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DISRUPTION OF LARGE-SCALE NEURAL NETWORKS IN NON-FLUENT/AGRAMMATIC VARIANT PRIMARY PROGRESSIVE APHASIA ASSOCIATED WITH FRONTOTEMPORAL DEGENERATION PATHOLOGY

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Abstract

Non-fluent/agrammatic primary progressive aphasia (naPPA) is a progressive neurodegenerative condition most prominently associated with slowed, effortful speech. A clinical imaging marker of naPPA is disease centered in the left inferior frontal lobe. We used multimodal imaging to assess large-scale neural networks underlying effortful expression in 15 patients with sporadic naPPA due to frontotemporal lobar degeneration (FTLD) spectrum pathology. Effortful speech in these patients is related in part to impaired grammatical processing, and to phonologic speech errors. Gray matter (GM) imaging shows frontal and anterior-superior temporal atrophy, most prominently in the left hemisphere. Diffusion tensor imaging reveals reduced fractional anisotropy in several white matter (WM) tracts mediating projections between left frontal and other GM regions. Regression analyses suggest disruption of three large-scale GM-WM neural networks in naPPA that support fluent, grammatical expression. These findings emphasize the role of large-scale neural networks in language, and demonstrate associated language deficits in naPPA.

Keywords

primary progressive aphasia; non-fluent; agrammatic; MRI; diffusion tensor imaging; frontotemporal lobar degeneration

INTRODUCTION

The non-fluent/agrammatic variant of primary progressive aphasia (naPPA), also known as progressive non-fluent aphasia (PNFA), is characterized by effortful, slowed speech that is produced at about one-third the rate of healthy adults. This is accompanied by a disorder of grammar. In oral speech expression, there are grammatical simplifications as well as frank grammatical errors. The presence of a grammatical comprehension deficit emphasizes that this is a central disorder of language that cannot be attributed entirely to a motor impairment. Language output in naPPA also may be characterized by speech errors known

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as apraxia of speech (AoS). A clinical imaging marker associated with these speech and language characteristics is left frontal gray matter (GM) disease. In this paper, we examine GM and white matter (WM) imaging evidence for disruption of large-scale neural networks underlying the effortful, grammatically-limited speech of patients with sporadic naPPA due to frontotemporal lobar degeneration (FTLD) spectrum pathology.

CLINICAL CHARACTERISTICS OF naPPA

Current recommendations for identifying naPPA emphasize three clinical features: Effortful speech, a disorder of grammar, and AoS (Gorno-Tempini et al., 2011). While effortful speech has been recognized clinically (Grossman et al., 1996; Snowden, Neary, Mann, Goulding, & Testa, 1992), quantification of slowed speech rate has been documented only recently (Ash et al., 2006; Ash et al., 2009; Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011; Wilson, Henry, et al., 2010). Speech is produced at an average rate of about 45 words per minute (WPM) by naPPA patients in comparison to about 140 WPM for healthy adults. While there are many lengthy pauses in their effortful speech, speech remains significantly slowed even when pauses >2 sec duration are taken into consideration (Ash, et al., 2009).

Careful analyses have allowed investigators to test several hypotheses about the basis for the slowed, effortful speech found in naPPA. One essential characteristic of speech that is highly correlated with effortfulness is its grammatical characteristics (Ash, et al., 2006; Ash, et al., 2009; Gunawardena et al., 2010; Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011; Wilson, Henry, et al., 2010). The variety of grammatical forms in sentences is impoverished, and grammatical forms are simplified, with fewer sentences containing features like a subordinate clause or the passive voice. Grammatical simplifications also result in a shortened mean length of utterance (MLU). When syntactic features are produced, they often contain errors. Grammatical morphemes may be omitted, particularly free-standing morphemes such as “was” and articles like “a,” inappropriate grammatical inflections may be used, and words may be inserted in the incorrect grammatical slot in a sentence.

Evidence that effortful speech in naPPA is not determined entirely by a motor disorder comes at least in part from the observation of grammatical comprehension difficulty in these patients. Impaired grammatical comprehension was first described using a task that is entirely language-based, where a simple question about “who did what to whom” probed brief sentences varying in grammatical complexity (Grossman, et al., 1996). In the sentence “Boys that girls kick are unfriendly,” for example, naPPA patients often err when asked: “Who did the kicking?” This finding has been replicated more recently in a larger cohort of patients with naPPA (Peelle et al., 2008). These patients also have difficulty pointing to one of several pictures based on a sentence, where selecting the correct picture depends on appreciating the sentence’s grammatical structure (Wilson, Dronkers, et al., 2010). Another study used an anagram task to show that naPPA patients have difficulty ordering words printed on cards into a grammatically complex question about a picture (Weintraub et al., 2009). Grammatical difficulties such as this can be used to distinguish naPPA from other PPA variants (Mesulam et al., 2009; Peelle, et al., 2008). Moreover, naPPA is a *progressive* disorder of language, and two studies have shown progressive decline of grammatical comprehension in naPPA (Grossman & Moore, 2005; Rogalski, Cobia, Harrison, Wieneke, Weintraub, et al., 2011).

Additional evidence consistent with a “central” disorder of grammatical processing difficulty comes from several sources. Measures like those described above are off-line and therefore depend in part on task-related resources. Indeed, neuropsychological studies demonstrate deficits on measures of working memory and executive functioning in naPPA

that can compromise task performance (Libon et al., 2007). To deal with these confounds, several investigations minimized task-related resources by examining “on-line” processing of grammatical materials in sentences. One study showed slowed processing of grammatical agreements in subordinate clauses of sentences containing a prepositional phrase that elongates the gap between long-distance, syntactically-dependent words (Grossman, Rhee, & Antiquena, 2005). This study suggested degradation of long-distance grammatical representations in working memory in naPPA. A second study demonstrated insensitivity to lexical grammatical category violations (e.g. a noun occurring in a verb sentential slot) but normal sensitivity to lexical semantic violations (Peelle, Cooke, Moore, Vesely, & Grossman, 2007).

Some naPPA patients also may have a motor disorder contributing to their effortful speech. AoS is a clinical condition involving impaired coordination and planning of the motor articulators. This results in the production of incorrect speech sounds and sequences of sounds that do not occur in the speaker’s native language, groping for the correct sound of a word, pauses in the speech stream, and other distortions of speech. This is consistent with the observation that some patients with naPPA have an extrapyramidal disorder such as progressive supranuclear palsy or corticobasal degeneration that can result in poor motor speech control (Josephs, Duffy, et al., 2006), although AoS certainly can occur without a concurrent motor disorder and may be found independently of other disorders of language (Josephs et al., 2012; J. D. Rohrer, Rossor, & Warren, 2010b). We noted above the frequent pauses that occur in naPPA speech (Ash, et al., 2009), although pauses may occur for a variety of reasons, and we are aware of only one attempt to examine qualitatively distinct speech errors consistent with AoS in naPPA (Ash et al., 2010). This study distinguished between phonetic errors that involve misarticulated speech sounds that are not part of the English speech sound system and therefore are likely to be due to misplacement of the articulators by an impaired motor coordination system; and phonemic errors that are governed by the abstract rules of the phonologic system for representing and combining sounds in language expression and comprehension. The analysis revealed that naPPA patients produce significantly more speech errors than controls, consistent with other observations (Josephs, Duffy, et al., 2006; J. D. Rohrer, Rossor, & Warren, 2010a; J. D. Rohrer, et al., 2010b). However, an overwhelming number of their speech errors are phonemic in nature, qualitatively similar to controls’ errors, while only 21% of speech errors in naPPA can be clearly attributed to a motor speech planning disorder because they were distortions that are not part of the English speech sound system. While using these rigorous criteria for subcategorizing speech errors may exclude other examples of AoS, speech errors consistent with AoS certainly occur in naPPA but do not appear to be very common.

