Supplementary Material

Methods

Participants

Participants were excluded if they demonstrated clinical evidence of unstable medical or psychiatric illness, alcohol or drug abuse within the past year, learning or developmental disability requiring special education, history of another neurological condition, inability to undergo MRI scanning, and use of prescription antipsychotic medications within the past six months or phenothiazine-derivative antiemetic medications more than three times per month. Participants for this study were selected from a larger dataset of 32 gene-negative controls and 52 gene-positive prodromal Huntington's participants. The final sample was selected to minimize group differences in age while maintaining an equivalent number of subjects in each group.

All participants were administered the Motor Assessment section of the Unified Huntington's Disease Rating Scale (UHDRS), which contains 31 items that assess chorea, bradykinesia, rigidity, dystonia, and oculomotor function on a four-point scale (0 = normal; 4=greatest impairment). The UHDRS Motor Score is the sum of these items.

Disease Burden Score

The CAG-Age Product (CAP) score is a disease burden score (DBS) that purports to index the cumulative toxicity of exposure to the CAG expansion. As discussed by Ross and colleagues (Ross *et al.*, 2014), CAP is consistent with the general form of DBS, which is DBS = age × (CAG - L), where L is a constant used by different researchers. Based on the validation study of Zhang et al. (Zhang *et al.*, 2011) with an earlier PREDICT-HD data cut, the constant was estimated as L = 33.66. This is similar to the constant proposed several year earlier by Penney et al. (Penney, Jr. *et al.*, 1997), L = 35.50, and used in other longitudinal studies as an index of progression level (Tabrizi *et al.*, 2013). It can be shown that the aforementioned values of L will produce similar DBS, so there is an approximate equivalence among the different scores. Thus, the PREDICT-HD CAP score can be compared to other DBS allowing for direct comparisons among studies and similar indexing of progression level. CAP scores can be converted to a scaled score based on a 5-year probability of diagnosis. Cut-offs for the three CAP groups were based on an optimization algorithm from the larger PREDICT-HD cohort (N > 1,000). Based on

this stratification the estimated time to diagnosis is >12.78 years, 12.78 to 7.59 years, and <7.59 years for the Low, Medium, and High groups, respectively.

When studying only gene expanded people, grouping is generally not needed and not desirable. Treating CAP as a continuous variable rather than a grouping variable will tend to increase statistical power and allow for the use of regression methods. The correlations we report between CAP score and functional imaging measures were computed among the subsample of gene positive individuals. The goal was to directly assess the magnitude of associations between disease burden and connectivity metrics for those individuals for which disease burden can be defined. We argue that the results from both the grouping approach and the continuous approach are internally consistent. CAP indeed is a continuous variable, but it is undefined for negative-gene expanded people, for which CAG length does not index disease burden. Incomplete penetrance notwithstanding, CAG = 36 is treated as the threshold for defining negative gene expanded and positive gene expanded groups. Thus, whenever negative and positive gene expanded people are studied it is natural to compare them at the group level. An important caveat is that not all gene positive people are alike in our sample, because they entered the parent study with different levels of progression. To account for the progression variability and still maintain the group concept, the gene positives are divided into low/medium/high progression groups based on the algorithm discussed by Zhang and colleagues (Zhang *et al.*, 2011). The grouping has been used in numerous studies of prodromal Huntington's disease (e.g., Harrington *et al.*, 2012; Paulsen *et al.*, 2013; Rao *et al.*, 2014; Matsui *et al.*, 2014; Epping *et al.*, 2013; Williams *et al.*, 2015). In our study, we sought to account for natural aging by including gene negative individuals and to study gene-positive progression level. It was important to examine which gene-positive progression groups showed differences relative to the gene negatives to better understand how Huntington's disease progresses as indexed by imaging markers.

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Neuroimaging Protocol

Quality Assurance

Both sites used identical scanners and a comparison of phantom data between the sites indicated similar image quality and signal-to-noise ratio. Frequent quality assurance scans were also performed at each institution to ensure that imaging data were free of scanner artifacts and were comparable across sites. For each of the functional connectivity measures, we conducted ANOVAs to test for the main effect of site. Scanner site was not significantly associated with any of the measures (uncorrected for multiple comparisons).

