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From structure to function in the human

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Background. The amygdala is a crucial structure for several aspects of cognitive and affective functioning (Pessoa, 2010). These functions are supported by complex connectivity patterns to other brain regions, stemming from distinct subnuclei with unique microstructural properties (Kedo et al., 2017). However, current investigations of structure-function coupling in this region are limited by a lack of datasets and tools for individualized and observer-independent delineation of amygdala subregions. Given the strong inter-individual variability of this region, more personalized approaches are needed to reliably study the microstructural determinants of amygdala functions and connectivity. Our overall goal is to study how the amygdala's complex microarchitecture gives rise to its function and dynamic connectivity to other brain regions. This goal is addressed in two main steps, harnessing postmortem histological data as well as ultra high-resolution myelin-sensitive and resting-state functional imaging data.
Step 1: Data-driven mapping of amygdala microstructure. Capitalizing on a combination of advanced image processing (radiomics; (van Griethuysen et al., 2017)) and dimensionality reduction methods (UMAP, (McInnes et al., 2018)), we designed a novel method to capture variations in regional microstructure within the amygdala (Fig 1B-C). This approach was applied to the BigBrain dataset (Amunts et al., 2013), a unique resource offering unprecedented spatial resolution to study the neuronal organization of the human brain (100 m3 voxels) (Fig 1A). We identified two dimensions (U1 and U2) capturing large spatial variations in amygdala cytoarchitecture, which were consistent with gold standard labels built from detailed visual inspections of series of postmortem specimens (Amunts, Mohlberg, Bludau, & Zilles, 2020; Amunts, Mohlberg, Bludau, Caspers, et al., 2020, Fig 2A-B) . We also assess the generalizability of these results to in vivo data, specifically leveraging myelin-sensitive contrasts (quantitative T1 imaging) collected at a field strength of 7 Tesla (7T; 500 m3 voxels) (Fig 3A-C). Subsequent analysis correlating postmortem and in vivo findings indicate promising replicability (n=10 healthy participants), specifically, the axis which could best describe spatial variation in histology (U1) was found to have very similar correlations to the coordinate axes of all 10 subjects (Fig 3D). This highlights the potential of this approach for personalized investigations of regional microstructure.
Step 2: Correspondence of amygdala microstructure and functional network organization. We then leverage data-driven and subject-specific representations of amygdala microstructure computed in aim 1 to map large-scale changes in this region's functional connectivity to other brain regions. Specifically, by isolating then contrasting the highest and lowest 25% of U1 values for each participant in the amygdala mask brought to functional space (Fig 4A-C). Our 7T scanning protocol includes repeated resting-state functional acquisitions. Notably, all sequences were designed to enhance signal-to-noise (e.g., via the use of multi-echo acquisitions), an important consideration when studying mesio-temporal structures.
Conclusion. We propose a theoretically-grounded approach for data-driven explorations of subcortical cytoarchitecture applied to the human amygdala. This approach generalized to microstructurally-sensitive in vivo MRI data and could delineate distinct functional network embeddings. The present work thus offers a first step towards an integrated account of the amygdala's microstructural composition and functional organization.

Primary author: AUER, Hans

Co-authors: BERNHARDT, Boris (Mcgill); PAQUOLA, Casey (INM-1, Forschungszentrum Jülich); Mrs GIFT CABALO, Donna (McGill University); Ms ROYER, Jessica (McGill University); DEKRAKER, Jordan (McGill Uni-

versity); Dr BENKARIM, Oualid (McGill University); VALK, Sofie L (Research Center Jülich); WANG, Yezhou (McGill university)

Presenter: AUER, Hans

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