IMAGING FEATURES OF naPPA

What is the neuroanatomic basis for this pattern of language difficulty in sporadic naPPA? There is extensive imaging evidence to suggest that a clinical marker for naPPA is focal disease localized to the left frontal lobe. Several imaging techniques have helped specify the anatomic distribution of disease associated with naPPA. Structural MRI studies have emphasized gray matter (GM) atrophy in the inferior frontal region of the left hemisphere (Gorno-Tempini et al., 2004; Peelle, et al., 2008; J. D. Rohrer et al., 2009; Sapolsky et al., 2010; Sonty et al., 2003). This typically involves adjacent areas such as frontal operculum and anterior insula, may extend more dorsally and anteriorly into left prefrontal regions, and may encompass superior portions of the left anterior temporal lobe (Gunawardena, et al., 2010; Rogalski, Cobia, Harrison, Wieneke, Weintraub, et al., 2011). These structural findings are confirmed by functional imaging techniques such as arterial spin labeling (ASL) and positron emission tomography (PET), showing functional deficits in the left inferior

frontal lobe, including the frontal operculum and the anterior insula, as well as the anterior-superior temporal lobe (Grossman, et al., 1996; Nestor et al., 2003).

Several approaches have been employed to investigate more directly the role of left inferior frontal atrophy in the language deficits of naPPA patients. Regression analyses thus have related grammatical difficulties directly to GM atrophy in left inferior frontal and anterior-superior temporal regions (Gunawardena, et al., 2010; Peelle, et al., 2008; Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011; Wilson, Dronkers, et al., 2010; Wilson, Henry, et al., 2010). Other work has related speech errors to the left frontal lobe (Ash, et al., 2010; Josephs, Duffy, et al., 2006; J. D. Rohrer, et al., 2010a).

Functional MRI also has been used to assess the neuroanatomic basis for grammatical processing in naPPA. These studies emphasize that disease in left inferior frontal cortex alone does not fully explain the deficits of these patients. In one study, healthy controls and patients with naPPA silently read sentences that feature a complex grammatical structure and a prepositional phrase that lengthens the distance between grammatically linked elements in the sentence (Cooke et al., 2003). Healthy controls activated both ventral portions of the left frontal lobe associated with grammatical processing and dorsal left frontal regions associated with working memory. By comparison, naPPA patients did not activate the ventral frontal region associated with grammatical processing, although they recruited dorsal portions of the left frontal lobe associated with working memory and left posterior-superior temporal regions associated with sentence processing. Another fMRI study showed grammatically simple sentences and grammatically complex sentences to naPPA patients and healthy controls (Wilson, Dronkers, et al., 2010). Controls showed greater left inferior frontal activation during grammatically complex sentences compared to simple sentences, while naPPA patients did not show a difference in left inferior frontal activation for these types of sentences. The left posterior-superior temporal region was equally activated by naPPA patients and healthy controls. Findings such as these suggest that the language impairment in naPPA is due in part to disruption of large-scale peri-Sylvian neural networks that support language processing, and that disrupted networks consist of multiple brain regions including the inferior frontal lobe and posterior-superior temporal cortex (Friederici, 2011; Hickok & Poeppel, 2007).

While previous imaging studies in naPPA suggest that disease in inferior frontal cortex may disrupt one component of a large-scale neural network that underlies language processing, relatively little work has investigated how disease in white matter (WM) projections between inferior frontal cortex and other GM regions contributes to the pattern of language impairment in naPPA. There is an increasing body of research using diffusion tensor imaging (DTI) to evaluate disorders of fractional anisotropy (FA) in WM tracts. FA is a measure of linear water diffusivity that is reduced when WM tracts are distorted by disease. These studies suggest that FA is reduced in naPPA in regions related to the inferior frontal lobe (Agosta et al., 2011; Duda et al., 2008; Galantucci et al., 2011; Schwindt et al., 2011). However, previous work has not directly related language disorders to reduced FA. In the present study, we examine how both GM disease and WM disease contribute to degraded large-scale networks involved in language and thus characterize the neuroanatomic basis for speech deficits associated with naPPA.

PATHOLOGY IN naPPA

Clinical-pathological investigations have emphasized that the underlying pathology of naPPA is heterogeneous. Most cases of naPPA are sporadic, although naPPA may be associated with several genetic mutations (Boeve et al., 2005; Mesulam et al., 2007; J.D. Rohrer et al., 2010; Snowden et al., 2012). In this report, we restrict our assessment to individuals with sporadic disease. Clinical-pathological series suggest that the majority of

naPPA cases are due to underlying FTLN spectrum pathology (Grossman et al., 2008; Josephs, Petersen, et al., 2006; Knopman et al., 2005; Mesulam et al., 2008; J. D. Rohrer et al., 2011). In a large autopsy series of 23 naPPA patients, for example, a majority exhibited FTLN-tau pathology (Knibb, Xuereb, Patterson, & Hodges, 2006). Two reviews of clinical-pathological series have suggested that about 70% of naPPA patients have tau-immunoreactive histopathology (Grossman, 2010; Josephs et al., 2011). Another large clinical-pathological series found that the majority of patients with naPPA have pathology related to tau-DNA binding protein of approximately 43 kD (TDP-43) (Snowden et al., 2011). The remaining naPPA patients in these autopsy series have Alzheimer disease (AD) pathology.

To minimize potential confounds associated with heterogeneous pathology in clinical-imaging studies such as the present one, we focus on sporadic naPPA patients associated specifically with FTLN spectrum pathology. Several previous studies emphasize the importance of this. For example, the anatomic distribution of GM disease varies in naPPA depending on the underlying pathology. naPPA associated with AD thus appeared to have significantly greater parietal disease than naPPA due to FTLN spectrum pathology (Hu et al., 2010; Nestor et al., 2007). Moreover, a recent multimodal neuroimaging study showed that patients with FTLN spectrum pathology are much more likely to have WM disease than patients with AD pathology (C. McMillan et al., 2012). We are not aware of detailed clinical-imaging studies of sporadic naPPA restricted to patients who are likely to have FTLN spectrum pathology. In this report, we investigate language and multimodal imaging characteristics of naPPA patients with autopsy-proven FTLN or who have a cerebrospinal fluid (CSF) profile that is not seen in AD and instead is strongly associated with FTLN spectrum pathology based on a cohort with known pathology (Irwin et al., 2012). We hypothesized that both GM and WM disease play a role in the disruption of large-scale neural networks contributing to the language processing deficits in naPPA due to FTLN spectrum pathology.

METHODS

SUBJECTS

We identified 15 sporadic patients (8 males) in our database who met published clinical criteria for naPPA (Gorno-Tempini, et al., 2011). As detailed below, they also had autopsy-proven FTLN-tau pathology (n=4, including corticobasal degeneration (n=2), progressive supranuclear palsy (n=1), dementia with Pick bodies (n=1)) or with pathology-validated CSF consistent with a non-Alzheimer form of dementia (n=11, including patients with a clinical diagnosis of naPPA related to frontotemporal degeneration (n=9), corticobasal syndrome (n=1), or progressive supranuclear palsy syndrome (n=1)). Clinical and demographic characteristics are provided in Table 1. Five cases were 65 years of age at the time of evaluation, consistent with previous clinical observations that naPPA patients tend to be a little older on average than other patients with presumed FTLN spectrum pathology (Johnson et al., 2005). Six cases were high school-educated, and the remainder had at least college-level education. These cases were minimally demented when evaluated for this study, according to the MMSE. Clinical evaluation, confirmed by consensus assessment of two independent reviewers, revealed that all of these patients had effortful, non-fluent speech associated with grammatical difficulty, together with grammatical comprehension deficits or speech errors, consistent with naPPA (Gorno-Tempini, et al., 2011). Patients were minimally medicated at the time of evaluation, and were not taking any sedating medications. There were no other contributing neurologic, primary psychiatric or medical conditions. Healthy control subjects (n=10) were matched with naPPA for age, gender and education (Table 1). Although MMSE was significantly lower in naPPA than controls, the average MMSE score of naPPA patients was within the normal range.

NEUROPATHOLOGICAL AND CSF VALIDATION OF COHORT

All naPPA patients in this study were sporadic and had autopsy-confirmed FTLT-tau or CSF analytes consistent with FTLT spectrum pathology. CSF was obtained in a standard manner described previously (Bian et al., 2008; Irwin, et al., 2012) and analyzed using previously reported methods with ELISA (INNOTEST®, Innogenetics, Ghent, Belgium) (Bian, et al., 2008) or Luminex xMAP platform (INNO-BIA AlzBio3™, Innogenetics-Fujirebio, Ghent, Belgium) (Shaw et al., 2009) immunoassays to measure total-tau (t-tau), tau phosphorylated at threonine 181 (p-tau), beta-amyloid (A₁₋₄₂), and the calculated t-tau/A₁₋₄₂ ratio. ELISA values were transformed into equivalent units detected by the xMAP system in a validated manner (Irwin, et al., 2012). A pathology-validated cutoff of 0.34 for t-tau/A₁₋₄₂ ratio achieved >90% sensitivity and specificity for both training and test cohorts at identifying individuals with likely FTLT spectrum pathology. All cases reported in this study had a CSF t-tau/A₁₋₄₂ ratio <0.34. CSF biomarker data were obtained within six months of neuropsychological testing and imaging (see below).