Motion

Several procedures were used to carefully screen rs-fMRI scans for motion. Screening involved visual inspection of the rs-fMRI time series and subsequent correlation maps. Inspection included meticulous assessments of the each individual rs-fMRI scan to screen for head movements during the time series and potential motion-related artifacts such as rings of correlation around the outside of the head, correlation in the ventricles, connectivity in only part of the brain, and rapid correlation pattern changes from slice to slice. AFNI 3dvolreg (Cox, 1996) was used to retrospectively correct volumetric-level motion. The 3dvolreg program realigns subsequent volumes of time series data to a base volume and outputs volumetric motion parameters for rotation and displacement of each volume to the base volume. These volumetric parameters were then trigonometrically converted to voxel-level displacement and a model of the signal fluctuations was regressed from the time series at each voxel (Bullmore *et al.*, 1999). ANOVAs demonstrated that the groups did not differ in mean [Negative: 0.31 mm (0.11); Low: 0.33 mm (0.12); Medium: 0.29 mm (0.08); High: 0.40 mm (0.17)] or maximum [Negative: 0.70 mm (0.24); Low: 0.71 mm (0.19); Medium: 0.66 mm (0.25); High: 0.86 mm (0.35)] peak-to-peak displacement during the rs-fMRI scan ($p > 0.163$).

Resting State Image Analysis

Post processing of the rs-fMRI data included the removal of the first 4 volumes of the time series. Physiologic noise was estimated using PESTICA (Beall and Lowe, 2007) and was regressed out at the voxel level using RETROICOR (Glover *et al.*, 2000). Using the BOLD-weighted time series data, PESTICA generates two fast-sampled signals matching the periodicity of the heart and respiration cycles. These signals can then be used in the model-based correction with the same efficiency as if the pulse and respiration had been recorded in parallel. We

consider this the most effective method of reducing individual and group effects associated with physiologic noise.

Cortical and Subcortical Parcellation

To derive measures of functional connectivity, we subdivided the cortical surface and subcortical structures into parcels or nodes. The choice of a parcellation is important for accurate mapping of interregional functional connectivity, as imprecise node definition can influence the observed network measures (Zalesky *et al.*, 2010). Clinical studies commonly use anatomical atlas-based parcellations (e.g., Automatic Anatomical Labeling) that have a relatively coarse resolution (90 regions) and do not necessarily map to the underlying functional-brain organization (Fornito *et al.*, 2010). The present study used a medium-density resolution of 300 nodes, which was derived using a spatially constrained clustering method described by Craddock and colleagues (Craddock *et al.*, 2012) that subdivides regions into similarly sized parcels while optimizing the homogeneity of correlations among voxels within each node.

A group parcellation of 300 regions was based on the 16 HD negative subjects. First, a grey-matter mask was created from the average anatomical image and was restricted to areas where all subjects had adequate resting-state data. Resting time courses in individual hemispheres were resampled to 2mm cubic voxels and parcellated into 150 clusters in each hemisphere separately using two-level t-corr clustering (Craddock et al., 2012). This method attempts to create similarly sized parcels with high homogeneity of correlations among voxels. A group parcellation approach was desirable to compare functional connectivity in specific regions across groups of subjects. However, our main effect tests of group for graph-theory derived measures were largely reproducible when we conducted individual subject parcellations using the current method (Craddock et al., 2012) and another approach described by Blumensath and colleagues that maximizes homogeneity without the constraint of similar parcel sizes (Blumensath *et al.*, 2013) (Supplementary Table 1).

Network Topology Analysis

Average time courses from each region were then extracted and a 300 x 300 matrix of t-statistics for the Pearson correlation was created for each subject. A Gaussian fit restricted to the full-width at half-maximum (FWHM) of the t distribution of the correlations was used to create connectivity z-scores, which became the weighted connectivity matrix used in the between-subject analyses (Lowe *et al.*, 1998).

