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HOT TOPICS

# Unexpected circuit-level tradeoffs in human stress resilience

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Much of the psychiatric literature indicates that stress resilience requires effective regulation of negative emotion, and continued capacity for positive emotion. This model heavily influences our understanding of affective disorders. However, emerging evidence suggests that the picture is more complex, and that boosting emotion regulation circuits may even be harmful in some cases. Neural circuits supporting stress resilience change over the course of recovery, and certain features are adaptive in some individuals but not in others. We conceptualize these differences in terms of brain circuit-level tradeoffs.

## TEMPORAL TRADEOFFS

A recent systematic review of human neural circuits involved in resilience identified a set of core features that predict stress resilience in a time-invariant manner, including threat-regulation and reward circuits (Fig. 1a) [1]. However, two circuits, the default-mode (DMN) and salience networks (SN), appear to change in response to trauma and during recovery, with concordant changes in their effects on mental health (Fig. 1b) [1]. In the first few weeks post-trauma, lower DMN connectivity predicts resilience, possibly indicating lower self-reflection or rumination early post-trauma. However, this early phenotype does not predict long-term recovery. Instead, individuals who initially show high DMN engagement and high symptoms of PTSD early post-trauma end up with the greatest long-term resilience, with fewer symptoms at two years post-trauma and a reduction of within-network connectivity over time [2].

Prior to trauma, SN engagement during rest or conflict processing predicts later stress-susceptibility, but post-trauma SN engagement consistently predicts a resilient adaptation to stress [1]. It may be that individuals with trait-like low SN engagement are resilient, but are also more likely to upregulate SN following a major stressor.

## PERSON-LEVEL TRADEOFFS

Large-cohort longitudinal studies of traumatic stress strengthen the evidence that core resilience features are maladaptive in some individuals (Fig. 1c). Lebois et al. [3] investigated the role of dissociative symptoms following trauma. Participants in the multi-site AURORA investigation were scanned two weeks following an emergency department visit, and dissociation and PTSD symptoms were assessed longitudinally. Interestingly, vmPFC engagement did not predict resilience. Instead, early dissociation predicted a greater vmPFC response to threat cues, which in turn predicted later PTSD symptoms. Prefrontal down-regulation of threat reactivity is needed to cope with traumatic stress, but magnifies symptoms in some individuals.

With the same AURORA cohort, data-driven clustering identified three groups with different profiles of neural responses to threat, reward, and inhibition tasks [4]. Of the three "biotypes", one group concurred with common resilience models, showing relatively high vmPFC and hippocampus engagement during inhibition, and the fewest symptoms across depression, anxiety, and PTSD. However, the group with the greatest risk for chronic PTSD and anxiety symptom trajectories showed strong engagement of the nucleus accumbens to reward, and amygdala and SN to threat. Similar findings are seen in childhood trauma survivors with high inflammation [5]. Because accumbens response to reward and vmPFC engagement during threat are considered core features of resilience, these are striking examples of heterogeneity.

Resilience research will advance with models that account for both temporal and inter-person complexity. These factors must be considered in the design of effective early interventions for trauma.

