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Quantifying Cortico-subcortical Co-Maturation in the PFC: A Proposal for a Novel Developmental Metric

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The human prefrontal cortex (PFC) plays a central role in cognitive control and emotion regulation, supported by a protracted and heterogeneous maturation across its subregions (e.g., dorsolateral vs. ventromedial, medial vs. lateral) [1, 2]. This intra-PFC variability is a hallmark of its functional specialization [3, 4]. Importantly, the developmental trajectory of the PFC is shaped not only by intrinsic cortical mechanisms but also through dynamic interactions with subcortical structures such as amygdala, thalamus, and basal ganglia [5]. Yet, most current models of brain development remain cortico-centric, frequently overlooking how the timing and strength of subcortical inputs influence the specialization of different PFC subregions. To address this gap, we propose a novel framework for quantifying cortico-subcortical co-maturation using the Wasserstein distance, a metric from optimal transport theory [6]. This approach is designed to measure divergence between normative developmental trajectories of cortical and subcortical regions, enabling a more precise mapping of how subcortical inputs scaffold PFC maturation. We will apply this framework to high-resolution morphometric and diffusion MRI data from large-scale open-access datasets, including the Human Connectome Project –Youth and Young Adult cohorts [7, 8]. Analyses will examine whether mismatches in maturation patterns differentiate PFC subregions. Methodologically, our approach will be compared to existing tools such as MIND (Morphometric INverse Divergence) to assess robustness [9]. Crucially, we will validate anatomical plausibility against the histological BigBrain dataset, focusing on laminar thickness, cytoarchitectural boundaries, and regional differentiation within the PFC [10]. By anchoring MRI-based maturation measures to cellular-scale histology, we aim to ensure that our framework captures biologically meaningful patterns of development. Conceptually, this project contributes a methodological foundation for modeling cortico-subcortical co-development at high spatial resolution. Beyond advancing basic neuroscience, it may provide insights into sensitive developmental periods and mechanisms of neuropsychiatric vulnerability.

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