The atrophy pattern in Alzheimer-related PPA is more widespread than that of the frontotemporal lobar degeneration associated variants

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ABSTRACT

Objective: The three recognized variants of primary progressive aphasia (PPA) are associated with different loci of degeneration—left posterior perisylvian in logopenic variant (lvPPA), left frontal operculum in non-fluent variant (nfvPPA), and left rostroventral-temporal in semantic variant (svPPA). Meanwhile, it has become apparent that patients with lvPPA, in which Alzheimer pathology is the norm, frequently have more extensive language deficits—namely semantic and grammatical problems—than is captured in the strict diagnostic recommendations for this variant. We hypothesized that this may be because the degeneration in AD-related PPA typically extends beyond the left posterior perisylvian region.
Methods: Magnetic resonance images from 25 PPA patients (9AD-related PPA, 10 svPPA, 6 nfvPPA) and a healthy control cohort were used to calculate cortical thickness in three regions of interest (ROIs). The three ROIs being the left-hemispheric loci of maximal reported degeneration for each of the three variants of PPA.
Results: Consistent with past studies, the most severe cortical thinning was in the posterior perisylvian ROI in AD-related PPA; the ventral temporal ROI in svPPA; and the frontal opercular ROI in nfvPPA. Significant cortical thinning in AD-related PPA, however, was evident in all three ROIs. In contrast, thinning in svPPA and nfvPPA was largely restricted to their known peak loci of degeneration.
Conclusions: Although cortical degeneration in AD-related PPA is maximal in the left posterior perisylvian region, it extends more diffusely throughout the left hemisphere language network offering a plausible explanation for why the linguistic profile of lvPPA so often includes additional semantic and grammatic deficits.

1. Introduction

The diagnostic recommendations for primary progressive aphasia (PPA) propose three subtypes: namely semantic variant (svPPA), non-fluent/agrammatic variant (nfvPPA), and logopenic variant (lvPPA) (Gorno-Tempini et al., 2011). While svPPA and nfvPPA are typically associated with pathologies in the spectrum of frontotemporal lobar degeneration (FTLD) (Hodges et al., 2004; Yokota et al., 2009), lvPPA is most frequently associated with Alzheimer pathology (Grossman, 2010; Harris and Jones, 2014).

Although there is clear evidence that PPA can be associated with Alzheimer pathology, and, that when it is, the clinical syndrome is typically neither sv- nor nfvPPA (Josephs et al., 2008; Rabinovici et al., 2008), defining a precise clinical profile of lvPPA has proven

problematic. When the proposed lvPPA criteria are strictly applied, studies have sometimes struggled to identify this group (Giannini et al., 2017; Mesulam et al., 2012; Sajjadi et al., 2014). Moreover, data-driven analysis of clinical features has suggested that the proposed features of nfvPPA and svPPA cluster together as they should, whereas those for lvPPA do not (Sajjadi et al., 2012). A recent clinico-pathological study, meanwhile, found that most patients with PPA and AD pathology had more extensive language features than is captured by the criteria for lvPPA leading the authors to coin the term "lvPPA+" (Giannini et al., 2017). This finding resonates with an earlier clinical series that found that, while it was hard to find patients meeting criteria for lvPPA, a large number of patients had a "mixed" PPA that was separate from nfvPPA and svPPA (Sajjadi et al., 2012). One study even proposed a solution that largely abandoned the criteria for lvPPA and instead

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Table 1
demographic variables from the MRI control group and the three patient groups.

Group	Control (N = 42)	AD-PPA (N = 9)	svPPA (N = 10)	nfvPPA (N = 6)
Age	68.4(± 4.9)	68.8(+/− 6.4)	65.3(± 6.4)	68.2(± 7.0)
Sex (M/F)	19/23	4/5	5/5	6/0
Symptom duration (years)	–	2.3(± 0.9)	4.6(± 2.5)	3.2(± 1.7)

proposed a hierarchical diagnostic algorithm where it was essentially defined by the absence of sv- or nfvPPA (Leyton et al., 2011).

