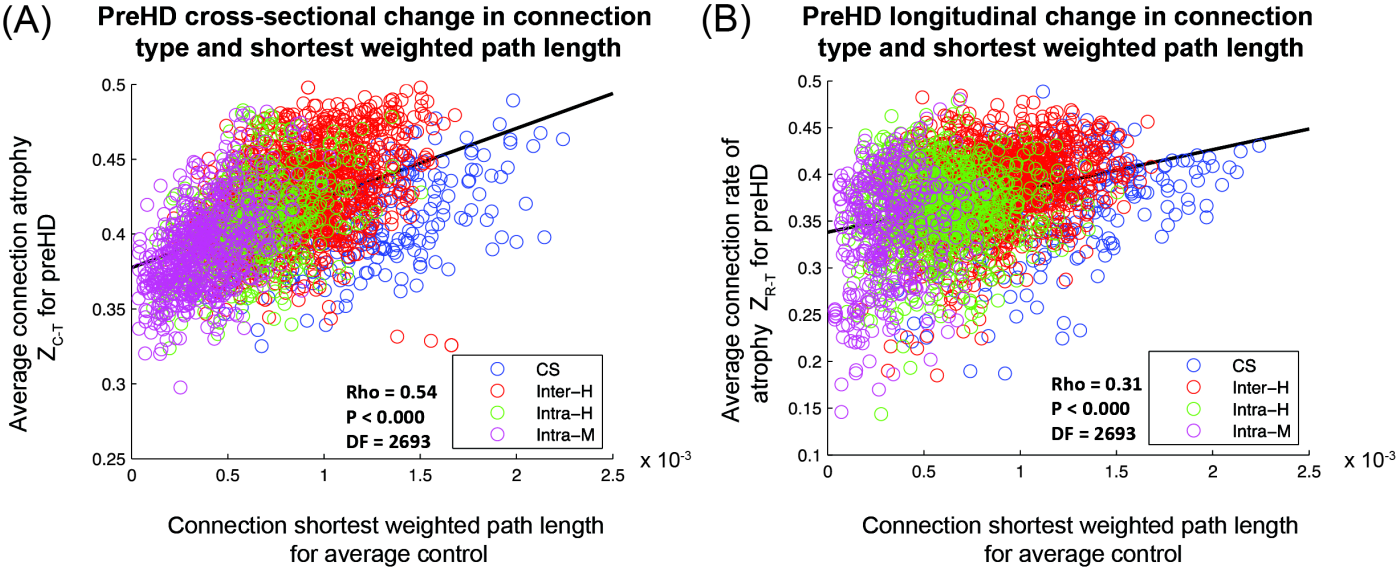
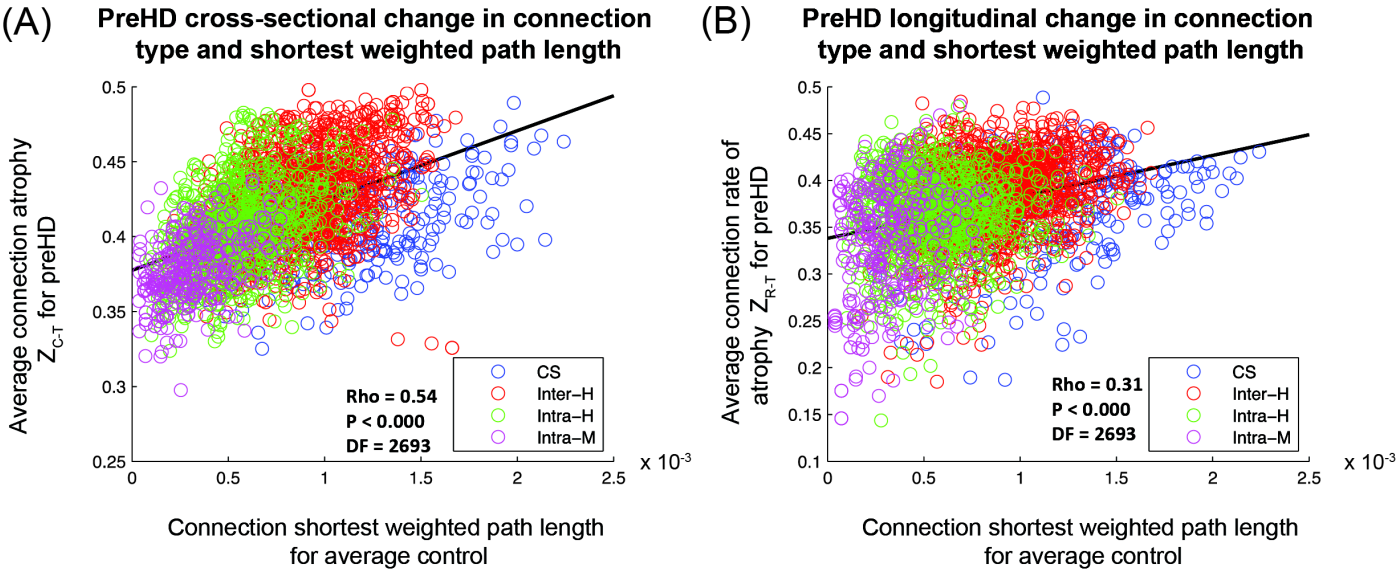
Supplemental Data

