Neurobiological Markers of Resilience to Early Life Adversity During Adolescence

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Abstract

Early life adversity (ELA) exposure (including trauma, abuse, neglect or institutional care) is a precursor to poor physical and mental health outcomes, and is implicated in 30% of adult mental illness. In recent decades, ELA research has increasingly focused on characterizing factors that confer resilience to ELA, and on identifying opportunities for intervention. In this review, we describe recent behavioral and neurobiological resilience work that suggests adolescence (a period marked by heightened plasticity, development of key neurobiological circuitry, and sensitivity to the social environment) may be a particularly opportune moment for ELA intervention. We review intrapersonal factors associated with resilience that become increasingly important during adolescence (specifically, reward processing, affective learning, and self-regulation), and describe the contextual factors (family, peers, and broader social environment) that modulate them. Additionally, we describe how the onset of puberty interacts with each of these factors, and explore recent findings that point to possible "pubertal recalibration" of ELA exposure as an opportunity for intervention. Lastly, we conclude by describing considerations and future directions for resilience research in adolescents, with a focus on understanding developmental trajectories using dimensional, holistic models of resilience.

Early life adversity (ELA) exposure is associated with poor mental and physical health outcomes, and is implicated in 30% of adult mental illness (1–3). Exposure to ELA (e.g., trauma, abuse, neglect or institutional care) is the normative experience in the United States and worldwide, with half of children reporting one or more such events (3,4). However, individuals vary greatly in their responses to ELA, and many demonstrate resilience in one or more domains following ELA exposure. Current ELA research is increasingly focused on identifying factors that promote resilience or may be targets for concurrent and retrospective intervention (5).

Adolescence is a developmental period marked by heightened plasticity, sensitivity to the social environment, and the rapid development of critical functions related to self-regulation, reward processing, and affective learning (6). Adolescence may present a unique opportunity for cultivating resilience by targeting the aforementioned domains, particularly in light of recent evidence that puberty provides a "recalibration" window for specific biological systems following ELA (7). Intervention during adolescence may be particularly beneficial given that the transitions associated with this developmental stage are normatively stressful, and the onset of anxiety, mood, and substance use disorders is most common during this period (8).

This review highlights individual and contextual factors[1] that promote resilience, which we define as positive physical and mental health outcomes following ELA (5,9). According to

[1] Given our focus on neurodevelopmental effects of ELA, we use "resilience factors" to describe both characteristics that may be stable or trait-like in adulthood (e.g. cognitive emotion regulation ability or capacity) and the adaptive behaviors these traits may promote in practice (e.g. use of emotion regulation ability to reduce a response to a particular stressor), as these have yet to be fully parsed in the developmental literature (see (9) for discussion in adults).

recent scientific consensus, resilience is not a personality trait (and not the responsibility of individuals to cultivate), but rather various domain-specific adaptations that improve post-ELA outcomes in the short or long term (9). Under this definition, resilience in a given domain arises from individual and contextual factors that contribute to adaptation to and/or recovery from exposures, and may vary over time. As a result, we operationalize resilience as distinct from the inverse of an individual's vulnerability (9).

In neurodevelopment, resilience can manifest in reduced impact of ELA on a circuit, through neurobehavioral adaptations that promote better outcomes, or through adaptations that confer risk or benefit depending on the current context. These processes are modulated by local, community, and societal level contextual factors. Rather than providing a systematic review of all factors associated with resilience, here we highlight a subset of domains fundamental to adolescent neurodevelopment that are promising candidates for intervention: specifically, reward-processing, affective learning, and self-regulation (6). An overview of these resilience factors, the neural circuits they rely on, and candidate techniques for intervention during adolescence are depicted in Figure 1. While we focus primarily on neurobiological and behavioral resilience markers, we also highlight other systems implicated in stress neurobiology, including the immune and neuroendocrine systems. Given that this literature is still nascent, we review resilience to all ELA, but when possible identify which dimensions of ELA – threat or deprivation, for example – may benefit from a particular resilience factor (10,11). Lastly, we describe future directions for this area of research.