Characteristic loci of neurodegeneration are associated with each of the PPA subtypes. Imaging studies reveal atrophy and/or hypometabolism that is maximal in and around the left frontal operculum in nfvPPA (Gorno-Tempini et al., 2004a, 2004b; Nestor et al., 2003; Sajjadi et al., 2013); in the left rostral temporal lobe in svPPA (Acosta-Cabronero et al., 2011; Diehl et al., 2004; Gorno-Tempini et al., 2004a, 2004b) of which anterior fusiform degeneration appears critical to the emergence of the clinical syndrome (Mion et al., 2010); and in left posterior perisylvian region in those designated lvPPA (Gorno-Tempini et al., 2004a, 2004b; Mesulam et al., 2012). Those classified as having a 'mixed PPA' because their deficits extended beyond that which can be captured with the strict consensus definition of lvPPA, nonetheless show the same lesion as that reported for lvPPA suggesting that such cases are the same as those labelled 'lvPPA' by others (Sajjadi et al., 2014).

Although these imaging findings are highly replicated, it should be noted that they refer to the peak areas of neurodegeneration as defined by the most statistically significant abnormalities in group-averaged data. Therefore, it does not follow that there cannot be other areas of significant degeneration. The problem of understanding the full extent of cortical degeneration associated with any particular syndrome is compounded by the methods of reporting; typically whole-brain studies report maps of statistical significance but this approach means that abnormal brain regions can appear unaffected by increasing the stringency of the statistical threshold. The present study investigated cortical thinning in the three peak atrophy sites associated with the three PPA subtypes. The aim was to test the specific hypothesis that, although the left posterior perisylvian region is the maximal site of damage, degeneration affects the left hemisphere language network more diffusely in AD-related PPA, compared to sv- and nfvPPA. This, in turn, would offer a possible explanation for why patients in this category often have a more mixed aphasic syndrome (including semantic and grammatic deficits) and so fail to meet strict lvPPA criteria. In contrast, we predicted that in svPPA and nfvPPA degeneration would be more restricted to the respective sites of peak degeneration.

2. Material & methods

2.1. Participants

31 patients with the root diagnosis primary progressive aphasia were recruited. Patients underwent neuropsychological assessment, magnetic resonance imaging, and, as part of their clinical diagnostic work-up, ^{18}F-Florbetaben positron emission tomography (PET.) Visual rating of the PET was performed to assess the amyloid-status by raters who had undergone the tracer manufacturer's rater-training course; scans were, accordingly, classified as amyloid positive or negative. Six participants had to be excluded: three because of contraindication to MRI; one who did not have PET; and two with amyloid-negative PET whose PPA syndrome was unclassifiable (i.e. neither sv- nor nfv-PPA), leaving 25 patients in the study.

All patients fulfilled the core diagnostic features of a PPA syndrome. Sv- and nfvPPA patients were classified according to consensus recommendations for the respective syndrome (Gorno-Tempini et al., 2011) and by having a negative Florbetaben-PET result. In this cohort,

no svPPA or nfvPPA patient had a positive Florbetaben-PET. The AD-related PPA patients were defined when the criteria for either svPPA or nfvPPA were not fulfilled and the Florbetaben-PET result was positive. Although word-finding difficulty and anomia were the main features of the AD-PPA group, all participants showed additional grammatical and/or semantic deficits meaning they corresponded to what has been described as "mixed" (Sajjadi et al., 2012; Sajjadi et al., 2014) or "lvPPA + " (Giannini et al., 2017) in previous studies.

Age-matched healthy controls (N = 42) were recruited from the local community for the MRI examination. These participants had no history of neurological disorders or major psychiatric illness. Cognitive testing was performed and all participants scored in the normative range. Demographics of patient groups and controls are found in Table 1.

Written informed consent was obtained from all participants or their legal representative. The study was approved by the local ethics committee.

2.2. Neuropsychological assessment

The general neuropsychological assessment comprised Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Digit Symbol Substitution test (DSS), as well as copy, immediate recall, and delayed recall of the Rey complex figure.

Linguistic neuropsychology included Boston Naming test (30 items); verbal digit span (forward & backward); category and letter fluency test (1 min each); "Kaffee & Kuchen"-test (a local German version of the Camel & Cactus test (Bozeat et al., 2000) that tests semantic associative knowledge); the Repeat & Point test (Hodges et al., 2008); a sentence repetition task, (also a local German test comprising 5 sentences, of increasing word/syllable count—6, 7, 8, 9 and 10 syllables respectively—with one point awarded for each fully repeated sentence); and the German version of the Sentence Comprehension Test-Visual version (SECT-V) (Billette et al., 2015).

