APPENDIX 1

Grey matter density. T1-weighted MRI images were acquired with a Siemens 3T Trio scanner with 1-mm slice thickness and a 192 x 256 matrix using an MPRAGE protocol (TR = 1620 ms, TE = 3.87 ms, flip angle = 15°, resolution = 1 mm isotropic). We used *PipeDream* (https://sourceforge.net/projects/neuropipedream/) and Advanced Normalization Tools (ANTS, http://www.picsl.upenn.edu/ANTS/) to perform the most stable and reliable multivariate imaging normalization and structure-specific processing currently available [1, 2]. PipeDream deforms each individual dataset into a standard local template space in a canonical stereotactic coordinate system. Core processing involves mapping T1 structural MRI to a population-specific, unbiased, average-shape and -appearance image at $1mm^3$ resolution derived from a representative local population consisting of 25 healthy seniors and 25 FTD patients [3]. The algorithm begins by registering the subject image to the local template, after which the subject space can be mapped directly to MNI space by combining the subject-to-template and template-to-MNI transformations. The coordinate deformation is diffeomorphic, that is, smooth and invertible; symmetric, so that it is not biased towards the reference space for computing the mappings; and topology-preserving, to capture the large deformation necessary to aggregate images in a common space. Next, segmentation is performed in subject space using the Atropos tool in ANTS. Prior probability images for gray matter, white matter, and cerebrospinal fluid, previously defined in the local template, are warped into the subject image to guide the segmentation and compute GM probability [4]. GM probability images

were resampled to 2 mm isotropic voxels. To minimize individual gyral variations, the GM probability images were smoothed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) using a 5 mm full-width half-maximum Gaussian kernel.

In SPM8, two-sample t-tests contrasted GM density between each of the patient groups (naPPA, lvPPA, svPPA, and bvFTD) and 36 healthy controls. An explicit mask defined using a gray matter prior probability map limited the analysis to voxelwise comparisons within gray matter. For the patient groups, the analysis included all clusters surviving an FDR-corrected statistical threshold and a 50 adjacent voxel extent criterion. We roughly equated the total volume of significant atrophy identified in each of these contrasts in an attempt to minimize any bias in the analyses as a result of different numbers of participants in each group. As a consequence, the cluster-level statistical height thresholds were: naPPA = $q < 0.025$, lvPPA = $q < 0.001$, svPPA = $q < 0.0005$, and bvFTD = $q < 0.00001$. SPM8 then performed regression analyses relating markers of fluency, grammatical complexity, and lexical access to GM density, using a height threshold of $p < 0.05$ (uncorrected) and a 10-voxel extent. For each of these analyses, peak voxel thresholds were set at a Z-score > 3.09 (equivalent to $p < 0.001$) unless otherwise noted. We interpreted these regressions only in areas of reduced GM density because it is only these areas that are abnormal in patients.

White matter fractional anisotropy. Diffusion-weighted images were acquired with either a 30-directional or 12-directional acquisition sequence. The 30-directional sequence included a single-shot, spin-echo, diffusion-weighted

echo planar imaging sequence (FOV = 245 mm; matrix size = 128 × 128; number of slices = 57; voxel size = 2.2 mm isotropic; TR = 6700 ms; TE = 85 ms; fat saturation). In total, 31 volumes were acquired per subject, one without diffusion weighting (b = 0 s/mm2) and 30 with diffusion weighting (b = 1000 s/mm2) along 30 non-collinear directions (for 11 patients, an additional 4 volumes without diffusion weighting were collected). The 12-directional sequence included a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (matrix size = 128 × 128, number of slices = 40, voxel size = 3 mm isotropic; TR = 6500 ms, TE = 99 ms). In total 12 non-collinear, non-coplanar, isotropic diffusion encoding directions were acquired. All patient DTI scans were 30-directional; for the healthy seniors group, 8 were 12-directional and 28 were 30-directional. To minimize any potential bias associated with a DTI sequence, we included a nuisance covariate for DTI sequence in all patient-control DTI analyses.