Individual Factors Affecting Resilience

Reward Processing

Adolescence is marked by increased behavioral and neural reward sensitivity, defined as enhanced arousal in response to and heightened motivation to seek rewards (13). While increased reward sensitivity is often described as a risk factor in adolescents (13), it also confers benefits (maximizing exploration and reward optimization, for instance; 14), and in adversity-exposed adolescents may be a source of resilience. Across species, reward processing is guided by a mesocorticolimbic dopaminergic system that includes the basal ganglia (including the ventral striatum, commonly associated with reward processing), the orbitofrontal cortex (involved in contingency representation and reward learning), ventromedial prefrontal cortex (vmPFC; linked to self-referential thinking, reward processing, and emotional learning), and limbic regions including the amygdala (implicated in affective valuation, particularly threat and reward) and the hippocampus (associated with learning and memory, alongside biological tuning of the hypothalamic-pituitary-adrenal, or HPA, axis, which coordinates stress responses) (15,16). Functional magnetic resonance imaging (fMRI) studies of adolescents indicate that early deprivation (e.g. institutional orphanage care) and trauma dampen behavioral and neural sensitivity to rewards and weaken reward-based learning (17–19). These effects are linked to anhedonia, which mediates relationships between ELA and psychopathology, social challenges, and substance abuse (17,20–24).

Conversely, heightened reward sensitivity (behavioral and neural, particularly in the striatum) predicts concurrent and longitudinal resilience for adolescents exposed to ELA, in part through reductions in anhedonia (25–28). Reward sensitivity also increases positive affect and

the propensity to appraise events positively following ELA, which in turn predict better mental and physical health (26,29,30).[2] The aforementioned findings suggest that reward processing interventions may support adolescent ELA resilience. Candidate interventions include positive affect treatment, which enhances reward anticipation, reward learning, and savoring of positive experiences (32), and behavioral activation therapy (currently being evaluated in maltreated adolescents), which emphasizes positive reinforcement to reduce anhedonia and enhance motivation and pleasure (33,34).

Affective Learning

Preliminary evidence from fear conditioning research in humans and non-human animals points to fear learning as a possible ELA intervention target. Converging classical conditioning work has implicated the amygdala in producing and storing fear memories, the hippocampus in context learning, and various prefrontal cortex (PFC) regions (including vmPFC) in increasingly inhibiting fear expression across adolescence (35). Across species, adolescents exposed to ELA exhibit accelerated development of fear learning behaviors and medial PFC, hippocampus and amygdala circuitry (10,36). In human adolescents, childhood maltreatment has been associated with threat discrimination difficulty and reduced amygdala and hippocampal volumes (37). By contrast, youth exposed to deprivation (specifically previously institutionalization; PI) show a positive relationship between aversive learning behavior and anxiety, though those that show stronger (i.e., more "mature") vmPFC-hippocampus functional coupling are buffered against anxiety two years later (38). Similarly, maternally separated rats that exhibit increased amygdala-

[2] While early threat exposure may alter related systems like the salience network, such evidence is limited, particularly in regards to adolescent resilience (31).

PFC functional coupling during fear learning display decreased anxiety behaviors (described in 39). However, current evidence is more mixed about whether non-affective forms of memory and learning that rely on hippocampus-PFC circuits also contribute to resilience (31). Overall, the extant data suggest that accelerated development of fear learning may confer resilience for adolescents exposed to ELA (particularly deprivation), and thus, extinction-enhancing exposures might improve outcomes in this population (34).

