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Abstract

Primary Progressive Aphasia (PPA) is an overarching term for a heterogeneous group of neurodegenerative diseases which affect language processing. Impaired picture naming has been linked to atrophy of the anterior temporal lobe in the semantic variant of PPA. While atrophy of the anterior temporal lobe proposedly impairs picture naming by undermining access to semantic knowledge, picture naming also entails object recognition and lexical retrieval. Using multivariate analysis, we investigated whether cortical atrophy relates to different types of naming errors generated during picture naming in 43 PPA patients (13 semantic, 9 logopenic, 11 nonfluent and 10 mixed variant). Omissions were associated with atrophy of the anterior temporal lobes. Semantic errors, e.g. mistaking a rhinoceros for a hippopotamus, were associated with atrophy of the left mid and posterior fusiform cortex and the posterior middle and inferior temporal gyrus. Semantic errors and atrophy in these regions occurred in each PPA subtype, without major between-subtype differences. We propose that pathological changes to neural mechanisms associated with semantic errors occur across the PPA spectrum.

Keywords: primary progressive aphasia, volumetric analysis, picture naming, semantic errors, semantic dementia, language

Non-standard abbreviations: nonfluent variant (NFV), semantic variant (SV), logopenic variant (LV), mixed variant (MV), anterior temporal lobe (ATL), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), sparse canonical correlation analysis (SCCAN)

1. Introduction

Impaired picture naming is a core feature in the clinical presentation of Primary Progressive Aphasia (PPA). Virtually all PPA patients demonstrate impaired picture naming albeit for different reasons: picture naming entails correct object identification, access to semantics, phonological retrieval and speech production. Here, we use multivariate analysis to identify in which regions cortical atrophy is associated with specific naming errors during picture naming. Studying error types (e.g. semantic errors, circumlocutions, omissions; Table 1 for classification) instead of total naming accuracy brings us one step closer to understanding which neural mechanisms are impaired. We hypothesize that the neural correlates of naming errors will provide us with an opportunity to study the effect of regional atrophy on language impairment in PPA.

PPA is an overarching clinical term for acquired language disorders caused by different neurodegenerative diseases, such as tauopathies, TDP43-proteinopathies and Alzheimer's disease (Gorno-Tempini et al., 2011; Grossman, 2010). PPA can manifest as different phenotypes, with the main subtypes being the nonfluent variant (NFV), the semantic variant (SV) and the logopenic variant (LV). Recently, the mixed variant (MV) has been introduced as an additional subtype which groups certain cases which were previously unclassifiable (Mesulam et al., 2014). While anomia has often linked to regional atrophy of the anterior temporal lobe (ATL) in PPA, especially in SV (Lambon Ralph et al., 2010; Mion et al., 2010; Patterson et al., 2007), some neuroimaging studies in stroke patients suggest that the size of left-lateralized lesions may well be just as important as the exact location to predict overall naming accuracy (Bruffaerts et al., 2014; Capitani et al., 2009; Schwartz et al., 2011; Thye and Mirman, 2018). Part of the explanation for this difference is that ATL atrophy reflects a loss of semantic knowledge in SV while in stroke, impaired executive control and selection processes might play a larger role (Jefferies and Lambon Ralph, 2006). From a neurolinguistic

perspective, it is worthwhile to investigate whether regional atrophy outside of the ATL contributes to impaired picture naming. Across 50 patients with Alzheimer's Disease (AD), Frontotemporal degeneration (FTD) and corticobasal degeneration (CBD), Grossmann et al. (2004) observed that naming accuracy correlated with cortical atrophy in the left lateral temporal lobe, indicating that the neural basis for impaired naming partially overlaps. Common damage across the PPA spectrum can be highly informative to elucidate the neurobiology of PPA (Mesulam et al., 2014). Amici et al. (2007) and Race et al. (2013) noted that atrophy in left middle temporal gyrus (MTG) and inferior temporal gyrus (ITG) are linked to naming accuracy across all PPA subtypes, whereas Migliaccio et al. (2016) only observed this correlation in LV, but not SV and NFV. Furthermore, education seems to play a role in this relationship (Riello et al., 2018). Left MTG/ITG has also been linked to naming accuracy in stroke patients (Baldo et al., 2013; Hillis et al., 2006) and patients with brain tumors (Sierpowska et al., 2019).

A smaller number of studies characterized different types of naming errors in PPA. Naming errors are more frequent in SV than in other subtypes (Gorno-Tempini et al., 2011; Grossman, 2018; Leyton et al., 2011; Rogers et al., 2006). Early in the disease, semantic errors and circumlocutions occur, but with disease progression superordinate errors dominate (Hodges et al., 1995). Word frequency, familiarity and age of acquisition predict naming success (Lambon Ralph et al., 1998). Accordingly, SV generate responses with higher familiarity during fluency tasks (Rofes et al., 2019). The incorrect responses generated during picture naming by SV have a higher typicality index than the correct responses, reflecting a loss of fine-grained semantic knowledge (Woollams et al., 2008). In LV, a mixed mechanism of anomia and word-selection deficits impairs picture naming (Gorno-Tempini et al., 2008). In MV, object recognition and comprehension deficits exist in combination with distorted speech or agrammatism (Mesulam et al., 2014, 2012). In SV and MV, semantic distractors related to the more dominant meaning

of a homonym were the prime source of errors during single-word comprehension (Schaeverbeke et al., 2018), suggesting a shared mechanism. When directly comparing between PPA subtypes, semantic errors were common in all subtypes, whereas circumlocutions were more frequent in LV and SV versus speech production errors in NFV (Budd et al., 2010).

As impaired picture naming is a clinical characteristic across several PPA subtypes, we hypothesize that part of the neuroanatomical changes occurring in PPA will take place in overlapping cortical regions regardless of the specific underlying neurodegenerative disease. Our work differs from most prior research by including not only SV, but all PPA subtypes (13 SV, 11 NFV, 10 MV, 9 LV, 24 healthy controls; Table 2). Second, we focused on the neuroanatomy of different naming errors rather than overall picture naming accuracy. We used a multivariate approach, sparse canonical correlation analysis (SCCAN) (Avants et al., 2010; Lê Cao et al., 2009; Witten et al., 2009) to identify the cortical regions in which atrophy correlates with naming errors (error percentage for omissions, semantic errors, superordinate errors, circumlocutions only; these are the most common and well-characterized error types). SCCAN is a dimensionality-reduction technique which avoids voxel-wise testing and the associated multiple comparisons problem. Another advantage of this method is that the extent of the cortical region can be determined in a data-driven way, which is important since lesion studies have demonstrated the impact of lesion size on picture naming (Capitani et al., 2009; Schwartz et al., 2011). SCCAN has been applied to a dataset containing 108 patients with different neurodegenerative diseases (AD, FTD, PPA) and 56 controls (Avants et al., 2014). Compound language scores mapped to the left inferior and posterior temporal cortex. Here, we focus on impaired picture naming and use the same approach to untangle the neuroanatomical basis of different naming errors. We used the error classification proposed by Woollams et al. (2008) for SV to define naming errors generated during the 60-item Boston Naming Test (BNT) (Kaplan et al., 1983). While the BNT is the most popular confrontation naming test in clinical

practice (Rabin et al., 2005), it has been criticized because it may not sample widely enough across diverse entities (Harry and Crowe, 2014), some entities may be redundant (Pedraza et al., 2011), or BNT score may not good be a good proxy for daily-life speech because the entities are unlikely to occur in everyday conversation (Brookshire and Nicholas, 1995). We motivate our choice for the BNT because it is a reliable (Strauss et al., 2006) and routinely used clinical tool in the assessment of PPA, norms are available, and responses can readily be compared across participants, in contrast to less constrained tasks.

