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In vivo signatures of nonfluent/agrammatic primary progressive aphasia caused by FTLD pathology

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ABSTRACT

Objective: To identify early cognitive and neuroimaging features of sporadic nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) caused by frontotemporal lobar degeneration (FTLD) subtypes.

Methods: We prospectively collected clinical, neuroimaging, and neuropathologic data in 11 patients with sporadic nfvPPA with FTLD-tau (nfvPPA-tau, n = 9) or FTLD–transactive response DNA binding protein pathology of 43 kD type A (nfvPPA-TDP, n = 2). We analyzed patterns of cognitive and gray matter (GM) and white matter (WM) atrophy at presentation in the whole group and in each pathologic subtype separately. We also considered longitudinal clinical data.

Results: At first evaluation, regardless of pathologic FTLD subtype, apraxia of speech (AOS) was the most common cognitive feature and atrophy involved the left posterior frontal lobe. Each pathologic subtype showed few distinctive features. At presentation, patients with nfvPPA-tau presented with mild to moderate AOS, mixed dysarthria with prominent hypokinetic features, clear agrammatism, and atrophy in the GM of the left posterior frontal regions and in left frontal WM. While speech and language deficits were prominent early, within 3 years of symptom onset, all patients with nfvPPA-tau developed significant extrapyramidal motor signs. At presentation, patients with nfvPPA-TDP had severe AOS, dysarthria with spastic features, mild agrammatism, and atrophy in left posterior frontal GM only. Selective mutism occurred early, when general neurologic examination only showed mild decrease in finger dexterity in the right hand.

Conclusions: Clinical features in sporadic nfvPPA caused by FTLD subtypes relate to neurodegeneration of GM and WM in frontal motor speech and language networks. We propose that early WM atrophy in nfvPPA is suggestive of FTLD-tau pathology while early selective GM loss might be indicative of FTLD-TDP. *Neurology*® 2014;82:239–247

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GLOSSARY

AOS = apraxia of speech; **CBD** = corticobasal degeneration; **DTI** = diffusion tensor imaging; **4R** = 4 repeat; **FTD** = frontotemporal dementia; **FTLD** = frontotemporal lobar degeneration; **FWE** = familywise error; **GM** = gray matter; **IFG-po** = pars opercularis of the inferior frontal gyrus; **MAC** = Memory and Aging Center; **nfvPPA** = nonfluent variant of primary progressive aphasia; **PSP** = progressive supranuclear palsy; **SLF** = superior longitudinal fasciculus; **SMA** = supplementary motor area; **TDP** = transactive response DNA binding protein of 43 kD type A; **UCSF** = University of California, San Francisco; **VBM** = voxel-based morphometry; **WM** = white matter.

The nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA)[1,2] falls under the umbrella of clinical syndromes caused by frontotemporal lobar degeneration (FTLD) pathology.[3–5] The major molecular classes of FTLD associated with nfvPPA are microtubule-associated protein tau (either 3 repeat [3R] or 4 repeat [4R])[5,6] (FTLD-tau) and transactive response DNA binding protein of 43 kD (TDP-43) type A (TDP-A)[7] (FTLD-TDP).[8,9]

Several studies have evaluated speech and language, and/or anatomical data, in pathologically confirmed cases of nfvPPA.[9–13] However, studies including complete datasets of prospectively collected cognitive, neuroimaging, and pathologic data are still scarce. Furthermore, the distinctive features characterizing sporadic nfvPPA caused by different FTLD pathologic subtypes

Supplemental data at www.neurology.org

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are still not established. Some authors have proposed that agrammatism might be a marker for FTLD-TDP pathology,[12] whereas motor speech deficits would be more typical of FTLD-tau.[14] Pathologic and neuroimaging evidence in a variety of frontotemporal dementia (FTD)-spectrum disorders suggests that greater white matter (WM) than gray matter (GM) changes might be characteristic of the FTLD-tau subtype.[15–17]

Here, we present a prospective cognitive and neuroimaging study of 11 patients with nfvPPA with sporadic disease and pathologically confirmed FTLD-tau (nfvPPA-tau) or FTLD–TDP-A (nfvPPA-TDP). The aim of the study was to identify antemortem clinical and neuroimaging features suggestive of each FTLD pathologic subtype in this comprehensively characterized, homogeneous clinical group.

METHODS

Subjects. We recruited 11 subjects (7 women, mean age 68.5 ± 7.6 years) diagnosed with nfvPPA at the University of California at San Francisco (UCSF) Memory and Aging Center (MAC) (table 1). Inclusion criteria involved clinical diagnosis based on current criteria,[18] the availability of speech and language and cognitive testing, an MRI scan within 6 months of first visit to the UCSF MAC, and postmortem pathologic FTLD diagnosis. Exclusion criteria included family history for dominantly inherited FTD or dementia at an early age of onset, and the presence of a known genetic mutation.

