

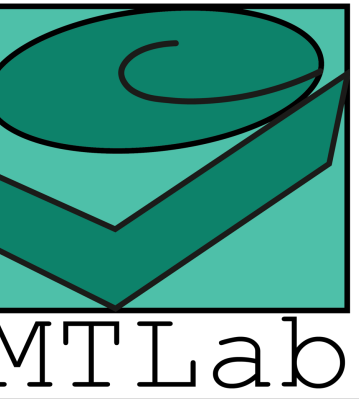


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Structural Heterogeneity of Human Amygdala Subregions: High-Resolution Postmortem MRI of Amygdala Morphometry

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Background

- The amygdala is a structurally complex region, but its morphometry is understudied in neuroimaging research, despite growing interest¹
- In vivo imaging is constrained by limited resolution and histological findings are difficult to bridge to in vivo inference leading to a heterogeneous anatomical account across studies
- High-resolution anatomical descriptions are needed to bride ex vivo with in vivo work and thereby lay the foundation for a reference of the amygdala and its interindividual variability

Aims

- To quantify both the shared organization and the inter-individual variation of amygdala and its subregions using 3D reconstruction and quantitative morphometry
- To establish a systematic morphometric reference that supports anatomical interpretation across ex vivo and in vivo imaging

Methods

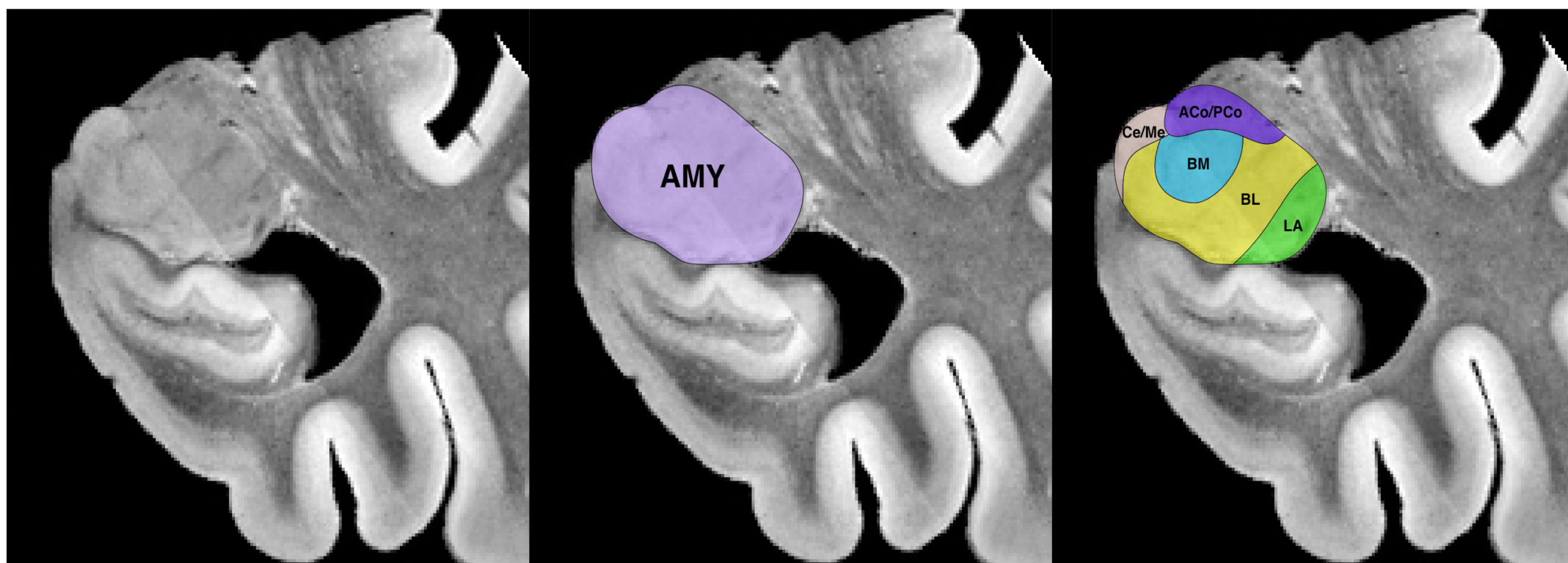


- 9.4T (0.2x0.2x0.2 mm³) postmortem magnetic resonance images of nine cognitively healthy individuals were obtained and manually segmented using an in-house developed segmentation protocol²

