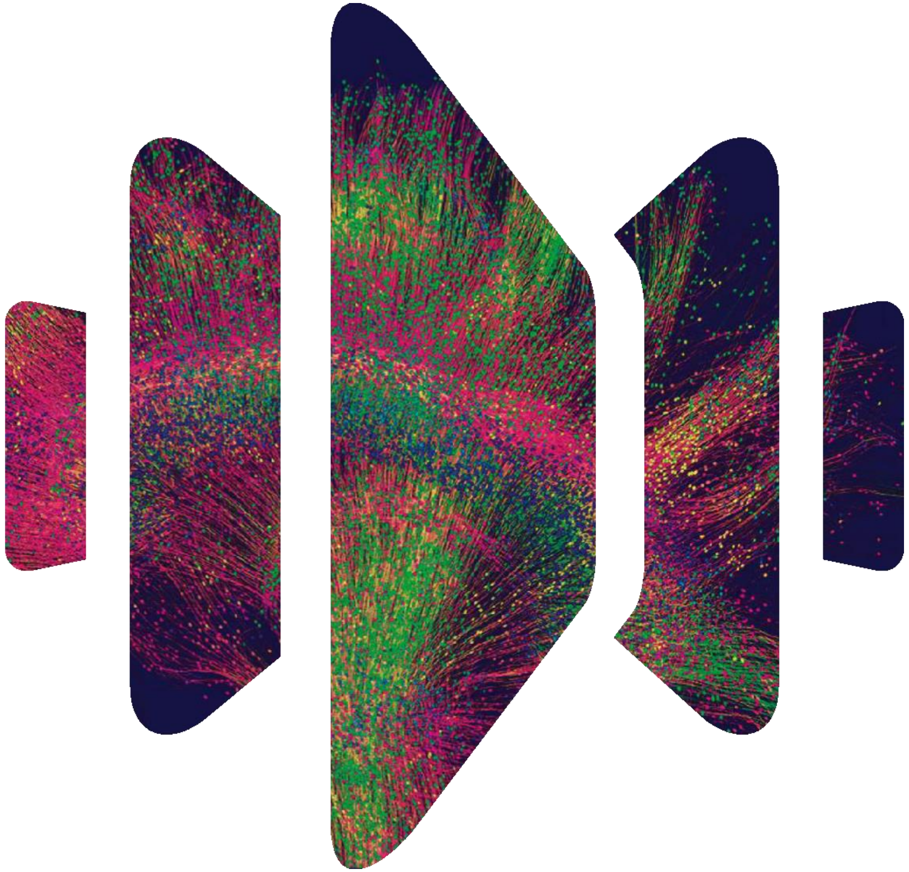


HD-IH Consortium:

Harmonizing volumetric Imaging across Track-, Predict- and Image-HD

Marina Papoutsi

15th September 2022

Overview

IXICO

- **Background:**
  - Joint IXICO, Pharma and CHDI initiative aims to address unmet industry need for a large volumetric imaging dataset
  - CHDI holds a repository from three major natural history studies in HD: TRACK-/TrackOn-, PREDICT-, IMAGE-HD
  - Important studies for understanding disease progression and identifying important disease biomarkers, including neuroimaging biomarkers (e.g. Caudate BSI)
  - However:
    - different studies used different volumetric methods in primary analyses
    - harmonized available dataset used outdated and less accurate, automated methods (e.g. Freesurfer)

TRACKHD

PREDICT-HD

Overview

- **Aim:**
  - Re-analyze ~6000 datasets from both people with HD and healthy controls
  - Create a highly curated dataset using methods aligned with those applied in clinical trials
  - Calculate volumetric cut-off values for HD-ISS to ensure compatibility with these segmentation methods

Group	Baseline	Follow-Up (up to 12 years)**
Control	489	1,239
HD - Prior to clinical motor diagnosis*	1,243	2,326
HD - After clinical motor diagnosis*	194	634

* "Prior to clinical motor diagnosis" defined as DCL < 4; "After clinical motor diagnosis" defined as DCL = 4
** 16.5% of baseline data have 8 or more years follow-up

- **Value:**
  - **Clinical trials:**
    - Historical/External control arm
    - Clinical trial design
    - Participant selection, stratification and enrichment
  - **R&D:**
    - Method/Biomarker development and validation
    - Disease modelling

Analysis

Highlights:

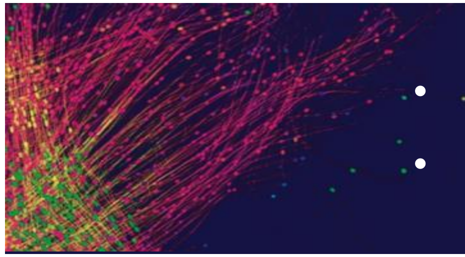
- Visual quality control (QC) of all images and endpoints
- Leverage novel AI technology (IXIQ.Ai) to produce high-quality automated segmentations
- Manual correction of selected regions, where needed
- 95% of baseline segmentations available for four core regions: caudate, putamen, whole brain and lateral ventricles

Volumetric Endpoints:

- **Caudate**
- **Putamen**
- **Whole brain**
- **Lateral ventricles**
- Thalamus
- White matter
- Hippocampus

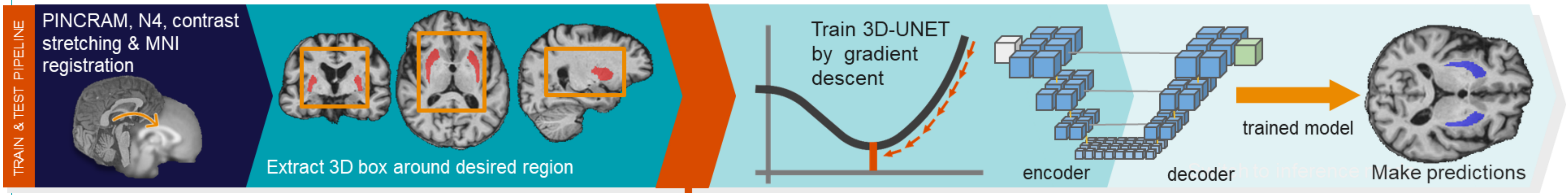
	Region	Cross-sectional segmentation method	Longitudinal measurement method
Core regions	Whole brain	IXIQ.Ai + manual at all timepoints	generalized Boundary Shift Integral (gBSI)
	Ventricles		
	Caudate		
	Putamen		NA
Secondary regions	Thalamus		
	White matter	LoAD	Jacobian
	Hippocampus	LEAP	LLEAP

