8th BigBrain Workshop - Challenges of Multimodal Data Integration



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Neuropil distributions in the human brain predict resting-state functional networks

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The human brain is intrinsically organized as (anti-)correlated regions as shown repeatedly by resting-state fMRI (Biswal et al. 2010), where these regions are thought to represent activity fluctuations of neuronal populations across large cortical swathes (Chen et al. 2020). Yet elucidating properties of these functional networks based on neuroanatomy has remained elusive. Prior attempts to predict functional connectivity from structural connectivity, specifically DTI-measured long-range associations, have failed (Honey et al. 2009). We hypothesized if microscopic connectivity of neuropil in the human brain can recapitulate dominant resting-state fMRI networks.

The most popular functional network is the default mode network (DMN) which has been primarily observed in the cerebral cortex (Shulman et al. 1997, Buckner et al. 2008, Thatcher et al. 2014), but also in the subcortex (Li et al. 2021, Seoane et al. 2024). Other examples of functional networks (Lawrence et al. 2023, Mulders et al. 2015) include the language network (LN), salience network (SN), and central executive network (CEN). Hardwired networks range from medial and basolateral limbic systems (LIMBm, LIMBb) to primary/secondary visual cortex (VN) and somatosensory/motor cortex (SMN).

Neuropil density is fundamental for in silico modeling of brain energy metabolism as it represents the infrastructure necessary for brain function (Hyder et al. 2013). The metabolic cost of electrical activity at the neuropil involves several processes, which collectively comprise an "energy budget" (Yu et al. 2018). Bottom-up energy budgets require a certain level of understanding of cellular (CellDen) and synaptic (SynDen) densities (Yu et al. 2023). Prior budgets utilized generalized neuropil density representing prototypical measures of CellDen and SynDen to model the brain's energetic metabolism. To consider how these densities vary across regions, we created a machine learning algorithm that predicts neuropil density (CellDen, SynDen) from in vivo MRI scans, where ex vivo Merker staining (BigBrain) and in vivo synaptic vesicle glycoprotein 2A PET imaging (SV2A-PET) were reference standards for CellDen and SynDen, respectively (Akif et al. 2024). We used these neuropil data to examine if major resting-state fMRI networks are revealed in human brain.

In vivo MRI datasets from 64 healthy control subjects (Akif et al. 2024) were selected from the ADNI database (adni.loni.usc.edu) of whom 10 were randomly selected for training. Using 54 normal human brain neuropil data, we generated 54 datasets each for CellDen and SynDen. Using these data as subject series, we investigated the presence of networks. The neuropil data revealed both correlated and anti-correlated networks, which are comprised of limbic/sensory systems, but also functional networks (LN, SN, CEN, DMN) commonly identified by resting-state fMRI (Figure 1).

These findings address puzzling results of prior studies that report structural networks cannot fully predict functional networks. Furthermore, the intermediary of the metabolic network created by the energy budget, we demonstrate the promise of individualized anatomic/metabolic datasets to gain insights of microscopic effects underlying mesoscopic measures of functional networks on a per subject basis. Understanding mechanisms of how the human brain is inherently organized as functional networks has major consequences for neuroimaging markers of brain function.

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