2.3. Image acquisition

Imaging was performed at the German Center for Neurodegenerative Diseases (DZNE) in Magdeburg (Germany) on a 3 T Siemens VERIO system using a 32-channel head coil. The acquired sequence was a T1-weighted 3-dimensional magnetization-prepared rapid gradient echo sequence (TR = 2500 ms, TE 4.37 ms, flip angle = 7°, voxel matrix = 192x256x256 with 1 mm isotropic voxels).

2.4. Image processing

The anatomical MRIs were processed with the open source software suite Freesurfer (version 6.0.0, https://surfer.nmr.mgh.harvard.edu). Cortical reconstruction was performed automatically according to standard pipeline (Fischl and Dale, 2000), including automatic cortical parcellation (Fischl et al., 2004). Average cortical thickness for regions of interest (ROIs) is estimated as distance between pial surface and grey/white matter boundary. A smoothing kernel of 20 mm full width at half-maximum (FWHM) was used for the whole brain analyses (Diaz-De-Grenu et al., 2014).

ROIs of the cortical ribbon were automatically extracted from parcellation of the Desikan-Killiany atlas (Desikan et al., 2006) or the

Destrieux atlas (Destrieux et al., 2010). The average cortical thickness for three ROIs, corresponding to the three key loci of degeneration in the three clinical groups, was extracted and entered statistical analysis. From the Desikan-Killiany atlas, the areas labelled pars triangularis and pars opercularis were combined to represent the left inferior frontal gyrus (IFG) as the critical site of degeneration in nfvPPA. Also from the Desikan-Killiany atlas, the regions defined as supramarginal gyrus and inferior parietal cortex—which includes the angular gyrus—were combined to create a left posterior perisylvian ROI (PPS) region as the main site of degeneration in AD-related PPA. SvPPA is associated with extensive rostral temporal degeneration. The peak atrophy, however, is the anterior fusiform area (AFA) (Chan et al., 2001), and this region has been shown to be the neural substrate for the cognitive deficit in svPPA (Mion et al., 2010). To this end, the region designated anterior transverse collateral sulcus in the Destrieux atlas was chosen as it corresponds to the AFA; this also meant that the ROI was of a similar size order to those for IFG and PPS.

2.5. Statistical analysis

To contextualise the current cohorts with previous group studies we performed whole brain analyses of cortical thickness. A general linear model was applied to analyse vertex-wise whole-brain cortical thickness between groups; false discovery rate (FDR) was set to $p < .001$ to adjust for multiple comparisons.

Statistical analyses of cortical thickness in ROIs and neuropsychological tests were performed using SPSS version 21(IBM, Chicago,IL). Symptom duration and cortical thickness of the ROIs was assessed for normality with Shapiro-Walk test and subsequently analysed with Kruskal-Wallis test followed by pair-wise comparison with Dunn's test. Bonferroni correction was applied for adjustment of multiple comparisons and the level of significance was set at $p < .05$. Neuropsychological tests were analysed separately with one-way ANOVAs and post hoc *t*-tests for pairwise comparison and Bonferroni correction at the significance level $p = .05$ for multiple comparison adjustment.

3. Results

Mean age was similar in all groups. Controls, AD-PPA and svPPA had approximately equal gender distribution, whereas the nfvPPA group consisted exclusively of males. Symptom duration was longest for svPPA patients and shortest in the AD-PPA group though these differences were not significant ($X^2(2) = 3.77$, $p = .15$) (Table 1).

3.1. Neuropsychological performance

The detailed results of the neuropsychological data are provided in Table 2. MMSE and GDS were similar across all patient groups, indicating mild-to-moderate cognitive impairment and no major depressive state. As expected, the svPPA group's deficits were most pronounced in tests tapping semantic knowledge: category fluency; Boston naming test; Kaffee & Kuchen-test; and the semantic (point) component of the Repeat & Point test. NfvPPA deficits were most pronounced for span; repetition of single words (repeat component of the Repeat & Point test) and sentences; as well as grammatical comprehension (SECT-V). The linguistic performance of the AD-PPA group tended to show impairments across that board with the most pronounced deficit in the sentence repetition task.

3.2. Whole brain analysis of cortical thinning

All three patient groups had asymmetric, left hemisphere dominant, significant cortical thinning (FDR-corrected $p < .001$) with subtype-specific peak atrophy sites (Fig. 1). The AD-PPA group had most significant cortical thinning at the left temporoparietal junction (posterior

perisylvian area), encompassing the superior and middle temporal lobe as well as inferior parietal lobe, left dorsolateral prefrontal cortex and inferior frontal gyrus. The svPPA group revealed significant, bilateral (left worse than right) temporal cortex thinning that particularly involved fusiform, inferior temporal, middle temporal, and the anterior portion of the superior temporal gyrus. The atrophy pattern in nfvPPA encompassed dorsolateral prefrontal cortex (left worse than right), left dorsomedial, and opercular frontal regions and left superior temporal gyrus. The same analyses using a 10 mm smoothing kernel are shown in Fig. 2.

