Commentary

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Neurobiological Underpinnings of Adolescent Susceptibility to Stress

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Adolescence is a developmental stage marked by significant neurobiological changes, including the maturation of brain regions involved in emotion regulation and responses to stress (1). It is also a period of heightened susceptibility to socioenvironmental stressors, which can predispose individuals to psychiatric disorders later in life (2,3). Decades of studies have identified neural systems affected by stress during adolescence (4,5), but a clear picture of the neural underpinnings of adolescent vulnerability has been elusive. In new work published in *Biological Psychiatry: Global Open Science*, Colodete *et al.* (6) designed an interesting set of experiments to directly test the hypotheses that adult perineuronal nets (PNNs) surrounding parvalbumin interneurons (PVIs) in the ventral hippocampus (vHIP) are protective against stress effects in rats, and their lack of maturation in adolescence confers vulnerability. PNNs are extracellular matrix elements that surround inhibitory interneurons, stabilizing their connections and protecting against oxidative stress (7). In different cortical regions, PNNs are established at different developmental windows, typically when an area of the cortex reaches its mature state following a critical developmental period (8). In the prefrontal cortex and likely its associated hippocampal region (the anterior hippocampus in humans, the vHIP in rodents), the critical period occurs during adolescence (7), a time when the sensory and motor cortices have reached their maturity. Because of this delayed maturation, these regions are still at risk for aberrant developmental trajectories during adolescence, and animal model work has shown that prefrontal and hippocampal PVIs are sensitive to oxidative stress in adolescence (9). Colodete *et al.* showed that PNNs offer an adult-like protection against the loss of PVI function and other downstream effects.

The study employed a stress protocol with male rats during either adolescence or adulthood and assessed behavioral outcomes related to anxiety, sociability, and cognition, along with neurophysiological changes in the vHIP. Adolescent stress was found to induce anxiety-like behaviors, reduced sociability, and cognitive deficits, accompanied by overactivity of dopamine neurons in the ventral tegmental area. Adolescent stress led to a decrease in both PVIs and their PNNs in the vHIP. In contrast, adult stress did not produce the same extent of behavioral deficits or neurophysiological changes as those observed with adolescent stress, suggesting a critical period-specific vulnerability. Moreover, the study explored the protective role of PNNs by selectively degrading them using ChABC (chondroitinase ABC) in adult rats, which effectively recreated an adolescent-like phenotype of stress susceptibility. This manipulation underscored the importance of PNNs in mitigating stress-induced damage to PVIs during critical developmental periods.

The results raise several interesting possibilities for our understanding of the neurobiological underpinnings of neuropsychiatric conditions. Do adult stress–triggered conditions or the adult persistence of adolescent-onset conditions depend on abnormal PNNs in specific brain circuits? The data in Colodete *et al.* (6) indicate that loss of PNNs in an adult brain renders it into a state of adolescent-like vulnerability to stress, suggesting that this may be the case. How can the impact of abnormal PNNs be detected? Because PNNs protect interneurons, their improper configuration may affect interneuron physiology, yielding an abnormal excitation/inhibition balance, which could be captured with electrophysiological tools. In humans, gamma band oscillations and some evoked potentials are thought to reflect adequate excitation/inhibition balance (10). It will be of interest to explore electroencephalography/physiological correlates of circuits with poor PNN configuration.

Another consideration worth investigating is whether sex plays a role in PNN-related stress vulnerability. The authors ran their experiments only in male rats for the sake of data homogeneity and given the higher vulnerability of males to the effects of adolescent stress. Sex differences in response to stress and age of onset of serious mental conditions are well documented. Are there sex differences in PNN configuration or vulnerability? A response to this key question may offer insight into precision treatment approaches that may rely on different sex vulnerabilities.

Overall, understanding the neurobiological underpinnings of stress vulnerability in adolescence has significant implications for advancing novel therapies in a field where very little has been added despite extensive advancements in neuroscience. Targeting neurobiological vulnerabilities identified during adolescence may enable early interventions to mitigate the long-term impact of stress on mental health outcomes. Recognizing individual differences in stress susceptibility based on neurobiological markers that capture PVI function and/or PNN state could inform personalized treatment strategies tailored to mitigate risk and promote resilience. Lastly, developing preventive measures that enhance PNN integrity or promote neuroplasticity during adolescence could potentially reduce the incidence and severity of stress-related psychiatric disorders. The time for precision psychiatry has arrived; studies like that of Colodete *et al.* pave the way for neurobiology-based identification of patient subsets and preventive approaches.

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