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Longitudinal gray matter contraction in three variants of primary progressive aphasia: A tenser-based morphometry study

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ABSTRACT

The present study investigated the pattern of longitudinal changes in cognition and anatomy in three variants of primary progressive aphasia (PPA). Eight patients with the non-fluent variant of PPA (nfvPPA), 13 patients with the semantic variant (svPPA), seven patients with the logopenic variant (lvPPA), and 29 age-matched, neurologically healthy controls were included in the study. All participants underwent longitudinal MRI, neuropsychological and language testing at baseline and at a 1-year follow-up. Tenser-based morphometry (TBM) was applied to T1-weighted MRI images in order to map the progression of gray and white matter atrophy over a 1-year period. Results showed that each patient group was characterized by a specific pattern of cognitive and anatomical changes. Specifically, nfvPPA patients showed gray matter atrophy progression in the left frontal and subcortical areas as well as a decline in motor speech and executive functions; svPPA patients presented atrophy progression in the medial and lateral temporal lobe and decline in semantic memory abilities; and lvPPA patients showed atrophy progression in lateral/posterior temporal and medial parietal regions with a decline in memory, sentence repetition and calculations. In addition, in all three variants, the white matter fibers underlying the abovementioned cortical areas underwent significant volume contraction over a 1-year period.
Overall, these results indicate that the three PPA variants present distinct patterns of neuroanatomical contraction, which reflect their clinical and cognitive progression.

1. Introduction

Primary progressive aphasia (PPA) is a syndrome characterized by isolated speech and language symptoms for the first 2 years of the disease (Mesulam, 2003). Three main clinical variants with specific features at presentation have been described: the nonfluent/agrammatic variant of PPA (nfvPPA), semantic variant of PPA (svPPA), and the logopenic variant of PPA (lvPPA) (Gorno-Tempini et al., 2011). Different linguistic features, patterns of atrophy and underlying pathology characterize each variant (Josephs et al., 2008).

nfvPPA is characterized by effortful speech, agrammatism in production and apraxia of speech, and has been associated with gray matter atrophy in the left premotor, anterior insula and inferior frontal regions (Gorno-Tempini et al., 2004b; Josephs et al., 2006; Wilson et al., 2009, 2011), as well as severe white matter changes in the dorsal language network (superior longitudinal fasciculus and its components) (Galantucci et al., 2011). Some reports suggest that as nfvPPA progresses, patients often develop Parkinsonism and other clinical features suggestive of either a corticobasal syndrome or progressive supranuclear palsy (Gorno-Tempini et al., 2004c; Josephs et al., 2005, 2006). nfvPPA patients may become functionally mute early in the disease, while other language functions are still relatively spared (Gorno-Tempini et al., 2004b, 2006). Consistently, nfvPPA has often been found to have tau-positive pathology at autopsy (Josephs et al., 2006).

svPPA presents with anomia and loss of semantic memory, as well as bilateral atrophy in the anterior temporal lobes (Gorno-Tempini et al., 2004b; Hodges et al., 1992; Mummery et al., 2000; Rosen et al., 2002) and significant involvement of the white matter fiber bundles of the uncinate fasciculus and the inferior longitudinal fasciculus bilaterally (Galantucci et al., 2011). Over time, in addition to the progressive semantic deficits, patients also develop behavioral symptoms (Neary et al., 1998; Seeley et al., 2005) and show progression of atrophy in

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the initially less-affected anterior temporal lobe and orbitofrontal regions (Brambati et al., 2009c). From a pathological point of view, approximately 75% of cases have features conforming to type C of the TDP-43 proteinopathies (Cairns et al., 2007; Grossman, 2010; Mackenzie et al., 2011; Sampathu et al., 2006). Only a minority of cases have been associated with Pick's disease and Alzheimer's disease pathology (Davies et al., 2005; Grossman, 2010; Hodges et al., 2010; Mesulam et al., 2008).

lvPPA (Gorno-Tempini et al., 2004b, 2011), presents with word finding pauses, poor repetition and comprehension of sentences, and has been associated with left temporo-parietal atrophy (Gorno-Tempini et al., 2004b; Wilson et al., 2009, 2011) and white matter damage, mainly in the temporoparietal component of the left superior longitudinal fasciculus and in the left arcuate fasciculus (Galantucci et al., 2011). Over time, lvPPA shows a generalized cognitive decline including language functions (naming, sentence repetition and comprehension), attention, memory recall, and visuo-spatial abilities (Leyton et al., 2013; Rohrer et al., 2013). Anatomically, disease progression is associated with a progression of atrophy in the left temporal, parietal, frontal and caudate areas, and in the right posterior cingulate/precuneus (Rohrer et al., 2013). Converging evidence indicates that Alzheimer's disease pathology with an atypical presentation may be responsible for lvPPA (Josephs et al., 2008; Mesulam et al., 2008; Rabinovici et al., 2008b; Rohrer et al., 2012, 2013).

PPA syndromes can be quite heterogeneous in terms of disease duration and symptom progression. A better understanding of anatomical disease progression could significantly help predict the time course of the disease, the symptoms that may arise in these patients and could also have a major impact on caregiver education and support. Furthermore, tracking the disease over time could shed light on the possible mechanisms involved in the spreading of the disease. In this framework, the characterization of the pattern of atrophy progression represents a major challenge in the study of PPA patients. To date, only a few studies have investigated the progression of gray matter atrophy over time in a single variant of PPA, such as svPPA (Brambati et al., 2009c; Chan et al., 2001b; Whitwell et al., 2004) and lvPPA (Rohrer et al., 2013). However, none of these studies have investigated both GM and WM tissue contraction over time in the three clinical variants of PPA.

Neuroimaging MRI techniques, such as tenser-based morphometry (TBM), have been developed to allow for objective and automated mapping of tissue loss over time (Chan et al., 2001a; Fox et al., 2000, 2001; Fox and Freeborough, 1997; Freeborough et al., 1996; Kipps et al., 2005; Leow et al., 2006; Studholme et al., 2001). TBM as implemented in Statistical Parametric Mapping (SPM), has been successfully applied to identify areas of gray matter contraction in neurodegenerative disorders such as pre-symptomatic carriers for Huntington's disease gene mutation (Kipps et al., 2005), frontotemporal dementia (Brambati et al., 2007), svPPA (Brambati et al., 2009c), and lvPPA (Rohrer et al., 2013). In the present study we used TBM as implemented in SPM in order to map the gray and white matter atrophy progression over 1 year following diagnosis in 28 PPA patients compared to 29 healthy age-matched controls.

