Supplementary Material

Methods

Statistical analysis

Generalised least squares regression models (adjusted for age, gender and study site) were fitted to the regional thickness data to assess between-group differences. Statistical maps of the clinical associations were also processed in FreeSurfer. For this, data from all HD gene-carriers was pooled to create a study-specific group template. Average thickness data was overlaid on this template and smoothed with a 10mm full width at half maximum Gaussian kernel before clinical associations were computed.

Supplementary Table 1. Paced Tapping and cognitive scores within each study group.

	Controls	preHD			HD		
		preHD-A	preHD-B	Combined	HD1	HD2	Combined
Paced Tapping (Deviation from target interval)	13.43 (23.61) -83.37-69.60 (N=97)	5.81 (29.09) -95.35-79.79 (N=51)	9.41 (31.74) -81.10-100.09 (N=58)	7.72 (39.44) -95.35-100.09 N=109	9.83 (45.71) -106.56-104.37 (N=40)	105.49 (154.98) -75.32-532.69 (N=29)	50.03 (115.55) -106.56-532.69 N=69
SDMT (Number correct)	54.26 (10.15) 32.00-84.00 (N=97)	54.76 (8.78) 30.00-69.00 (N=49)	50.54 (12.05) 22.00-88.00 (N=56)	52.50 (10.81) 22.00-88.00 (N=105)	38.51 (9.13) 22.00-61.00 (N=39)	29.03 (10.52) 13.00-59.00 (N=29)	34.47 (10.77) 13.00-61.00 (N=68)
Stroop Word Reading (Number correct)	106.95 (15.45) 60.00-148.00 (N=97)	103.16 (15.67) 70.00-134.00 (N=49)	97.41 (17.18) 60.00-141.00 (N=56)	100.10 (16.66) 60.00-141.00 (N=105)	82.92 (18.73) 30.00-115.00 (N=39)	66.14 (22.13) 38.00-121.00 (N=29)	75.76 (21.76) 30.00-121.00 (N=68)
Trails A (Time in seconds)	25.87 (11.01) 11.00-84.00 (N=97)	26.76 (7.41) 14.00-45.00 (N=49)	29.39 (11.15) 13.00-61.00 (N=56)	28.16 (9.63) 13.00-61.00 (N=105)	34.95 (12.98) 16.00-75.00 (N=39)	50.28 (15.34) 18.00-70.00 (N=29)	41.49 (15.88) 16.00-75.00 (N=68)
Map search (Number correct)	69.08 (9.82) 36.00-80.00 (N=97)	68.09 (10.77) 29.00-79.00 (N=47)	63.18 (12.68) 24.00-80.00 (N=56)	65.42 (12.04) 24.00-80.00 (N=103)	54.89 (15.6)1) 20.00-74.00 (N=38)	39.28 (14.60) 19.00-66.00 (N=29)	48.13 (16.97) 19.00-74.00 (N=67)
Mental Rotation (Percent correct)	0.74 (0.15) 0.13-0.96 (N=97)	0.73 (0.15) 0.46-0.96 (N=49)	0.71 (0.15) 0.40-1.00 (N=56)	0.72 (0.15) 0.40-1.00 (N=105)	0.59 (0.11) 0.42-0.94 (N=39)	0.57 (0.10) 0.48-0.96 (N=29)	0.58 (0.11) 0.42-0.96 (N=68)
Spot the Change (Percent correct)	83.28 (11.63) 50.00-100.00 (N=97)	82.41 (9.29) 59.38-96.88 (N=51)	76.29 (10.27) 53.13-93.75 (N=58)	79.16 (10.25) 53.13-96.88 (N=109)	70.08 14.89 31.25-93.75 (N=40)	66.27 (11.61) 43.75-90.63 (N=29)	68.48 (13.65) 31.25-93.75 (N=69)

Supplementary Table 2. Adjusted between-group differences in Paced Tapping and cognitive measures. Dark grey highlights associations significant to p<0.01 whilst light grey highlights those significant at the p<0.05 level.

