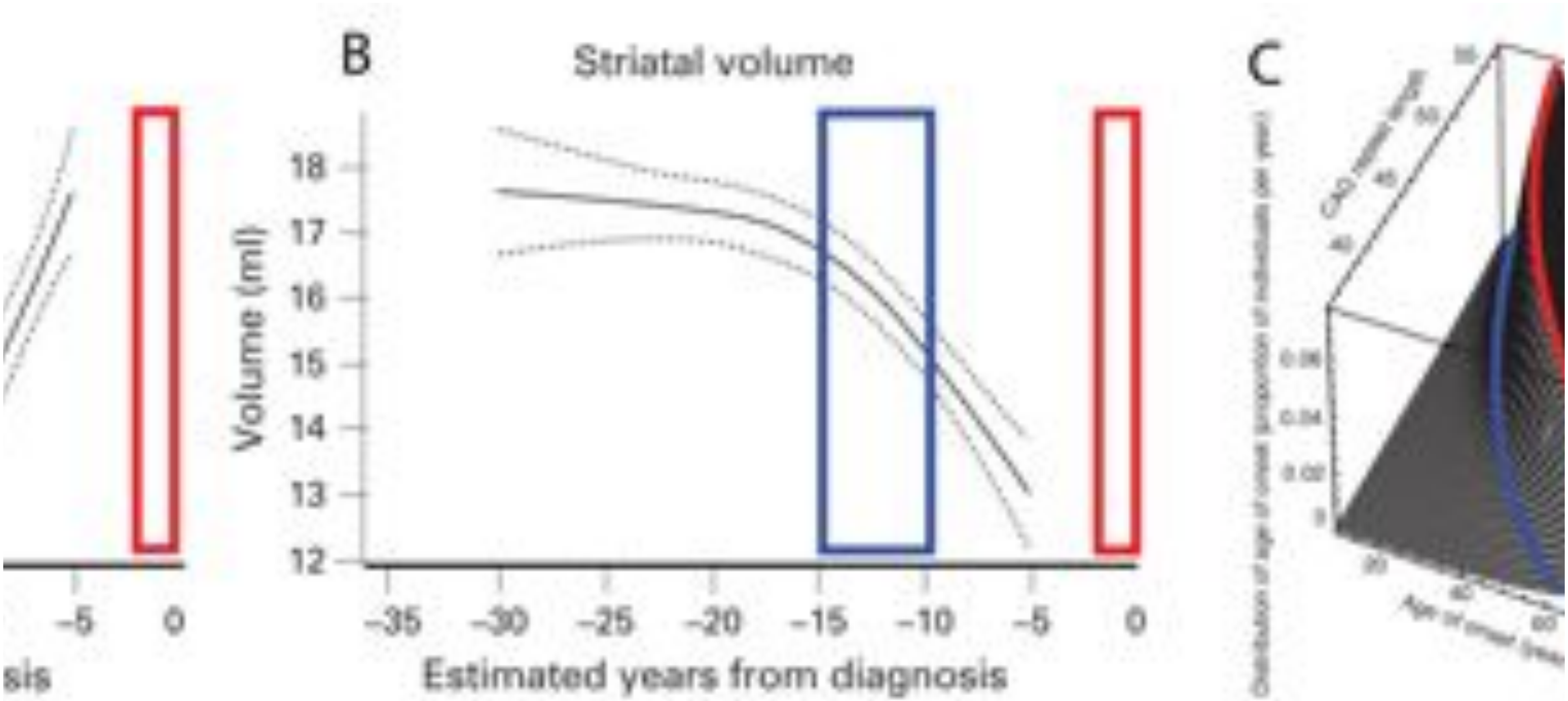
# Builds on PREDICT-HD

- The NIH-funded project “Neurobiological Predictors of Huntington’s Disease” (PREDICT-HD) studies Huntington’s disease (HD), a neurodegenerative genetic disorder that affects muscle coordination, behavior, and cognitive function, and causes severe debilitating symptoms by middle age.

