

# Volumetric change across the different Stages of the Huntington's disease Integrated Staging System (HD-ISS) defined at baseline



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The HD Integrated Staging System (HD-ISS; Tabrizi et al. 2022) enables classification of people with HD into four disease stages based on quantitative landmark assessments. Here we characterized volume change over time in the caudate nucleus, putamen, lateral ventricles, and whole-brain across participants starting in each of the different HD-ISS Stages at baseline and compared to healthy controls (HC).

We used a subset of data from TRACK-HD/ON and PREDICT-HD studies, which have been processed as part of the HD Imaging Harmonization (HD-IH) consortium. Volumetric analyses were performed using deep-learning (IXIQ.Ai; Weatheritt et al., 2020) and the generalized Boundary Shift Integral (gBSI; Prados et al., 2015) methods.

## METHODS

We analysed data from 482 controls and 1,219 participants with HD across the four HD-ISS stages. Demographic details at baseline entry into the study are provided in the table below. Visits up to 6.5 years were included in the analyses. To enable differentiation between HD-ISS Stages 0 and 1 within the HD-IH consortium data, new cut-off values were calculated based on the control study participants for the HD-ISS Stage 1 landmarks, ie the putamen and caudate volume, adjusted by the affine scaling factor (ASF; Buckner et al. 2004), using the IXIQ.Ai methods.

Variables	Controls (HC)	HD-ISS Stage 0	HD-ISS Stage 1	HD-ISS Stage 2	HD-ISS Stage 3
N at Baseline	482	244	378	375	205
N Follow-Up visits	939	327	582	524	320
Years on Study (time from baseline) – Mean (SD)	3.1 (1.6)	3.2 (1.6)	3.2 (1.6)	3.0 (1.5)	2.5 (1.4)
Age – Mean (SD)	44.4 (11.6)	35.4 (9.6)	40.2 (9.5)	40.6 (10.0)	45.5 (9.7)
Sex (%F)	61.8%	74.2%	53.7%	60.5%	60.5%
CAG – Median (min-max)	-	42 (40 – 49)	42 (40 – 50)	43 (40 – 50)	43 (40 – 50)

Linear mixed models (LMMs) with random intercept and slope were used to estimate the rate of change in regional brain volume across the four HD-ISS stages and controls at baseline (first visit). The outcome was regional volume in mm<sup>3</sup> for the four regions of interest (ROIs): whole-brain, lateral ventricles, caudate and putamen. The predictors were time from baseline (years), group (baseline HD-ISS Stage and controls), time by group interaction. For the whole brain we also added a quadratic effect of time. The models were adjusted for sex, time from baseline (in years), baseline age (centred at 44), site, MRI scanner field strength and their interactions with time. **Separate models were fit for each ROI.**

The R model equation is depicted below.

$$\text{Volume change} = 1 + \text{sex} + \text{time} \times (\text{group} + \text{baseline age} + \text{site} + \text{scanner field strength}) + (1 + \text{time} | \text{participant})$$