Routine neuropathological examination was performed on a subset of cases (n=4) using standard techniques and established monoclonal antibodies, including monoclonal antibodies specific for pathogenic tau (Forman et al., 2006) and p409/410 for phosphorylated TDP-43 (CNDR) (Neumann et al., 2006). Semi-quantitative scores (0=none, 1=mild, 2=moderate, and 3=severe) for burden of neuropathologic features were recorded at the time of microscopic diagnosis. Data for neuronal loss, gliosis, and inclusion severity were used in the analysis as a measure of disease burden.

Gross pathology in naPPA is illustrated in Figure 1. As can be seen, there was substantial focal atrophy in the inferior frontal and anterior-superior temporal regions of the left hemisphere, areas that were found to be atrophied in MRI images (see below).

Microscopic pathology is summarized in Figure 2. Dense tau pathology was evident in all sampled cortical regions. This was generally accompanied by ubiquitin. Neuron loss and gliosis was more evident in cortical regions than in the striatum, but was not as profound as the immunoreactive staining. There was also substantial white matter disease (not illustrated) in these cases. We found no evidence for TDP-43 histopathology in these cases, and our autopsy series does not include sporadic naPPA cases due to TDP-43 pathology.

BEHAVIORAL MATERIALS

Patients were evaluated on several language and neuropsychological measures. Speech was assessed with a 90-second description of the Cookie Theft Scene from the Boston Diagnostic Aphasia Exam (Goodglass & Kaplan, 1983). We quantified WPM, MLU, percent of grammatically well-formed utterances, and nouns and verbs produced per 100 words. Grammatical comprehension was assessed with one of two versions of the Test for the Reception of Grammar: One version examined accuracy matching a sentence to one of four pictures (Bishop, 1989); a second version assessed accuracy matching a sentence to one of two pictures, systematically manipulating whether sentences had a cleft structure or contained a subordinate clause, and systematically including an additional prepositional phrase strategically placed between grammatically linked noun phrases in half of each type of sentence. Language measures also included an assessment of visual confrontation naming with a 30-item version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). Episodic memory was assessed with the Philadelphia Verbal Learning Test, a 9-word list presented during 5 learning trials, and we report short delayed recall, long delayed recall following an interference trial, and recognition memory (Libon et al., 1996). Executive functioning and working memory were assessed with digit span forward and reverse (Wechsler, 1995), letter-guided category naming fluency for one minute each for the target

letters F-A-S (Lezak, 1983), and semantically-guided category naming fluency for one minute each for Animals, Vegetables, and Tools (Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994). We attempted to administer all of these measures during a single session, but this was not always possible. Not all patients were able to perform all tasks for a variety of reasons (e.g. scheduling conflict, medical illness, technical difficulty), and the number of patients with ascertainable data is provided in Tables 2 and 4.

IMAGING PROCEDURES

Gray Matter Imaging—Twelve participants underwent a structural T1-weighted MRI sequence for GM with a SIEMENS 3.0T Trio scanner, including one autopsy-confirmed case and 11 CSF-confirmed cases. In this retrospective clinical-pathological series, we also included two additional imaging datasets obtained with a GE 1.5T Horizon Echospeed scanner; both were autopsy-confirmed cases. All imaging was obtained within 6 months of neuropsychological testing. On the SIEMENS Trio, we acquired an MPRAGE sequence using an 8-channel coil with the following parameters: repetition time=1620 msec; echo time=3 msec; slice thickness=1.0 mm; flip angle=15°; matrix=192×256, and in-plane resolution=0.9×0.9 mm. On the GE Horizon Echospeed, a 3D spoiled gradient echo sequence was acquired with the following parameters: repetition time=35 msec; echo time=6 msec; slice thickness=1.3 mm; flip angle=30°; matrix size=128×256; and in-plane resolution=0.9×0.9mm.

Whole-brain MRI volumes were preprocessed with PipeDream (<https://sourceforge.net/projects/neuropipedream/>) and Advanced Normalization Tools (<http://www.picsl.upenn.edu/ANTS/>) using a procedure described elsewhere (Avants, Epstein, Grossman, & Gee, 2008; Klein et al., 2010). Briefly, PipeDream deformed each individual dataset into a standard local template space in a canonical stereotactic coordinate system. A diffeomorphic deformation was used for registration that is symmetric to minimize bias toward the reference space for computing the mappings, and topology-preserving to capture the large deformation necessary to aggregate images in a common space. These algorithms allow template-based priors to guide GM segmentation and compute GM probability which reflects a quantitative measure of GM density. Images were downsampled to 2 mm³ and smoothed using a 5 mm full-width half-maximum Gaussian kernel.

Analyses were performed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). The two-samples t-test module was used to compare GM probability in patients relative to 28 healthy seniors, using a local template consisting of 28 seniors and 12 patients obtained at 3T. Differences were evaluated using an explicit mask to constrain voxelwise comparisons to regions of GM, and a nuisance covariate was included in the model to minimize bias introduced by scanner type and sequence parameters for the two naPPA studies obtained at 1.5T. We report clusters that survive a threshold of $q < 0.005$ (FDR-corrected) and contain a minimum of 400 adjacent voxels.

We additionally performed linear regression analyses using SPM8's multiple regression module to relate language performance to regions of significant GM disease. We constrained our regression analyses to regions of disease using an explicit mask generated from the results of direct comparisons with healthy controls because it would otherwise have been difficult to interpret a regression result in an area without disease. For example, a significant brain-behavior relationship in areas without disease could be attributed to a variety of non-disease factors such as healthy aging. For the regression analyses, we accepted clusters significant at the $p < 0.01$ level where the peak voxel in a cluster is significant at $p < 0.001$ and the cluster extent contains > 50 adjacent voxels.

White Matter Imaging—Diffusion-weighted imaging (DWI) datasets were acquired in seven patients with the SIEMENS 3.0T Trio scanner with a 30-directional acquisition sequence. In addition, in this retrospective clinical-pathological study, 12-directional DWI datasets were acquired in two additional patients on the 3.0T scanner. The former included a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (FOV=245mm; matrix size=128 × 128; number of slices=57; voxel size=2.2mm isotropic; TR=6700ms; TE=85ms; 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 DTI-sequence included a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (matrix size=128 × 128, number of slices=40, FOV=220mm; slice thickness=3mm; TR=6500ms, TE=99ms). In total, 12 volumes were acquired per subject, one without diffusion-weighting ($b=0$ s/mm²) and 12 with diffusion-weighting ($b=1000$ s/mm²) along 12 non-collinear directions.

DWI images were preprocessed using ANTS (Avants, et al., 2008; Klein, et al., 2010) and Camino (Cook et al., 2006) within the associated PipeDream (<http://sourceforge.net/projects/neuropipedream/>) analysis framework. Motion and distortion artifacts were removed by affine co-registration of each DWI to the unweighted ($b=0$) image. Diffusion tensors were computed using a weighted linear least-squares algorithm implemented in Camino. Images were smoothed at 4 mm FWHM. Each participant's T1 image was warped to the template via the symmetric diffeomorphic procedure in ANTS described above. Distortion between participants' T1 and DT images was corrected by regularized intrasubject registration of 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.