Using the Brain Connectivity Toolbox, the clustering coefficient, global efficiency, and rich-club coefficient weighted measures were computed as a ratio of each measure to the mean value derived from 100 random networks (Rubinov and Sporns, 2010), because measures of network organization should not be interpreted in isolation. For instance, an increase in a measure such as the global efficiency is not necessarily beneficial, especially if it is accompanied by a simultaneous reduction in other measures, such as the clustering coefficient. Indeed random graphs have very high global efficiency, but very low clustering coefficients, reflecting an imbalance between integration and segregation. Random networks were constructed using null_model_und_sign.m, an algorithm that preserves node degrees and connection weights, and closely approximates node strengths, thereby allowing for more rigorous hypothesis tests on weighted networks (Rubinov and Sporns, 2011).

Structural MRI Analyses of Brain Morphometry

MRI scans were analyzed to examine group differences in regional cortical volume and thickness as well as subcortical volumes. Cortical volume and thickness were derived from the Desikan atlas parcellation method (Desikan *et al.*, 2006) incorporated in FreeSurfer 5.1 software (Fischl *et al.*, 2004), which demonstrates good test-retest reliability across scanners and sites (Han *et al.*, 2006). We analyzed bilateral regional volume/thickness in homologous areas, since hemispheric asymmetries have not been noted across multiple studies (Harrington *et al.*, 2014; Nopoulos *et al.*, 2010; Aylward *et al.*, 2012). Cortical and subcortical volumes were adjusted for total intracranial volume [(volume/intracranial volume) *100)]. ANCOVAs (age adjusted) tested for the main effect of group for each of the 34 cortical thickness and volume measures and five subcortical volumes (putamen, globus pallidus, caudate, accumbens, thalamus), using the false discovery rate (FDR) correction for multiple comparisons. Each subject's MRI was initially analyzed in original space. Processing included removal of non-brain tissue by a hybrid watershed/surface deformation procedure, segmentation of subcortical structures (Fischl *et al.*,

2002), and further intensity normalization. This was followed by white-matter segmentation, tessellation of the grey-white matter boundary, and automated topology correction (Fischl *et al.*, 2001). Then surface deformation following intensity gradients optimally placed the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models were complete, deformable procedures performed additional data processing and analysis, including parcellation of the cerebral cortex into 34 conventional gyral- and sulcal-based neuroanatomical regions in each hemisphere based on the Desikan atlas, which is sensitive to structural changes in the cortex of individuals with prodromal Huntington's disease (Harrington et al., 2014). Intensity and continuity information from the segmentation and deformation procedures produced representations of cortical thickness, which were calculated as the closest distance from the grey-white matter boundary to the grey-CSF boundary at each vertex on the tessellated surface. FreeSurfer also outputs subcortical volumetric measures.

Results

Network Topology

Unadjusted group means are shown in Supplementary Table 2 for global and intermediate network measures.

Rich club anatomy. Preliminary analyses explored whether variations in the cutoff value of node strength (k) for different proportions of subjects (e.g., k>130 and 90% of subjects in one or more groups versus k >210 in 67% of subjects in one or more groups) substantially altered the anatomy. Despite variations in the number of nodes identified, rich club anatomy remained remarkably similar irrespective of the threshold. The criterion adopted in our study was chosen because it placed 17% of the nodes in the rich club, which is comparable to an anatomical rich club of 15% of the nodes (van den Heuvel and Sporns, 2011). Our rich club anatomy was also largely compatible with rich club structures identified by others (Tomasi and Volkow, 2010; Achard *et al.*, 2006; Tomasi and Volkow, 2011; Grayson *et al.*, 2014; Hagmann *et al.*, 2008; van den Heuvel and Sporns, 2013; Crossley *et al.*, 2013). Moreover, node strength (summed z-score) did not significantly differ among the groups for any of the 50 nodes, which provides converging evidence that the density of connections between the rich-club nodes specifically decreased with proximity to diagnosis. This result further supports the validity of the

rich club anatomy identified in this study. The location of rich clubs was similar within and across groups.

Whole-brain functional connectivity of aberrant nodes

The NBS analyses identified functional connectivity disturbances in prodromal Huntington's that were characterized by weaker (Negative > prodromal Huntington's disease) or stronger (prodromal Huntington's disease > Negative) connections relative to the Negative group. Supplementary Table 3 lists the regional distributions of weakened and strengthened functional connectivity (i.e., percentages of nodes exhibiting abnormal connectivity within a region of the brain relative to the total number of aberrant nodes) in the Medium and High groups.