Self-Regulation

Successful self-regulation (including cognitive control and regulation of negative emotion) may also buffer against ELA. Emotion regulation is defined as a collection of implicit (automatic) and explicit (deliberate) strategies that modify the intensity, valence or timing of an emotional response (40), and cognitive control as mechanisms (including response inhibition, cognitive flexibility, attentional control and working memory) that facilitate overriding automatic mental or behavioral responses in accordance with one's goals (41).

Although cognitive control functions emerge during childhood, they undergo protracted development during adolescence (42,43). These functions are supported by a broad network that includes fronto-parietal regions (including the dorsolateral PFC, dorsomedial PFC, the anterior cingulate cortex, and superior parietal cortex), the basal ganglia, and the thalamus (42). Neuropsychological testing, electroencephalography, and fMRI evidence suggests that exposure to both threat and deprivation diminishes behavioral and neurocognitive markers of cognitive

control (44–47),[3] but also that ELA-exposed youth with strong cognitive control display fewer internalizing symptoms (10,49).

While less commonly explored, emerging work suggests cognitive control may contribute to neurodevelopmental resilience during adolescence. Initial fMRI studies have shown decreased PFC recruitment during cognitive control in adolescents exposed to early threat (50–53) and deprivation (46). Though not an explicit evaluation of neural functioning during cognitive control, a large-scale structural analysis (N = 1870) found that adolescents who were resilient across social, academic, and risk-taking domains had increased gray matter volumes in multiple dorsolateral PFC regions associated with cognitive control (54). Cognitive control may also interact with other resilience factors during adolescence: one recent study found that adolescents with high amygdala threat responses and decreased striatum reward responses reported increased anxiety, unless they displayed robust dlPFC recruitment during executive control (55). ELA-exposed youth may therefore benefit from existing well-validated cognitive control interventions (e.g., task-switch and working memory training; (42).

A larger body of work has explored emotional control and regulation as sources of resilience to ELA. During adolescence, age-related improvements in implicit and explicit emotion regulation behavior are mirrored by the emergence of negative functional coupling between the amygdala and vmPFC and ventrolateral prefrontal cortex (vlPFC), respectively (56–58). Converging evidence from human lesion work, meta-analysis of fMRI emotion regulation studies, and neuroanatomical tracing in non-human primates suggests that negative PFC-amygdala functional coupling during emotional events likely reflects the PFC exerting inhibitory

[3] Although some recent findings suggest cognitive control deficits following ELA may be linked to systemic barriers (e.g. low-SES) that increase risk of ELA, rather than ELA itself (48)

control over amygdala activity (59–62). Negative PFC-amygdala coupling is broadly considered the mature emotion regulation phenotype, as it emerges during the transition to adolescence and predicts both better regulation of negative affect and reduced risk for internalizing psychopathology (56,63–66). Similarly, disruption to (behavioral and neural) emotion regulation processes constitutes a transdiagnostic mechanism connecting ELA and psychopathology risk (67–70).

Although early deprivation and trauma reduce self-regulation ability and confer increased risk for psychopathology at the population level, in individuals there is marked variability in self-regulation capacity, and successful regulation appears to buffer against negative outcomes (71,72). In young adults who experienced early deprivation (e.g. low socioeconomic status), adaptive coping strategies confer benefits for both mental and physical health (e.g. reduced inflammatory activity) (73–75). A systematic review of child and adolescent studies found that emotion regulation success reduces psychopathology risk post-ELA (76), and use of adaptive emotion regulation strategies is associated with resilience to psychopathology in adolescents who experienced childhood poverty (77,78) or war (79).

Similarly, ELA-exposed individuals who display neural phenotypes associated with effective emotion regulation show greater resilience to psychopathology. This effect has primarily been observed in neuroimaging studies examining cognitive reappraisal, an explicit emotion regulation strategy that involves reinterpreting emotional events through lateral PFC regulation of amygdala responses (59). Although ELA (abuse and poverty) confers risk for weak lateral prefrontal recruitment during reappraisal (68,80), adolescents exposed to ELA who exhibit robust lateral prefrontal recruitment and attenuated amygdala reactivity during cognitive reappraisal are at decreased risk for depression (81) and anxiety (82).