DTI statistical analyses of FA were performed in SPM8 using a whole-brain approach. We used a whole-brain approach rather than a tract-specific approach such as tract-specific analysis (Yushkevich, Zhang, Simon, & Gee, 2008) or tract-based specific segmentation (Agosta et al., 2010) in order to minimize the risk of missing a significant deficit in a tract that is not among the restricted subset of tracts in tract-specific approaches, and we used a smaller Gaussian kernel for smoothing to minimize extension of the smoothing kernel beyond the anatomic limits of a tract, based on preliminary comparative studies using tract-based and whole-brain approaches (Brun, McMillan, Yushkevich, Gee, & Grossman, 2012; Powers et al., 2012). The ICBM-DTI-81 template was used as an explicit mask in order to constrain comparisons to regions of known WM tracts and to localize results to specific probabilistically-defined WM tracts (Oishi et al., 2008). Comparisons of naPPA patients relative to 25 30-directional and three 12-directional datasets from healthy seniors used a $q<0.05$ (FDR-corrected) threshold and a 200 adjacent voxel extent, including a nuisance covariate for the datasets acquired with a 12-direction sequence to minimize potential sequence bias. For regression analyses relating behavior to FA, we performed a linear regression analysis using SPM8 to relate language performance to regions of WM tracts with significantly reduced FA. We report a $p<0.05$ threshold with clusters containing a peak-voxel that is greater than $p<0.001$ and a minimum of 50 adjacent voxels.

RESULTS

LANGUAGE AND COGNITIVE RESULTS

Sentence Expression and Comprehension—Every naPPA patient in this study had clinical evidence for effortful, non-fluent speech. Quantitative assessment of speech rate using WPM revealed a significant deficit compared to healthy seniors (Table 2: $t(17)=7.72$; $p<0.001$). A z-score analysis relative to the healthy seniors participating in this study

showed that each individual naPPA patient is significantly slowed (at least at the $p < 0.01$ level) in their speech (z-score range -2.35 to -3.91).

We found evidence relating reduced WPM in naPPA to deficits in grammatical expression in our quantitative analysis of semi-structured speech samples. As summarized in Table 2, naPPA patients had a significantly reduced MLU [$t(17)=3.69$; $p < 0.002$], where shorter sentences reflect simplified grammatical forms. We also examined grammatical processing more directly by assessing whether utterances were grammatically well-formed or contained grammatical errors. We found that naPPA patients have a significantly reduced rate of producing grammatically well-formed utterances [$t(17)=2.50$; $p < 0.02$]. A correlation analysis showed that WPM correlates with measures reflecting grammatical competence in speech, including both MLU and the proportion of grammatically well-formed sentences (Table 3). Thus, effortful speech in naPPA appears to be related at least in part to a deficit in grammatical expression.

Grammatical limitations in slowed speech may have had an indirect impact on lexical retrieval. naPPA patients thus did not differ from healthy seniors in their retrieval of nouns per 100 words or verbs per 100 words (Table 2), although these patients approached significance in their relative difficulty with confrontation naming compared to healthy seniors (Table 4: $t(22)=1.89$; $p=0.071$). Nevertheless, lexical retrieval for nouns was inversely correlated with speech rate (Table 3). As speech slowed, these patients produced an *increased* number of nouns. This may reflect their reduced production of grammatical morphemes as well as their reasonably preserved lexical semantic access.

Confirming the deficit for a grammatical deficit in expression, we also found evidence for grammatical comprehension difficulty in naPPA. Overall sentence-picture matching accuracy approached a significant level of impairment in these patients relative to healthy seniors [Table 2; $t(18)=1.98$; $p=0.06$]. While naPPA patients were not significantly impaired for control sentences that do not involve a grammatical manipulation [$t(12)=1.63$; ns], they were significantly impaired relative to healthy seniors in the comprehension of sentences with a cleft structure [$t(12)=2.71$; $p < 0.02$] or a center-embedded structure [$t(12)=2.57$; $p < 0.03$]. Comprehension of sentences with an additional prepositional phrase inserted between grammatically-linked noun phrases also were significantly impaired [$t(12)=2.30$; $p < 0.04$]. This may reflect in part their working memory limitations (see below). We also found that slowed speech rate correlates significantly with reduced sentence-picture matching accuracy for grammatically-mediated comprehension, including sentences with cleft structures and center-embedded clauses (Table 3). Grammatical comprehension and grammatical expression thus may share in part a common source of impairment.

Another criterion for naPPA is the presence of speech errors reflecting AoS (Gorno-Tempini, et al., 2011). Among the naPPA patients participating in this study, we found significantly more speech errors than in healthy seniors [$t(17)=3.17$; $p < 0.01$]. It should be noted, however, that the speech errors produced by these naPPA patients were virtually all phonemic errors; phonetic errors consistent with AoS were extremely rare. Speech errors nevertheless correlated with slowed speech rate in naPPA (Table 3). Thus, difficulty implementing the linguistic rules needed to combine speech sounds into words also may contribute to effortful speech in naPPA, although this does not necessarily reflect a motor speech disorder related to AoS.

Dementia, Episodic Memory, and Executive Functioning—naPPA patients also have executive and working memory limitations, but these patients do not appear to be demented in a traditional sense and do not have episodic memory deficits. Patients with naPPA thus had worse scores than healthy seniors on the MMSE (Table 1), a brief survey

measure of cognitive functioning [$t(22)=2.98$; $p<0.01$]. Nevertheless, these patients on average were not “demented” in the traditional sense at the time of assessment since their overall level of cognitive functioning averaged within the normal range. Only 6 (40%) of the 15 naPPA patients in this study had a MMSE score <24 , and only 2 an MMSE score <20 . This is not surprising given that all but one of 30 points on the MMSE are mediated by language, although the modest level of overall impairment emphasizes that traditional definitions of dementia as measured by the MMSE are difficult to apply to naPPA patients likely to have FTD spectrum pathology rather than AD pathology. In line with this perspective, MMSE scores did not correlate with the speech characteristics of naPPA such as slowed speech rate (Table 3).

We also found that patients with naPPA are reasonably preserved in their episodic memory. As summarized in Table 4, their verbal recall and recognition memory did not differ from that of healthy controls, consistent with the low likelihood that any of these patients have AD. Moreover, measures of episodic memory did not correlate with slowed speech (Table 3). Using z-scores based on the healthy, age- and education-matched seniors participating in this study, only 1 (6.7%) of the naPPA patients had a deficit that differed from controls at the $p<0.01$ level ($z<-2.32$) for long delayed recall and recognition memory. This 69 year old, high school-educated individual had a MMSE of 22. It is possible to speculate that he may have had sufficient non-AD pathology in the hippocampus to warrant a traditional diagnosis of dementia, as can occur in some patients with FTL spectrum pathology (Graham et al., 2005).

Despite reasonably normal performance on dementia screening measures and episodic memory, Table 4 shows that patients with naPPA have difficulty on measures of executive functioning and working memory. naPPA patients thus are significantly impaired in their performance on a digit span task, including both digits repeated forward and digits reproduced in the reverse order. They had greater difficulty with reverse digit span compared to forward digit span [$t(11)=4.99$; $p<0.001$]. However, this differential deficit with reverse digit span compared to forward digit span was also found in controls [$t(4)=4.00$; $p<0.01$], and relative difficulty with reverse digit span compared to forward digit span using a difference score was comparable in controls and naPPA patients [$t(15)=1.01$; ns]. naPPA patients thus may have a short-term memory impairment independent of the need to manipulate information maintained in an active mental state. Digit span performance did not correlate with slowed speech rate (Table 3). However, naPPA patients did have difficulty with grammatical comprehension when sentences were lengthened in the critical portion between grammatically-linked words, and this may have been due in part to the working memory limitations for grammatical processing in naPPA (Grossman, et al., 2005).

Patients with naPPA also were significantly impaired in their category naming fluency relative to healthy seniors. This includes both letter-guided fluency [$t(21)=7.68$; $p<0.001$] and semantically-guided fluency [$t(21)=3.55$; $p<0.002$]. The discrepancy between letter-guided and semantically-guided fluency was significantly greater in naPPA than healthy seniors [$t(13)=3.36$; $p<0.001$]. This may reflect the fact that naPPA patients are able to use relatively preserved access to semantic representations of superordinate categories like “animal” and “vegetable” to help retrieve additional category members in a semantically-guided fluency task. Their deficit retrieving words beginning with the letter “F” nevertheless suggests that naPPA patients are impaired in their performance on measures of mental planning. Category naming fluency did not correlate with slowed speech rate (Table 3), suggesting that performance on executive measures contributes minimally to effortful speech in naPPA.

