**ONLINE-ONLY MATERIAL**

**Sensitivity analysis results**

Alternative models were explored in the sensitivity analysis as follows: (1) non-linearity. We fitted a "lowness" curve to each patient's data (not reported) and checked if the assumption of two linear trends before/after human foetal striatal transplantation would be reasonable. We also fitted a non-linear non-parametric model (by a cubic spline with 5 knots) over time since onset of symptoms. The transplantation effect changed from -0.9 (95%CI -1.6;-0.2) to -1.0 (95%CI -1.9;-0.2) for total motor scores and from 2.7 (95%CI 0.1;5.3) to 3.0 (95%CI 0.2;5.8) for total cognitive scores. (2) The goodness-of-fit R-squared based on the log-likelihood ratio was 0.76 for total motor and 0.56 for total cognitive scores. The change-in-slope was -0.8 (-1.4;-0.2) (deleting 7 outlying/influential observations) *vs.* -0.9 (-1.6;-0.2) for total motor score, and 3.9 (95%CI 1.7;6.2) (deleting 4 observations) *vs*. 2.7 (0.1;5.3) for total cognitive score. (3) The inclusion of a subject-specific random effect for deterioration over time did not alter the main results – for total motor scores on the whole patients' series the change-in-slope was -1.1 unit/year (95% CI -1.9;-0.4) *vs.* -0.9 (-1.6;-0.2). (4) heterogeneity among subjects of transplantation effect. Fitting a random slope model for foetal striatal grafting, we still found a transplantation effect on average (the change-in-slope is -1.5 unit/year, 95% CI -2.7;-0.3 for total motor scores) and a heterogeneity standard deviation of 0.56 years. The change-in-slope 80% population interval is $-1.5 \pm 0.56 \times 1.282 = \{-0.8;-2.2\}$ unit/year. That is 80% of patients had a predicted transplantation effect between -0.8 and -2.2 and 10% above -0.8. Since a clinically significant effect (Table 3B of the main manuscript) is recorded for a change-in-slope of -0.8 or less, we estimated that one patient in 10 will not experience a clinical benefit. (5) confounding control. We used a propensity score for total motor scores which included age at onset, sex, disease burden at onset, time since onset of symptoms and total cognitive scores. The change-in-slope was -0.7 (95%CI -1.5;0.0) instead of -0.9 (-1.6;-0.2). (6) standard errors estimates. We have a relatively small sample size and multivariate models, we checked the stability of our results, especially for accurate estimate of standard errors, by using a bootstrap/jackknife approach (for total motor score the standard error for the change-in-slope was 0.41 *vs*. 0.37 and the 95%CI were -1.7;-0.1 *vs.* -1.6;-0.2).

**Table 1A** Frequency of Unified Huntington's Disease Rating Scale assessments in 10 Huntington's disease patients who underwent human foetal striatal transplantation and in 16 Huntington's disease not-transplanted patients

| **Outcome** | **Per-year frequency of measurements** | |
|---|---|---|
| **UHDRS total scores** | **Grafted patients** | **Not-grafted patients** |
| | Mean (range) | Mean (range) |
| Functional | 2.0 (1.7-2.5) | 0.9 (0.4-1.7) |
| Behavioural | 2.0 (1.4-2.5) | 1.0 (0.8-1.7) |
| Cognitive | 1.4 (0.6-2.5) | 0.9 (0.6-1.7) |
| Motor | 2.5 (1.7-3.3) | 1.1 (0.8-1.7) |

**Table 1B** Follow-up times and frequency of measurements of neuroimaging studies in 10 Huntington's Disease patients who underwent human foetal striatal transplantation

| **Outcome** | **Frequency of measurements** |
|---|---|
| Magnetic Resonance | Pre-transplantation, at 1 week, 3rd, 6th month, then annually |
| [18F]Fluorodeoxyglucos Positron Emission Tomography | Pre-transplantation, at 24th and 48th month |
| [123I]Iodobenzamide Single Photon Emission Computed Tomography | Pre-transplantation, at 12th, 18th and 24th month |

