Validation of IXIQ.Ai+gBSI: an automated framework for caudate atrophy measurement in Huntington's disease

M. Papoutsi[1,2], D. Pustina[3], E.C. Gantman[3], R.I. Scahill[2], R. Wolz[1,4]
[1]IXICO plc, London UK; [2]University College London, London, UK, CHDI Management/CHDI Foundation, New York, NY, USA [4]Imperial College London, London UK

HUNTINGTON'S DISEASE CENTRE

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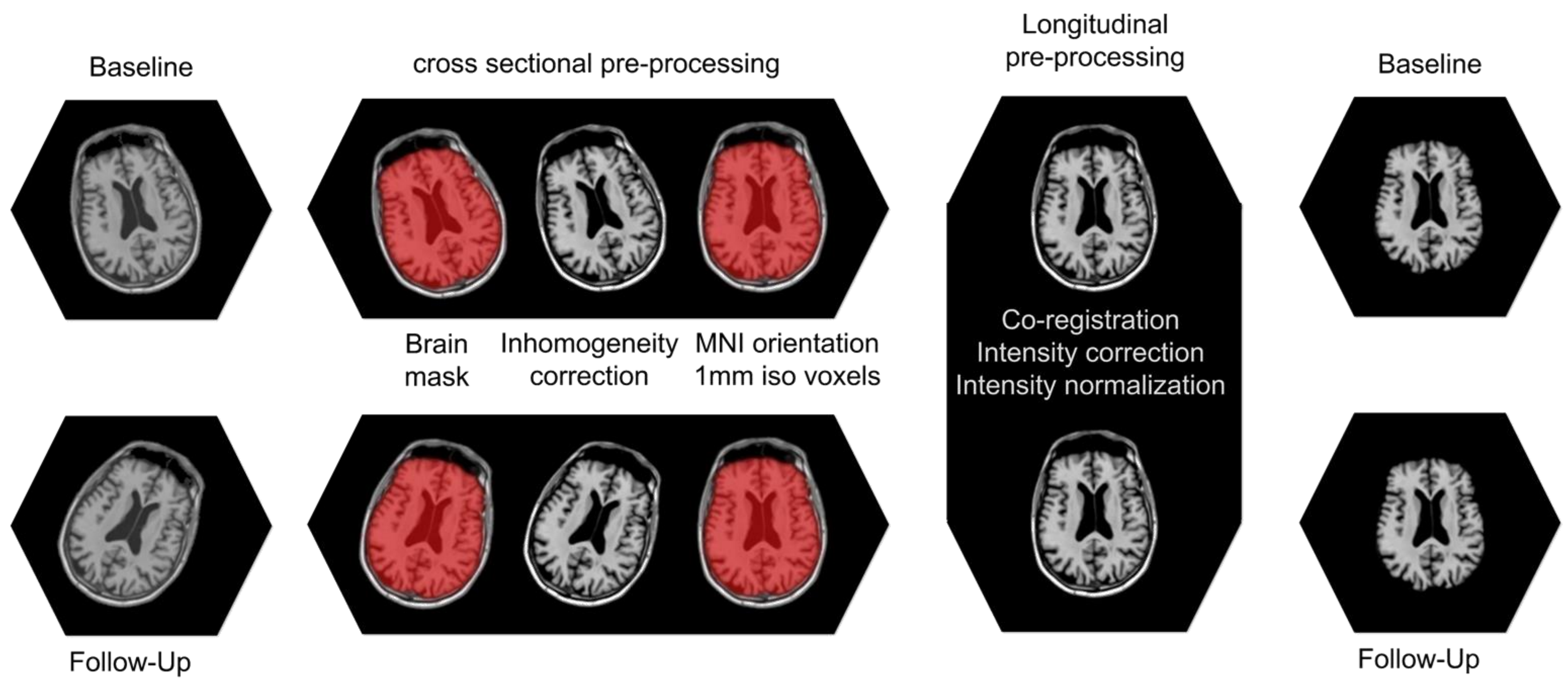
Caudate volume is a well-established biomarker in Huntington's disease (HD) used to assess disease progression and potential efficacy of interventions. The gold standard requires manual segmentation at baseline followed by application of the Boundary Shift Integral method (man+BSI; Hobbs et al., 2009; Mansoor et al, 2021). This process is slow and requires significant expertise and is therefore not easily scalable to accommodate large clinical trials or the need for disease progression modelling using big datasets, which requires rapid and accurate estimation of baseline volume and longitudinal volume change.

