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Longitudinal Imaging and Deterioration in Word Comprehension in Primary Progressive Aphasia: Potential Clinical Significance

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Abstract

Background—Three variants of primary progressive aphasia (PPA), distinguished by language performance and supportive patterns of atrophy on imaging, have different clinical courses and the prognoses for specific functions. For example, semantic variant PPA alone is distinguished by impaired word comprehension. However, sometimes individuals with high education show normal performance on word comprehension tests early on, making classification difficult. Furthermore, as the condition progresses, individuals with other variants develop word comprehension deficits and other behavioral symptoms, making distinctions between variants less clear. Longitudinal brain imaging allows identification of specific areas of atrophy in individual patients, which identifies the location of disease in each patient.

Aims—We hypothesized that the areas of atrophy in individual PPA participants would be closely correlated with decline in word comprehension over time. We propose that areas where tissue volume is correlated with word comprehension are areas that: (1) are essential for word comprehension, (2) compensate for word comprehension in some individuals with semantic variant PPA early in the course; and (3) show atrophy in individuals with logopenic and nonfluent variant PPA only late in the course.

Methods and Procedures—Fifteen participants with PPA (5 logopenic variant PPA; 8 semantic variant PPA; 2 nonfluent/agrammatic variant PPA; mean age 67.8), underwent high resolution MRI and cognitive tests at least 9 months apart. The correlations between change in regional volumes and change in auditory word comprehension scores were investigated using Spearman test.

Outcomes & Results—While scores on auditory word comprehension at Time 1 were correlated with volume loss in right and left temporal pole and left inferior temporal cortex (areas of atrophy associated with semantic variant PPA), deterioration in auditory word comprehension

from Time 1 to Time 2 was associated with individual atrophy in left middle temporal cortex, left angular gyrus, and right inferior and middle temporal cortex.

Conclusions—Progressive atrophy in focal areas surrounding left temporal pole and left inferior temporal cortex, and right homologous area is closely related to progressive decline in auditory word comprehension. These correlations likely reflect areas that help support auditory word comprehension, effectively compensating for subtle deficits in some individuals early in the course of semantic variant PPA, as well as areas that are critical for auditory word comprehension that eventually atrophy in individuals with other variants of PPA. Individual patterns of atrophy also help us understand and predict the clinical course of individuals, such as associated behavioral or motor deficits.

Keywords

primary progressive aphasia; MRI; brain mapping

Introduction

Primary progressive aphasia (PPA) is a clinical syndrome with a heterogeneous course, both in terms of duration and the symptoms that develop over time. There are three main variants that are distinguished by their key features and supporting brain imaging characteristics, which are generally associated with distinct underlying pathologies (Gorno-Tempini et al., 2011). These variants provide clues to the likely clinical course, as well as the associated pathology and potential underlying genetic mutations (Leyton et al., 2011). For example, semantic variant PPA (svPPA), distinguished by early word comprehension impairments or modality-independent semantics (Binney et al., 2010; Bozeat et al., 2000; Corbett, et al., 2009; Jefferies & Lambon Ralph, 2006; Jefferies, Patterson, Jones, & Lambon Ralph, 2009; Patterson, Nestor, & Rogers, 2007), is often associated with TDP-43¹ pathology and sometimes the progranulin gene mutation (see Kirshner, 2010 for review) or C9ORF72 mutations (Boeve et al., 2012). Individuals with svPPA are more likely than others with PPA to develop disinhibition, aberrant behavior, or abnormal eating behaviors (Rosen et al., 2006). The combination of word comprehension and behavioral deficits severely compromises safety in living alone, or possibly even the ability to be cared for by a healthy but elderly spouse. Behavioral deficits, typical of behavioral variant frontotemporal dementia (Rascovsky et al., 2011) are thought to reflect bilateral orbitofrontal dysfunction. Nonfluent agrammatic variant PPA (nfaPPA), is characterized by agrammatic spoken production and/or apraxia of speech (Grossman, 2012; Hodges & Patterson, 1996; Josephs et al., 2006; Rohrer, Rossor, & Warren, 2010; Thompson et al., 1997), and often impaired comprehension of syntactically complex sentences (Hodges & Patterson, 1996; Grossman, 2012; Grossman & Moore, 2005). This variant is frequently associated with tau pathology of corticobasal degeneration or frontotemporal lobar degeneration-tau² (FTLD-t) and sometimes with MAPT³ mutations (Kirshner, 2010). Logopenic variant PPA (lvPPA), with

¹TPD-43, or transactive response DNA binding protein 43 kDa, is the major disease protein in ubiquitin-positive, tau-, and alpha-synuclein-negative frontotemporal dementia, and in amyotrophic lateral sclerosis.

