

Supplemental Table 1: Neuropsychological assessments in Community Controls (Com-CON) and Gene-Negative controls from HD families (Gen-Neg-CON)

	<i>Com-CON</i> (<i>n</i> = 12)	<i>Gen-Neg-CON</i> (<i>n</i> = 15)	<i>p</i> ^a
<i>Cognition</i>			
MMSE	30.0 (28.5-30.0)	30.0 (30.0-30.0)	n.s.
RAVLT (total A1-A5)	57.25 ± 10.49	54.60 ± 6.97	n.s.
RAVLT retention A7	12.67 ± 1.92	13.07 ± 1.67	n.s.
RAVLT recognition A8	15.0 (14.0-15.0)	15.0 (15.0-15.0)	n.s.
BNT	57.0 (55.0-58.0)	56.0 (52.0-58.0)	n.s.
TMT A (sec)	29.58 ± 12.79	28.6 ± 7.9	n.s.
TMT B (sec)	49.0 (43.5-58.5)	58.5 (51.0-63.0)	n.s.
STROOP word reading	44.42 ± 7.20	42.33 ± 7.56	n.s.
STROOP color naming	55.92 ± 13.84	51.20 ± 8.90	n.s.
STROOP interference	83.17 ± 18.16	82.80 ± 14.89	n.s.
NART	45.17 ± 4.11	50.0 (49.0-50.0)	0.01
DS forward	6.5 (5.0-7.0)	6.53 ± 1.19	n.s.
DS backward	5.17 ± 1.34	5.0 (4.0-6.0)	n.s.
VF animal	21.5 (21.0-25.5)	24.33 ± 5.63	n.s.
VF N	12.67 ± 4.31	12.27 ± 6.06	n.s.
VF A	12.08 ± 3.42	13.73 ± 2.31	n.s.
VF K	13.83 ± 5.13	14.73 ± 4.35	n.s.
Digit symbol	78.75 ± 17.05	85.27 ± 11.66	n.s.
Block patrons	67.5 (65.0-68.0)	67.0 (61.0-68.0)	n.s.
<i>Mood and Behaviour</i>			
BDI	2.0 (1.0-7.5)	1.0 (0.0-4.0)	n.s.
STAI 1	47.00 ± 3.02	46.33 ± 4.48	n.s.
STAI 2	47.58 ± 4.25	48.00 ± 3.66	n.s.
PBA-HD total	1.0 (0.0-2.0)	3.08 ± 3.15	n.s.
PBA-HD apathy	0.0 (0.0-0.0)	0.0 (0.0-0.0)	n.s.
PBA-HD irritability	0.0 (0.0-0.0)	0.0 (0.0-0.0)	n.s.
PBA-HD depression	0.0 (0.0-1.0)	1.0 (0.0-1.0)	n.s.

Normally distributed data are reported as mean \pm standard deviation. Skewed data are reported as median (quartile 1 – quartile 3).

^a Results surviving Kruskal-Wallis test and Bonferroni test for correction for multiple comparisons.

n.s. = not significant (even before post-hoc testing); Com-CON = community control group; Gene-Neg-CON = gene-negative controls from HD families; MMSE = Mini-Mental State Examination, RAVLT = Rey Auditory Verbal Learning Test; BNT = Boston Naming Test; TMT = Trail Making Test; NART = National Adult Reading Test; DS = Digit span; VF N, A, K = verbal fluency for the letters N, A and K; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; PBA = Problem Behavior Assessment.