	preHD vs controls	HD vs controls	preHD vs HD	preHD-A vs controls	pre-HD-B vs controls	HD1 vs preHD-B	HD2 vs HD1
Paced Tapping (Deviation from target interval)	-7.69 (-15.17,-.0) p=.043 ES=-.22 (-.49,.02) N=206	18.64 (5.65,31.64) p=.005 ES= .176 (.06,.26) N=166	40.93 (14.35,67.51) p=.003 ES=.386 (.14,.57) N=178	-11.88 (-21.04,-2.72) p=.011 ES=-.434 (-.72,-.07) N=148	-2.53 (-7.21,2.14) P=.289 ES=-.083 (-.23,.10) N=155	-4.20 (-20.57,12.16) P=.615 ES=-.101 (-.52,.35) N=98	89.70 (38.95, 140.46) p<0.001 ES=-.697 (-.264,1.04) N=69
SDMT (Number correct)	-3.83 (-6.51,-1.16) p=.005 ES= -.374 (-.65,-.08) N=202	-9.49 (-10.99,-7.99) p<.001 ES=-.932 (-1.13-.72) N=165	-17.24 (-20.52,-13.96) p<.001 ES=-1.766 N=173	-2.60 (-5.52,.32) p=.081 ES=-.320 (-.72,.10) N=146	-2.68 (-4.47, -.89) P=.003 ES=-.229 (-.41, -.04) N=153	-13.22 (-17.61,-8.83) p<0.001 ES=-1.514 (-2.07, -.95) N=95	-8.33 (-12.78, -3.89) p<0.001 ES=-.938 (-1.66, .14) N=68
Stroop Word Reading (Number correct)	-7.19 (-11.45,-2.93) p=.001 ES=-.477 (-.75,-.17) N=202	-15.23 (-17.99,-12.47) p<.001 ES=-.797 (-.94-.61) N=165	-25.21 (-31.00,-19.41) p<.001 ES=-1.326 (-1.66,-.95) N=173	-5.36 (-10.65,.07) p=.047 ES=-.359 (-.69,.06) N=146	-4.83 (-7.33,-2.33) p<0.001 ES=-.328 (-.51,-.11) N=153	-17.41 (-24.42,-10.40) P<.001 ES=-1.050 (-1.45, -.53) N=95	-12.87 (-21.66,-4.08) p=0.004 ES=-.691 (-1.37, .08) N=68
Trails A (Time in seconds)	3.41 (.64,6.18) p=.016 ES=.358 (-.00,.61) N=202	7.53 (5.54,9.52) p<.001 ES=.533 (.37,.67) N=165	12.68 (8.60,16.76) p<.001 ES=.905 (.57,1.17) N=173	2.47 (-.54,5.48) p=.108 ES=.326 (-.06,.69) N=146	2.28 (.49, 4.07) P=0.012 ES=-.207 (.04,.36) N=153	6.04 (.98, 11.10) P=0.019 ES=.518 (-.04, .97) N=95	12.45 (6.15,18.76) p<0.001 ES=-.961 (.34, 1.61) N=68
Map search (Number correct)	-6.41 (-9.03,-3.79) p<.001 ES=-.601 (-.80,-.36) N=199	-9.88 (-11.99,-7.79) p<.001 ES=-.611 (-.73,-.45) N=163	-13.95 (-18.62,-9.27) p<.001 ES=-.864 (-1.16,-.54) N=170	-4.30 (-7.51,-1.09) p=.009 ES=-.452 (-.78,-.11) N=143	-4.16 (-5.82,-2.50) p<.001 ES=-.376 (-.50,-.22) N=152	-5.45 (-11.51,.72) p=.084 ES=-.360 (-.79,.08) N=94	-15.15 (-22.49,-7.80) p<0.001 ES=-1.09 (-1.79,-.39) N=67
Mental Rotation (Percent correct)	-.04 (-.08,.00) p=.064 ES=-.279 (-.57,.07) N=201	-.07 (-.09,-.05) p<.001 ES=-715 (-.99,-.44) N=164	-.11 (-.15,-.07) p<.001 ES=-1.11 (-1.65,-.58) N=173	-.03 (-.08, .02) p=.205 ES=-.234 (-.62, .19)	-.02 (-.05, -.00) p=0.047 ES=-.174 (-.35,.01) N=152	-.10 (-.15,-.04) p<0.001 ES=-.850 (-1.45, -.11) N=95	-.03 (-.07, .02) p=0.278 ES=-.334 (-1.14, .48) N=68
Spot the Change (Percent correct)	-6.16 (-9.01,-3.30) p<.001 ES=-.624 (-.91,-.31) N=206	-7.16 (-8.99,-5.32) p<.001 ES=-.564 (-.71,-.39) N=166	-8.38 (-12.12,-4.64) p<.001 ES=-.667 (-1.00,-.28) N=178	-3.67 (-7.04,-.30) p=.033 ES=-.402 (-.75,-.00) N=148	-4.27 (-5.93,-2.61) p<.001 ES=-.441 (-.62,-.23) N=155	-4.07 (-9.07,.93) p=.110 ES=-.321 (-.80,.15) N=98	-2.85 (-9.06,3.36) p=.368 ES=-.238 (-.86,.39) N=69

Data are coefficients (95% CI), p-values and effect sizes (bootstrapped 95% CIs) of between-group differences in Paced Tapping and performance on cognitive tasks. Coefficients and p-values were calculated using generalised least squares regression adjusted for age, gender, education and study site. Effect sizes were calculated as the estimated absolute adjusted mean difference of the metric between the HD and control groups, divided by the estimated residual SD of the HD group. These are reported with bias corrected and accelerated bootstrapped 95% CIs based on 2000 replications (Carpenter and Bithell, 2000).