We followed patients for an average of 4.5 years and evaluated trajectories of clinical progression by considering data from longitudinal neurologic examinations.

Cognitive testing. Cognitive functioning at presentation was assessed using the UCSF neuropsychological and speech and language batteries described elsewhere[2,19] (appendix e-1 on the *Neurology*® Web site at www.neurology.org).

Cognitive data from 10 age-matched, right-handed healthy subjects (3 men, mean age 70.1 ± 6.6 years) were used as control for the cognitive analysis. We compared cognitive scores between subjects with nfvPPA and controls at presentation using the Kruskal-Wallis and Mann-Whitney *U* tests (table 1). Furthermore, each patient's scores on speech and language tests were transformed into standardized *z* scores (table 2).

Neuropathology. Autopsies were performed at UCSF (n = 7), University of Pennsylvania (cases 1, 3, and 5), and Vancouver General Hospital (case 7) (table 3). Pathologic diagnosis was based on consensus criteria for FTLD[20] and Alzheimer disease[21] following standard procedures described elsewhere.[22] Nine patients

Table 1 Demographic and cognitive data in nfvPPA groups vs controls at presentation

	All nfvPPA	nfvPPA-tau	nfvPPA-TDP	Controls
Demographic				
Sex, n, M/F	4/7	4/5	0/2	3/7
Handedness, n, R/L	11/0	9/0	2/0	10/0
Education, y	15.5 ± 3.2	15.5 ± 3.3	15.5 ± 4.9	17.6 ± 2.2
Illness duration, y	3.2 ± 1.1	3.2 ± 1.3	3 ± 0	NA
Age at onset, y	65.6 ± 7.8	65.7 ± 9.1	65 ± 2.8	NA
Age at evaluation, y	68.7 ± 7.6	68.6 ± 8.7	69 ± 4.2	70.1 ± 6.6
Survival, y	7.5 ± 1.7	6.8 ± 1	10.5 ± 0.7	NA
General functioning and cognition				
MMSE	24.5 ± 4.5[a]	24.4 ± 5.1[a]	25 ± 4.24[a]	29.7 ± 0.7
CDR total	0.3 ± 0.2[a]	0.3 ± 0.25[a]	0.5 ± 0[a]	0
GDS	8.1 ± 5.7[a]	7.6 ± 5.1[a]	10 ± 9.9[a]	3.6 ± 3.5
NPI	9.4 ± 9.3[a]	10.5 ± 10.6[a]	5 ± 7.1[a]	0
Benson Figure Copy	14.8 ± 1.9	14.7 ± 2.1	15.5 ± 2.1	16.1 ± 1.4
Benson Figure Recall	10.4 ± 3.5	10.5 ± 4.1	10 ± 0	12.6 ± 3.7
CVLT-MS 10′-FR	6.1 ± 1.8	5.5 ± 1.6[a]	8.5 ± 0.7	7.7 ± 1.4
Digits Backward	2.6 ± 1.4[a]	2.7 ± 1.4[a]	3.5 ± 0.7	5.4 ± 1.3
Modified trails (lines per min)	9.9 ± 9.4[a]	7.6 ± 7.4[a]	22.9 ± 5.5[a]	34.2 ± 16
Calculation	4.2 ± 1.2	4 ± 1.3	5 ± 0	4.9 ± 0.3

Abbreviations: CDR = Clinical Dementia Rating; CVLT-MS 10′-FR = California Verbal Learning Test–Mental Status 10 minutes free recall; GDS = Geriatric Dementia Scale; MMSE = Mini-Mental State Examination; NA = not applicable; nfvPPA = nonfluent variant of primary progressive aphasia; NPI = Neuropsychiatric Inventory; TDP = transactive response DNA binding protein of 43 kD type A.
Values are mean ± SD unless marked otherwise. Illness duration is defined as years from onset to first visit. Survival is defined as years from onset to death.
[a] $p < 0.05$ vs controls.

Table 2 Summary of language scores at first evaluation in each patient with nfvPPA

	Pathologic group										
	nfvPPA-tau									nfvPPA-TDP	
	1	2	3	4	5	6	7	8	9	10	11
MMSE	28	26	28	28	27	23	20	27	13	22[a]	28
CDR	0.5	0	0	0.5	0.5	0.5	0.5	0	0.5	0.5	0
Language and speech											
Boston Naming Test (15)	13[b]	11[b]	15	12[b]	11[b]	14	11[b]	15	7[b]	15[a]	13[b]
Phonemic fluency (D words)	2[b]	2[b]	9	5[b]	5[b]	3[b]	1[b]	4[b]	0[b]	0[b]	7[b]
Semantic fluency (animals)	7[b]	6[b]	13[b]	11[b]	12[b]	9[b]	4[b]	7[b]	1[b]	0[b]	12[b]
Speech fluency (WAB, 10)	6	9	9	10	5	9	4	9	3	0	NA
Agrammatism in production[c]	−	+	−	+	+	+	+	+	+	+	−
AOS (MSE, 7)	4	4	2	1	1	2	1	2	1	7	4
Dysarthria rating (MSE, 7)	7	5	0	0	2	3	0	0	6	NA	4
Repetition (WAB, 100)	52[b]	86[b]	88[b]	96[b]	67[b]	88[b]	96[b]	97[b]	53[b]	NA	100
Word recognition (WAB, 60)	60	60	60	60	60	60	55[b]	60	60	60	60
Sequential commands (WAB, 80)	69[b]	72[b]	67[b]	72[b]	68[b]	80	49[b]	63[b]	63[b]	70[b]	80
Syntactic comprehension (CYCLE, 55)	44[b]	45[b]	45[b]	52	41[b]	51[b]	36[b]	37[b]	NA	53	53
PPT (52)	52	50	51	49	51	51	NA	NA	34[b]	49	51