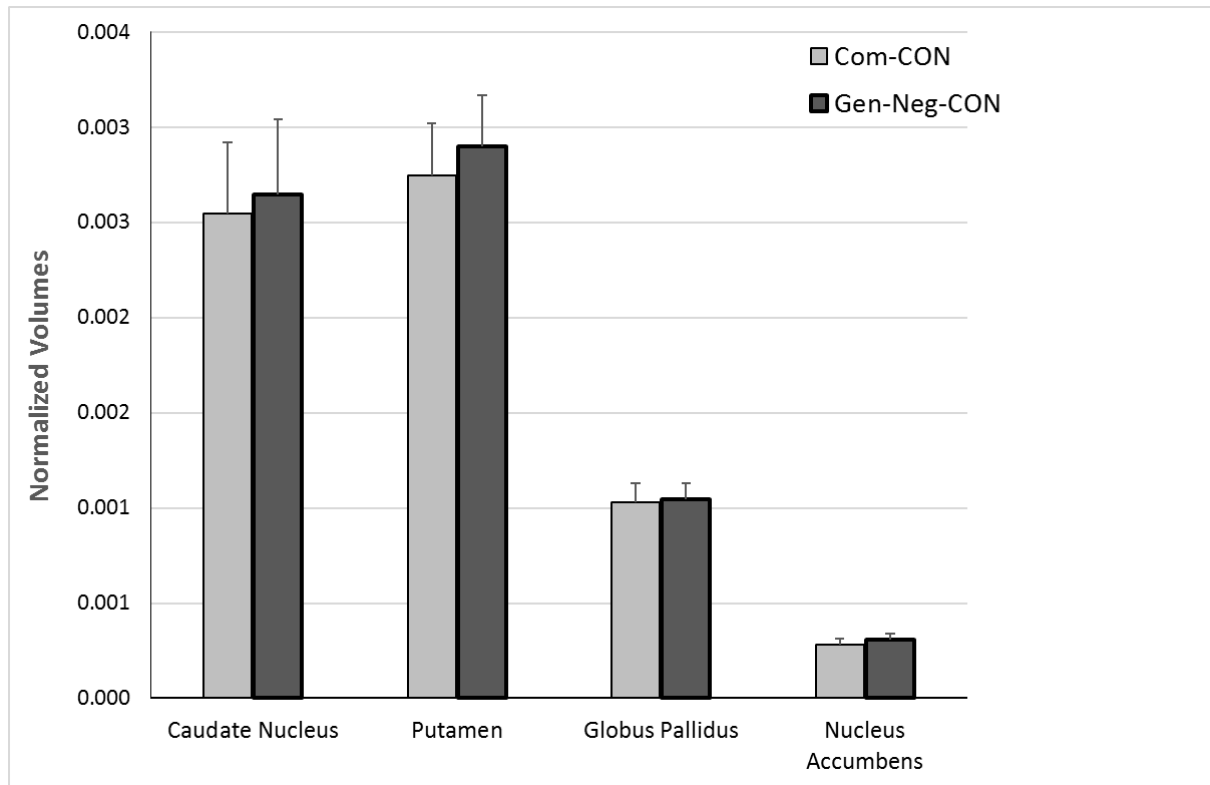
Supplemental Table 2: Grey matter volume differences between premanifest Huntington's disease subjects (preHD) and healthy controls (CON).

Cluster-level		Voxel-level		Peak voxel MNI coordinate			Cluster location
p _{cor}	k _E	p _{unc}	T	x	y	z	
<i>preHD < CON</i>							
2.10 ⁻⁶	1188	5.10 ⁻⁵	4.28	26	14	8	R anterior putamen
		1.10 ⁻⁴	3.99	20	17	-11	R nucleus accumbens
		4.10 ⁻⁴	3.66	17	3	-11	R amygdala
		5.10 ⁻⁴	3.58	23	20	2	R anterior putamen
		7.10 ⁻⁴	3.42	18	20	0	R caudate nucleus
		0.001	3.23	24	2	-6	R globus pallidus
		0.002	3.12	11	23	5	R caudate nucleus
		0.002	3.07	9	6	-9	R nucleus accumbens
		0.003	2.92	26	0	11	R posterior putamen
1.10 ⁻⁶	1561	7.10 ⁻⁵	4.24	-23	11	8	L anterior putamen
		1.10 ⁻⁴	4.06	-20	15	-12	L anterior orbitofrontal gyrus (BA 11)
		1.10 ⁻⁴	3.98	-21	21	-2	L anterior putamen
		2.10 ⁻⁴	3.82	-23	17	-2	L anterior putamen
		3.10 ⁻⁴	3.71	-21	14	-8	L anterior putamen
		4.10 ⁻⁴	3.65	-11	18	-5	L nucleus accumbens
		0.001	3.55	-29	-2	11	L posterior putamen
		0.001	3.45	-23	-6	8	L posterior putamen
		0.001	3.23	-29	-12	11	L posterior putamen
		0.002	3.00	-8	5	-5	L globus pallidus
0.025	482	2.10 ⁻⁴	3.89	-38	15	35	L middle frontal gyrus (BA 44)
		3.10 ⁻⁴	3.77	-33	14	33	L middle frontal gyrus (BA 44)
		3.10 ⁻⁴	3.75	-38	15	29	L middle frontal gyrus (BA 44)
		4.10 ⁻⁴	3.63	-41	12	30	L middle frontal gyrus (BA 44)
		0.001	3.50	-33	14	24	L insula
		0.001	3.47	-41	8	29	L insula