IXIQ.Ai cross sectional segmentation



- **Deep learning framework for improved segmentation of challenging brain structures**
- **Dedicated models for caudate, putamen, thalamus, whole brain, lateral ventricles**

- Dedicated convolutional neural network (CNN) per brain structure
- Trained on expert annotations on data across multiple neurodegeneration disorders, including HD
- Combined with manual edits to improve accuracy and maximise usable data for challenging images



[1] Kinnunen *et al.* CHDI 2020, [2] Weatheritt *et al.* MIUA 2020, [3] Reinwald *et al.* HSG 2020, [4] Weatheritt *et al.* HSG 2020, [5] Weatheritt *et al.* ADPD 2021

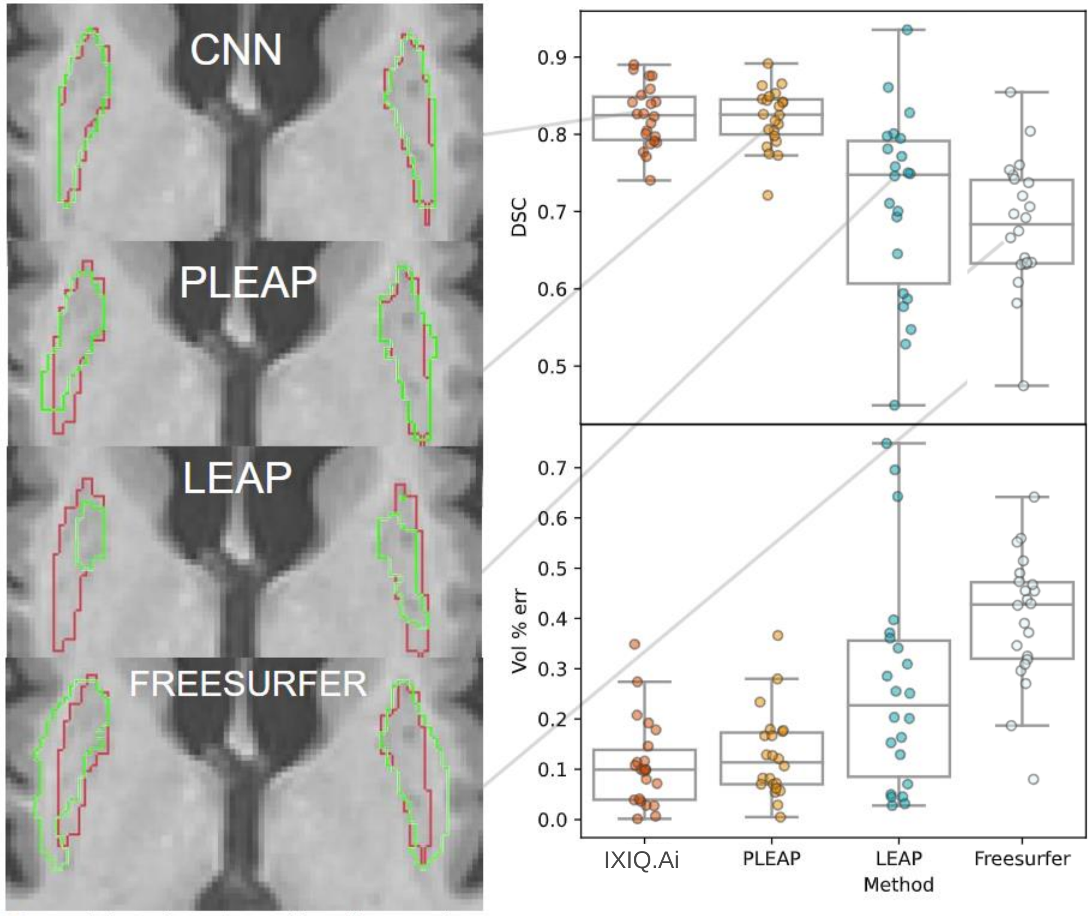
Putamen

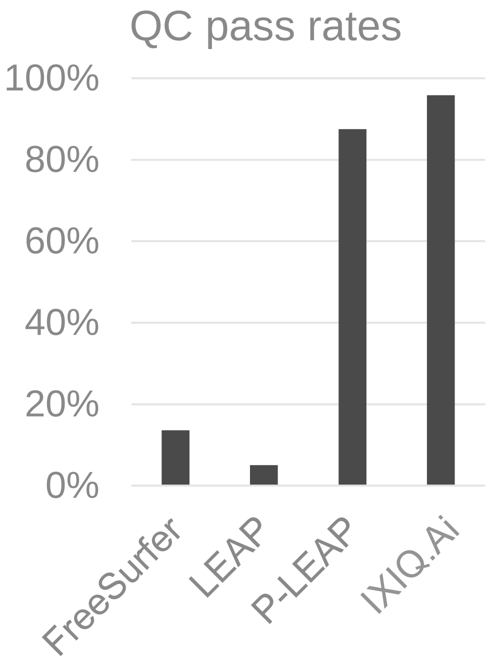
Dataset

- 28 cases
- Early clinically diagnosed HD

Methods

- LEAP
- P-LEAP
- FreeSurfer
- IXIQ.Ai