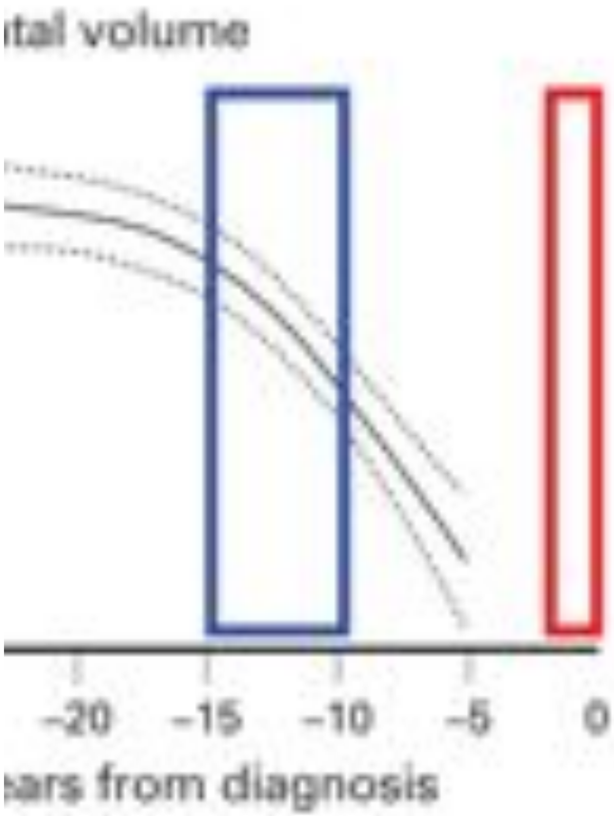
# HD Background

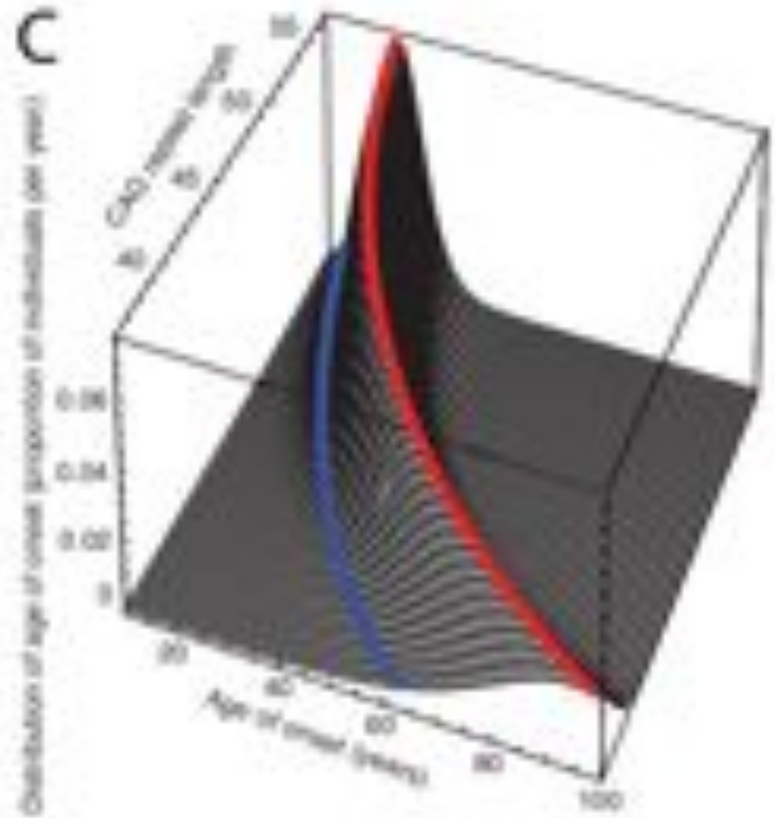


# HD Background



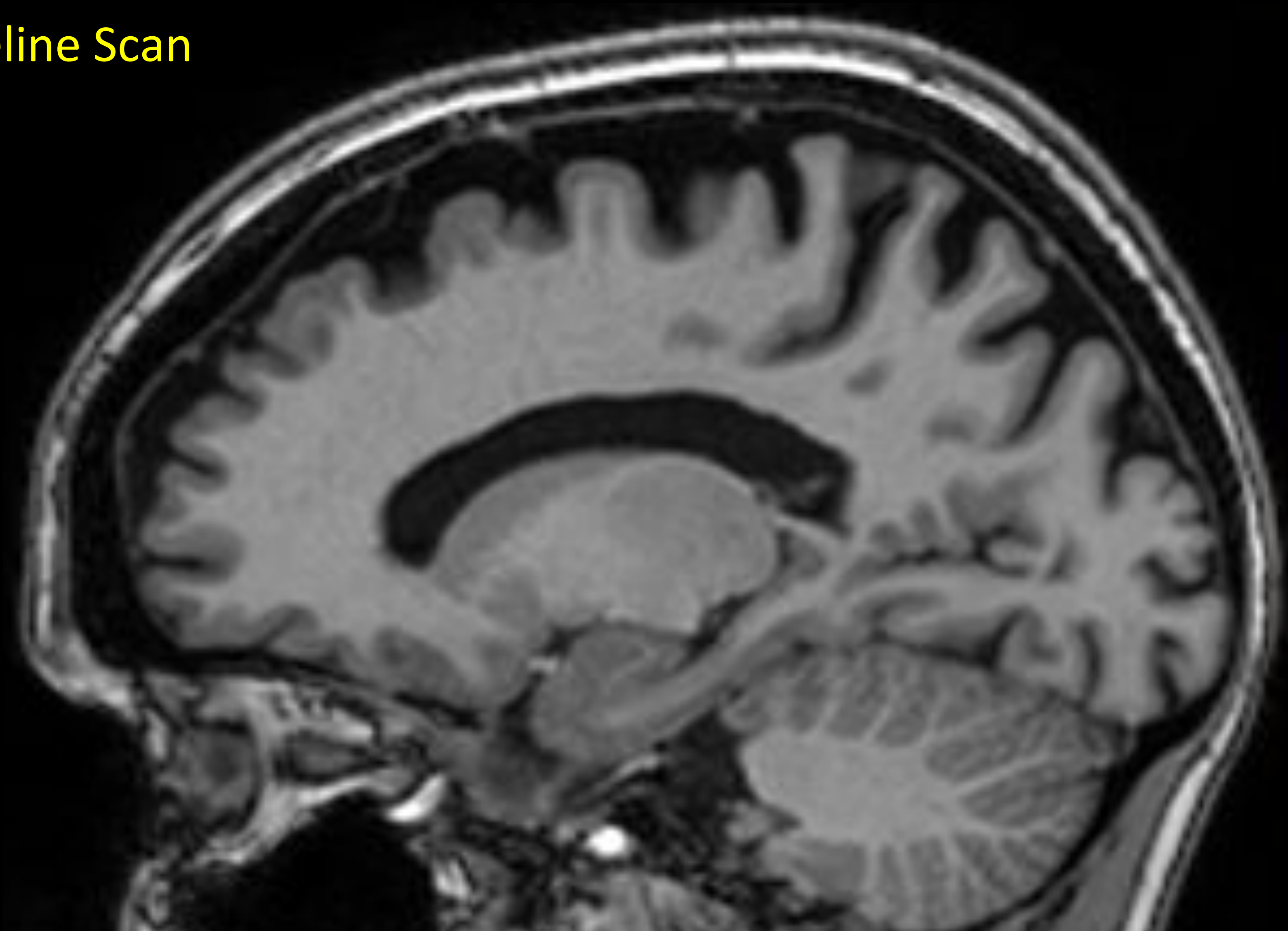
# HD Background



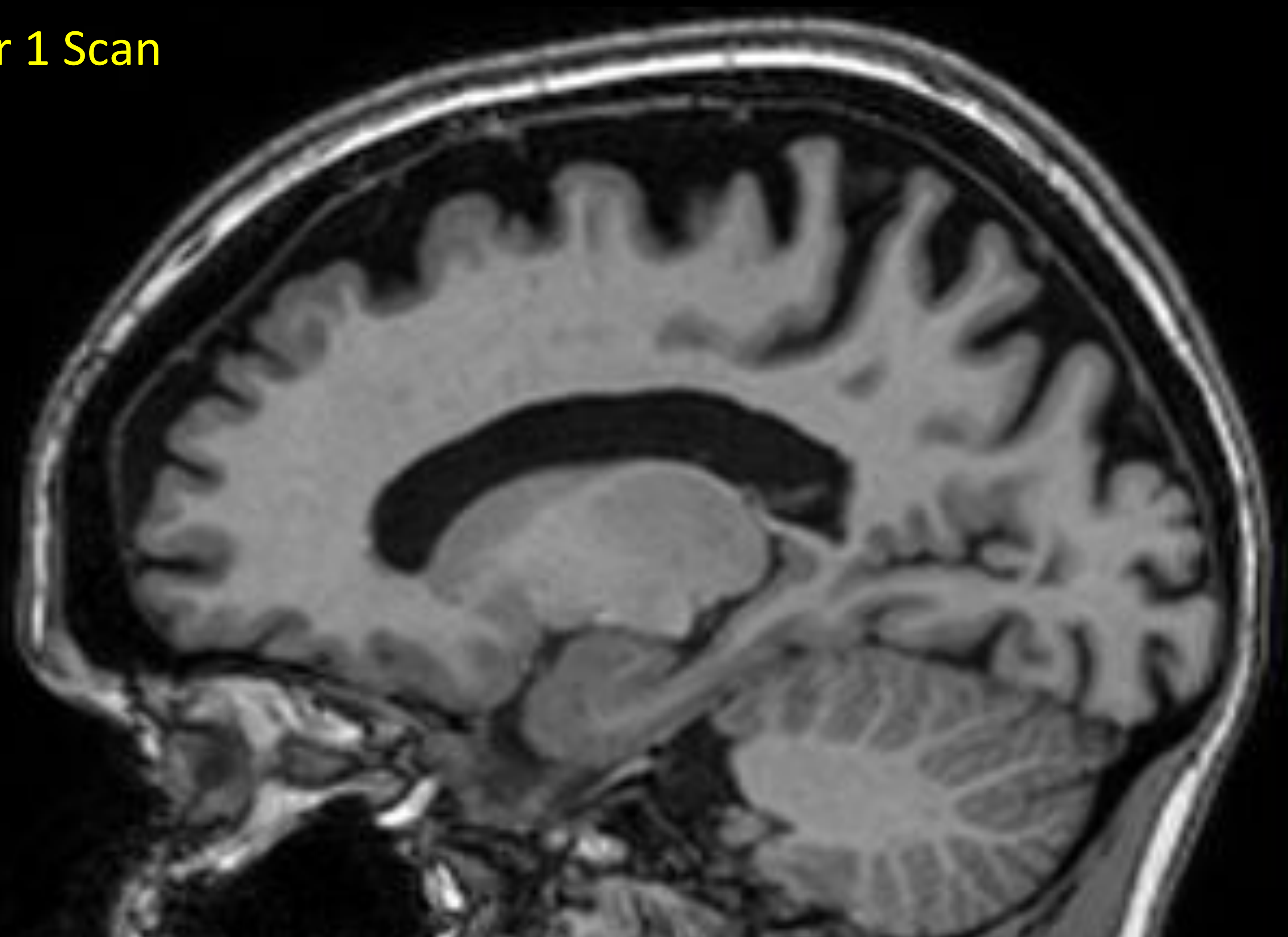
# TRACK-HD Stage 1 HD Subject

Baseline Scan

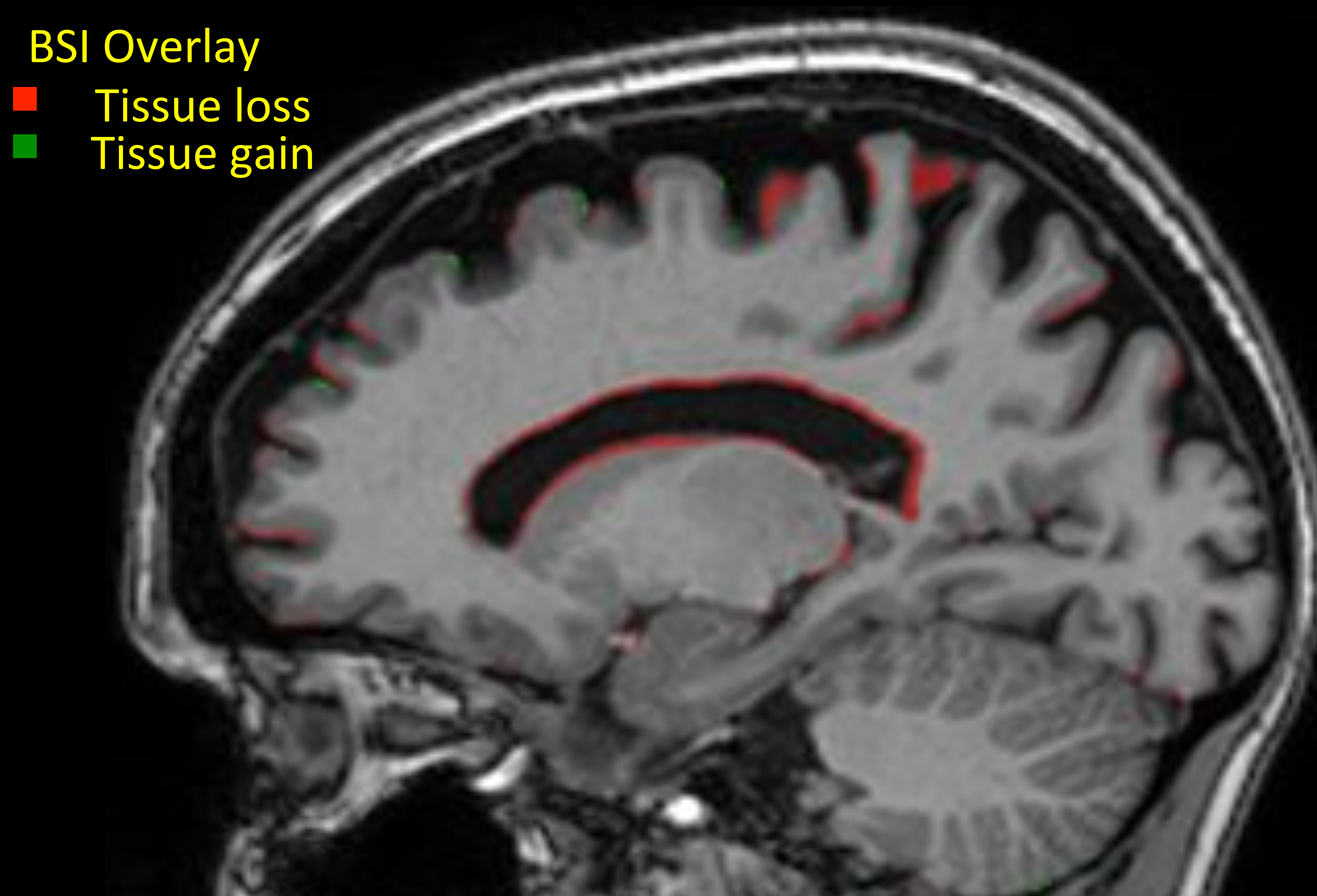


# TRACK-HD Stage 1 HD Subject

Year 1 Scan

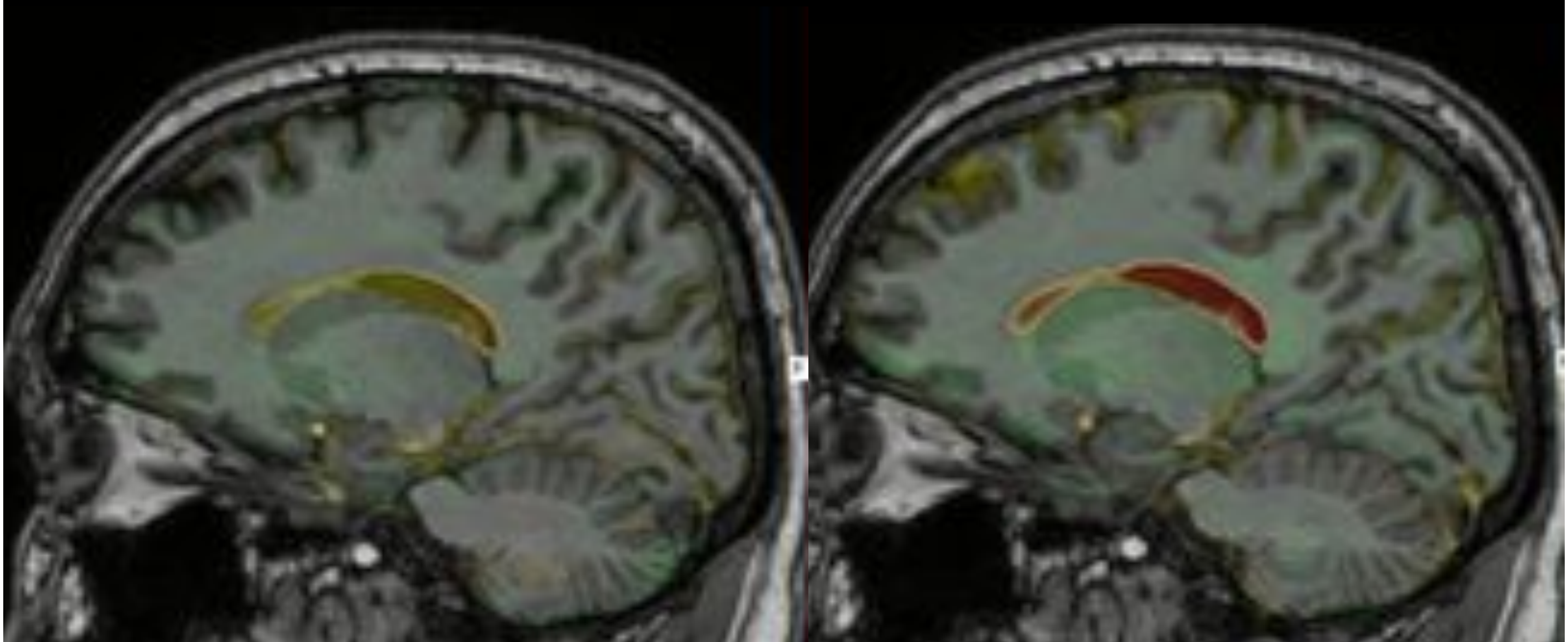


# TRACK-HD Stage 1 HD Subject



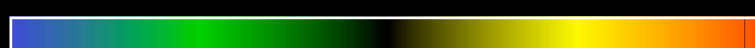