N	age	females, n (%)	ABC=0/ ABC=1 n (%)
9	73.6±11.8[57-93]	15 (33%)	5 (56%)/ 4 (44%)

Note. Sample demographics including ABC scores of all cases included. A=Amyloid Beta Plaques (Thal Phases) ; B=Neurofibrillary Tangles (Braak Staging) ; C=Cortical Neuritic Plaques (CERAD Criteria)³

- Volumes of the whole amygdala (Figure 1b) and five amygdala subregions (Figure 1c)
 - i. lateral (La), ii. basolateral (BL), iii. basomedial (BM), iv. cortical (Co), v. centralmedial (Ce/Me)



Note. Example case and segmentation of the amygdala and subregions in the coronal plane of OA. Abbreviations: AMY=amygdala, BL=basolateral, BM=basomedial, ACo/PCo (Co)=(anterior/posterior) cortical, Ce/Me=centromedial, OA=older adults with no known neurological disease, La=lateral.

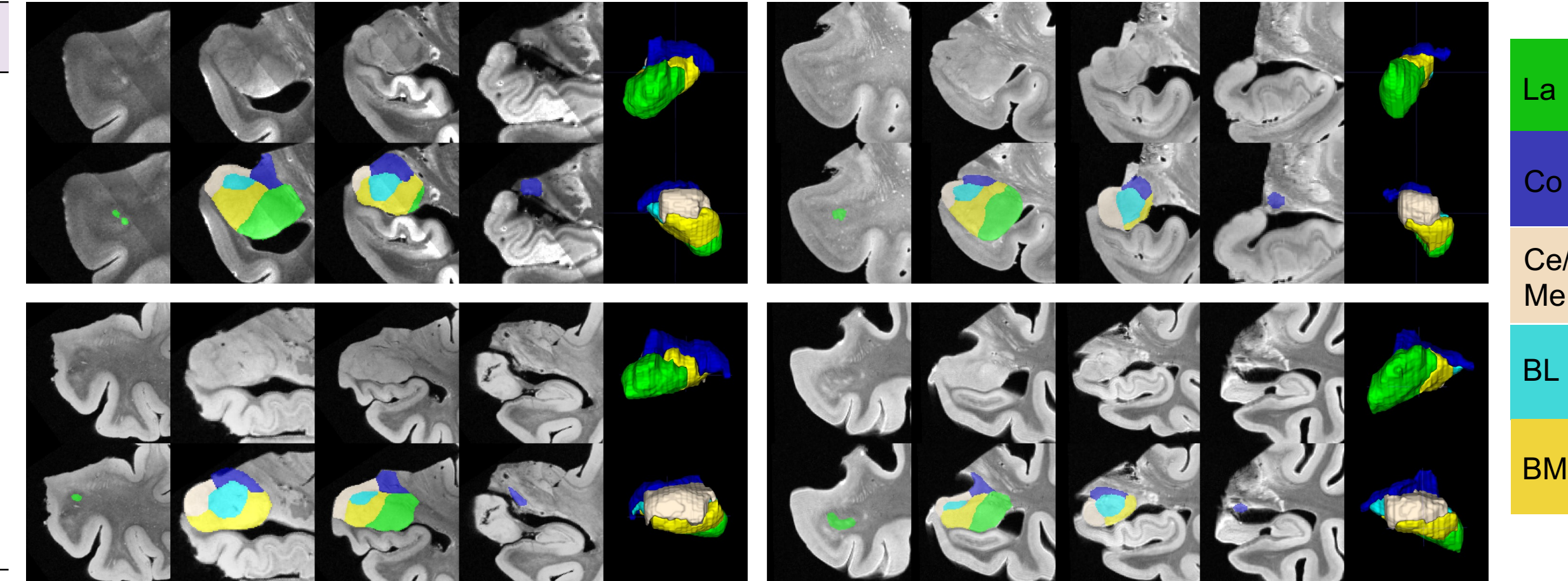
- Quantitative analyses of subregions and whole amygdala
 - Proportional subregional composition within the amygdala in
 - Z-scored proportions across cases for whole amygdala and subregions
 - Subregional extend in OA measured in distance to La
- Statistical shape modelling of the whole amygdala shape