3.3. ROI analysis

Statistically significant differences between groups were present in all ROIs: the IFG ($X^2(3) = 25.6$, $p < .001$), the PPS ($X^2(3) = 34.6$, $p < .001$), and the AFA ($X^2(3) = 39.8$, $p < .001$). Post-hoc pairwise comparisons with Dunn's test ($p < .05$, corrected) revealed that, compared to the control mean, the IFG showed a significant mean thickness reduction of 16% in the nfvPPA group ($p < .001$); 9% in the AD-PPA group ($p < .05$); and a non-significant 4% reduction in svPPA (Fig. 3a). In the AFA, mean reduction was 31% for svPPA ($p < .001$); 14% for AD-PPA group ($p < .005$); and a non-significant 8% for nfvPPA (Fig. 3b). The PPS thickness was mostly severely reduced in the AD-PPA group (15%, $p < .001$) with reductions also reaching significance in both non-AD groups: 8% in nfvPPA and 5% in svPPA (each $p < .05$) (Fig. 3c).

4. Discussion

Consistent with prior knowledge, the ROI analysis found that for each region maximal cortical thinning corresponded to the expected syndrome: the most severe IFG thinning was in the nfvPPA group; likewise for AFA thinning and svPPA; and, PPS thinning and AD-PPA. Significant cortical thickness reductions, however, were evident in all three ROIs in AD-PPA. This result confirmed the prediction that, while the left posterior perisylvian region is the most severely affected area in AD-related PPA, degeneration diffusely affects the left hemisphere language network. In contrast, there was no significant AFA abnormality in nfvPPA nor, vice versa, for the IFG in svPPA. Both nfvPPA and svPPA did, however, show mild, but statistically significant, thickness reductions in the PPS. The whole-brain analyses also highlighted far more diffuse left hemisphere changes in AD-PPA when contrasted to the other two patient groups.

Previous whole-brain analyses of cortical thickness in AD-PPA (confirmed by either post-mortem or Alzheimer's biomarkers) revealed a similar pattern to that found in the present analysis (Rohrer et al., 2010, 2012). Likewise, the voxel-based morphometry method also identified reduced grey matter density to be maximal in the posterior temporoparietal region in AD-PPA (Josephs et al., 2008) although this analysis method is less sensitive than the cortical thickness approach at capturing degeneration in the cortical ribbon (Diaz-De-Grenu et al., 2014; Rohrer et al., 2010). The limitation of only reporting statistical maps, however, is that there is a degree of arbitrariness in what gets defined as the extent of the degenerated region; the stringency of the applied statistical threshold, for instance, along the number of subjects (i.e. power) and even the degree of smoothing will influence the results. On this last point, the default smoothing kernel in the Freesurfer method of 10 mm appears to underestimate the extent of neurodegeneration in AD by giving patchy, and thus non-biological-looking blobs (Fig. 2 and see (Diaz-De-Grenu et al., 2014) for further discussion). In contrast, studies using large smoothing kernels (20 mm FWHM), such as the present study and others (Leyton et al., 2016; Rohrer et al., 2010, 2012) yield confluent areas of cortical thinning.

Regarding the whole-brain analyses of the other two groups, svPPA was associated with left worse than right and rostral worse than caudal cortical thinning in the temporal lobes as has been well documented in

Table 2

Results from the neuropsychological assessment. Normative data are collapsed from cognitive healthy participants in the range 60–80 years ($N = 25$–33); data = mean (SD); "Kaffee&Kuchen"-test for one nfvPPA patient was not recorded due to technical problems.

