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“Associations Between Neonatal Pain-Related Stress, Neonatal Brain Structural Connectome, and Behavior at School Age in Children Born Very Preterm”

Introduction: Internalizing behaviors (anxiety, depressive symptoms) and executive function difficulties are prevalent in children born very preterm (≤ 32 weeks gestation). Procedural pain/stress during neonatal intensive care unit (NICU) stay is associated with regionally-specific neonatal brain microstructure alterations, hypothalamic-pituitary-adrenal (HPA) axis functioning (cortisol), and behavior problems in childhood.

Hypotheses: 1. Greater NICU pain-related stress will be related to neonatal structural network alterations, beyond clinical factors associated with prematurity 2. Structural brain organisation will be related to child cortisol levels, internalizing behaviors and executive functioning at 4 years.

Study Population: N = 50 infants born very preterm recruited from the BC Women's Hospital Level III NICU.

Methods: Neonatal chart review (e.g. pain/stress [number of invasive procedures], infection), and whole-brain tractography in early life and term equivalent age (MRI/DTI), parent report of internalizing behaviors, executive functioning, and salivary cortisol at 4-years.

Results: Whole-brain network integration (global efficiency) and segregation (transitivity) decreased with greater neonatal pain/stress. Partial-Least Squares Correlation analysis showed clinical factors including neonatal pain/stress were related to change in 128 region-pair connections (normalized streamline count; 69% intrahemispheric, 82% cortico-cortical) across the neonatal period. Relative to weeks between scans, smaller increases in connectivity were primarily related to frontal-limbic (25%) regions, with less decrease in frontal-limbic (14%) and frontal-temporal (15%) regions. Analyses to 4-year behavior and cortisol are in progress.

Implications: Our study advances understanding of the effects of early life pain/stress on brain circuitry during a critical developmental window. Findings will elucidate associations of such alterations with behavior and physiological stress regulation.