

***The effects of stress on the developing prefrontal cortex:
parallels between humans and animals and how stress, immune dysfunction,
and timing influence psychiatric disorders and addiction.***

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Motivational anhedonia is the diminished desire to engage in activities one used to enjoy and is a key feature of a number of psychiatric disorders (depression, anxiety) and addiction. Exposure to drugs or poor social interactions during development can have a unique influence on a given brain area. If this disturbance occurs during a sensitive period associated with active maturation, the outcome will 1) be relatively permanent, 2) emerge during adolescence, and 3) manifest differently than if experienced in adulthood. Moreover, this process is conserved across species. Here, we characterized the mechanisms underlying the effects of early adversity on anhedonic behavior that can facilitate depression and addiction during a sensitive period.

Methods: Sprague-Dawley rat pups underwent maternal separation (MS) for four hours a day between postnatal (P) day P2-20. A separate cohort was socially isolated (ISO) between P20-40. MS females demonstrate an anhedonic-like depression. On P42, both conditions and their controls were exposed to their peers being shocked on day 1, followed by assessment of escape from shock on day 2. The prefrontal cortex was analyzed for the fast-spiking GABAergic interneuron parvalbumin and TrkB (the BDNF receptor) with Western immunoblot and immunohistochemistry/stereology. For MS subjects only, stereological assessment of double-labeled D1 receptors on prelimbic cortical inputs to the accumbens core was conducted as this pathway is involved in motivational drive.

Results: Individual parvalbumin levels were highly correlated with an anhedonic-like depression in the prefrontal cortex in MS rats ($r=0.93$; $n=9$), but not controls ($r=0.13$; $n=9$). No such effects were found following ISO. ISO females did not demonstrate an anhedonic depressive phenotype, but were helpless in the triadic model. ISO females had no significant change in parvalbumin levels, although TrkB levels were significantly lower. Finally, MS subjects had fewer D1 labeled projections from the prelimbic cortex to the accumbens.

Discussion: The effects of exposure to adversity during a sensitive period is highly conserved, and now we provide behavioral data of anhedonia in females and its relationship to GABA/parvalbumin in rats that parallels those in humans (Gabbay et al., 2017). Exposure to MS decreased prefrontal cortical parvalbumin levels (Brenhouse et al., 2011), which are related to increased cytokine IL-6 levels. Both parvalbumin and depressive behavior can be restored to control levels with an anti-inflammatory agent given during the peri-adolescent period. The loss of D1 on prelimbic projections provides a mechanism underlying anhedonic/amotivational effects.

References

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