- A canonical oval shape was observed throughout 3D reconstruction
- Subregional organization was largely consistent, with the cortical subregion extending most posteriorly and the lateral subregion anteriorly
- Within this shared organization, inter-individual variation in shape and size remained evident

1. Subregional composition is conserved across cases despite variation in shape and size

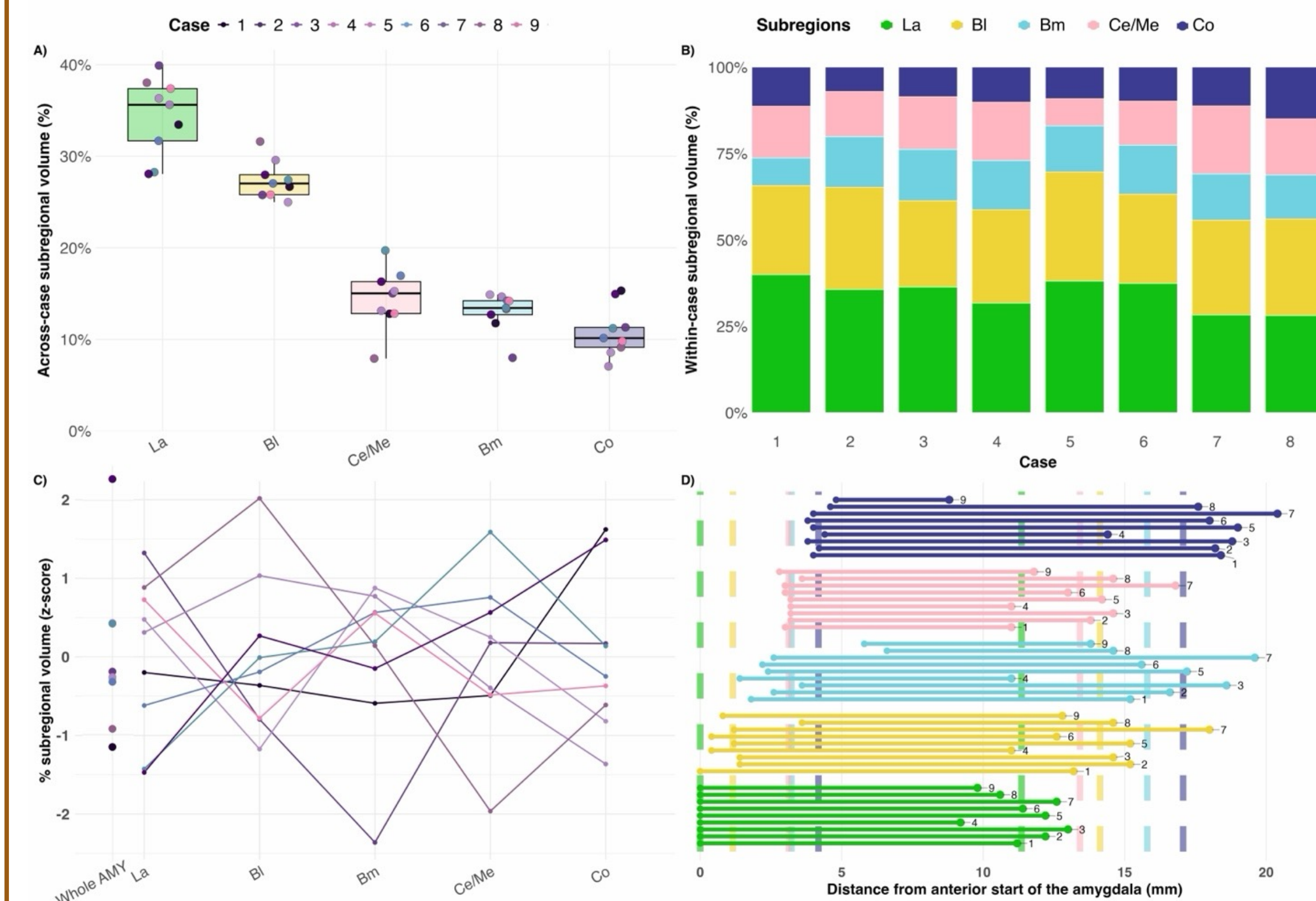
Subregion	Mean mm ² ± SD (SE)	Mean % ± SD (SE%)	Range
La	434.00 ± 55.70 (18.60)	34.30 ± 4.24 (1.41)	0.28–0.40
BL	350.00 ± 58.90 (19.60)	27.40 ± 2.07 (0.69)	0.25–0.32
Bm	167.00 ± 37.50 (12.50)	13.00 ± 2.12 (0.71)	0.08–0.15
Co	140.00 ± 51.20 (17.10)	10.80 ± 2.77 (0.92)	0.07–0.15
Ce/Me	187.00 ± 61.30 (20.40)	14.40 ± 3.32 (1.11)	0.08–0.20
Total	1307.00 ± 184.00 (29.20)	100 ± 00 (00)	—

