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# Driving Biological Problem Huntington's Disease



THE UNIVERSITY  
OF IOWA

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# **Builds on PREDICT-HD**

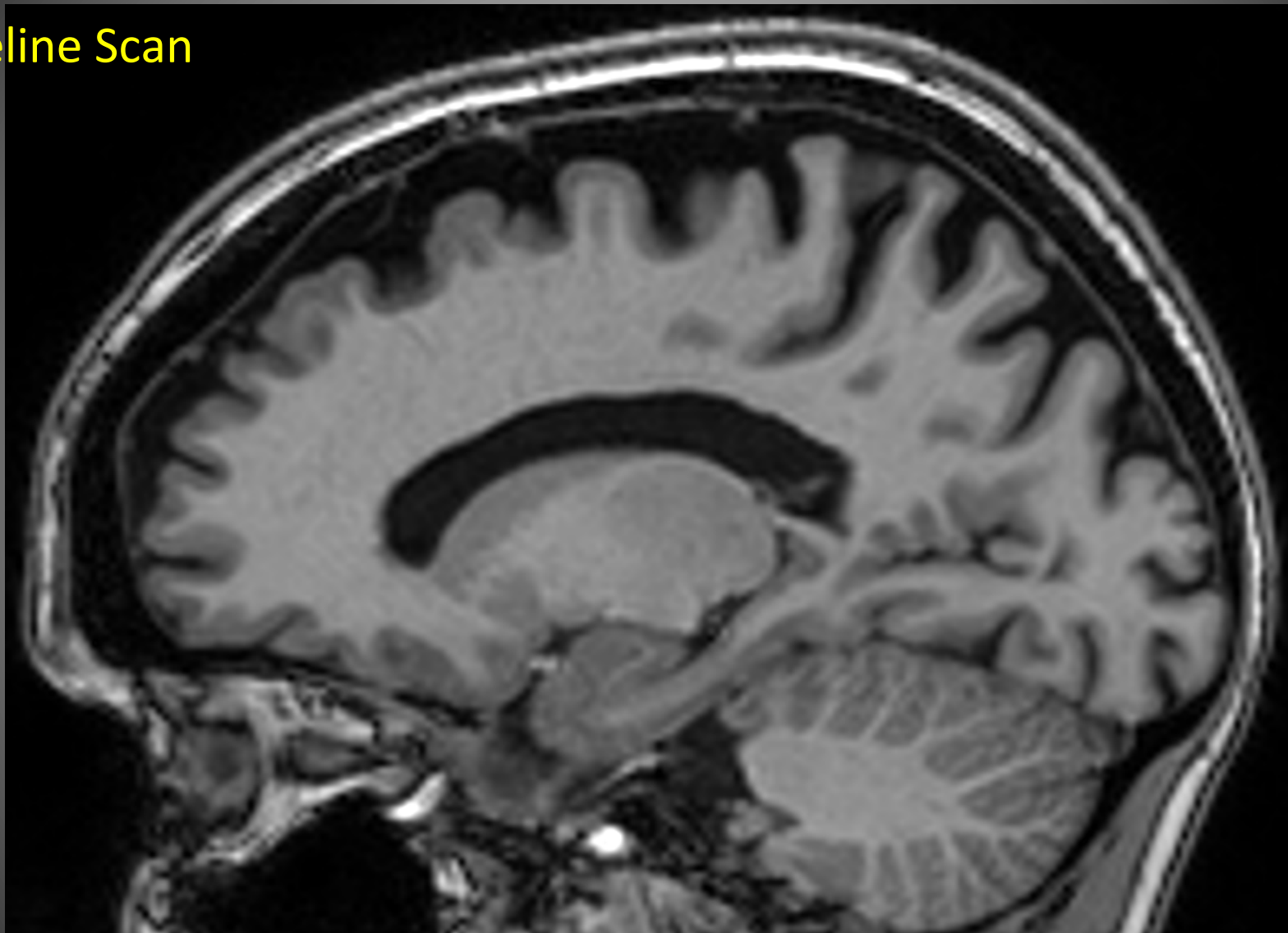
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The NIH-funded project “Neurobiological Predictors of Huntington’s Disease” (PREDICT-HD) studies Huntington’s disease (HD), a neurodegenerative genetic disorder that affects muscle coordination, behavior, cognitive function, and causes severe debilitating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

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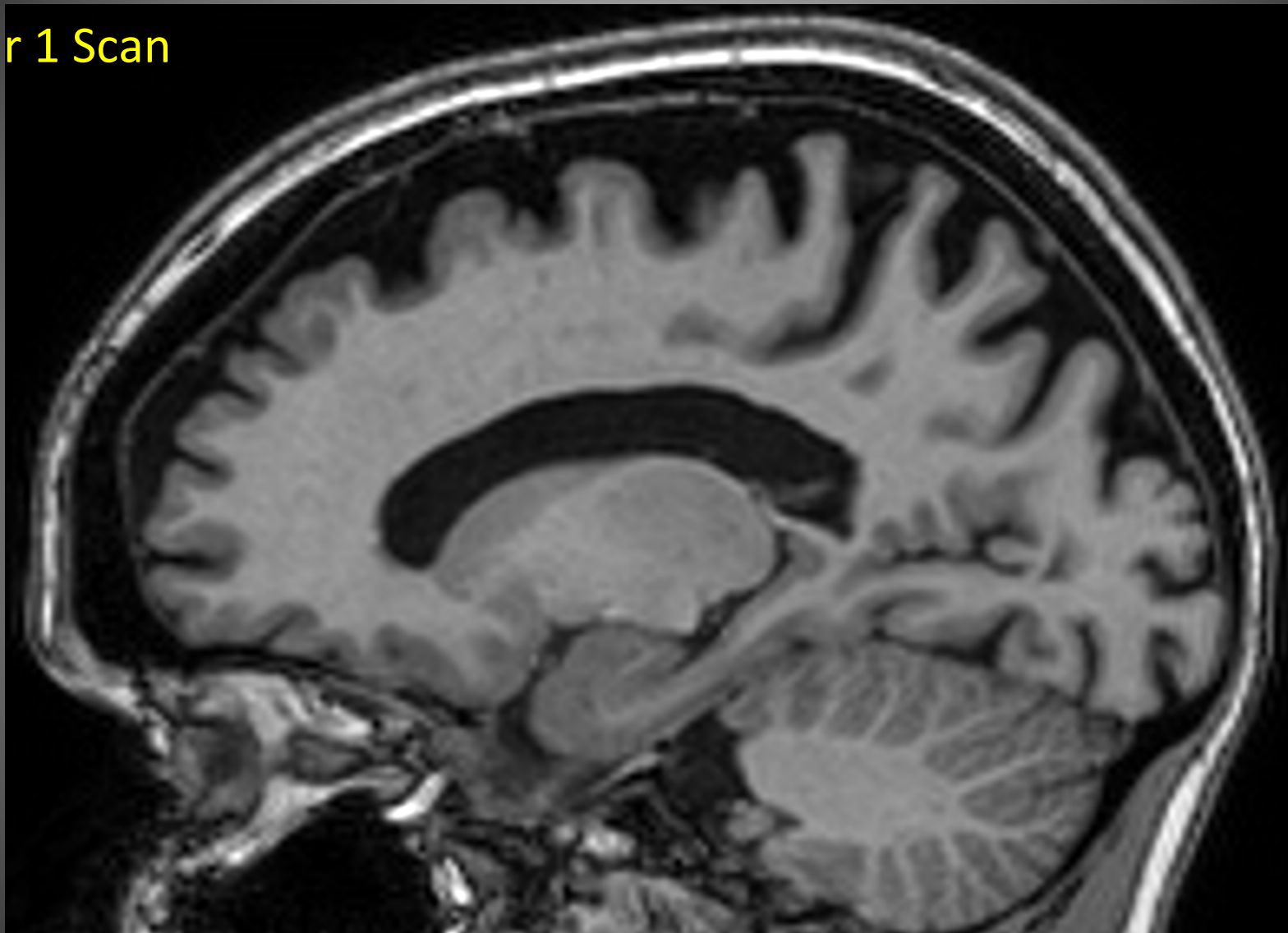
# TRACK-HD Stage 1 HD Subject