While neuroimaging research on ELA and explicit emotion regulation is relatively nascent, far more work has examined interactions between ELA and implicit forms of emotion regulation, including discrimination learning, extinction, and automatic regulation of emotional threat responses. In contrast to reappraisal, which strongly recruits lateral PFC, implicit regulation processes rely heavily upon vmPFC-amygdala interactions (83). Cross-species models of caregiving deprivation suggest that ELA accelerates development of vmPFC-amygdala networks underlying implicit emotion regulation (84). For example, PI youth display negative (mature) vmPFC-amygdala functional coupling patterns during childhood, in contrast with the positive coupling observed in comparison children (38,85). Importantly, PI youth who demonstrate the mature phenotype display decreased anxiety symptoms relative to those who do not (38,85). Thus, accelerated development of vmPFC-amygdala circuitry may be an adaptive response to the need for self-regulation in the absence of a caregiver (84), given that parental presence tunes such networks in typical development (86,87).

Together, these findings highlight self-regulation training as a candidate intervention in adolescents. In particular, cognitive behavioral therapy (CBT) relies upon ingredients ascribed to both explicit (i.e., reframing emotional events) and implicit (i.e., gradual exposure to emotional triggers) emotion regulation (88). Trauma-focused CBT, which is well-validated in children, may promote resilience through relaxation and emotion regulation (34,89,90). Likewise, transdiagnostic treatment approaches that focus more squarely on reappraisal and relaxation[4] may support self-regulation development (91,34). However, because such treatments target

[4] e.g., the FIRST program, which promotes calmness, changing thoughts, and problem solving (91)

multiple domains, more work is needed to assess the utility of interventions specifically targeting emotion regulation (e.g. 92) to confer resilience.

Contextual Factors Affecting Resilience

Development of the individual resilience factors reviewed above is scaffolded by one's social context. Because adolescence confers increased sensitivity to the social environment (6), this developmental period provides a unique opportunity for the cultivation of resilience factors supported by the social context.

High-quality caregiving and a supportive family environment promote resilience following ELA. Caregivers buffer biological stress responses in childhood (93), and scaffold the development of affective (fear) learning, emotion regulation, and cognitive control (94–97), as well as the development of vmPFC-amygdala circuitry during childhood (84,87). Similarly, high-quality caregiving and attachment promote resilience during childhood and adolescence (30,98,99), although individuals vary in their tendency to demonstrate parental buffering effects to stress (86). The family environment (e.g., positive parenting, cohesion and involvement) plays a critical role in resilience and can buffer ELA-exposed adolescents against psychopathology (100). Critically, the family context during adolescence not only protects mental health concurrently – perhaps partially by diminishing sensitivity to other adversities (101) – but into adulthood as well. Indeed, one study found that a family-based parenting intervention in early adolescence was associated with improved self-regulation (and consequently, vmPFC-hippocampal functional coupling) at age 25 (102).

While far more work has examined how social support, particularly caregiving, sculpts fear behavior and vmPFC-amygdala circuitry, emerging evidence suggests positive social contexts also promote adaptive reward-motivated behavior. For example, caregiver presence increases adolescents' ventral striatal activity when making safe choices but decreases said activity during risky choices (103), and adolescents with a greater sense of family obligation display decreased striatal activity during risk taking (104). Although the presence of peers generally increases reward sensitivity in adolescents (105), in ELA-exposed youth peer effects are less well understood. While preliminary evidence suggests that as children become adolescents, peers increasingly modulate biological stress processes (106,107) and resilience factors (105,108–110), reported effects are mixed (and paradigms disproportionately employ social evaluative stressors over other stressors like shared threats). A systematic review found that peer relationships do not modulate adolescent resilience to ELA (100), although this may partially reflect social challenges experienced by ELA-exposed youth (111).