Note for figure in the right corner. Figure shows four representative cases demonstrating anatomical heterogeneity. For each case, subregions are shown in the coronal plane with corresponding three-dimensional reconstructions in medial (top) and lateral (bottom) views. All segmentations are color-coded for the five segmented amygdala subregions and were delineated using ITK-Snap.



1.2 Structural variability exists within shared subregional organization

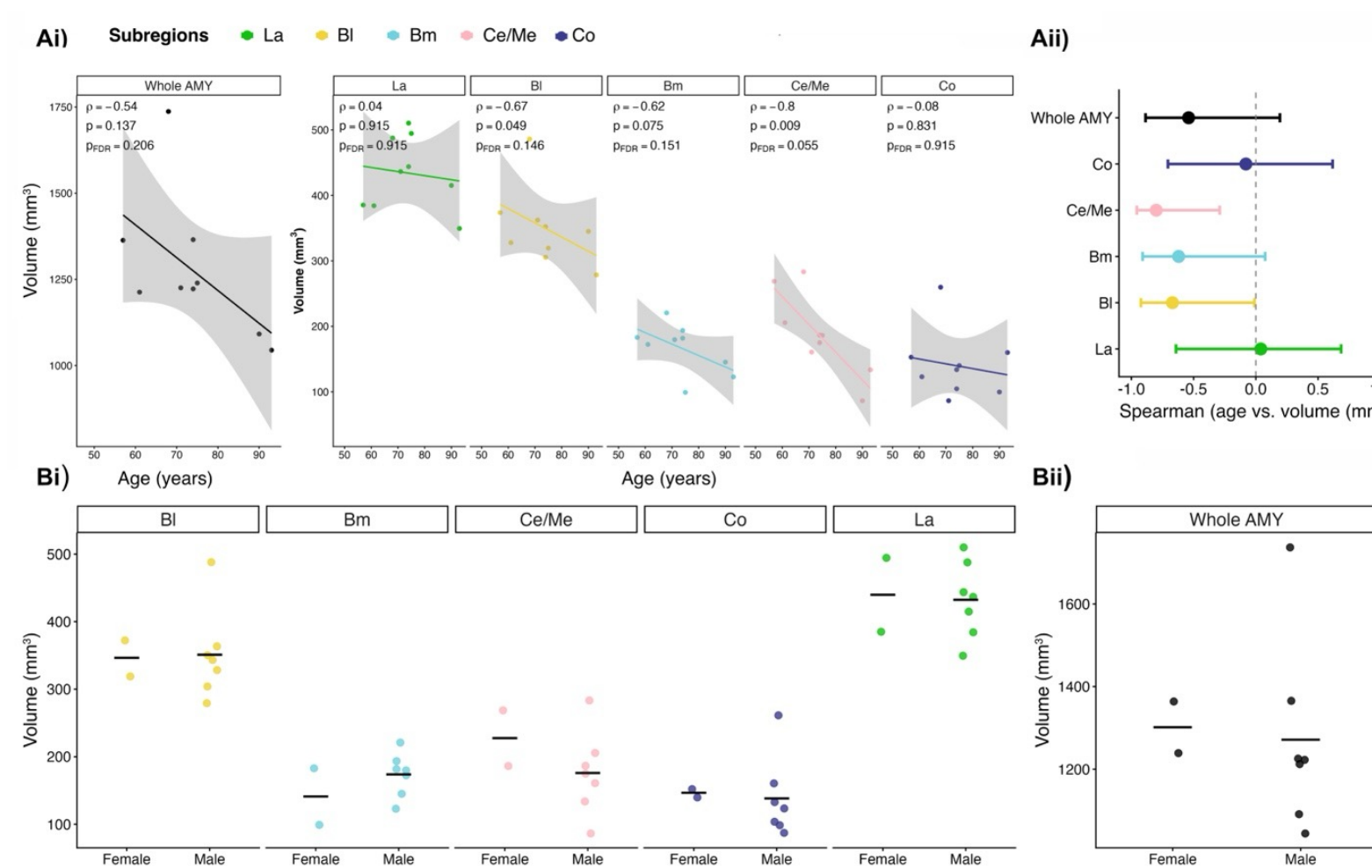
- Quantitative analysis revealed a shared subregional organization with variation in subregional volumes, anterior to posterior extent and relative composition
- Cortical and basomedial subregions showed the least relative deviation in size
- Basomedial and basolateral subregions showed greatest posterior extent



