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Bridging histology with structural MRI in the human amygdala

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Introduction Buried in the temporal lobes, the amygdala is a crucial structure for emotion and social cognition. Detailed post mortem studies have highlighted several subdivisions within the amygdala, each with distinct cytoarchitectural characteristics and distinguishable connectivity profiles to other regions of the brain (Kedo et al., 2017). However, these atlases rely on labour-intensive visual inspections of histological specimens performed by expert neuroanatomists. Here, we build a multiscale framework grounded in foundational histological studies of the neocortex to map amygdala cytoarchitecture in a data-driven manner. We cross-reference this approach against manually segmented labels provided in established atlases of amygdala anatomy(Amunts et al., 2020).

Methods. Histological data of the amygdala was obtained from the 100µm BigBrain dataset (Amunts et al., 2013) (Fig1A), in which image intensity values provide direct measurements of brain cytoarchitecture (soma size and density). The amygdalae were isolated using an existing manual segmentation of subcortical structures (Xiao et al., 2019). This segmentation was warped to BigBrain histological space using co-registration strategies aggregated in the BigBrainWarp toolbox (Paquola et al., 2021). Guided by prior neuroanatomical studies of cortical histology (Palomero-Gallagher Zilles, 2018), we built a histological feature bank of the amygdala. Specifically, feature selection leveraged the parameterization of central moments mapping intensity variations across the amygdala. We used a radiomics approach (van Griethuysen et al., 2017) to compute voxel-based maps for each of the selected first-order features (mean, variance, skewness, and kurtosis) at 5 different kernel sizes. This resulted in 20 distinct feature maps, reflecting variations in intensity distributions within the amygdala from finer to coarser scales (Fig1A). To capture and visualize the underlying structure of amygdala cytoarchitecture, we applied UMAP, a non-linear dimensionality reduction technique (McInnes et al., 2018), to our microstructural feature bank (Fig1B). We then leveraged openly available probabilistic maps of amygdala subnuclei (1,8,9) labelling each voxel to its highest probability subdivision (Fig1C). For further neuroanatomical contextualization, correlations were calculated between voxel-wise UMAP components values and corresponding spatial coordinates (Fig1C). These steps were then repeated with 7T quantitative T1 (qT1) images of 6 subjects (Fig1D).

Results. Our data-driven process could partly recover ground-truth anatomical subdivisions of the amygdala. Notably, the three anatomical subdivisions seemed to primarily follow the direction of U2 (Fig1C). Furthermore, U1 seemed to primarily vary on the medial-lateral axis (r=0.3186), whereas U2 was primarily and highly correlated to the inferior-superior axis (r=0.88), both correlations were statistically significant with a variogram matching test. UMAP-driven visualizations of the histological feature space suggest our dimensionality reduction approach could capture global intensity covariations across moments. When reproducing the analyses on qT1 images, the UMAP components illustrated similar trends from their respective feature banks (Fig1D). U2 generally captures more inferior-superior gradients and U1 more medial-lateral variance. Statistical analysis of these similarities is currently being investigated.

Conclusions. We propose data-driven approach for investigations of amygdala cytoarchitecture. This novel method, together with the reproducible findings found in qT1 images, shows great potential for an efficient and accurate representations of cytoarchitecture that can support investigations of subject-specific structure-function coupling in subcortical structures.

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