	Normative data	AD-PPA (N = 9)	SvPPA (N = 10)	NfvPPA (N = 6)	Omnibus significance
General neuropsychological assessment					
MMSE /30[*]	29.1	19.3	21.0	20.8	$F(3,54) = 23.542, p < .001$
	(0.8)	(5.0)[a]	(5.9)[a]	(7.4)[a]	
GDS /15[*]	0.6	4.2	2.4	4.0	$F(3,54) = 8.079, p < .001$
	(0.8)	(4.5)[a]	(1.7)	(4.0)[c]	
Digit Symbol Substitution	11.3	6.2	9.7	6.3	$F(3,54) = 25,324, p < .001$
	(1.8)	(1.8)[a]	(1.6)[d]	(2.3)[a,h]	
Rey copy /36[*]	32.3	22.6	33.6	27.9	$F(3,53) = 13.784, p < .001$
	(2.7)	(8.5)[a]	(1.6)[d]	(5.2)	
Rey immediate recall /36[*]	18.5	7.5	14.0	14.8	$F(3,53) = 10.571, p < .001$
	(5.8)	(4.9)[a]	(4.2)	(4.3)	
Rey delayed recall /36[*]	17.8	7.1	12.0	14.3	$F(3,53) = 11.895 p < .001$
	(5.0)[i]	(5.7)[b]	(4.1)[c]	(5.3)[f]	
Linguistic neuropsychological assessment					
Letter fluency	12.8	6.4	5.7	2.7	$F(3,49) = 32.135, p < .001$
	(2.3)	(4.5)[a]	(3.3)[a]	(1.8)[a]	
Category fluency	18.2	7.4	5.9	7.8	$F(3,44) = 34.802, p < .001$
	(4.1)	(3.1)[a]	(3.5)[a]	(4.4)[a]	
Boston naming /30[*]	27.4	16.4	4.7	22.7	$F(3,54) = 97.082, p < .001$
	(2.4)	(6.3)[a]	(4.5)[a,d]	(4.4)[c,f,g]	
Kaffee & Kuchen /30[*]	27.8	22.9	17.0	24.7	$F(3,45) = 37.486, p < .001$
	(1.6)	(2.0)[a]	(5.0)[a,d]	(2.4)[g]	
Digit span forward /8[*]	6.2	4.1	5.6	3.3	$F(3,54) = 23.313, p < .001$
	(1.0)	(0.9)[a]	(1.0)[e]	(0.8)[a,g]	
Digit span backward /7[*]	4.4	2.8	4.2	2.2	$F(3,54) = 14.087, p < .001$
	(0.7)	(1.2)[a]	(0.9)[f]	(1.5)[a,g]	
Sentence repetition /5[*]	4.9	2.5	4.5	1.5	$F(3,49) = 15.840, p < .001$
	(0.3)	(1.3)[a]	(0.7)[d]	(2.1)[f]	
Repeat & point (repeat) /10[*]	9.9	6.6	9.6	4.5	$F(3,46) = 21.860, p < .001$
	(0.4)	(2.4)[a]	(0.7)[e]	(3.7)[a,g]	
Repeat & point (point) /10[*]	9.8	8.7	5.8	9.0	$F(3,46) = 13.597, p < .001$
	(0.4)	(1.3)	(2.6)[a,d]	(2.0)[h]	
SECT-V /48[*]	45.2	36.1	43.0	36.0	$F(3,42) = 22.119, p < .001$
	(2.2)	(3.1)[a]	(5.1)[d]	(5.1)[a,h]	

Abbreviations: MMSE = Mini-Mental State Examination, GDS = Geriatric Depression Scale, SECT-V = visual version of the Sentence Comprehension Test, AD-PPA = Alzheimer-related PPA, svPPA = semantic variant of PPA, nfvPPA = nonfluent/agrammatic variant of PPA.

[*] Represents the maximum score for the test.
[a] $p < .001$ compared with normative data.
[b] $p < .01$ compared with normative data.
[c] $p < .05$ compared with normative data.
[d] $p < .001$ compared with AD-PPA.
[e] $p < .01$ compared with AD-PPA.
[f] $p < .05$ compared with AD-PPA.
[g] $p < .001$ compared with svPPA.
[h] $p < .01$ compared with svPPA.
[i] $p < .05$ compared with svPPA.

this syndrome (e.g. Acosta-Cabronero et al., 2011). In the nfvPPA group, maximal thinning was observed in the caudal middle frontal gyrus and on the dorso-mesial surface of the frontal lobe; this pattern has been reported with corticobasal degeneration pathology, a well-recognized association with nfvPPA (Lee et al., 2011).

The novelty of the present study was in quantifying the severity of cortical thinning in the key loci for each of the three PPA groups. This approach was also employed in a post-mortem study although the "semantic" ROI was the temporal pole rather than the anterior fusiform (Leyton et al., 2016). Nonetheless, the results were similar to the present findings in that AD-PPA showed significant atrophy at the putative svPPA and nfvPPA loci.