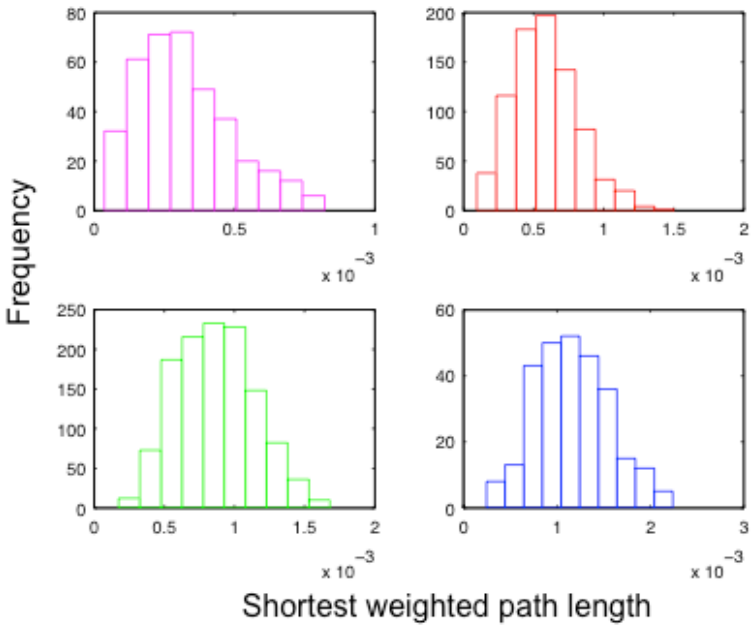
Supplemental Figure 1. Four cortical module analysis. Connection length correlates with rate of connection degeneration over 2 years in preHD. (A) Cross sectional analysis: Z-scores, denoting loss of connection strength, were transformed into positive atrophy measures using a logistic transform. Average transformed connection strength Z-score for preHD participants was plotted against connection weighted path length for average control. Connections colour coded according to type**. (B) Longitudinal analysis:** Z-scores, denoting connection rate of atrophy over 3 time points, were transformed into a positive rate of atrophy measure using a logistic transform. Average transformed connection rate of change Z-score for preHD participants were plotted against connection weighted path length for average control and Spearman rank correlations performed**.** For both (A) and (B) each data point represents a brain connection. Intra-M – intra-modular (magneta), Intra-H –intra-hemispheric (green), Inter-H – inter-hemispheric (red), CS – cortico-striatal (blue). The black line represents a least squares linear regression line. rho = correlation, p = p-value, DF = degrees of freedom. Please note that data points and rho values are same for cortical module analyses 4, 6 and 8 as the module assignment does not alter the connection atrophy measures or the shortest weighted path length. Differing module partitions changes the assignment of connection type, specifically whether a connection is classed as intra-modular or inter/intra-hemispheric.