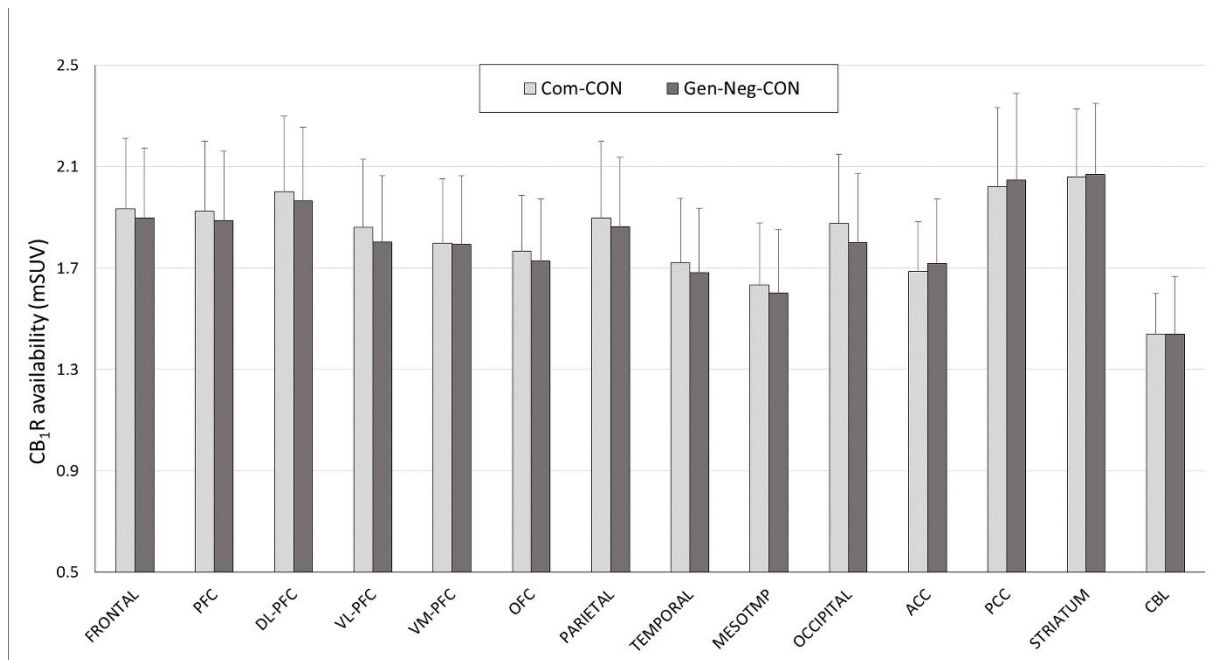
Detailed cluster peak locations and p-values of the voxel-based morphometry analysis at $p_{unc} < 0.005$ with cluster extent (K_E) 250 voxels.

K_E , cluster size extent (number of $2 \times 2 \times 2 \text{ mm}^3$ voxels); p_{cor} , corrected for multiple comparisons; p_{unc} , uncorrected for multiple comparisons; L, left; R, right.

Supplemental Fig 1 Striatal grey matter volumes (normalized to total intra-cranial volume) in community controls (Com-CON) and gene-negative controls from HD families (Gen-Neg-CON).