Atrophy Rate: 1.9%    Premanifest Rate: 0.7%    Control Rate: 0.2%

# TRACK-HD Premanifest A Subject: voxel-compression mapping



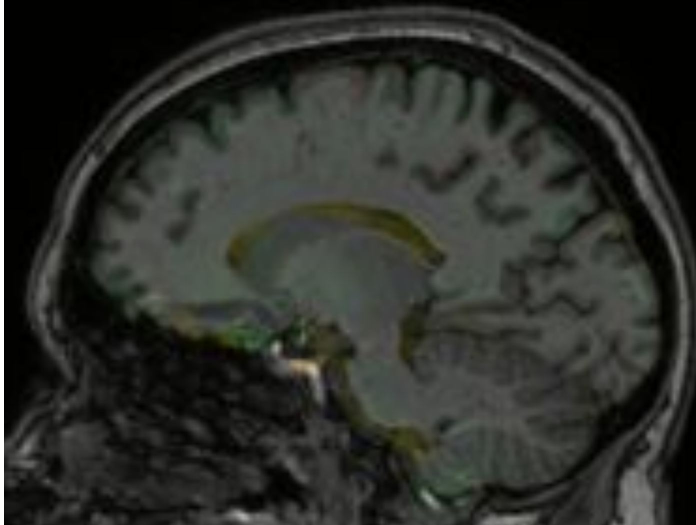
12-month atrophy

24-month atrophy

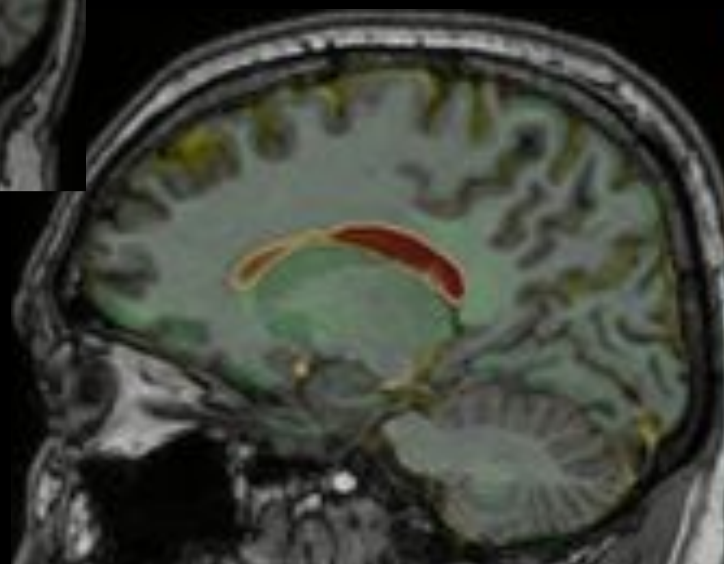
Contraction ≤ 20%  Expansion ≥ 20%

# 24-month voxel-compression mapping

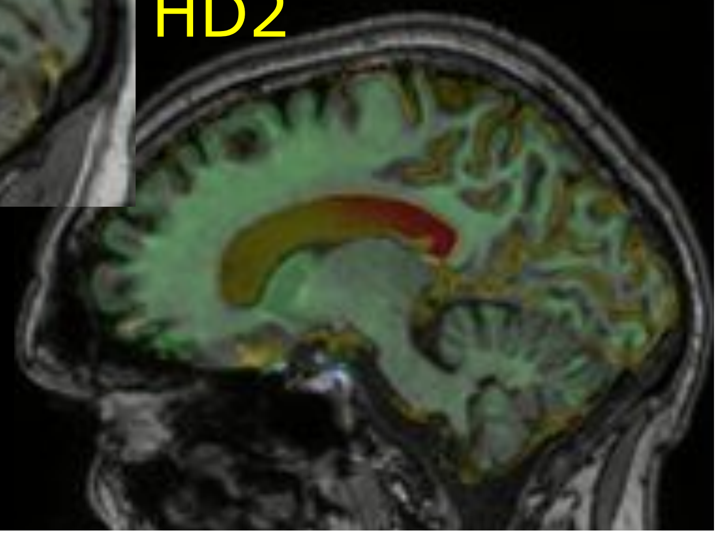
Control

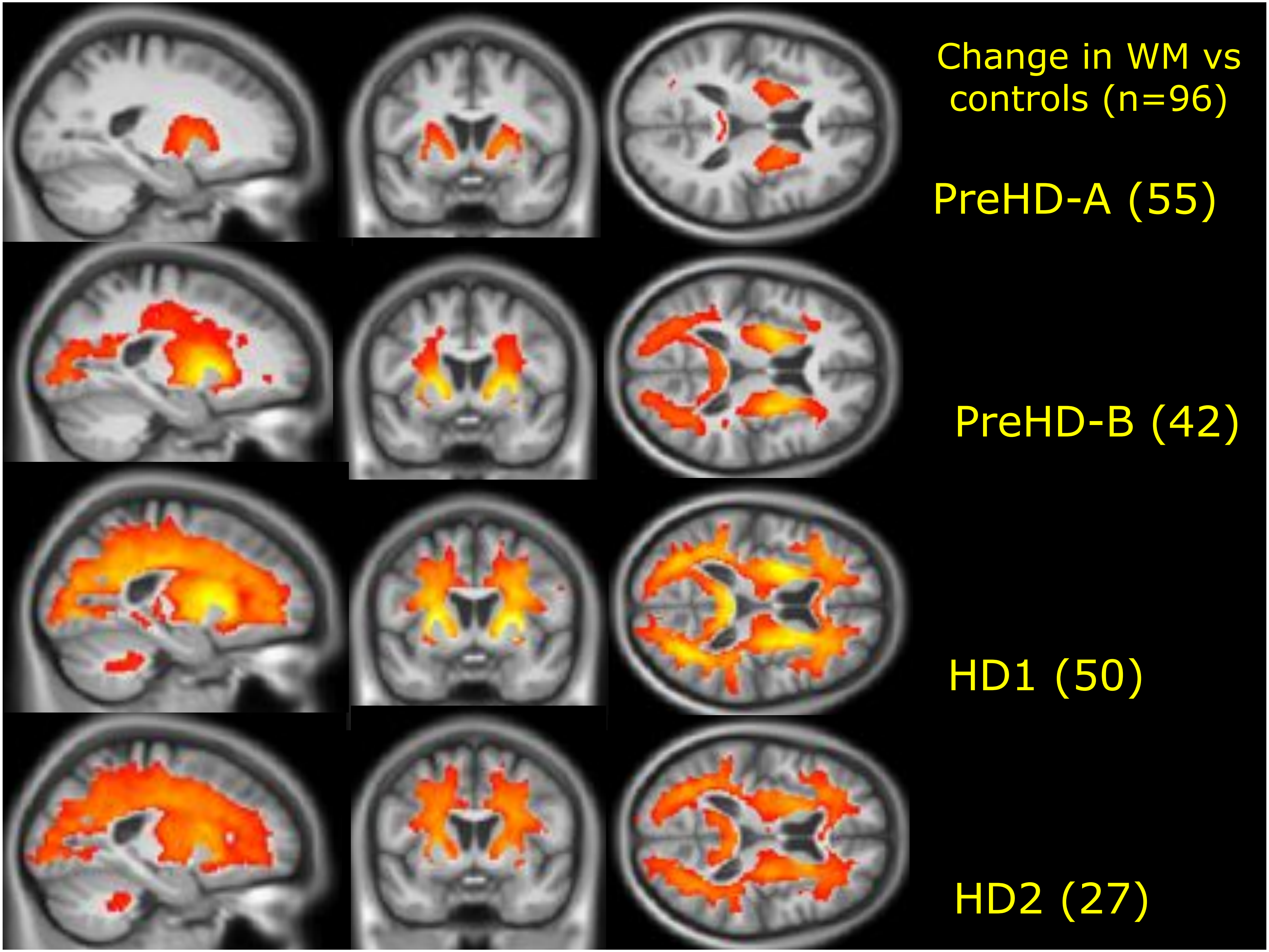


PreA



HD2




Change in WM vs
controls (n=96)
PreHD-A (55)
PreHD-B (42)
HD1 (50)
HD2 (27)