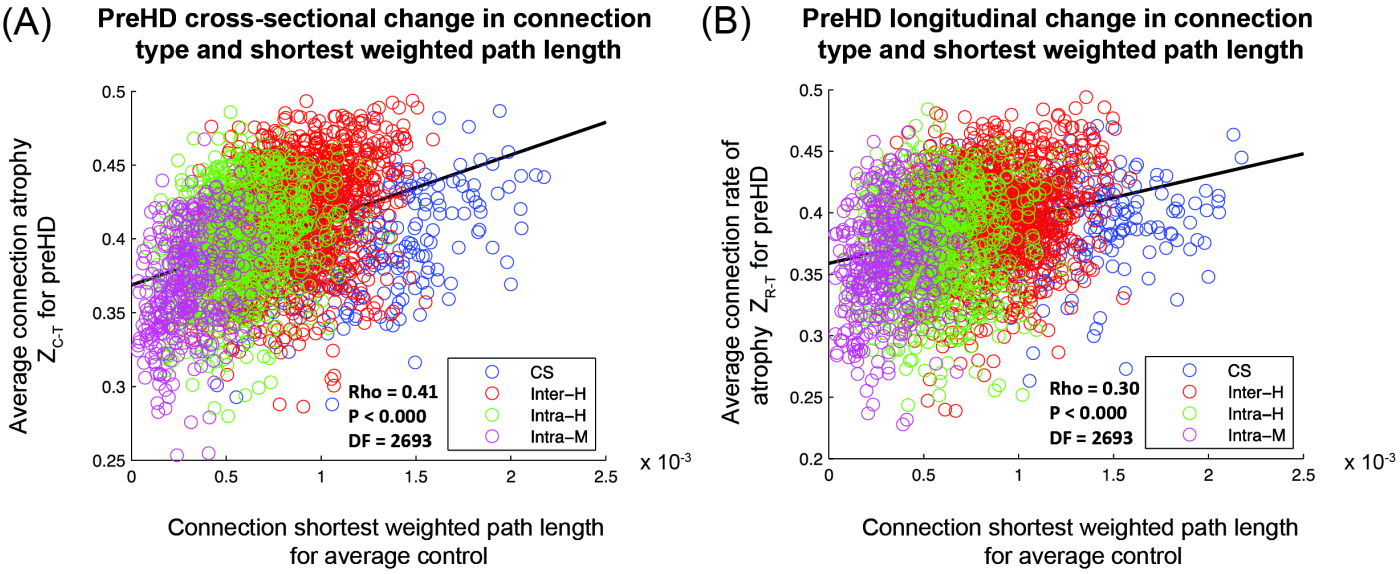
Supplemental Figure 2. Eight cortical module analysis. Connection length correlates with rate of connection degeneration over 2 years in preHD. (A) Cross sectional analysis: Z-scores, denoting loss of connection strength, were transformed into positive atrophy measures using a logistic transform. Average transformed connection strength Z-score for preHD participants was plotted against connection weighted path length for average control. Connections colour coded according to type**. (B) Longitudinal analysis:** Z-scores, denoting connection rate of atrophy over 3 time points, were transformed into a positive rate of atrophy measure using a logistic transform. Average transformed connection rate of change Z-score for preHD participants were plotted against connection weighted path length for average control and Spearman rank correlations performed**.** For both (A) and (B) each data point represents a brain connection. Intra-M – intra-modular (magneta), Intra-H –intra-hemispheric (green), Inter-H – inter-hemispheric (red), CS – cortico-striatal (blue). The black line represents a least squares linear regression line. rho = correlation, p = p-value, DF = degrees of freedom. Please note that data points and rho values are same for cortical module analyses 4, 6 and 8 as the module assignment does not alter the connection atrophy measures or the shortest weighted path length. Differing module partitions changes the assignment of connection type, specifically whether a connection is classed as intra-modular or inter/intra-hemispheric.