IMAGING RESULTS

Gray Matter Imaging—GM atrophy is illustrated in Figure 3, and anatomic locations of clusters are summarized in Table 5. As can be seen, there was considerable GM atrophy in the left frontal lobe. This was centered in ventral lateral and opercular portions of frontal cortex as well as the insula. Atrophy extended from this inferior frontal region into dorsal and anterior regions of the left frontal lobe, and ventrally into the anterior-superior regions of the left temporal lobe. Significant atrophy also was seen in the right inferior frontal lobe.

Regression analyses demonstrate that slowed speech rate and grammatical expression are related to this distribution of GM atrophy. Anatomic locations of these clusters are summarized in Table 5. Figure 3 Panel B thus shows that reduced WPM was associated with GM atrophy in lateral portions of left inferior frontal cortex. This overlapped with regressions relating grammatical deficits in expression to GM atrophy. Figure 3 Panel C shows significant regressions relating reduced proportion of grammatically well-formed utterances to similar portions of left lateral frontal cortex. Figure 3 Panel D relates reduced MLU to significant atrophy in lateral portions of left inferior frontal cortex as well. Thus, atrophy in left frontal GM regions appears to be related to the language expression deficits in naPPA.

White Matter Imaging—Reduced FA in WM tracts is summarized in Table 6 and illustrated in Figure 4. Axial diffusivity, radial diffusivity and mean diffusivity are presented in Appendix 1. Panel A illustrates tracts that are relatively medial and Panel B shows tracts that are located more laterally. Glass brains of these areas of reduced FA can be found in Appendix 2. In Panel A, significantly reduced FA can be seen in the anterior half of the corpus callosum bilaterally that integrates left and right frontal regions. Reduced FA also is seen in the cingulum and fornix on the left. Panel B shows significantly reduced FA in the anterior portion of the arcuate/superior longitudinal fasciculus that subserves a dorsal stream projecting between inferior and dorsal frontal regions and posterior-superior temporal regions. Reduced FA also is present in the inferior frontal-occipital fasciculus that courses through the external capsule and subserves a ventral stream projecting between inferior frontal and anterior-superior temporal regions and posterior-superior temporal regions. Finally, there is reduced FA in the uncinate fasciculus that carries projections between the inferior frontal region and the anterior temporal lobe. Reduced FA is also present in the right cingulum and right inferior longitudinal fasciculus (not illustrated).

Regression analyses were performed to relate language deficits to FA in tracts where there is significantly reduced FA. These regression analyses, summarized in Table 6, suggest that white matter structural damage contributes to the language characteristics seen in naPPA. Thus, Figure 4 Panel C shows that reduced WPM was related to reduced FA in the left anterior corpus callosum. Figure 4 Panel D shows reduced FA in the arcuate/superior longitudinal fasciculus, the inferior frontal-occipital fasciculus and the uncinate fasciculus (not illustrated) that was related to a reduced proportion of grammatically well-formed utterances. Finally, reduced FA in the anterior corpus callosum, inferior frontal-occipital fasciculus, and the cingulum were related to shortened MLU, as shown in Figure 4 Panel E. Thus, there appears to be reduced FA in WM tracts that link areas of frontal GM disease to temporal GM regions involved in sentence expression, and regression analyses relate these areas of reduced FA in WM projections to impairments on the same language measures that are associated with GM atrophy in naPPA.

DISCUSSION

naPPA is a common form of PPA. The different forms of PPA are important to recognize because they may serve as a clinical screen for a specific histopathologic abnormality. While

there are differences from center to center around the world, it appears that about 70% of naPPA cases are associated with FTLN spectrum pathology (Grossman, 2010; Josephs, et al., 2011). Most of the remaining cases appear to have an unusual aphasic variant of AD. Since FTLN and AD associated with naPPA appear to have different anatomic distributions of disease (Hu, et al., 2010; C. T. Mcmillan et al., 2012; Nestor, et al., 2007), clinical-imaging work in this group of patients would benefit from analyses restricted to FTLN. Unfortunately, few studies have provided a comprehensive characterization of sporadic naPPA associated with FTLN spectrum histopathology. The present report follows up our previous series (Turner, Kenyon, Trojanowski, Gonatas, & Grossman, 1996) by investigating the breakdown of large-scale neural networks associated with the clinical characteristics of 15 patients who have sporadic naPPA due to FTLN spectrum pathology.

CLINICAL AND LANGUAGE CHARACTERISTICS OF naPPA

Using recently described consensus criteria, we found that patients with sporadic naPPA due to FTLN are slightly older than many other patients with an FTLN spectrum disorder. Some of these patients have an akinetic-rigid disorder such as corticobasal syndrome or progressive supranuclear palsy syndrome, but this represents a minority of cases in our series. This cohort otherwise resembles the demographic characteristics of other patients with an FTLN spectrum disorder.

naPPA patients are distinguished from other patients with PPA by the specific features of their speech and language. In this study, we focus on language expression. These patients have profoundly effortful speech. The average speech rate is less than one word/second. Using a semi-structured speech sample, we found a significantly slowed speech rate in each and every individual that we assessed. This replicates our prior work with a lengthy speech sample that gives patients ample opportunity to demonstrate the full range of their linguistic skills (Ash, et al., 2009; Gunawardena, et al., 2010), and receives support from other reports demonstrating similar quantitative findings with a short speech sample (Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011; Wilson, Henry, et al., 2010).

It is important to quantify speech rate for several reasons. First, this appears to be a robust way to identify patients with naPPA. This deficit was present to a significant extent in 100% of our patient cohort. Second, this measure requires little technical or linguistic expertise, and thus can be used in the clinic as a screening tool that would signal the need for additional diagnostic studies. Third, this is a potentially important method for distinguishing between naPPA due to FTLN spectrum pathology and logopenic variant PPA (lvPPA). lvPPA can present clinically with slowed speech (Hu, et al., 2010; Nestor, et al., 2007), and although this is not a qualitatively distinct feature, quantification shows that the speech of lvPPA is not as slowed as that of naPPA. This distinction between naPPA and lvPPA is important because naPPA is commonly associated with FTLN spectrum pathology while lvPPA is more often associated with underlying AD pathology (Grossman, 2010; Mesulam, et al., 2008).

The basis for slowed, effortful speech in naPPA has been a matter of some debate. We and others find that effortful expression is related in part to a grammatical processing impairment (Gunawardena, et al., 2010; Mesulam, et al., 2009). The formulation of a sentence depends on grammatical processing to identify the major grammatical category associated with a word, and to organize the set of words contributing to a sentence in a syntactically coherent manner that supports long-distance grammatical relations. This is essential to sentence meaning, since this determines *who is doing what to whom*. This is an extraordinarily complex and demanding process. The overwhelming majority of utterances in our speech are unique: We say them once, and the identical utterance is never repeated. This linguistic creativity depends in part on complex grammatical processing, and this

involves greater computational time if the device supporting this mechanism is compromised. Healthy seniors use grammatical devices such as subordinate clauses, cleft structures and the passive voice not infrequently – in fact, these features are present in up to 35% of healthy seniors' utterances in extended speech samples (Gunawardena, et al., 2010). naPPA patients have lengthy pauses more frequently in their speech than other PPA patients and controls (Ash, et al., 2009), and this can reduce apparent speech fluency on quantitative measures that count words per minute. However, correcting for pauses >2 sec does not eliminate the fact that these patients have a significantly reduced speech rate (Ash, et al., 2009).

In the present study, we analyzed two measures of grammatical processing in a semi-structured speech sample to assess the basis for effortful speech in patients with FTL spectrum pathology. The first measure showed that naPPA patients have a significantly reduced MLU. MLU was advanced in the developmental psycholinguistic literature as a measure to characterize sentence-level, grammatically-mediated language acquisition. Sentence length is reduced in the grammatically simplified utterances of children because there are fewer grammatical morphemes and syntactic structures available to lengthen a sentence with prepositional phrases, subordinate clauses, passive voice and other syntactic devices. A grammatical limitation also appears to be implicated in part in the reduced MLU of naPPA patients. Thus, these patients have simplified grammatical forms in their speech (Ash, et al., 2009; Gunawardena, et al., 2010).

