Spatial-temporal subtypes of amyloid deposition show distinct baseline and longitudinal cognitive profiles

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Background

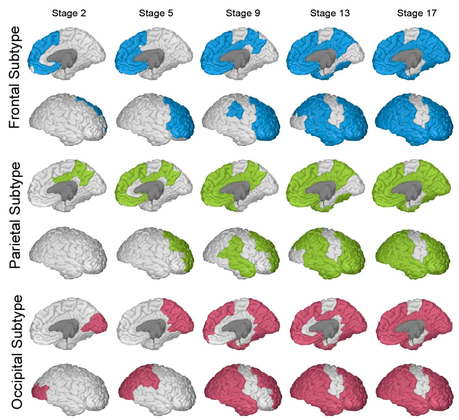
We recently identified three distinct spatial-temporal trajectories of amyloid deposition through the application of a machine-learning model (i.e., Subtype and Stage Inference [SuStaIn]) to amyloid positron emission tomography (PET) data[1]. These included Frontal, Parietal, and Occipital subtypes, defined by the earliest brain regions to show abnormality. To date, the clinical relevance of these amyloid subtypes remains to be determined.

Aim

To investigate whether subtypes of amyloid deposition hold value in predicting baseline and longitudinal cognitive functioning in addition to a validated measure of global amyloid burden (Centiloids [CL])

Material and Methods

Sample: The Frontal, Parietal, and Occipital SuStaIn subtypes were applied to z-scored amyloid-PET standard uptake value rations (SUVr) of 2,510 subjects from 3 cohorts (ADNI, EMIF-AD, OASIS-3). Of these, 570 subjects with a high subtype probability assignment (>50%), assigned stage ≥ 1, and available cognition were included in the analyses.



Cognition: Subtypes were compared on global cognition (MMSE) and several cognitive domains including memory, attention, executive functioning, language, and visuospatial functioning. Domains were computed as the average of z-scored neuropsychological tests based on a cognitively unimpaired (CU) amyloid-negative (CL <21) reference group.

Statistical analysis: To assess whether subtype assignment added to baseline CL in predicting baseline and longitudinal cognition (range follow-up=0.4-11 years), linear models (predictors: subtype and CL) and linear mixed models (predictors: subtype*time and CL*time) were performed, respectively. All models were adjusted for baseline age, sex, education, and baseline cognitive stage.

Occipital amyloid subtype shows greater language and attention impairment at baseline

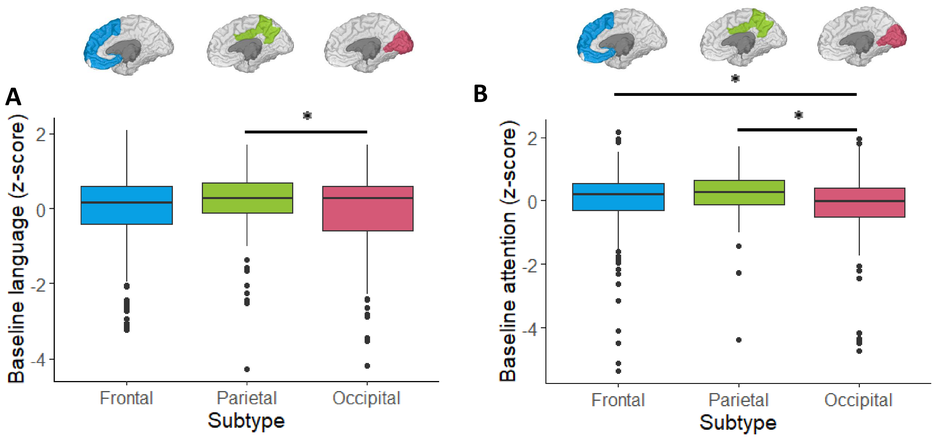


Figure 1. Differences in subtypes are shown for **A)** baseline language and **B)** baseline attention. Z-scores are adjusted for baseline Centiloids, baseline age, sex, education, and baseline cognitive status. * indicates significant differences.