2. Methods

2.1. Subjects

Fifty-seven subjects participated in the neuroimaging study: 28 PPA (8 nfvPPA, mean age 67.9 ± 10.4; 13 svPPA, mean age 62.6 ± 6.4; 7 lvPPA, mean age 64.3 ± 7.2) and 29 age-matched neurologically-normal individuals (mean age 65.6 ± 7.5) recruited from the Memory and Aging Center (MAC) at the University of California, San Francisco. At the time of enrollment in the study, all research participants underwent a detailed clinical evaluation including a thorough history, neurological examination, cognitive and neuropsychiatric evaluation. The results of the evaluation were reviewed by a multidisciplinary team in order to formulate a consensus diagnosis. A diagnosis of PPA required progressive deterioration of speech and/or language functions, and that deficits be largely restricted to speech and/or language for a period of at least 2 years (Mesulam, 1982, 2003). Patients were diagnosed with non-fluent, semantic or logopenic variants of PPA based on recent guidelines (Gorno-Tempini et al., 2011).

Subjects who had had two structural MRIs 1 year apart (the first at the time of diagnosis and the second at 1-year follow-up, mean time interval 12.7 ± 3.3 months) were included in the study. All participants signed a written informed consent that had been approved by the local Committee on Human Research.

2.2. Neuropsychological testing: cognitive and language evaluation

All participants received a 1-hour standardized neuropsychological assessment as part of either a research or clinical visit. The specific methods regarding neuropsychological testing at the MAC have been described in previous studies (Brambati et al., 2007, 2009c; Gorno-Tempini et al., 2004a). Briefly, tests assessed multiple cognitive domains and included the MMSE (Folstein et al., 1975), the CVLT-Short Form (total number of words recalled over 4 learning trials, 30-s free recall, 10-minute free recall, and recognition), the Modified Rey–Osterrieth Figure (copy performance, 10-minute recall), the Modified Trail Making Test (Total Time, number of correct lines), the DKEFS Design Fluency Filled Dots Condition (number of correct designs), the Stroop Interference (number correct), calculations, praxis, lexical Fluency (number of 'D' words in 60″), semantic Fluency (number of Animals in 60″), 15-Item Boston Naming Test (BNT), Sentence Repetition, and Clinician Rating of Language Symptoms (melody, phrase length, grammar, paraphasic errors, word-finding difficulties, comprehension; 0 = maximal impairment, 4 = normal).

The patients also underwent a comprehensive language evaluation as part of an ongoing research study. The language battery has been described in detail in a previous study (Gorno-Tempini et al., 2004b) and included the Western Aphasia Battery (WAB) (Kertesz, 1980) with the following subtests: Spontaneous Speech (Information content and Fluency), Yes/No Comprehension, Auditory Word Recognition Total Score, Sequential Commands Total Score, Repetition Total Score. Additional measures included the Motor Speech Evaluation (MSE) Apraxia of Speech Rating, the MSE Dysarthria Rating (Mack et al., 1992), and the total score for 11 of the CYCLE-R syntactic comprehension subtests (Curtiss and Yamada, 1988).

2.2.1. Longitudinal changes in cognitive and language profiles: data analysis

All neuropsychological and language variables were examined for normality and most variables were found to be non-normally distributed. Given the non-normal distributions and relatively small samples sizes, we elected to use nonparametric tests to examine differences between the performance at the time of diagnosis and follow-up. In addition, due to small sample sizes we chose to examine patterns of change within each group, rather than group by time interactions. Thus, for each dependent variable, we used a Wilcoxon test to compare performance at the time of diagnosis and at 1-year follow-up within each diagnostic group. Original means and standard deviations can be found in Tables 1 and 2, along with notations of significant findings. To perform the statistical analysis SPSS, STATA, and R software were used (Team, 2008).

2.3. Imaging

2.3.1. Image acquisition

The brain structural MRI scans at the time of diagnosis (baseline image) and 1-year follow-up were obtained with a 1.5 Tesla Magneton

VISION system (Siemens Inc., Iselin, NJ). A volumetric magnetization prepared rapid gradient echo (MP-RAGE) MRI was used to obtain a T1-weighted image of the entire brain, using acquisition parameters described elsewhere (Gorno-Tempini et al., 2004b).

2.3.2. Tensor based morphometry pre-processing

Pre-processing TBM procedures are described in detail in previous articles (Brambati et al., 2007, 2009c; Kipps et al., 2005). Briefly, we applied a bias correction to the follow-up T1-weighted scan previously co-registered with the baseline image. As a result of this procedure, a version of the follow-up image that had the same bias as that of the baseline image was obtained. Using a high dimensional intra-subject deformation based on the 'Deformation tool' of SPM2, we warped the follow-up image to match the image at the time of diagnosis (Ashburner and Friston, 2000). This approach minimizes the mean squared difference between the images. A regularization step was also included in the function, which kept the deformations smooth, and enforced a one-to-one mapping. The tradeoff between the mean squared difference among the images and the smoothness of the deformations was defined by a regularization parameter, which was set to four. Based on previous studies (Brambati et al., 2007, 2009c; Kipps et al., 2005), eight iterations of the algorithm were considered sufficient to model the deformations that were likely to occur within a subject over time. The amount of volume change was quantified by taking the determinant of the gradient of deformation at a single-voxel level (Jacobian determinants). The following formula was applied to the segmented gray matter image that was obtained from the first scan (Ashburner and Friston, 2003) and the Jacobian determinant map: (Jacobian value-1) * gray (or white) matter segments of the scan at the time of diagnosis. The resulting product image represented a measure of the specific gray matter volume change between the first and second scan. A study-specific template and a-priori images were created by averaging each subject's baseline and follow-up T1-weighted images after normalization and segmentation using the Montreal Neurological Institute (MNI) brain and a-priori images provided with SPM. The normalization parameters were estimated by matching the customized gray matter template with the segmented gray matter image from the baseline scan. The normalization parameters were then applied to the product image (Ashburner and Friston, 1999). Normalized images were smoothed using a 12 mm isotropic Gaussian kernel, consistent with previous studies using the same methodological approach in neurodegenerative diseases (Brambati et al., 2007, 2009c; Kipps et al., 2005).