The second measure of grammatical processing assessed the proportion of grammatically well-formed utterances. Here too we found that naPPA patients produce significantly fewer grammatically well-formed utterances. This is due in large part to the production of sentences with various grammatical errors. We found that healthy seniors consistently produce about 10% of their utterances with grammatical errors. However, naPPA patients produce over four times this number of grammatical errors in their speech samples. In a semi-structured speech sample such as ours, patients have an option to simplify their speech and thus minimize the risk of producing utterances with grammatical errors. The observation of grammatical errors is all the more striking because naPPA patients appear to take advantage of this strategy and produce grammatically simplified speech, with fewer grammatically complex utterances than healthy seniors (Ash, et al., 2009; Gunawardena, et al., 2010). Both reduced MLU and reduced grammatically well-formed sentences correlated with WPM, emphasizing the contribution of grammatical difficulty to the effortful speech in naPPA.

Additional evidence consistent with a grammatical account for effortful speech expression comes from the finding of impaired grammatical comprehension in these patients. Here we found that naPPA patients have difficulty matching a sentence to a picture. Their poor performance involved grammatically complex sentences rather than simpler sentences. An important caveat to keep in mind is that our measure of grammatical comprehension was performed “off-line” and may not fully reflect day-to-day natural language use. Thus, the sentences were presented at a normal speech rate, but task performance was mediated in part by an executive resource system that is making conscious, deliberative decisions about sentences, and as noted below, naPPA patients have limited executive resources and working memory that can confound interpretation of performance on these language tasks. Other measures of grammatical processing also are heavily resource-demanding since they involve deliberative word ordering in an anagram task that is constrained to formulate a wh-question (Weintraub, et al., 2009). With this important caveat in mind, it is important to point to a handful of studies that probed grammatical processing in an “on-line” manner that minimizes executive resource demands during task performance (Grossman, et al., 2005;

Peelle, et al., 2007). Additional work is needed to specify the precise basis for the grammatical deficit in naPPA.

Other factors have been proposed to account for slowed, effortful speech in naPPA. We found that naPPA patients produce speech sound errors. However, these errors were phonemic in nature, reflecting difficulty in the linguistic processing system governing the rules for combining speech sounds into words. These errors consisted of exchanges, insertions, omissions and substitutions of allowable English speech sounds in speech sequences that are allowable in English. While these occur in most English speakers, they were significantly more common in naPPA than healthy controls. The production of these speech errors correlated with WPM, suggesting that the computational demands associated with phonologic processing also may detract from fluent speech in naPPA. However, this mechanism is different from the speech slowing that may be observed in association with a motor coordination impairment due to AoS. Additional work is needed to investigate the nature of phonological processing deficits in naPPA.

A second alternate explanation for effortful speech in naPPA could be the executive and working memory limitations seen in these patients. We found that naPPA patients have a reduced digit span. Unlike patients with executive disorders due to extensive prefrontal disease, there was not disproportionate difficulty with reverse digit span. Instead, forward and reverse digit spans were both reduced, while maintaining the same relative levels of performance as found in controls. Although we did not find a correlation with speech rate, this pattern of reduced working memory may play a role in lengthy sentences involving long-distance syntactic dependencies. naPPA patients encountered difficulty with strategically lengthened sentences on the sentence-picture matching task, for example, and we previously reported a deficit processing strategically lengthened sentences such as these in naPPA for both off-line and on-line measures of sentence comprehension (Grossman, et al., 2005; Peelle, et al., 2008).

We also found that patients with naPPA have reduced category naming fluency, a classic measure of planning and mental organization. This has been related to frontal and temporal atrophy in FTLT (Libon et al., 2009). A similar deficit in planning may contribute to the patients' deficit in connected speech. For example, a planning deficit may interfere with rapid, coordinated lexical retrieval during on-going speech. However, we did not find a correlation between performance on these category naming measures and slowed speech rate. This replicates our previous work (Gunawardena, et al., 2010). Instead, we found that naPPA patients retrieve the same number of nouns per 100 words as controls, and their retrieval is inversely correlated with speech fluency. This may reflect in part their relative difficulty retrieving free-standing grammatical morphemes, with a relative increase in retrieval of content words such as nouns. This may be related in part to relatively preserved lexical semantic access. Thus, it appears that effortful speech in naPPA is related primarily to linguistic processes such as impaired grammatical processing rather than motor or non-linguistic cognitive deficits.

DEGRADED LARGE-SCALE NEURAL NETWORKS UNDERLIE LANGUAGE DEFICITS IN naPPA

We examined the anatomic basis for expression difficulty in sporadic naPPA associated with FTLT spectrum pathology. We employed two imaging methods – one sensitive to GM abnormalities, and a second sensitive to disease in WM tracts projecting between GM regions that are essential for sentence processing. We confirmed a frequently reported MRI finding that naPPA patients have GM disease that is most evident in the left frontal lobe (Gorno-Tempini, et al., 2004; Peelle, et al., 2008; J. D. Rohrer, et al., 2009; Sapolsky, et al., 2010; Sonty, et al., 2003). Atrophy is evident in inferior frontal regions and the adjacent

frontal operculum and anterior insula. Atrophy in these patients was not restricted to the classic posterior-inferior frontal region known as Broca's area, and this may explain some of the discrepancies between effortful speech in stroke aphasics compared to naPPA patients who have a progressive neurodegenerative disease. Thus, atrophy also extended superiorly and anteriorly into dorsolateral portions of the left frontal lobe. Disease also extended into the anterior-superior regions of the left temporal lobe. This corresponds well to the anatomic distribution of gross atrophy seen in autopsy cases of naPPA associated with a tauopathy (e.g. Figure 1). There was also some atrophy in the right inferior frontal region.

Regression analyses helped us establish the portion of this area of GM atrophy that is most relevant to patients' effortful speech. Specifically, we hoped to establish a causal link directly relating a quantitative measure of slowed speech expression with the amount of GM atrophy in a specific neuroanatomic region, and thus begin to define the large-scale neural networks important for language that are disturbed in naPPA. We found that effortful speech is related to specific areas within left inferior and lateral prefrontal regions of atrophy in naPPA. Previous work from our lab and elsewhere has demonstrated a direct association between effortful speech and this left frontal distribution of disease (Gunawardena, et al., 2010; Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011; Wilson, Henry, et al., 2010).

Behavioral assessments underlined the contribution of grammatical processing deficits to the characteristically effortful speech of naPPA, and we assessed this from an anatomic perspective by examining regression analyses relating atrophy to two measures of grammatical processing difficulty in expression. Regression analyses directly related grammatical deficits on both measures to left frontal disease. Moreover, we observed a close overlap between the anatomic regression for effortful speech and regressions relating grammatically well-formed utterances and MLU to GM atrophy. Work from our lab and elsewhere also has shown an overlap of the anatomic regions associated with speech fluency and with grammatical processing in left inferior frontal regions (Gunawardena, et al., 2010; Wilson, Henry, et al., 2010). This is similar to areas activated in fMRI studies of healthy controls during challenges intended to engage the grammatical processing system (Friederici, 2011; Grodzinsky & Friederici, 2006). However, this differs from the finding of another study that associated grammatical processing with an extensive area involving the parietal lobe (Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011). This discrepancy may have been related in part to their use of a grammatical measure – MLU – to quantify speech fluency and a resource-demanding anagram test to assess grammatical processing, and to their use of a region of interest analysis rather than a regression direct relating performance to anatomy using a voxel-based morphometric approach. This discrepancy also may be related in part to the assessment of clinically-ascertained patients, where parietal involvement may have reflected that some patients had underlying AD (Hu, et al., 2010; Nestor, et al., 2007), compared to our use of patients highly likely to have FTLT pathology. Additional comparative work is needed to evaluate naPPA patients with FTLT or AD pathology.

We also observed significant WM disease in naPPA. This involved WM projections related to the frontal GM disease seen in these patients. Moreover, regression analyses related both GM regions and WM regions to disorders of similar language characteristics. This is consistent with the breakdown of large-scale neural networks for language expression in naPPA. We found disruption of three large-scale GM-WM networks. First, we observed reduced FA in the anterior corpus callosum. Regression analyses showed that reduced FA in this location is related to the slowed, effortful speech rate in naPPA. Regression analyses also associated effortful speech with left inferior frontal cortex. Slowed, effortful speech in naPPA from this perspective may due in part to interruption of a bilateral frontal network

mediated by projections through the anterior corpus callosum. There is much evidence in the stroke literature implicating right frontal regions in the non-fluent speech found in the syndrome known as Broca's aphasia (Hamilton et al., 2010; van Oers et al., 2010; Winhuisen et al., 2005). These regression analyses also relate callosal dysfunction to performance on grammatical measures. Although additional work is needed to establish the precise role of the components of this network in the slowed, effortful speech rate of naPPA, our findings suggest that disruption of this large-scale neural network in naPPA is important for their rate of speech expression.