**Table 2A** Human foetal striatal transplantation effect on Unified Huntington's Disease Rating Scale total scores

| | | Total HD patients' series | | | Grafted HD patients' series | |
|---|---|---|---|---|---|---|
| | Slope (95% CI) | $\Delta_{intercept}$ (95% CI) | $\Delta_{slope}$ (95% CI) | Slope (95% CI) | $\Delta_{intercept}$(95% CI) | $\Delta_{slope}$ (95% CI) |
| Functional | -0.7 (-1.0;-0.4) P<0.001 | -1.0 (-1.9; -0.1) P=0.022 | 0.1 (-0.1; 0.2) P=0.483 | -0.9 (-1.2; -0:5) P<0.001 | -0.6 (-1.6; 0.3) P=0.198 | 0.2 (0.0; 0.4) P=0.050 |
| Behavioural | -1.1 (-2.2; 0.01) P=0.052 | -1.0 (-4.5; 2.6) P=0.583 | 0.2 (-0.5; 0.9) P=0.548 | 0.3 (-1.2; 1.8) P=0.706 | -3.3 (-7.0; 0.4) P=0.083 | -0.5 (-1.3; 0.2) P=0.178 |
| Cognitive | -11.5 (-16; -7.3) P<0.001 | -2.0 (-14.4; 10.3) P=0.748 | 2.7 (0.1; 5.3) P=0.042 | -15.0 (-20; -9.5) P<0.001 | 7.4 (-5.2; 20.1) P=0.250 | 4.1 (1.8; 6.5) P=0.001 |
| Motor | 5.2 (3.9; 6.5) P<0.001 | -2.3 (-5.8; 1.2) P=0.189 | -0.9 (-1.6; -0.2) P=0.017 | 6.7 (5.1; 8.3) P<0.001 | -6.8 (-10.6; -3.0) P=0.001 | -2.0 (-2.8; -1.2) P<0.001 |

In Columns 2 and 5 we report the variation ("slope", in units/year) of functional, behavioural, cognitive, and motor total scores of the Unified Huntington's Disease (HD) Rating Scale – functional and cognitive score decrease indicate deterioration (better up), behavioural and motor score increase indicate deterioration (better down) – over time since onset of symptoms.

In Columns 3,4 and 6,7 we report the transplantation effect measures: change-in-intercept and change-in-slope. Left panel results are based on total HD patients' series; right panel results on grafted patients only, see text. CI: 95% confidence intervals (light-blue shade if false discovery rate <0.10). $\Delta_{intercept}$: average difference in total scores at time of transplantation. $\Delta_{slope}$: difference in slope before/after transplantation. P: P-values

**Table 2B**. Human foetal striatal transplantation effect on the motor Items of the Unified Huntington's Disease Rating Scale scores

| | Total HD patients'series | | Grafted HD patients' series | |
|---|---|---|---|---|
| | Slope (95% CI) | Δ (95% CI) | Slope (95% CI) | Δ (95% CI) |
| Chorea | 0.03 (-0.4; 0.4)<br>P=0.902 | -0.2 (-0.4;0.1)<br>P=0.215 | 0.2 (-0.4; 0.8)<br>P=0.463 | -0.4 (-0.7; -0.1)<br>P=0.020 |
| Dystonia | 0.4 (0.1; 0.8)<br>P=0.012 | -0.1 (-0.3; 0.2)<br>P=0.577 | 0.6 (0.1; 1.0)<br>P=0.013 | -0.2 (-0.5; -0.01)<br>P=0.041 |
| Gait | 0.3 (0.19; 0.34)<br>P<0.001 | 0.02 (-0.03;0.06)<br>P=0.480 | 0.3 (0.2; 0.4)<br>P<0.001 | -0.03 (-0.08; 0.02)<br>P=0.290 |
| Ocular pursuit | 0.2 (0.04; 0.4)<br>P=0.018 | -0.1 (-0.2; 0.04)<br>P=0.216 | 0.4 (0.2; 0.7)<br>P=0.001 | -0.1 (-0.3; -0.004)<br>P=0.043 |
| Saccade initiation | 0.4 (0.2; 0.6)<br>P<0.001 | -0.1(-0.2; 0.003)<br>P=0.057 | 0.6 (0.4; 0.8)<br>P<0.001 | -0.2 (-0.3; -0.05)<br>P=0.005 |
| Saccade velocity | 0.3 (0.1; 0.5)<br>P=0.005 | -0.2 (-0.3; -0.03)<br>P=0.013 | 0.4 (0.2; 0.7)<br>P=0.001 | -0.2 (-0.4; -0.1)<br>P=0.001 |
| Dysarthria | 0.2 (0.1; 0.3)<br>P<0.001 | 0.06 (0.005; 0.12)<br>P=0.034 | 0.3 (0.2; 0.5)<br>P<0.001 | 0.03 (-0.04; 0.1)<br>P=0.465 |
| Tongue protrusion | 0.1 (-0.01; 0.2)<br>0.2 P=0.080 | -0.02 (-0.08; 0.05)<br>P=0.626 | 0.2 (0.1; 0.4)<br>P=0.001 | -0.1 (-0.2; -0.01)<br>P=0.029 |
| Finger taps | 0.4 (0.2; 0.6)<br>P<0.001 | -0.1 (-0.2;0.02)<br>P=0.099 | 0.6 (0.4; 0.8)<br>P<0.001 | -0.2 (-0.3; -0.1)<br>P=0.002 |
| Pronate/Supinate hands | 0.6 (0.4; 0.7)<br>P<0.001 | 0.0 (-0.1; 0.1)<br>P=0.863 | 0.7 (0.4; 0.9)<br>P<0.001 | -0.1 (-0.2; 0.01)<br>P=0.065 |
| Luria | 0.2 (0.1; 0.3)<br>P<0.001 | -0.05 (-0.1; 0.01)<br>P=0.085 | 0.2 (0.1; 0.3)<br>P<0.001 | -0.06 (-0.1; -0.001)<br>P=0.047 |
| Rigidity | 0.3 (0.1; 0.5)<br>P<0.001 | 0.04 (-0.06; 0.1)<br>P=0.475 | 0.4 (0.2; 0.6)<br>P=0.001 | 0.02 (-0.1; 0.1)<br>P=0.733 |
| Bradykinesia | 0.3 (0.2; 0.4)<br>P<0.001 | -0.04 (-0.1; 0.05)<br>P=0.439 | 0.2 (0.1; 0.3)<br>P=0.001 | -0.05 (-0.1; 0.02)<br>P=0.184 |
| Tandem walk | 0.2 (0.1; 0.3)<br>P<0.001 | -0.02 (-0.1; 0.05)<br>P=0.616 | 0.3 (0.1; 0.4)<br>P<0.001 | -0.1 (-0.2; 0.01)<br>P=0.103 |
| Retropulsion | 0.3 (0.2; 0.4)<br>P<0.001 | 0.02 (-0.04; 0.08)<br>P=0.562 | 0.5 (0.3; 0.6)<br>P<0.001 | -0.03 (-0.1; 0.05)<br>P=0.470 |
| Dystonia axial | 0.1 (-0.02; 0.2)<br>P=0.114 | 0.0 (-0.1; 0.1)<br>P=0.875 | 0.1 (0.01; 0.2)<br>0.2 P=0.031 | -0.05 (-0.1; 0.04)<br>P=0.292 |
| Dystonia articular | 0.3 (-0.04; 0.6)<br>P=0.091 | -0.04 (-0.2; 0.2)<br>P=0.715 | 0.2 (-0.2; 0.6)<br>P=0.392 | -0.1 (-0.4; 0.1)<br>P=0.203 |
| Chorea axial | 0.1 (-0.2; 0.3)<br>P=0.581 | -0.2 (-0.4; -0.05)<br>P=0.009 | 0.1 (-0.1; 0.4)<br>P=0.403 | -0.3 (-0.5; -0.1)<br>P=0.002 |
| Chorea limbs | -0.2 (-0.4; 0.3)<br>P=0.891 | -0.2 (-0.4; 0.06)<br>P=0.140 | -0.2 (-0.3; 0.6)<br>P=0.479 | -0.4 (-0.6; -0.1)<br>P=0.012 |

