e-Appendix

Neuropathological Diagnosis.

Neuropathologic diagnoses of FTLD-Tau and FTLD-TDP were established according to consensus criteria[1] by expert neuropathologists (J.Q.T.; E.B.L.) using immunohistochemistry with established monoclonal antibodies specific for pathogenic tau (mAb PHF-1)[2] and TDP-43 (mAbs p409/410 or 171)[3], as previously reported.[4] Twenty patients had a primary FTLD-spectrum neuropathologic diagnosis at autopsy including corticobasal degeneration (CBD; N=2), PSP (N=5), Pick's disease (N=3), referred to here collectively as FTLD-Tau disorders, or FTLD with TDP-43 inclusions (N=10), designated here as FTLD-TDP. Among those individuals with neuropathological confirmation of FTLD, five also had genetic mutations (see below).

Genetic Screening.

DNA was extracted from peripheral blood or brain tissue following the manufacturer's protocols (Flexigene (Qiagen) or QuickGene DNA whole blood kit (Autogen) for blood, and QIAsymphony DNA Mini Kit (Qiagen) for brain tissue). Samples were genotyped for the *C9orf72* hexanucleotide-repeat using a modified repeat-primed polymerase-chain reaction and the *MAPT (exons 1, and 9-13), GRN* (entire coding region), and *TARDBP* genes were sequenced to identify pathogenic mutations as previously described.[4] Sequencing data was analyzed using Mutation Surveyor software (Soft Genetics, State College, PA). Genetic screening revealed that a total of 40 patients (five also with neuropathological confirmation) had a known pathogenic mutation associated with FTLD-Tau or FTLD-TDP disorders, including mutations in *MAPT* (N=7),[5] as well as *C9orf72* expansions (N=20)[6,] or mutations in the *GRN* (N=11),[7] or *TARDBP* (N=2)[8] genes, respectively.

Neuropsychological Assessment.

Letter fluency is a measure of executive control and verbal ability[9] and was assessed by the number of unique words beginning with "F" a patient was able to generate in one minute (excluding proper nouns and numbers). The MMSE is a 30-point questionnaire that evaluates global dementia severity.[10] Forward digit span, a measure of auditory-verbal short-term memory,[11] was assessed with repetition of increasingly longer sequences until the patient erred; the maximum number of digits on a correct trial was recorded. Rey figure copy, a measure of visuospatial constructional ability,[12] required patients to copy a modified Rey complex figure and was scored for accuracy on a 12-point scale. The Boston Naming Test, a measure of confrontational word retrieval, required patients to orally name 30 line drawings; the total number of correct responses made without aid of a stimulus cue was recorded.[13]

Neuroimaging Acquisition and Preprocessing.

High-resolution T1-weighted MPRAGE structural scans were acquired using a 3T Siemens Tim Trio scanner with an 8-channel head coil, with T=1620ms, T=3.09ms, flip angle=15°, 192x256 matrix, and 1mm^3 voxels. T1-weighted MRI images were then preprocessed using ANTs Cortical Thickness software.[14] Briefly, each individual dataset was deformed into a standard local template space in a canonical stereotactic coordinate system. Advanced Normalization Tools (ANTs) provides a highly accurate registration routine using symmetric and topology-preserving diffeomorphic deformations to minimize bias toward the reference space for computing the mappings and to capture the large deformation necessary to aggregate images in a

common space. Then, we used N4 bias correction to minimize heterogeneity,[15] the ANTs Atropos tool to segment images into six tissue classes (cortex, white matter, CSF, subcortical grey structures, brainstem, and cerebellum) using template-based priors and to generate probability maps of each tissue. GM probability images, the sum of the cortical, subcortical, and brainstem probability images, were then transformed into Montreal Neurological Institute (MNI) space, smoothed using a 2 sigma full-width half-maximum Gaussian kernel, and downsampled to 2mm isotropic voxels.

Post Hoc Analyses for Education and Occupation.

While our primary analyses use a CR index, we performed *post hoc* analyses to evaluate whether education and occupational attainment alone are similarly related to neuroimaging results (see Table e-2 and Figure e-2). These *post hoc* analyses largely converge with our CR index analyses: when considered separately, educational and occupational category are positively associated with GM density in right frontal cortical regions similar to results obtained when using the CR index. We also observed that each of these measures has some distinct frontal associations with GM. Educational category also positively relates to GM density in the right caudate and left premotor cortex, and occupational category also positively relates to regions in bilateral temporal cortices and in the left frontal cortex. Future work evaluating the difference between these measures would be valuable.

e-Appendix References

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Table e-1: Results of two whole-brain regression analyses examining CR index relative to whole-brain GM density in FTLD patients and in controls. We report clusters that survive a $p<0.05$ (uncorrected) threshold and cluster extent threshold of >50 adjacent voxels relative to 10,000 random permutations. Regression analysis in patients included disease duration and age at MRI as nuisance covariates, and regression analysis in healthy controls included age at MRI as a nuisance covariate.