Baseline Scan



# TRACK-HD Stage 1 HD Subject

Year 1 Scan

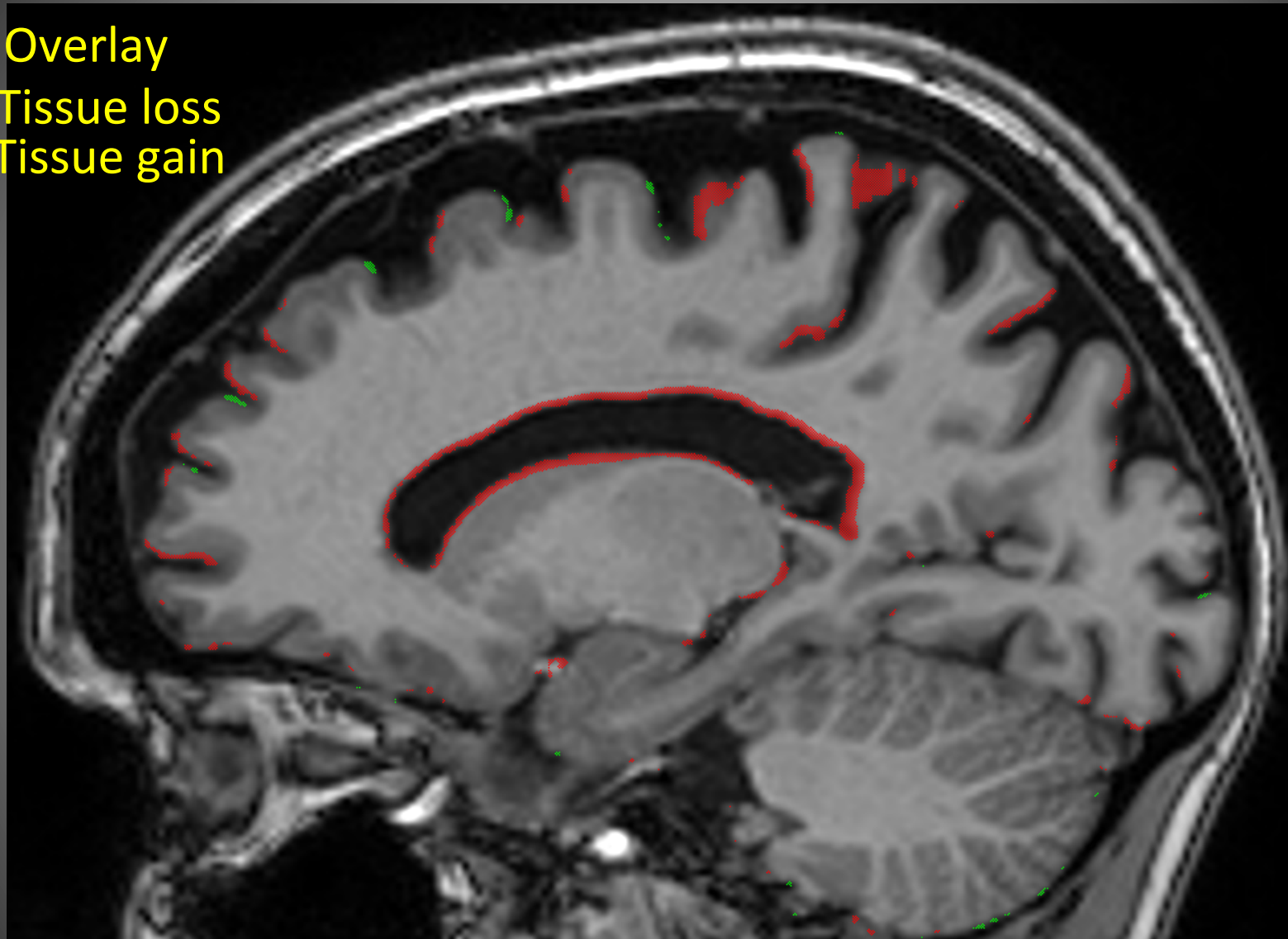




# TRACK-HD Stage 1 HD Subject

BSI Overlay

- Tissue loss
- Tissue gain

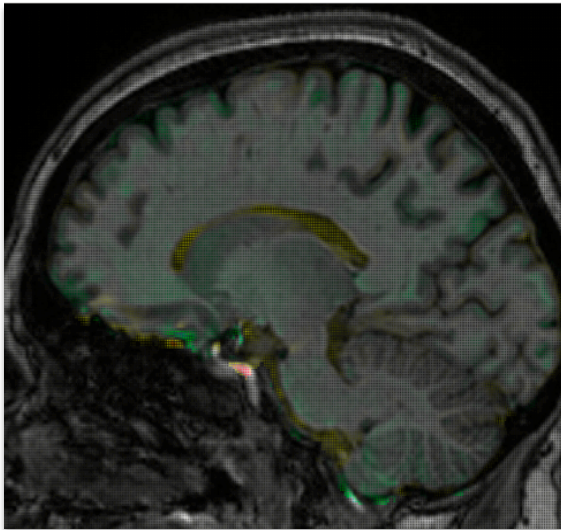


Atrophy Rate: 1.9%    Premanifest Rate: 0.7%    Control Rate: 0.2%

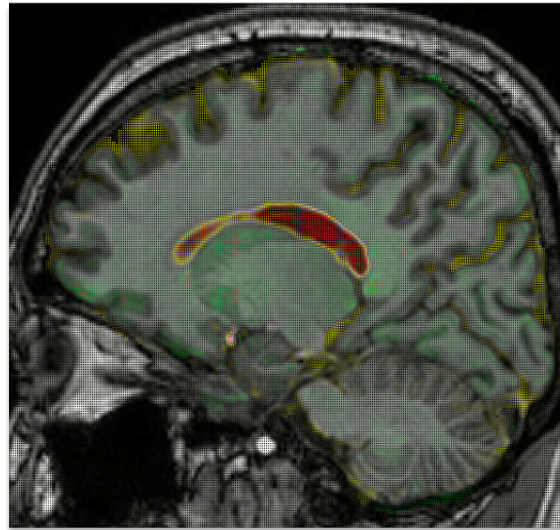


# 24-month voxel-compression mapping

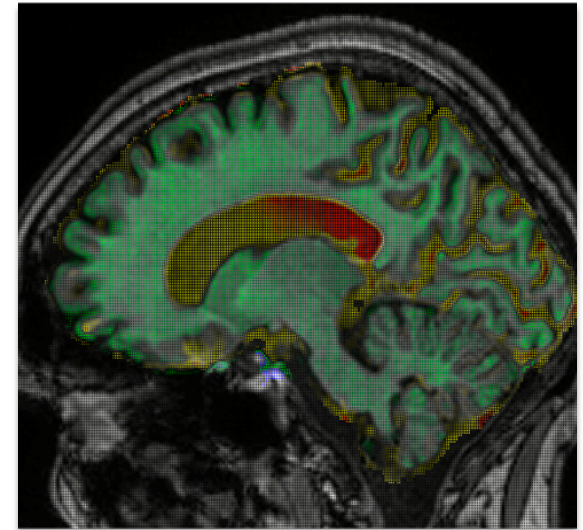
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Control



