Appendix e-1. Neuropsychological Testing

Subjects were evaluated on the MMSE(e-1) and on further tests of executive functioning, memory, and lexical access. Tests of executive functioning included the following measures: letter-guided naming fluency, a test of mental search capability in which subjects have 60 sec to name as many words as possible that begin with each of the letters F, A, and S(e-2); category naming fluency, a test of the mental planning needed to search a semantic field, in which subjects name as many different animals as they can in 60 sec(e-2); and reverse digit span, a measure of working memory involving repetition of a sequence of numbers reversing the order of presentation(e-3). Forward digit span was used as a brief test of short-term verbal memory(e-3). Lexical access was assessed by means of the Pyramids and Palm Trees test, averaged for presentation by words and pictures, a test of associative object knowledge(e-4).

Appendix e-2. Fluency Disruptions

Examples of fluency disruptions, spoken by three different lvPPA patients, are given in (1)-(3). Incomplete words are shown in italics, hesitation markers are underlined, and extraneous words are shown in boldface.

(1) DH19786
and he's on **a-** one of those things that you *sta-* stand up to get up to the top **of the, we** uh- uh in that room.

(2) JB19542
Okay, the mother **is- is** doesn't know what she's doing because it's, *g-* um going over the water and everything like that.

(3) AL19375
Uh, mother is uh washing dishes **and-** while the kids are climbing around **on-** making a *ne-* nuisance of themselves, uh with uh the, uh cookies, eh trying to get into the cookie jars.

Appendix e-3. Imaging Analysis

Gray 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 ms, flip angle = 15°, resolution = .9 × .9 × 1 mm). 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(e-5, e-6). 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(e-7). 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(e-8). GM probability images were smoothed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) using a 5mm full-width half-maximum

Gaussian kernel to minimize individual gyral variations.

In SPM8, two-sample t-tests contrasted GM density between the three PPA patient groups and 25 healthy controls. An explicit mask defined by a gray matter prior probability map in SPM8 limited the analysis to voxelwise comparisons within gray matter. For the three patient groups, the analysis included all clusters surviving a $p<.025$ height threshold (FDR corrected) and a 50 voxel-extent criterion. SPM8 then performed a regression analysis relating markers of fluency, grammatical complexity, and lexical access to GM density, using a height threshold of $p<.05$ uncorrected. We interpreted these regressions only in areas of reduced GM density because it is only these areas that are abnormal in patients. For each of these analyses, thresholds were set at a peak voxel Z-score > 3.09 (equivalent to $p<0.001$) and a 50-voxel extent.

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. 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=3mm; TR = 6500ms, TE = 99ms). In total 12 non-colinear, non-coplanar, isotropic diffusion encoding directions were acquired. Different proportions of DTI data from each sequence were available for the different subject groups. For naPPA, all 8 were 30-directional; for

lvPPA, 2 were 12-directional and 9 were 30-directional; and for svPPA, 5 were 12-directional and 6 were 30-directional. To minimize any potential bias associated with a DTI sequence, we additionally included a nuisance covariate for DTI sequence in DTI analyses for lvPPA and svPPA.

Diffusion-weighted images were preprocessed using ANTS(e-9) and Camino(e-10) 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(e-11) 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(e-12).

DTI analyses of fractional anisotropy were performed in SPM8 using the two-samples t-test module. DTI volumes were analyzed using an explicit mask in order to constrain comparisons to regions of known white matter tracts and to localize results to specific probabilistically defined WM tracts(e-13). Comparisons of patient groups relative to healthy seniors for naPPA and lvPPA used a $q<0.01$ (FDR-corrected) height threshold and a 200-voxel extent; for svPPA, we used a $p<.005$ height threshold and 200-voxel extent. For WM regressions, we used a $p<.01$ height threshold and 50-voxel extent.