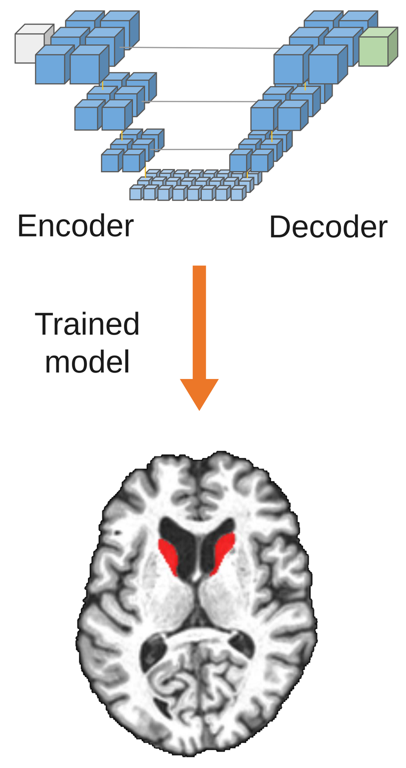
Here we present **an automated workflow for estimation of cross-sectional volume and volume change in the caudate** using deep-learning (Weatheritt et al., 2020) and the generalized Boundary Shift Integral (Prados et al., 2015; IXIQ.Ai+gBSI).

As part of the validation of IXIQ.Ai+gBSI we retrospectively analysed 581 T1-weighted (T1W) MRI scans from 259 participants with up to 3-years follow-up from Track- and TrackOn-HD (Tabrizi et al., 2013; Langbehn et al., 2019) and compared the sensitivity of IXIQ.Ai+gBSI with the sensitivity of man+BSI algorithms to detect disease progression over time.