Abbreviations: AOS = apraxia of speech; CDR = Clinical Dementia Rating; CYCLE = Curtiss-Yamada Comprehensive Language Evaluation; MMSE = Mini-Mental State Examination; MSE = Motor Speech Evaluation; NA = not applicable; nfvPPA = nonfluent variant of primary progressive aphasia; PPT = Pyramid and Palm Trees Test-3 pictures; TDP = transactive response DNA binding protein of 43 kD type A; WAB = Western Aphasia Battery.
[a] Written responses are allowed.
[b] Abnormal scores in reference to control group data (2 SD below) when applicable.
[c] + = present; − = absent.

with nfvPPA had FTLD-tau, and 2 had FTLD-TDP pathology. Among the FTLD-tau group, 2 had progressive supranuclear palsy (PSP) (cases 1 and 2), 6 had corticobasal degeneration (CBD) (cases 3–8), and one had an unclassifiable 4R tauopathy (case 9). Both TDP cases (cases 10 and 11) were classified as TDP-A.

MRI acquisition and analysis. All images were acquired on a 1.5T Siemens Magnetom VISION system (Siemens, Iselin, NJ) using a magnetization-prepared rapid gradient echo sequence.[2]

We used voxel-based morphometry (VBM)[23] in SPM8 (Statistical Parametric Mapping; Wellcome Department of Imaging

Table 3 Findings on neurologic examination at first and last visits at the UCSF MAC and language deficits in the nfvPPA cohort

Case (pathology)	Neurologic examination at first visit (2.8 ± 1.2 y from onset)	Neurologic examination at last visit (2.4 ± 2 y to death)
1 (PSP)	+ EMA; + R limb Ri	+++ EMA; +++ R limb Ri; ++ axial Ri; ++ R hand dystonia; +++ gait and balance
2 (PSP)	+ EMA; + R limb Ri	+++ EMA; +++ R limb Ri; ++ axial Ri; ++ R hand dystonia; +++ gait and balance
3 (CBD)	Unremarkable	+++ EMA; +++ R limb Ri; ++ axial Ri; ++ R hand dystonia; ++ R alien limb phenomenon; +++ gait and balance; R visual hemineglect
4 (CBD)	Unremarkable	++ EMA; +++ R limb Ri; +++ gait and balance; R visual hemineglect
5 (CBD)	Unremarkable	+ R arm Ri
6 (CBD)	+ R arm Ri	++ R arm Ri; ++ R hand dystonia
7 (CBD)	Unremarkable	+++ R limb Ri; +++ R arm dystonia; +++ gait and balance
8 (CBD)	Unremarkable	+ Gait and balance; + swallowing difficulties
9 (4R-unclassifiable tauopathy)	Unremarkable	+ Masked face, + EMA, ++ R > L arm Ri; + R > L arm bradykinesia; + R arm myoclonus
10 (TDP-A)	Unremarkable	++ R arm Ri; + gait and balance; ++ swallowing difficulties
11 (TDP-A)	Unremarkable	+ R limb Ri; +++ swallowing difficulties

Abbreviations: CBD = corticobasal degeneration; EMA = extraocular movement abnormalities; 4R = 4-repeat; MAC = Memory and Aging Center; nfvPPA = nonfluent variant of primary progressive aphasia; PSP = progressive supranuclear palsy; Ri = rigidity; TDP-A = transactive response DNA binding protein type A; UCSF = University of California, San Francisco.
Mild (+), moderate (++), severe (+++).

Neuroscience, London, UK) to investigate volume differences in GM and WM using standard methods.[24,25] The VBM control group included 53 age- and sex-matched, right-handed healthy subjects (16 men, mean age 68.5 ± 8.6 years).

Statistical analyses first compared all 11 cases of nfvPPA with controls. We then separated the nfvPPA-tau (n = 9) from the nfvPPA-TDP (n = 2) cases and compared each pathologic subtype with controls.

We accepted a level of significance of $p < 0.05$, corrected for familywise error (FWE). Subsequently, VBM results were tested at $p < 0.001$, uncorrected, to avoid false negatives that can occur in single-subject or small-group VBM analyses.

