Impact of early life experience on prefrontocortical circuits

Epigenetic regulation in the prefrontal cortex: relevance to schizophrenia

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Epigenetic mechanisms are involved in the regulation of brain development. Findings from a neurodevelopmental model of schizophrenia (MAM-E17) showed changes in a dynamic of histone H3 methylation during the rat prefrontal cortex maturation. Impairments in histone H3 methylation at lysine 4 (H3K4me3) affected expression of genes (Gad1, parvalbumin) in the adult MAM-E17 cortex. Adolescent environmental factors (enriched environment, social isolation) influenced on H3K4me3 protein level that resulted in altered gene expression in the adult MAM-E17 cortex. Thus, modifications in histone methylation during prefrontal cortex development changed trajectory of interneurons maturation, and malfunction of prefrontal cortex might be related to schizophrenia-like abnormalities observed in the MAM-E17 model.

Bator, E., Latusz, J., Wędzony, K., Maćkowiak, M. (2018). Adolescent environmental enrichment prevents the emergence of schizophrenia-like abnormalities in a neurodevelopmental model of schizophrenia. Eur Neuropsychopharmacol., 28(1), 97-108. doi: 10.1016/j.euroneuro.2017.11.013.

Impact of early aversive experiences on the structure, connectivity and plasticity of prefrontocortical neurons

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The prefrontal cortex continues to develop after birth, during the infancy and the adolescence and, consequently, aversive experiences such as chronic stress can affect the final steps of its construction. These alterations lead to permanent alterations in the structure and physiology of the adult prefrontal cortex, which may contribute to the development of certain psychiatric disorders. Recent work in our laboratory has shown that different forms of chronic stress during early life have a strong impact on prefrontocortical inhibitory circuits and their plasticity, particularly on parvalbumin expressing interneurons.

Garcia-Mompo C, Curto Y, Carceller H, Gilabert-Juan J, Rodriguez-Flores E, Guirado R, Nacher J. Transl Psychiatry. Δ-9-Tetrahydrocannabinol treatment during adolescence and alterations in the inhibitory networks of the adult prefrontal cortex in mice subjected to perinatal NMDA receptor antagonist injection and to postweaning social isolation. 2020 Jun 1;10(1):177. doi: 10.1038/s41398-020-0853-3.
Carceller H, Guirado R, Ripolles-Campos E, Teruel-Marti V, Nacher J. Perineuronal Nets Regulate the Inhibitory Perisomatic Input onto Parvalbumin Interneurons and γ Activity in the Prefrontal Cortex. J Neurosci. 2020 Jun 24;40(26):5008-5018. doi: 10.1523/JNEUROSCI.0291-20.2020. Epub 2020 May 26.

Adolescent stress and disruption of prefrontal inhibitory maturation

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During adolescence, the prefrontal cortex gains inhibitory control through the maturation of its GABAergic system. This gain of prefrontal inhibitory control contributes to the maturation of executive functions. It is agreed upon that stress during adolescence impairs these cellular and behavioral maturational processes, potentially leading to cognitive deficits as observed in schizophrenia. The molecular mechanisms driving stress-induced abnormal development of prefrontal inhibitory circuits and associated executive functions remain to be determined. Using genetic, behavioral and molecular approaches in mice, my lab has shown that the transcription factor Npas4 regulates of normative prefrontal circuits maturation during adolescence and mediates the effects of adolescent chronic stress on executive functions deficits.

Shepard R, Heslin K, Coutellier L. (2017) The transcription factor Npas4 contributes to adolescent development of prefrontal inhibitory circuits, and to cognitive and motional functions: Implications for neuropsychiatric disorders. Neurobiol Dis. 99:36-46. doi: 10.1016/j.nbd.2016.12.012.

Page CE, Alexander J, Shepard R, Coutellier L. Npas4 deficiency interacts with adolescent stress to disrupt prefrontal GABAergic maturation and adult cognitive flexibility. Genes Brain Behav. 17(6):e12459. doi: 10.1111/gbb.12459.

Child abuse associates with increased recruitment of perineuronal nets in the ventromedial prefrontal cortex: evidence for an implication of oligodendrocyte progenitor cells

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Child abuse (CA) is a strong predictor of psychopathologies and suicide, and can lastingly alter normal trajectories of brain development, in particular in areas closely linked to emotional responses such as the ventromedial prefrontal cortex (vmPFC). I will present evidence that a history of CA is specifically associated with increased recruitment and maturation of perineuronal nets (PNNs) around parvalbumin-immunoreactive interneurons in human vmPFC, and that oligodendrocyte progenitor cells (OPCs) are involved in this phenomenon. These findings suggest that early-life adversity may lead to persistent patterns of maladaptive behaviours by reducing the neuroplasticity of cortical circuits through the enhancement of developmental OPC-mediated PNN formation.

Child abuse associates with increased recruitment of perineuronal nets in the ventromedial prefrontal cortex: evidence for an implication of oligodendrocyte progenitor cells. Arnaud Tanti, Claudia Belliveau, Corina Nagy, Malosree Maitra, Fanny Denux, Kelly Perlman, Frank Chen, Refilwe Mpai, Candice Canonne, Maria Antonietta Davoli, Gustavo Turecki, Naguib Mechawar. bioRxiv 2020.10.19.345355; doi: https://doi.org/10.1101/2020.10.19.345355

Child abuse associates with an imbalance of oligodendrocyte-lineage cells in ventromedial prefrontal white matter. Tanti A, Kim JJ, Wakid M, Davoli MA, Turecki G, Mechawar N. Mol Psychiatry. 2018 Oct;23(10):2018-2028. doi: 10.1038/mp.2017.231. Epub 2017 Nov 21.