2.3.3. Tenser-based morphometry statistical analysis

The pattern of gray and white matter progression in different variants of PPA was assessed using 'condition and covariates' statistical model, entering sex, age and total intracranial volume at the time of

Table 1
Demographics and neuropsychological screening results in each of the three PPA variants at the time of diagnosis (baseline) and at 1 year follow-up.

	nfvPPA ($N = 8$)		svPPA ($N = 13$)		lvPPA ($N = 7$)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Demographics						
Age	67.9 ± 10.4		62.6 ± 6.4		64.3 ± 7.2	
Education	16.1 ± 3.0		16.6 ± 2.7		17.4 ± 3.5	
Gender (M/F)	2/6		9/4		5/2	
Handedness (R/L)	8/0		13/0		6/1	
Global function						
MMSE (30)	27.9 ± 1.7	23.1 ± 7.5	23.3 ± 6.3	17.5 ± 8.8[a]	21.6 ± 5.0	16.9 ± 6.8[a]
Memory						
CVLT total learning (36)	25.1 ± 6.4	23.4 ± 9.7	13.2 ± 5.2	8.9 ± 6.2[a]	14.2 ± 4.8	6.8 ± 9.0[b]
CVLT 30 s recall (9)	7.1 ± 1.9	6.5 ± 3.0	2.5 ± 2.0	1.1 ± 1.8[a]	3.0 ± 2.4	1.8 ± 3.0[b]
CVLT 10 minute recall (9)	7.1 ± 2.1	5.8 ± 4.1	1.6 ± 2.1	0.7 ± 1.7	2.2 ± 1.9	1.0 ± 2.2[b]
Modified Rey 10 minute recall (17)	10.5 ± 4.0	8.5 ± 5.9	7.5 ± 4.3	8.4 ± 5.6	8.7 ± 4.0	8.0 ± 5.6
Language						
Boston naming test (15)	12.8 ± 2.1	12.5 ± 1.8	4.0 ± 3.4	2.9 ± 2.7	10.4 ± 3.3	7.9 ± 2.9 [b]
D word fluency	5.9 ± 3.9	6.3 ± 4.2	7.2 ± 4.3	5.9 ± 3.5	8.9 ± 4.9	5.4 ± 6.1
Animal fluency	11.9 ± 5.1	8.1 ± 5.5[a]	6.1 ± 2.7	4.7 ± 2.4	8.9 ± 4.6	6.1 ± 6.9
Sentence repetition (3)	2.3 ± 1.4	2.1 ± 1.2	2.4 ± 1.0	2.3 ± 0.9	1.2 ± 1.0	1.3 ± 0.8
Examiner's rating: melodic (4)	2.3 ± 1.4	1.4 ± 1.3	3.9 ± 0.4	3.9 ± 0.3	3.3 ± 0.5	2.0 ± 0.8[b]
Examiner's rating: phrase length (4)	2.6 ± 1.1	2.1 ± 1.5	3.8 ± 0.5	3.4 ± 1.0	3.0 ± 0.8	1.8 ± 0.5[b]
Examiner's rating: grammar (4)	2.9 ± 0.8	2.4 ± 1.5	3.4 ± 1.0	3.1 ± 1.3	3.3 ± 0.8	1.8 ± 1.0[b]
Examiner's rating: paraphasic errors (4)	2.5 ± 1.7	2.6 ± 1.8	3.0 ± 0.7	2.4 ± 1.1	2.0 ± 0.8	1.5 ± 1.3
Examiner's rating: word finding (4)	2.3 ± 1.2	2.7 ± 1.4	2.4 ± 1.3	2.2 ± 1.2	2.8 ± 1.0	1.0 ± 0.8[b]
Examiner's rating: comprehension (4)	3.6 ± 0.5	3.3 ± 0.8	2.7 ± 1.3	1.9 ± 1.4[a]	3.0 ± 0.8	2.0 ± 0.0[b]
Executive function						
Modified trails Time (120")	60.4 ± 39.3	82.4 ± 45.3[b]	65.4 ± 31.2	77.3 ± 41.7	91.3 ± 45.4	91.7 ± 49.1
Modified trails # correct (14)	9.1 ± 6.7	8.1 ± 6.4	12.7 ± 3.8	11.9 ± 3.6	12.7 ± 2.3	7.3 ± 6.1
Stroop interference # correct	25.8 ± 12.3	22.0 ± 8.4	27.3 ± 15.4	32.1 ± 16.6	13.8 ± 7.7	6.5 ± 7.9[b]
Design fluency # correct	7.5 ± 3.3	5.3 ± 2.3[a]	7.8 ± 3.5	6.4 ± 3.4	6.3 ± 3.1	4.0 ± 1.7
Digits backward (span)	3.0 ± 1.6	3.0 ± 1.7	4.7 ± 1.4	4.8 ± 0.7	2.7 ± 1.0	1.7 ± 1.4
Other						
Modified Rey figure copy (17)	15.0 ± 1.3	11.6 ± 5.4[b]	16.4 ± 0.9	16.5 ± 0.8	13.8 ± 3.8	13.0 ± 6.4
Calculations (5)	4.6 ± 1.1	3.6 ± 1.3[a]	4.6 ± 0.8	4.6 ± 0.5	2.9 ± 1.6	2.3 ± 1.3
Praxis (14)	10.1 ± 3.8	10.4 ± 2.9	12.7 ± 2.6	10.6 ± 2.6[b]	12.8 ± 1.9	7.8 ± 4.0[b]

Abbreviations: nfvPPA = non-fluent variant PPA, svPPA = semantic variant PPA, lvPPA = logopenic variant PPA, MMSE = Mini-Mental State Examination, CVLT = California Verbal Learning Test.

[a] T1 vs. T2 comparison significant at $p < 0.05$.

[b] T1 vs. T2 comparison a trend at $p < 0.10$.

Table 2
Language battery results in each of the three PPA variants at baseline and 1-year follow-up.

	nfvPPA		svPPA		lvPPA	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
WAB Information Content (10)	8.0 ± 3.0	5.9 ± 3.8[a]	8.7 ± 0.8	7.5 ± 2.1[a]	8.3 ± 1.9	7.2 ± 1.8[a]
WAB Fluency (10)	7.3 ± 3.2	4.8 ± 4.1[a]	8.7 ± 1.2	8.5 ± 1.5	7.7 ± 1.8	5.5 ± 3.1[b]
WAB Spontaneous Speech Total (20)	15.3 ± 5.8	10.6 ± 7.7[a]	17.4 ± 1.6	16.0 ± 3.1	16.0 ± 3.5	12.7 ± 4.8[a]
WAB Yes–No Comprehension (60)	57.4 ± 4.1	57.6 ± 3.4	57.0 ± 4.6	49.1 ± 12.2[a]	57.8 ± 4.5	48.0 ± 24.0
WAB Auditory Word Recognition (60)	59.8 ± 0.7	56.9 ± 3.3[a]	52.8 ± 6.4	40.0 ± 12.8[a]	57.0 ± 2.9	57.0 ± 2.2
Sequential Commands (80)	74.0 ± 5.3	73.9 ± 7.6	75.43 ± 8.0	50.3 ± 24.2[a]	66.0 ± 11.3	48.4 ± 24.2[a]
Repetition (100)	83.7 ± 17.8	68.0 ± 36.6[b]	90.6 ± 13.2	82.3 ± 13.9[b]	69.0 ± 16.1	58.8 ± 26.8[a]
MSE apraxia of speech (7 = max deficit, 0 = normal)	3.5 ± 2.2	5.0 ± 2.1[a]	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 1.5	1.0 ± 2.0
MSE dysarthria rating (7 = max deficit, 0 = normal)	2.6 ± 2.7	1.6 ± 2.5[b]	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
CYCLE-R syntax comprehension (55)	49.6 ± 4.3	45.3 ± 7.9[a]	54.0 ± 1.1	45.0 ± 10.8[b]	41.7 ± 7.2	35.0 ± 4.4