We applied the Montreal Neurological Institute coordinate system for GM atrophy localization, and attempted attribution of WM volume loss to the main fasciculi using the JHU-MNI-ss atlas (http://cmrm.med.jhmi.edu).

Standard protocol approvals, registrations, and patient consents. All participants gave written informed consent, and the study was approved by the Committee on Human Research at UCSF.

RESULTS

Demographic data. All nfvPPA cases (7 women and 4 men) were right-handed with at least a high school level of education (12 years) (table 1). No significant differences were found between subjects with nfvPPA-tau and those with nfvPPA-TDP for age at onset, illness duration (years from symptom onset to first neurologic evaluation), or education.

Cognitive findings. ***All nfvPPA-FTLD.*** At first visit, the whole nfvPPA group showed a neuropsychological profile (table 1) consistent with previous reports using the same battery.[2] Symptoms of apraxia of speech (AOS) and/or dysarthria were present in all patients with nfvPPA. Clear agrammatism in production or comprehension was detected in all nfvPPA-tau and in one of the 2 nfvPPA-TDP cases (table 3). Case 11 was the only patient who did not show clear grammatical deficits at presentation but developed some difficulties 6 months later. In this cohort, agrammatism never occurred in isolation, without motor speech impairment. Case 7 (CBD), previously described because of her artistic talent,[26] was the only patient who showed mild AOS but severe agrammatism, with production limited to single words. Further details and evolution of language symptoms are discussed below.

nfvPPA-tau. All nfvPPA-tau cases presented with varying degrees of motor speech impairment (table 2) consistent with either isolated AOS (4 CBD cases) or mixed AOS and dysarthria (2 CBD + 2 PSP + 1 unclassifiable 4R tauopathy). Speech was characterized by slowed rate, delayed initiation, prosodic insufficiency, and frequent pauses, with increased intra- and intersegment duration. Patients with nfvPPA-tau showed visible groping, especially on syllable-initial consonant clusters, and sequencing errors that were particularly evident on multiple repetitions of multisyllabic words. Motor speech evaluations revealed the presence of both sound distortions (including prolongations, particularly for consonants) and phonemic errors (including sound substitutions, i.e., "g*l*ass" for "grass" and insertions "pi*nknic*" for "picnic").

Dysarthria presented with mixed prominent hypokinetic (monopitch, reduced stress, monoloudness, inappropriate silence, and speech festination) and spastic features (strained, harsh vocal quality, hypernasality, bursts of loudness, low pitch, slowed rate, and imprecise articulation). Furthermore, 5 patients with nfvPPA-tau showed mild buccofacial apraxia at first visit.

At presentation, agrammatism in production was detected in 7 of 9 patients with nfvPPA-tau. The 2 patients who did not have initially detectable agrammatic errors in language production nevertheless showed impaired comprehension of syntactically complex sentences. Later in the disease course, both patients developed agrammatism in oral and written samples. All patients with nfvPPA-tau presented with various degree of impairment in comprehension of syntactically complex sentences.

Over the course of their disease, all patients with nfvPPA-tau developed buccofacial apraxia that gradually worsened over time. They remained able to execute simple mouth movements on command until very late in the disease course. Performance on single-word comprehension and semantic tasks remained relatively spared.

nfvPPA-TDP. The 2 nfvPPA-TDP cases showed the most severe speech output deficits (table 3) and buccofacial apraxia that led to mutism without any extrapyramidal motor deficits affecting everyday life. Below we report their detailed clinical features.

One patient, case 10, was first seen at the Alzheimer's Disease Center of the Northwestern University Feinberg School of Medicine reporting 2 years of progressive language output difficulties. She was then diagnosed as having PPA with moderately severe motor speech impairment and mild agrammatism. Speech was characterized by slow rate, sequencing errors, and distortions suggestive of AOS. She also showed features of spastic dysarthria, such as weak and hoarse voice. Minor grammatical difficulties were observed on written samples. Comprehension of syntactically complex statements was also impaired. In subsequent months, speech continued to deteriorate and at her first language evaluation at the UCSF MAC (approximately 1 year later and 3 years after onset) she was functionally mute (table 3). She could only produce a few sounds and answer yes or no with great effort. Dysarthria could no longer be classified because of insufficient production, but the patient's voice was clearly weak and hypernasal. Written production was much more preserved than spoken output but few agrammatic errors were detected.

Comprehension of syntactically complex sentences was impaired but lexical retrieval abilities, semantic memory, and single-word comprehension were spared. At 1-year follow-up, she was unable to produce any speech sounds, despite other cognitive and language domains being unchanged. Buccofacial apraxia had worsened to the point that the only movement she could perform on command was to open her mouth. She reported some swallowing difficulties. EMG was performed and found to be negative.

