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THE MULTISCALE ARCHITECTURE OF THE SALIENCE NETWORK SUPPORTS A BRAIN-WIDE "SWITCH" FUNCTION

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Background. Recent neuroimaging research has witnessed a surge of studies aiming to shed light on principles of structure-function coupling in the human brain. Central to these investigations is understanding how relatively fixed anatomical features contribute to highly dynamic patterns of activity (1). This question remains particularly elusive in transmodal areas supporting higher-order cognitive functions such as memory, executive function, and attention (2, 3). Among these regions, the salience network (SN) has been proposed to mediate switching between functional states (as proposed in the triple network model (4) and large-scale signal propagation frameworks (5)), making it an ideal system-level model of dynamic structure-function coupling. Yet, the neuroanatomical features enabling the SN to regulate brain-wide transitions remain poorly understood.

Aims/hypotheses. We will develop a novel multiscale connectomics framework to investigate how fixed microarchitectural and connectivity features support flexible functional dynamics. Focusing on the SN and its role in regulating transitions between the default mode network (DMN) and central executive network (CEN), we hypothesize that the SN exhibits characteristic microarchitectural and connectomic features that allow it to mediate transitions between large "task-positive" and "task-negative" systems.

Methods. We will integrate state-of-the-art methodologies across multiple brain organization levels. First, SN microarchitecture will be characterized using intracortical profiling of post-mortem histology, leveraging the BigBrain (6) and AHEAD (7) datasets. These findings will be extended in vivo using 7T (8) myelin-sensitive MRI to quantify microstructural variability within the SN across individuals and evaluate robustness of histological findings. Our preliminary findings show that specific subregional patterns of local circuit properties within the SN support its flexible engagement with distributed functional systems. Second, we will comprehensively map SN connectivity, by modeling white matter pathways with diffusion MRI tractography and local connections using surface geometry eigenmodes (9). Together, these approaches will determine whether the SN occupies a topologically advantageous position within the structural connectome, facilitating parallel interactions across systems. Third, we will investigate how the structural architecture of the SN shapes functional dynamics and supports network switching. We will simulate whole-brain state transitions using network control theory (10). Specifically, we will examine the capacity of SN nodes to facilitate transitions between empirically defined brain states, such as shifts from DMN to CEN states. This approach will test whether the SN's structural embedding and microarchitecture confers the SN a unique capacity to coordinate large-scale functional reconfigurations.

Outcomes. Our work proposes a novel framework for understanding the joint contributions of microarchitecture, geometry, and connectivity to dynamic cross-network interactions in the human brain. It will provide a foundational account of how subregional patterning of the SN may contribute to its capacity to modulate the engagement of distinct macroscale functional systems. More broadly, our findings will demonstrate how local structural topography and connectivity shape and constrain large-scale neural dynamics, opening new areas of investigation into the structural basis of cognitive flexibility (11).

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