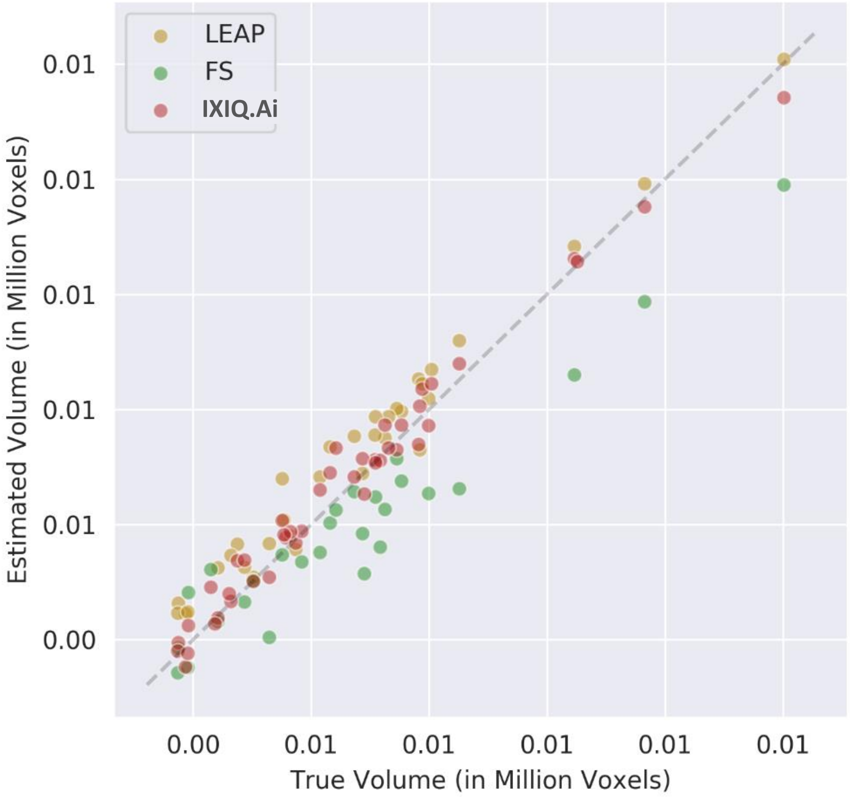
Caudate

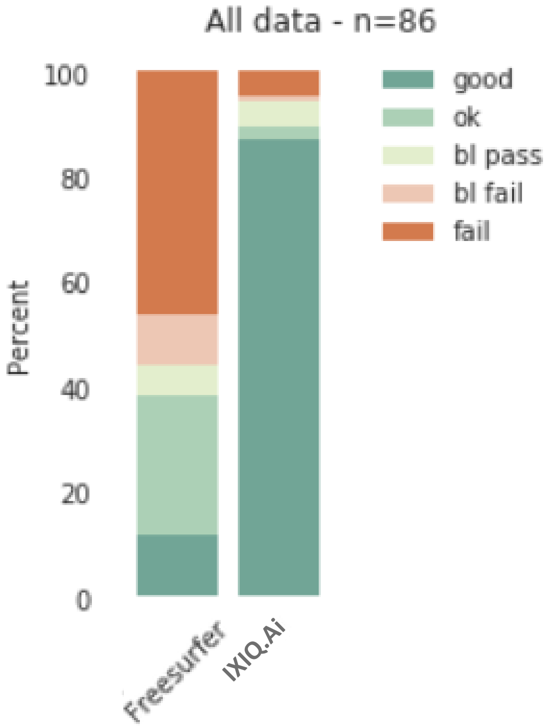
Dataset

- 43 early clinically diagnosed HD

Methods

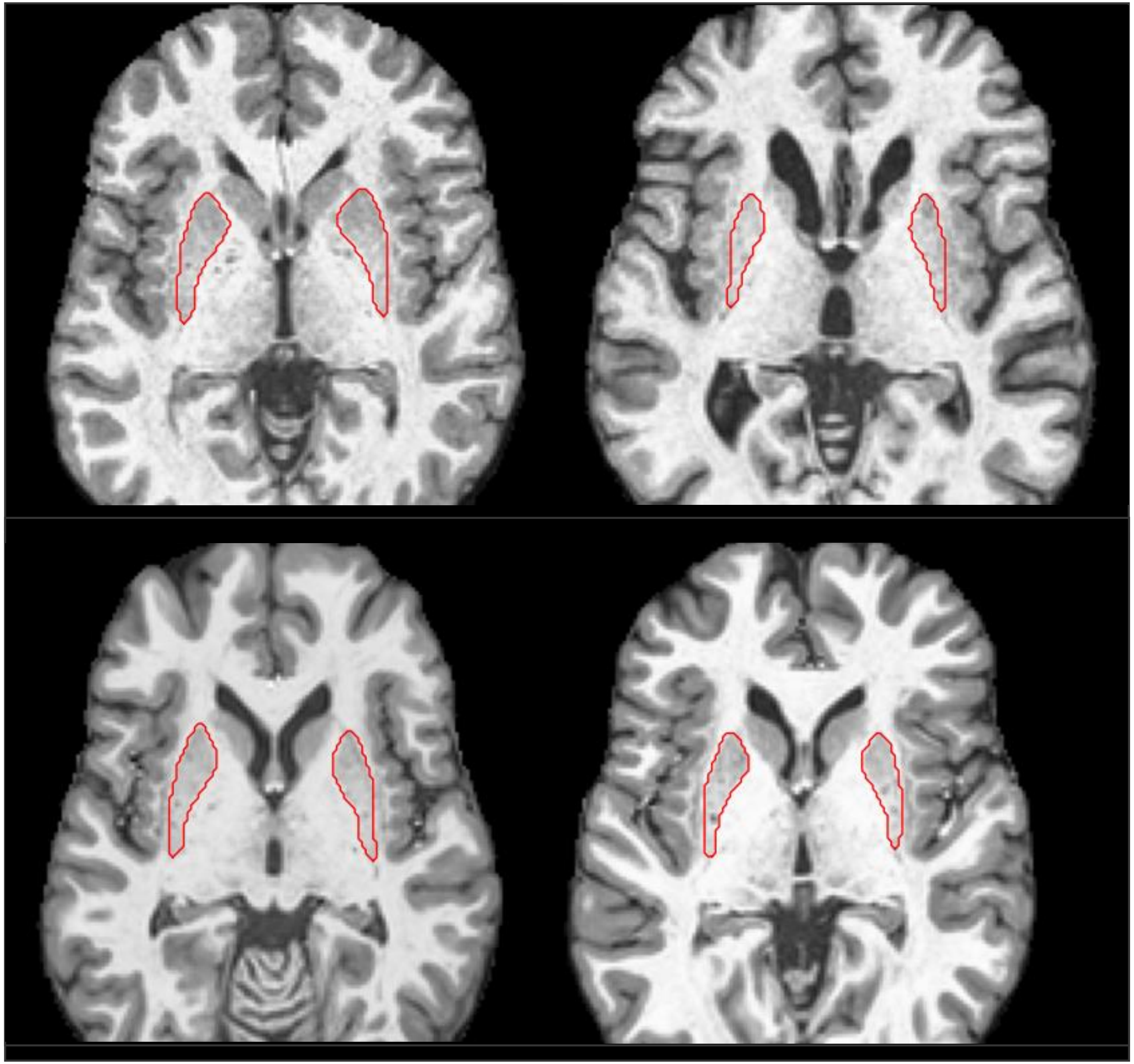
- C-LEAP
- FreeSurfer
- IXIQ.Ai



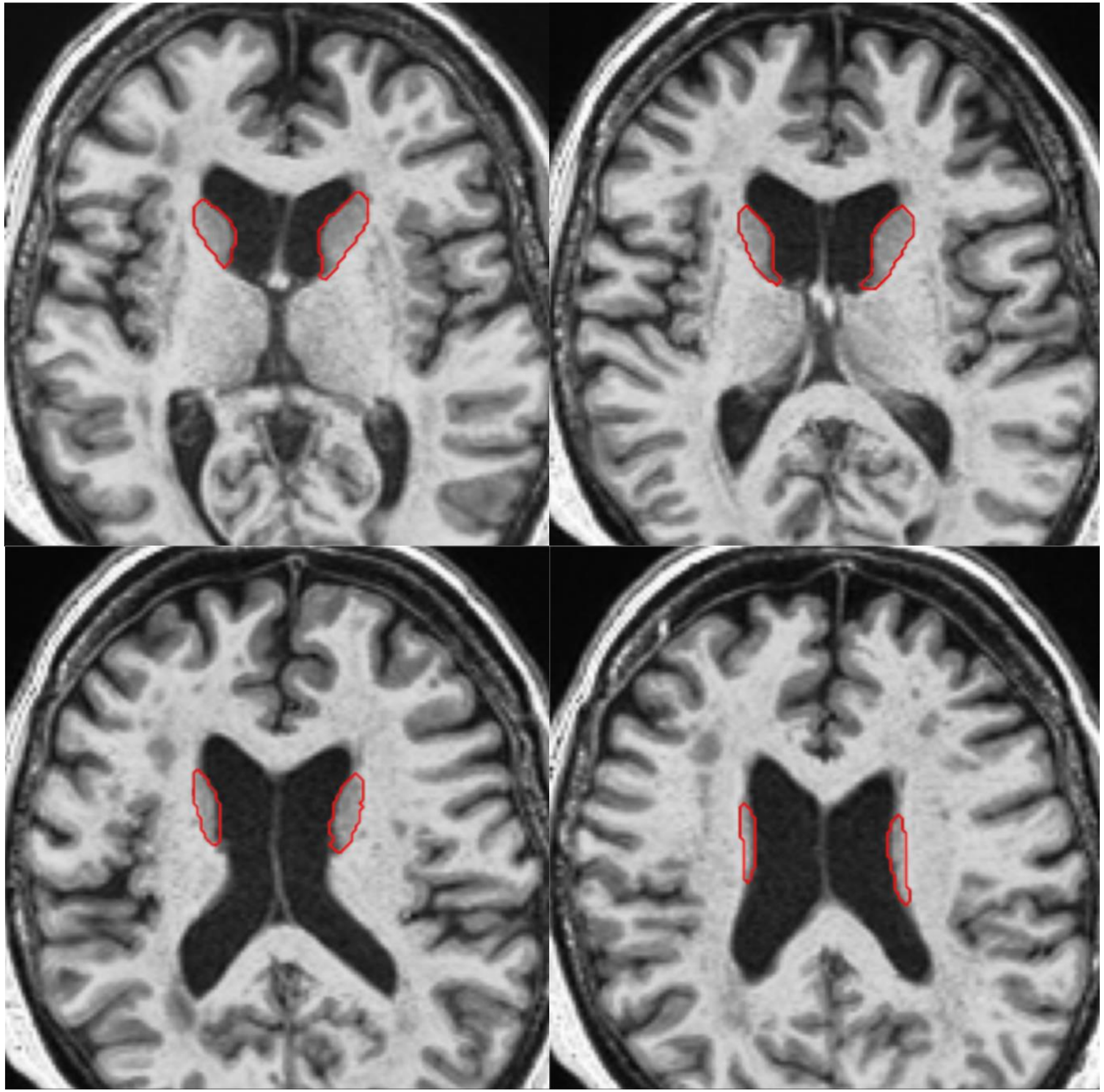


	Dice Score Mean (SD)	% Volume difference from GT Mean (SD)
C-LEAP	0.811 (0.046)	9.6% (6.5%)
FS 7.x	0.813 (0.039)	11.5% (7.9%)
IXIQ.Ai	0.925 (0.014)	4.5% (3.8%)