PreA

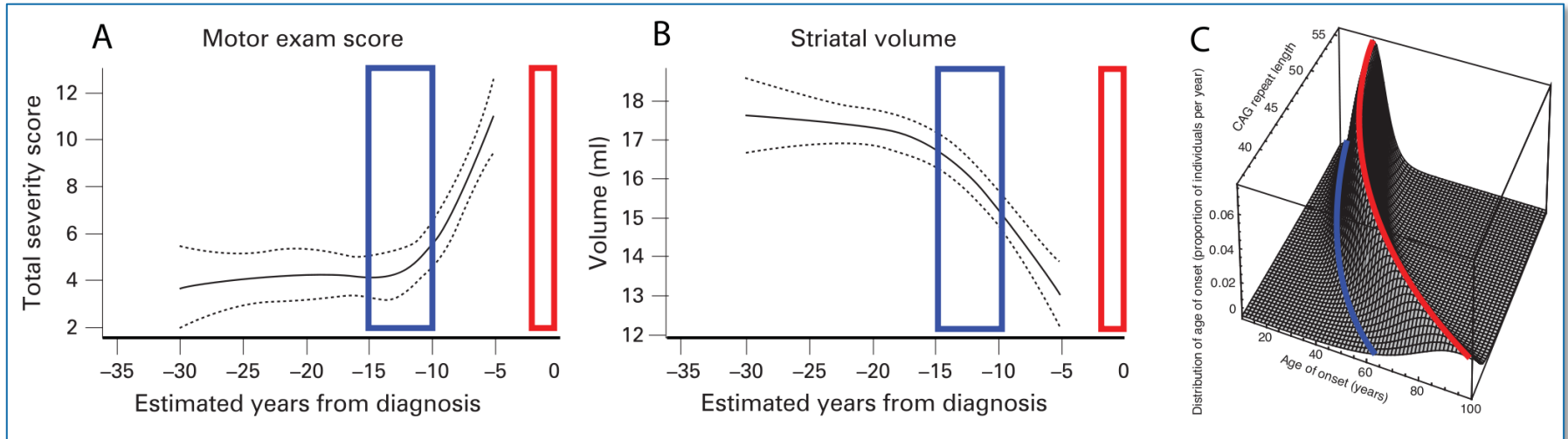


HD2

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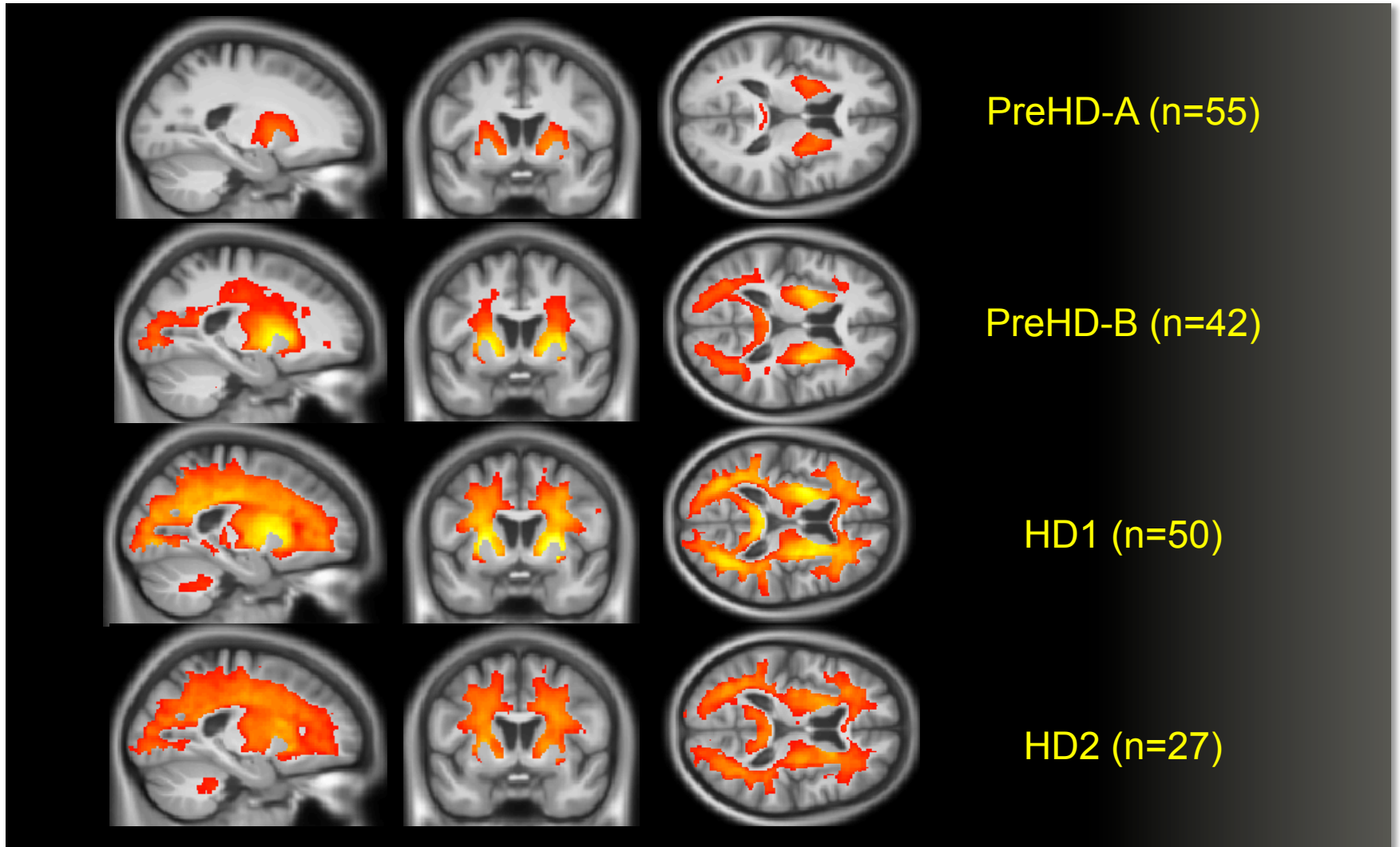
# HD Background



The relationship between estimated years to diagnosis of HD and motor exam score and striatal volume (A,B). Distribution of age of onset for subjects with 36-56 GAC repeats (C). Red box indicates most likely time of diagnosis, blue box is the proposed time that intervention would have the greatest impact.