ERROR	COMMENTS	EXAMPLE RESPONSES
OMISSION	No time limit was set for response generation	"I don't know", no response
SEMANTIC	Semantic relation of target	Rhinoceros => "Hippopotamus"
SUPERORDINATE	Category name of target	Cactus => "plant"
CIRCUMLOCUTION	Multiword response that circles target	Coat hanger => "it is used for hanging clothes"
OTHER	- Neologism: possible but nonexistent single word (not found in dictionary); shares less than 50% of phonemes with the target	Octopus => "eightarm"
	- Phonological error: unintended phonemic insert, omission, substitution, transposition or repetition; shares at least 50% of phonemes with the target; sound occurs in the speaker's language	Seahorse => "seehouse"
	- Speech production error/performance error: distortions that are slurred/stuttered due to apraxia of speech or dysarthria, e.g. syllable segregation, articulatory groping, phonetic errors (sounds that do not occur in the speaker's language)	Stethoscope => "ste…tho…scope"

	-Visual error: visual but non semantic relation to target, includes partonomic errors	Pretzel => "snake" Tree => "leaves"
UNRELATED	No relation to target	Trellis => "pliers"

Table 1: Error classification following Woollams et al. (2008) for SV. The "other" errors were classified using the definitions proposed by Corina et al. (2010) & Ash et al (2010). The examples responses contains the target and actual responses generated by PPA patients (quotes).

2. Materials & methods

2.1 Participants

The study was approved by the Ethics Committee, University Hospitals Leuven. All participants provided written informed consent in accordance with the Declaration of Helsinki. PPA patients were recruited via the memory clinic University Hospitals Leuven and through referrals from other centers between 2010 and 2019. A consecutive series of 43 patients who fulfilled the international consensus criteria for PPA (Gorno-Tempini et al., 2011) enrolled for the experiment. Prior to study enrollment, each PPA patient was classified according to the Gorno-Tempini et al. (2011) and Mesulam et al. (2014) recommendations into NFV, MV, LV and SV. The classification relied on the clinical evaluation by an experienced neurologist (R.V.), in combination with neurolinguistics assessment and clinical MRI, as well as, where available, [^{18}F]fluorodeoxyglucose PET ([^{18}F]-FDG PET), CSF AD biomarkers and [^{11}C]-Pittsburgh compound B amyloid PET. Thirteen cases were classified as SV, eleven as NFV, ten as MV and nine as LV (Table 2). It is of note that the MV subtype (Mesulam et al., 2014, 2012)

was described after enrollment for our study started. It is possible that some MV enrolled before 2014 were classified as NFV (5/11 NFV were recruited before 2014). However, we chose not to perform post-hoc reclassification to avoid introducing bias. Out of the 43 participants, 36 were included in previously published work (Grube et al., 2016; Nelissen et al., 2011; Schaeverbeke et al., 2018). Twenty-four healthy controls (HC), matched for age, gender and education (Table 2), performed the same test battery as the patients.

	HC	LV	NFV	SV	MV
N	24	9	11	13	10*
AGE (Y)	62.0 (7.9)	65.9 (7.3)	66.3 (8.1)	64.9 (8.1)	67.3 (8.8)
GENDER (M:F)	13:11	5:4	4:7	5:8	5:5
EDUCATION (Y)	13.9 (2.4)	14.4 (2.6)	12.3 (3.0)	12.7 (3.3)	13.5 (2.6)
DISEASE DURATION (Y)	-	2.8 (2.5)	3.8 (1.3)	4.1 (2.2)	2.8 (1.3)
MMSE (/30)	29.3 (0.9)	**27.0 (2.3)**	**24.6 (5.3)**	**25.7 (3.3)**	**22.8 (7.5)**
ASSOCIATIVE SEMANTIC TASK (/30)	27.7 (1.6)	**26.3 (1.6)**	**23.7 (7.9)**	**21.5 (6.6)**	**23.0 (3.4)**
WP MATCHING (/40)	39.8 (0.5)	39.2 (1.2)	**36.6 (5.6)**	**28.9 (9.9)**	**38.2 (1.4)**
FLUENCY	28.3 (7.3)	**13.5 (6.9)**	**7.2 (5.0)**	**10.3 (5.5)**°	**9.4 (4.2)**
REPETITION (/160)	153.3 (7.2)	**146.2 (7.6)**	**125.4 (45.7)**°	**143.7 (14.7)**	**104.4 (51.3)**
OBJECT DECISION (/64)	56.9 (2.9)	54.1 (3.8)	53.5 (7.5)°	**45.2 (6.2)**°	**49.2 (5.2)**
CPM (/36)	33.1 (2.3)	30.8 (7.2)	**25.0 (9.0)**°	31.7 (4.2)°	**25.4 (6.8)**

*Table 2: Patient and control demographics and neuropsychological test scores (mean and s.d.). WP matching: auditory word-picture matching task; CPM: Raven's Colored Progressive Matrices. Bold indicates worse performance compared to controls (P<0.05, Wilcoxon or Student t test depending on normality of distribution). *One MV patient in an advanced stage performed only the picture naming task. °Score missing for a single participant in this group (fatigue).*

2.2 **Experimental design**

The 60-item version of the BNT was performed and audio recordings were collected. Test administration was halted when requested by the patient or when the patient did not generate a response in more than 8 consecutive trials. The full neuropsychological test battery also included the Mini Mental State Examination (Folstein et al., 1975) as a general test of cognitive function, and Raven's Colored Progressive Matrices (CPM) as a test of non-verbal executive function. Neurolinguistic testing was performed using a selection of tests from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Bastiaanse et al., 1995). In the auditory word-picture matching task (PALPA 45), a concrete noun was presented together with a target picture and four distractors (2 semantically related, 1 perceptually related, 1 unrelated). Participants had to point to the target. In the associative-semantic task (PALPA 49), a noun is presented visually together with four-choice noun stimuli (a target noun, a semantically related noun and 2 unrelated nouns). The participant had to indicate the noun that matched the sample stimulus most closely in meaning, for a total of 15 word series with high imageability and 15 words series with low imageability. In the repetition task (PALPA 9), the examiner pronounces 80 nouns and 80 pseudowords which the participant has to repeat. The Birmingham Object Recognition Battery (parts hard (A) and easy (B)) (Riddoch and Humphreys, 1993) was performed to measure object identification abilities. For every drawing, the participant has to indicate whether an animal or tool which is depicted is real or unreal. Finally, animal verbal fluency was determined in all participants.