Appendix e-4. Anatomic Locations of Gray Matter and White Matter Atrophy and Regressions Relating Atrophy to Language Production

Table e-1. Peak Anatomic Locations of Gray Matter Atrophy and Regressions Relating Atrophy to Speech Production in naPPA

Anatomic Locus (Brodmann Area)	MNI Coordinates			Z-score	Cluster Size (voxels)
	X	Y	Z		
naPPA Gray Matter Atrophy					
L anterior cingulate (32)	-8	44	4	4.65	200
L dorsolateral prefrontal (8)	-16	40	52	5.44	52
L orbitofrontal (47)	-56	38	0	4.27	84
L putamen	-24	14	6	4.03	153
L insula (13)	-36	8	8	5.71	2663
L superior temporal (22)	-60	-24	0	4.15	396
L superior temporal (22)	-50	-56	12	4.19	85
L inferior parietal (40)	-64	-22	18	4.6	231
L inferior parietal (40)	-56	-38	44	4.15	183
L thalamus	-20	-34	4	3.81	66
L somatosensory (3)	-30	-38	54	4.36	56
L precuneus (7)	-24	-64	62	4.45	215
R anterior cingulate (32)	22	26	36	4.23	85
R dorsolateral prefrontal (9)	42	34	34	4.1	52
R inferior frontal (44)	36	12	26	3.84	62
R inferior frontal (6)	36	-4	52	4.52	522
R claustrum	30	10	10	3.45	50
R putamen	22	2	8	3.58	64
R posterior cingulate (31)	14	-22	44	5.76	1692
R primary motor (4)	40	-24	36	4.73	66
Regression Relating Grammaticality* to Atrophy in naPPA					
L inferior frontal (6)	-30	-6	46	3.90	205
L inferior frontal (6)	-52	2	40	3.76	64
L inferior frontal (44)	-42	4	28	3.39	55
L dorsolateral prefrontal (46)	-48	38	20	3.67	150
L dorsolateral prefrontal (9)	-24	38	28	3.60	198
L insula (13)	-36	14	4	3.17	176
L middle temporal (21)	-62	-24	-10	3.14	53
Regression Relating Speech Errors per 100 Words to Atrophy in naPPA					

L anterior cingulate (32)	−14	42	4	3.26	54
L insula (13)	−38	28	6	3.35	88
R middle frontal (6)	38	10	56	4.00	78

* The Grammaticality score is the average of the Z-scores for MLU, % well-formed sentences, and proportion of dependent clauses per utterance.

Table e-2. Peak Anatomic Locations of Gray Matter Atrophy and Regressions Relating Atrophy to Speech Production in lvPPA

Anatomic Locus (Brodmann Area)	MNI Coordinates			Z-score	Cluster Size (voxels)
	X	Y	Z		
lvPPA Gray Matter Atrophy					
L dorsolateral prefrontal (46)	-40	24	24	5.45	9140
L putamen	-26	8	8	4.08	50
L caudate	-18	0	20	3.15	55
L hypothalamus	-2	-4	-12	3.84	60
L primary motor (4)	-34	-22	48	3.64	70
L hippocampus	-30	-32	-2	4.25	250
L cingulate (31)	-8	-54	30	4.76	740
L precuneus (7)	-30	-64	56	4.26	130
R dorsolateral prefrontal (46)	40	42	8	4.07	203
R dorsolateral prefrontal (8)	20	26	40	4.46	216
R dorsolateral prefrontal (9)	36	10	30	4.86	1724
R caudate	18	8	16	3.46	75
R putamen	20	4	4	3.61	55
R inferior frontal (6)	58	0	12	3.94	53
R insula (13)	48	-14	0	3.96	143
R postcentral (2)	48	-20	32	4.6	143
R thalamus	18	-34	6	3.47	52
R superior temporal (22)	46	-40	6	4.27	110
R angular gyrus (39)	52	-58	38	4.31	456
R inferior parietal (40)	62	-46	28	4.21	189
R precuneus (7)	4	-62	36	3.62	89
Regression Relating Grammaticality* to Atrophy in lvPPA					
L inferior parietal (40)	-60	-52	24	4.17	1026
Regression Relating Dysfluencies to Atrophy in lvPPA					
L superior temporal (22)	-60	-42	20	3.51	58
L angular gyrus (39)	-56	-68	18	3.58	170

* The Grammaticality score is the average of the Z-scores for MLU, % well-formed sentences, and proportion of dependent clauses per utterance.