# Change in White Matter vs Controls (n=96)





# Specific Aims

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- Perform individualized longitudinal shape change quantification from multi-modal data.
  - Complete full brain Diffusion Tensor Imaging tractography analysis.
  - Deploy extensible tools for sharing source data, derived data, algorithms and methods to multi-site analysis teams.
-





## Methods: Aim 3.

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- Deploy the XNAT environment.
  - Extend the NA-MIC data-sharing tools to disseminate raw scan data, derived datasets, and measurement scores for Aims 1 and 2.
  - Incorporate existing morphometric analysis pipelines into XNAT.
-



# Sharing HD Data

[http://www.na-mic.org/Wiki/index.php/2011\\_Summer\\_Project\\_Week](http://www.na-mic.org/Wiki/index.php/2011_Summer_Project_Week)

## Data Files

- File:Anonymized factorsExternalIDs with blage mriDate scanID daysSince.xlsx
- File:NAMIC+Factors.doc
- File:NAMIC HD DWI DTI.xlsx
- File:NAMIC HD DataDescription.pdf
- File:ANN Segmentation thesis.pdf
- File:20111102 ANNSegmentation.pptx

Subjects [X] SELECT [v]

<< first < prev 1 2 3 4 5 next > last >> 20 [v] 1 of 6 Pgs (115 Rows) Reload Options [v]

Subject	M/F	Hand	YOB	MR Sessions
10001	U	U		6
10002	U	U		6
10003	U	U		6
10004	U	U		6
10005	U	U		4
10006	U	U		6
10007	U	U		4
10008	U	U		5
10009	U	U		6
10010	U	U		6
10011	U	U		6
10012	U	U		8
10013	U	U		6
10014	U	U		6
10015	U	U		8
10016	U	U		6
10017	U	U		6



# Shared Sites (14 labs)

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Tallahassee, Florida 32306-4330  
*Department of Statistics*  
(850) 644-3218



School of Electrical and Computer Engineering  
College of Engineering



MAX-PLANCK-GESELLSCHAFT



BRIGHAM AND  
WOMEN'S HOSPITAL

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# Currently Shared Data

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- Anonymized Raw Scan data
- Derived Data





## NeuroImage

Volume 54, Issue 1, 1 January 2011, Pages 328–336



## Fully automated analysis using BRAINS: AutoWorkup

Ronald Pierson<sup>a</sup> ·  · , Hans Johnson<sup>a</sup>, Gregory Harris<sup>a</sup>, Helen Keefe<sup>a</sup>, Jane S. Paulsen<sup>a, c</sup>, Nancy C. Andreasen<sup>a</sup>, Vincent A. Magnotta<sup>b</sup>

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# Improving shared derived data processing

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## Documentation-Rons-Rules-For-Tools

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Documentation-Rons-Rules-For-Tools

### Introduction

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"Rules for tools" is an informal set of rules that developers should keep in mind when working on **interactive tools** for translational clinical research. If you follow them, you will create tools that many people will use.

1. You make it, I break it. <sup>[1]</sup>
2. Your tool does not exist, until it works on my laptop with my data. <sup>[2]</sup>
3. I am lazy. I do not like to move the mouse or to type. <sup>[3]</sup>
4. No more than one simple parameter. <sup>[4]</sup>
5. I have ADD. Make your algorithm fast. <sup>[5]</sup>

#### HOW TO MAKE ALGORITHMS ROBUST

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- Build a case library with 10 or more cases
  - Use half for development, cycle through the cases daily
  - Use the other half for testing
-



# Improving shared derived data processing

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- Convert brains2 internal tools auto workup into fully NA-MIC compliant tool suite
    - Convert major applications to SEM compliance (Decouple SEM from Slicer)
    - Use SimpleITK to replace brains2 basic image processing building blocks
    - Transition Slicer to ITKv4 (Thanks Bill Lorensen)
    - Define workflows in NiPype (Thanks Satra Ghosh)
-



# NiPype Key Features

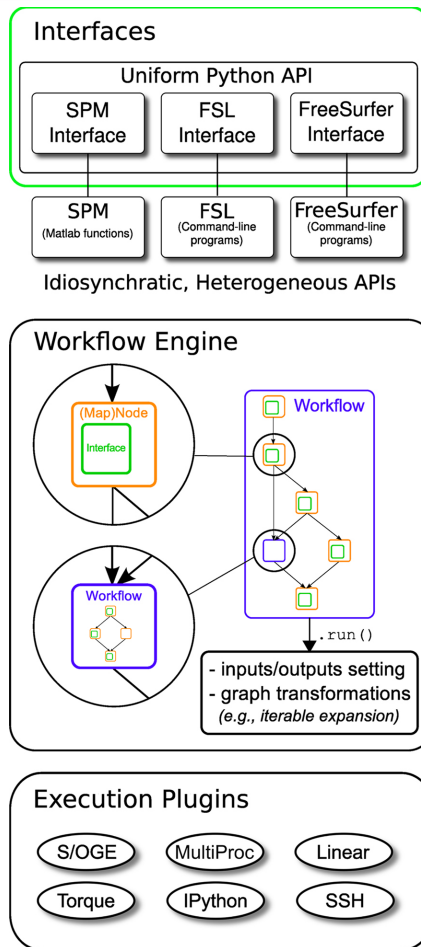
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- Naïve Approach
    - Smooth, denoise, etc.
    - Mask brain
    - Register to Atlas
    - ...
  - Better Approach
    - Some images have noticeable field bias
    - Insert N4 bias correction step
-



# NiPype: Large catalog of tools with a uniform interface



- **Batch processing**
  - Distributed processing plugins
  - Reruns affect updated/edited node connections ONLY!
- **Uniform node creation**
  - Stable API
  - Nipype's Function node allows easy integration of CLI tools
- **Pipeline complexity**
  - Iterables, MapNodes
  - Nested workflows



# NiPype: Can be seamlessly integrated With many of the other NA-MIC tools

```
import regexNode, n4correct # Scripted modules
import BRAINSFit           # Nipype API wrapped module
import nipype.pipeline.engine as pe
from nipype.interfaces.utility import Function, IdentityInterface

registration = pipe.Workflow(name = "registration")

filesNode = pe.Node(name = "filesNode", IdentityInterface(fields = ["filename"]))
filesNode.iterables = ("filename", inputFiles)

regexNode = pe.Node(name = "regexNode", Function(function = fileRegex,
                                                input_names = ["filename"],
                                                output_names = ["outputVolume", "outputLabel"]))
```

```
n4bias = pe.Node(name = "N4BiasCorrection", Function(function = n4correct,
                                                    input_names = ["inputVolume",
                                                                    "labelVolume"],
                                                    output_names = ["outputVolume"]))

n4bias.inputs.convergenceThreshold = 0.0005
n4bias.inputs.bSplineOrder = 6
```

Create the  
pipeline  
node

```
bFit = pe.Node( name = "BRAINSFit", interface = BRAINSFit())
```