# Interest in DWI

- Diffusion-weighted (DW) MRI
- How DWI is often used: investigate progression of white matter changes during disease progression
  - Detect varying levels/changes of anisotropic diffusion *in vivo*
  - Changes in diffusion reflect tissue integrity
  - Tissue integrity can provide information on disease state
- Published knowledge on DWI is based on smaller studies
  - Smaller = simpler to manage
  - Fewer subjects
  - One site, one scanner
  - Uniformity in problems encountered

# More interest in DWI

| **Needs of expanding DWI studies** | **Solution** | **New Problem** |
|---|---|---|
| Need more data sooner or subjects are geographically spread out | Collect data at multiple sites simultaneously | Different scanner produces data incompatible with processing software |
| Need data on new type of subject | Collect data on new type of subject | Different subject requires different assumptions in analysis |
| Advanced application of DWI: surgical planning | Acquire pre-operative or (perhaps intra-operative) DWI data | Must process DWI data faster |
| **Need more data** | **Collect more data** | **TONS OF DATA WITH ABOVE PROBLEMS** |

# Typical DWI data processing pipeline

**Scanner**

↓

**DICOM files**

↓

**Artifact correction (coregistration)**

↓

**Tensor files**

↓

**Anatomical alignment**

↓

**Scalars**
**Fiber tracking**

ERROR

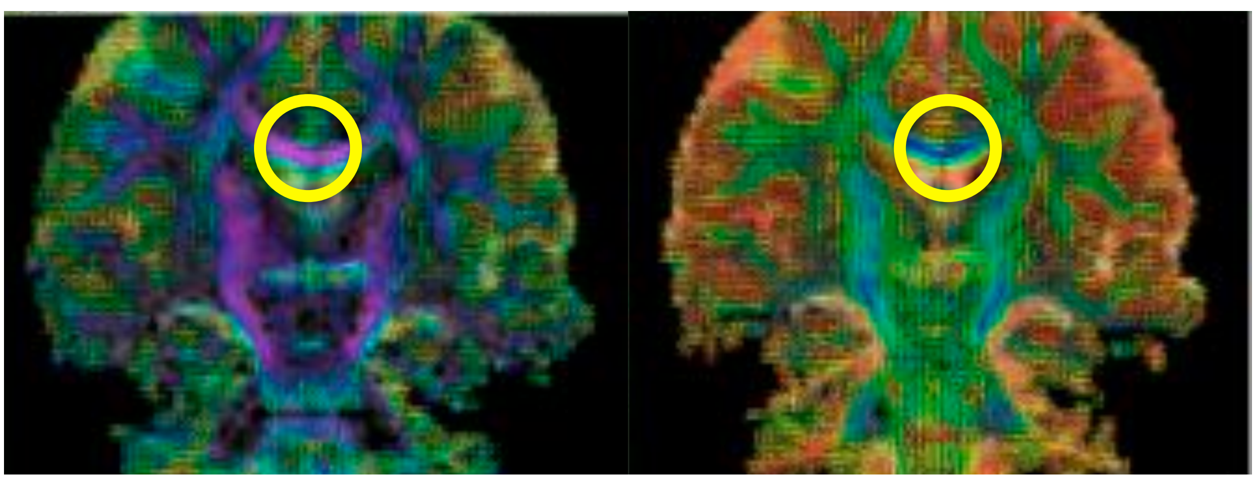
**Problem #1:** Extracting proper information from DICOM files