2.3 Behavioral analysis

Dutch norms (Mariën et al., 1998) were used to identify responses that qualified as a correct answer. Errors were classified based on the audio recordings according to the classification proposed for SV by Woollams et al. (2008). Different errors types included in this classification are omissions, semantic errors, superordinate errors, circumlocutions, other errors and unrelated responses (Table 1). We report also some additional error types to characterize our sample of patients because we included not only SV, but also MV, NFV and LV: neologisms, phonological errors, speech production errors/performance errors and visual errors (Table 1). We added visual and phonological errors because they were mentioned as specific types of "other" errors in the Woollams et al. (2008) classification. Partonomic errors (where patients identify one part as if it were a whole stimulus) were included as a subtype of visual errors because they may result from simultanagnosia (Bergmans et al., 2016; Riddoch and Humphreys, 2004). Finally, we added neologisms and speech production errors/performance errors based on the classifications by Corina et al. (2010) (for epilepsy patients) and Ash et al. (2010) (for NFV). Speech production errors include phonetic errors: in the case of a phonological error, the unintended sound is a well-formed phoneme of the language, whereas in the case of a phonetic error, the sound does not occur in the speaker's language (Ash et al., 2010). In the event that a sequence of responses was generated for one trial, the first response was scored, even for self-corrections.

First, we report the total accuracy and absolute numbers of different error types for every group (Fig 1A) and describe effects of lexical parameters on naming accuracy for comparison to previous work. Log word frequency was derived from the SUBTLEX-NL database for Dutch words (Keuleers et al., 2010) and age of acquisition was based on ratings from 74 native Dutch speakers (Brysbaert et al., 2014). Word length was used as a proxy for articulatory difficulty level. In the subsequent analyses, we used the percentage error scores (absolute number of errors divided by total number of trials completed by participant) (Fig 1B), to correct for the

lower number of trials in patients who did not complete all trials. Statistical comparison of percentage error score differences between PPA subtypes was performed by means of a one-way ANOVA followed by post hoc Tukey-Kramer pairwise comparison of subtypes ($P<0.05$). Additionally, we tested the correlation between percentage error score and disease duration.

2.4 **Acquisition & preprocessing of MRI data**

All participants received a high resolution T1-weighted structural MRI. Twenty-nine patients and all controls were scanned on a 3 T Philips Intera system equipped with an 8-channel receive-only head coil (Philips SENSitivity Encoding head coil). Fourteen patients were scanned on a 3 T Philips Achieva dstream scanner equipped with a 32-channel head volume coil. For structural imaging, an identical 3D turbo field echo sequence was used on both systems (coronal inversion recovery prepared 3D gradient-echo images, inversion time (TI) 900 ms, shot interval = 3000 ms, echo time (TE) = 4.6 ms, flip angle 8 degrees, 182 slices, voxel size 0.98 x 0.98 x 1.2 mm^3). Segmentation was performed used the CAT12 toolbox (Structural brain mapping group, Jena, Germany, http://www.neuro.uni-jena.de/cat), an extension of SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm). Segmentation was performed in CAT12 using a default tissue probability map. Local adaptive segmentation was used at default strength (medium) and a Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL) was used for registration to the default template (IXI555_MNI152). Voxel size for normalized images was set at 1.5 mm (isotropic) after internal resampling at 1mm. Images were smoothed using a 8 x 8 x 8 mm^3 Gaussian kernel.

2.5 **Statistical analysis: sparse Canonical Correlation Analysis (SCCAN)**

This multiple regression tool is an extension of canonical correlation analysis (Hotelling, 1935), which is itself an extension of principal component analysis. Recently, SCCAN has been implemented for neuroimaging (Avants et al., 2010). Univariate techniques such as voxel-based-morphometry (VBM) require correction for multiple comparisons and subsequent clustering of significant voxels. In contrast, SCCAN first decomposes neuroimaging data to obtain clusters in a data-driven way (Avants et al., 2014). Second, hypothesis testing is performed at cluster-level. As input, we used the smoothed grey matter maps of the PPA patients produced by CAT12, masked by the grey matter mask provided with the SCCAN toolbox (binarized and resliced to 272705 voxels of 1.5 x 1.5 x 1.5 mm^3). SCCAN was run using R v3.4.4 for linux and ANTsR v0.4.8. The PPA dataset (n = 43) was randomly split in half into a training PPA dataset (n = 22) and a test PPA dataset (n = 21). The control dataset (n = 24) was used as a second test dataset. First, SCCAN was used to compute an eigenvector in the training set which maximizes the Pearson correlation between the input modalities (here, imaging and percentage error score). Although it is possible to introduce prior knowledge about neurobiology when using SCCAN (Avants et al., 2014), we employed a strictly data-driven approach. Default settings (Tustison, 2017) for orthogonality and gradient descent were applied: this means that orthogonality is enforced on the sparse eigenvectors as well as on the low-dimensional outcomes generated by application of the eigenvector to the input data (Kandel et al., 2015) and that a negative gradient descent parameter is introduced, which iteratively optimizes the model to minimize the error. For the neuroimaging data, a minimum cluster extent was set at 200 voxels to avoid single voxels appearing in the eigenvector. For the behavioral data, sparseness was fixed at 0.9 (default setting). For every error type (omissions, semantic errors, superordinate errors, circumlocutions), the optimal sparseness was determined separately, namely the sparseness at which the linear correlation between the percentage error

score and the predicted scores derived from the neuroimaging data was maximal in the training PPA dataset. We studied each error type separately: the rationale is that we did not want to make assumptions about whether the resulting eigenvectors for different error types should overlap or have equal sizes (as determined by the sparseness value). To obtain the optimal sparseness, correlations between neuroimaging and behavioral data were calculated for a range of candidate sparseness values between 0.001 (99.9% sparse, or 0.1% non-zero values in the neuroimaging modality) and 0.1 (90% sparse) in the training PPA dataset. This procedure resulted in a sparse projection vector (eigenvector) acting on voxels that taken as a set, maximally correlated with each error type in the training dataset. The eigenvector can be reinterpreted as a weighted average of values over a restricted region of voxels, which can be visualized. The significance of SCCAN results can be determined using permutation testing when large samples (>1000) are available by comparing the true correlation value to a distribution of correlation values obtained by random permutation labelling (Avants et al., 2014). Examples of SCCAN combined with random permutation labelling are Avants et al. (2010), Sintini et al. (2019), Kang et al. (2018), Jang et al. (2017) and McMillan et al. (2014). Given the smaller sample in our case, we are using a training set and an independent test dataset as proposed by Avants et al (2014) and Tustison (2017). For each error type, the eigenvector determined on the training PPA dataset was applied to the test PPA dataset and the test control dataset to calculate the weighted average of values based on the test neuroimaging data, i.e. the predicted score. In each test dataset, a single one-tailed Pearson correlation was performed between the scores predicted from the neuroimaging data and the behavioral data for each error type (preset threshold of $P < 0.05$, no correction for multiple comparisons used for 4 error types). The eigenvectors were visualized using MRIcroGL (http://www.mricro.com). Additionally, we evaluated to which degree PPA subtype-specific atrophy patterns contributed to the multivariate results. This was tested by comparing grey matter volumes in the regions

defined by the eigenvectors by means of a one-way ANOVA. Grey matter volumes for each PPA subtype in the regions defined by the eigenvectors were compared to elderly controls (two-sample t-test, uncorr. P<0.05). Finally, exploratory plots including PPA subtypes (NFV, MV, LV, SV) were created to visualize the correlations between the percentage error scores and the predicted scores in the training and test datasets. Age, scanner type and total intracranial volume (TIV, calculated using the CAT12 toolbox) were added as variables of no interest in all multivariate analyses.