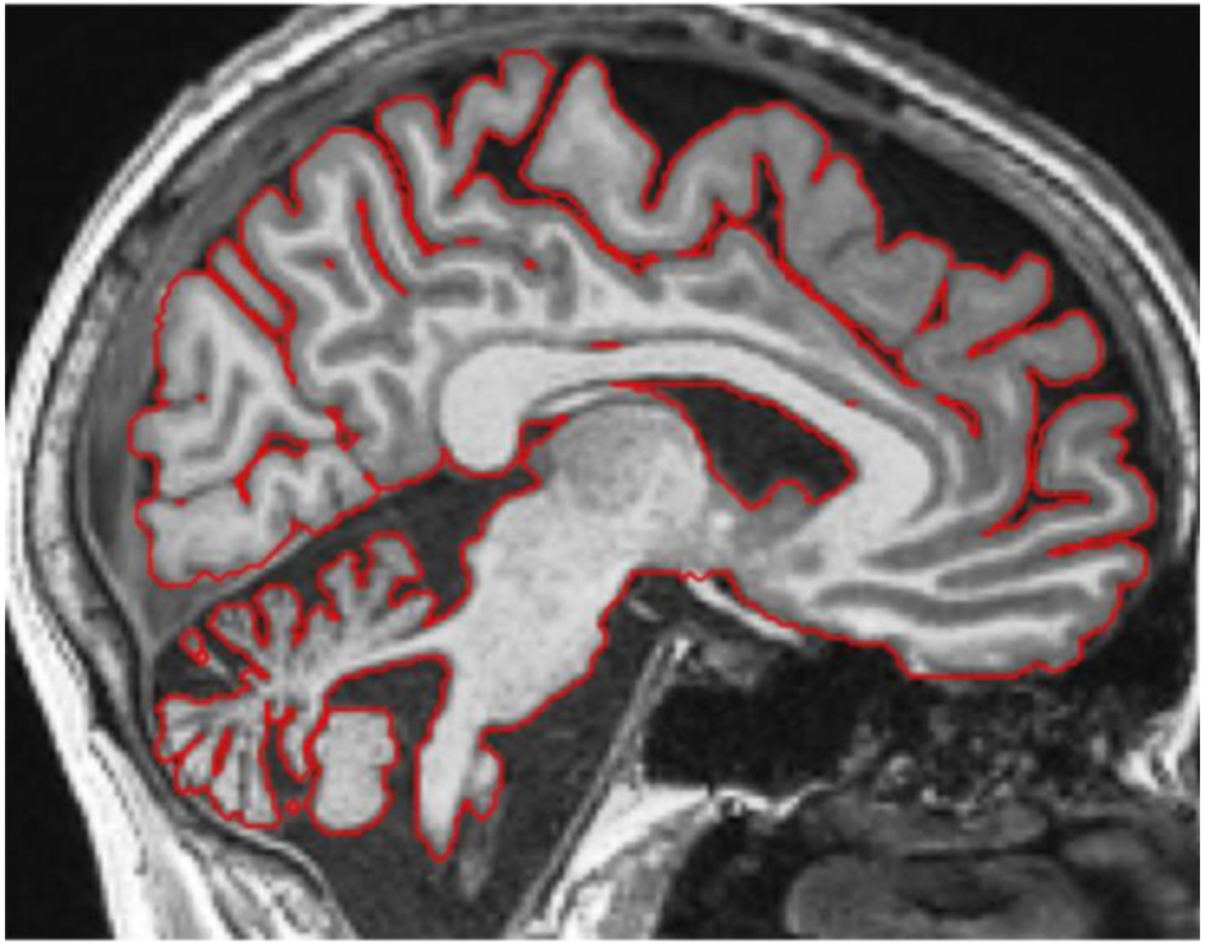
Example Segmentations: Putamen



Example Segmentations: Caudate

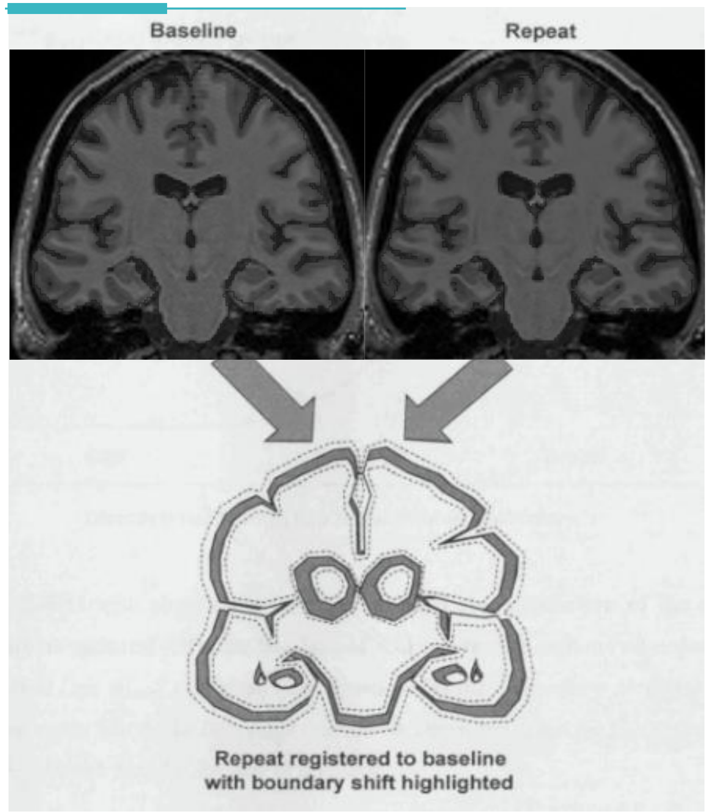


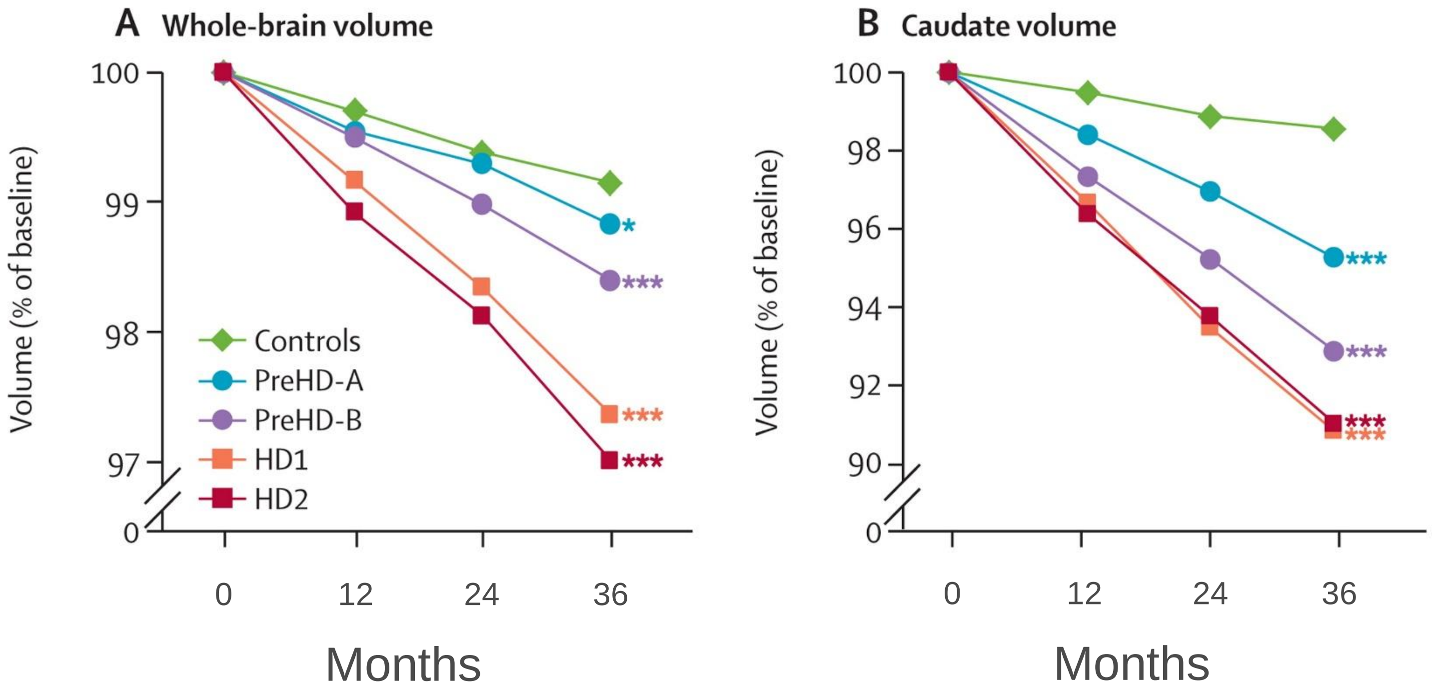
Example Segmentations: Whole Brain



Boundary Shift Integral (BSI)

- Current "best practice" method of measuring longitudinal brain volume change [1]