²Tau proteins are abundant in neurons and stabilizes microtubules. Diseases such as fronto-temporal dementias can result if tau is defective.

³MAPT (microtubule-associated protein tau) is the gene that codes tau

the key characteristics of anomia and impaired sentence repetition, is often associated with Alzheimer's disease pathology (and thus occasionally associated with amyloid precursor protein or presenilin mutations).

The location of atrophy also helps to support the PPA classification (Gorno-Tempini et al., 2011). Classification of nfaPPA is supported by left posterior frontal and insular atrophy; while svPPA is associated with left greater than right anterior and inferior temporal atrophy. In contrast, lvPPA is associated with posterior temporal and inferior parietal atrophy (Gorno-Tempini et al., 2008; Wilson et al., 2009; Rohrer et al., 2013).

Although identification of the variant provides some clues regarding the subsequent course, classification into one of the three main variants is not always possible and is not always adequate for prognosis. Classification is not always possible for two reasons. First, early in the course, individuals may only show anomia and/or dysgraphia, two deficits that are common to all three variants and arise early in all three types of PPA. Although the character of the naming and spelling deficits may be somewhat different across variants (Budd et al. 2010; Sepelyak et al., 2011), there is not a one:one correspondence between the naming type or spelling type and the variant of PPA. Likewise, late in PPA, the boundaries between variants become less distinct. For example, although word comprehension deficits are the hallmark of semantic variant PPA, individuals with other variants of PPA develop word comprehension deficits later in the course of PPA.

We have also noted that identification of the variant alone is inadequate for prognosis. For example, an atypical form of lvPPA has been identified, with a distinct longitudinal course - a relatively long, slow progression (Machulda et al., 2013). Likewise, the associated symptoms that an individual will develop depend on where the pathology spreads in the brain. For example, individuals with svPPA have atrophy in left temporal cortex. If the disease spreads dorsally and posteriorly, to affect the occipitoparietal cortex, the individual will develop visuospatial difficulties. On the other hand, if the underlying disease spreads more anteriorly and bilaterally, to the prefrontal and orbitofrontal cortex, the individual will likely develop change in personality and comportment, as well as a change in executive function. Ideally, we would like to precisely identify the location of focal atrophy - where it begins to spread is where it will likely continue. This localization would aid prediction of the kinds of impairments that are likely to occur with deterioration over time (see Table 1).

However, because of the large normal variation of brain volumes, particularly in elderly population, it is often difficult to detect the location of PPA-specific atrophy in conventional MRI scans with the human eye. In an older individual, one is often unsure how much "shrinkage" of an area is due to normal aging, versus how much is PPA-related. Comparing the brain to a "normal" brain or atlas is limited by the fact that patients with PPA (like patients with stroke and healthy controls) have brains of different sizes and shapes, and so the scans must be registered to the atlas or "normal" brain using global or focal warping methods. Even when the atlas or normal brain is age-and gender-matched, it is difficult to be sure the voxels identified as atrophy are truly atrophied, or simply areas where the individual's brain was congenitally smaller. Furthermore, there is no one method of registration that is perfect; different registration methods yield significantly different results

in structure-function mapping studies (Anticevic, et al., 2008; Pantazis et al., 2010). Additionally, there is quite a bit of overlap between atrophy in frontotemporal dementia and PPA and normal aging (Chow et al., 2008). Moreover, atrophy in the three variants may lose their distinctiveness over time, as atrophy becomes more diffuse (Rogalski et al., 2011).

Longitudinal imaging avoids some of these difficulties in localizing atrophy. First, it is not necessary to register the scan to an atlas or normal brain, but only to register the individual's subsequent scans to that person's initial scan. Then it is possible to identify which voxels or areas have actually atrophied in that individual over time. Areas where there is disproportionate atrophy on the left, or atrophy that correlates with decline in language performance, likely represent areas where there is disease. The site of disease provides prognostic clues about what symptoms are likely to arise next, as well as supportive evidence for the variant of PPA (and thus the underlying pathology and the potential genetic basis), which itself provides clues regarding prognosis.