2.6 Voxel-based morphometry (VBM)

To compare the SCCAN results to a univariate approach, we conducted a traditional univariate VBM analysis using CAT12. Multiple linear regression was used to evaluate the relationship between percentage error score for each error type and atrophy (smoothed grey matter maps) in all 43 PPA patients. A one-tailed significance threshold was set at voxel-level uncorrected P<0.001 and cluster-level FWE-corrected P<0.05 (Poline et al., 1997). In the control group, the resulting clusters derived in PPA patients were used as regions of interest, in which the correlation between percentage error score and atrophy was assessed. Age, scanner type and TIV were added as variables of no interest in all univariate analyses.

2.7 Code accessibility

Scripts to perform SCCAN are available online (https://github.com/stnava/sccan) as well as a tutorial (Tustison, 2017).

3. Results

3.1 Behavioral analysis

Out of the 43 PPA patients, 36 (83.7%) completed all 60 items of the BNT, the remaining 7 patients (1 NFV, 5 SV, 1 MV) completed between 15 and 49 items. Mean accuracies were highest in LV (69.3%, s.d. 18.1%), compared to NFV (63.0%, s.d. 24.8%), MV (56.2%, s.d. 19.0%) and SV (47.4%, s.d. 17.2%), but no large between-group differences were observed ($F(3,39)=2.34$, $P = 0.089$). In every PPA subtype, higher accuracy for individual words correlated with higher word frequency (all $P<0.002$) and lower age of acquisition (all $P<0.001$). Higher accuracy correlated with shorter word length in LV ($r = -0.38$, $P = 0.003$), NFV ($r = -0.27$, $P = 0.036$) and MV ($r = -0.46$, $P < 0.001$), but not in SV ($P > 0.1$).

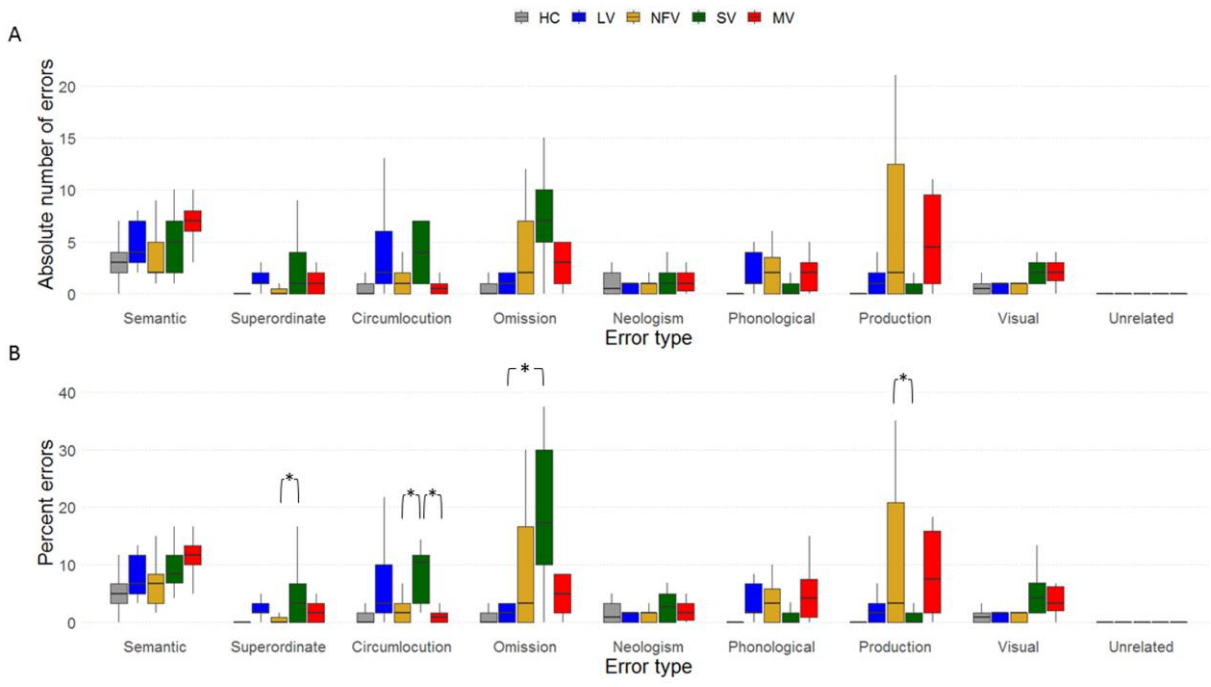

Fig. 1: Errors across PPA variants. A) Absolute number of errors per error type. B) Percent errors per error type. Boxplot shows median and interquartile range. (*) between-subtype difference using a post hoc Tukey-Kramer pairwise comparison (P<0.05)

Unrelated errors were only observed twice in one NFV patient in an advanced stage: "pliers" for trellis and "mouse" for igloo (Fig 1A). The "unrelated" error type was thus excluded from further analysis. A specific subtype of semantic error is the "associate error", which is semantically related but from a different category and altogether rare in PPA (Jefferies and Lambon Ralph, 2006): this occurred twice in total (one occurrence in LV, one in NFV). Partonomic errors, classified as a subtype of visual errors, were also rare (mean error percentage across PPA subtypes: 0.56%).

The percentage of omissions differed between the 4 PPA subtypes ($F(3,39)=2.95$, $P = 0.044$, Fig. 1B). A post-hoc Tukey test showed significantly more omissions in SV than LV ($P<0.05$). The percentage of circumlocutions differed between the 4 subtypes ($F(3,39)=4.56$, $P = 0.008$), with more circumlocutions in SV than NF and MV ($P<0.05$). The percentage of superordinate errors differed between the 4 subtypes ($F(3,39)=3.17$, $P = 0.035$), with more superordinate errors in SV than NFV ($P<0.05$). Speech production errors differed between subtypes ($F(3,39)=4.14$, $P = 0.012$), with more errors in NFV compared to SV. No between-group differences were found for semantic errors ($F(3,39)=1.27$, $P = 0.298$), neologisms ($F(3,39)=1.08$, $P = 0.370$), phonological errors ($F(3,39)=2.15$, $P=0.101$) or visual errors ($F(3,39)=1.68$, $P = 0.186$).

In summary, omissions, circumlocutions, and superordinate errors were more frequent in SV, and speech production errors were more prevalent in NFV.

PPA subtype groups did not significantly differ in MMSE or disease duration (defined as years from reported onset of symptoms). Disease duration correlated negatively with accuracy ($r = -0.455$, $P = 0.002$) and positively with the percentage of omissions ($r = 0.432$, $P = 0.004$) and circumlocutions ($r = 0.302$, $P = 0.049$). These effects remained unchanged even when subtype was introduced as a covariate of no interest.

3.2 Sparse Canonical Correlation Analysis (SCCAN)

The percentage of semantic errors correlated with atrophy within the left mid and posterior fusiform cortex (mainly BA20), as well as the left posterior MTG/ITG (mainly BA37) and middle occipital gyrus and parietooccipital fissure, left middle frontal gyrus and bilateral anterior cingulate cortex (sparseness: 0.041, meaning 4.1% of all voxels, 11181 voxels, Fig 2AB). All PPA subtypes contributed to the correlation between percentage error score and predicted score based on regional atrophy (Fig 3AC). There was no between-subtype difference in atrophy within the regions derived using SCCAN ($F(3,39)=0.14$, $p=0.935$) (Fig 2C). In elderly controls, no correlation between regional atrophy and the percentage of semantic errors was observed (Fig 3E) and the atrophy in this region was greater for each PPA subtype compared to the control group (corr. for age, scanner type, TIV, $P<0.05$)(Fig 2C).