Case 11 had a comparable history. At presentation, she was 66 years old and reported a 3-year history of speech output difficulties. At her first language evaluation (table 3), she showed moderate AOS and her voice was soft and hypernasal, consistent with moderate spastic dysarthria. At that point, she did not show clear signs of agrammatism in spoken or written language, although her written picture description was short and simple. Syntactic comprehension was spared. At the 1-year follow-up visit, she was functionally mute, producing only a few sounds, which were weak and hypernasal. The speech pathologist who examined her defined her deficit as "apraxia of phonation." At that time, mild grammatical deficits appeared in writing and in sentence comprehension; single-word comprehension, confrontation naming, and semantic memory remained relatively spared. As in case 10, buccofacial apraxia became severe and she was unable to perform even simple mouth movements or cough on command or imitation. She reported loss of sensation in the lips and tongue and mild swallowing problems. EMG results were negative. At the last evaluation, when she was aphonic, general motor deficits were mild and she was still able to dance with her husband. She became progressively unable to swallow and in the last year of disease, a feeding tube was placed.

General cognitive evaluation was nonstandard because of severe motor speech deficits, but both patients appeared relatively spared in all domains.

Neurologic examination at presentation and follow-up. By definition, all patients with nfvPPA showed early, isolated speech or language difficulties that were the only cause of limitation of daily living activities. The review of longitudinal neurologic evaluations revealed that, during the disease course, all patients developed various degrees of motor impairment (table 3), as previously reported for FTD-spectrum disorders.[27,28] However, the trajectory appeared different in the 2 nfvPPA-FTLD subtypes. At first visit, 3 nfvPPA-tau cases (cases 1, 2, and 6) showed mild extrapyramidal motor signs on neurologic examination only, with no subjective complaints or functional impact (table 3). All patients with nfvPPA-tau developed a moderate to severe extrapyramidal syndrome within a mean of 3 years from (language) symptom onset. Five subjects with nfvPPA-tau (cases 1–4 and 7) were wheelchair-bound approximately 5 years after (language) symptom onset.

The nfvPPA-TDP cases did not show extrapyramidal motor signs at first evaluation, despite having moderate to severe motor speech deficits (table 2). They developed early mutism, when general neurologic examination still only showed decreased finger dexterity in the right hand. Extrapyramidal signs remained mild for most of the disease course. At last evaluation before death (8 years from language symptom onset), case 10 showed moderate right limb rigidity and needed some assistance in walking, and case 11 was still able to walk autonomously and dance with her husband 6 years from the onset of language symptoms.

Mean survival (years from onset to death) of the entire nfvPPA group was 7.5 years. Patients with nfvPPA-TDP lived almost 3 years longer than those in the nfvPPA-tau group.

Neuroimaging. ***All nfvPPA-FTLD vs controls.*** VBM analysis revealed GM atrophy in patients with nfvPPA-FTLD along left motor and premotor cortices, including precentral gyrus, superior frontal gyrus, middle frontal gyrus, pars opercularis of the inferior frontal gyrus (IFG-po), supplementary motor area (SMA), dorsal anterior insula, and basal ganglia ($p < 0.05$, FWE).