Variation (slope, in units/year) of selected motor items of the Unified Huntington's Disease (HD) Rating Scale – increase indicate deterioration (better down) – over time since onset of symptoms. Transplantation effect measure: change-in-slope. Left panel results are based on total HD patients' series, right panel results on grafted patients only, see text. CI: 95% confidence intervals (light-blue shade if false discovery rate <0.10). □: difference in slope before/after transplantation. P: P-values

**Table 2C** Human foetal striatal transplantation effect on the cognitive items of the Unified Huntington's Disease Rating Scale scores

| | Total HD patients' series | | Grafted HD patients' series | |
|---|---|---|---|---|
| | Slope (95% CI) | Δ (95% CI) | Slope (95% CI) | Δ (95% CI) |
| Phonemic verbal fluency | -0.7 (-1.2; -0.2)<br>P=0.011 | 0.4 (0.0; 0.8)<br>P=0.055 | -1.2 (-1.9; -0.4)<br>P=0.002 | 0.4 (0.0; 0.8)<br>P=0.047 |
| Stroop reading fluency | -1.8 (-2.9; -0.8)<br>P<0.001 | 0.7 (-0.2;1.6)<br>P=0.125 | -3.3 (-4.8; -1.9)<br>P<0.001 | 0.8 (0.1; 1.5)<br>P=0.033 |
| Stroop color naming | -3.3 (-5.0; -1.6)<br>P<0.001 | 1.1 (-0.3; 2.5)<br>1.2 P=0.114 | -5.4 (-7.5; -3.3)<br>P<0.001 | 1.3 (0.2; 2.3)<br>1.4 P=0.025 |
| Stroop interference | -1.1 (-2.0; -0.3)<br>P=0.006 | 0.7 (-0.0; 1.4)<br>P=0.060 | -2.0 (-3.1; -0.9)<br>P<0.001 | 0.8 (0.2; 1.3)<br>P=0.007 |
| Symbol digit combination | -1.6 (-2.1; -1.0)<br>P<0.001 | 0.8 (0.4; 1.2)<br>P<0.001 | -2.7 (-3.6; -1.9)<br>P<0.001 | 0.8 (0.4; 1.2)<br>P<0.001 |