...

```
registration.connect([(filesNode, regexNode, [("filename", "filename")]),
                      (regexNode, n4bias, [("outputLabel", "labelVolume"),
                                           ("outputVolume", "inputVolume")]),
                      (n4bias, bFit, [("outputVolume", "inputVolume")]) ])
```

Connect  
the node



# Methods: Aim 1

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- 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.
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# Timeline: Year 1

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- 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
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# Brain Sub-Cortical Structures: BRAINSCut

Developed

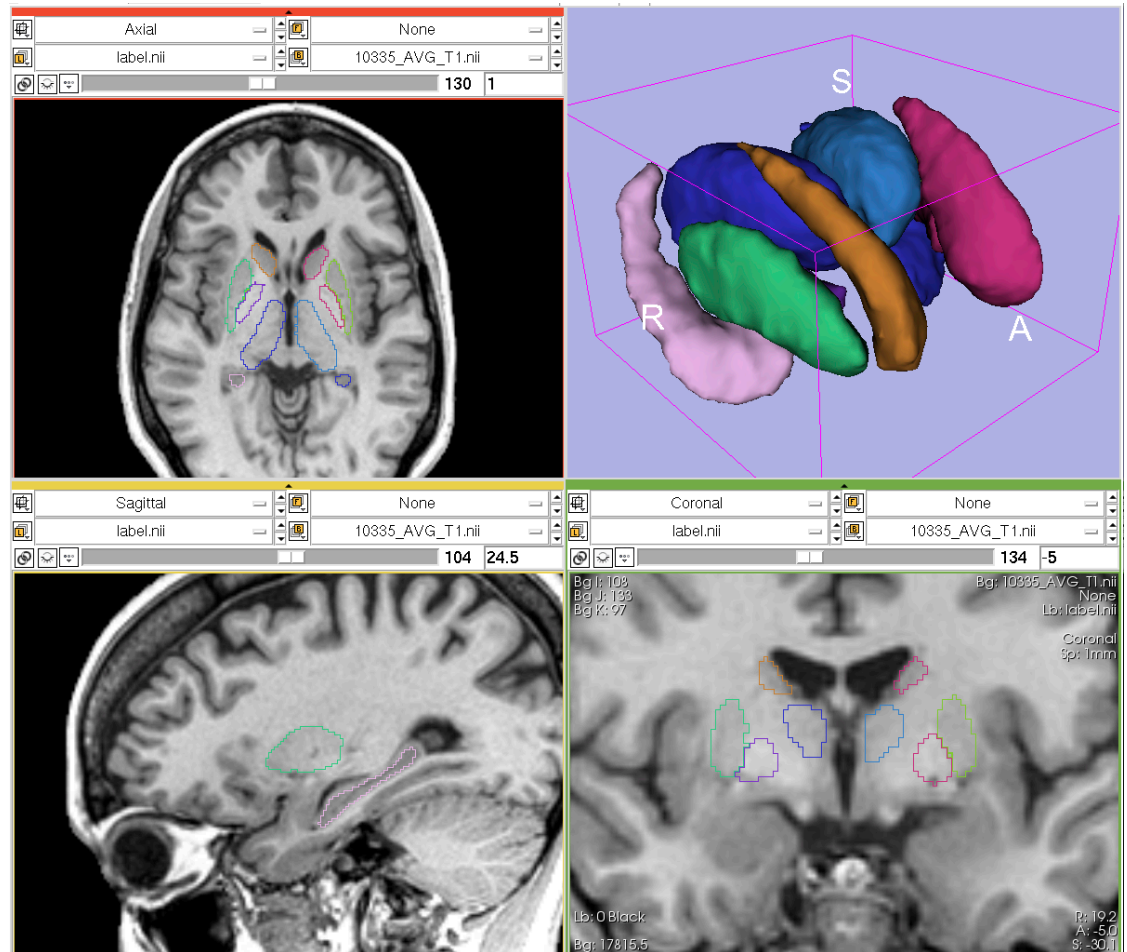
- Caudate
- Putamen
- Thalamus

New structure

- Hippocampus

On going

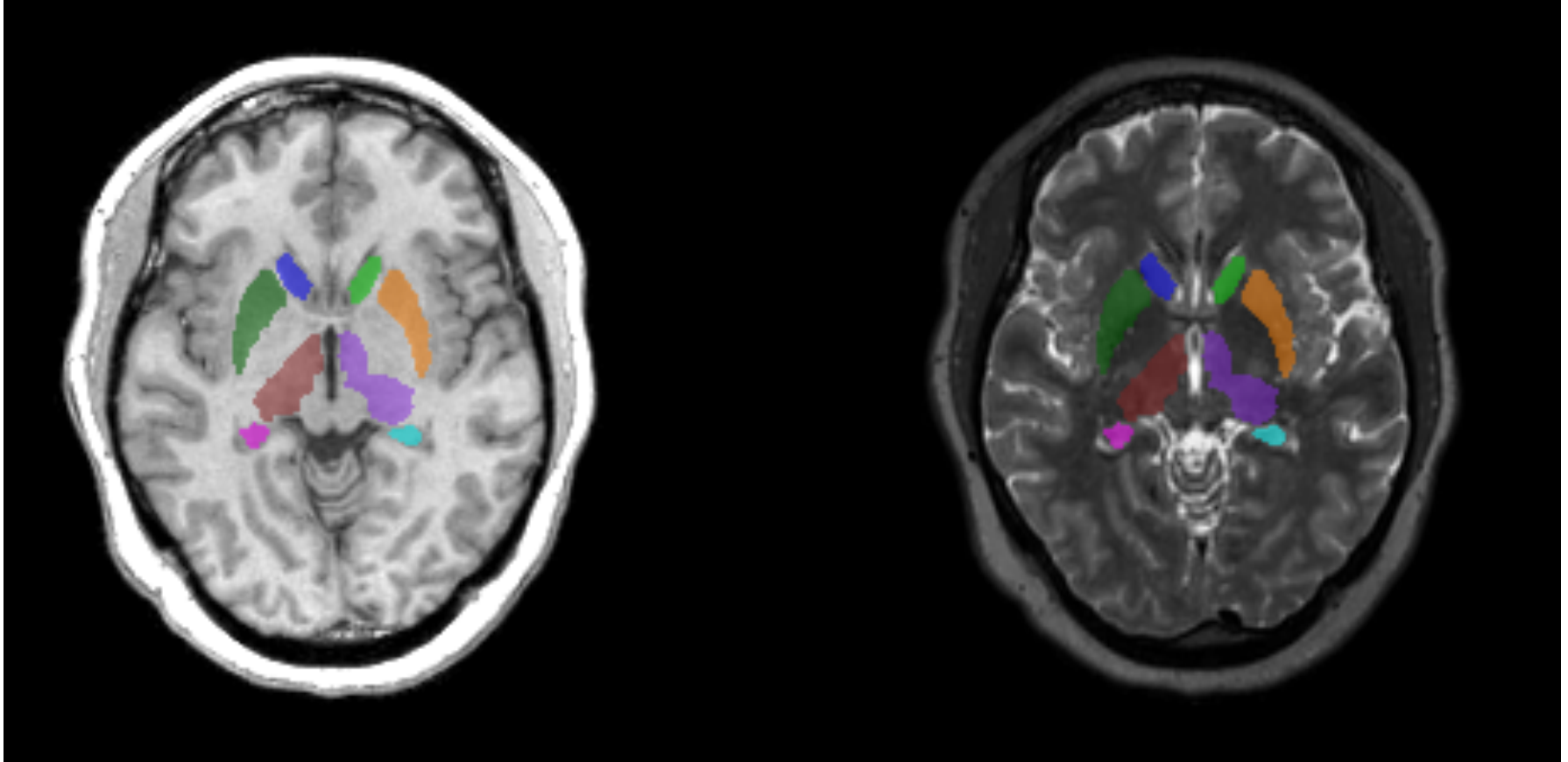
- Globus
- Accumbens
- And more...