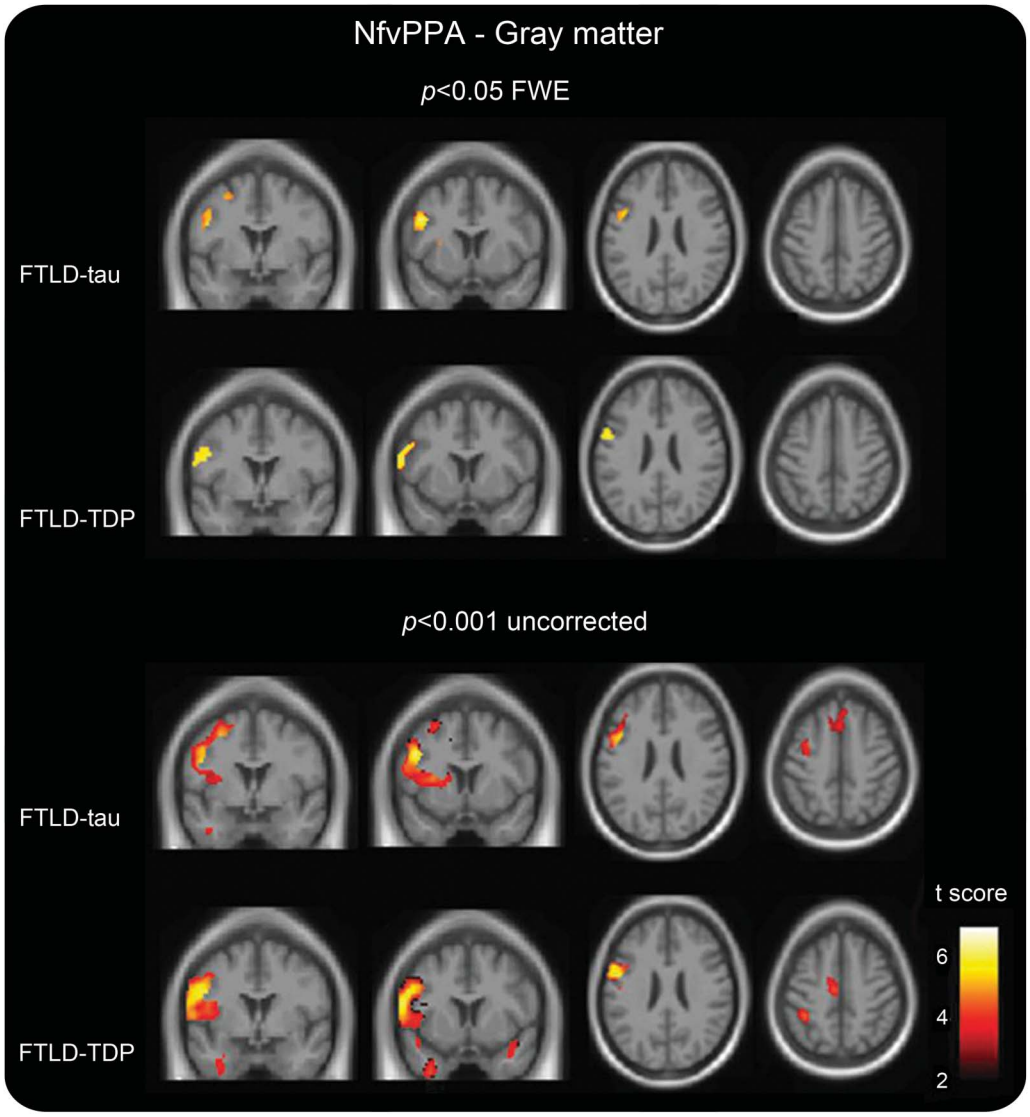
WM atrophy was extensive within the left frontal lobe. The JHU-MNI-ss atlas placed the atrophy in the superior longitudinal fasciculus (SLF), corona radiata, and the body of the corpus callosum ($p < 0.05$, FWE). At an uncorrected threshold, WM atrophy was also detected in the right frontal region and left brainstem, likely the cerebral peduncle (figure e-1).

nfvPPA-tau vs controls. Subjects with nfvPPA-tau showed GM atrophy in the left premotor cortex, comprising the precentral gyrus, IFG-po, superior frontal gyrus, middle frontal gyrus, and putamen (figure 1, table e-1). At an uncorrected threshold, the left SMA, middle cingulate cortex, dorsal anterior insula, and caudate were also involved.

WM atrophy was severe in subjects with nfvPPA-tau and mirrored the pattern of the entire group (figure 2), including part of the SLF, corona radiata, and the body of the corpus callosum ($p < 0.05$, FWE). At an uncorrected threshold, WM atrophy was also detected contralaterally and in the left brainstem.

nfvPPA-TDP vs controls. GM atrophy was found in the left posterior, inferior frontal area, including IFG-po and the posterior part of precentral gyrus, in the face, mouth, and pharyngeal motor representations

