Association between regional volume change and clinical change in Huntington's disease HD-ISS Stage 2 and Stage 3 participants

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Caudate, putamen, and whole-brain volume are important biomarkers in Huntington's disease (HD) and could play an important role as reasonably likely surrogate endpoints in clinical trials. We provide preliminary results on the relationship between caudate, putamen, and whole-brain volume change and change with the composite Unified HD Rating Scale (cUHDRS), Total Functional Capacity (TFC), Total Motor Score (TMS), and Symbol Digit Modalities Test (SDMT) scores in the HD Integrated Staging System (HD-ISS) Stage 2 and 3 participants (Tabrizi et al. 2023) at study entry.

We used a subset of data from TRACK-HD/TrackOn-HD 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 (Weatheritt et al., 2020) and the generalized Boundary Shift Integral (Prados et al., 2015) methods (IXIQ.Ai+gBSI).

METHODS

We analysed data from 315 HD-ISS Stage 2 and 169 Stage 3 participants. Demographic and clinical details at entry are provided below.

Variables	HD-ISS Stage 2	HD-ISS Stage 3
N at Baseline	315	169
Years on Study (time from baseline) – Mean (SD)	2.4 (1.0)	2.2 (1.0)
Age – Mean (SD)	40.8 (9.9)	45.4 (9.6)
Sex (%M)	41.0%	40.2%
CAG – Median (min-max)	43 (40 – 61)	43 (40 – 59)
cUHDRS – Mean (SD)	15.3 (1.7)	12.9 (2.9)
TFC – Mean (SD)	13.0 (0.1)	10.8 (1.4)
SDMT – Mean (SD)	43.8 (10.6)	39.3 (12.0)
TMS – Mean (SD)	10.3 (7.5)	17.3 (13.0)

We performed a "change-with-change" analysis in which regional volume change was predicted by clinical variable change. Linear mixed models (LMMs) with random intercepts were used. The outcome was volume change from baseline from the 3 regions of interest (ROIs): whole-brain, caudate and putamen. The predictors of interest were change in each of the clinical scores: cUHDRS, TFC, SDMT and TMS. Clinical scores were partitioned into the mean between-subject effect and change relative to the mean (within-subject effect; Fitzmaurice et al., 2011). The models were adjusted for baseline HD-ISS Stage, sex, time from baseline (in years), baseline age, baseline ROI volume, MRI scanner field strength change (1.5T → 3T, treated as a binary time-varying variable) and their interactions with time. **Separate models were fit for each outcome and predictor of interest**. The full model is depicted below.

$$
\begin{aligned}
&Volume\ change \\
&= 1 + sex + field\ strength\ change\ + time \\
&\times\ (baseline\ age\ + baseline\ volume + baseline\ HDISS\ stage\ ) \\
&+ baseline\ HDISS\ stage \times (mean\ clinical\ score + clinical\ score\ change) \\
&+ (1\ |\ participants)
\end{aligned}
$$

For the whole brain we also added a quadratic effect of time.