# Sub-Cortical Structures: BRAINSCut: Detailed View

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# Brain Sub-Cortical Structures: BRAINSCut: Reliability

Testing data includes  
Multi-sites, which  
means:

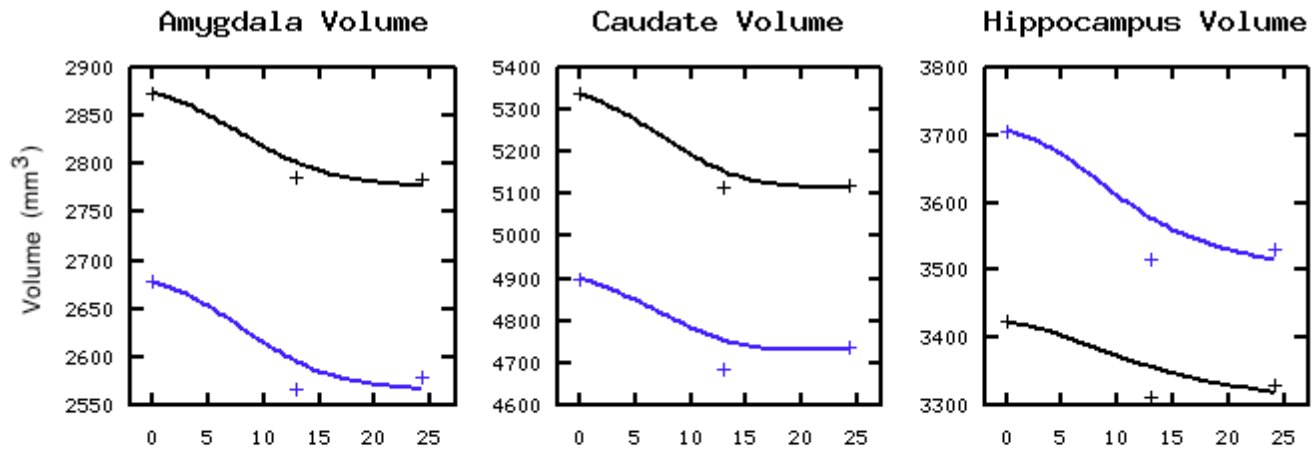
- Different protocols
- Variation of subjects!!!