Other fiber pathways also appear to have reduced FA in naPPA, and these too are implicated in specific aspects of language processing that are also related to GM disease in the left frontal lobe. Previous studies of WM in naPPA reported reduced FA in the arcuate/superior longitudinal fasciculus complex (Galantucci, et al., 2011; Schwindt, et al., 2011). This is the so-called dorsal stream, the second large-scale neural network that is disrupted in naPPA. The arcuate/superior longitudinal fasciculus contains projections that link frontal brain regions with language areas in the posterior-superior temporal lobe. We too found reduced FA in this tract. It has been proposed that this dorsal stream mediates long-distance syntactic dependencies (Friederici, 2011). Moreover, we found evidence for direct statistical associations between reduced FA and grammatical processing in projections contributing to the dorsal stream – in particular, for grammatically well-formed sentences. We also found that atrophy in left inferior frontal cortex is related to an impairment of this grammatical aspect of speech. Some work in stroke patients has provided evidence for a role of these tracts in syntactic processing (Rolheiser, Stamatakis, & Tyler, 2011), and regression analyses relating grammatical processing to FA in the arcuate/superior longitudinal fasciculus in the present study provide converging evidence for a functional role of these compromised projections in naPPA. Important to consider is that this projection also may mediate a left frontal-parietal verbal working memory system that appears to contribute to difficulty processing long-distance syntactic dependencies in sentences in naPPA (Grossman, et al., 2005; Peelle, et al., 2008), and may play a role in auditory-motor associations important for speech fluency (Hickok & Poeppel, 2007). Regardless of the specific role of this dorsal stream, evidence of reduced FA in the arcuate/superior longitudinal fasciculus in naPPA suggests disruption of a second large-scale neural network in naPPA involved in speech expression (Ash, et al., 2009; Grossman, et al., 2005; Gunawardena, et al., 2010; Peelle, et al., 2008; Wilson, Henry, et al., 2010).

Our study involved a whole brain analysis, resembling one previous study (Schwindt, et al., 2011), but unlike prior work that restricted analyses to specific pathways (Agosta, et al., 2011; Galantucci, et al., 2011). In whole brain approaches, we and others observed reduced FA in projections mediating connectivity in the ventral stream between, on the one hand, inferior frontal and anterior-superior temporal regions, and on the other hand, other temporal regions critical for language processing. This is the third large-scale neural network that is disrupted in naPPA, and includes the inferior frontal-occipital fasciculus coursing through the external capsule to posterior-superior temporal regions. Regression analyses related reduce FA in this fasciculus to both reduced MLU and difficulty with grammatically well-formed sentences. As noted above, left inferior frontal atrophy in naPPA was related to impairments on these measures as well. This inferior frontal-occipital pathway may support lexical representations that include the major grammatical category of words in sentences (Friederici, 2011; Hickok & Poeppel, 2007). This aspect of grammatical processing was compromised in an on-line study of naPPA (Peelle, et al., 2007). The uncinate fasciculus projecting to anterior temporal regions also was directly related to grammatical difficulty in naPPA. The anterior temporal area also may be implicated in the representation of major lexical grammatical category knowledge (Friederici, 2011). Although additional work is needed to help specify more precisely difficulty with major lexical grammatical category

knowledge in naPPA, these findings point to a third large-scale neural network that may be compromised in these patients.

Some pathways with reduced FA do not appear to have any obvious relationship with the clinical characteristics of naPPA. This includes the cingulum and the fornix. There is significant WM disease in tauopathies such as tau plaques and microglial inclusions (Forman et al., 2002), and these occur independently of Wallerian degeneration in WM that may occur as a result of GM-related disease. Additional clinical-pathological studies are needed with larger samples of patients to evaluate the contribution of disease in various WM tracts to the deficits found in naPPA.

Additional shortcomings should be kept in mind when considering our findings. Thus, we reported a fairly comprehensive language and cognitive evaluation, but we did not obtain any on-line measures of sentence processing in these patients. The disrupted large-scale neural networks that we associated with speech expression difficulties are not necessarily identical to the large-scale neural networks mediating grammatical comprehension. Additional work thus is needed to specify the scope of the neural substrate for grammatical processing we identified in naPPA. While we obtained multiple imaging modalities, we did not include any functional imaging. Thus, there may be additional regions of functional GM impairment that are contributing to the language deficit of naPPA. Our autopsy sample was small.

Keeping in mind these and other caveats mentioned above, our findings suggest that patients with sporadic naPPA due to FTL spectrum pathology have effortful speech that is related to a deficit in grammatical processing. Multimodal imaging studies supplemented by regression analyses appear to associate this deficit with the disruption of three large-scale neural networks in naPPA. One network mediated by the anterior corpus callosum involves bi-frontal processing of fluent speech; a second network mediated by the arcuate/superior longitudinal fasciculus appears to play a role in long-distance syntactic dependencies; and a third network mediated by the inferior frontal-occipital fasciculus may contribute to lexical representations including grammatical category information. The observation of significant regressions implicating the same characteristics of speech expression in measures of both GM and WM disease in these networks is an important demonstration of the role of large-scale neural networks for language in the deficits of patients with naPPA. Moreover, this work provides important converging evidence from a brain-damaged population that is consistent with the contribution of large-scale neural networks seen in fMRI studies of language in healthy adults.

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APPENDIX 1

MEAN, AXIAL, AND RADIAL DIFFUSIVITY IN WHITE MATTER CLUSTERS

naPPA < Elderly				
	MEAN	AXIAL	RADIAL	# VOXELS
Corpus callosum	0.00111	0.00169	0.00089	13982
B fornix	0.00183	0.00238	0.00165	599
L cingulum	0.00407	0.00442	0.00400	226
L cerebral peduncle	0.00083	0.00123	0.00072	420
L inferior frontal-occipital fasciculus	0.00085	0.00120	0.00077	1131
L fornix	0.00137	0.00176	0.00128	1227
L superior longitudinal fasciculus	0.00075	0.00111	0.00067	264
L arcuate fasciculus	0.00073	0.00111	0.00066	263
R inferior frontal-occipital fasciculus	0.00077	0.00112	0.00068	257
L uncinate	0.00066	0.00123	0.00046	814
Words per Minute Regression in naPPA				
Corpus callosum	0.00077	0.00118	0.00068	58
Grammatically Well-Formed Regression in naPPA				
L inferior longitudinal fasciculus	0.00112	0.00160	0.00099	124
L superior longitudinal fasciculus	0.00077	0.00120	0.00067	62
Mean Length of Utterance Regression in naPPA				
Corpus callosum	0.00117	0.00194	0.00086	61
L cingulum	0.00076	0.00110	0.00069	80
L inferior frontal-occipital fasciculus	0.00090	0.00121	0.00080	63

APPENDIX 2

GLASS BRAIN REPRESENTATIONS OF WHITE MATTER CLUSTERS

PANEL A – REDUCED FRACTIONAL ANISOTROPY

PANEL B - WPM

PANEL C - WELL-FORMED

PANEL D MLU

HIGHLIGHTS

- We examined non-fluent/agrammatic primary progressive aphasia in FTL
- The core clinical characteristic is slowed, effortful expression
- This is related to impaired grammatical processing
- Disruption of 3 large-scale neural networks contributes to naPPA expression

FIGURE 1. GROSS ANATOMY OF THE LEFT HEMISPHERE IN A PATIENT WITH naPPA
Atrophy in the inferior frontal and anterior superior temporal region is indicated by asterisk.

FIGURE 2. DENSITY OF PATHOLOGY IN SAMPLED ANATOMIC REGIONS OF naPPA BRAINS

Histopathologic features are indicated by histograms on a 0–3 severity scale. Note the widespread distribution of histopathologic disease that is most pronounced for tau-immunoreactive changes.

FIGURE 3. GRAY MATTER ATROPHY IN naPPA

Panel A: Whole brain analysis of reduced gray matter density (green). Panel B: Regression analysis relating slowed speech (words per minute) to gray matter atrophy (red); Panel C: Regression analysis relating a measure of grammatical expression (mean length of utterance) to gray matter atrophy (yellow); Panel D: Regression analysis relating a measure of grammatical competence in expression (percent grammatically well-formed utterances) to gray matter atrophy (blue).