Pre-processing

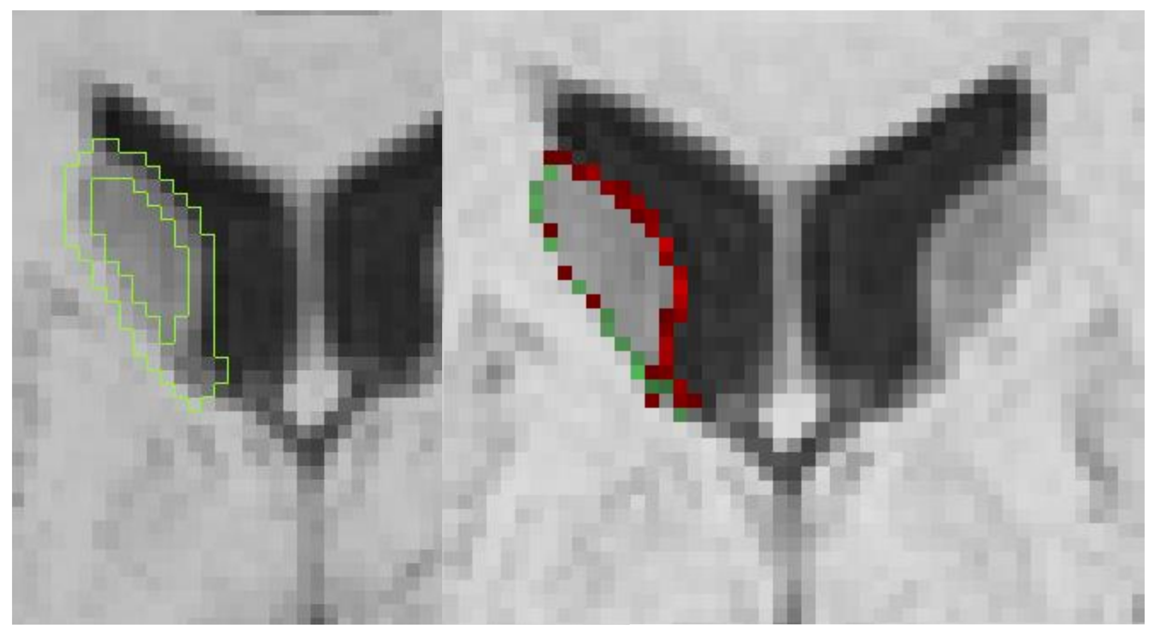


Regional Segmentation



Boundary Shift Integral

BSI estimation within regional boundary



Red = volume decrease; Green = volume increase

Methods

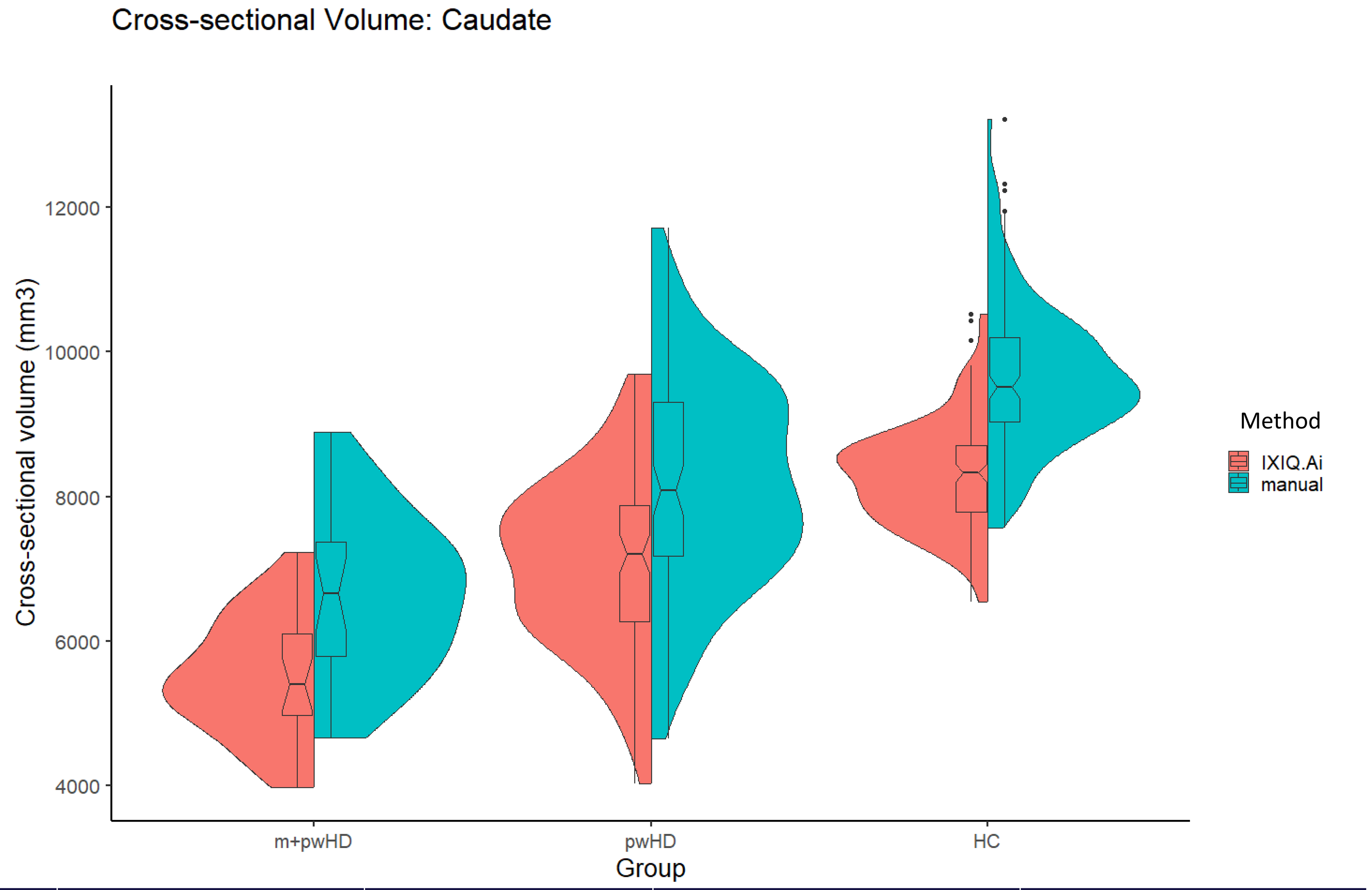
As part of the HD-Imaging Harmonisation consortium (HD-IH) study we used IXIQ.Ai+gBSI to segment T1W images from 142 healthy controls (HC: CAG repeat length<36), 93 people with HD prior to clinical motor diagnosis (pwHD: CAG>=39 and diagnostic confidence level<4), and 24 pwHD with clinical motor diagnosis (m+pwHD, diagnostic confidence=4). Details are provided in Table 1. Man+BSI measurements were also available for all these images.