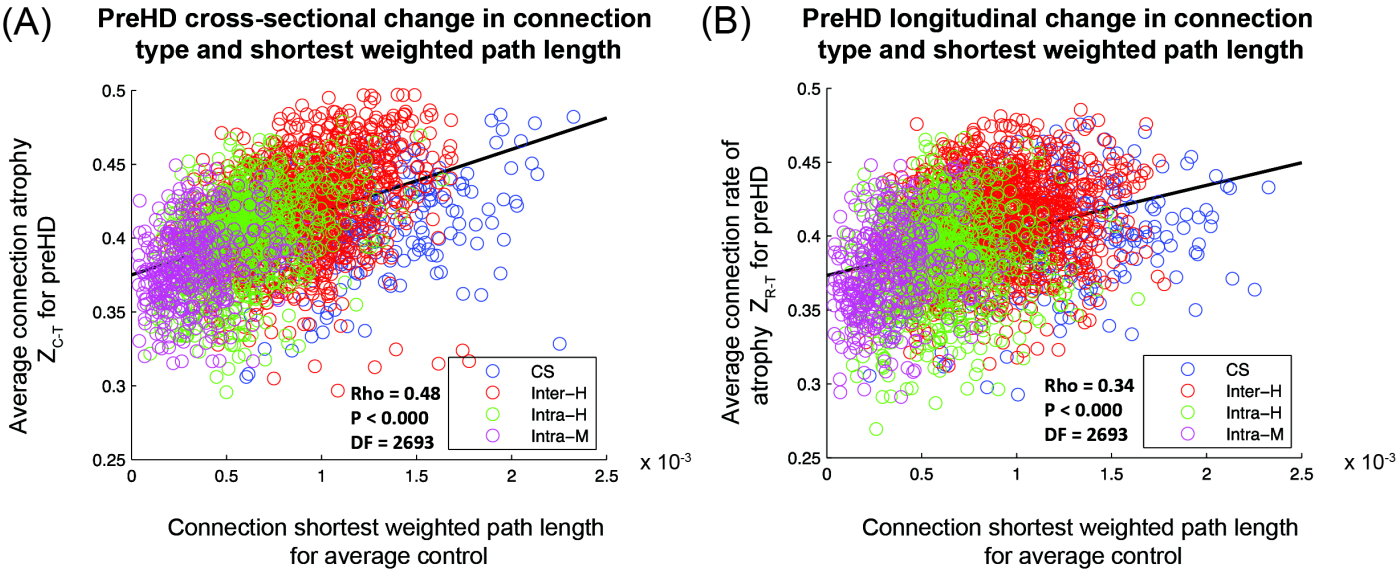
Supplemental Figure 3. Histograms of *shortest weighted path length* for different classes of connection. Intra-modular (magneta), Intra-hemispheric (green), Inter-hemispheric (red), Cortico-striatal (blue). Y-axis: frequency of connection length in a given interval (intervals generated automatically by MATLAB hist function in order to cover range of values in data). X-axis: *shortest weighted path length*



Supplemental Figure 4. Split site Leiden-Vancouver analysis. Connection length correlates with rate of connection degeneration over 2 years in preHD. (A) Cross sectional analysis: Z-scores, denoting loss of connection strength, were transformed into positive atrophy measures using a logistic transform. Average transformed connection strength Z-score for preHD participants was plotted against connection weighted path length for average control. Connections colour coded according to type**. (B) Longitudinal analysis:** Z-scores, denoting connection rate of atrophy over 3 time points, were transformed into a positive rate of atrophy measure using a logistic transform. Average transformed connection rate of change Z-score for preHD participants were plotted against connection weighted path length for average control and Spearman rank correlations performed**.** For both (A) and (B) each data point represents a brain connection. Intra-M – intra-modular (magneta), Intra-H –intra-hemispheric (green), Inter-H – inter-hemispheric (red), CS – cortico-striatal (blue). The black line represents a least squares linear regression line. rho = correlation, p = p-value, DF = degrees of freedom.



Supplemental Figure 5. Split site London-Paris analysis. Connection length correlates with rate of connection degeneration over 2 years in preHD. (A) Cross sectional analysis: Z-scores, denoting loss of connection strength, were transformed into positive atrophy measures using a logistic transform. Average transformed connection strength Z-score for preHD participants was plotted against connection weighted path length for average control. Connections colour coded according to type**. (B) Longitudinal analysis:** Z-scores, denoting connection rate of atrophy over 3 time points, were transformed into a positive rate of atrophy measure using a logistic transform. Average transformed connection rate of change Z-score for preHD participants were plotted against connection weighted path length for average control and Spearman rank correlations performed**.** For both (A) and (B) each data point represents a brain connection. Intra-M – intra-modular (magneta), Intra-H –intra-hemispheric (green), Inter-H – inter-hemispheric (red), CS – cortico-striatal (blue). The black line represents a least squares linear regression line. rho = correlation, p = p-value, DF = degrees of freedom.



