Developmental neuroplasticity and adversity-related risk for psychopathology

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The origin of individual differences in psychopathology has been of perennial interest for researchers seeking to improve treatments for psychiatric disorders. Early-life adversity is a potent risk factor for psychopathology, yet significant heterogeneity remains in outcomes following exposure. The timing of adversity exposure—and its intersections with circuit-level neuroplasticity—may be a key factor contributing to this heterogeneity. Sensitive periods of heightened neuroplasticity are 'experience expectant,' requiring environmental input to support the development and calibration of a specific function in a circuit-specific, time-bounded manner [1]. By contrast, 'experience dependent' mechanisms of neuroplasticity may respond throughout the lifespan following impactful experiences such as adversity. Critically, the *timing* of sensitive periods (i.e., onset, duration, and offset) is itself experience-dependent. Thus, *when during development* adversity occurs could contribute to individual differences in risk and resilience by exacerbating or mitigating effects on a developing circuit and mental health (e.g., when function-relevant adversity occurs during or outside of a sensitive period, respectively), as well as by influencing the timing of sensitive periods (**Figure 1**) [1]. Here, we highlight cross-species advances probing how adversity can impact plasticity, neurodevelopment, and youth mental health.

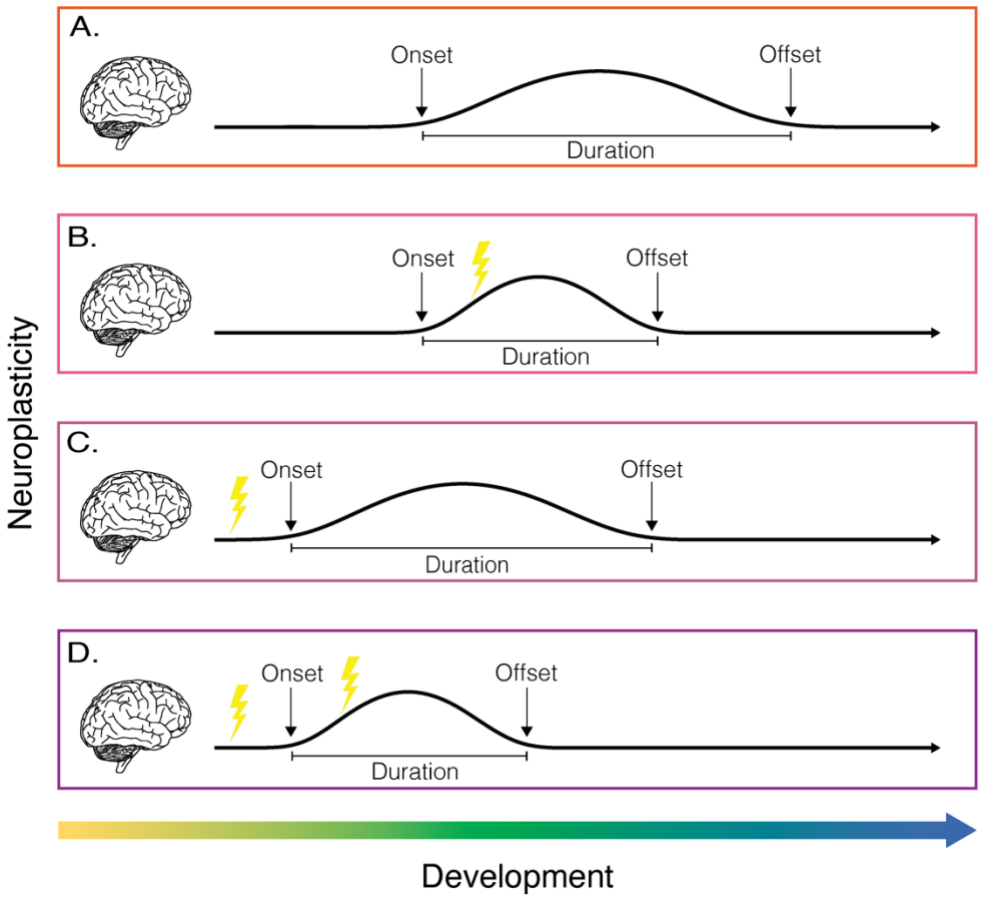

Figure 1. *Experiences such as adversity exposure (depicted as a lightning bolt) can impact the timing of sensitive periods. A) A sensitive period unimpacted by adversity. B) Function-relevant adversity* experienced during an open sensitive period might accelerate its closing and shorten its duration. C) Adversity experienced prior to a sensitive period might accelerate its onset. D)*

*Prior adversity and ongoing function-relevant adversity might both accelerate the onset of a sensitive period and shorten its duration. While the present figure focuses on adversity-related acceleration of sensitive periods, delays in sensitive period onset and offset have also been observed, particularly in the context of sensory deprivation. Further work parsing how changes to sensitive period timing may be modulated by specific characteristics of adverse exposures is required [1]. *Here, 'function-relevant' is used to specify adverse events with characteristics pertaining to the developing circuit and function undergoing a sensitive period.*

Cellular-level mechanisms that govern plasticity inform how adversity affects neural and behavioral development. Among these, myelination is an experience-dependent process that also contributes to attenuating neuroplasticity. In mice, acute stress triggers neuropeptide release that initiates the proliferation of oligodendrocyte progenitor cells and subsequent myelination of active neurons [2]. This molecular cascade might impact risk for psychopathology following stress exposure by altering myelin content of a circuit, accelerating closure of a sensitive period, and contributing to individual differences in neural structure. Parvalbumin-expressing (PV+) inhibitory interneurons also regulate plasticity; their emergence signals opening of a sensitive period, and their eventual formation of perineuronal nets marks closure of a sensitive period. Exposure to early-life adversity can accelerate the emergence of PV+ cells in the basolateral amygdala in mice [3], underscoring the experience-dependent nature of sensitive period timing.

Large-scale developmental neuroimaging studies suggest that early-life adversity can also accelerate neurodevelopment in humans. High levels of prenatal adversity predict accelerated structure-function decoupling in preschool-aged youth [4], and greater adversity exposure confers a more mature corticolimbic functional connectivity phenotype in adolescents [5]. In both studies, adversity-exposed youth with "accelerated" neural phenotypes displayed lower psychiatric symptoms, suggesting that experience-dependent shifts in neurodevelopmental tempo may represent an adaptive response to challenging environments in the short term. Further, youth living in more disadvantaged neighborhoods showed reduced intrinsic fMRI activity in association cortices, potentially reflecting accelerated regional development [6]. As decreases in intrinsic fMRI activity associate with increases in intracortical myelin and may signal a reduction in plasticity consistent with attenuation of a sensitive period, it is possible that adversity-induced changes in the pace of neurodevelopment encompass accelerated timing of sensitive periods as well.

Mechanistic, cross-species characterization of how adversity impacts neurodevelopment and sensitive period timing will be important for understanding how such alterations propagate individual differences in risk for and resilience against psychopathology over the lifespan. Given the prevalence of adversity and the immense burden of psychopathology among youth worldwide, delineating the neurobiological implications of adversity exposure timing can inform efforts to parse heterogeneity and develop tailored interventions to promote resilience and better support youth mental health throughout development.

Competing Interests

The authors report no competing interests.

Author Contributions

LMS and DGG conceptualized the manuscript; LMS drafted the manuscript; and LMS and DGG edited the manuscript.

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