An inspection of the results from the NBS analysis revealed that some nodes exhibited abnormal connectivity with multiple regions in the Medium and/or High groups. As disturbances in these nodes might be an important source of abnormal communication, we explored the effects of disease burden on whole-brain connectivity of this subset of nodes. To identify these nodes, the frequency by which each of the 300 nodes appeared in an aberrant connection in the Medium and/or High group was plotted. The cut off criterion for nodes with the most aberrant connections was based on the point at which the frequency distribution of the number of aberrant edges began to asymptote (range of aberrant connections = 8 to 25). Supplementary Table 4 lists the nodes with the highest number of weakened and strengthened aberrant connections. We calculated the sum of z-scores for each of these nodes and its edges to obtain a composite measure that quantified functional connectivity of a node with the *whole brain*, in contrast to the group NBS comparisons of node-to-node functional connectivity.

Group differences were found for 10 nodes that showed weakened whole-brain connectivity (Supplementary Table 4). Only the Low and High groups showed weakened left anterior cingulate connectivity, whereas only the Medium group showed weakened left middle occipital gyrus (MOG) connectivity. All prodromal Huntington's groups showed weakened left hippocampus, right thalamus, bilateral insula, left IFG, and right Heschl's gyrus connectivity relative to the Negative group. CAP scores did not correlate with the summed z-scores for any of these regions. As for enhanced connectivity, only whole-brain connectivity of the right IPL differed in prodromal Huntington's, with the High group showing enhanced right IPL connectivity, the strength of which also positively correlated with CAP scores ($r = 0.31$, $p = .032$).

Brain structure

Results from ANCOVAs (age adjusted) testing group differences in cortical volume and thickness are summarized in Supplementary Tables 5 and 6, respectively. Two regions showed group differences in cortical volume and eleven regions showed group differences in cortical thickness ($p < 0.05$, uncorrected). However, none of these regions survived an FDR correction for multiple comparisons, which were applied separately to the cortical volume and thickness measures. Though we did not find significant cortical thinning and volume loss in the prodromal Huntington's group, our study may be underpowered in this respect, owing to reports of cortical thinning and volume loss in studies of large prodromal Huntington's disease samples ($n > 300$) (Nopoulos et al., 2010; Harrington et al., 2014). Group differences in volumes of bilateral putamen, globus pallidus, caudate, and nucleus accumbens were found (Supplementary Table 7), largely due to atrophy in the High group compared to the Negative and/or Low groups.

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Supplementary Table 1: Summary statistics for network measures in gene Negative and prHD groups as a function of the parcellation method.

Network Statistic/Parcellation Method	Negative	Low	Medium	High	p value
Density (weighted)					
Craddock Group	0.498 (0.840)	-0.181 (0.808)	-0.200 (0.998)	-0.128 (1.252)	0.115
Craddock Individual Subjects	0.503 (0.713)	-0.124 (0.882)	-0.404 (0.973)	0.020 (1.262)	0.091
Blumensath Individual Subjects	0.105 (0.967)	-0.151 (1.151)	0.064 (0.863)	-0.018 (1.108)	0.873
Global efficiency (weighted)					
Craddock Group	-0.550 (0.732)	-0.017 (1.222)	0.091 (0.874)	0.481 (0.944)	0.022
Craddock Individual Subjects	-0.544 (0.736)	-0.057 (1.197)	0.067 (0.812)	0.537 (0.997)	0.022
Blumensath Individual Subjects	-0.452 (0.852)	-0.083 (0.972)	-0.060 (0.749)	0.594 (1.193)	0.065
Average clustering coefficient (weighted)					
Craddock Group	0.135 (1.220)	-0.002 (1.167)	0.186 (0.788)	-0.318 (0.805)	0.476
Craddock Individual Subjects	0.163 (1.292)	0.025 (1.093)	0.231 (0.800)	-0.420 (0.702)	0.248
Blumensath Individual Subjects	0.401 (1.039)	0.086 (1.114)	-0.230 (0.859)	-0.255 (0.947)	0.182
Rich club AUC (weighted)					
Craddock Group	0.686 (0.809)	0.100 (1.091)	-0.281 (0.840)	-0.506 (0.915)	0.004
Craddock Individual Subjects	0.662 (1.023)	0.070 (1.015)	-0.248 (0.735)	-0.485 (0.915)	0.011
Blumensath Individual Subjects	0.504 (1.036)	-0.179 (0.913)	-0.065 (1.143)	-0.260 (0.815)	0.044

Age-adjusted means (SD) are presented for each of the network measures as a function of the parcellation method that was used, including the Craddock et al. method for group and individual subjects and the Blumensath et al. method for individual subjects. P-values are from the Kruskall-Wallis nonparametric permutation tests for the main effect of group.