The percentage of omissions correlated with atrophy in the bilateral medial ATL extending posteriorly, overlapping with the perirhinal cortex and parahippocampal gyrus (mainly BA36/BA30), as well as the right angular gyrus (sparseness: 0.021, 5727 voxels, Fig 2DE, Fig 3BD). The between-subtype difference in atrophy within the regions derived using SCCAN was significant ($F(3,39)=7.55$, $p<0.001$). A post-hoc Tukey test confirmed that the atrophy in SV was greater than in LV. In the group of elderly controls, no correlation between regional atrophy and the percentage of omissions was observed (Fig 3F), and grey matter volume was smaller in SV and MV compared to controls ($P<0.05$)(Fig 2F). The neural correlates for semantic errors and omissions did not overlap. For circumlocutions and superordinate errors no neural correlate was revealed. Removal of the participants who completed <60% of trials, did not substantially change the results for semantic errors, whereas the correlation was weaker in the test PPA dataset for omissions ($P = 0.09$).

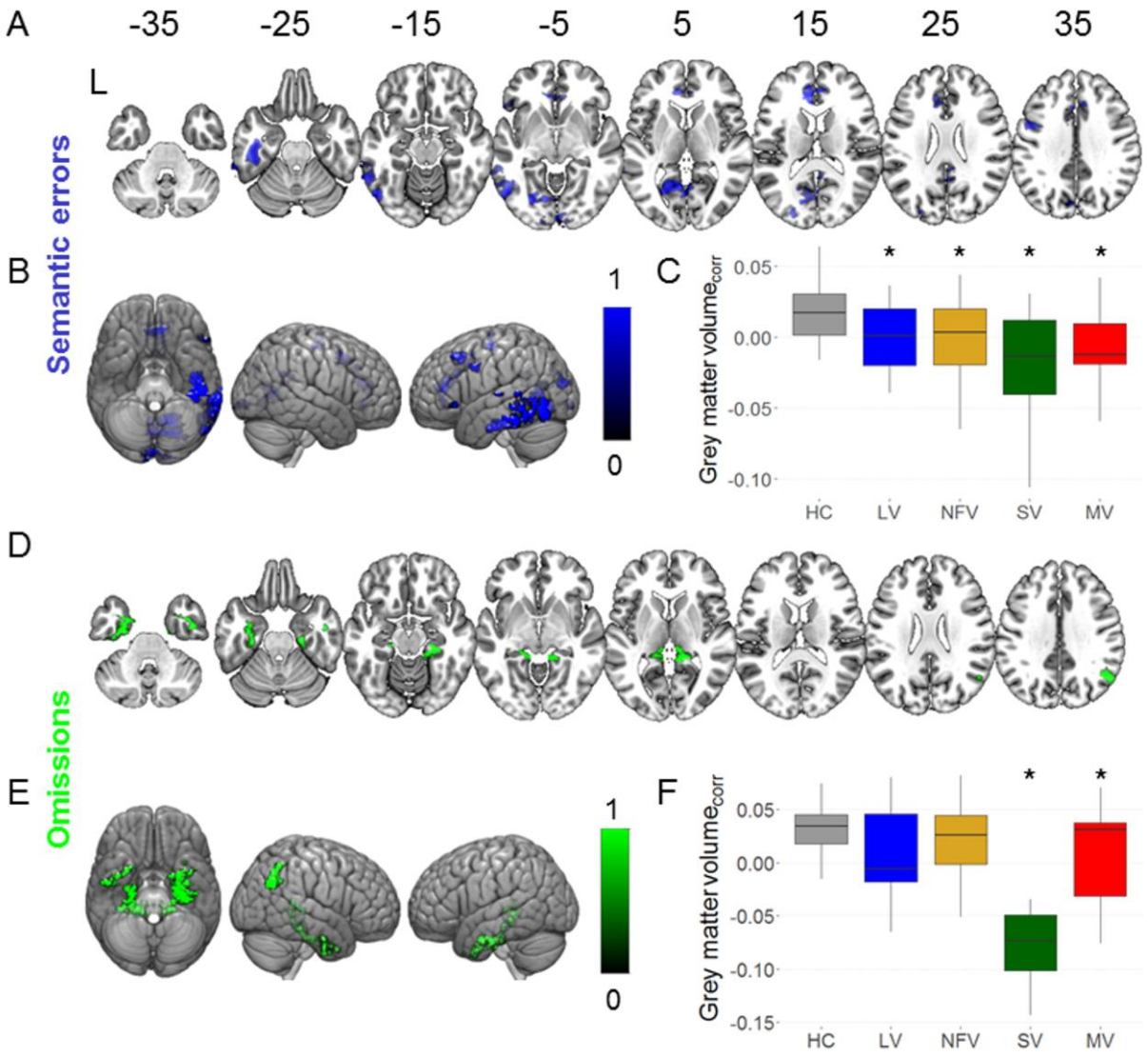

Fig. 2: Eigenvectors determined in the training dataset for semantic errors and omissions. AD) Axial slices at selected MNI z-coordinates. BE) Renderings are partly translucent to visualize medial regions. The colorbar displays the normalized vector weights. CF) Boxplot of average grey matter volume, corrected for TIV, scanner type and age, in the region defined by the eigenvector. (*) indicates grey matter volume in the PPA subtype group is lower compared to the control group ($P<0.05$).