There have been previous longitudinal imaging studies of particular variants of PPA (e.g. Rohrer et al. 2012; Whitwell et al., 2004) or of all PPA subtypes (e.g. Knopman et al., 2009; Rogalski et al., 2011). However, these studies have not evaluated correlations between specific language functions over time and atrophy in particular areas. They also have not demonstrated the usefulness of longitudinal imaging in individuals with PPA.

In the present study, we correlate the progression of brain atrophy and language deficits in patients with PPA. Based on evidence from previous lesion and functional imaging studies, we hypothesized that change in a word comprehension task would correlate with change in volume of several segments of the left temporal cortex, which would be greatest in svPPA, but not limited to those with svPPA. We also hypothesized that this focal atrophy could be demonstrated on individual "difference maps" in patients who show marked decline in auditory word comprehension- a deficit critical to daily functioning. If confirmed, the study would provide preliminary data in support of the proposal that longitudinal imaging of individual PPA patients can provide a useful adjunct to PPA classification, and reflects the localization of disease in each patient. We also illustrate how distinct patterns of localized atrophy across individuals can provide clues regarding future course of the disease in individuals with PPA.

Methods

Participants

We enrolled 15 participants with PPA (5 logopenic variant PPA; 8 semantic variant PPA; 2 nonfluent/agrammatic variant PPA). The mean age was 67.8 years (Range = 57–77). Nine participants were female (Please see Table 2 for details). This study was approved by our Institutional Review Board, and participants or their spouses provided informed consent to the procedures. All participants underwent high resolution MRI and a battery of language and cognitive tests at least 9 months apart. We report only the subset of the test results in this paper that were critical to our hypothesis or provide important information about the character of the patients' language profiles.

Cognitive and Language Testing

Auditory word comprehension was tested by subtest from the Western Aphasia Battery (Kertez, 1982). Scores on additional tests are reported in Table 2, just to give the reader an idea of the severity and character of the language performance of the patients. Tests that were administered included: Repetition and auditory word comprehension subtests from the Western Aphasia Battery - WAB⁴ (Kertez, 1982), Digit Span testing (forward and backward), and oral and written naming of 30 pictured objects and 30 pictured actions (Zingeser & Berndt, 1990). Scores for objects and actions are collapsed in Table 2. Participants were given unlimited time to respond in the naming test. They were permitted to self-correct. The final response was scored. All test scores were converted into percent correct scores.

Imaging—This study was based on high resolution T1-weighted images (MPRAGE) following our regular clinical protocol. The images were acquired using a 3T whole body MRI scanner (Philips Medical Systems, Best, The Netherlands), with axial orientation, image matrix of 256 × 256 mm, field of view of 212×212 mm and 120–140 slices of 1.1 mm thickness. The imaging post-process, performed using DiffeoMap (www.MriStudio.org), consisted in an initial alignment of the second time point to the first using 9-parameter AIR (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998) followed by a large deformation diffeomorphic metric mapping LDDMM (Miller, Beg, Ceritoglu, & Stark, 2005). As a quantitative metric of local volume changes, we used the Jacobian determinant (i.e., the local expansion factor) of the LDDMM deformation fields. The Jacobian maps indicate local tissue expansion (Jacobian>1) or shrinkage (Jacobian<1) relative to the template (Chung et al., 2001; Riddle et al., 2004; Thompson et al., 2000) that allows identification of localized volume increases/reductions at the voxel level

The Jacobians were averaged and total volumes obtained by gyri. The gyri were defined by registering each brain to multiple geriatric atlases (Djamanacova et al, submitted; Mori et al., 2008), extensively parceled and labeled to 254 regions (Oishi et al., 2008). Inversely, this parcellation map was warped to the original MRI data, thus automatically parceling each of our subject's brains. For details, please read our previous publications (Faria et al., 2010, 2011, 2012; Oishi et al., 2009). Note that the aim of mapping each brain image to a common template was to be able to group voxels into structures pre-defined in this template, therefore reducing the dimensionality of the data and improving the signal-to-noise. As previously mentioned, the longitudinal degree of atrophy was obtained by an "intra-subject" registration (by mapping the second time point to the first), therefore overcoming the issues pointed out in the introduction of co-registering atrophic brains to common healthy templates. Only cortical areas (50 regions) were considered in the current study. Cerebrospinal fluid was excluded using tissue maps obtained with SPM.. The initial degree of atrophy was calculated based on a group of healthy controls, paired by age and gender.