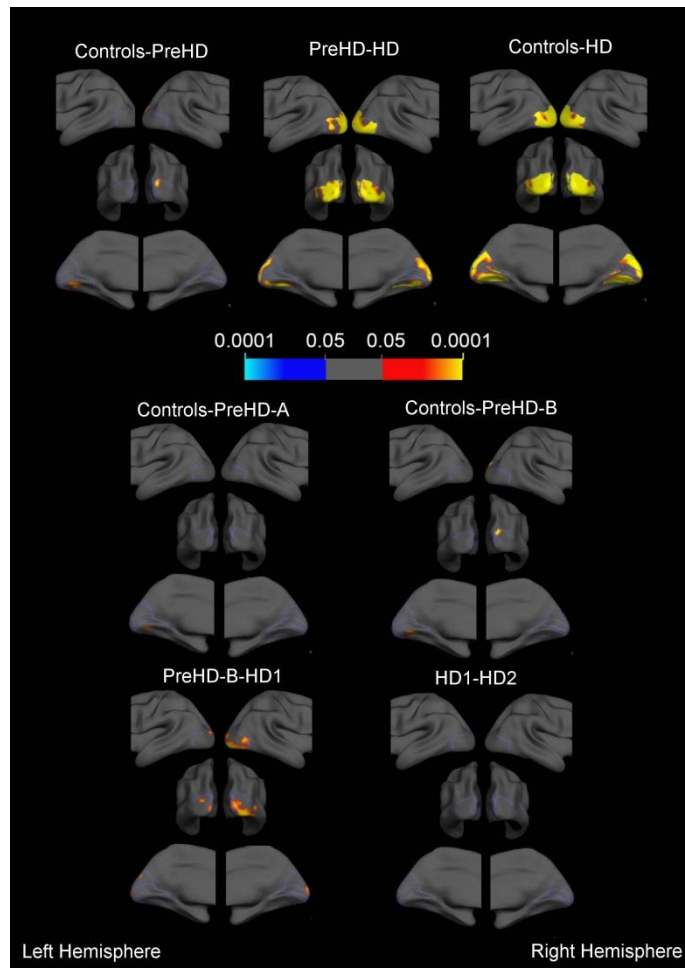Supplementary Table 3. Occipital and frontal cortex regional thickness measures (mm) within each study group.

	Controls	preHD-A	preHD-B	preHD	HD1	HD2	HD
N	N=97	N=51	N=58	N=109	N=40	N=29	N=69
Occipital cortex	2.00 (.10)	1.98 (.14)	1.93 (.09)	1.96 (.12)	1.82 (.11)	1.77 (.13)	1.80 (.12)
Cuneus	1.79 (.13)	1.79 (.16)	1.75 (.10)	1.77 (.13)	1.66 (.11)	1.62 (.11)	1.64 (.11)
Lateral occipital cortex	2.21 (.13)	2.18 (.17)	2.13 (.12)	2.16 (.15)	1.99 (.15)	1.92 (.16)	1.96 (.16)
Lingual	2.01 (.11)	1.99 (.14)	1.94 (.11)	1.96 (.12)	1.85 (.13)	1.77 (.16)	1.82 (.14)
Pericalcarine	1.52 (.13)	1.53 (.12)	1.50 (.10)	1.51 (.11)	1.42 (.09)	1.43 (.10)	1.42 (.09)
N		N=48	N=51	N=99	N=37	N=24	N=61
Caudate Volume	-	6426.68 (921.64)	5826.90 (1111.90)	6117.71 (1062.50)	4772.81 (1103.46)	4346.96 (945.91)	4574.93 (1052.54)

Regional thickness estimates outputted from FreeSurfer cortical analysis masked with the Desikan-Killiany Atlas and manually measured Caudate Volume for all gene-carriers

Supplementary Table 4. Adjusted between-group differences in occipital volume and thickness measures. Dark grey highlights associations significant to p<0.01 whilst light grey highlights those significant at the p<0.05 level.