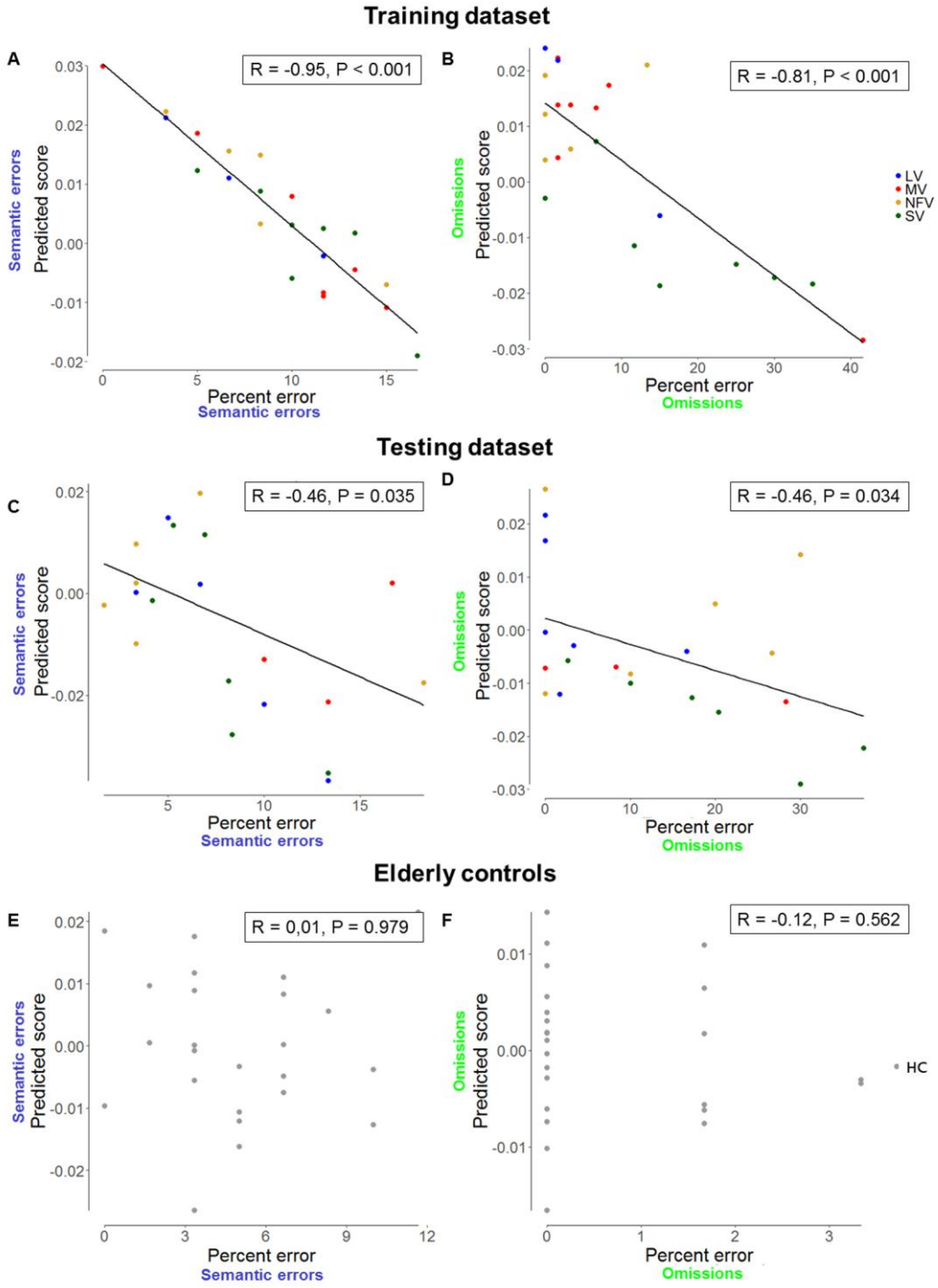

Fig. 3: Correlation between percentage error scores and the predicted scores based on cortical atrophy (Fig. 2) in the training PPA dataset (AB) , test PPA dataset (CD) and test elderly control dataset (EF) for semantic errors (ACE) and omissions (BDF).

3.3 Voxel-based morphometry

The percentage of omissions correlated with clusters in the left medial ATL (MNI –23,-33,-14, k_E = 6429, Z = 4.30, cluster-level $P_{FWE\text{-}corr} < 0.001$) and the right medial ATL (MNI 21,-12,-36, k_E = 1222, Z = 4.05, cluster-level $P_{FWE\text{-}corr} = 0.022$; Fig 4AB, Fig 5A) (mainly BA36/BA30). Similar to the multivariate findings, the between-subtype difference in atrophy within the regions derived using univariate analysis was significant ($F(3,39)=11.78$, $p<0.001$), with greater atrophy in SV compared to LV (Fig 4C). In elderly controls, no correlation between percentage of omissions and atrophy in these regions was observed (Fig 5C) and grey matter volume was smaller in SV and MV compared to controls ($P<0.05$)(Fig 4C). The percentage of superordinate errors correlated with atrophy of the superior and medial part of the left superior temporal gyrus adjacent to the insula (MNI -44,-11,-12 k_E = 1125, Z = 3.86; Fig 4DE, 5B, cluster-level $P_{FWE\text{-}corr} = 0.029$)(BA48). Again, the between-subtype difference in atrophy within these regions was significant ($F(3,39)=9.81$, $p<0.001$), with greater atrophy in SV compared to LV (Fig 4F).When the two SV with the highest percentage of superordinate errors were removed, the correlation was weaker ($r = -0.325$, $P = 0.038$). In elderly controls, no correlation was observed (Fig 5D) and atrophy across and grey matter volume was smaller in SV and MV compared to controls ($P<0.05$)(Fig 4F). No significant results were found for semantic errors and circumlocutions. For the sake of comparison to the SCCAN results (Avants et al., 2010), we show the univariate analysis for semantic errors at a very low threshold (uncorr. $P<0.05$ with cluster threshold of 200 voxels)(Fig 6). This reveals similar regions to the SCCAN analysis and additional right-sided regions. Removal of the participants who completed <60% of trials, did not substantially change the results of the univariate analysis.

