Evaluating the Impact of Scanner Harmonisation with ComBat on Longitudinal Brain Volume Measures in Huntington's Disease

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Regional brain atrophy measures are widely used to monitor disease progression in Huntington's disease (HD). However, scanner-related variability in multicentre studies may reduce sensitivity to longitudinal change. We assessed the relative contributions of scanner-related effects on regional brain volume change and evaluated whether longitudinal harmonisation using ComBat improves sensitivity to disease progression. We compared harmonized vs unharmonized volumetric results for the **caudate**, **putamen**, **whole brain** and **lateral ventricles** across 73 unique combinations of site, scanner vendor, model and magnet field strength. We used data from the Track-/TrackOn-HD, Predict-HD and Image-HD studies analyzed as part of the HD-IH consortium.

METHODS

We included in our analyses 482 controls and 918 participants with HD across the four HD-ISS stages using monotonic staging at the baseline visit. Demographic details at baseline entry into the study are provided in the table below. Visits up to 9 years and only scanners with at least 2 scans across different timepoints were included in the analyses.

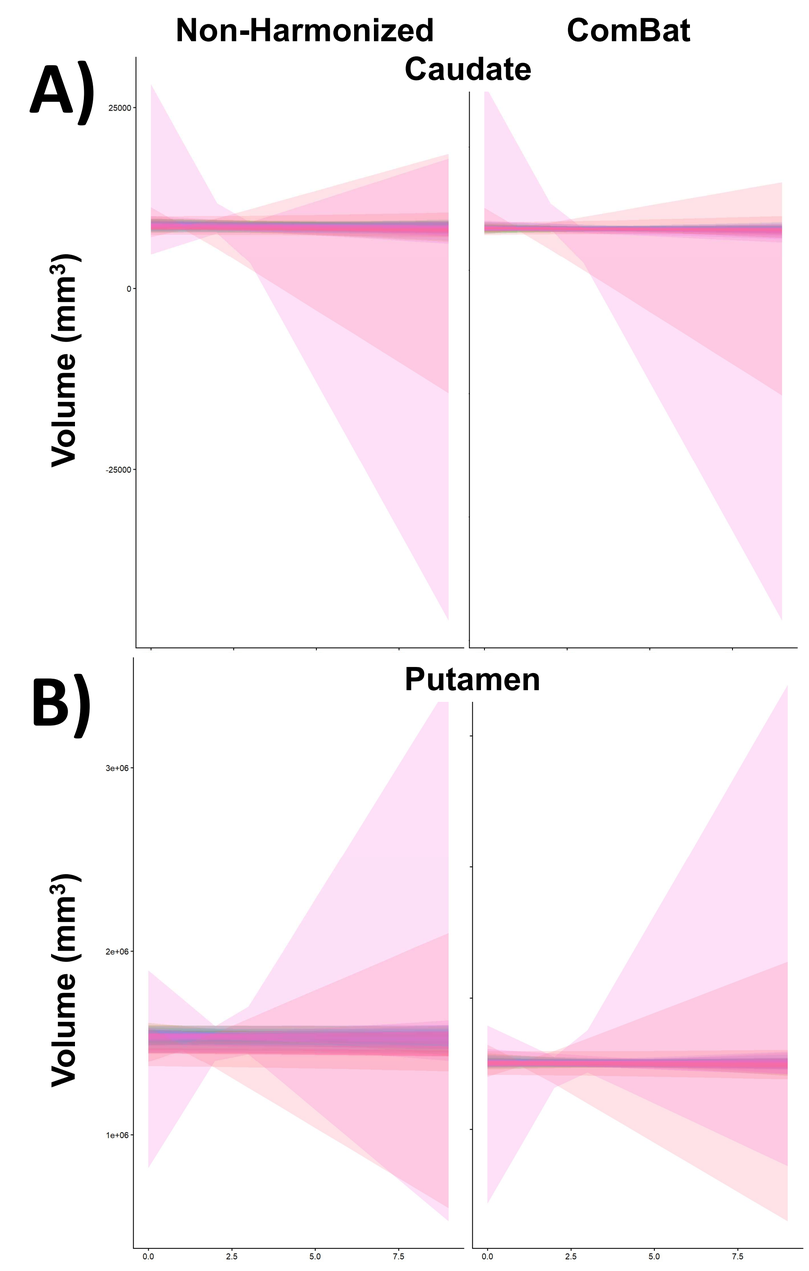
Variables	Controls (HC)	HD-ISS Stage 0	HD-ISS Stage 1	HD-ISS Stage 2	HD-ISS Stage 3
N at Baseline	482	185	324	254	155
N Follow-Up visits	1207	479	806	542	274
Years on Study (time from baseline) – Mean (SD)	3.4 (1.9)	4.0 (2.1)	3.6 (2.0)	3.6 (2.1)	2.4 (1.4)
Age – Mean (SD)	44.4 (11.6)	36.9 (9.1)	41.1 (9.2)	41.7 (9.7)	46.3 (10.0)
Sex (%M)	38.2%	26.5%	45.4%	43.3%	42.6%
CAG – Median (min-max)	-	42 (40 – 52)	42 (40 – 50)	43 (40 – 61)	43 (40 – 59)
N scanners at Baseline	49	35	36	39	38
N scanners at Follow-Up	59	53	56	50	39