Abbreviations: nfvPPA = non-fluent variant PPA, svPPA = semantic variant PPA, lvPPA = logopenic variant PPA; WAB = Western Aphasia Battery, MSE = Motor Speech Evaluation, CYCLE-R = Curtiss–Yamada Comprehensive Language Evaluation-Receptive.
[a] T1 vs. T2 comparison significant at $p < 0.05$.
[b] T1 vs. T2 comparison a trend at $p<0.10$.

the first scan as confounding variables. Regionally specific differences in gray matter volumes were assessed using the general linear model (Friston et al., 1994) and the significance of each effect was determined using the theory of Gaussian fields (Friston et al., 1996). Specific statistical analyses were performed to map the progression of both gray and white matter volume change in the three PPA variants compared to controls over the 1-year period. We accepted a level of significance of $p < 0.001$, uncorrected at whole-brain level. The anatomical localization of the gray matter voxels was assigned using with the Duvernoy Human Brain Atlas (Duvernoy, 1999, 1998), while Mori's Atlas of Human White Matter was used to identify the location of the white matter voxels (Mori et al., 2005).

3. Results

3.1. Language and cognitive profile at the time of diagnosis

There were no significant effects of diagnosis on age or gender at the time of diagnosis. Thus, these variables were not included as covariates in any of the following analyses.

As per classification criteria, language evaluation showed that 1) nfvPPA cases manifested impairments in speech production (Spontaneous Speech Fluency, MSE Ratings of Apraxia of Speech & Dysarthria), altered grammar, and decreased phonemic fluency, probably due to apraxia of speech and/or dysarthria, 2) svPPA had defective word recognition, comprehension skills, naming, and verbal fluency (semantic > phonemic) in the context of relatively spared visual–spatial and executive abilities, and 3) lvPPA showed difficulties on tasks of naming, sentence repetition, sequential commands, and syntax comprehension.

Nonetheless, the cognitive assessment revealed that 1) nfvPPA patients had mild executive dysfunction (e.g., trails, design fluency) in the context of relatively spared global abilities, including memory and visual-spatial function, 2) svPPA had relative deficits in memory, and 3) lvPPA was associated with more global difficulties relative to nfvPPA or svPPA, including decreased memory, executive function (e.g., Stroop interference, digits backward span), figure copy, and calculations.

3.2. Longitudinal changes in cognitive and language profile

3.2.1. Non-fluent/agrammatic variant PPA

At follow-up, nfvPPA was associated with a significant decline ($p < 0.05$) in WAB Information, WAB Fluency, Auditory Word Recognition, MSE Apraxia of Speech rating, syntax comprehension, animal fluency, calculations, and design fluency (see Table 2 and Fig. 1). There were trends ($p < 0.10$) for a decline in constructional praxis (modified Rey copy) and set-shifting (modified trails). Although not significant, longitudinal decline was also observed in the clinician ratings of melody, phrase length, and grammar. The areas of relative strengths for nfvPPA were comprehension tasks (Yes/No Comprehension, Auditory Word Recognition, Sequential Commands), global cognition (MMSE), verbal (CVLT) and visual memory (Modified Rey-copy), naming (BNT), and clinician rating of comprehension skills.

3.2.2. Semantic variant PPA

On language tests, svPPA was associated with significant decline ($p < 0.05$) in Information Content, Yes–No Comprehension, Auditory Word Recognition, and Sequential Commands (see Table 2 and Fig. 1). At a more general cognitive level, significant decline was also observed in global cognition (MMSE), verbal memory (CVLT total learning and 30-s recall), and clinician rating of comprehension skills. There was a trend ($p < 0.10$) for a decline in praxis. Unfortunately, many of the svPPA scores were at floor level at the time of diagnosis, which made it difficult to detect any longitudinal decline. Visual–spatial and executive skills remained areas of relative strength.

3.2.3. Logopenic variant PPA

At follow-up, lvPPA was associated with significant decline ($p < 0.05$) in spontaneous speech Information Content, Sequential Commands, sentence repetition (see Table 2 and Fig. 1) and on the MMSE. Additionally, there were trends ($p < 0.10$) for decline in verbal memory (learning), naming, Stroop interference, praxis, and poorer clinician ratings of melody, phrase length, grammar, and word-finding. Although not significant, additional numerical decline was observed in verbal fluency, design fluency, digits backward, and calculations. Of note, the amount of change in each lvPPA patient's longitudinal profile appeared to be quite variable relative to svPPA and nfvPPA, which likely made it more difficult to see consistent and significant change when looking at the longitudinal lvPPA data at the group level. Overall, these findings suggest that lvPPA patients tend to show relatively more diffuse cognitive impairment in comparison to the other two PPA variants.

In summary, although many of the longitudinal analyses within each diagnostic group were not statistically significant, the general pattern of results was as expected. Specifically, nfvPPA showed progression in speech fluency and executive dysfunction, while svPPA showed decline in MMSE, memory and comprehension. lvPPA was more variable, but as a group showed decline in repetition, fluency, comprehension, and the MMSE, with trends for additional decline in memory, naming, praxis, and executive function.