Note. A) Distribution of subregional volumes across individuals ordered by descending median. B) Within-case amygdala compositional profiles depicting the proportional volume of subregions. C) Z-scored subregional volumes showing case specific deviations from group means across subregions as well as the z-scores of absolute whole amygdalae. D) Order of first appearance and total length of each amygdala subregion from the anterior border. 0 mm is set as the anterior starting point of the amygdala for each case. Dashed lines show mean value for subregional start and end point. Numbers on the right side of each line display case numbers.

1.3 Limited age and sex associations with subregional volumes

- Age showed a significant negative association with basolateral and centromedial volumes, though this did not survive FDR correction
- Qualitatively, no sex differences were observed for both subregional or whole amygdala volume

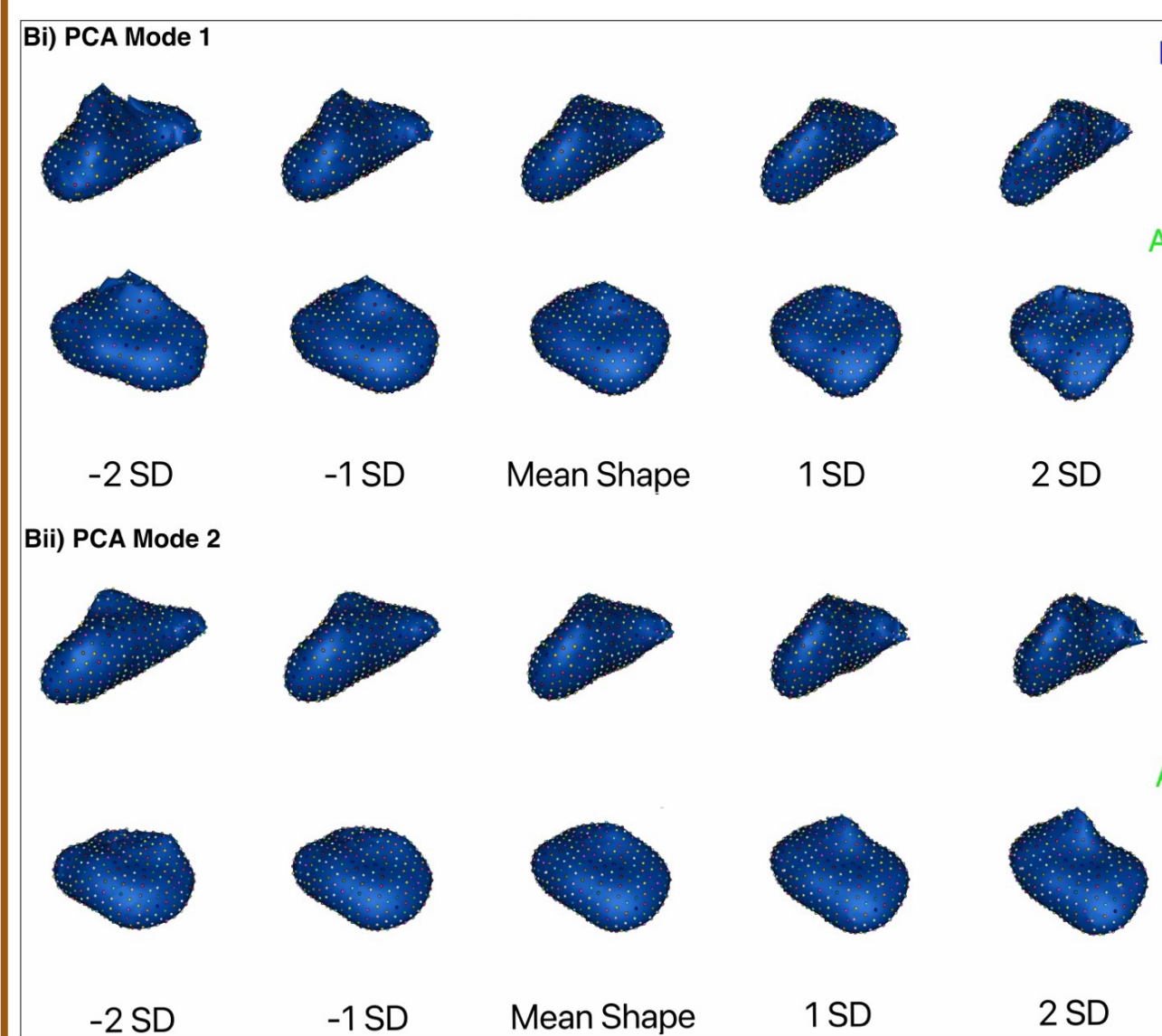
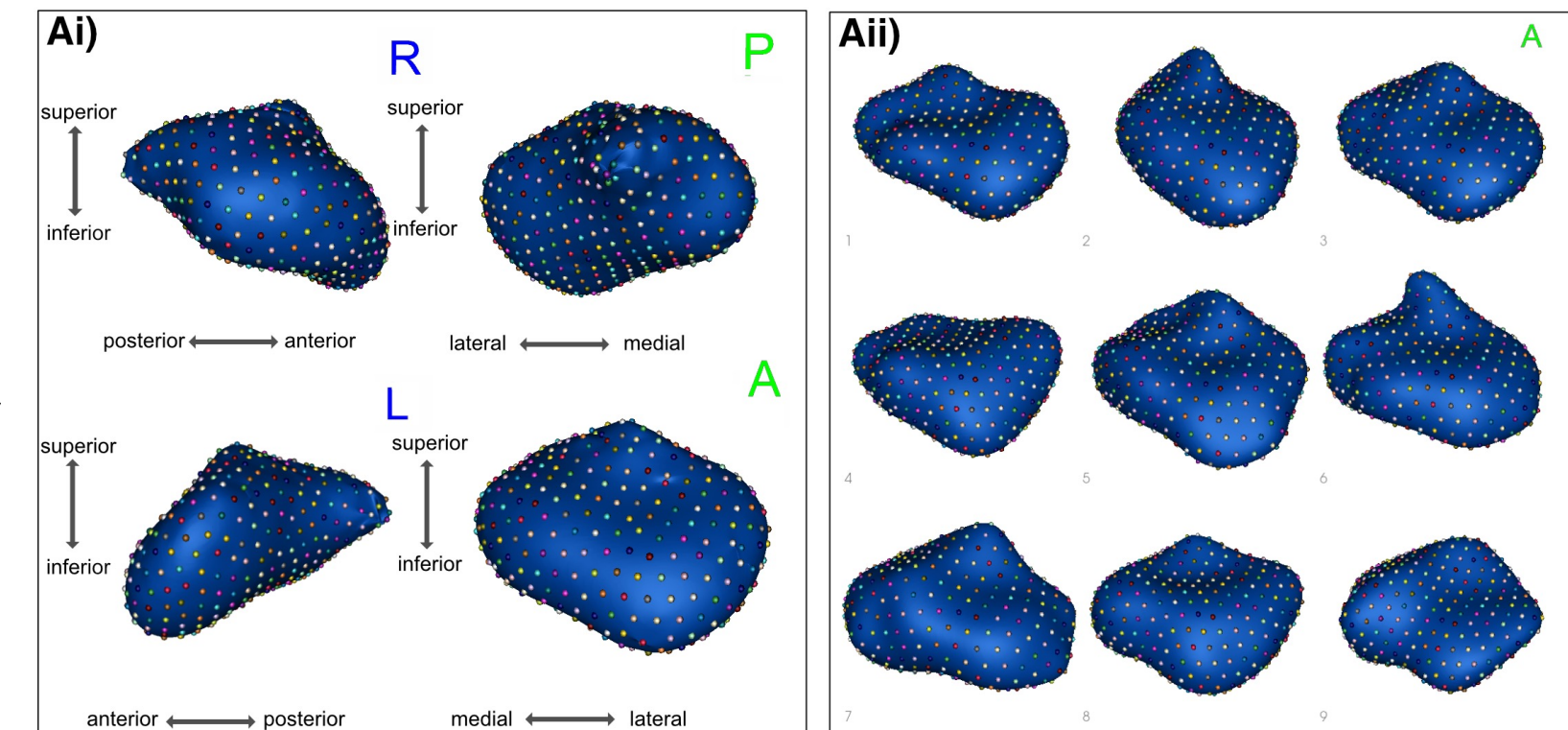


