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Deconstructing the transdiagnostic nature of language symptoms in frontotemporal dementias

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Introduction

- Frontotemporal lobar degeneration (*FTLD*) related syndromes featuring primary language impairments are known as primary progressive aphasia (*PPA*).
- PPA is classified into three variants: semantic (*sv*), non-fluent (*nfv*), and logopenic (*lv*). Yet their language profiles overlap, and some patients do not fit any variant (i.e., 'mixed' PPA).
- Language deficits also can occur across other FTLD-related syndromes like progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), suggesting that language symptoms are transdiagnostic.
- Note that lvPPA is usually associated with Alzheimer's disease (AD) pathology, even if it falls under clinical FTD-PPA syndromes. Similarly, CBS can be underpinned by AD.
- Though brain atrophy determines PPA language deficits, similar lesion profiles often have different language deficits, while different lesions can cause similar impairments (e.g. lvPPA / nfvPPA).
- We apply a multimodal approach to behavioural and neuroimaging data (cf. Ingram et al 2020, Brain; Murley et al 2020, Brain):

To link language dimensions of variations across FTD-PPA spectrum to their underlying neuroanatomical factors.

Methods

Participants: Patients and healthy controls (HC)

Demographic	Mean (std)					
Variables	***svPPA***	***nfvPPA***	***lvPPA***	***CBS***	***PSP***	***HC***
Age	66.3 (1.8)	71.2 (1.6)	70.2 (1.4)	70 (1.8)	68 (2.0)	65.6 (1.1)
Education (y)	18.9 (0.8)	17.3 (0.7)	19.2 (0.6)	18.3 (0.8)	17.1 (0.9)	21.1 (0.5)
Female/Male	7/6	10/5	6/16	6/7	4/6	**13/19**
Sample size	13	15	21	13	10	**32**

Behaviour: Participants completed the Mini-linguistic State Examination (Patel et al 2021, Brain Communications).

Neuroimaging: T1-MRI, DW-MRI.

Analyses: GM segmentations and FA maps were calculated and used to estimate the degree of abnormality for each brain voxel (fuzzy lesion map).

a) Principal component analysis (PCA) of fuzzy lesion maps and MLSE metrics to identify covarying patterns of language and brain abnormalities.
b) Voxel-based correlation mapping of emergent language dimensions (GM/FA maps combined).
c) Multiple regression analysis with regions of interest (ROI) to pinpoint brain-language associations.

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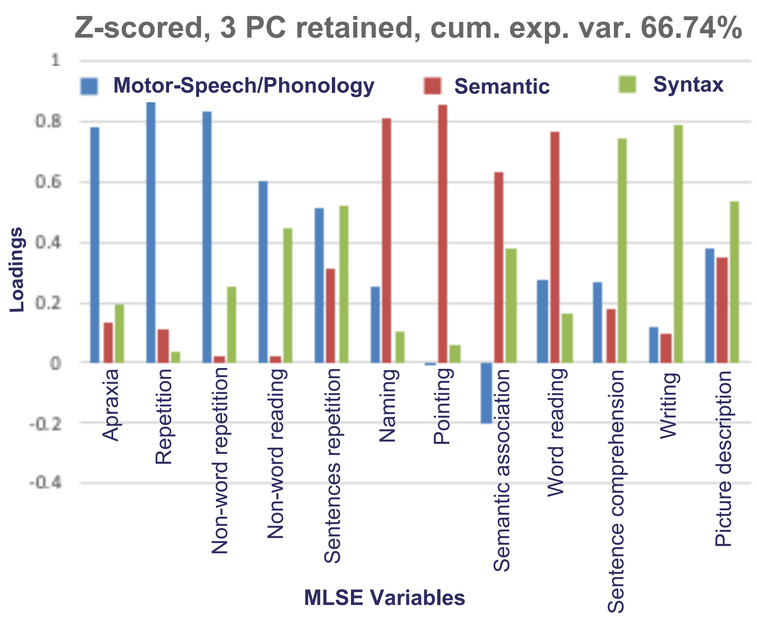
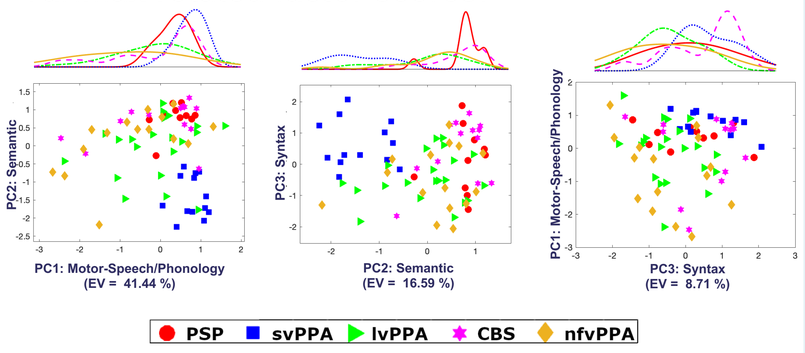
Language symptoms dimensions