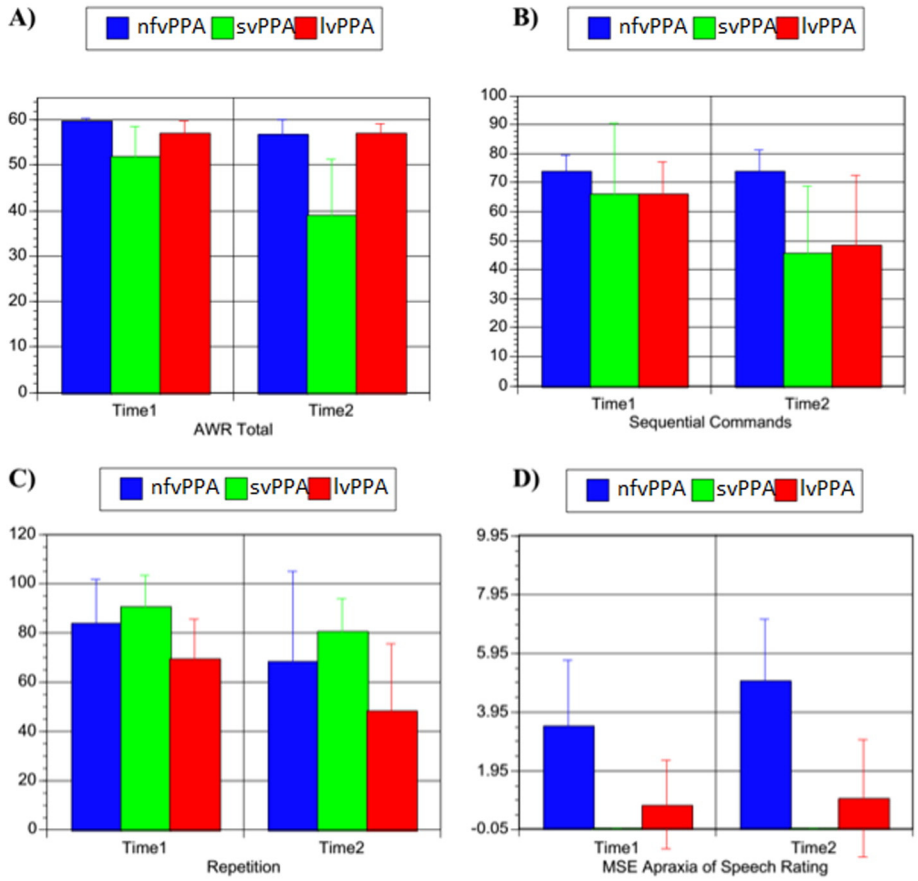

Fig. 1. Mean scores of four language tests, at baseline (light gray) and at follow-up (dark gray), in each of the three PPA variants.

3.3. Imaging

3.3.1. Gray and white matter atrophy progression

3.3.1.1. Gray matter. The TBM analysis of the gray matter showed a distinct pattern of progressive atrophy in each of the three PPA variants (see Table 3 and Fig. 2).

3.3.1.1.1. nfvPPA vs. controls. In nfvPPA, over 1 year from initial diagnosis, significant gray matter (GM) contraction was found in the left frontal lobe, and more specifically in the inferior frontal gyrus, pars triangularis (45), rolandic operculum (6) and precentral gyrus (6). Within the temporal lobe, significant GM contraction was observed in the anterior portion of the fusiform gyrus (20). Regions of progressive GM contraction were observed in some subcortical structures such as the bilateral hippocampus/amygdala, right thalamus, and bilateral cerebellum ($p < 0.05$, FWE-corrected).

3.3.1.1.2. svPPA vs. controls. Patients with svPPA showed significant GM contraction over time bilaterally in the anterior temporal lobes including the superior (22), middle (21) and inferior (20) temporal gyri, fusiform gyrus (20/37), temporal pole, and parahippocampal gyrus. Regions of GM contraction over time were also observed in the basal ganglia (left bilateral putamen, left pallidum, and right thalamus) and in the left frontal lobe including medial orbital gyrus (25), superior medial frontal gyrus (32), anterior cingulate (32), and bilateral insula ($p < 0.05$, FWE-corrected). When we lowered the threshold to a less conservative one of $p < 0.001$ uncorrected, further areas of GM contraction were observed in the right inferior frontal gyrus, pars opercularis (44), supramarginal gyrus (40), angular gyrus (39), and superior frontal gyrus (9).

3.3.1.1.3. lvPPA vs. controls. No significant regions of GM contraction over 1-year period following diagnosis were observed in the lvPPA group at the pre-established threshold of $p < 0.05$ FWE-corrected, probably due to the small sample size. For exploratory analysis, we lowered the level of significance to a more permissive threshold of $p < 0.001$ uncorrected in the regions that have shown progressive GM contraction over time in a previous study of our group (Rohrer et al., 2013). Within our regions of interest, lvPPA showed gray matter contraction bilaterally in the anterior portion of the left superior temporal gyrus, and in left inferior temporal and fusiform gyri (0.001 uncorrected). Due to our hypothesis regarding Alzheimer's disease as a frequent underlying pathology in lvPPA (Rabinovici et al., 2007, 2008a), an exploratory analysis was performed to examine whether lvPPA patients showed gray matter contraction in the hippocampus. Significant changes in GM volume over 1 year following diagnosis were observed in left hippocampus at a threshold of $p < 0.005$ uncorrected.

Overall, these results suggest differential patterns of longitudinal gray matter contraction over 1 year following diagnosis in the three PPA variants. Specifically, nfvPPA showed progressive GM volume contraction mainly in left prefrontal regions, svPPA in bilateral temporal and insular cortex, and the basal ganglia, while lvPPA showed contraction mainly in left temporal regions and hippocampus.

3.3.1.2. White matter. The white matter analysis revealed differential patterns of white matter contraction over a 1-year period in the three diagnostic groups (see Table 4 and Fig. 2).

3.3.1.2.1. nfvPPA vs. controls. nfvPPA had a greater progression of atrophy in the left superior region of the corona radiata ($p < 0.05$, FWE-corrected). Other areas associated with greater gray matter contraction were the superior longitudinal fasciculi bilaterally, the right anterior portion of the corpus callosum, the right middle cerebellar peduncle and the left corticospianal/corticobulbur tract at the midbrain level ($p < 0.001$, uncorrected).

Table 3
Voxel of significant gray matter contraction over 1 year in each of the three PPA variants vs. controls.

Region (BA)	H	x	y	z	T	Z
nfvPPA vs CTRL						
Inferior frontal gyrus, pars triangularis (45)	L	−47	17	8	7.2	6.0
Rolandic operculum (6)	L	−51	0	11	8.1	6.4
Precentral gyrus (6)	L	−42	8	41	7.8	6.3
Fusiform gyrus, anterior portion (20)	L	−36	−5	−29	7.0	5.8
Hippocampus/amygdala	L	−19	−4	−11	6.4	5.4
	L	−23	−31	4	7.6	6.1
	R	21	−36	7	6.7	5.6
Thalamus	R	13	−22	16	6.7	5.6
Cerebellum	R	2	−43	−43	5.9	5.1
	L	−9	−62	−41	3.7	3.5*
svPPA vs CTRL						
Superior temporal gyrus (22)	L	−46	−10	−1	6.4	5.4
	L	−34	6	−27	9.3	7.0
Middle temporal gyrus, anterior portion (21)	L	−61	−27	−15	6.1	5.3
	R	55	−2	−20	7.4	6.1
Inferior temporal gyrus, anterior portion (20)	L	−49	9	−43	6.6	5.6
	L	−58	−12	−24	6.4	5.5
	R	39	2	−37	10.2	7.4
Fusiform gyrus (20/37)	L	−34	−39	−23	11.1	7.8
	R	27	17	−43	7.8	6.3
Temporal Pole (20/38)	R	51	9	−14	7.3	6.0
	R	45	23	−31	6.0	5.2
	R	31	19	−42	7.7	6.2
Parahippocampal gyrus	L	−28	−13	−28	10.3	7.5
	L	−20	−41	−7	7.1	5.9
	R	27	−24	−26	9.2	6.9
	R	17	−4	−24	9.8	7.3
Putamen	L	−17	15	3	8.5	6.6
	R	19	15	7	7.2	5.9
Pallidum	L	−15	1	−5	6.6	5.5
Thalamus	R	12	−8	6	6.9	5.7
	R	9	−3	−1	6.4	5.4
Insula (13)	L	−33	15	−11	8.1	6.4
	R	45	11	−11	6.4	5.4
Medial orbital gyrus (25)	L	−11	14	−14	10.3	7.5
Superior medial frontal gyrus (32)	L	−7	41	31	6.2	5.3
Anterior cingulate (32)	L	−5	49	8	6.6	5.5
Inferior frontal gyrus, pars opercolaris (44)	R	57	13	20	5.2	4.6*
Supramarginal gyrus (40)	L	−58	−33	39	4.5	4.1*
Angular gyrus (39)	L	−41	−70	45	3.9	3.6*
Superior frontal gyrus (9)	R	19	46	36	5.0	4.5*
	L	−18	46	35	3.8	3.6*
lvPPA vs CTRL						
Superior temporal gyrus, anterior portion (20)	R	51	6	−9	3.6	3.4*
	L	−33	8	−27	3.5	3.3*
Inferior temporal gyrus (20)	L	−44	−38	−23	4.8	4.4*
Fusiform gyrus (37)	L	−35	−37	−23	4.6	4.1*
Hippocampus	L	−23	−1	−19	3.4	3.3§

nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, lvPPA = logopenic variant of primary progressive aphasia, CTRL = age- and sex-matched healthy control.
* $p < 0.001$ uncorrected for multiple comparison.
§ $p < 0.005$ uncorrected for multiple comparison.

3.3.1.2.2. svPPA vs. controls. svPPA was associated with a progressive reduction of the white matter underlying the temporal lobe (left inferior fronto-occipital fasciculus, uncinate fasciculus, and bilateral inferior longitudinal fasciculus; $p < 0.05$, FWE-corrected). In addition, svPPA showed white matter contraction in the left corpus callosum (genu, body and splenium), bilateral anterior thalamic projection, right corticospinal tract, bilateral superior longitudinal fasciculi ($p < 0.05$, FWE-corrected). Other areas associated with white matter progression were right inferior cerebellar peduncle and left superior longitudinal fasciculus ($p < 0.001$, uncorrected).

3.3.1.2.3. lvPPA vs controls. lvPPA showed greater white matter progression in the right superior longitudinal fasciculi and left posterior cingulate ($p < 0.05$, FWE-corrected). At a lower level of significance ($p < 0.001$, uncorrected) also left inferior longitudinal/inferior fronto-occipital fasciculus was associated with white matter contraction.

Overall, these results suggest differential patterns of longitudinal WM contraction over 1 year following diagnosis in the three PPA variants. Specifically, nfvPPA showed progressive WM volume contraction bilaterally in the frontal lobes, svPPA in the temporal lobes, while lvPPA in WM regions in correspondence to temporo-parietal regions.

4. Discussion

In the present study, we used TBM to track the progression of brain tissue contraction over 1 year following the diagnosis in the three clinical variants of PPA (Gorno-Tempini et al., 2011), including eight patients with nfvPPA, 13 with svPPA and seven with lvPPA. The current study showed that the three variants have distinct and only partially overlapping patterns of gray and white matter atrophy progression. More specifically, the results revealed a pattern of GM atrophy progression within the brain regions that are generally first targeted by each variant, i.e., the left prefrontal cortex and subcortical regions in nfvPPA, the anterior temporal lobes in svPPA and the posterior middle and superior temporal gyrus in the lvPPA. Moreover, GM contraction spreads over time towards nonadjacent regions such as the insular cortex and the basal ganglia in svPPA and in the left inferior temporal regions and the hippocampus in lvPPA. In all three variants, the white matter fibers underlying the abovementioned cortical areas underwent significant volume reduction in 1 year. In the following paragraphs, we describe the gray and white matter progression together with their clinical implications for each of the three PPA variants.

4.1. Nonfluent variant PPA (nfvPPA)

nfvPPA cases showed greater gray matter contraction in left frontal and subcortical regions. White matter progression was seen in left corona radiata, underlying the motor cortex and the supplementary motor area, which are fibers that connect frontal areas with subcortical nuclei and the spinal cord (Mori et al., 2005). These results extend cross-sectional imaging studies that found the left posterior frontal cortical and subcortical regions to be the most affected area in nfvPPA (Gorno-Tempini et al., 2004b; Josephs et al., 2006; Nestor et al., 2003). The brain regions that showed significant progression in nfvPPA represent a large network involved in speech production (Hickok, 2009; Price, 2010), grammar comprehension (Amici et al., 2007; Caplan, 1992; Wilson et al., 2010a,b, 2011, 2012b) and working memory (Amici et al., 2007; Jonides et al., 1993, 1998; Wilson et al., 2010a). Nonetheless, significant progression of WM volume loss was observed in dorsal language tracts that have been shown to connect brain regions that are critically involved in syntactic processing (Wilson et al., 2011). These anatomical changes likely contribute to the observed decreases in grammar, phrase length and melody of speech, and to the decline in executive skills. Our findings are also in line with previous pathologically-confirmed case observations. In fact, atrophy of the perirolandic region, middle and inferior frontal gyrus, thalamus and bulbar brainstem involvement has been found in nfvPPA pathologically confirmed cases (Josephs et al., 2006). These regions are also most involved in 4R tauopathies such as progressive supranuclear palsy (Boxer et al., 2006; Brenneis et al., 2004; Cordato et al., 2005; Padovani et al., 2006) and cortico-basal degeneration (Boxer et al., 2006), which is the most common pathology associated with nfvPPA (Josephs et al., 2006).

4.2. Semantic variant PPA (svPPA)

svPPA patients demonstrated longitudinal gray matter contraction in several regions of the lateral and medial temporal lobes, insula and ventromedial cortex. Main areas of WM contraction over time were observed bilaterally in the inferior longitudinal fasciculus connecting occipital and anterior temporal regions, and in the uncinate fasciculus