The broader social environment also affects resilience. Adolescents who belong to marginalized groups (particularly racial/ethnic minorities) often face ongoing discrimination and systemic barriers that prevent access to therapeutic resources. Such ongoing stress can affect physical and mental health in adolescence and beyond (112–114). While addressing oppression of minority and low-income groups will require large-scale sociopolitical changes, interventions that target systemic inequalities can confer great benefit. For example, regular small unconditional cash transfers to low-income families improve maternal mental health and reduce depression rates in adolescent boys (115,116). Likewise, animal models suggest that peripubertal environmental enrichment may reverse negative effects of ELA on hippocampal development,

HPA-axis reactivity, cognitive functioning, and play behaviors (117–119). Additionally, interventions that target identity development may contribute to resilience in adolescents. Community-based interventions like the Strong African-American Families (SAAF) program, which supports positive parenting, body image and adolescent pride in racial identity have been shown to reduce risk-taking, depression, and conduct disorders, and improve neural, endocrine, immune, and biological aging outcomes more than a decade later (120,121,121–123). Given that identity development is a prominent developmental task during adolescence that relies on circuits underlying individual resilience factors described above (including vmPFC, dmPFC, ACC, and the striatum; 124), it may be a particularly important intervention focus (6). Community-based interventions like SAAF have the added benefit of cultivating resilience in families, which may support more sustainable resilience in youth. Parents of children exposed to ELA are disproportionately likely to have experienced adversity themselves, and community interventions may therefore foster resilience in both youth and their caregivers, potentially mitigating cross-generational adversity transmission (5).

Pubertal Stress Recalibration Hypothesis

In normative development, puberty is associated with dramatic changes in the brain, neuroendocrine system, and HPA axis (125,126). Puberty alters the function of each of these systems and their interactions – for example, circulating sex hormones and inflammatory markers predict brain function related to emotion regulation and executive control in adolescence (127,128). Accumulating cross-species work suggests that ELA not only modulates brain and biology concurrently, but also may have ongoing or novel effects during and after puberty. In primates (including humans), trauma and psychosocial stress may even accelerate pubertal onset,

particularly in girls (129–131). While the aforementioned work has focused on identifying mechanisms of risk, emerging evidence indicates puberty may offer a window of resilience for adolescents exposed to ELA (129,132,133). Recent research in internationally-adopted PI youth suggests that pubertal onset may present a stress recalibration opportunity for HPA axis functioning (specifically, cortisol reactivity to a social stressor) (7,134). These adolescents experienced extreme social deprivation during early HPA axis development, followed by high-resource environments post-adoption (135). While in this study PI children displayed blunted cortisol responses to stressors, as they progressed through puberty they began to show more normative cortisol responses, suggesting that puberty constitutes a second sensitive period for HPA development that facilitates recalibration to the current environment (7).

The onset of puberty (and thus the beginning of adolescence) may be an ideal intervention opportunity for developing the intrapersonal resilience factors reviewed above. Developmental trajectories of self-regulation appear synchronized to pubertal onset, pointing to a possible pubertal interaction: cognitive reappraisal ability develops rapidly around age 10 and increases across adolescence, and mPFC-amygdala functional coupling patterns associated with implicit emotion regulation ability shift from positive coupling during childhood to negative coupling (the adult phenotype) at approximately the same age (56–58), with similar patterns in cognitive control development (42,43). Similarly, recent developmental theory posits that because puberty initiates peak behavioral and neural reward sensitivity (136), adolescents may be particularly amenable to interventions utilizing "health promoting" rewards like prosocial behavior (132,137).