ERROR

**Problem #2:** No removal of artifacts or automated quality control step

# Proposed Pipeline: DicomToNrrdConverter

- Properly converts DICOM data to NRRD files for 12 types of data (Siemens, Philips, and GE)
- Back-calculates diffusion-sensitizing gradient coordinates from **b** matrix when coordinates are incorrect in DICOM header

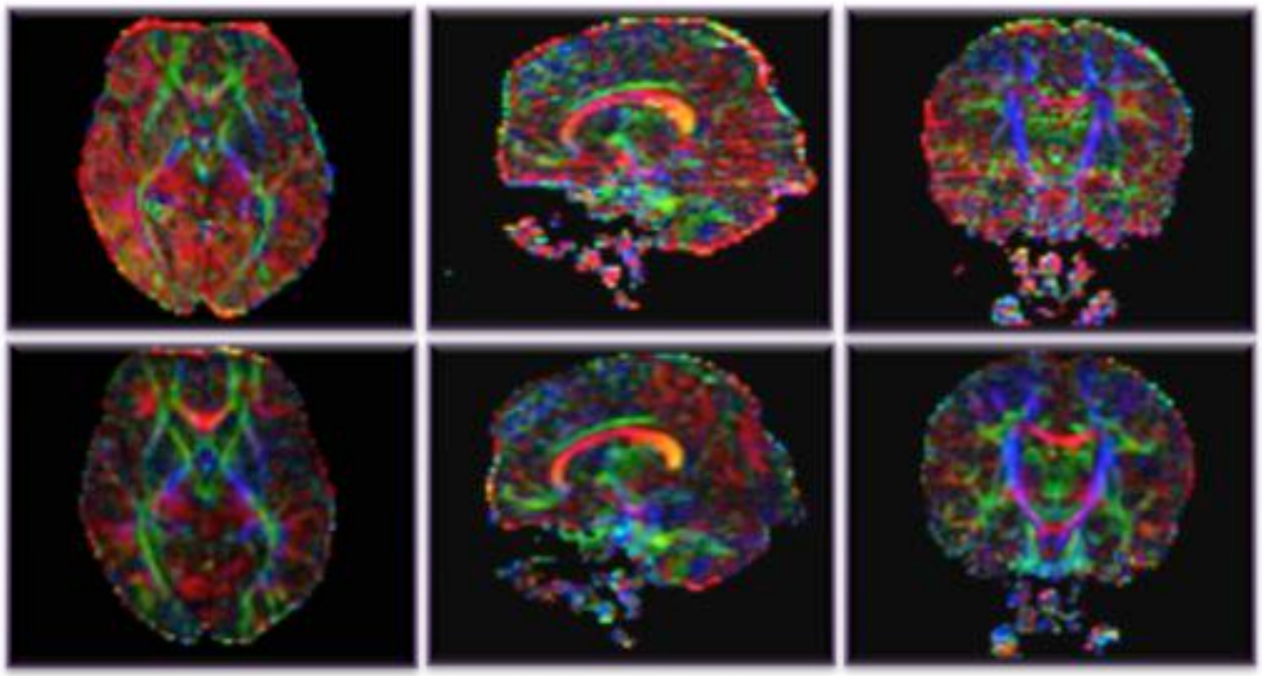


# Proposed Pipeline: DTIPrep

- Promising results: less noisy tensor image

**Before**

**After**

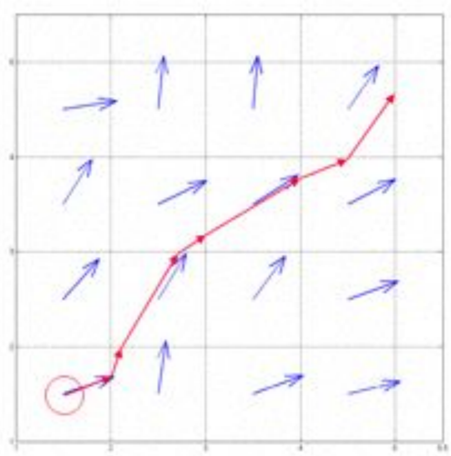


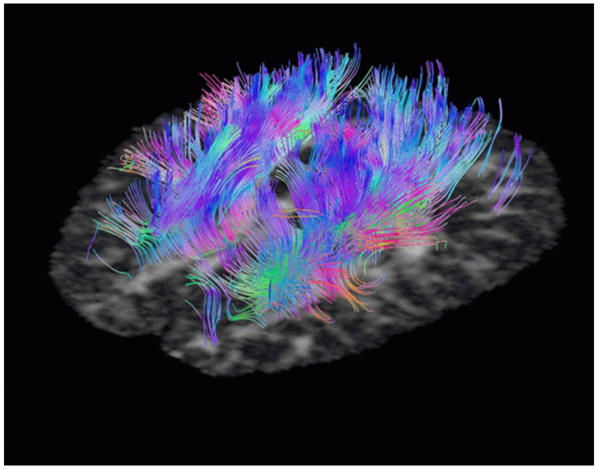
# Background: Quantifying diffusion

- Diffusion anisotropy indices

| DAI Name | Formula | Interpretation |
|---|---|---|
| Mean diffusivity (MD) or ADC | $MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$ | Average of diffusion tensor trace; size of diffusion |
| Fractional anisotropy (FA) | $FA = \frac{\sqrt{3[(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2]}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$ | Shape of diffusion |
| Radial diffusivity (RD) | $RD = \lambda_2 + \lambda_3$ | Transverse diffusion |
| Axial diffusivity (AD) | $AD = \lambda_1$ | Longitudinal diffusion |

- Fiber tracking





# Proposed Pipeline: Future Work

- Identify and Implement Improved fiber tracking
  - GTRACT (Iowa)
    - Graph search tracking: finds tracts in tensor image
    - Guided tracking: incorporates anatomical information about the track orientation using initial guess of fiber track (graph search)
  - Two tensor model
    - Use already encountered fiber orientations to continue fiber tracking
    - Reduces signal reconstruction error and improve angular resolution at crossing and branchings
- Test fiber tracking methods on wide-range of data