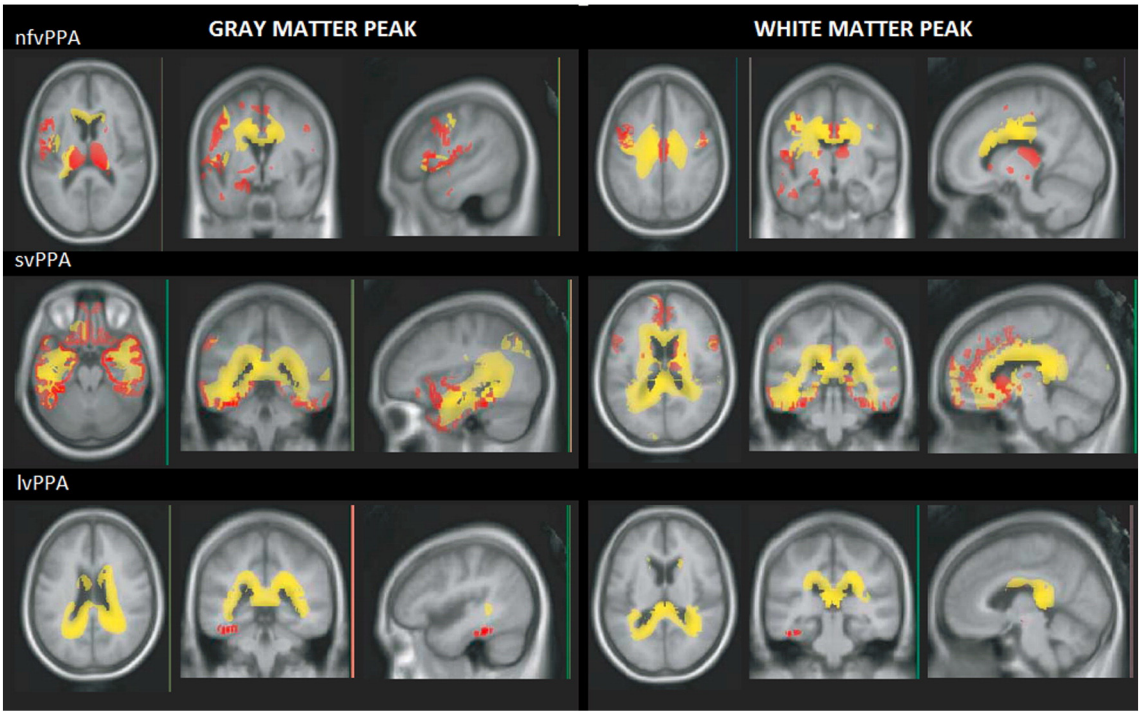

Fig. 2. Transverse, coronal and sagittal slices of the main peak of gray matter (shown in red) and white matter (shown in yellow) contraction in nfvPPA (first row), svPPA (second row), and lvPPA (third row) versus controls. The results are superimposed on a section of the study-specific template. The x, y, and z values reported in the figure represent the position of slices within the Montreal Neurologic Institute (MNI) stereotaxic space. The threshold is set at $p < 0.001$ uncorrected for display purpose.

connecting the anterior temporal regions with the frontal lobe. Both of these GM and WM brain structures have been shown to be affected in svPPA patients even at early stages of the disease (Agosta et al., 2010; Borroni et al., 2007; Gorno-Tempini et al., 2004b; Mummery et al., 2000; Rosen et al., 2002). Overall, our findings seem to indicate that the regions usually atrophic in svPPA patients become more atrophic after 1 year and the atrophy spread both medially and posteriorly within the temporal lobe together with the white matter bundles that connect the temporal lobe with the frontal and occipital cortex. These results are consistent with previous DTI (Agosta et al., 2010; Borroni et al., 2007), fluid registration (Whitwell et al., 2004) and TBM findings (Brambati et al., 2009c).

The areas that underwent major atrophic changes in svPPA, ventral and lateral temporal lobes, are part of a network involved in semantic memory (Butler et al., 2009; Mummery et al., 1999; Williams et al., 2005), exception word reading (Brambati et al., 2009b; Wilson et al., 2012a), identification of visual attributes (D'Esposito et al., 1997; Vandenbulcke et al., 2006), famous faces (Brambati et al., 2010; Gesierich et al., 2012; Gorno-Tempini et al., 1998; Kanwisher et al., 1997), buildings and landscapes (Epstein and Kanwisher, 1998). The progressive volume contraction in these areas is clinically associated with worsened single word comprehension abilities.

Other regions that showed greater progression were the insula, the ventromedial frontal and anterior cingulate, which have been associated with behavioral symptoms, emotional processing, mood regulation, and eating behavior (Rosen et al., 2005; Williams et al., 2005; Woolley et al., 2007) and less associated with executive function deficits (Possin et al., 2009). The medial frontal atrophy is likely associated with the development of behavioral and social dysfunction observed in this population (Seeley et al., 2005, 2008; Seeley, 2010).

Our longitudinal findings seem to provide critical support to the recently proposed pathophysiological model of svPPA progression (Fletcher and Warren, 2011). According to this model, the anterior temporal lobe would be vulnerable to the neurodegenerative effects of TDP-43-C (Mackenzie et al., 2006; Mesulam et al., 2014; Rohrer et al., 2010; Whitwell et al., 2010). However, the development of the semantic PPA manifestations would arise from disintegration of a distributed neural network with specific intrinsic anatomical and functional connectivity with the ATL (Fletcher and Warren, 2011). Consistently with this hypothesis, Guo and colleagues, report that svPPA patients showed reduced intrinsic connectivity throughout a distributed set of regions connected with the anterior temporal lobe in healthy controls (Guo et al., 2013). Nonetheless, the same authors reported that scores on semantic tasks correlated with physiological deficits *outside* the anterior temporal lobe, suggesting that the severity of the semantic impairments in svPPA is associated with the spread of the disease to cortical areas connected to the ATL (Guo et al., 2013). Interestingly, the set of regions whose physiological deficits correlate with the severity of the impairments in the semantic representations of emotions in the study by Guo and colleagues (i.e. insula, anterior cingulated, medial frontal cortex), also present with progressive volume contraction over a 1-year period in the present study.

Different possible candidates have been identified as potentially responsible for the spreading of the disease from the ATL to connected brain regions, including axonal degeneration, transynaptic spreading of abnormal protein, or abnormal folding in tau molecules induced by nearby folded tau (Bartz et al., 2002; Frost et al., 2009; Salehi et al., 2009) (see Fletcher and Warren, 2011 for a review). However, the precise molecular mechanisms leading to large-network distraction in svPPA still remain largely unknown.

4.3. Logopenic variant PPA (lvPPA)

lvPPA showed main GM volume reduction over 1 year following diagnosis in the left temporal lobe and hippocampus. White matter progression was present in the right superior longitudinal fasciculus and left posterior cingulum. The superior longitudinal fasciculus is a large bundle that connects perisylvian frontal, parietal and temporal cortex (Catani and Mesulam, 2008; Dejerine, 1895; Duffau, 2008; Petrides and Pandya, 1984). The arcuate fasciculus is part of the superior

Table 4
Voxels of significant white matter contraction over 1 year in the three PPA variants.