Supplementary Table 2. Summary statistics for network properties in gene Negative and prHD groups.

Network Statistic	Negative	Low	Medium	High	p	CAP r
Weighted density	153.033 (16.384)	141.340 (15.889)	139.829 (19.878)	139.936 (25.054)	0.115	-0.003
Global efficiency (weighted)	0.794 (0.036)	0.820 (0.061)	0.826 (0.043)*	0.846 (0.047)*	0.022	.33*
Average clustering coefficient (weighted)	1.486 (0.171)	1.493 (0.184)	1.503 (0.120)	1.405 (0.130)	0.476	-0.14
Rich club AUC (weighted)	138.238 (2.567)	136.024 (3.380)[a]	135.132 (2.665)*	134.749 (2.899)*	0.004	-.32*

Global efficiency, average cluster coefficient, and rich club AUC represent ratios of actual measure relative to the average of 100 random networks.

Tabled values are the mean (standard deviations) for the unadjusted values. Nonparametric permutation tests of the main effect of group (Negative, Low, Medium, High; FDR corrected) were conducted on the standardized residuals (age adjusted), the means for which are graphed in Figure 1. AUC = area under the curve

* For variables demonstrating a significant main effect of group, asterisks denote significant differences in the means between the Negative group and each of the prHD groups ($p<.05$). Asterisks also designate significant Pearson correlations.

[a] Nonsignificant trend for a difference between the Low and Negative groups ($p=0.093$).

Supplementary Table 3. Regional distributions of weakened and strengthened functional connectivity in prHD.

	Medium	High
Negative > prHD		
Number of aberrant edges	96	130
Frontal cortices & insula	52%	95%
Memory areas (hippocampus, parahippocampus)	26%	19%
Parietal cortex	3%	5%
Ventral attention areas (occipital, lateral temporal)	42%	0%
Thalamus	8%	18%
Basal ganglia	0%	4%
Cerebellum & brainstem	13%	5%
prHD > Negative		
Number of aberrant edges	0	122
Frontal cortices		39%
Parietal		37%
Ventral attention areas (occipital, lateral temporal, fusiform)		75%
Thalamus		21%
Basal ganglia		1%
Cerebellum		20%

Aberrant functional connectivity was identified by comparing the matrix z-score correlations for all edges connecting the 300 nodes between the Negative group with each of the prHD groups (Low, Medium, High). Aberrant edges were identified using network based statistics (NBS). The percentage of nodes exhibiting abnormal connectivity within an area of the brain, relative to the total number of aberrant nodes, is tabulated for weakened (Negative > prHD) or strengthened (prHD > Negative) functional connectivity.

Supplementary Table 4. Whole-brain functional connectivity of nodes with the highest number of aberrant connections in prHD.

Region	Talairach Coordinates			Number of Connections	Group			
	x	y	z					
Negative > prHD						*Negative > Low*	*Negative > Medium*	*Negative > High*
L Anterior Cingulate	-6	43	4	20	0.009	0.007		0.004
L Hippocampus	-19	-18	-15	18	0.016	0.027	0.008	0.008
R Inferior Frontal Gyrus	51	11	10	18	0.0004	0.0004	0.017	0.0004
L Middle Frontal Gyrus	-26	39	29	15				
R Thalamus	7	-13	-2	15				
R Parahippocampal Gyrus	33	-29	-13	12				
L Middle Occipital Gyrus	-26	-86	8	11	0.024		0.004	
L Hippocampus	-30	-28	-13	10	0.050	0.049	0.013	0.019
R Heschl's gyrus	54	-7	7	10	0.033	0.009	0.011	0.005
R Insula	48	4	-2	9	0.020	0.012	0.021	0.005
L Inferior Frontal Gyrus	-45	22	6	8	0.002	0.012	0.002	0.009
L Calcarine	-8	-85	-2	8				
L Insula	-40	8	-2	8	0.003	0.001	0.002	0.011
R Thalamus	10	-27	-3	8	0.039	0.034	0.006	0.023
prHD > Negative						*Low > Negative*	*Medium > Negative*	*High > Negative*
R Iinferior Parietal Lobule	45	-54	42	25	0.014		0.014	0.001
L Thalamus	-9	-19	11	17				
L Medial Superior Frontal Gyrus	-6	34	46	16				
L Fusiform	-34	-67	-14	13				
L Lingual	-19	-81	-7	9				
R Cuneus/Precuneus	7	-76	35	9				
R Thalamus	10	-18	11	8				