⁴Auditory comprehension was measured by using the auditory word recognition subtest of WAB. There are 60 items which consisted of word to picture/object matching with 5 semantically related foils.

Statistical Analyses

The correlation between local volume changes and clinical scores were established by Spearman correlation coefficients. The threshold for significance was p -value <0.05 after correction for multiple comparison with False Discovery Ratio, FDR.

Results

Correlation between longitudinal atrophy and changes in clinical performance: change in accuracy of word comprehension was strongly associated with change in volume of left middle temporal cortex ($r=.793$; $p=0.01$), left angular gyrus ($r=0.788$; $p=0.01$), and right inferior temporal and middle temporal gyri after correction for multiple comparisons (Table 3 and Figure 1, right panel).

Correlation between atrophy and clinical performance at the first time point: the areas of atrophy associated with change in comprehension over time were somewhat different to those areas of atrophy that were associated with initial error rates on word comprehension at Time 1 (Table 4 and Figure 1, left panel). At Time 1, the areas associated with impaired word comprehension included left and right temporal pole and left and right inferior temporal cortex, areas frequently atrophied in svPPA, as well as left middle temporal gyrus.

Individual “difference” scans were created to show areas that atrophied (became smaller, shown in blue) or areas such as ventricles or sulci that enlarged due to atrophy (shown in red). Along with longitudinal testing of auditory word comprehension, these difference scans illustrate the correlations revealed by the group data. Furthermore, these individual difference scans helped us to understand the course of PPA for individual patients, and often helped us predict problems that would follow, based on the location of atrophy.

Case 1 (Figure 2): JRH: unclassifiable at Time 1, svPPA at Time 2

At the time of initial testing, JRH was 65 years old, and working as a lawyer, living alone. He had fluent, but anomie speech with occasional semantic paraphasias. He had no deficits in attention, orientation, learning, episodic memory, or executive functions. He had no auditory word comprehension impairment or repetition impairment on testing, although he had marked naming impairment and surface dysgraphia which had been progressive over at least 8 years. His PPA was unclassifiable, as he did not have the key features of any variant; although svPPA was suspected on the basis of his pattern of atrophy, with focal atrophy of the left temporal pole. At Time 2, 19 months later, he continued to live alone. He was no longer working or driving, but he was paying his bills, preparing his own meals, and effectively using public transportation. He remembered his appointments, and arrived on time. Longitudinal imaging showed diffuse atrophy, including atrophy in bilateral orbitofrontal cortex, as well as bilateral temporal cortex and left angular gyrus that correlated with a decline in auditory word comprehension. His speech was fluent and grammatical, well-articulated, with frequent semantic paraphasias and circumlocutions. It was sometimes jargon. He now met criteria for svPPA. On the basis of the diffuse atrophy, it was concluded that his disease had spread diffusely and that he would likely show more diffuse cognitive and behavioral change in the near future, necessitating a change in living

situation. He moved in with family. Shortly thereafter, he began to show inappropriate and unsafe behaviors, including wearing very inappropriate clothing for the weather, poor problem-solving, and inability to prepare his own meals.

Case 2 (Figure 3): JWE: SvPPA with normal behavior at Time 1, abnormal behavior at Time 2, 9 months later, with marked decline in word comprehension

At Time 1, JWE was 65 years old, and had svPPA with fluent, well-articulated, grammatical speech and frequent semantic paraphasias and occasional English jargon. He made occasional errors in word comprehension, that had become more apparent even in conversation over the past few years. He lived with his wife, but was independent in basic activities of daily living. He was very pleasant, amiable, and showed little change in personality or comportment. By the time of his second MRI, his word comprehension had deteriorated considerably, along with further atrophy in left inferior and middle temporal cortex and to a lesser degree, right inferior and middle temporal cortex. Moreover, he showed bilateral orbitofrontal cortex atrophy. His wife reported that he had become quite disinhibited, and difficult to control. He could not understand when she tried to calm him. His focal atrophy in the orbitofrontal cortex bilaterally helped us understand that the disease had spread to these regions, affecting his behavior. Shortly thereafter, he had to be placed in a nursing home, as his wife was unable to take care of him at home.

