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Integration of cytoarchitecture and brain-wide connectivity reveals topographic organization of macaque insula networks

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One of the major challenges to carrying out in vivo neuroanatomical analyses is that there is significant regional cytoarchitectural variation that is often difficult to capture by MRI. As a result, parcellation of brain regions is often limited to a scale too coarse for the understanding of their functions. While this is a challenge for many regions of the brain, the insula is one such region that is known to be cytoarchitecturally heterogeneous in which cellular variation is believed to be related to variation in function. Different regions of the insula support specific functions that are critically important for understanding a broad array of psychological functions, and may ultimately be targets of interventions for neuropsychiatric diseases. In order to capture such heterogeneity among sub-insular regions, it is necessary to collect neuroanatomical data at different resolutions and with different modalities from the same subjects. We present our first Integrated *Mic*(ro) to *Mac*(ro) Macaque brain dataset, here called *MicMac*. *MicMac* is an extendable workflow, represented by a within-subject whole brain dataset that integrates aligned multi-parametric in vivo MRI, high resolution ex vivo MRI, and histology within a single, standardized space.

In establishing the study protocol, all multiparametric MRI and histology data were obtained from a 10.3 year old healthy female rhesus macaque. In vivo MRI scans were performed on a Siemens 3T equipped with an 8-channel monkey head coil. Ex vivo MRI were conducted on a Bruker 7T using a 72mm volume coil. Both in vivo and ex vivo imaging protocols were harmonized, and optimized for experimental factors such as tissue fixation. Multi-shell dMRI was acquired for structural connectivity analysis using fiber tractography. Complete 3D histological volumes were reconstructed from a stack of cell-body (Nissl) and myelin-stained (Gallyas) 2D microscopy sections (2x2 micron in plane, 40 micron slice thickness, 400 micron interslice spacing) with optical-balancing to account for histological staining artifacts. All processed data were spatially aligned in a common in vivo reference space using an adapted image registration framework that was previously established for the human BigBrain project (Amunts et al, 2013).

The 15 cytoarchitectonically-defined insula subregions (Evrard et al, 2014) were specified on the histological images, rendered in the surface space defined by CIVET-Macaque (Lepage et al, 2021), and used as seed-regions for diffusion MRI (dMRI) tractography to reconstruct the connections between these subregions with other cortical areas.

Results demonstrate excellent correspondence of insula connectivity that align with macaque histological tract tracing studies (Mesulam and Mufson, 1982) and previous human dMRI and resting-state MRI studies (Menon et al, 2020). The specificity of these projections, even for small subregions, was well-defined and occupied distinct patterns across the cortex with minimal overlap. Despite the focus on insula for this application, the workflow demonstrated here (Fig. 1) could be done for any other brain region, although it is currently unknown how well this would translate due to variations in cellular structure and network connectivity.

Fig 1. Cytoarchitectonically-defined fiber tracking was performed in the insula using the *MicMac* dataset.

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