Nodes with the highest number of weakened and strengthened aberrant connections in one or more of the prHD groups, based on simple functional connectivity analyses. Anatomical location of the nodes is displayed in Figure 6. For each node, whole-brain functional connectivity was computed (summed z-scores). Group column tabulates the p-value for significance tests of the main effect of group (Negative, Low, Medium, and High) in summed z-scores (age-adjusted residuals). The remaining columns to the right tabulate the significance of planned comparisons between the Negative group and each of the prHD groups. The top rows show nodes in which functional connectivity was weakened in the prHD groups (Negative > prHD) and the bottom rows show nodes in which functional connectivity was strengthened in the prHD groups (prHD > Negative).

Supplementary Table 5. Group differences in cortical volumes (ICV-corrected) derived from FreeSurfer parcellations.

	NEGATIVE		LOW		MEDIUM		HIGH		p	η_p^2
Desikan Region	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Caudal anterior-cingulate cortex	0.261	0.038	0.301	0.047	0.302	0.034	0.274	0.045	**0.013**	0.121
Transverse temporal cortex	0.148	0.014	0.149	0.022	0.156	0.023	0.137	0.020	**0.036**	0.083
Rostral anterior cingulate cortex	0.328	0.031	0.362	0.031	0.350	0.035	0.335	0.050	0.053	0.061
Posterior-cingulate cortex	0.427	0.041	0.464	0.061	0.454	0.055	0.422	0.060	0.076	0.034
Supramarginal gyrus	1.478	0.137	1.551	0.232	1.502	0.187	1.409	0.142	0.085	0.005
Parahippocampal gyrus	0.301	0.042	0.322	0.033	0.308	0.034	0.294	0.035	0.092	0.005
Superior temporal gyrus	1.599	0.190	1.636	0.148	1.638	0.167	1.519	0.171	0.096	0.031
Rostral middle frontal gyrus	2.142	0.213	2.252	0.180	2.139	0.189	2.104	0.216	0.134	0.013
Superior frontal gyrus	2.969	0.218	3.119	0.232	3.023	0.288	2.952	0.293	0.153	0.006
Insula	0.932	0.054	0.984	0.081	0.955	0.063	0.942	0.087	0.173	0.023
Banks superior temporal sulcus	0.337	0.035	0.369	0.065	0.341	0.052	0.341	0.041	0.184	0.025
Middle temporal gyrus	1.527	0.190	1.626	0.200	1.600	0.210	1.511	0.139	0.196	0.013
Lateral orbital frontal cortex	0.988	0.093	1.052	0.102	1.023	0.108	0.992	0.097	0.203	0.015
Pars opercularis	0.618	0.085	0.639	0.085	0.604	0.060	0.584	0.096	0.227	0.014
Entorhinal cortex	0.268	0.031	0.272	0.034	0.247	0.036	0.256	0.051	0.247	0.055
Cuneus cortex	0.439	0.060	0.438	0.049	0.402	0.050	0.431	0.076	0.265	0.066
Lateral occipital cortex	1.595	0.123	1.616	0.135	1.525	0.136	1.537	0.218	0.292	0.041
Paracentral lobule	0.491	0.065	0.532	0.080	0.518	0.059	0.497	0.070	0.296	0.023
Medial orbital frontal cortex	0.711	0.061	0.748	0.060	0.721	0.071	0.721	0.052	0.378	0.031
Isthmus–cingulate cortex	0.335	0.029	0.356	0.041	0.350	0.049	0.337	0.041	0.407	0.012
Frontal pole	0.121	0.019	0.133	0.021	0.125	0.027	0.126	0.013	0.461	0.023
Precentral gyrus	1.815	0.172	1.877	0.160	1.808	0.196	1.793	0.193	0.519	0.006
Fusiform gyrus	1.371	0.157	1.412	0.110	1.401	0.161	1.348	0.142	0.529	0.005
Pars triangularis	0.541	0.080	0.566	0.080	0.534	0.075	0.544	0.058	0.567	0.039
Inferior parietal cortex	1.952	0.182	2.000	0.208	1.953	0.228	1.905	0.211	0.606	0.002
Pars orbitalis	0.315	0.042	0.328	0.034	0.319	0.046	0.315	0.035	0.685	0.006
Pericalcarine cortex	0.325	0.053	0.327	0.045	0.314	0.042	0.335	0.065	0.724	0.033
Caudal middle frontal gyrus	0.843	0.107	0.878	0.126	0.886	0.107	0.875	0.161	0.725	0.058
Temporal pole	0.320	0.040	0.328	0.040	0.313	0.060	0.314	0.038	0.769	0.007
Precuneus cortex	1.375	0.125	1.399	0.139	1.395	0.142	1.358	0.112	0.784	0.004
Superior parietal cortex	1.919	0.204	1.954	0.124	1.919	0.165	1.893	0.221	0.824	0.004
Postcentral gyrus	1.362	0.141	1.360	0.106	1.327	0.161	1.363	0.142	0.842	0.050
Lingual gyrus	0.930	0.115	0.952	0.100	0.955	0.157	0.924	0.129	0.869	0.004
Inferior temporal gyrus	1.492	0.195	1.516	0.155	1.515	0.156	1.490	0.168	0.948	0.012