Figure 1 Gray matter atrophy in nfvPPA pathologic subtypes vs controls



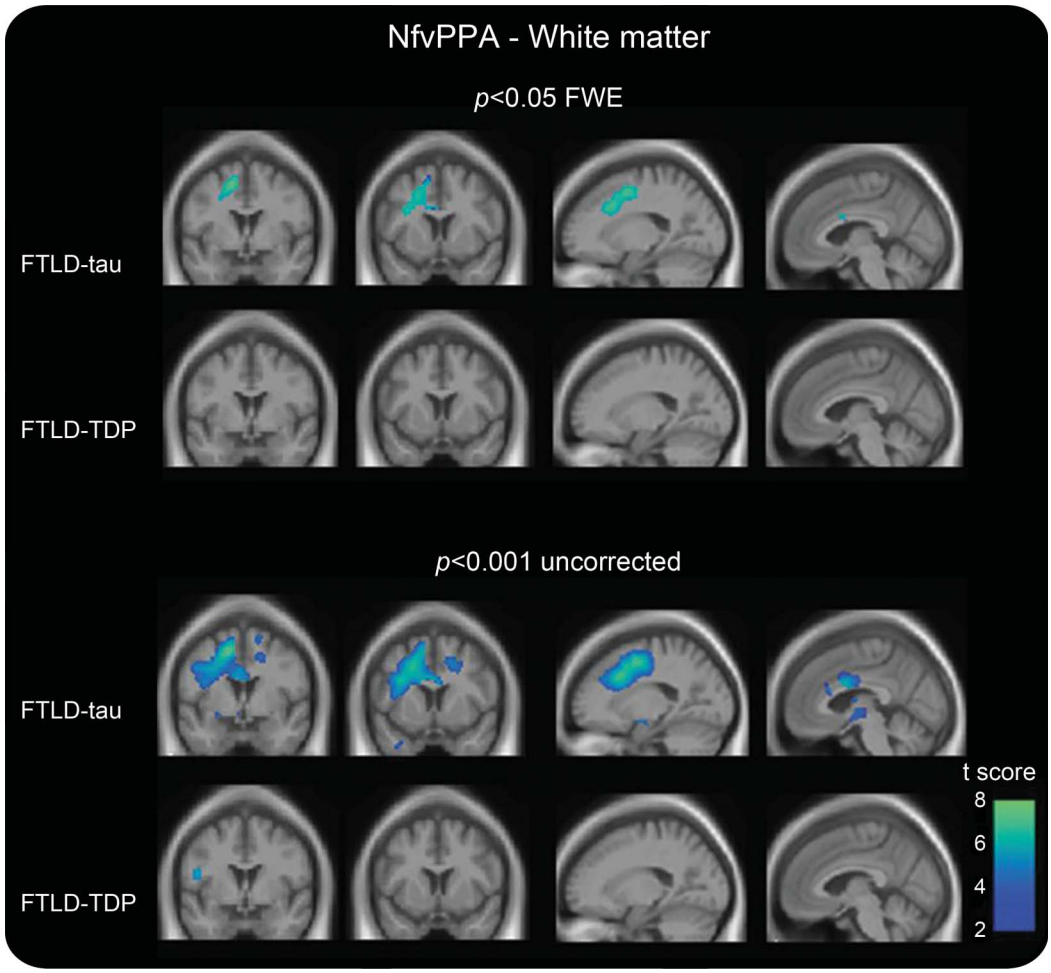
Voxel-based morphometric analysis on gray matter regions in nfvPPA pathologic subtypes relative to healthy controls. Statistical maps have been thresholded at $p < 0.05$ for FWE (top) and at $p < 0.001$ uncorrected (bottom). Statistical maps have shown in the coronal (coordinates [mm]: +0, +8) and axial (coordinates [mm]: +24, +48) sections of a T1-weighted MRI template image in DARTEL space. The color bar (hot) represents the *t* score. DARTEL = diffeomorphic anatomical registration through exponentiated lie; FTLD = frontotemporal lobar degeneration; FWE = familywise error; nfvPPA = nonfluent variant of primary progressive aphasia; TDP = transactive response DNA binding protein of 43 kD type A.

($p < 0.05$; figure 1, table e-1). At $p < 0.001$ uncorrected, atrophy included the posterior part of the left SMA, insula, middle cingulum, bilateral inferior parietal lobule (IPL), and inferior temporal and right supramarginal gyri.

The nfvPPA-TDP cases did not show WM atrophy at $p < 0.05$ FWE (figure 2). Even at an uncorrected threshold, only a small area in the left frontal region was detected, suggesting that the WM atrophy seen in the overall nfvPPA-FTLD group derived from the nfvPPA-tau cases.

DISCUSSION We report clinical, cognitive, and neuroimaging findings in a cohort of patients with sporadic nfvPPA with autopsy-confirmed FTLD-tau or FTLD–TDP-A pathology. The aim of the study was to identify early clinical and neuroimaging nfvPPA features associated with each molecular FTLD subtype. Our data show that AOS is the most frequent manifestation of nfvPPA caused by both FTLD-tau and -TDP pathology. Distinctive features of nfvPPA-TDP cases included early mutism with severe buccofacial apraxia, spastic dysarthria, and selective inferior frontal GM atrophy with relative sparing of WM. Typical nvfPPA-tau features included extensive frontal WM damage, early mixed dysarthria with prominent hypokinetic features, and later development of significant extrapyramidal

Figure 2 White matter atrophy in nfvPPA pathologic subtypes vs controls



Voxel-based morphometric analysis on white matter regions in nfvPPA pathologic subtypes relative to healthy controls. Statistical maps have been thresholded at $p < 0.05$ for FWE (top) and at $p < 0.001$ uncorrected (bottom). Statistical maps have shown in the coronal (coordinates [mm]: +0, +8) and sagittal (coordinates [mm]: −18, −4) sections of a T1-weighted MRI template image in DARTEL space. The color bar (winter) represents the *t* score. DARTEL = diffeomorphic anatomical registration through exponentiated lie; FTLD = frontotemporal lobar degeneration; FWE = familywise error; nfvPPA = nonfluent variant of primary progressive aphasia; TDP = transactive response DNA binding protein of 43 kD type A.

motor signs. We propose that earlier and greater WM damage in nfvPPA-tau could explain the subtle distinctions between the clinical manifestations of nfvPPA-tau and -TDP.

AOS is a disorder characterized by an impaired ability to coordinate articulatory movements. It can occur in isolation without other speech, language, or movement deficits and is associated with damage in the left inferior frontal/insular region. AOS has been previously reported as a common clinical feature in nfvPPA.[2,11] Our findings suggest that it is associated with both FTLD-tau and -TDP, likely in relation to left inferior frontal atrophy, which is common to both pathologic subtypes.