Left		Right		Left Results										Right Results										Progress
SSE	thrsd	SSE	thrsd	mean	SI		ICG		Linear Fit		kauffDi	SI		ICG		Linear Fit		kauffDi	Progress					
					SI	thrsd	Agmt	thrsd	icpd	thrsd	Slope	Intercep	SI	thrsd	Agmt	thrsd	icpd	thrsd	Slope	Intercep	kauffDi			
0.06	98	0.06	99	98.5	0.895	0.6	0.944	0.5	0.945	0.5	0.96	190.1	0.891	0.6	0.958	0.6	0.958	0.5	1	135.6	done	apply		
0.05	99	0.05	66	82.5	0.901	0.6	0.949	0.5	0.949	0.5	0.99	122.2	0.895	0.6	0.954	0.5	0.962	0.5	1.02	65.78	done	apply		
0.05	91	0.05	95	93	0.907	0.6	0.944	0.5	0.946	0.4	0.98	110.2	0.9	0.6	0.957	0.5	0.956	0.4	1.02	62.33	done	apply		
0.05	99	0.05	98	98.5	0.912	0.6	0.945	0.5	0.951	0.4	0.98	106.6	0.905	0.6	0.956	0.5	0.956	0.5	1	71.32	done	apply		
0.04	94	0.05	99	96.5	0.915	0.6	0.943	0.5	0.943	0.5	0.95	157.3	0.908	0.6	0.96	0.5	0.959	0.5	1.01	53.54	done	apply		
0.04	76	0.05	90	83	0.915	0.5	0.951	0.5	0.951	0.4	0.95	166.8	0.909	0.6	0.959	0.5	0.959	0.5	1	60.94	done	done		
0.04	60	0.05	82	71	0.914	0.5	0.946	0.5	0.946	0.4	0.96	143.7	0.91	0.5	0.954	0.5	0.954	0.5	0.99	85.48	done	done		
0.04	62	0.05	97	79.5	0.915	0.5	0.942	0.5	0.942	0.5	0.95	163.1	0.911	0.6	0.956	0.5	0.958	0.4	0.99	76.63	done	done		
0.04	50	0.05	95	72.5	0.915	0.5	0.942	0.5	0.942	0.5	0.96	133.6	0.912	0.5	0.96	0.5	0.96	0.5	1	52.5	done	done		
0.05	62	0.05	62	62	0.903	0.5	0.944	0.5	0.946	0.7	1.12	-244	0.896	0.5	0.952	0.5	0.959	0.7	1.15	-221	done	done		
0.04	89	0.04	95	92	0.918	0.5	0.945	0.5	0.951	0.7	1.09	-185	0.91	0.5	0.947	0.5	0.955	0.8	1.1	-214	done	done		
0.04	95	0.04	92	93.5	0.922	0.5	0.947	0.5	0.947	0.6	1.06	-143	0.915	0.5	0.947	0.5	0.955	0.8	1.09	-210	done	done		
0.04	93	0.04	86	89.5	0.924	0.5	0.944	0.5	0.95	0.8	1.05	-111	0.919	0.5	0.949	0.5	0.956	0.8	1.08	-182	done	done		
0.04	76	0.04	100	88	0.928	0.5	0.951	0.5	0.956	0.8	1.05	-119	0.921	0.5	0.949	0.5	0.957	0.8	1.07	-185	done	done		
0.04	92	0.04	86	89	0.929	0.5	0.95	0.5	0.958	0.9	1.05	-128	0.922	0.5	0.949	0.5	0.957	0.8	1.08	-193	done	done		
0.03	53	0.04	62	57.5	0.93	1	0.995	1	0.996	1	1.05	-125	0.922	0.5	0.949	0.5	0.955	0.8	1.07	-189	done	done		
0.03	68	0.04	40	54	0.931	0.5	0.95	0.5	0.953	0.8	1.04	-94.5	0.922	0.5	0.951	0.5	0.957	0.8	1.08	-193	done	done		
0.03	41	0.04	89	65	0.93	0.5	0.95	0.5	0.955	0.8	1.04	-107	0.923	0.6	0.951	0.5	0.96	0.8	1.06	-160	done	done		
0.03	81	0.04	31	56	0.931	0.5	0.95	0.5	0.956	0.9	1.04	-106	0.922	0.5	0.95	0.5	0.957	0.9	1.06	-172	done	done		
0.05	87	0.05	98	92.5	0.899	0.6	0.937	0.6	0.941	0.6	1.15	-294	0.896	0.5	0.946	0.6	0.95	0.7	1.16	-313	done	done		
0.04	100	0.04	99	99.5	0.916	0.5	0.944	0.5	0.946	0.6	1.08	-157	0.909	0.5	0.946	0.6	0.951	0.8	1.1	-200	done	done		
0.04	100	0.04	76	88	0.92	0.6	0.944	0.5	0.948	0.7	1.05	-115	0.913	0.6	0.947	0.5	0.953	0.8	1.09	-199	done	done		
0.04	75	0.04	95	85	0.924	0.5	0.946	0.5	0.954	0.8	1.08	-176	0.917	0.6	0.949	0.5	0.954	0.8	1.09	-200	done	done		
0.04	94	0.04	99	96.5	0.927	0.5	0.951	0.5	0.953	0.7	1.04	-99.6	0.92	0.5	0.95	0.5	0.954	0.7	1.08	-198	done	done		
0.04	55	0.04	92	73.5	0.928	0.5	0.95	0.5	0.953	0.8	1.05	-122	0.919	0.5	0.948	0.5	0.951	0.8	1.07	-159	done	done		
0.04	80	0.04	98	89	0.929	0.6	0.95	0.5	0.953	0.8	1.05	-112	0.92	0.5	0.95	0.5	0.956	0.8	1.07	-166	done	done		
0.04	51	0.04	46	48.5	0.927	0.5	0.945	0.5	0.947	0.7	1.04	-102	0.922	0.5	0.95	0.5	0.954	0.8	1.07	-176	done	done		
0.04	46	0.04	91	68.5	0.928	0.5	0.949	0.5	0.952	0.8	1.05	-103	0.921	0.6	0.949	0.6	0.954	0.8	1.08	-179	done	done		
0.04	39	0.04	31	35	0.929	0.5	0.952	0.5	0.959	0.8	1.05	-104	0.919	0.5	0.946	0.5	0.953	0.8	1.08	-175	done	done		
0.05	94	0.05	89	91.5	0.902	0.5	0.945	0.5	0.95	0.7	1.11	-228	0.894	0.4	0.942	0.6	0.951	0.7	1.15	-333	done	done		
0.04	90	0.04	100	95	0.917	0.5	0.946	0.5	0.95	0.7	1.06	-131	0.911	0.5	0.949	0.5	0.958	0.8	1.11	-228	done	done		
0.04	97	0.04	80	88.5	0.924	0.5	0.949	0.5	0.951	0.7	1.06	-148	0.917	0.5	0.949	0.5	0.959	0.8	1.09	-207	done	done		
0.04	80	0.04	71	75.5	0.927	0.5	0.95	0.5	0.953	0.8	1.06	-148	0.918	0.5	0.951	0.5	0.957	0.8	1.08	-193	done	done		
0.04	84	0.04	88	86	0.928	0.5	0.951	0.5	0.955	0.8	1.04	-99.3	0.92	0.5	0.953	0.5	0.959	0.8	1.08	-203	done	done		
0.03	78	0.04	84	81	0.929	0.5	0.954	0.5	0.956	0.8	1.04	-106	0.921	0.5	0.951	0.5	0.958	0.8	1.07	-187	done	done		
0.03	30	0.04	84	57	0.928	0.5	0.947	0.5	0.952	0.8	1.05	-121	0.922	0.5	0.952	0.5	0.96	0.9	1.07	-190	done	done		
0.03	57	0.04	68	62.5																				
0.03	90	0.04	55	72.5																				
0.03	42	0.04	48	45																				
0.934	0.6	0.971	0.6		0.888	0.5	0.94	0.5	0.939	0.4	0.87	276.9												
0.935	0.5	0.975	0.5		0.889	0.5	0.933	0.5	0.934	0.4	0.84	327.2												
0.934	0.6	0.97	0.6		0.888	0.5	0.929	0.5	0.928	0.5	0.84	330.9												
0.935	0.6	0.974	0.6		0.889	0.5	0.937	0.5	0.938	0.5	0.86	298.4												
0.934	0.6	0.973	0.6																					

Intra class correlation  $\approx$   
0.92~0.93



# Longitudinal Shape





# Diffusion Data: Summary of Work

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- Design image processing pipeline and longitudinal statistical analyses for large amounts of multi-site diffusion-weighted data
    - Data used: ~260 scan sessions
      - Collected at 2 PREDICT-HD sites
      - Cases and controls
      - Up to 4 data acquisitions at 1 year intervals
      - Included structural and clinical data
  - Apply/extend pipeline and analyses to larger PREDICT-HD data set
    - Data that will be used: 813 scan sessions + ~13 new per week
      - Collected at 31 PREDICT-HD sites over
      - Cases and controls
      - Includes structural and clinical data
-



# Diffusion Data: Completed Work

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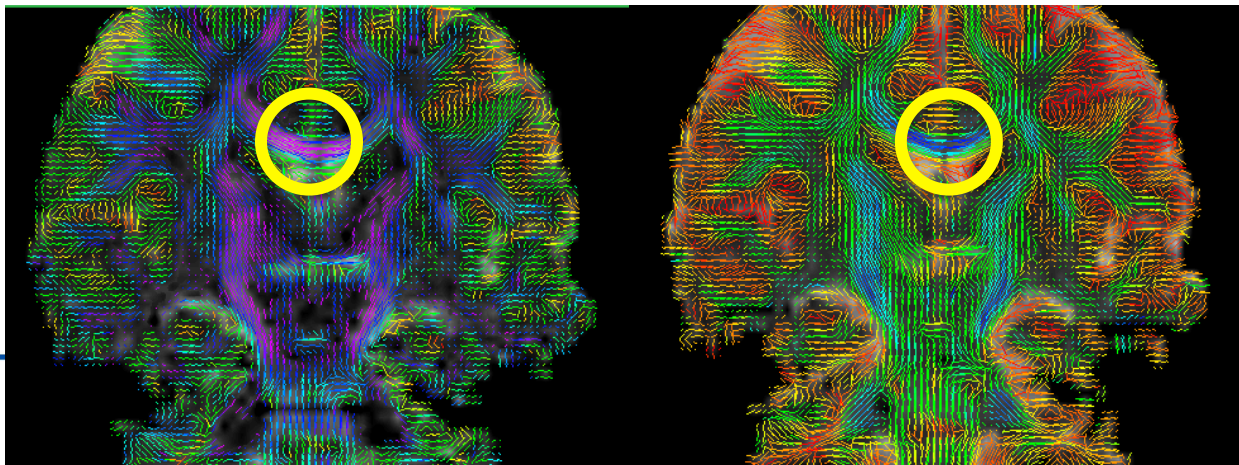
- Designed image pre-processing pipeline
    - Proper and consistent conversion of DICOM diffusion data to NRRD
      - DicomToNrrdConverter (Xiaodong Tao, UNC, Iowa)
    - Quality control
      - Manual visual inspection of raw DWI data (Iowa)
      - Removed bad data: DTIPrep (UNC)
  - Designed techniques for extracting DTI scalar measurements from ROIs
    - Label statistics (SimpleITK)
    - Segmented preliminary ROIs: caudate, putamen, white matter by lobe
-