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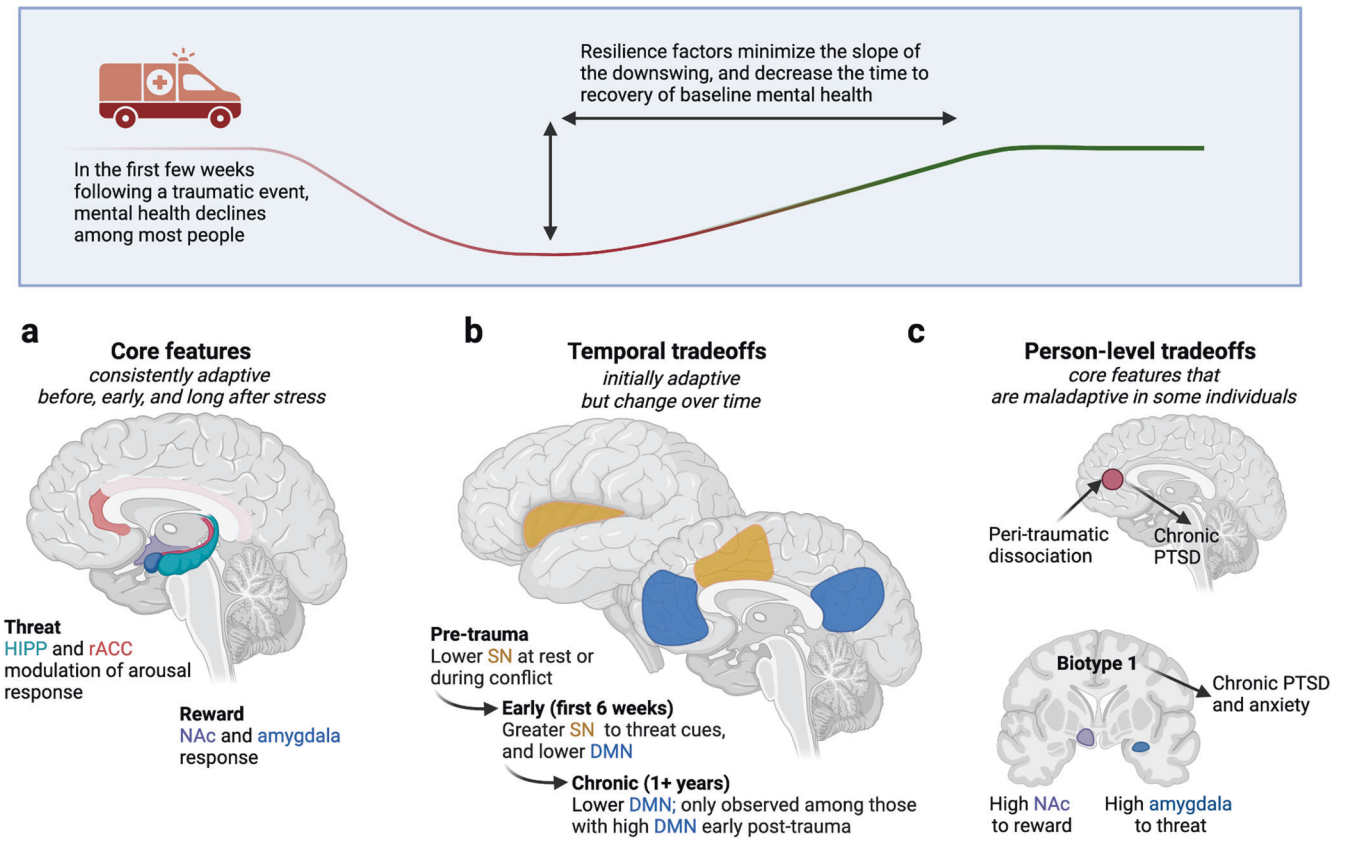


**Fig. 1 Relationship of neural circuits to the timeline of resilience. a** Core features include negative emotion regulation via rostral anterior cingulate cortex (rACC) and hippocampal (HIPP) regulation of the amygdala, and a preserved reward response via nucleus accumbens (NAc) and amygdala reactivity. These features are temporally consistent pre-trauma, peri-trauma, and post-trauma. **b** Temporal tradeoffs are observed in the changing roles of the default-mode network (DMN) and salience network (SN). The DMN includes medial prefrontal cortex and posterior cingulate/precuneus, with additional nodes in temporal cortex. The DMN is engaged at rest, and is implicated in autobiographical memory, self-reflection, and planning [6]. The SN includes dorsal anterior cingulate cortex and bilateral insula, and is involved in processing internal and external stimuli that have homeostatic or survival-related relevance [6]. Temporal tradeoffs may indicate a strong stress response leading to metabolic exhaustion in the early post-stress window, followed by later recovery processes, similar to the building of a muscle after exercise. Alternatively, they may reflect the value of an early heavy allocation of resources to process or reflect upon stressful events, creating an initial mental health cost followed by longer-lasting gains. **c** Person-level tradeoffs are most striking when core features of stress resilience are maladaptive in sub-sets of individuals. Here we illustrate cases from individuals with high peri-traumatic dissociation, and those with an fMRI-defined biotype of high threat and reward responsivity following trauma. Person-level tradeoffs may result from differences in temperament, early development of brain networks, or development of different strategies to deal with environmental stressors.

## REFERENCES

1. Roeckner AR, Oliver KI, Lebois LAM, van Rooij SJH, Stevens JS. Neural contributors to trauma resilience: A review of longitudinal neuroimaging studies. Transl Psychiatry. 2021;11:508 https://doi.org/10.1038/s41398-021-01633-y
2. Ke J, et al. A longitudinal fMRI investigation in acute post-traumatic stress disorder (PTSD). Acta Radiol. 2016;57:1387–95.
3. Lebois LAM, et al. Persistent dissociation and its neural correlates in predicting outcomes after trauma exposure. Am J Psychiatry. https://doi.org/10.1176/appi.ajp.21090911.
4. Stevens JS, et al. Brain-based biotypes of psychiatric vulnerability in the acute aftermath of trauma. Am J Psychiatry. 2021;178:1037–49. https://doi.org/10.1176/appi.ajp.2021.20101526
5. Miller GE, White SF, Chen E, Nusslock R. Association of inflammatory activity with larger neural responses to threat and reward among children living in poverty. Am J Psychiatry. 2021;178:313–20.
6. Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3:472–80. https://doi.org/10.1016/S2215-0366(15)00579-9

## AUTHOR CONTRIBUTIONS

JSS and ARR identified the topic area, wrote and edited the article, and JSS created the figure.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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