Previous studies have shown significant WM damage in patients with clinically diagnosed nfvPPA.[29–31] One recent diffusion tensor imaging (DTI)-MRI study revealed WM damage in an nfvPPA cohort including patients with FTLD-tau pathology or non-Alzheimer CSF biomarkers.[13] We suggest that in nfvPPA-tau, early GM and WM degeneration produces a network-level dysfunction in both motor speech and language systems. GM degeneration of cortical regions and disconnection between cortical and basal ganglia motor control systems would result in AOS and hypokinetic dysarthria first[32,33] and, later in the disease course, in the development of a generalized extrapyramidal motor syndrome. GM damage in more anterior portions of the IFG and disconnection between frontal and temporal language areas caused by pathology in the SLF[32] could instead result in early grammatical deficits.

By contrast, at presentation, patients with nfvPPA-TDP showed atrophy only in the GM of the left inferior motor and premotor regions without significant WM involvement. The early clinical

features of nfvPPA-TDP might thus be related to focal damage to these specific cortical hubs rather than to a network-level dysfunction. Both patients showed severe AOS, spastic dysarthric features, and severe buccofacial apraxia, as previously shown in patients with focal lesions of the inferior frontal region.[34,35] Agrammatism was present but mild, possibly because damage to a single cortical hub within the distributed grammar network is not sufficient to cause severe deficits.[36] Similarly, patients with nfvPPA-TDP did not show dysarthric features typical of subcortical damage, nor development of a prominent general extrapyramidal syndrome, even later in the disease, if not very close to death. This nfvPPA-TDP clinical picture resembles an upper motor neuron variant of amyotrophic lateral sclerosis, with which the nfvPPA variant shares common TDP-related pathology.[9]

Biological features of FTLD-tau and -TDP molecules support our neuroimaging findings. The widespread WM damage in patients with FTLD-tau early in the disease is consistent with the hypothesis that tau deposition might primarily affect the axon, with retrograde GM degeneration, as suggested by previous studies in animal models.[37,38] Pathology could then spread in a "prion-like" manner[39] along connected networks,[40] in our case those related to motor and language functions. In contrast, TDP-43 is a nuclear protein[7] that is redistributed from the nucleus to the cytoplasm and dendritic processes during neurodegeneration. However, despite these differences in cellular pathogenesis, caution should be used in this interpretation because GM and WM are both heavily involved in FTLD-tau and FTLD-TDP in late-stage disease, when pathologic analysis occurs.

This study has some clear limitations. First, the patient group was small, reflecting the rarity of the disease and our strict inclusion criteria. We believe that the strengths of our study are the selection of a homogeneous patient cohort and the extensive clinical characterization. Specific hypotheses based on such detailed assessment of a small cohort can eventually be tested in larger, less extensively studied patient cohorts. The second limitation is that DTI data were not available. Nevertheless, VBM proved sensitive for detecting WM atrophy in the FTLD-tau group and GM damage in both groups, consistent with recent DTI findings in a more heterogeneous clinical population. We do believe that DTI could enable even earlier detection of WM damage in FTLD.

Our results suggest that AOS and agrammatism are not distinctive features of an underlying FTLD-tau or FTLD–TDP-A pathology. Early WM damage on neuroimaging might provide a biomarker for FTLD-tau pathology in the nfvPPA syndrome and might be associated with subtle differential clinical features.

Because future treatments will be directed toward specific molecules, predicting pathology in nfvPPA is an increasingly important endeavor.

AUTHOR CONTRIBUTIONS

Francesca Caso: study concept and design, acquisition of data, drafting/revising the manuscript for content, analysis or interpretation of data, statistical analysis. Maria Luisa Mandelli: acquisition of data, drafting/revising the manuscript for content, statistical analysis. Maya Henry: acquisition and analysis of data, drafting/revising the manuscript for content. Benno Gesierich: acquisition and analysis of data, revising the manuscript for content. Brianne M. Bettcher: acquisition and analysis of data, drafting/revising the manuscript for content. Jennifer Ogar: acquisition and analysis of data, revising the manuscript for content. Massimo Filippi: drafting/revising the manuscript for content. Giancarlo Comi and Giuseppe Magnani: revising the manuscript for content. Manu Sidhu, John Q. Trojanowski, Eric J. Huang, and Lea T. Grinberg: acquisition and analysis of data, revising the manuscript for content. Bruce L. Miller: acquisition of data, drafting/revising the manuscript for content. Nina Dronkers: acquisition and analysis of data, revising the manuscript for content. William W. Seeley: acquisition and analysis of data, drafting/revising the manuscript for content. Maria Luisa Gorno-Tempini: study concept and design, revising the manuscript for content, analysis or interpretation of data, study supervision or coordination, obtaining funding.

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