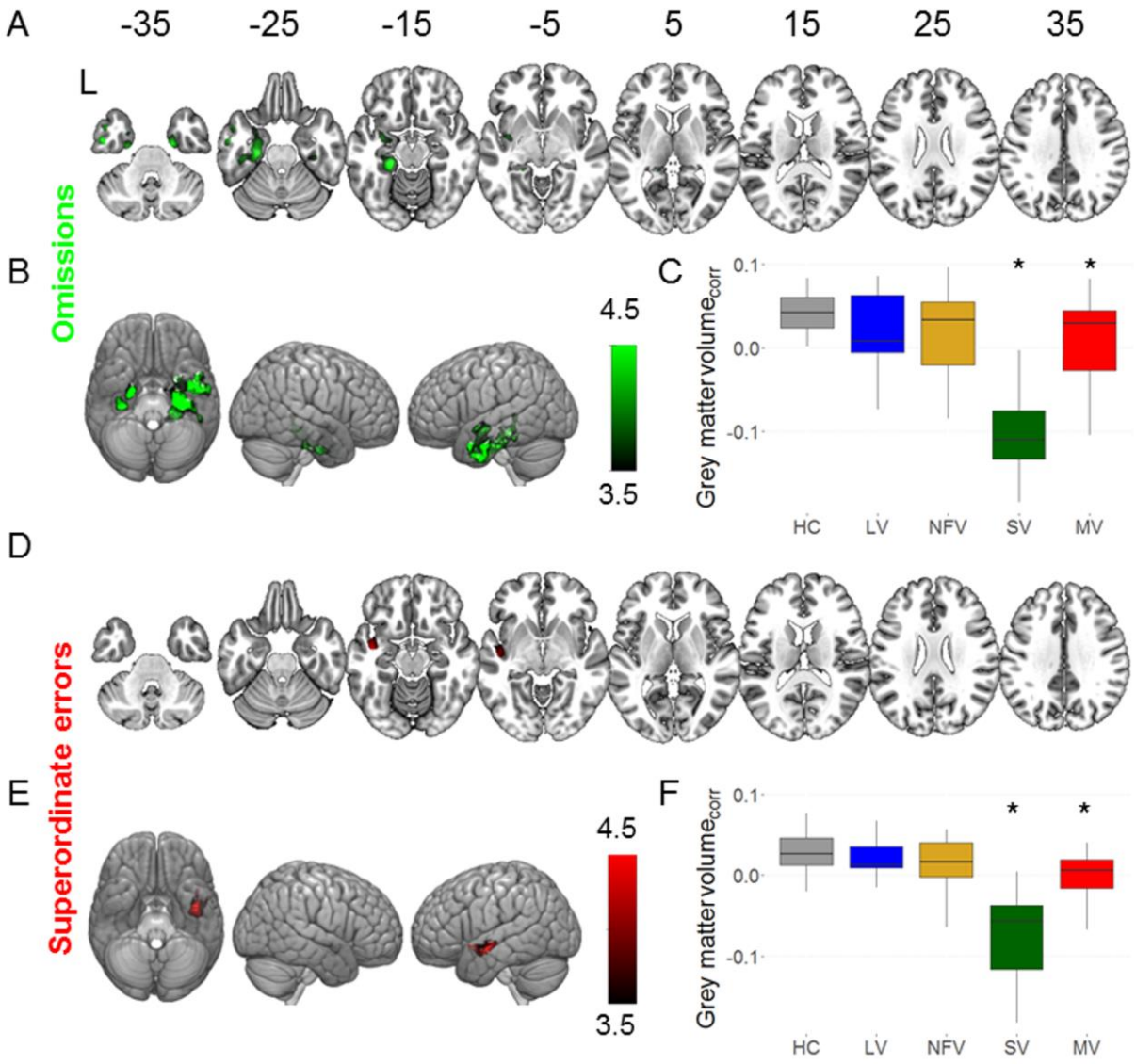

Fig. 4: VBM at a threshold of voxel-level uncorrected P<0.001 and cluster-level FWE-corrected P<0.05 (Poline et al., 1997) for omissions and superordinate errors. AD) Axial slices at selected MNI z-coordinates. BE) Renderings. Colorbars display t-scores. CF) Boxplot of average grey matter volume, corrected for scanner type, TIV and age, in the regions defined by the VBM analysis. (*) indicates grey matter volume in the PPA subtype group is lower compared to the control group (P<0.05).

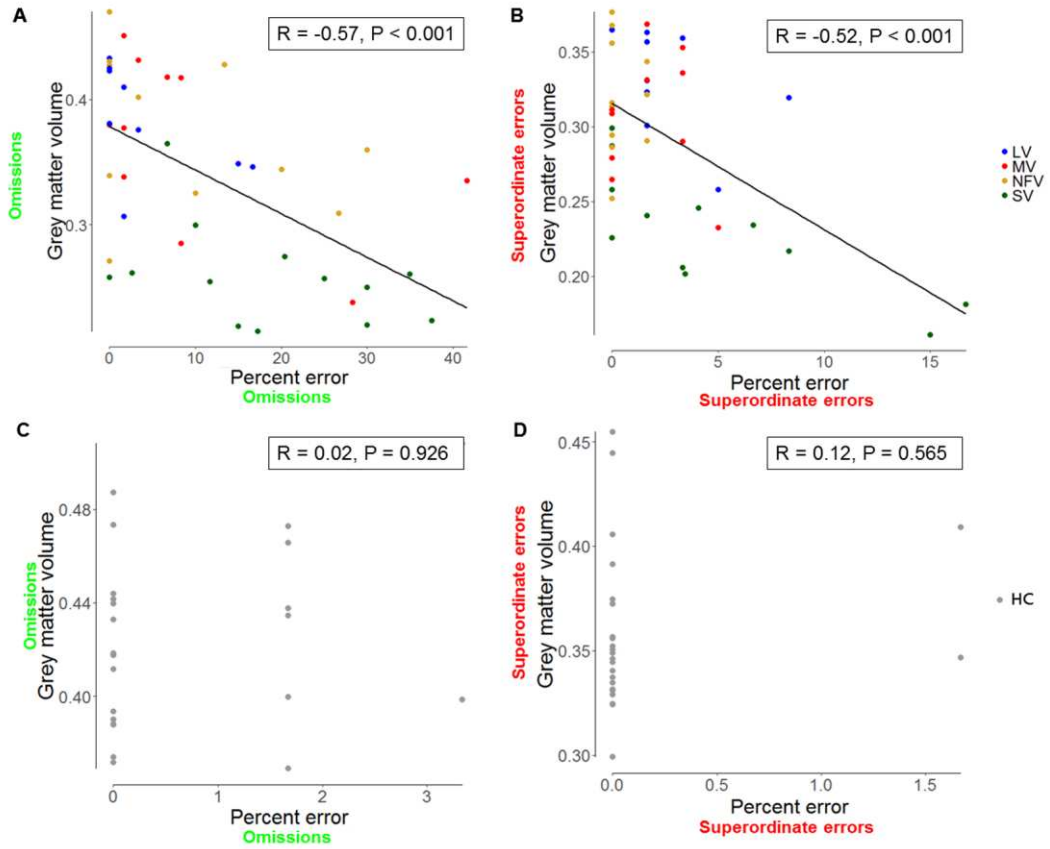

Fig. 5: Correlation between percentage error scores and mean grey matter volume in the regions of interest calculated from VBM (Fig. 4) for omissions (AC) and superordinate errors (BD) in PPA (AB) and healthy elderly controls (CD).

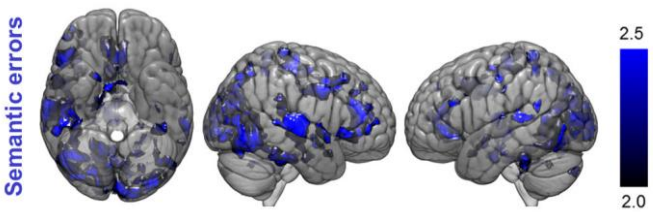

Fig. 6: VBM for semantic errors at a threshold of voxel-level uncorrected P<0.05 for comparison to Fig 2B. Colorbar displays t-scores.

4. Discussion

The aim of this study is to increase our understanding of the language impairment in PPA associated with regional atrophy patterns. In a data-driven whole-brain analysis, which was replicated in an independent dataset, we observed that the neuroanatomical substrate of semantic errors is different from the neuroanatomical substrate of omissions in PPA. Omissions were associated with atrophy of the bilateral medial ATL and the right angular gyrus (Fig 2D). Semantic errors during picture naming were associated with atrophy of the left mid and posterior fusiform cortex and left posterior MTG/ITG (Fig 2B). Our dataset identifies a shared pattern of atrophy for semantic errors across the PPA spectrum regardless of the underlying pathology, suggesting shared neural mechanisms. Semantic errors were found across all PPA subtypes (Fig 1) with no major difference between PPA subtypes, in accordance with prior work by Budd et al. (2010). Similarly, regional atrophy in the left mid and posterior fusiform cortex and left posterior MTG/ITG was observed in all PPA subtypes (Fig 2C). Our multivariate results replicate the findings of Grossman et al. (2004), who observed that across AD, FTD and CBD, left posterior MTG/ITG atrophy correlates with naming. Additionally, we identified an another neural correlate of semantic errors, namely atrophy in the left mid and posterior fusiform cortex. Previously, Ding et al. (2016) observed a correlation in SV between atrophy in the left fusiform gyrus and a compound score derived from picture naming, sound naming, picture matching, word matching, word-picture verification and naming to definition. Our findings are also in accordance with the seminal PET study in SV by Mummery et al. (1999), which showed that in SV compared to controls, posterior MTG/ITG is less active during a semantic versus a visual decision task. We further expand on these prior results by demonstrating that across all PPA subtypes, this pattern of regional atrophy is associated with semantic errors.