The findings of the present study, in which the AD-PPA group showed significant involvement of the regions characteristically associated with nfvPPA and svPPA, offers a plausible explanation for why the language deficit in AD-PPA is often more extensive than is captured in the current conceptualisation of lvPPA (Gorno-Tempini et al., 2011). Core features of nfvPPA and svPPA, respectively, focus on grammatical and semantic knowledge impairments (Gorno-Tempini et al., 2011). To this end, it is notable that in this new, prospective cohort study, both

the AD-PPA and the nfvPPA groups showed significant impairments in grammatical comprehension (the SECT-V test) whereas svPPA did not; similarly, the AD-PPA and svPPA groups showed significant impairments in semantic associative knowledge whereas the nfvPPA group did not. In other words, there was evidence for a double dissociation between grammatical and semantic comprehension between nfvPPA and svPPA whereas AD-PPA showed impairments in both domains.

Remaining with the cognitive features, one recent study proposed that impaired forward digit span was a marker of AD-PPA (Giannini et al., 2017). The present study confirmed that significant deficits in this measure are, indeed, a feature of AD-PPA but also highlighted a problem with using it in isolation as a marker for this group. The case for forward digit span was made by contrasting AD versus non-AD PPA and finding that impairments were far more common in the former (Giannini et al., 2017). The authors collapsed, however, non-AD PPA (including nfv-, sv- and unclassifiable) cases into a single group. The problem with this approach is illustrated in the current cohort in which one can see that while the svPPA group was not significantly impaired in forward span, the nfvPPA group (n.b. who in the present study were all amyloid negative) actually performed worse as a group than AD-
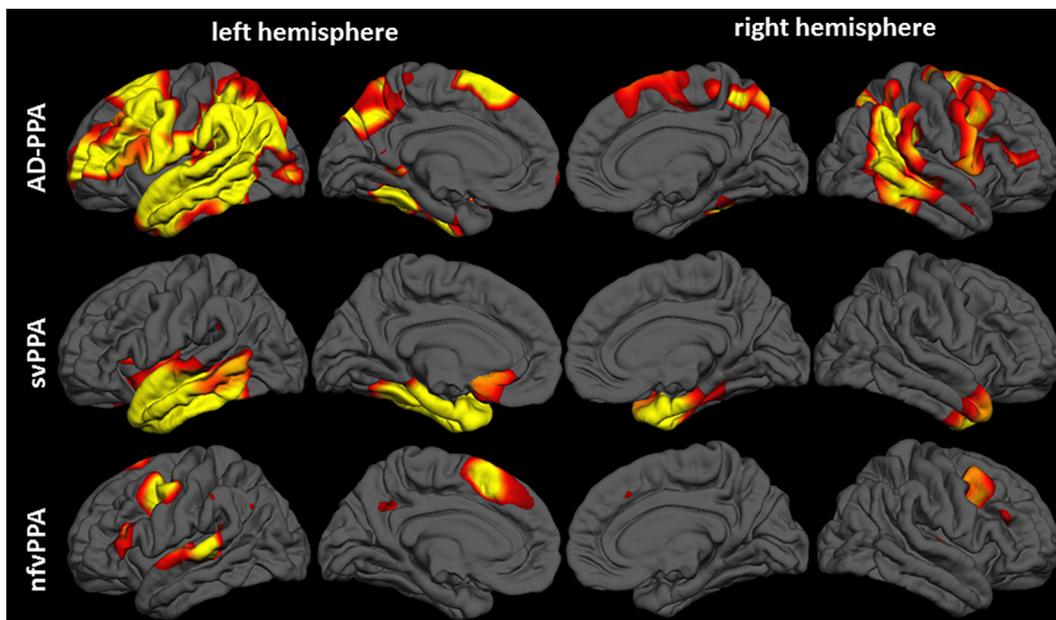
Fig. 1. Whole-brain cortical thinning displayed on the pial surface for every PPA variant compared to a cohort of healthy age-matched volunteers. FDR-corrected (p < .001).
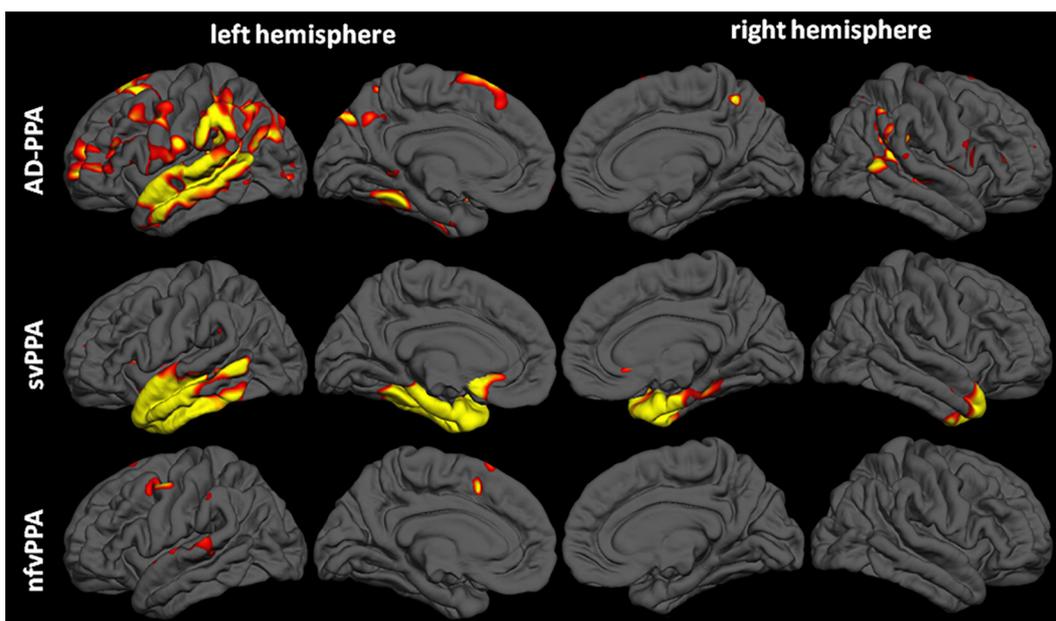