Diffusion-weighted images were preprocessed using ANTS [5] and Camino [6] within the associated PipeDream (http://sourceforge.net/projects/neuropipedream/) analysis framework. Motion and distortion artifacts were removed by affine co-registration of each diffusion-weighted image to the unweighted (b=0) image. Diffusion tensors were computed using a linear least squares algorithm [7] implemented in Camino. Each participant's T1 image was warped to the template via the symmetric diffeomorphic procedure in ANTS (as above). Distortion between participants' T1 and DT images was corrected by registering the FA image to the T1 image. The DT image was then warped to template space by applying both the intra-subject

(FA to participant T1) and inter-subject (participant T1 to template) warps. Tensors were reoriented using the preservation of principal directions algorithm [8]. Reduced FA images were smoothed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) using a 4 mm full-width half-maximum Gaussian kernel to minimize individual tract variations.

DTI analyses of fractional anisotropy were performed in SPM8 using the two-samples t-test module. DTI volumes were analyzed using an explicit mask to constrain comparisons to regions of known white matter tracts and to localize results to specific probabilistically defined WM tracts [9]. Comparisons of patient groups to healthy seniors were performed at a height threshold of $q < 0.01$ (FDR-corrected) with a 200-voxel extent. For regression analyses, the full WM template was used as an explicit mask as described above. The regression module of SPM8 related markers of fluency, grammatical complexity, and lexical access to WM tracts with significantly reduced FA in the patient groups. We used a height threshold of $p < 0.005$, a peak voxel threshold of Z-score > 3.09 (equivalent to $p < 0.001$), and a 50-voxel extent.

APPENDIX 2

ANATOMIC LOCATIONS OF SIGNIFICANT GRAY MATTER ATROPHY AND REDUCED WHITE MATTER FRACTIONAL ANISOTROPY

Anatomic Locus (Brodmann Area)	MNI Coordinates			Z score	Cluster Size (voxels)
	x	y	z		
GRAY MATTER ATROPHY					
naPPA < Eld Atophy					
L prefrontal (9)	-46	20	36	4.51	359
L prefrontal (9)	-28	50	30	3.98	62
L prefrontal (8)	-40	18	48	4.46	57
L premotor (6)	-50	-12	38	4.00	65
L motor (4)	-36	-10	46	4.58	58
L anterior cingulate (24)	-2	28	18	4.19	356
L superior temporal (21)	-52	-28	-2	Inf	2600
L middle temporal (20)	-52	-4	-34	5.48	101
L parahippocampal (27)	-22	-32	-6	5.41	402
L putamen	-26	12	4	3.82	83
L caudate	-20	0	18	3.41	90
R inferior frontal (44)	38	8	26	5.28	1770
R inferior frontal (44)	52	18	18	4.26	86
R prefrontal (46)	26	46	16	4.65	69
R premotor (6)	42	-8	34	4.11	64
R anterior cingulate (6)	6	-8	50	4.85	162
R anterior cingulate (32)	10	20	38	4.34	184
R superior temporal gyrus (22)	56	-60	20	4.62	61
R parahippocampal (27)	20	-34	-4	4.79	145
R inferior parietal (40)	62	-44	24	4.49	86
lvPPA < Eld Atrophy					
L inferior frontal (44)	-50	2	18	6.01	264
L inferior frontal (45)	-40	22	24	5.65	267
L prefrontal frontal (8)	-26	14	42	5.03	75
L prefrontal frontal (46)	-44	36	24	4.90	63
L prefrontal (9)	-22	38	28	5.39	66
L anterior cingulate (32)	-12	44	12	6.58	233
L middle temporal (21)	-54	-28	0	6.86	2860
L middle temporal (21)	-64	-48	-10	5.93	205
L hippocampus	-30	-30	-4	6.57	366
L claustrum	-28	12	0	4.24	55
R inferior frontal (44)	38	8	28	5.44	102
R middle frontal (46)	42	44	6	5.10	64
R anterior cingulate (32)	12	34	24	5.44	142
R insula	30	22	8	4.64	58
R middle temporal (21)	52	-28	-2	5.64	91