Supplemental Table 1. Cortical module assignments

	Cortical Region		Cortical Region
Module 1	L.caudalanteriorcingulate L.caudalmiddlefrontal L.lateralorbitofrontal L.medialorbitofrontal L.parsopercularis L.parsorbitalis L.parstriangularis L.rostralanteriorcingulate L.rostralmiddlefrontal L.superiorfrontal L.frontalpole L.insula	**Module 2**	R.caudalanteriorcingulate R.caudalmiddlefrontal R.lateralorbitofrontal R.medialorbitofrontal R.parsopercularis R.parsorbitalis R.parstriangularis R.posteriorcingulate R.rostralanteriorcingulate R.rostralmiddlefrontal R.superiorfrontal R.frontalpole
Module 3	L.bankssts L.entorhinal L.fusiform L.inferiortemporal L.middletemporal L.parahippocampal L.superiortemporal L.temporalpole L.transversetemporal L.hippocampus	**Module 4**	R.hippocampus R.bankssts R.entorhinal R.fusiform R.inferiortemporal R.middletemporal R.parahippocampal R.superiortemporal R.temporalpole R.transversetemporal R.insula
Module 5	L.cuneus L.inferiorparietal L.isthmuscingulate L.lateraloccipital L.lingual L.paracentral L.pericalcarine L.postcentral L.posteriorcingulate L.precentral L.precuneus L.superiorparietal L.supramarginal	**Module 6**	R.cuneus R.inferiorparietal R.isthmuscingulate R.lateraloccipital R.lingual R.paracentral R.pericalcarine R.postcentral R.precentral R.precuneus R.superiorparietal R.supramarginal

Supplemental Table 2. Cross-sectional mixed linear model results: Cortico-striatal (VCP) and intra-modular connections. γ – estimated group intercept difference (preHD minus control; see Equation 1), SE – standard error of the difference, p-value – probability value, q-value – FDR corrected p-value. Cross-sectional group difference at first visit was defined as the intercept main effect of group in the full linear mixed effects model.

Cortico-striatal connection (VCP)	γ	SE	p-value	q-value
Left striatum fronto-cingulate	-0.159	0.020	$1.2x10^{-14}$	$7.23x10^{-14}$
Right striatum fronto-cingulate	-0.061	0.009	$2.23x10^{-10}$	$6.69x10^{-10}$
Left striatum temporal	-0.046	0.014	$1.1x10^{-3}$	$1.1x10^{-3}$
Right striatum temporal	-0.049	0.009	$2.48x10^{-7}$	$4.95x10^{-7}$
Left striatum motor-occipital-parietal	-0.067	0.020	$6.37x10^{-4}$	$7.64x10^{-4}$
Right striatum motor-occipital-parietal	-0.043	0.010	$2.37x10^{-5}$	$3.55x10^{-5}$
Intra-modular connection	γ	**SE**	**p-value**	**q-value**
left fronto-cingulate	325.299	4496.184	0.942	0.942
right fronto-cingulate	6126.354	4248.015	0.150	0.300
left temporal	-3548.794	5525.934	0.521	0.625
right temporal	-13643.181	6685.873	0.042	0.251
left motor-occipital-motor	-6054.634	6344.644	0.340	0.511
right motor-occipital-motor	-9391.770	6333.663	0.139	0.300

Supplemental Table 3. Longitudinal mixed linear model results: Inter-hemispheric and Intra-modular connections. δ – parameter estimate, SE – standard error, p-value – probability valve, q-value – FDR corrected p-value. Longitudinal change was defined as a significantly superior fit for the full LMER compared to the reduced LMER omitting group * time interaction.