Puberty also marks a shift in environmental modulation of resilience factors. In childhood, caregiver presence reduces HPA reactivity to stressors, but this dampening diminishes after middle childhood – an effect driven primarily by pubertal onset, rather than chronological age (93,96,138). Likewise, while children display similar stress-induced cortisol responses in the presence of peers and strangers, peers increasingly modulate HPA stress responses in adolescence (although effects vary across populations) (106,107,139,140). Similarly, although parental presence scaffolds negative mPFC-amygdala coupling in children, it does not in adolescents, implying parents impact emotion regulation circuitry to a lesser degree after puberty (141). These findings motivate investigation of interactions between puberty and social context effects on resilience, which may facilitate intervention development (132).

Future Directions

Just as ELA research has embraced dimensional models of risk conferred by different features of stress (e.g., type, timing, severity, controllability) (11,142,143), so too has resilience work begun to adopt a similar approach, assessing resilience with consideration for the type and severity of ELA experienced, and jointly investigating "bottom-up" (e.g. polygenetic and epigenetic) and "top-down" resilience factors (e.g., social environment) (144). Evaluating functioning across biobehavioral systems may be particularly important for understanding resilience, as resilience in one domain may come at the expense of outcomes in another. For example, in low-SES youth, higher self-regulation predicts positive psychosocial outcomes, but also accelerated epigenetic aging (78). Similarly, a recent network analysis revealed that 10 commonly studied resilience factors were all positively associated in non-adversity-exposed adolescents, but showed more antagonistic associations in adversity-exposed adolescents (100).

While recent work has probed interactions between neurobiological resilience and resilience in other systems (epigenetics, for example, see 145), there has not been systematic evaluation of neurobiological resilience factors within individuals (e.g., between accelerated development of emotion regulation circuitry as compared to fear learning circuitry; 146). Future work should evaluate the interplay between resilience factors (particularly following differing ELA exposures) to examine whether they are synergistic, antagonistic or orthogonal to each other. Lastly, these holistic approaches should assess possible pubertal recalibration of stress-related biobehavioral processes across domains (147, for example), and subsequent opportunities for tailored intervention work (7).

Future research should also probe how the biological manifestation and relative impact of specific resilience factors may change and interact across development to predict varying outcomes across the lifespan. Although evidence for sensitive periods of ELA exposure is mixed (despite indication that there may sensitive periods for the effects of caregiver deprivation), future investigations should consider that ELA may shift the timing of neural and biological sensitive periods, including puberty (148,129,38,149,150). These shifts may be adaptive in the short-term (e.g. the absence of a caregiver), but long-term effects are not well characterized. This is particularly relevant to adolescence, given the biological and social transitions that occur during this period. Lastly, parsing the contributions of ongoing and resolved sources of adversity may inform adolescent resilience research, given adolescence's temporal proximity to childhood and the frequent co-occurrence of ELA and complex or chronic stress exposures (as with persistent systemic inequalities). Further evaluation of developmental timing effects may therefore inform resilience models and later intervention design.

Taken together, these findings point to the continued need to employ long-term, large-scale longitudinal studies that evaluate a) resilience given severity and type of ELA exposure b) resilience factors across multiple levels (genetic, immune, neurological, behavioral, and social), with an eye to pubertal effects, c) developmental trajectories for each resilience factor and d) the interplay between resilience sources across developmental stages. Information gleaned from this work may inform targeted interventions and improved understanding of resilience during development.