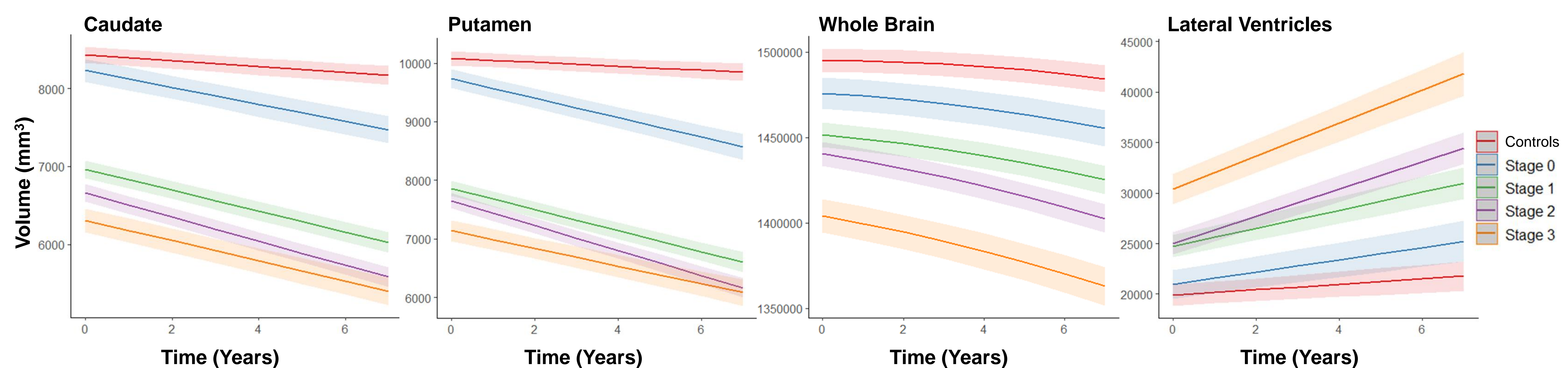
The plots below show the marginal means with age held constant at 44 years old and categorical variables held constant at their proportions.

## RESULTS

For all regions, there was a significant main effect of group, time, and group by time interaction (all p<0.001 Bonferroni corrected for four ROIs).

The table below reports the results from the post-hoc comparisons of the group by time interaction within the HD-ISS groups. Comparisons against the control group were all significant (all p < 0.01 corrected). P-values were Tukey-adjusted for a family of 5 estimates and then Bonferroni corrected for four ROIs.

ROI	Result	Stage 0 vs Stage 1	Stage 1 vs Stage 2	Stage 2 vs Stage 3	Stage 0 vs Stage 2	Stage 0 vs Stage 3	Stage 1 vs Stage 3
Caudate	P-value (Bonferroni corr.)	0.06	0.072	0.048	<0.001	0.604	1
	T-value	3.14	3.09	-3.20	5.59	2.28	-0.56
	Contrast Estimate (SE) in mm <sup>3</sup>	25.49 (8.12)	20.13 (6.52)	-24.45 (7.64)	45.62 (8.16)	21.17 (9.27)	-4.33 (7.77)
Putamen	P-value (Bonferroni corr.)	1	0.080	<0.001	0.012	1	0.652
	T-value	1.08	3.06	-4.83	3.60	-1.01	-2.25
	Contrast Estimate (SE) in mm <sup>3</sup>	13.72 (12.73)	32.71 (10.70)	-61.40 (12.72)	46.43 (12.90)	-14.97 (14.82)	-28.69 (12.75)
Whole Brain	P-value (Bonferroni corr.)	0.248	<0.001	1	<0.001	<0.001	<0.001
	T-value	2.65	6.14	1.50	7.91	8.06	6.63
	Contrast Estimate (SE) in mm <sup>3</sup>	818.07 (308.47)	1649.69 (268.46)	479.02 (319.98)	2467.77 (311.96)	2946.79 (365.72)	2128.71 (321.21)
Lateral Ventricles	P-value (Bonferroni corr.)	0.068	<0.001	0.092	<0.001	<0.001	<0.001
	T-value	-3.10	-5.76	-3.00	-8.06	-9.48	-7.78
	Contrast Estimate (SE) in mm <sup>3</sup>	-280.87 (90.72)	-456.84 (79.17)	-283.53 (94.43)	-736.70 (91.41)	-1020.24 (107.65)	-739.37 (95.07)



## SUMMARY

Post-hoc comparisons between the HD-ISS groups showed that as Stage increased, mean volume differed significantly for all regions. However, for rate of change, there were differences between regions. For the whole brain and lateral ventricles, Stage 2 and 3 participants had faster rate of change than Stage 0 and 1. For the caudate and putamen, Stage 2 participants have faster rate of atrophy compared to Stage 0, and also compared to Stage 3. Our results therefore suggest there is acceleration of striatal volume change during Stage 2, which slows down at Stage 3, whereas for the whole brain and lateral ventricles rate of change accelerates at Stage 2 and continues at the same rate in Stage 3.