# 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



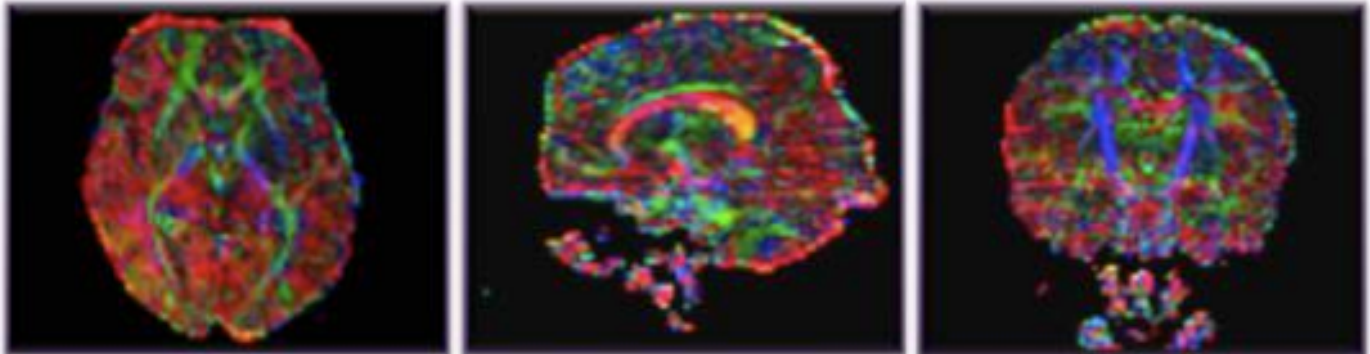


# Diffusion Data: Completed Work

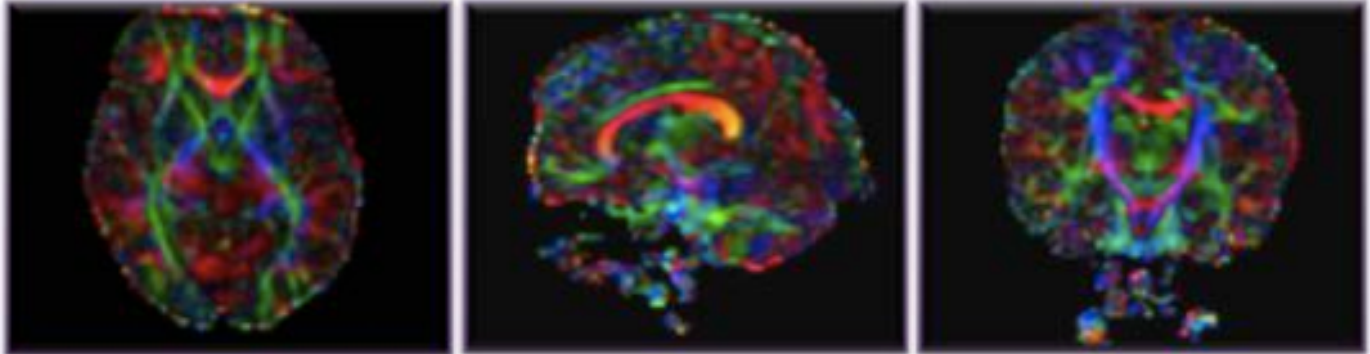
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Results of quality control steps

**Before**



**After**

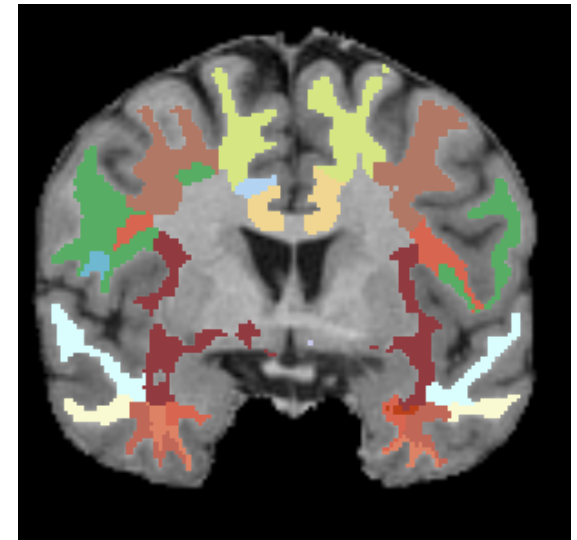
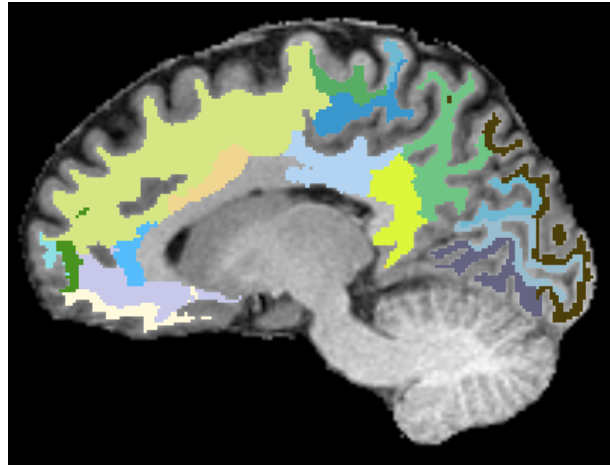
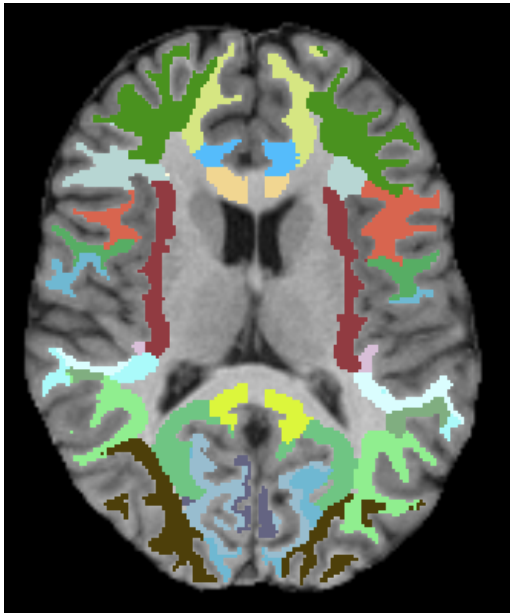






# Diffusion Data: Completed Work

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# Diffusion Data: Future Work

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- Design processing pipeline for fiber tracking analysis
    - DWI/DTI atlas building with population (dwiAtlas, UNC)
    - Incorporation of multiple tensor data
    - Fiber tracking on atlas
    - Propagation of fibers to individual subjects
    - Examine scalar values along tracts in individual subjects
  - Apply/extend full processing pipeline to full PREDICT-HD data set
  - Design longitudinal statistical analyses
-



## Methods: Aim 2.

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- Construct an HD-specific
  - 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 2

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- 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
-