Case 3 (Figure 4): LLD: svPPA with normal behavior at Time 1 and Time 2, with marked deterioration in word comprehension

LLD was 57 years old at time point 1, with a post-graduate degree. She had a fairly typical pattern of language performance for svPPA, with fluent, well-articulated speech that was often “empty” or hard to follow. It had deteriorated over several years. She made frequent semantic paraphasias. She had marked impairment in word comprehension and showed both surface dyslexia and surface dysgraphia. She was very pleasant and cooperative, although she occasionally showed somewhat odd or socially/semantically inappropriate behavior (e.g. eating beans with her fingers). Her husband, who read quite a bit about PPA on line, wondered if she would develop behavioral problems, making it difficult for him to care for her at home. Longitudinal imaging, 36 months later, revealed marked atrophy in left and right middle temporal cortex that correlated with further decline in word comprehension. However, there was not substantial atrophy in orbitofrontal cortex, making it less likely that disease had spread to this area. It was predicted that she would not likely develop disruptive behavior in the near future. Her comportment remained unchanged, and she remained at home for the subsequent two years.

Case 4. (Figure 5): DUE: IvPPA at Time 1 and Time 2 (with minimal change in word comprehension)

At the time of initial testing, DUE was 68 years old, and had experienced progressive difficulty with word-retrieval for more than 5 years. She had hesitant, anomie speech that was well-articulated. Naming was substantially impaired. She had no deficits in learning or episodic memory, but she had impaired sentence repetition. She was very active in the community and volunteer work, independent in all activities, including driving and cooking. On the basis of her pattern of performance on language testing and support from imaging

that showed atrophy in left posterior superior temporal gyrus, she was classified as having lvPPA. Longitudinal imaging and language testing, 9 months later, revealed further deterioration in repetition and digit span, consistent with lvPPA. She showed mild atrophy in left temporal cortex and inferior parietal cortex over time, with an increase in size of the left more than right lateral ventricle (voxels in red). She made very occasional errors in word comprehension in conversation, associated with mild atrophy in left and right middle temporal cortex. She never showed any change in behavior or personality between Time 1 and Time 2 (or in the subsequent year that we followed her), consistent with the lack of atrophy in the frontal cortex.

Case 5 (Figure 6): PZR: Nonfluent/agrammatic PPA at Time 1 and Time 2, with unchanged word comprehension and behavior

At Time 1, PZR was 66 and presented with apraxia of speech. She had simplified sentence production, but most sentences were grammatical. Her digit span was below normal, and she had experienced progressive dysgraphia for about two years. She had otherwise normal language performance. Her MRI showed widening of the left lateral ventricle compared to the right. Longitudinal imaging over 20 months showed minimal atrophy with further widening of the left more than right lateral ventricle (particularly in the frontal horn) and only slight decrease in volume of the left insula and cingulate, over a period of time when she showed mild deterioration in motor speech, but no change in auditory word comprehension or behavior. She remained independent in all daily activities, including driving and shopping. Two years later, she still has not developed any associated changes in motor function, comportment, or comprehension.

Discussion

We found that progressive atrophy in left and right middle temporal cortex and left angular gyrus in PPA was closely related to decline in auditory word comprehension in uncategorized PPA patients. Additionally, we confirmed that at a single time point, auditory word comprehension errors were correlated with volume loss in bilateral temporal poles and inferior temporal cortex, areas typically atrophied in svPPA, as well as left middle temporal cortex. It is likely that many of the patients who showed decline in auditory word comprehension already had atrophy in bilateral temporal poles and inferior temporal cortex, and may not have been able to show further atrophy in these areas if the atrophy time course follows a logarithmic model and is regionally dissimilar. Although this conclusion is intuitive, it has not been demonstrated previously. This means that the atrophy at a single time point is not sufficient to predict the atrophy course forward. The surrounding areas (bilateral middle temporal cortex) and/or left angular gyrus may be important for compensating, at least temporarily, for auditory comprehension deficits. As these areas atrophy, auditory word comprehension declines further. Alternatively or additionally, the correlation between decline in auditory word comprehension between Time 1 and Time 2 and angular gyrus atrophy could (hypothetically) reflect the decline in word comprehension sometimes seen later in the course of lvPPA patients, who typically have atrophy in superior temporal gyrus and inferior parietal lobule (angular gyrus and supramarginal gyrus). As their atrophy worsens, their word comprehension may decline. However, inspection of Figure 1