Bold Italics indicate significant group differences ($p < 0.05$) based on oneway ANCOVA with age as covariate, uncorrected for multiple comparisons. Main effects of group did not survive the FDR correction for any of the regions.

Note. Regions ranked from lowest to highest p-values.

ICV correction = regional volume/intracranial volume.

η_p^2 = partial eta-squared, a measure of effect size.

Supplementary Table 6. Group differences in cortical thickness derived from FreeSurfer parcellations.

	NEGATIVE		LOW		MEDIUM		HIGH		***p***	η_p^2
Desikan Region	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Pars opercularis	5.176	0.281	5.415	0.203	5.271	0.175	5.214	0.168	**0.008**	0.083
Lateral occipital cortex	4.549	0.190	4.548	0.124	4.596	0.192	4.386	0.207	**0.009**	0.129
Superior frontal gyrus	5.474	0.256	5.656	0.188	5.424	0.254	5.429	0.225	**0.013**	0.076
Medial orbital frontal cortex	4.787	0.245	5.034	0.246	4.839	0.201	4.940	0.238	**0.020**	0.132
Rostral anterior cingulate cortex	5.571	0.292	5.916	0.324	5.778	0.368	5.644	0.328	**0.022**	0.095
Banks superior temporal sulcus	5.136	0.282	5.333	0.304	5.166	0.248	5.057	0.230	**0.029**	0.049
Middle temporal gyrus	5.770	0.241	5.914	0.235	5.861	0.288	5.698	0.191	**0.043**	0.027
Supramarginal gyrus	5.231	0.244	5.359	0.185	5.283	0.191	5.162	0.225	**0.046**	0.020
Caudal middle frontal gyrus	5.142	0.298	5.323	0.185	5.096	0.250	5.155	0.253	**0.047**	0.070
Superior temporal gyrus	5.568	0.301	5.669	0.241	5.614	0.295	5.427	0.265	**0.048**	0.021
Rostral middle frontal gyrus	4.743	0.209	4.937	0.207	4.828	0.182	4.774	0.223	**0.050**	0.070
Caudal anterior-cingulate cortex	5.045	0.287	5.333	0.311	5.281	0.408	5.314	0.334	0.062	0.108
Lingual gyrus	4.123	0.223	4.207	0.153	4.276	0.352	4.085	0.112	0.077	0.066
Pars orbitalis	5.270	0.321	5.533	0.319	5.386	0.275	5.361	0.294	0.091	0.050
Isthmus–cingulate cortex	4.807	0.254	5.039	0.223	4.956	0.312	4.911	0.257	0.092	0.062
Pars triangularis	5.053	0.324	5.244	0.248	5.099	0.265	5.048	0.221	0.097	0.017
Posterior-cingulate cortex	4.988	0.224	5.167	0.284	5.068	0.301	4.972	0.255	0.123	0.016
Entorhinal cortex	6.912	0.463	7.030	0.624	6.824	0.534	6.589	0.501	0.135	0.070
Fusiform gyrus	5.391	0.353	5.553	0.143	5.528	0.329	5.381	0.210	0.140	0.027
Paracentral lobule	4.764	0.263	4.949	0.167	4.854	0.328	4.783	0.223	0.145	0.029
Inferior parietal cortex	5.148	0.248	5.262	0.162	5.176	0.225	5.110	0.185	0.179	0.011