# Traveling Human Phantom (THP) Study

- Objectives of study
  - Evaluate site and vendor variation of DTI in the same set of human volunteers
  - Determine minimum number of concatenated scans required for optimal DTI studies (rotationally invariant scalars, fiber tracking)
- Methods
  - Data from 8 sites
  - 5 healthy subjects
  - Data from both Philips (3) and Siemens (5) 3T scanners
  - Each subject at each site received 4 31-direction scans and 2 71-direction scans
  - High resolution T1 and T2 anatomical images
  - Comparison of data processed with and without DTIPrep

# THP data is available upon request.

# Specific Aim #1

- Perform individualized longitudinal shape change quantification from multi-modal data.

**Shape Analysis**

Goals: Tools for a longitudinal shape analysis pipeline to identify localized changes in basal ganglia tracts that have strong co-morbid degenerative timelines. Enable the use of the advanced SPHARM & particle shape analysis processing in NA-MIC within PREDICT HD.

Steps/Modules:

- 2011-04-01 (Slicer Team/Core2):Sun Grid Engine compatibility
- 2011-04-01 (Clement): Clean up existing tools for deployment at Iowa
  - Individual SPHARM tools (exists, needs polishing)
  - SPHARM shape summary tool (exists, needs polishing)
  - Statistical Shape Analysis Tools (exists, needs polishing)
    - CSV files as part of Slicer standards (Paths, variables, group associations, etc)
- 2012-01-01 (Mark): Analyze 225 subjects with Cross sectional tools
  - With between 3-6 longitudinally collected scans.
  - With Caudate/Putamen/Thalamus
- 2013-08-01 (Clement): Add support for particle shape analysis (new Slicer module)
  - Target of 2011-01-14: have feasibility shape analysis done to identify outstanding work that needs to be done.

# Specific Aim #2

- Complete full brain Diffusion Tensor Imaging tractography analysis.

**DTI Processing**

Goals: Tools for a longitudinal analysis pipeline of changes measured by fiber tractography to identify white matter tracts that have strong co-morbid degenerative timelines compared to subcortical degeneration over time. Enable the use of the advanced DTI processing in NA-MIC within PREDICT HD. Specifically, adapt all NA-MIC tools to work as individual external Slicer modules (in part they already exist, but need further work), as well as combine them into a single Slicer DTI processing wizard.

Steps/Modules:

- 2010-12-15 (Mark, Joy, UNC Team): Write Tutorial for DTIPrep
  - Create Media Wiki version of documentation with screen shots describing how visual inspections are to occur.
  - Create PPT presentation for DTIPrep.
- Process data from raw DICOM data (enhanced DicomToNRRDConverter)
  - 2010-11-30 (Mark, Joy): Add testing data suite to DicomToNRRDConverter (Joy to identify, Mark to implement)
  - Target 2010-12-31(Mark): CMake URL data download mechanisms (Look at Titan CMake has examples of this).
  - Target 2010-12-31 (Clement): Document how to interpret B-Matrix for Siemens (extration from dicom) on the DicomToNrrd Wiki page
  - Target 2010-12-31 (Clement) Investigate DicomToNRRDConverter use of B-Matrix for vb13 data DTI_THP Iowa data.
- Target 2011-03-01 (Clement): DTI noise estimation, Rician noise filtering
  - Review status of code to determine how to modularize into stand alone library and executable
  - Include directly into DTI-PREP

# Specific Aim #3

- Deploy extensible tools for sharing source data, derived data, algorithms and methods to multi-site analysis teams.

**Data**

Is the image data already in hand?

- Yes. Over 2900 scan sessions collected. We will need to identify the meaningful subset of this data, get final approval from the Predict Steering Committee for that subset,and then re-deidentify it and post to XNAT for NA-MIC purposes.
- (Target date of 2010-12-10) Identified the FMRI_024 data (77 subjects, 2-3 years longitudinal) as a good candidate data set for collaborative algorithm development platform. This data set has 3 71direction+8B0 DTI data sets, 2 1.0^3 T1 data sets, and a 0.56x0.56x1.4 T2 data set.
  - Will likely need to collect clinical data for shape analysis work that includes: (Age, Gender, Dx, Burdon Score, Motor Score).
  - Will need to re-de-identify all the data to be used here.
  - Will need to run auto-workup for generating Caudate/putamen/hippocampus/thalmus masks.
  - Data exchange will be done through XNAT, including derived data.
- (Target date of 2011-01-14): Share all DTI_THP to wide NAMIC group for validation of tools being developed.

# Methods: Aim 1

- Use shape analyses to create a normative model.
- Changes in an individual's scores can then be used to inform clinical counseling and intervention scheduling decades before a neurological motor diagnosis is made.

# Methods: Aim 2.

- Create tools for longitudinal analysis of changes in fiber tractography
- Perform whole brain longitudinal analysis of DTI connectivity using stochastic tractography tools for network and pathology detection.

# Timeline: Year 1

- Aim1: Apply preliminary tools for longitudinal shape change to existing data
- Aim2: Create a quality control pipeline of DTI datasets.
- Aim3: Deploy XNAT instance and populate with PREDICT-HD data

# Timeline: Year 2

- Aim1: Improve shape analysis tools and apply to larger cohort with multiple study visits
- Aim2: Longitudinal analysis of fiber tracts
- Aim3: Incorporate aim one and two workflows into XNAT instance

# Timeline: Year 3

- Aim1: Create normative models of shape change in healthy aging and disease (HD)
- Aim2: Develop workflow of optimized longitudinal white matter analysis for whole brain tractography
- Aim3: Documentation, training, and data sharing.