indicates that it was the further deterioration of word comprehension in participants with svPPA that primarily accounted for the correlation with atrophy in left angular gyrus, indicating that svPPA patients also show atrophy in angular gyrus late in the course of the disease. Individuals with nfaPPA also can show decline of word comprehension in late stage PPA; however, the two participants with nfaPPA in this study did not show decline in word comprehension during the course of this study.

Individual “difference” maps illustrated the various relationships between decline in impaired word comprehension and individual patterns of atrophy. Additionally, we showed how these “difference maps” can reveal very different patterns of atrophy even within a variant of PPA. For example, two patients with svPPA (JRH and JWE) showed marked bilateral orbitofrontal atrophy that signaled an impending or current change in comportment and social behavior that required a change in living situation. In contrast, two other patients with svPPA (LLD and DCR) showed no orbitofrontal atrophy and no change (present or future) in behavior or social function. All four patients showed marked decline in auditory word comprehension associated with atrophy in bilateral middle temporal cortex (which was most pronounced in LLD and DCR).

Earlier longitudinal imaging studies have investigated a single variant of PPA (e.g. Rohrer et al. 2012; Whitwell et al., 2004) or of all variants of PPA (e.g. Knopman et al., 2009; Rogalski et al., 2011). The focus of these studies has been to characterize the clinical and anatomical progression of the subtypes, which is also a valuable enterprise. For example, Rohrer and colleagues (2012) found different rates of atrophy in different lobes of the brain in distinct subtypes of frontotemporal lobar degeneration (FTLD), with svPPA showing fastest rates of atrophy in the temporal lobe, followed by frontal, then parietal, then occipital lobe. In contrast, nfvPPA participants showed fastest rates of atrophy in frontal lobe, followed by temporal and parietal, then occipital lobe. Both groups showed faster left than right hemisphere atrophy (see also Whitwell et al, 2004 for distinct patterns of atrophy over time in variants of FTLD). However, changes in whole brain volume and ventricular volume were similar across the three variants over one year (Knopman et al., 2009). The contribution of the current study, in contrast, is to show the clinical utility of individual “difference maps” created by longitudinal imaging, both for prognosis and for selection into pharmacological or genetic interventions targeted to specific neuropathologies when these become available, as well as to show how longitudinal imaging can contribute to understanding of decline in auditory word comprehension observed across variants of PPA.

There are several limitations of this study, including the relatively small number of participants and limited testing of auditory word comprehension. The MRI scans were not separated by exactly the same time (although given that rate of atrophy varies across individuals it is not clear that the precise timing makes a difference, as long as there is adequate time between scans/testing to capture atrophy and decline in function). The purpose of the study was to illustrate the feasibility and clinical usefulness of longitudinal imaging. The figures also demonstrate how individual “difference images” can be useful for identifying precisely where an individual has shown atrophy over time, which can be useful both clinically and for research. Future studies will evaluate how well this imaging truly predicts future quantifiable changes in social, language, or cognitive function.

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A) Correlation between initial volume, compared to age-paired controls (y-axis) and Auditory Word Comprehension scores (x-axis)

B) Correlation between changes in volume (y-axis) and change in Auditory Word Comprehension scores (x-axis)

Figure 1.

Scatter plots showing the significant correlation between volumes and scores in language tests converted to percentages a) at Time 1 and b) for Time 2 – Time 1

Figure 2.
Case 1 (JRH). T1-weighted MRIs acquired in the first (first row) and second (second row) time points and the Jacobians from the longitudinal deformation fields (third row) demonstrating the expansion (red) or atrophy (blue) over time

Figure 3. Case 2 (JWE). T1-weighted MRIs acquired in the first (first row) and second (second row) time points and the Jacobians from the longitudinal deformation fields (third row) demonstrating the expansion (red) or atrophy (blue) over time.