- Widely deployed in HD research [2-5] and clinical trials



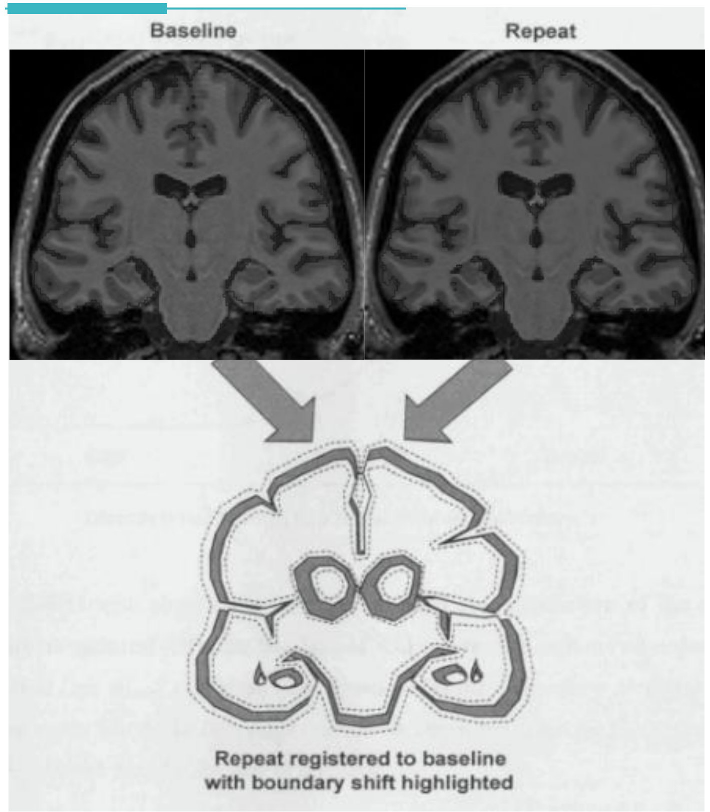


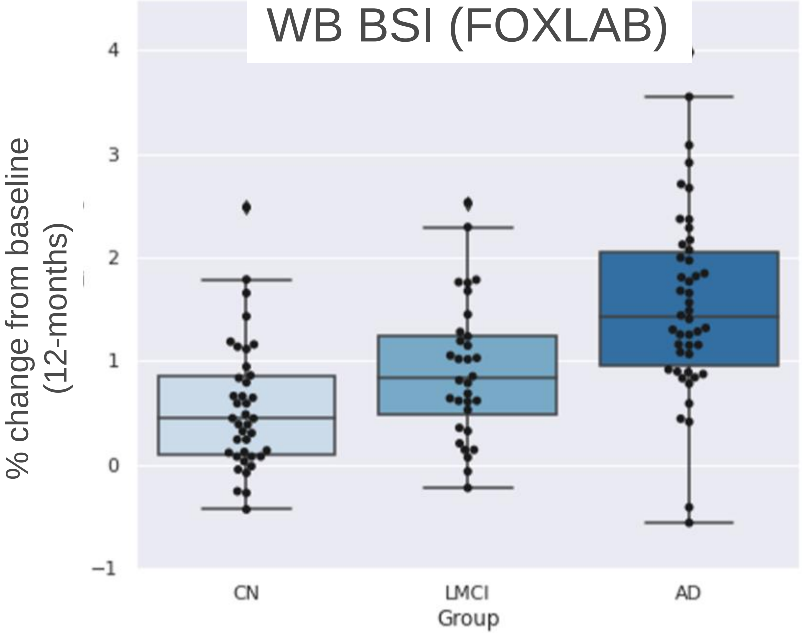
[1] P. Freeborough and N. Fox, 1997 [2] Hobbs et al, 2009; [3-5] Tabrizi et al., 2011, 2012 and 2013)

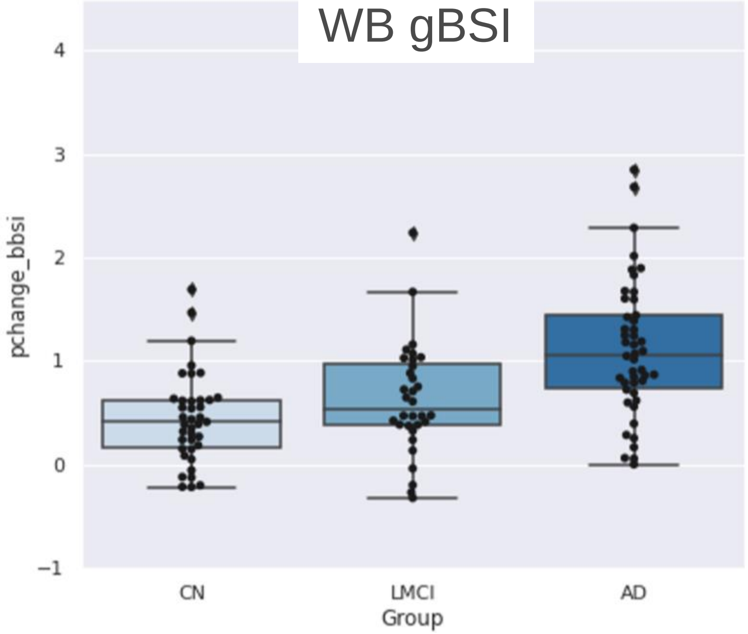
Boundary Shift Integral (BSI)