Inter-hemispheric connection	δ	SE	p-value	q-value
left fronto-cingulate right fronto-cingulate	-8.548	1064.484	0.994	0.994
left temporal right temporal	7.415	28.474	0.795	0.946
left motor-occipital-parietal right motor-occipital-parietal	123.274	614.003	0.841	0.946
left fronto-cingulate right motor-occipital-parietal	-112.598	143.000	0.431	0.647
right fronto-cingulate left motor-occipital-parietal	-281.773	184.737	0.128	0.383
left fronto-cingulate right temporal	-52.692	40.285	0.192	0.383
right fronto-cingulate left temporal	-39.018	20.837	0.062	0.383
left temporal right motor-occipital-parietal	-135.995	97.276	0.162	0.383
right temporal left motor-occipital-parietal	-158.435	127.021	0.213	0.383
Intra-modular connection	δ	**SE**	**p-value**	**q-value**
left fronto-cingulate	3977.641	2647.570	0.134	0.401
right fronto-cingulate	2250.200	2861.948	0.432	0.520
left temporal	2698.917	4211.651	0.523	0.522
right temporal	3901.665	4978.346	0.434	0.520
left motor-occipital-motor	6834.844	4460.051	0.126	0.401
right motor-occipital-motor	4121.240	4923.315	0.403	0.520

Supplemental Table 4. Tukey-Kramer post hoc analysis of differences in connection length between different connections types. Intra-M –intra-modular, Intra-H –intra-hemispheric, Inter-H – inter-hemispheric, CS – cortico-striatal. CI – confidence interval.

Group 1	Group 2	95% lower CI	Mean difference	95% CI upper	p-value
Intra-M	Intra-H	-0.000302067	-0.000259613	-0.000217159	3.77E-09
Intra-M	Inter-H	-0.000582694	-0.000542553	-0.000502413	3.77E-09
Intra-M	CS	-0.000897343	-0.000843599	-0.000789855	3.77E-09
Intra-H	Inter-H	-0.000313728	-0.00028294	-0.000252152	3.77E-09
Intra-H	CS	-0.000631157	-0.000583986	-0.000536816	3.77E-09
Inter-H	CS	-0.000346146	-0.000301046	-0.000255947	3.77E-09

Supplemental Table 5. Baseline demographic information. SD = standard deviation, M = male, F = female, N = number. ISCED = International standard classification of education. CAG = CAG repeat expansion length, DBS = disease burden scale (Penney, et al., 1997)

	Premanifest HD	Control	Statistical test	P-value
N	72	85	-	-
Age (SD)	43.3 (9.2)	48.8 (9.8)	T-test	0.0004
Gender (M/F)	38/34	32/53	Chi-square	0.057
Study Site (N) (Leiden/London/Paris/Vancouver)	14/25/18/15	20/26/23/16	Chi-square	0.89
ISCED (2/3/4/5/6)	5/16/23/27/1	8/16/29/30/2	Chi-square	0.94
CAG (SD)	42 (2.3)	-	-	-
DBS (SD)	317 (55)	-	-	-

Supplemental Table 6. Rate of connection atrophy longitudinal cohort. SD = standard deviation, M = male, F = female, N = number. ISCED = International standard classification of education. CAG = CAG repeat expansion length, DBS = disease burden scale (Penney, et al., 1997)

	Premanifest HD	Control	Statistical test	P-value
N	56	65	-	-
Age (SD)	43.6 (9.3)	49.2 (9.7)	T-test	0.002
Gender (M/F)	30/26	24/41	Chi-square	0.066
Study Site (N) (Leiden/London/Paris/Vancouver)	8/22/16/10	15/20/20/10	Chi-square	0.57
ISCED (2/3/4/5/6)	5/13/14/23/1	5/16/22/20/2	Chi-square	0.74
CAG (SD)	42.8 (2.4)	-	-	-
DBS (SD)	316.7 (58)	-	-	10

Supplemental Table 7. Cross-sectional global cognitive composite effects in preHD: Cortico-striatal connections (VCP). γ – parameter estimate of baseline cognitive composite effect, SE – standard error, p-value – probability valve, q-value – FDR corrected p-value. Association between connection strength and cognition was assessed by the main effect of global cognitive composite score at baseline for the full LMER.