Neuroanatomic region (BA)	**L/R**	**MNI Coordinates**			***p* value**	**Voxels**
Higher GM density associated with higher CR in FTLD:		x	y	z		
Dorsolateral Prefrontal Cortex (9)	R	34	36	38	0.001	479
Rostral Frontal Cortex (10)	R	36	42	10	0.001	455
Visual Association Cortex (18)	L	-30	-90	-10	0.001	339
Fusiform Gyrus (37)	R	60	-40	-22	0.001	296
Visual Association Cortex (19)	R	36	-88	-14	0.001	234
Orbital Frontal Cortex (47)	R	50	28	-4	0.003	195
Premotor Cortex (6)	L	-26	0	64	0.001	115
Premotor Cortex (6)	R	58	2	44	0.003	110
Supramarginal Gyrus (40)	L	-54	-40	40	0.001	106
Premotor Cortex (6)	L	-10	-106	2	0.001	90
Premotor Cortex (6)	R	28	6	56	0.001	64
Supramarginal Gyrus (40)	R	56	-40	36	0.004	61
Middle Temporal Gyrus (21)	L	-62	-24	-16	0.002	60
Cerebellum	L	-34	-86	26	0.002	59
Rostral Frontal Cortex (10)	L	-44	46	22	0.004	59
Middle Temporal Gyrus (21)	L	-64	-38	-8	0.003	54
Supramarginal Gyrus (40)	R	50	-48	44	0.004	52
Higher GM density associated with higher CR in controls:						
Posterior Cingulate Cortex (31)	L	-8	-38	-44	0.001	392
Anterior Temporal Cortex (38)	R	46	22	-30	0.001	183
Inferior Frontal Gyrus (45)	L	-56	22	12	0.001	117
Visual Association Cortex (18)	L	-4	-96	-14	0.001	107
Visual Association Cortex (18)	L	-4	-96	14	0.004	74
Primary Visual Cortex (17)	R	8	-82	8	0.005	61
Orbital Frontal Cortex (11)	R	12	34	-26	0.003	56
Primary Sensory Cortex (1)	R	64	-18	34	0.001	52

Table e-2: Results of two regression analyses showing a positive relationship between GM density and education and occupation in regions from *Analysis 1* in FTLD patients. We report clusters that survive a $p<0.05$ (uncorrected) threshold and cluster extent threshold of >50 adjacent voxels relative to 10,000 random permutations. Regression analysis in patients included disease duration and age at MRI as nuisance covariates.

Neuroanatomic region (BA)	**L/R**	**MNI Coordinates**			***p* value**	**Voxels**
Higher GM density associated with higher education in FTLD:		x	y	z		
Inferior Frontal Gyrus (44)	R	58	10	22	0.002	316
Rostral Frontal Cortex (10)	R	42	44	10	0.001	194
Orbital Frontal Cortex (47)	R	50	34	-6	0.002	146
Caudate (48)	R	12	8	10	0.005	119
Premotor Cortex (6)	L	-50	0	50	0.006	66
Higher GM density associated with higher occupation in FTLD:						
Orbital Frontal Cortex (47)	R	44	30	-14	0.001	1310
Orbital Frontal Cortex (47)	L	-40	30	-16	0.001	508
Orbital Frontal Cortex (11)	R	8	36	-24	0.001	473
Middle Temporal Gyrus (21)	R	58	-8	-16	0.002	448
Inferior Frontal Gyrus (44)	R	58	10	20	0.001	436
Rostral Frontal Cortex (10)	L	-36	56	6	0.002	262
Anterior Temporal Cortex (38)	R	30	8	-40	0.004	135
Anterior Temporal Cortex (38)	L	-32	18	-36	0.007	87
Inferior Frontal Gyrus (44)	L	-62	-18	-22	0.003	74
Dorsolateral Prefrontal Cortex (46)	L	-40	30	22	0.005	65
Orbital Frontal Cortex (11)	L	-8	40	-24	0.007	52

Figure e-1. Results of a regression analysis in healthy controls (N=90) restricted to regions of reduced GM density from *Analysis 1* (pictured in white) demonstrating that GM density in the left inferior frontal gyrus is positively associated with Cognitive Reserve (CR) index (*Analysis 2b*). Color bar represents 1—p-value with yellow representing highest significance.

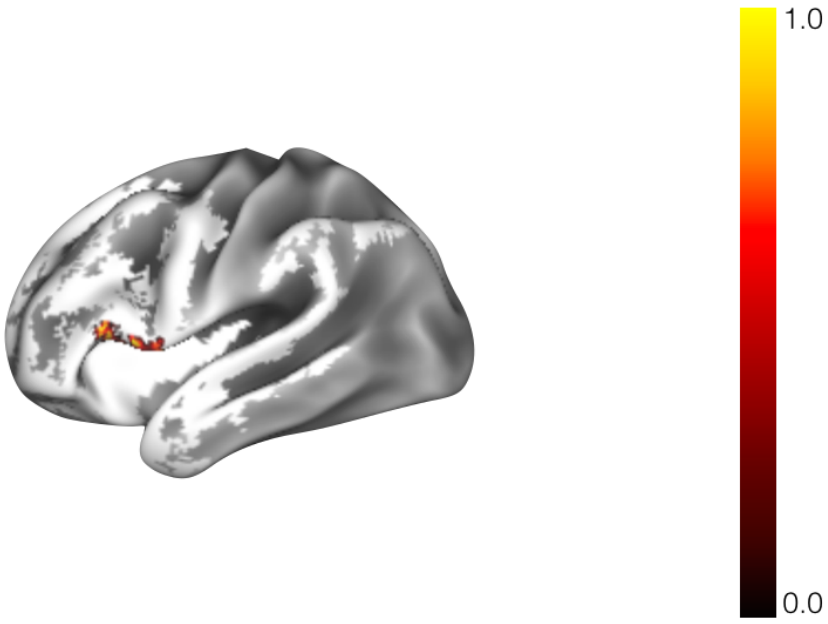

Figure e-2. Results of a regression analysis in FTLD patients (N=55) restricted to regions of reduced GM density from *Analysis 1* (pictured in white) demonstrating that when considered separately, educational category (A) and occupational category (B) each are significantly positively associated with right frontal cortex GM density, largely converging with our results using Cognitive Reserve (CR) index as a combined metric of educational and occupational category (*Post hoc Analyses*). Color bar represents 1—*p*-value with yellow representing highest significance.