How unpredictable, fragmented early-life experiences sculpt the developing brain

Annabel Short, Jenny Molet, Jessica Bolton, Yuncai Chen, Matt Birnie, Tallie Z. Baram *

University of California-Irvine, USA

Background: Mental and cognitive health and vulnerability to neuropsychiatric disorders involve an interplay of genes and environment, especially during sensitive developmental periods. Indeed, both genetic and environmental factors contribute to the development and maturation of neurons, synapses and the resulting brain circuits. Whereas the environmental signals for the sculpting of visual and auditory circuits are known (light, sound), the nature of the signals that influence normal or aberrant maturation of emotional and cognitive brain circuits has not been fully resolved. Early in life, crucial environmental signals arise from the principal care-taker, typically the mother. Thus, in rodent models, the crucial effects of the quantity and qualitative measures of maternal care are well established. However, which maternal signals are salient to optimal brain development, how these signals reach specific populations of neurons and how they influence neuronal and behavioral phenotype enduringly is unclear.

Methods: we employ both control animal model studies and prospective observational studies in human cohorts to examine the role of **patterns** of maternal behaviors, and specifically **fragmented and unpredictable** patterns in the normal maturation of brain circuits and cognitive and emotional outcomes.

Results: We find that fragmented and unpredictable maternal signals are a critical factor that influences neuronal circuit maturation and behavioral phenotype. We demonstrate that maternal signals influence the number and function of synapses abutting specific neuronal populations, which, in turn, is sufficient to initiate epigenetic programs within these neurons. The resulting enduring changes in gene expression translate into altered neuronal function as well as connectivity within brain circuits, and to altered cognitive and emotional behaviors.

Conclusions: Across humans and rodents, emerging evidence supports the importance of predictable sequences of maternal care to optimal cognitive and emotional brain development.

Supported by NS28912; MH73136 and P50 MH096889.