Varimax rotated factor loading:

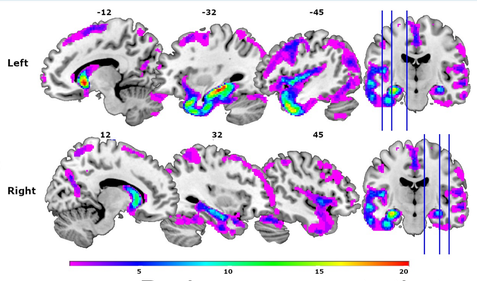


Varimax rotated factor scores:



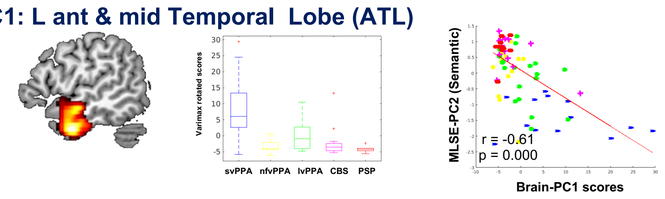
Brain atrophic dimensions

Atrophy Overlap Map

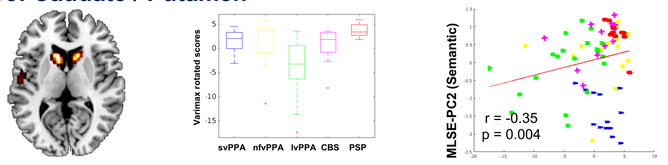


PCA on Lesion maps: Brain components that correlate with language components

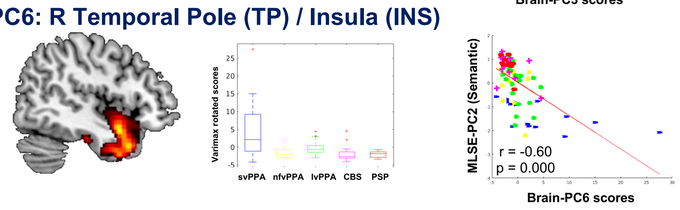
PC1: L ant & mid Temporal Lobe (ATL)



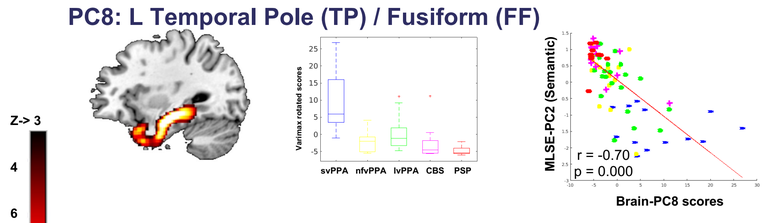
PC3: Caudate / Putamen



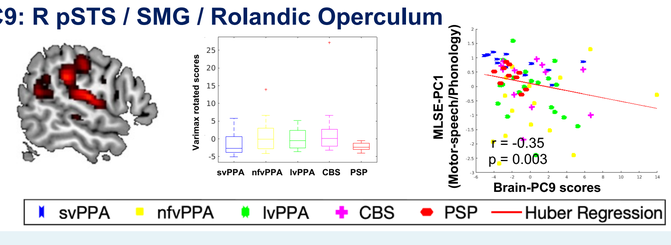
PC6: R Temporal Pole (TP) / Insula (INS)