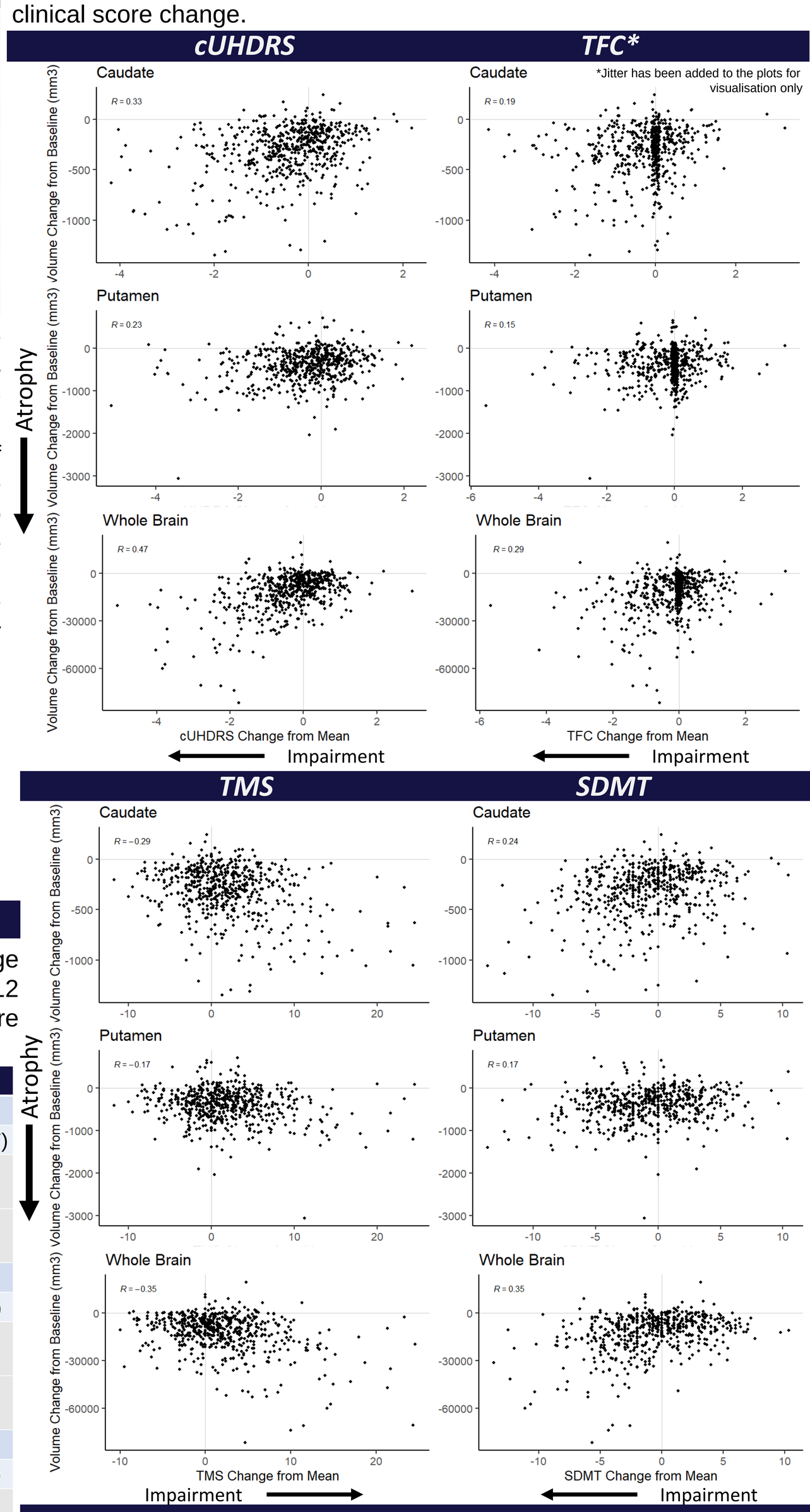
LMM RESULTS: clinical score change

The table below reports the LMM statistical results and volume change estimates for minimal clinically important difference (MCID) estimates at 12 months for each clinical score (Hamilton et al., 2023). P-values were Bonferroni corrected for three ROIs.

			Caudate	Putamen	Whole Brain
cUHDRS	P-value Bonferroni corr.		0.035	0.005	<0.001
	Beta (95 CI%) in mm^3		14.5 (3.2, 25.8)	30.8 (11.5, 50.0)	1594.3 (1049.9, 2137.7)
	Estimates (95% CI) in mm_3 at **cUHDRS MCID:**	***-0.64***	-179.9 (-208.6, -151.2)	-57.2 (-105.7, -8.7)	-13872.7 (-15605.4, -12139.9)
		-0.94	-185.6 (-215.0, -156.2)	-61.2 (-110.4, -11.9)	-14607.8 (-16363.0, -12852.5)
TFC	P-value Bonferroni corr.		0.971	0.008	<0.001
	Beta (95 CI%) in mm^3		6.7 (-6.6, 19.9)	34.0 (11.8, 56.2)	1189.9 (323.6, 1824.6)
	Estimates (95% CI) in mm^3 at **TFC MCID:**	***-0.55***	-184.2 (-213.6, -154.8)	-61.7 (-111.9, -11.45)	-14378.2 (-16156.8, -12600.2)
		-0.61	-184.6 (-214.4, -154.8)	-62.7 (-113.1, -12.3)	-144443.4 (-16224.1, -12662.6)
TMS	P-value Bonferroni corr.		0.003	0.066	<0.001
	Beta (95 CI%) in mm^3		-3.5 (-5.6, -1.4)	-4.3 (-7.9, -0.6)	-254.6 (-360.8, -148.3)
	Estimates (95% CI) in mm^3 at **TMS MCID**:	***2.1***	-176.0 (-204.1, -147.9)	-48.2 (-95.5, -0.9)	-13699.7 (-15420.5, -11979.0)
		3.6	-179.2 (-207.4, -151.1)	-50.5 (-98.0, -2.9)	-13959.4 (-15680.2, -12238.5)
SDMT	P-value Bonferroni corr.		0.057	0.313	<0.001
	Beta (95 CI%) in mm^3		3.3 (0.5, 6.0)	3.9 (-0.8, 8.5)	266.5 (129.8, 403.0))
	Estimates (95% CI) in mm^3 at **SDMT MCID**:	***-1.1***	-178.7 (-207.0, -150.4)	-55.9 (-103.5, -8.3)	-13978.9 (-15713.3, -12244.5)
		-1.9	-180.0 (-208.5, -151.6)	-56.4 (-104.2, -8.5)	-14219.9 (-15961.6, -12478.2)

RESULTS

The interaction between HD-ISS Stage and change in the clinical score was not significant after multiple comparisons correction for any of the clinical scores and ROIs. Therefore, we only present the main effect of clinical score change.



SUMMARY

For HD-ISS Stage 2 and Stage 3 participants, whole-brain volume shows significant association with clinical change for all four clinical variables examined here. For caudate and putamen volume, the association depended on the clinical variable. Our results provide further evidence on the use of volume change as a surrogate endpoint.

References: • Tabrizi et al., 2022, Lancet Neurology 12 (7) • Weatheritt et al., 2020, Neurotherapeutics, 17(S1); • Prados et al., Neurobiology of Aging, 2015, 36 ; • Fitzmaurice et al., 2011, Wiley 25; • Hamilton et al., 2023, Movement Disorders 38 (6)