Table e-3. Peak Anatomic Locations of Gray Matter Atrophy and Regressions Relating Atrophy to Speech Production in svPPA.

Anatomic Locus (Brodmann Area)	MNI Coordinates			Z-Score	Cluster Size (Voxels)
	X	Y	Z		
svPPA Gray Matter Atrophy					
L dorsolateral prefrontal (8)	-8	28	44	3.80	98
L dorsolateral prefrontal (46)	-40	20	22	3.71	64
L anterior cingulate (32)	-10	6	42	3.96	148
L middle temporal (21)	-56	-10	-30	5.75	9407
R temporopolar (38)	42	16	-36	3.95	286
R inferior temporal (20)	32	4	-40	3.64	183
Regression Relating Grammaticality* to Atrophy in svPPA					
L middle temporal (21)	-70	-26	-16	4.10	1667
L orbital frontal (11)	-24	28	-24	3.61	84
L inferior frontal (47)	-32	26	-8	3.58	343
Regression Relating Nouns per 100 Words to Atrophy in svPPA					
L middle temporal (21)	-62	-58	0	3.81	339
L fusiform (37)	-42	-46	-14	3.18	118
L orbital frontal (11)	-30	44	-14	3.40	73
L anterior cingulate (24)	-8	2	40	3.26	76

* The Grammaticality score is the average of the Z-scores for MLU, % well-formed sentences, and proportion of dependent clauses per utterance.

Table e-4. Peak Anatomic Locations of White Matter FA in PPA and Regressions Relating FA to Language Variables.

Neuroanatomic Region	MNI Coordinates of Peak Voxel			Z-score of Peak Voxel	Cluster Size (Voxels)
	X	Y	Z		
naPPA < Controls (FA)					
L anterior corona radiata	-18	24	18	4.39	653
L cingulum	-5	18	26	4.77	336
L cingulum	-5	-10	36	4.14	755
Genu of corpus callosum	-4	16	0	4.87	704
Genu of corpus callosum	-8	13	19	4.19	1781
R column and body of fornix	2	-4	16	4.68	490
Regression Relating Speech Sound Errors to FA in naPPA					
L anterior corona radiata	-10	28	-12	4.22	630
Body of corpus callosum	-17	-3	36	3.56	87
Body of corpus callosum	13	8	31	4.31	586
Genu of corpus callosum	9	23	12	3.23	136
R anterior corona radiata	23	32	-1	3.77	956
Regression Relating Grammaticality* to FA in naPPA					
L corona radiata	-17	-3	42	3.26	92
lvPPA < Controls (FA)					
L cingulum	-7	16	25	5.35	20685
L superior longitudinal fasciculus	-40	-15	25	3.90	215
L posterior corona radiata	-19	-50	33	4.94	265
L posterior thalamic radiation	-31	-60	3	3.50	425
Body of corpus callosum	-13	-20	29	3.59	320
Body of corpus callosum	15	-23	29	3.85	221
R column and body of fornix	2	1	8	4.51	463
Regression Relating Grammaticality* to FA in lvPPA					
L cingulum	-27	-21	-25	3.72	55
svPPA < Controls (FA)					
Body of corpus callosum	-7	16	25	3.51	971
L external capsule	-34	3	-8	3.86	681
L crus of fornix or stria terminalis	-33	-6	-19	3.62	589
L cingulum	-8	-21	33	3.53	364
Regression Relating Nouns per 100 Words to FA in svPPA					
L column and body of fornix	-1	-10	19	3.48	89

L posterior thalamic radiation	-26	-63	12	3.73	1350
Body of corpus callosum	-16	2	31	4.54	7319
Genu of corpus callosum	17	30	-2	4.18	1485
R corona radiata	19	-24	34	3.18	67

* The Grammaticality score is the average of the Z-scores for MLU, % well-formed sentences, and proportion of dependent clauses per utterance.

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