Lateral orbital frontal cortex	5.114	0.195	5.282	0.276	5.217	0.253	5.168	0.253	0.218	0.028
Insula	6.073	0.320	6.252	0.330	6.101	0.262	6.077	0.264	0.220	0.015
Frontal pole	5.424	0.348	5.647	0.430	5.507	0.504	5.375	0.307	0.259	0.038
Inferior temporal gyrus	5.657	0.305	5.750	0.304	5.740	0.354	5.564	0.250	0.274	0.022
Precuneus cortex	4.926	0.247	5.036	0.179	4.935	0.272	4.897	0.214	0.314	0.007
Transverse temporal cortex	4.783	0.349	4.852	0.274	4.860	0.410	4.702	0.224	0.330	0.029
Postcentral gyrus	4.395	0.201	4.479	0.199	4.470	0.260	4.377	0.164	0.395	0.015
Pericalcarine cortex	3.542	0.276	3.509	0.264	3.401	0.289	3.448	0.215	0.426	0.047
Precentral gyrus	5.089	0.294	5.170	0.181	5.082	0.383	5.019	0.207	0.483	0.005
Cuneus cortex	3.927	0.265	3.948	0.199	3.878	0.298	3.836	0.206	0.573	0.020
Parahippocampal gyrus	5.642	0.527	5.531	0.371	5.696	0.472	5.587	0.384	0.683	0.091
Temporal pole	7.347	0.266	7.204	0.514	7.232	0.777	7.139	0.408	0.732	0.021
Superior parietal cortex	4.710	0.273	4.734	0.108	4.719	0.223	4.661	0.259	0.817	0.014

Bold Italics indicate significant group differences ($p < 0.05$) based on oneway ANCOVA with age as covariate, uncorrected for multiple comparisons. Main effects of group did not survive the FDR correction for any of the regions.

Note. Regions ranked from lowest to highest p-values.

η_p^2 = partial eta-squared, a measure of effect size.

Supplementary Table 7. Group differences in subcortical volumes (ICV-corrected) derived from FreeSurfer parcellations.

	NEGATIVE		LOW		MEDIUM		HIGH									
FreeSurfer Region	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***p***	η_p^2	**NEG vs. LOW**	**NEG vs. MED**	**NEG vs. HIGH**	**LOW vs. MED**	**LOW vs. HIGH**	**MED vs. HIGH**
Putamen	0.734	0.066	0.747	0.081	0.652	0.061	0.594	0.098	***0.0000002***	0.339		>	>	>	>	
Pallidum	0.213	0.019	0.212	0.029	0.192	0.026	0.160	0.031	***0.0000004***	0.359			>		>	>
Caudate	0.503	0.050	0.526	0.064	0.476	0.063	0.433	0.067	***0.00052***	0.178			>		>	
Accumbens	0.069	0.010	0.072	0.009	0.065	0.007	0.060	0.015	***0.01***	0.089					>	
Thalamus	1.123	0.089	1.170	0.128	1.086	0.099	1.113	0.136	0.0594	0.112						

Bold-Italics indicate significant group differences ($p < 0.05$) based on oneway ANCOVA with age as covariate, corrected for multiple comparisons (False Discovery Rate).
Note. Regions ranked from lowest to highest p-values.
ICV correction = regional volume/intracranial volume.
η_p^2 = partial eta-squared, a measure of effect size.