Although picture naming is seemingly straightforward, it consists of neurobiologically diverse processes: visual object identification, access to semantics, lexical retrieval and speech production. Semantic errors can arise from disruption of the object naming pathway even when semantic knowledge is preserved (Cloutman et al., 2009; Hurley et al., 2012; Lambon Ralph et al., 2002). Our multivariate approach, identifying regions across the brain where atrophy covaries, does not discriminate between simultaneous impairment of the different neural processes relevant to picture naming. More concretely, atrophy in the left posterior MTG/ITG and the left mid and posterior fusiform cortex may disrupt correct picture naming through different neural mechanisms. The left posterior MTG/ITG is a candidate region for the amodal representation of semantic information (Devereux et al., 2013; Fairhall and Caramazza, 2013). This region might also play a role in lexical retrieval, as suggested by prior studies in stroke patients (Cloutman et al., 2009; Hillis et al., 2006, 2005), PPA patients (Grossman et al., 2004; Mummery et al., 1999) and epilepsy patients (Corina et al., 2010) as well as functional neuroimaging in controls (Cohen et al., 2004; Price, 2012). Atrophy in the left mid and posterior fusiform cortex possibly reflects deficits in visual object processing. In controls, the left mid and posterior fusiform cortex is known to contain visual and semantic information during picture naming (Clarke and Tyler, 2014). This information reflects the extraction of visual and semantic features from visual input within the left mid and posterior fusiform cortex (Bruffaerts et al., 2019a, 2019b; Clarke and Tyler, 2015). The mid fusiform cortex could also be involved in the representation of semantic information across modalities: this region has been referred to as the "basal temporal language area" because electrical stimulation may result in global aphasia (Lüders et al., 1991). Recently, Forseth et al. (2018) demonstrated that stimulation of the mid fusiform cortex impairs the access to semantic information during an auditory task, while sentence repetition is preserved. The neural processes cited here –lexical retrieval, representation of semantic information, visual object processing- are all central to picture

naming and pathological changes to each of these processes may result in a similar behavioral response, i.e. a semantic error.

What our study adds, is that cortical atrophy outside of the anterior temporal lobe contributes to the generation of semantic errors, not only in SV (Ding et al., 2016) but in all PPA subtypes. Regardless of the PPA subtype, regional atrophy in the left mid and posterior fusiform cortex and left posterior MTG/ITG may correlate to word finding difficulties reported by PPA patients. Our findings suggest that some neural mechanisms associated with semantic errors are shared across the PPA spectrum. However, we find no evidence that regional cortical atrophy is associated with naming errors in healthy elderly controls. Perhaps, a disease-specific mechanism of semantic interference might exist in PPA due to FTD. Behaviorally, presenting a semantically related prime negatively affects naming times in PPA, whereas a positive effect was found in AD (Vandenberghe et al., 2005). Other considerations are that accuracies are higher in controls, resulting in ceiling effects in which case SCCAN will fail to detect associations (Avants et al., 2010). Next, absence of regional cortical atrophy in elderly controls does not preclude that functional changes associated with picture naming might occur in these regions during healthy aging. Across the adult lifespan, a decrease in occipitotemporal fMRI activity was observed during picture naming, and this decrease correlated to naming accuracy at the individual level (Samu et al., 2017). Finally, word retrieval failure, which is considered an important factor in picture naming declines in healthy neurocognitive aging (Burke et al., 2008), might also be underpinned by neural correlates not typically affected across the PPA spectrum, such as the insula (Shafto et al., 2010).

Omissions were associated with regional atrophy of bilateral medial ATL including the perirhinal cortex (Fig 2E, Fig 4B) and similar results were obtained using univariate and multivariate analysis. While the correlation between omissions and the ATLs was driven by SV (Fig 2F), we point out that the participant with the highest percentage of omissions (41% of

trials, Fig 3D) was diagnosed with MV due to AD, based on positive amyloid imaging. At the time of study participation, this 64-year-old patient was already in an advanced stage of the disease with cognitive decline beyond the linguistic domain. The correlation of atrophy of the ATL and anomia fits well with the extensive literature on SV (Lambon Ralph, 2014; Lambon Ralph et al., 2017, 2010; Mion et al., 2010). The role of the perirhinal cortex in visual object discrimination (Kivisaari et al., 2012; Lee et al., 2006; O'Neil et al., 2009; Wright et al., 2015) and fine-grained representation of semantically related words (Bruffaerts et al., 2013; Clarke and Tyler, 2014; Liuzzi et al., 2015) has also been repeatedly demonstrated. The bilateral ATL involvement is not unexpected since the right ATL is involved in visual object recognition (Butler et al., 2009; Drane et al., 2013; Hoffman and Lambon Ralph, 2018; Rice et al., 2015; Snowden et al., 2004). In SV, atrophy of the right medial ATL occurs early-on (Bocchetta et al., 2019). Multivariate analysis additionally revealed that atrophy of the right angular gyrus is linked with the occurrence of omissions (Fig 2E). Using a resting-state analysis in SV, the ATL also belonged to the same network as the angular gyrus (Battistella et al., 2019). Furthermore, the link between naming deficits and damage to the ATL is not restricted to SV, but was also observed in patients with AD (Kivisaari et al., 2012), stroke (Wright et al., 2015), herpes encephalitis (Frisch et al., 2015; Warrington and Shallice, 1984) and epilepsy patients after unilateral anterior temporal lobe resection (Lambon Ralph et al., 2012; Rice et al., 2018; Visser et al., 2018), as well as in controls after application of TMS (Jackson et al., 2015; Whitney et al., 2011). Regarding PPA, our results confirm once more that the combination of ATL atrophy and failure to generate a response occurs predominantly in SV, is in keeping with the literature (Mesulam et al., 2009; Woollams et al., 2008), where the ATL is viewed as a semantic "hub" (Lambon Ralph, 2014; Lambon Ralph et al., 2010; Patterson et al., 2007). Nevertheless, we acknowledge that our study design is inadequate in capturing all possible neural mechanisms leading to omissions (or semantic errors). It is easy to imagine how omissions during picture

naming can result from damage to the occipital cortex ("visual form agnosia", (Farah, 1990)) or by other large lesions not included in our sample.

A limitation of our study is that our sample size was restricted to 43 PPA patients. A larger study population will increase the statistical power because the variability in the sample size will increase (Avants et al., 2010). With a substantially increased sample size, neural correlates for circumlocutions and superordinate errors might also be revealed using our approach (a correlation was found between atrophy and superordinate errors using VBM, which relied heavily on two SV patients). We looked at percentage error scores rather than absolute values to correct for seven patients (5 SV) who did not fully complete the BNT. In these cases, the percentages are based on the initial trials (with high word frequency): perhaps, the percentage error scores for different error types would have been different in these patients in case more trials were completed. Also, the error scores reported here may be increased compared to some prior studies because only the first response was scored, even for self-corrections. Given the low prevalence of PPA, subsequent studies would benefit from multicenter collaborative efforts. Another consideration is that lexical parameters such as word frequency and age of acquisition might differentially affect naming errors in the different PPA subtypes. While the effects of word frequency and age of acquisition on naming in SV have been documented earlier (Lambon Ralph et al., 1998), we also observed correlations with naming accuracy in the other PPA subtypes. A larger sample of PPA patients is required to address the relationship between lexical parameters and naming errors (and regional atrophy) for every subtype, because this interaction might be subtype-specific (Rofes et al., 2019).

In conclusion, multivariate analysis of grey matter atrophy revealed that the left mid and posterior fusiform cortex and posterior MTG/ITG are neural correlates for semantic errors across the PPA spectrum. These regions are likely to be involved in neural processes central to picture naming, such as representation of semantic information, lexical retrieval or visual object

processing. We propose that some neural mechanisms associated with semantic errors are shared across the PPA spectrum.

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