IXICO

- Current "best practice" method of measuring longitudinal brain volume change [1]
- Widely deployed in HD research [2-5] and clinical trials
- Generalised BSI (gBSI): Used in combination with CNN-based segmentation to achieve largely automated workflow [6]







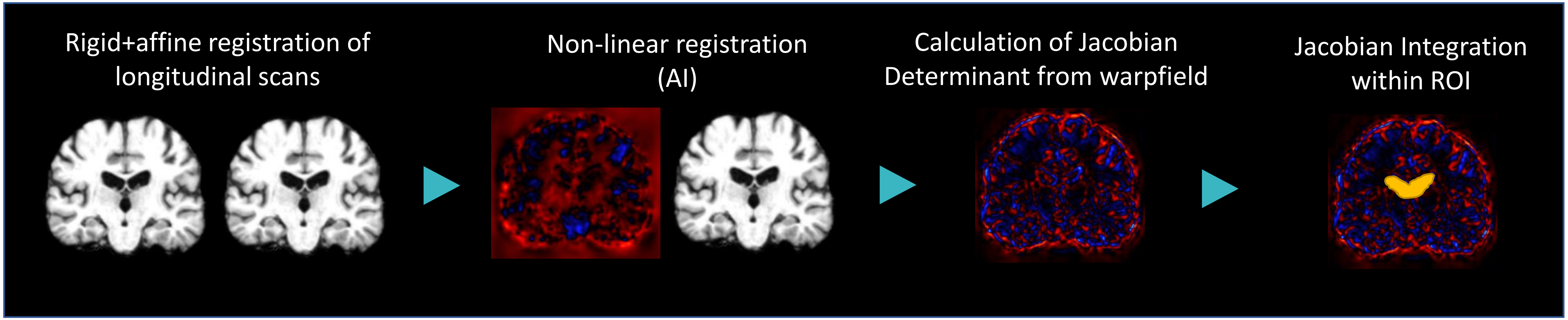
Method	% Change Mean +/- Std	Effect Size AD | MCI		Sample Size AD | MCI	
BSI (FOXLAB)	1.0 +/- 0.87	0.13	0.06	85	134
gBSI	0.76 +/- 0.62	0.11	0.04	86	180

[1] P. Freeborough and N. Fox, 1997 [2] Hobbs et al, 2009; [3-5] Tabrizi et al., 2011, 2012 and 2013); [6] Prados et al, 2015

LoAD & Jacobian Volume Change

- WM volume is computed from cross-sectional tissue class segmentation [1]
- Jacobian integration of deformation field provides voxel-wise measure of growth or shrinkage
- Application to the measurement of white matter volume change

- Well-established technique in HD research for white matter volume change [2-6]
- Fully-automated workflow

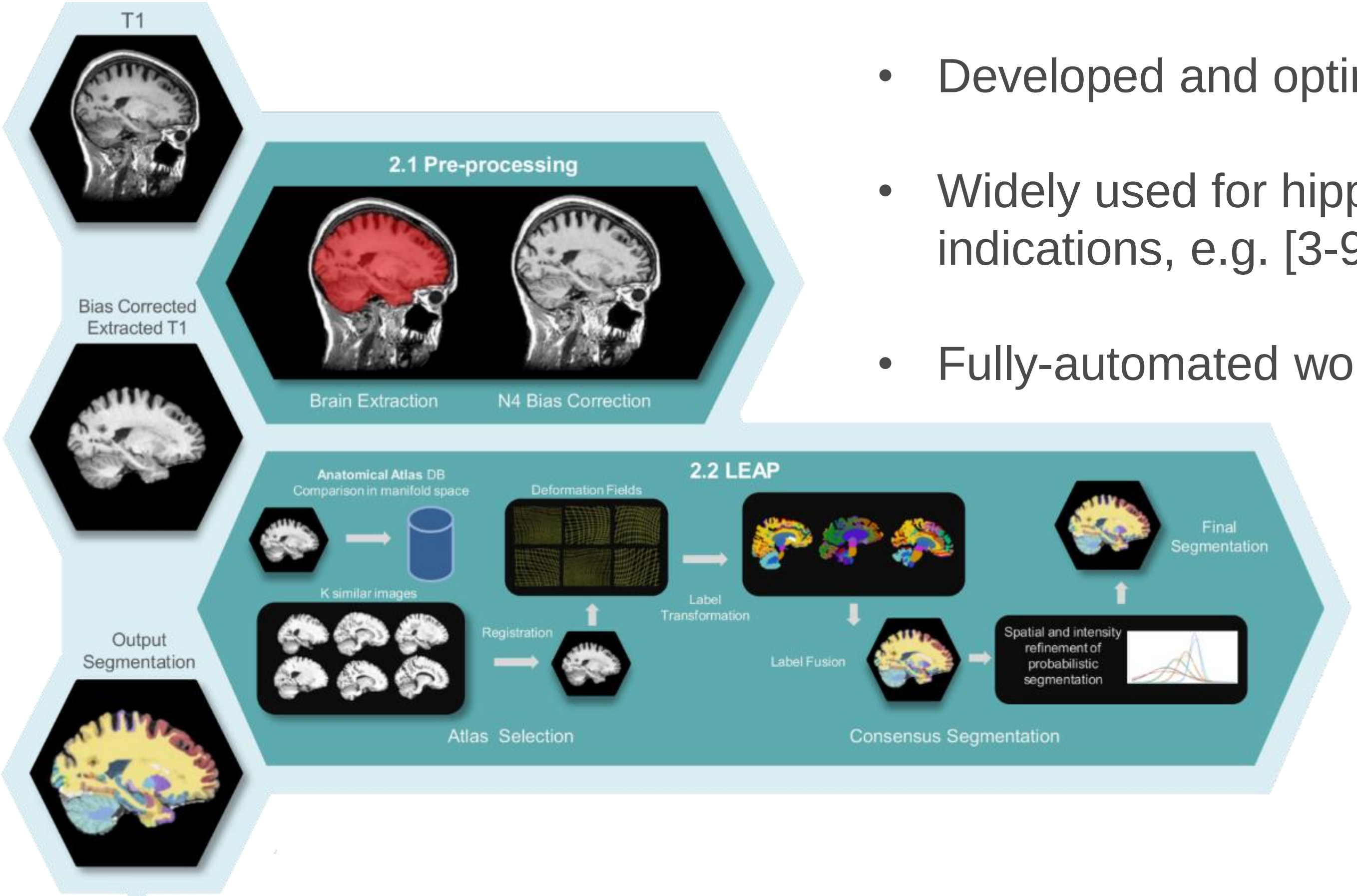


[1] Cardoso et al., 2011) [2-5] Tabrizi et al., 2009, 2011, 2012 and 2013. [6] Reilman et al., 2019