Figure

Figure 1. Schematic of resilience factors and associated neural systems and inte

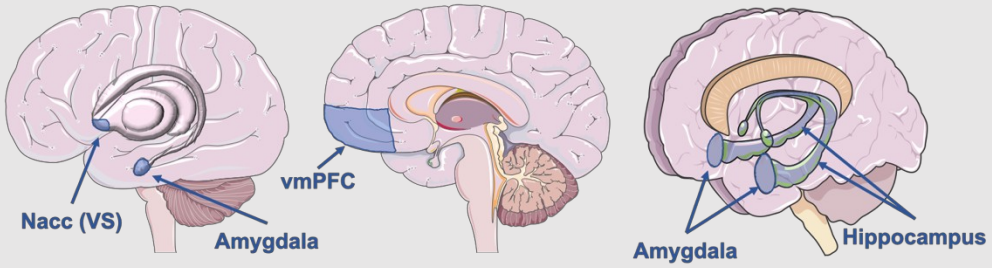
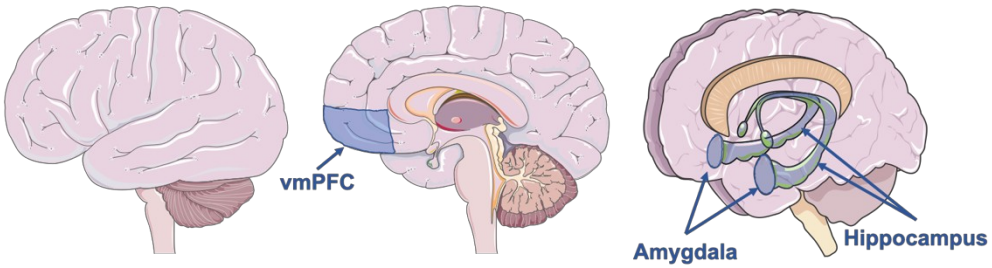
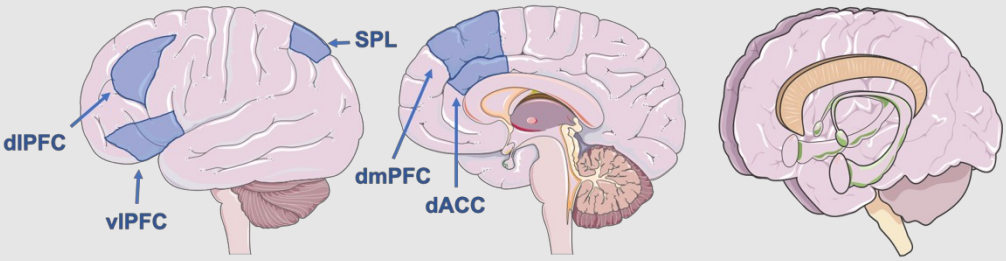
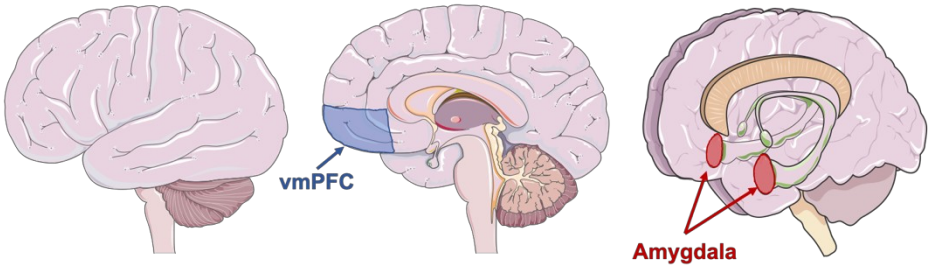
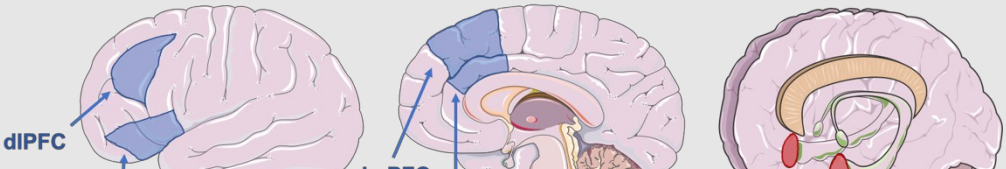
Resilience Factor	Neural System
Reward Processing	
Affective Learning*	
Cognitive Control	
Emotion Regulation <u>Implicit:</u>	
<u>Explicit:</u>	

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Figure Legends

Figure 1. Schematic of resilience factors and associated neural systems and interventions.