Cortico-striatal connection (VCP)	γ	SE	P-value	q-value
Left striatum fronto-cingulate	0.037	0.023	0.114	0.412
Right striatum fronto-cingulate	0.017	0.011	0.137	0.412
Left striatum temporal	0.009	0.014	0.528	0.723
Right striatum temporal	0.005	0.010	0.623	0.723
Left striatum motor-occipital-parietal	0.026	0.021	0.217	0.433
Right striatum motor-occipital-parietal	-0.004	0.012	0.723	0.723

Supplemental Table 8. Longitudinal global cognitive composite effects in preHD: Cortical connections. δ – parameter estimate of baseline cognitive composite effect, SE – standard error, p-value – probability valve, q-value – FDR corrected p-value. Longitudinal change was defined as a significantly superior fit for the full LMER compared to the reduced LMER omitting global cognitive composite * time interaction.

Inter-hemispheric connection	δ	SE	p-value	q-value
left fronto-cingulate right fronto-cingulate	290.472	1352.185	0.830	0.914
left temporal right temporal	-76.655	31.395	0.015	0.139
left motor-occipital-parietal right motor-occipital-parietal	582.052	780.157	0.456	0.781
left fronto-cingulate right motor-occipital-parietal	-18.155	168.517	0.914	0.914
right fronto-cingulate left motor-occipital-parietal	221.011	235.550	0.349	0.781
left fronto-cingulate right temporal	27.539	42.800	0.521	0.781
right fronto-cingulate left temporal	-9.478	21.281	0.657	0.844
left temporal right motor-occipital-parietal	-91.957	108.829	0.399	0.781
right temporal left motor-occipital-parietal	-286.764	140.863	0.043	0.193
Intra-hemispheric connection	δ	**SE**	**p-value**	**q-value**
left fronto-cingulate left temporal	-1138.861	586.779	0.054	0.225
left fronto-cingulate left motor-occipital-parietal	-343.698	1123.016	0.760	0.760
left temporal left motor-occipital-parietal	-2756.217	1581.689	0.083	0.225
right fronto-cingulate right temporal	-974.896	611.831	0.113	0.225
right fronto-cingulate right motor-occipital-parietal	-686.440	1115.276	0.539	0.647
right temporal right motor-occipital-parietal	-1664.563	1803.591	0.357	0.536
Intra-modular connection	δ	**SE**	**p-value**	**q-value**
left fronto-cingulate	-6636.924	3203.536	0.039	0.207
right fronto-cingulate	-3984.763	3729.899	0.286	0.430
left temporal	6582.062	5131.308	0.201	0.402
right temporal	548.183	5749.975	0.924	0.964
left motor-occipital-motor	-253.806	5633.787	0.964	0.964
right motor-occipital-motor	10993.406	6017.274	0.069	0.207

Supplemental Table 9. Longitudinal global cognitive composite effects in preHD: Cortico-striatal connections. δ – parameter estimate of baseline cognitive composite effect, SE – standard error, p-value – probability valve, q-value – FDR corrected p-value. Longitudinal change was defined as a significantly superior fit for the full LMER compared to the reduced LMER omitting global cognitive composite * time interaction.

Cortico-striatal connection (Connectome)	δ	**SE**	**P-value**	**q-value**
Left striatum fronto-cingulate	-431.959	444.913	0.333	0.909
Right striatum fronto-cingulate	-218.826	378.821	0.564	0.909
Left striatum temporal	-103.621	102.919	0.315	0.909
Right striatum temporal	47.646	180.734	0.792	0.909
Left striatum motor-occipital-parietal	18.488	158.160	0.907	0.909
Right striatum motor-occipital-parietal	-16.283	142.786	0.909	0.909
Cortico-striatal connection (VCP)	δ	**SE**	**P-value**	**q-value**
Left striatum fronto-cingulate	0.007	0.013	0.573	0.608
Right striatum fronto-cingulate	0.008	0.008	0.280	0.608
Left striatum temporal	-0.004	0.008	0.574	0.608
Right striatum temporal	0.003	0.006	0.608	0.608
Left striatum motor-occipital-parietal	-0.008	0.016	0.594	0.608
Right striatum motor-occipital-parietal	0.012	0.007	0.112	0.608

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