FIGURE 4. WHITE MATTER DISEASE IN naPPA

RGB images showing reduced fractional anisotropy (FA) in a diffusion tensor imaging analysis of whole brain diffusion-weighted imaging, where green = anterior-posterior diffusion, red = lateral (left-right) diffusion, and blue = superior-inferior diffusion. Ghost areas show white matter anatomic regions, and denser-colored portions of the ghost areas show regions of significantly reduced fractional anisotropy in the corresponding tract. Panel A: Reduced FA in medial tracts: red = corpus callosum; green = cingulum; light blue = fornix; Panel B: Reduced FA in lateral tracts: dark green = arcuate/superior longitudinal fasciculus; green = inferior frontal-occipital fasciculus; purple = uncinate fasciculus; Panel C: Regression analysis relating slowed speech (words per minute) to reduced FA in corpus callosum; Panel D: Regression analysis relating a measure of accurate grammatical expression (percent grammatically well-formed utterances) to reduced FA in inferior frontal-occipital fasciculus and arcuate/superior longitudinal fasciculus; Panel E: Regression analysis relating a measure of grammatical competence in expression (mean length of utterance) to reduced FA in inferior longitudinal fasciculus, corpus callosum, and cingulum.

TABLE 1MEAN ($\pm$ S.D.) CLINICAL AND DEMOGRAPHIC FEATURES^I

	naPPA	CONTROLS
Age (years)	69.7 (11.7)	69.9 (16.1)
Gender (M/F)	8/7	4/6
Education (years)	14.8 (2.6)	16.1 (2.7)
MMSE (max=30) *	24.2 (4.4)	28.8 (1.2)

NOTE

^I.* indicates a group difference significant at the p<0.05 level.

TABLE 2MEAN ($\pm$ S.D.) PERFORMANCE ON LANGUAGE MEASURES^I

	naPPA	CONTROLS
EXPRESSION (Cookie Theft picture description) (n=9)		
Words per minute (# words) *	52.9 (19.7)	144.9 (30.4)
Mean length of utterance (# words) *	7.8 (2.3)	11.5 (2.0)
Verbs per 100 words (# words)	15.1 (1.7)	15.5 (1.1)
Nouns per 100 words (# words)	22.5 (5.2)	18.7 (3.7)
Grammatically well-formed (% correct) *	61.0 (37.5)	91.1 (6.2)
Speech errors per 100 words (# words) *	2.7 (2.5)	0.2 (0.3)
COMPREHENSION (sentence-picture matching) (n=12)		
Overall sentence-picture matching (% correct)	88.1 (13.5)	97.9 (3.8)
Cleft comprehension (% correct) *	89.5 (8.6)	98.4 (3.0)
Center-embedded comprehension (% correct) *	81.9 (13.1)	95.8 (7.0)
Long-sentence comprehension (% correct) *	85.4 (12.6)	96.9 (5.8)

NOTE

^I.* indicates a group difference significant at the p<0.05 level.

TABLE 3

CORRELATIONS OF SPEECH FLUENCY (WORDS PER MINUTE) WITH LANGUAGE AND COGNITIVE MEASURES¹

	Correlation with words per minute
GRAMMATICAL EXPRESSION	
Mean length of utterance	0.59 *
Grammatically well-formed	0.74 *
GRAMMATICAL COMPREHENSION	
Sentence-picture matching – grammatically-dependent	0.64 *
SPEECH ERRORS	
Phonologic errors	-0.69 *
LEXICAL RETRIEVAL	
Lexical retrieval during speech for verbs/nouns	-0.21/-0.59 *
COGNITION, EPISODIC MEMORY, WORKING MEMORY AND EXECUTIVE FUNCTIONING	
MMSE	0.14
Recognition memory	0.49
Digits forward – reverse	0.07
Letter-guided category fluency	0.26

NOTE

¹* indicates a significant correlation at the p<0.05 level

TABLE 4MEAN ($\pm$ S.D.) NEUROPSYCHOLOGICAL PERFORMANCE¹

	naPPA	CONTROLS
EPISODIC MEMORY (n=10)		
Short delay (max=9)	5.2 (2.8)	5.7 (2.1)
Long delay (max=9)	5.1 (3.1)	6.1 (2.2)
Recognition (max=9)	8.0 (2.8)	8.1 (1.2)
EXECUTIVE		
Letter-guided category fluency (words/min; n=14) *	4.4 (2.9)	14.3 (3.2)
Semantic-guided category fluency ² (words/min; n=14) *	8.9 (4.1)	14.3 (2.7)
Digits forward (# words; n=10) *	4.6 (1.7)	7.4 (1.1)
Digits reverse (# words; n=10) *	2.1 (1.2)	5.8 (1.8)
NAMING		
Boston Naming Test ³ (% correct; n=15)	78.0 (26.1)	94.8 (5.6)

NOTES

¹. * indicates a group difference significant at the p<0.05 level.

². Four naPPA patients performed category naming fluency only for Animals

³. Four naPPA patients performed a 15-item version of the Boston Naming test

TABLE 5

GRAY MATTER ATROPHY AND REGRESSIONS RELATING GRAY MATTER

Anatomic Locus (Brodmann Area)	Talairach Coordinates			Cluster Size (# voxels)
	x	y	z	
naPPA < Elderly Atrophy				
L inferior frontal (44)	−49	8	15	27114
L insula	−33	20	8	Same cluster as L inferior frontal
L middle frontal (10)	−29	48	−5	1013
L inferior frontal (47)	−30	29	−16	1485
L orbital frontal (11)	−12	15	−19	2451
L medial frontal (10)	−12	47	4	14035
L superior temporal (22)	−56	0	−2	436
L middle temporal (21)	−56	−30	−2	4026
L inferior temporal (20)	−46	−1	−28	447
L fusiform (20)	−44	−25	−17	1150
L parahippocampal (28)	−23	−11	−17	4934
L uncus (28)	−30	−10	−28	559
L putamen	−19	13	9	2573
R middle frontal (9)	37	16	26	513
R orbital frontal (11)	11	15	−19	452
R premotor (6)	45	−7	34	479
R cingulate (24)	20	7	45	611
R middle temporal (21)	55	−6	−8	631
R insula	33	23	8	4143
R putamen	20	14	1	528
R putamen	18	9	12	982
Words per Minute Regression in naPPA				
L middle frontal (46)	−48	38	16	81
L inferior frontal (47)	−54	21	−1	91
L cingulate (24)	−21	5	43	67
L postcentral gyrus (40)	−58	−18	15	165
L insula	−31	23	3	54
Grammatically Well-Formed Regression in naPPA				
L inferior frontal gyrus (45)	−34	29	3	77
L middle frontal gyrus (10)	−39	43	21	98
L cingulate (24)	−22	5	43	73
L supramarginal (40)	−63	−18	17	103
Mean Length of Utterance Regression in naPPA				
L middle frontal (9)	−40	20	41	125

TABLE 6
ATROPHY TO SPEECH MEASURES

WHITE MATTER AREAS OF REDUCED FRACTIONAL ANISOTROPY AND REGRESSIONS
RELATING FRACTIONAL ANISOTROPY TO SPEECH MEASURES

naPPA < Elderly				
	x	y	z	# voxels
Corpus callosum	7	15	20	13982
B fornix	1	-8	11	599
L cingulum	-20	-20	-18	226
L cerebral peduncle	-16	-24	-9	420
L inferior frontal-occipital fasciculus	-31	10	-6	1131
L fornix	-29	-16	-10	1227
L superior longitudinal fasciculus	-14	7	37	264
L arcuate fasciculus	-42	-22	28	263
R inferior frontal-occipital fasciculus	30	7	-5	257
L uncinate	-9	3	4	814
Words per Minute Regression in naPPA				
Corpus callosum	-8	21	20	58
Grammatically Well-Formed Regression in naPPA				
L inferior longitudinal fasciculus	-39	-28	-11	124
L superior longitudinal fasciculus	-17	4	36	62
Mean Length of Utterance Regression in naPPA				
Corpus callosum	8	7	23	61
L cingulum	-8	14	24	80
L inferior frontal-occipital fasciculus	-25	31	4	63