	preHD vs controls	HD vs controls	preHD vs HD	preHD-A vs controls	preHD-B vs controls	HD1 vs preHD-B	HD2 vs HD1
	Thickness (mm)						
Occipital cortex	-.10	-.10	-.14	-.05	-.04	-.11	-.03
	(-.11, -.08)	(-.12, -.09)	(-.18, -.11)	(-.09, -.01)	(-.05, -.03)	(-.15, -.07)	(-.08, .02)
	p<0.001	p<0.001	p<0.001	p=0.015	p<0.001	p<0.001	p=0.264
	ES=-.653	ES=-.947	ES=-1.303	ES=-.411	ES=-.508	ES=-.979	ES=-.269
	(-.92, -.31)	(-1.17, -.68)	(-1.67, -.89)	(-.74, -.02)	(-.72, -.29)	(-1.50, -.38)	(-.83, .34)
LOC	-.12	-.13	-.18	-.06	-.05	-.15	-.04
	(-.14, -.10)	(-.15, -.11)	(-.23, -.14)	(-.10, -.01)	(-.06, -.03)	(-.20, -.10)	(-.11, .03)
	p<0.001	p<0.001	p<0.001	p=0.026	p<0.001	p<0.001	p=0.250
	ES=-.580	ES=-.896	ES=-1.268	ES=-.374	ES=-.431	ES=-1.133	ES=-.278
	(-.86, -.26)	(-1.11, -.66)	(-1.64, -.87)	(-.71, .02)	(-.62, -.22)	(-1.60, -.62)	(-.80, .36)
Lingual	-.09	-.10	-.12	-.06	-.05	-.08	-.05
	(-.11, -.08)	(-.12, -.08)	(-.16, -.08)	(-.09, -.02)	(-.06, -.03)	(-.13, -.03)	(-.11, .02)
	p<0.001	p<0.001	p<0.001	p=0.004	p<0.001	p=0.001	p=0.139
	ES=-.662	ES=-.758	ES=-.926	ES=-.501	ES=-.425	ES=-.682	ES=-.353
	(-.92, .36)	(-.98, -.53)	(-1.28, -.55)	(-.84, -.15)	(-.59, -.24)	(-1.16, -.23)	(-.93, .25)
Cuneus	-.08	-.08	-.11	-.04	-.03	-.09	-.02
	(-.09, -.06)	(-.09, -.06)	(-.15, -.08)	(-.08, .01)	(-.05, -.02)	(-.14, -.05)	(-.07, .03)
	p<0.001	p<0.001	p<0.001	p=0.132	p<0.001	p<0.001	p=0.459
	ES=-.441	ES=-.689	ES=-1.036	ES=-.261	ES=-.365	ES=-.826	ES=-.195
	(-.74, -.13)	(-.90, -.48)	(-1.41, -.67)	(-.62, .10)	(-.56, -.17)	(-1.25, -.38)	(-.81, .43)
Pericalcarine	-.05	-.05	-.08	-.02	-.02	-.08	.01
	(-.07, -.03)	(-.06, -.03)	(-.11, -.05)	(-.06, .03)	(-.04, -.001)	(-.11, -.04)	(-.03, .05)
	p<0.001	p<0.001	p<0.001	p=0.462	p=0.037	p<0.001	p=0.486
	ES=-.253	ES=-.576	ES=-.917	ES=-.139	ES=-.203	ES=-.979	ES=.168
	(-.60, .07)	(-.83, -.32)	(-1.30, -.48)	(-.52, .28)	(-.40, .004)	(-1.50, -.38)	(-.39, .82)

Data are coefficients (95% CI), p-values and effect sizes (bootstrapped 95% CIs) of between-group differences in occipital lobe volume and thickness measures. Coefficients and p-values were calculated using generalised least squares regression adjusted for age, gender and study site. Effect sizes were calculated as the estimated absolute adjusted mean difference of the metric between the HD and control groups, divided by the estimated residual SD of the HD group. These are reported with bias corrected and accelerated bootstrapped 95% CIs based on 2000 replications (Gomez-Tortosa et al., 1996).

Supplementary Figure 1: Significance maps of cortical thickness differences between groups (0.0001<p<0.05). comparisons were adjusted for age, gender, study site, education, CAG, and disease burden score, and corrected for multiple comparisons using Monte Carlo cluster-wise correction (p<0.05) across the four occipital regions.

Carpenter, J., Bithell, J., 2000. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. Stat Med 19, 1141–64.

Gomez-Tortosa, E., del Barrio, A., Barroso, T., Garcia Ruiz, P.J., 1996. Visual processing disorders in patients with Huntington's disease and asymptomatic carriers. J Neurol 243, 286–292.