Region	H	x	y	z	T	Z
nfvPPA vs CTRL						
Superior corona radiata	L	−12	−10	37	6.4	5.4
	R	14	−7	31	5.6	5.0*
Superior longitudinal fasciculus	R	47	−5	37	3.7	3.4*
	R	67	−20	−1	3.3	3.3*
	L	−43	−10	41	5.3	4.7*
	L	−30	−19	25	4.5	4.1*
	L	−49	15	3	3.7	3.5*
Anterior corpus callosum	R	13	17	18	5.3	4.7*
Middle cerebellar peduncle	L	14	−33	−33	4.0	3.8*
Corticospinal tract (midbrain level)	R	−14	−23	−14	4.7	4.2*
svPPA vs CTRL						
Inferior longitudinal fasciculus	L	−27	−7	−17	8.3	6.5
	L	−23	−9	−15	6.6	5.6
	L	−37	−43	−9	7.9	6.3
	L	−44	−23	−19	8.0	6.3
	R	39	1	−39	6.2	5.3
	L	−21	−13	−17	6.3	5.3
Anterior thalamic projection	R	15	−5	22	8.0	6.4
	L	−13	3	19	6.1	5.2
Uncinate fasciculus	L	−31	1	−23	7.9	6.3
	L	−29	−9	−15	7.8	6.3
Superior longitudinal fasciculus	R	33	−37	13	5.9	5.1
	L	−13	−1	21	6.3	5.3
	L	−13	3	19	6.0	5.2
	L	−13	7	17	5.9	5.1
Corticospinal tract	R	15	−5	22	7.7	6.2
Splenium of corpus callosum	L	−8	−34	17	8.6	6.7
Body of corpus callosum	L	−11	−5	25	6.7	5.5
	L	−9	1	25	6.0	5.2
	L	−9	11	19	6.0	5.2
	L	−9	7	21	5.9	5.1
Genu of corpus callosum	L	−11	15	17	6.1	5.2
	L	−15	23	11	6.1	5.2
	L	−14	21	15	6.0	5.2
Inferior cerebellar peduncle	R	11	−44	−43	4.0	3.7*
lvPPA vs CTRL						
Superior longitudinal fasciculus	R	25	−44	25	6.5	5.5
	R	24	−28	31	6.1	5.3
		−22	−33	33	4.6	4.2*
Posterior cingulum	L	−18	−52	26	6,1	5.2
	L	−20	−55	23	6.1	5.2
	R	7	−31	7	5.6	4.9*
Inferior longitudinal fasciculus	L	−34	−47	−8	4.2	3.9*

nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, lvPPA = logopenic variant of primary progressive aphasia, CTRL = age- and sex-matched healthy control.
* $p < 0.001$, uncorrected for multiple comparison.

longitudinal fasciculus and is typically damaged in vascular conduction aphasia (Catani et al., 2005; Geschwind, 1965; Hickok and Poeppel, 2004), which shares the repetition deficits of lvPPA (Geschwind, 1965; Gorno-Tempini et al., 2004b). Posterior cingulum white matter fibers connect the anterior thalamus, anterior cingulate cortex, temporal lobe, and hippocampus and are atrophic in both MCI and AD patients (Damoiseaux et al., 2009). The brain regions showing progressive tissue loss in our study do not represent the areas usually reported to be atrophic at the beginning of the disease in the cross-sectional study (Gorno-Tempini et al., 2008, 2004b; Rohrer et al. n/d), i.e. the left posterior superior temporal and inferior parietal area. During the 1-year interval following diagnosis, the atrophy spread anterior-inferiorly and medially in the temporal lobe together with the underlying white matter connections (e.g., posterior cingulate). These results are consistent with a previous longitudinal study of our group revealing very similar results (Rohrer et al., 2013).

In lvPPA, the areas more affected at follow-up represent a large network involved in episodic (Buckner et al., 1998; Desgranges et al., 1998; Henson et al., 1999; Rajah and McIntosh, 2008) and semantic memory. In accordance with these anatomical findings, the lvPPA patients manifested a decline in calculations, verbal and visual memory at follow-up of both neuropsychological and language assessments. The neuropsychological results are consistent with previous reports indicating that the progression of the disease is characterized by the appearance of verbal memory and calculation symptoms together with the worsening of anomia, repetition and fluency deficits (Roher et al., 2013). This would probably explain why the lvPPA group appears to have the greatest decline over the 12 month period. Nonetheless the areas showing progressive GM contraction over time in lvPPA belong to the network of regions usually damaged in Alzheimer's disease and its preclinical phases, i.e. mild cognitive impairment (Brambati et al., 2009a; Fox et al., 2001; Killiany et al., 2000; Minoshima et al., 1997; Seeley et al., 2009). Finally, increased rate of atrophy in individuals at risk for familial AD was found classically in the medial temporal lobe but also inferolateral temporal lobe (Fox and Rossor, 1999). This impressive neuroanatomical overlap between lvPPA and AD cases are consistent with the evidence that lvPPA and AD share the same underlying pathology (Josephs et al., 2008; Mesulam et al., 2008; Rabinovici et al., 2007, 2008a; Rohrer et al., 2012). Also the progression of gray matter in the hippocampus (albeit at a lower level of significance), is potentially consistent with underlying AD pathology. A possible explanation for slower progression in this area could be that in "atypical AD" cases presenting as fluent or non-fluent PPA, the medial temporal lobe is minimally affected (Galton et al., 2000).

4.4. Limitations

Future studies involving a greater number of patients matched by time of onset of symptoms and including a longer follow-up are necessary to further clarify the cognitive and anatomical progression of the disease in the three clinical variants of the disease. In particular, larger samples will allow us to run direct correlation analyses to test the association between the anatomical changes and the worsening of clinical symptoms over time and to compare the rate of cognitive and language decline among PPA variant subtypes. However, our sample size was comparable with previous anatomical studies in this patient population (Mandelli et al., 2014; Rogalski et al., 2014) and was a practical consequence of the rareness of the disease.

From a methodological point of view, a replication of the results and of the analysis of the longitudinal data using the DARTEL approach could be useful to validate the present findings.

Nonetheless, it must be noted that the white matter contraction pattern observed in our study sometimes involves regions adjacent to the ventricles, which raises the question of whether this result can be an effect of ventricle enlargement. It seems unlikely that this bias could entirely explain the present result given that different regions of WM contraction have been implicated in different PPA variants and that the total intracranial volume at the time of the first scan has been included as a covariate in the statistical model. However future studies that will specifically address this question could certainly elucidate the relationship between ventricle enlargement and longitudinal changes in WM tissue.

4.5. Conclusions

In the present study, we showed that nfvPPA, svPPA and lvPPA have different longitudinal patterns of neuroanatomical contraction that are related to their clinical and cognitive progression. nfvPPA progresses in areas involved in speech production and agrammatism; svPPA in areas associated to semantic memory, emotion processing and behavior, lvPPA in regions supporting repetition, episodic and semantic memory and attention. These findings can be crucial to develop intervention strategies, such as speech rehabilitation therapies that are tailored to patients' progression profiles, and to correctly inform families and

caregivers of the challenges they will eventually need to face with the patients. The proposed approach could be extremely useful to test the efficacy of intervention strategies aimed at slowing down the progression of the disease in these patients.

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