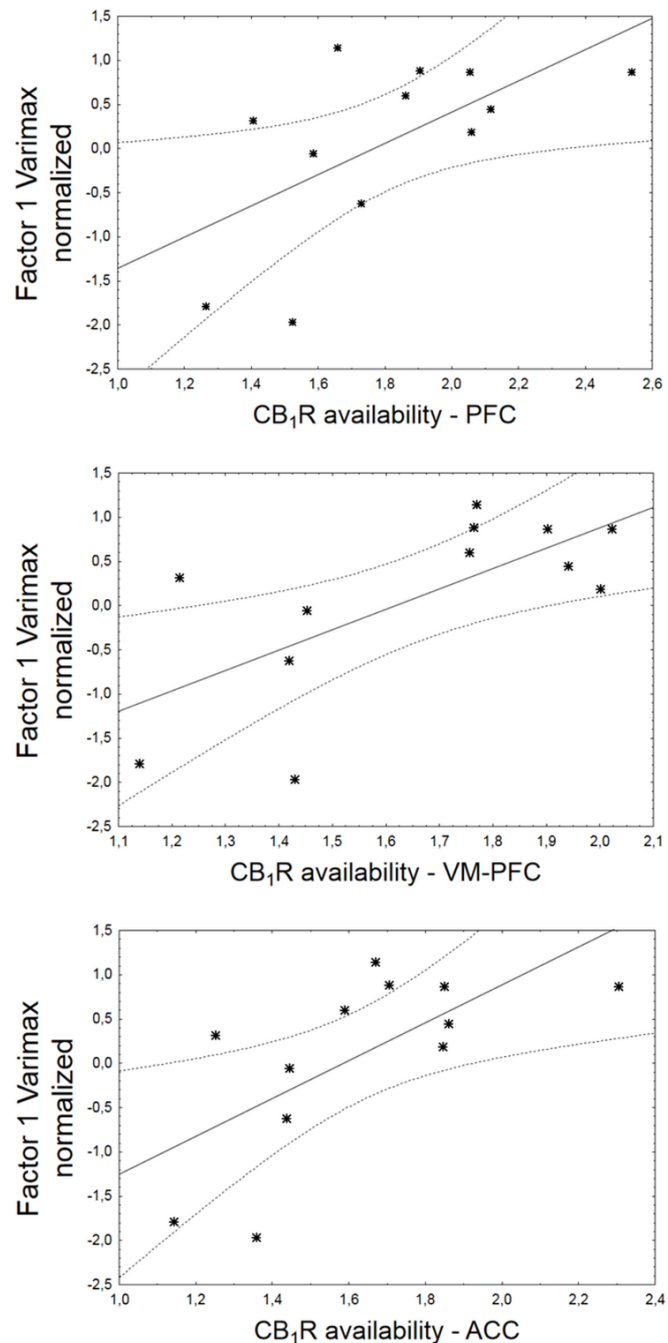
Supplemental Fig 2 CB₁ receptor (CB₁R) availability (expressed in modified standardized uptake value, mSUV) in community controls (Com-CON) and gene-negative controls from HD families (Gen-Neg-CON) after PVE correction.



There were no significant differences in any region (range $p = 0.5 - 0.9$).

PFC = prefrontal cortex; DL-PFC = dorsolateral prefrontal cortex; VL-PFC = ventrolateral prefrontal cortex; VM-PFC = ventromedial prefrontal cortex; OFC = orbitofrontal cortex; Mesotmp = mesotemporal lobe; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; CBL = cerebellum. Error bars represent SD.

Supplemental Fig 3 Positive correlations between individual scores for factor 1 varimax normalized and CB₁R availability in prefrontal cortex (PFC) regions (PFC: $r = 0.61$, $p = 0.036$; ventromedial prefrontal cortex, VM-PFC: $r = 0.69$, $p = 0.013$) and anterior cingulate cortex (ACC: $r = 0.67$, $p = 0.018$).



Solid lines represent linear regression curve and dotted lines represent 95% confidence interval.