Note. Partial spearman rank correlation between absolute volumes (mm³) of the whole amygdala and its five subregions in relation to age and descriptive depiction of amygdala and amygdala subregion volume by sex.

Results

2. Statistical Shape Modeling reveals primarily anterior-to-posterior individual variation

- Mean amygdala shape analysis reflected the oval form seen qualitatively (Ai)
- Individual shape modelling (anterior view) showed an inter-individual variation from the mean shape (Fig. Aii)



Deviation was confirmed by PCA, with two dominant modes of variation identified:

PCA Mode 1 & 2:

- Mode 1 capturing anterior-posterior elongation across cases
- Mode 2 capturing similar but more rounded (oval) elongation

*Shape modeling of individual subregions did not yield meaningful results, indicating that subregional variation was too large to detect group-level effects in this dataset

Note. Surface mesh reconstructions from the statistical shape model (SSM) of the whole amygdala, with mesh vertices (correspondence points) shown as dots of mean amygdala shape and individual amygdalae. Below first and second principal components, of the principal component analysis (PCA), show mean shape and reconstruction at ±1 and ± standard deviations (SD)

Conclusions

- Quantitative analyses reveals a mostly consistent subregional organization, size, and anterior-posterior extent with interindividual variability across cases
- Statistical shape modeling confirms an oval shape that differs mainly in elongation
- These results lay the foundation to characterize amygdala heterogeneity to be used as a reference to inform ex and in vivo imaging studies

References:

- Stouffer et al., 2023, *NeuroImage Clin*;
- Annettesdotter et al., 2024, *Alzheimer S & Dementia*
- Hyman et al, 2012, *Alzheimer S & Dementia*

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