Occipital amyloid subtype declines fastest over time in global cognition and language

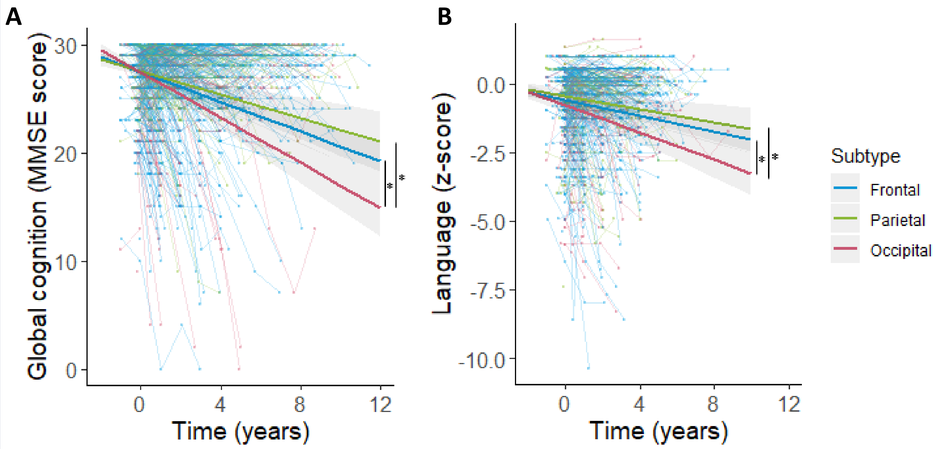


Figure 2. Differences in subtypes are shown for **A)** longitudinal decline in global cognition (MMSE) and **B)** longitudinal decline in language. Cognitive (z-)scores are adjusted for baseline Centiloids*time, baseline age, sex, education, and baseline cognitive status. In the background, subject-specific trajectories are shown.

Results

The majority of subjects was assigned to the **Frontal** subtype (*57%*), followed by **Occipital** (22%) and **Parietal** (20%). The **Frontal** subtype had a higher global amyloid burden and a higher proportion of amyloid-positive subjects (**Table 1**).

Table 1 Participant characteristics

	Total (*N*=570)	**Frontal** (*n*=325)	**Parietal** (*n*=116)	**Occipital** (*n*=129)	***P* value**
Diagnosis (baseline)	CU = 248 (43.5%) CI = 212 (37.2%) Dementia = 110 (19.3%)	CU = 144 (44.3%) CI = 124 (38.2%) Dementia = 57 (17.5%)	CU = 53 (45.7%) CI = 47 (40.5%) Dementia = 16 (13.8%)	CU = 51 (39.5%) CI = 41 (31.8%) Dementia = 37 (28.7%)	0.112
Age (baseline), years	74.0 (7.6)	74.1 (7.4)	73.5 (8.7)	74.2 (7.1)	0.902
Sex, n female (%)	298 (52.3%)	172 (52.9%)	63 (54.3%)	63 (48.4%)	0.835
Education, years	15.8 (3.1)	15.9 (3.2)	15.5 (2.9)	16.0 (2.8)	0.707
APOE e4 status, n carriers (%)	343 (60.2%)	210 (64.6%)	64 (55.2%)	69 (53.5%)	0.098
Aβ status (baseline)[a], n positive (%)	483 (84.7%)	295 (90.8%)	93 (80.2%)	95 (73.6%)	<0.001
Global amyloid burden, CL	56.8 (30.5)	60.9 (29.3)	50.3 (29.3)	52.4 (33.3)	0.003

Shown are mean ± standard deviation unless specified otherwise.
[a] Aβ positivity is defined as ≥ 21 Centiloids.

After adjusting for baseline CL, the **Occipital** subtype showed lower baseline language scores than the **Parietal** subtype (β=-0.34, p=.046) (**Fig-1A**) and lower baseline attention scores than both **Frontal** (β=-0.39, p=.047) and **Parietal** (β=-0.73, p=.002) subtypes (**Fig-1B**).

In addition, the **Occipital** subtype declined faster over time on global cognition (**Fig-2A**) and language (**Fig-2B**) as compared to the **Frontal** ($\beta_{global\ cognition}$=-0.35, $p_{global\ cognition}$=.007; $\beta_{language}$=-0.10, $p_{language}$=.015) and **Parietal** ($\beta_{global\ cognition}$=-0.50, $p_{global\ cognition}$=.002; $\beta_{language}$=-0.13, $p_{language}$=.015) subtypes.

Conclusion

Our results show the added value of amyloid subtype assignment on top of CL measures in predicting baseline and longitudinal cognition. Specifically, the Occipital subtype was associated with lower baseline performance and showed faster rates of cognitive decline.

Discussion

The observation of greater cognitive impairment at baseline and over time in the Occipital subtype might be explained by the presence of comorbidities, such as cerebral amyloid angiopathy (CAA) or lewy body dementia (LBD).

In future studies, we will compare the Frontal, Parietal, and Occipital subtypes on CSF biomarkers, tau PET, and neurodegeneration. In addition, we will repeat all analyses in an independent cohort (BioFINDER-2).

Academic partners
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[1] Collij, L.E. et al., Neurology, 2022

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