svPPA < Eld Atrophy					
L fusiform (20)	-44	-16	-28	Inf	4969
L inferior temporal (20)	-66	-36	-20	6.73	202
R inferior frontal (44)	38	8	30	6.36	129
R fusiform (21)	52	-8	-28	6.57	1111
R fusiform (37)	46	-42	-20	5.73	124
R middle temporal (37)	58	-44	-14	5.62	138
R hippocampus	30	-22	-26	5.99	214
bvFTD < Eld Atrophy					
L prefrontal (9)	-48	22	36	6.90	1647
L medial frontal (11)	-30	36	-14	6.24	179
L middle temporal (21)	-52	-10	-14	6.78	94
L middle temporal (21)	-56	-24	-10	5.93	55
L middle temporal (21)	-52	-38	2	5.48	58
L putamen	-22	18	-10	5.86	267
R inferior frontal (44)	40	10	26	Inf	2509
R prefrontal (9)	6	58	36	5.97	77
R prefrontal (9)	20	26	36	7.62	120
R medial frontal (11)	10	36	-24	5.88	187
R medial frontal (11)	26	34	-16	7.28	221
R anterior cingulate (24)	2	30	20	7.33	1657
R superior temporal (22)	50	-48	16	5.52	57
R middle temporal (21)	64	-30	2	6.40	541
R inferior temporal (20)	52	-4	-28	5.36	89
R inferior parietal (40)	36	-34	36	6.13	73
R putamen	22	18	-8	6.00	410
REDUCED FRACTIONAL ANISOTROPY					
naPPA < Eld					
L inferior frontal-occipital	-33	2	-8	4.77	497
L superior longitudinal	-43	-25	30	4.65	390
L uncinate	-30	-7	-18	4.51	443
L cingulum	-5	17	26	5.41	8802
L fornix/stria terminalis	-25	-34	4	4.44	360
B corpus callosum (genu)	-1	17	1	4.02	378
B fornix	2	-7	16	5.13	508
lvPPA < Eld					
L inferior frontal-occipital	-35	2	-9	5.39	826
L inferior frontal-occipital	-27	29	8	4.05	301
L inferior longitudinal	-37	-32	-8	5.06	882
L cingulum (hippocampal)	-22	-31	-17	4.43	201
L corpus callosum (genu)	-5	19	3	4.38	317
L corpus callosum (body-middle)	-5	2	25	3.95	226

B fornix	-1	-6	16	4.76	572
svPPA < Eld					
L uncinate	-31	-1	-13	6.11	735
L inferior longitudinal	-31	-6	-18	5.58	778
L corpus callosum (genu)	-8	23	2	4.02	367
L corpus callosum (body-anterior)	-8	8	23	3.80	300
B corpus callosum (body-posterior)	3	-29	22	4.72	867
B fornix	-1	-1	8	4.59	501
bvFTD < Eld					
L superior longitudinal/corona radiata	-32	11	21	5.14	261
L cingulum (hippocampal)	-25	-27	-21	5.00	447
L cingulum (hippocampal)	-9	-50	8	4.51	633
L fornix/stria terminalis*	-23	-34	9	5.54	N/A
L corpus callosum (tapetum)*	-26	-46	18	5.28	N/A
L inferior longitudinal*	-45	-31	-13	3.76	N/A
L inferior frontal-occipital*	-23	24	-6	3.56	N/A
R fornix/stria terminalis*	31	-18	-12	5.32	N/A
R corpus callosum (tapetum)*	27	-47	18	4.90	N/A
R uncinate*	37	-3	-16	4.13	N/A
R inferior frontal-occipital*	28	9	-12	3.95	N/A
B fornix	-1	-6	16	7.49	658
B corpus callosum (body-anterior)/corona radiata	5	17	13	6.53	42320
B corpus callosum (splenium)*	7	-41	8	4.02	N/A

* indicates a subpeak of the B corpus callosum cluster at this location

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