Variation (slope, in units/year) of selected cognitive items of the Unified Huntington's Disease (HD) Rating Scale – decrease indicate deterioration (better up) – over time since onset of symptoms. Transplantation effect measure: change-in-slope. Left panel results are based on total HD patients' series, right panel results on grafted patients only, see text. CI: 95% confidence intervals (light-blue shade if false discovery rate <0.10). □: difference in slope before/after transplantation. P: P-values

**Imaging procedures**

Magnetic resonance imaging examinations were performed with the patient breathing spontaneously, under mild sedation, on a 1.5 T unit (Siemens Symphony). The examination protocol included 5 mm thick T2 weighted (TR 4490 ms, TE 120 ms) fast spin echo images on the axial and coronal planes, coronal T1 weighted (TR 3000 ms, TI 400 ms, TE 28 ms) inversion recovery fast spin echo images and axial FLAIR (TR 5000 ms TI 1500 ms TE 60 ms) images. In addition a 3D T1-weighted MPRAGE sequence (TR 2100 ms TI 1000 ms TE 4.4 ms) with a slice thickness of 1 mm and a matrix of 256 x 256 after intravenous administration of Gadolinium chelate (0.1 mmol/kg) was acquired for computerized tomography co-registration and surgical planning.

Patients were injected with a dose of 370 MBq [$^{18}$F]fluorodeoxyglucose ([$^{18}$F]FDG) positron emission tomography (PET), in resting state, in a dimly lighted room with minimal background noise. [$^{18}$F]FDG PET scan was acquired 30 minutes after the tracer administration, lasting 20 minutes, using a GE Advance PET scanner (General Electric; Milwaukee, WI), or a Philips 16 TOF Gemini PET/CT scanner (Philips Medical Systems). A polycarbonate head holder was used to reduce head movements during the scan. [$^{18}$F]FDG PET images were coregistered with the individual MRI images obtained at the same time point. Anatomical volumes-of-interest (VOIs) were drawn using MRI, and copied onto the corresponding PET images. Anatomical VOIs were drawn on the head of the caudate nucleus, the putamen, the cerebellum, and all cortical regions (frontal, parietal, temporal and occipital lobes). Mean voxel values within each VOI were extracted from PET images and normalized to the cerebellum.

Subjects were injected with an average of 150 MBq (111-186 MBq) of [$^{123}$I]iodobenzamide ([$^{123}$I]IBZM) single photon emission computed tomography (SPECT) (GE Healthcare, Amersham, UK), after a 10-day drug wash-out period. Images were acquired 90 minutes after tracer injection using a three-headed camera (IRIX) equipped with ultra-high resolution collimators. Image data were reconstructed using FBP algorithm and corrected for attenuation using Chang algorithm ($\mu$=0.12 cm$^{-1}$). VOIs were drawn on the striata (caudate nucleus and putamen) and the cerebellum. Mean voxel values within each VOI were extracted from SPECT images and ratio of striatal values to the cerebellum was calculated to estimate $D_2$ receptor density.

**Protocol of foetal tissue collection and preparation**[1-3]

Foetal striatal tissue was obtained from the brains of legally aborted foetuses, according to the guidelines of the National Institute of Health (MD, USA). The use of human fetal tissue for research purposes was approved by the National Ethics Committee and the Committee for investigation in Humans of the University of Florence. Maternal donor serum was tested for a range of pathogens (HbsAg/Hb Ag HCV, HIV 1-2, HTLV I –II, CMV, toxoplasmosis and TPHA). Screening results were available prior to tissue collection. Permission to collect tissue from the maternal donor was requested and obtained at the end of the abortion procedure. For each procedure, both whole ganglionic eminencies were dissected from the floor of the forebrain ventricles. Estimation of fetal gestational age was determined by multiple parameters.[4] Immediately after isolation, the tissue was placed in 500 µl of physiological solution at 4°C and cut into small fragments, gently dissociated using firepolished Pasteur pipettes of decreasing bore diameters. Dissociated cells from striatal fragments were re-suspended in 500 µl of physiological solution (final grafting suspension) and triturated 5-10 times using a 200 µl disposable plastic pipette tip. Total nucleated cells were diluted 1:10 by trypan blue dye and transferred in a Burker chamber for counting at optic microscope. The average number of cells of 4 large squares has been used to calculate the cell concentration. A small aliquot was taken for assessment of cell viability by trypan blue dye exclusion and 7-Actinomycin D test, and a second aliquot was used for immuno-phenotype profile. A residual aliquot, after transplantation, was used for microbiological culturing (aerobic and anaerobic bacterial cultures). Another portion of the fetal tissue was used for HLA typing and for CAG-repeat count at the HD locus.

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