

## HOT TOPICS

# Developmental neuroplasticity and adversity-related risk for psychopathology

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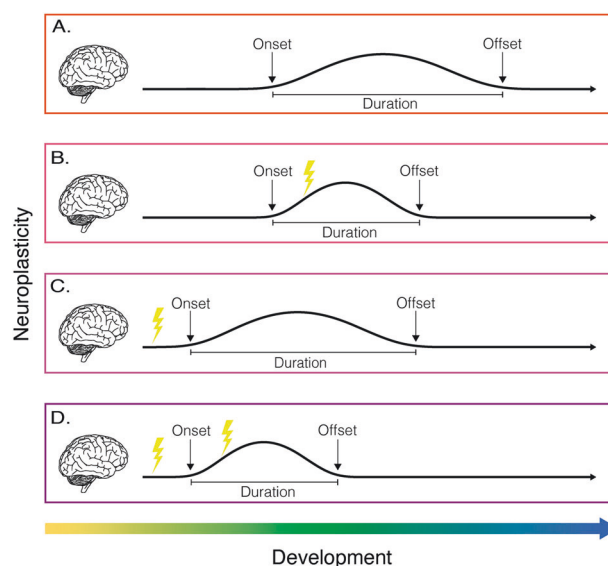
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Understanding individual differences in psychopathology is critical for improving treatments for psychiatric disorders. Early-life adversity is a potent risk factor for psychopathology, yet outcomes are heterogeneous following exposure. The timing of adversity exposure—and its intersections with circuit-level neuroplasticity—may centrally contribute 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 to experiences throughout the lifespan. Importantly, the *timing* of sensitive periods (i.e., onset, duration, and offset) is itself experience-dependent. Thus, *when during development* adversity occurs could shape 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 (Fig. 1) [1]. Here, we highlight cross-species advances probing how adversity can impact plasticity, neurodevelopment, and youth mental health.

Cellular-level mechanisms that govern plasticity inform how adversity affects neurobehavioral 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 the risk for stress-related psychopathology by altering the myelin content of a circuit, accelerating the closure of a sensitive period, and contributing to individual differences in neural structure. Parvalbumin-expressing (PV+) inhibitory interneurons also regulate plasticity; their emergence signals sensitive period opening, and their eventual formation of perineuronal nets marks sensitive period closure. Early-life adversity can accelerate PV+ cell emergence 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 prenatal adversity predicts accelerated structure-function decoupling in middle childhood [4], and greater adversity exposure confers a more mature corticolimbic functional connectivity phenotype in adolescence [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].



**Fig. 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 (i.e., adverse events with characteristics pertaining to the developing circuit and function) 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 the adversity-related acceleration of sensitive periods, delays in sensitive period onset and offset have also been observed. Further work parsing how changes to sensitive period timing may be modulated by specific characteristics of adverse exposures is required [1].

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As decreases in intrinsic activity are linked with increases in intracortical myelin and may signal a reduction in plasticity consistent with attenuation of a sensitive period, it is possible that adversity-related changes in neurodevelopmental tempo may also encompass accelerated sensitive period timing.

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 timing can inform efforts to parse heterogeneity and develop tailored interventions to promote resilience and better support youth mental health throughout development.

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## AUTHOR CONTRIBUTIONS

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

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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