Fig. 2. Whole-brain cortical thinning of the three PPA groups; this is the same analysis and statistical threshold as presented in Fig. 1, except that the default FreeSurfer 10 mm smoothing kernel was employed.

PPA. As such using forward span as a clinical marker for AD pathology will not work to differentiate it from non-AD nfvPPA. The AD-PPA group also showed some deficits on non-language tests including copy of the Rey figure. This suggests the emergence of some visuospatial/constructional deficits on formal testing in this group which, even if their clinical problem was PPA, is unsurprising with Alzheimer pathology. Interestingly as a group, nfvPPA displayed slight impairments copying the Rey figure with a mean score that was not significantly different from the AD-PPA group; this again is consistent with the speculation that some of the nfvPPA participants may have pathological corticobasal degeneration.

The most extreme lesion across all cohorts was AFA atrophy in the svPPA group. This result resonates with the well-documented finding of extreme rostroventral atrophy in this group. For instance, a recent

diagnostic study found that visual rating of individual patient MRI scans was highly sensitive for the atrophy pattern of svPPA but insensitive for the other clinical PPA subtypes (Sajjadi et al., 2017). Turning to the present nfvPPA group, in addition to the expected left lateral IFG atrophy, small areas of dorsomedial and dorsolateral frontal, and, superior temporal atrophy were evident in the whole brain analysis. All of these findings have been reported in past nfvPPA groups (Caso et al., 2014; Josephs et al., 2006; Leyton et al., 2016).