Demographics	HC	pwHD DCL < 4	m+pwHD DCL = 4
N	142	93	24
Years from Baseline - Mean (SD)	2.1 (0.7)	1.7 (0.7)	1.8 (0.8)
Age - Mean (SD)	45.7 (10.0)	37.4 (6.1)	42.6 (6.8)
Sex (%M)	41.5%	49.5%	29.2%
CAG - Median (SD)		44 (1.8)	44 (1.7)
DBS - Mean (SD)		307.1 (42.3)	361.5 (52.4)

Group differences in caudate volume at baseline and longitudinal volume change were analyzed using linear regression (mixed linear models were used for longitudinal analyses).

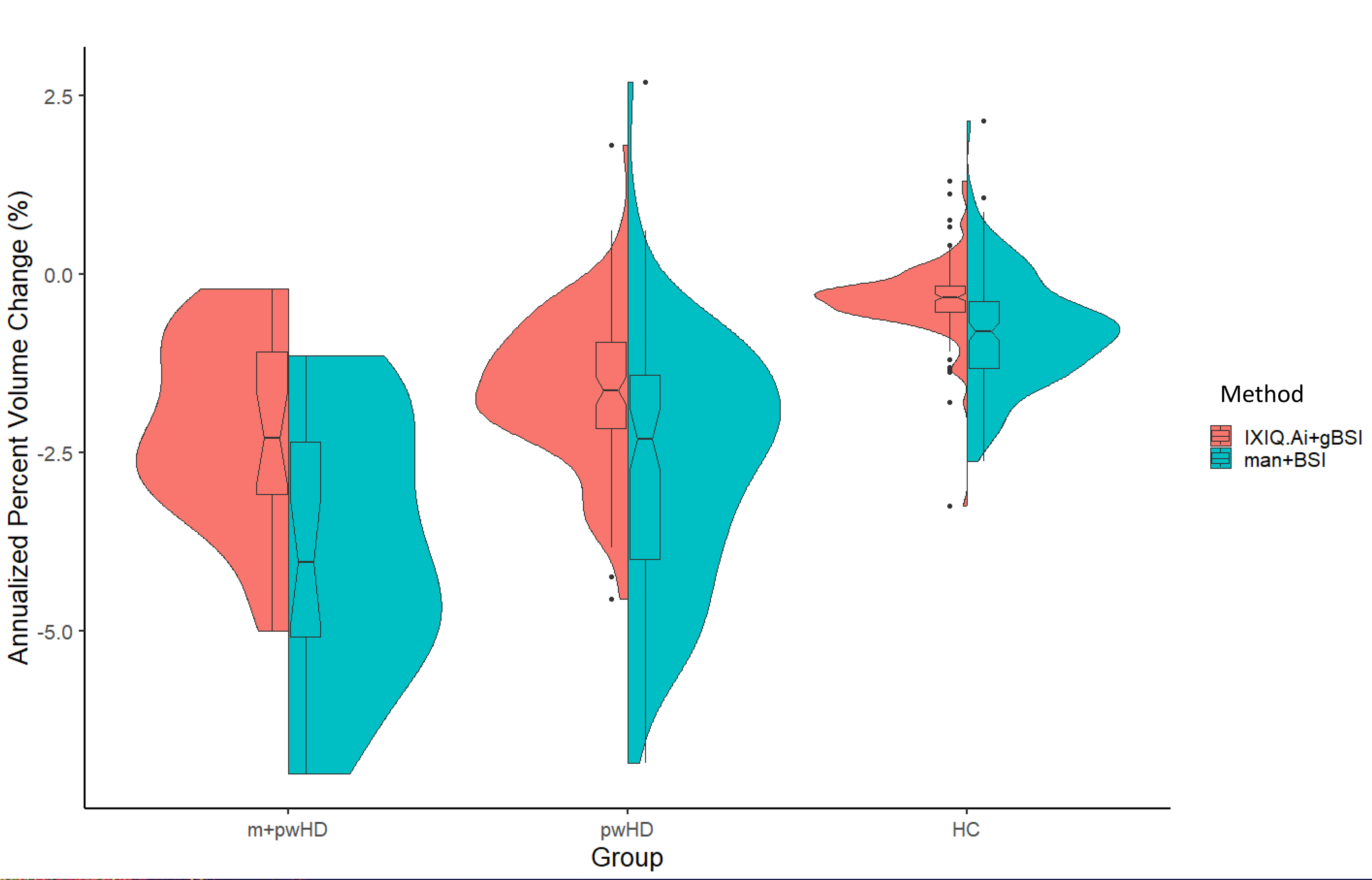
Volume estimates were normalized by the affine scaling factor to correct for head size, and adjusted for sex, baseline age and scanner manufacturer. Longitudinal models also included time (years from baseline) and its interaction with all other terms.