PC8: L Temporal Pole (TP) / Fusiform (FF)

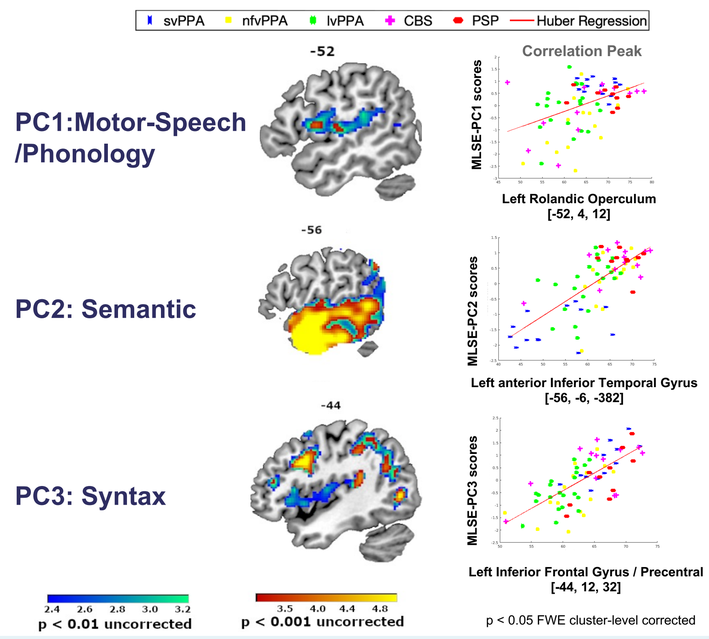


PC9: R pSTS / SMG / Rolandic Operculum



Voxel-based correlation mapping

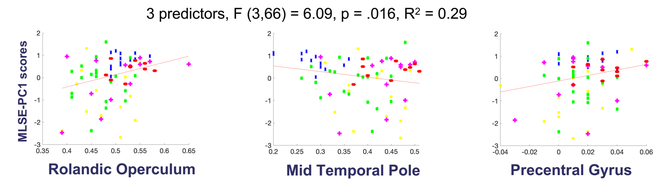
GM/FA intensity and PCA language performance:



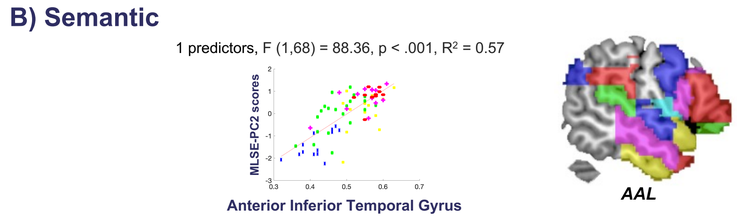
ROI-based multiple regression

15 bilateral GM ROIs to predict PCA language performance (stepwise regression):

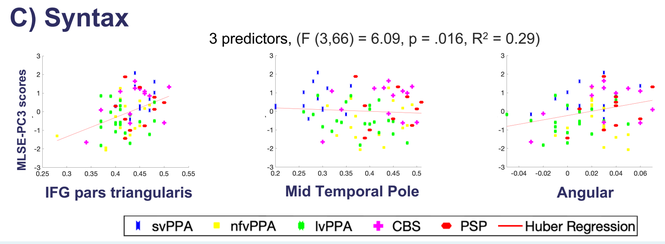
A) Motor-Speech/Phonology



B) Semantic



C) Syntax



Discussion

- As expected PCA found three language dimensions—***motor-speech/phonology***, ***semantics***, and ***syntax***—and thirteen brain atrophic dimensions, including ***temporal***, ***frontal***, and ***parietal*** regions.
- ***Semantic*** linked strongly with ***temporal lobe*** atrophy, but other atrophic and language dimensions did not, suggesting a non-one-to-one neural mapping of language functions.
- Multiple regression showed that atrophy in a distributed set of ***frontoparietal regions*** predicts ***motor-speech***, ***phonology***, and ***syntax*** deficits, while atrophy in ATL predicts semantic deficits.

Atrophy and language variations on across FTD-PPA syndromes are deconstructed on a brain-behaviour continuum, with only semantic variants being clearly separate.