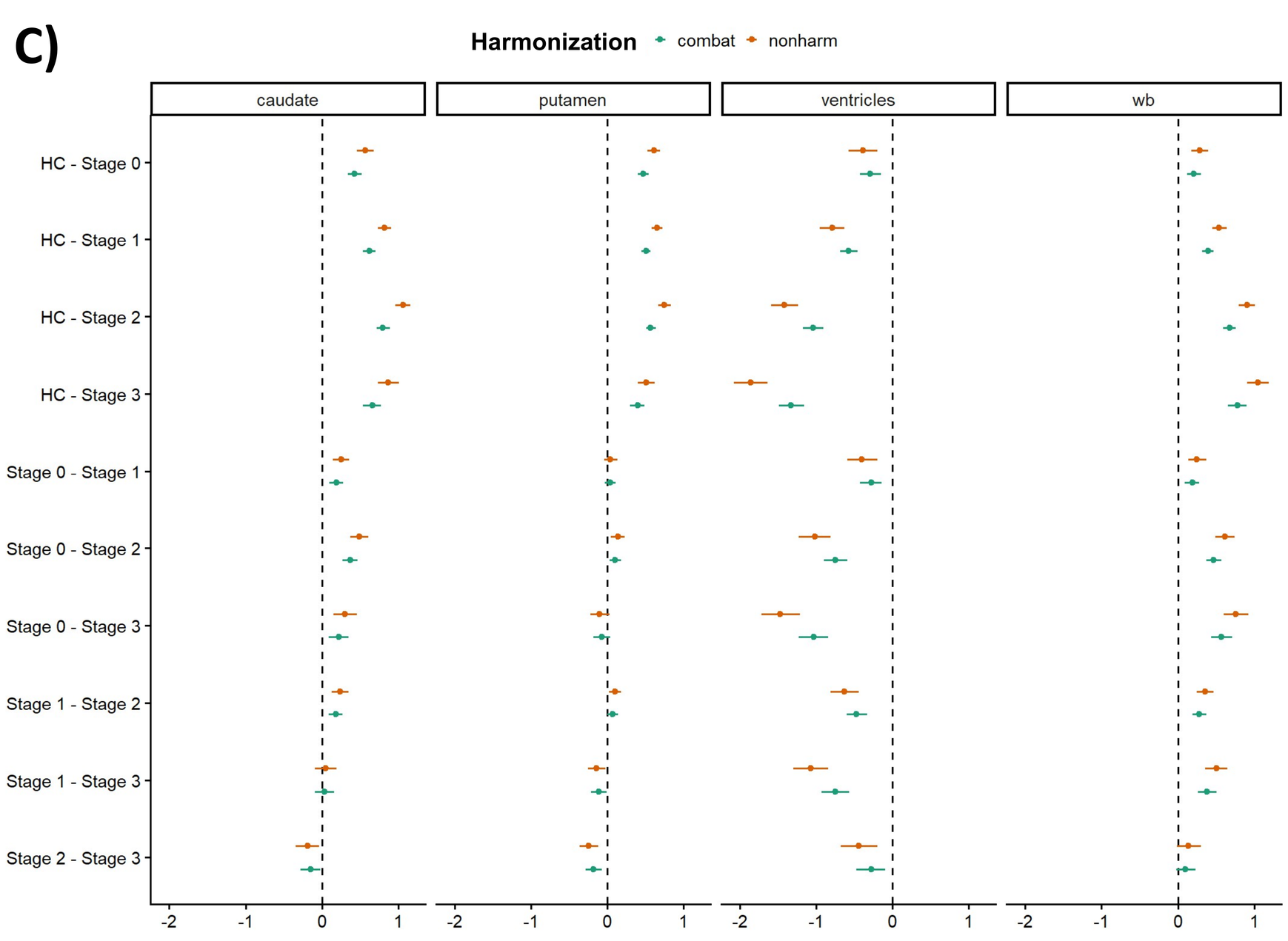
Regional volume and volume change were measured using IXI™ regional segmentation algorithms and generalized Boundary Shift Integral (gBSI). Linear mixed models (LMMs) with random intercept and slope were used to estimate the rate of change in regional brain volume across the four HD-ISS stages and controls. The outcome was regional volume in mm^3 adjusted for head size (Bucker et al. 2004) 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) and time by group interaction. The models were adjusted for sex, baseline age (centred at 42), scanner and their interactions with time. We used longitudinal ComBat (Beer et al, 2020) to adjust for scanner effects across the dataset and compared before and after harmonisation. The same predictors were included in the ComBat and LMM models. The LMM model equation is depicted below:

$$Regional\ Volume\ change = 1 + time \times (baseline\ age + sex + group + scanner) + (1 + time \mid participant)$$

RESULTS

- In the non-harmonised data both the main effect of scanner and the scanner by time interaction were significant for all regions (all p<0.001).
- Harmonisation significantly removed the scanner related main effects for all regions except the lateral ventricles ($p < 0.001$), but scanner by time interactions remained significant for all regions (all $p < 0.001$).
- Figures A and B show the time by scanner interactions before and after harmonization.
- Harmonisation did not improve sensitivity to disease progression for any region. Group-by-time interactions remained significant in all regions in both harmonized and non-harmonized datasets (all p<0.001), but effect sizes were reduced in most cases following harmonisation (see figure C).
- Analyses were repeated in Track-/TrackOn-HD and Predict-HD studies separately, with similar results even though patient characteristics were balanced across sites in Track-/TrackOn-HD.





SUMMARY

Although harmonisation with longitudinal ComBat reduced part of the scanner-related variability, it also potentially diminished sensitivity to disease-related effects. Therefore, its overall benefit for improving volumetric biomarkers in the HD-IH consortium data remains unclear and risks removing biological effects.

References: • Beer et al., 2020, Neuroimage 220 • Buckner et al., 2004, Neuroimage 23 (2)