Figure 4. Case 3 (LLD). T1-weighted MRIs acquired in the first (first row) and second (second row) time points and the Jacobians from the longitudinal deformation fields (third row) demonstrating the expansion (red) or atrophy (blue) over time

Figure 5.
Case 4 (DUE). T1-weighted MRIs acquired in the first (first row) and second (second row) time points and the Jacobians from the longitudinal deformation fields (third row) demonstrating the expansion (red) or atrophy (blue) over time

Figure 6. Case 5 (PZR). T1-weighted MRIs acquired in the first (first row) and second (second row) time points and the Jacobians from the longitudinal deformation fields (third row) demonstrating the expansion (red) or atrophy (blue) over time

Table 1

Summary of Potential Areas of Atrophy and Associated Consequences in Each Variant of PPA

PPA Variant	Typical Areas of Atrophy	Typical Consequences of Atrophy	Potential Areas of Spread	Potential Consequences of Spread in Atrophy
svPPA	Left > Right Anterior temporal; inferior temporal	Impaired word comprehension; impaired naming; impaired object semantics	Orbitofrontal gyrus	Change in comportment; Impaired empathy; hyperorality
			Right inferior temporal	Proposagnosia Object agnosia
nfvPPA	Left inferior Frontal gyrus & insula	Apraxia of speech and/or agrammatic speech	Left motor cortex	Right arm spastic monoplegia
			Left dorsomedial prefrontal cortex	Impaired executive functions
			Orbitofrontal cortex	Change in comportment; Impaired empathy; hyperorality
lvPPA	Left inferior parietal cortex & superior temporal cortex	Impaired sentence repetition; phonological errors in naming	Right (bilateral) inferior parietal cortex and superior temporal cortex	Impaired associative memory, executive function
			Mesial temporal cortex	Impaired learning, delayed recall
			Occipitoparietal cortex	Visuospatial deficits

Table 2

Demographic and language test scores

ID	Diagnosis	Age/Sex	Education (years)	Interval between tests (months)	Time Point 1				Time Point 2			
					Digit Forward	Repetition	Auditory Word Comp.	Oral Naming	Digit Forward	Repetition	Auditory Word Comp.	Oral Naming
BNR	LPA	75/F	16	21		20	100	87		20	100	80
DUE	LPA	68/F	18	9	6	88	100	77	2	56	100	42
FHY	LPA	74/M	18	26	5	78	100	100	3	78	100	95
KCE	LPA	67/F	18	12	3	20	80	84		0	80	90
KCR	LPA	77/F	18	19	4	96*	100	98*		100	95	81
DCR	SVPPA	60/F	18	19		60	65	47		50	0	10
JKS	SVPPA**	73/M	20	28	6	100	100	63	4	60	85	69
JRH	SVPPA**	65/M	20	19	6	100	100	70	6	100	77	13
JWE	SVPPA	65/M	16	9	6	92	92	50		40	47	33
LLD	SVPPA	57/F	18	36	4		73	20	3		0	0
MJE	SVPPA**	66/M	16	26	7	98	100	77		80		46
SKR	SVPPA**	74/M	16	25	4	100	100	100	3	60	90	70
TEY	SVPPA	64/F	16	15	3	70	93	90		100	82	40
PZR	NFVPPA	66/F	16	20	7	100	100	100	5	100	100	94
SRR	NFVPPA	66/F	16	14	4	82	100	95	3	0	100	43

* KCR's sentence repetition was only 80% correct at Time 1; Boston Test was 50% correct

** initially unclassifiable

Table 3

Correlation between change in volume and changes in Auditory Word Comprehension scores

Region	r	p-value
Middle temporal left	0.79	0.0004
Angular left	0.78	0.0004
Inferior temporal right	0.78	0.0005
Middle temporal right	0.74	0.0016

Table 4

Correlation between initial atrophy and Auditory Word Comprehension scores

Region	r	p-value
Middle temporal left	0.76	0.0008
Inferior temporal right	0.75	0.0012
Temporal pole right	0.75	0.0012
Temporal pole left	0.73	0.0016
Inferior temporal left	0.73	0.0019