LEAP and LLEAP

- Fully automated analysis pipeline for quantifying brain structural changes from MRI
- Multi-atlas registration and intensity refinement to obtain segmentation of a target structure

- Developed and optimised for hippocampal segmentation [1,2]
- Widely used for hippocampal segmentation across various indications, e.g. [3-9]
- Fully-automated workflow



[1-2] Wolz et al, NeuroImage 2010 a/b, [3-8] van Rossum et al, 2012, Clerx et al, 2013, Hill et al 2014, Bosco et al, 2017, Conrado et al, 2018, Douven et al, 2020, Ingala et al, 2021

Project stages

- **Current phase:**
  - CHDI shared data
  - 2 commercial partners selected participant-visits for analyses
  - IXICO completed set-up and selected additional participant-visits
  - Total number of unique participant-visits selected: 2,015
  - Expected completion of analyses: Q4 2022
  - Calculation of HD-ISS volumetric cut-offs compatible with these segmentation methods

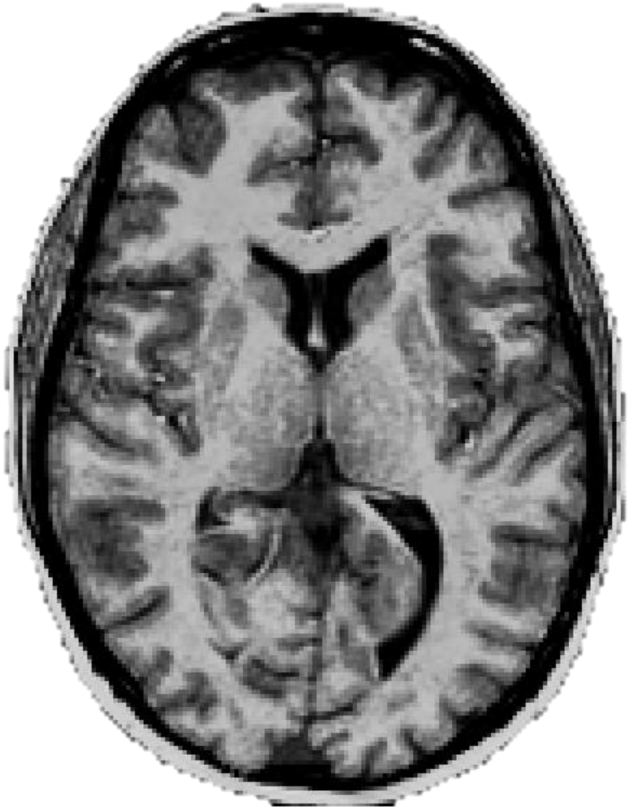
	Baseline	Follow-Up	Total
Control	478	250	728
HD - prior to clinical motor diagnosis	422	627	1,049
HD - after clinical motor diagnosis	89	148	237

* “Prior to clinical motor diagnosis” defined as DCL < 4;
“After clinical motor diagnosis” defined as DCL = 4

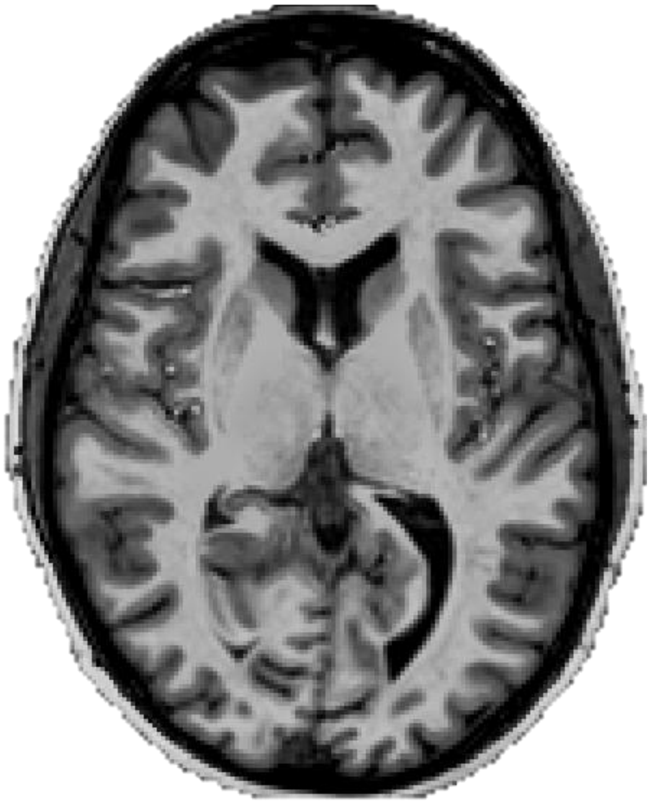
Project stages

- **Challenges:**
  - Data migration: fragmented data selection, data linking and database harmonizing
  - Variability in image quality in Predict-HD: artifacts, noise, lesions
  - Scanner and sequence parameter changes between visits in Predict-HD:
    - Change in sequence parameters, e.g. image resolution
    - Change from 1.5T to 3T MRI scanners (n = 949 change events vs 1554 no change events at follow-up)

Baseline 1.5T



After 3.5 Years 3T



Project stages

- **Next phase:**
  - Entry of additional commercial partners
  - Identification of additional participant-visits
  - Phase will close when all participant-visits available have been analysed

- **Data Availability:**
  - Following an embargo period the data will become widely available to the community via CHDI
  - Shared data will include volumetric results, ROI segmentations and relevant pipeline outputs

Thank you!