Cross-sectional Caudate Volume



		HC - pwHD	HC – m+pwHD	pwHD – m+pwHD
Manual	Contrast Mean (SE)	1674.1 (160) mm³	3304.1 (245) mm³	1629.9 (256) mm³
	P-value	<0.001	<0.001	<0.001
	Cohen's d (95%CI)	1.53 (1.22-1.85)	3.03 (2.51-3.54)	1.49 (1.01-1.98)
IXIQ.Ai	Contrast Mean (SE)	1366.4 (133) mm³	2908.6 (203) mm³	1542.2 (213) mm³
	P-value	<0.001	<0.001	<0.001
	Cohen's d (95%CI)	1.51 (1.19-1.83)	3.21 (2.69-3.73)	1.70 (1.22-2.19)

Longitudinal Caudate Volume Change



		HC - pwHD	HC – m+pwHD	pwHD – m+pwHD
Man +BSI	Contrast Mean (SE)	101.60 (11.8) mm³	142.25 (14.6) mm³	43.64 (12.7) mm³
	P-value	<0.001	<0.001	0.002
	Cohen's d (95%CI)	1.06 (0.81-1.31)	1.52 (1.21-1.83)	0.46 (0.19-0.72)
IXIQ.Ai +gBSI	Contrast Mean (SE)	70.60 (8.49) mm³	113.56 (10.56) mm³	42.96 (9.17) mm³
	P-value	<0.001	<0.001	<0.001
	Cohen's d (95%CI)	1.02 (0.77-1.27)	1.65 (1.33-1.96)	0.62 (0.36-0.89)

Both methods detected significant group differences in baseline volume and volume change with comparable effect sizes.

In conclusion, IXIQ.Ai+gBSI produced volume estimates equally sensitive to disease progression as the standard, man+BSI, but in a faster, automated, fashion.

References: • Hobbs et al., 2009, Neuroimage, vol. 47(4) ; • Mansoor et al., 2021, Frontiers in Neurology, 12; • Weatheritt et al., 2020, Neurotherapeutics, 17(S1); • Prados et al., Neurobiology of Aging, 2015, 36; • Tabrizi et al., 2013 Lancet Neurology, 12 (7); • Langbehn et al., 2019 JAMA Neurology, 76 (11)

Data used in this work were generously provided by the participants in the TRACK-HD study and made available by Professor Sarah Tabrizi, Principal Investigator, University College London.