The main limitation of the present study was the small number of patients in the nfvPPA group (N = 6). However, cognitive deficits and the atrophy pattern of our cohort correspond to previously published data. A further potential issue was that the pathological classification was made with an amyloid PET biomarker and not post-mortem examination. In such circumstances, it is possible that a patient with
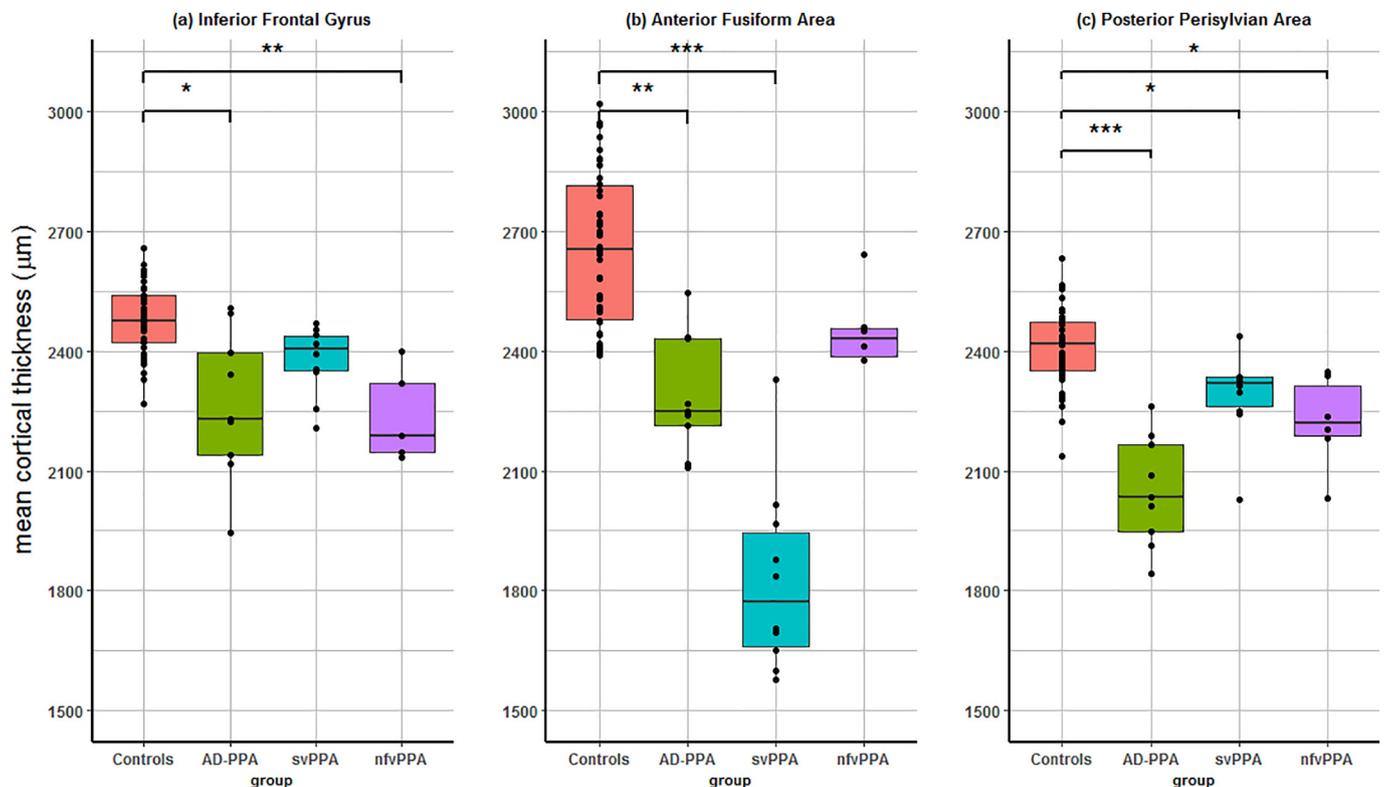
Fig. 3. Results from the ROI analysis for the ROIs a) IFG b) PPS c) AFA; boxplot = 1st, 2nd, 3rd quartile; whiskers 95% CI; * = p < .05; ** = p < .005; *** = p < .001.

positive amyloid PET has dual pathology (i.e. a patient, whose illness is driven by FLTD-related pathology, also has background AD pathology.) Arguing against this scenario in the current cohort was that none of the amyloid-positive PET group had svPPA or nfvPPA—the two recognized syndromes typically underpinned by an FTLD pathology.

In conclusion, in a new prospective cohort, evidence was identified to indicate diffuse involvement of the left hemisphere language network in AD-PPA which, we propose, likely explains why such patients often exhibit semantic and grammatical deficits beyond that which is captured in the consensus recommendations for lvPPA. The results highlight another way to consider the degeneration patterns of the PPAs in addition to the highly-replicated loci of maximal involvement for each syndrome: AD-PPA is associated with diffuse change when compared to FTLD-related PPAs in which the changes are much more focal.

Contributors

DP was involved in the study concept, literature search, collection of neuropsychological data, analysis and interpretation of the imaging data, statistical analysis, and conceptualisation/revision of the manuscript and study coordination. PJN was involved in the study concept, literature search, interpretation of the imaging data, conceptualisation/revision of the manuscript. OVB developed the "Kaffee & Kuchen"-test and the German version of the Sentence Comprehension Test-Visual version and was involved in the collection of neuropsychological data. AS was involved in patient recruitment. NS was involved in the analysis of the imaging data.

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Declaration of Competing Interest

None declared.

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