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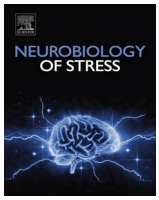

Enduring memory consequences of early-life stress / adversity: Structural, synaptic, molecular and epigenetic mechanisms

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ABSTRACT

Adverse early life experiences are strongly associated with reduced cognitive function throughout life. The link is strong in many human studies, but these do not enable assigning causality, and the limited access to the live human brain can impede establishing the mechanisms by which early-life adversity (ELA) may induce cognitive problems. In experimental models, artificially imposed chronic ELA/stress results in deficits in hippocampus dependent memory as well as increased vulnerability to the deleterious effects of adult stress on memory. This causal relation of ELA and life-long memory impairments provides a framework to probe the mechanisms by which ELA may lead to human cognitive problems. Here we focus on the consequences of a one-week exposure to adversity during early postnatal life in the rodent, the spectrum of the ensuing memory deficits, and the mechanisms responsible. We highlight molecular, cellular and circuit mechanisms using convergent trans-disciplinary approaches aiming to enable translation of the discoveries in experimental models to the clinic.

1. The association of early-life stress/adversity and cognitive function throughout life: Human studies

Early life adversity (ELA) includes traumatic events which encompass diverse types of physical and emotional stressors (Nelson et al., 2007; Pechtel and Pizzagalli, 2011; Short and Baram, 2019; Baldwin et al., 2024; Sheridan and McLaughlin, 2014; Felitti et al., 1998). Therefore, ELA is often an ambiguous term, frequently assessed from the perspective of the investigator to include physical stress, emotional stress and social disadvantages (Nelson et al., 2007). A holistic view of ELA may define it as any non-genetic factor that impacts or impedes the normal maturation and function of an individual (Felitti et al., 1998; Malave et al., 2022; Guadagno et al., 2018, 2021; VanTieghem and Tottenham, 2017; Peña et al., 2017; Molet et al., 2016a). Many studies in human and experimental animals categorize different types of ELA, looking for specificity both in terms of the scope of ELA's impact on brain development and in terms of specific domains of affected cognitive and emotional outcomes (Ellis et al., 2022; McLaughlin et al., 2021; Shackman and Pollak, 2014; Sheridan et al., 2012; Berman et al., 2022; Edwards et al., 2003). One example is the categorization proposed by Sheridan and McLaughlin (Sheridan and McLaughlin, 2014, 2016; Sheridan et al., 2017; Baldwin et al., 2021), in which high or low threat comprises one dimension of ELA, and the degree of deprivation is an orthogonal dimension. Other views emphasize the cumulative risk, i.e., the number of different types of adverse childhood experiences (ACEs) (Felitti et al., 1998; Evans et al., 2013). This has led to the development of additive scales of ACEs (Felitti et al., 1998; Dube et al., 2009) and the proposal that a larger number of ACEs leads to worse outcomes (Smith and Pollak, 2021). Whereas this approach has been proven at the population level, it does not predict outcomes of the individual child (Baldwin et al., 2021; Short et al., 2024). Importantly, while there is no consensus on the types and boundaries of ELA, a consistent aspect across all early life stressors is that they converge on activating the brain's own stress system (Joëls and Baram, 2009; Short et al., 2021; Feng et al., 2011; Raineki et al., 2010; Molet et al., 2014; McLaughlin et al., 2015). This activation in turn primes future programming, responsiveness, and function, setting in motion a cascade of molecular and cellular events that have the capability to affect memory, executive function and related cognitive behaviors (Pechtel and Pizzagalli, 2011; Bale et al., 2010; Parel and Peña, 2022; Lupien et al., 2009; Bos et al., 2011) (see Fig. 1).

A robust literature including large, longitudinal studies has documented effects of various types of ELA on cognitive development and function. De Bellis et al. (2009) and others, measured cognitive function

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in neglected children, finding that they scored significantly lower than controls in a battery of cognitive tests including learning and memory and attention and executive functioning (Sheridan et al., 2012; De Bellis et al., 2009; Danese et al., 2017; Luby et al., 2013). Similarly, studies of children who spent the first part of their life in institutionalized care showed decreased intellectual performance, poorer language skills, and deficits in cognitive abilities (Sheridan et al., 2012; Cohen et al., 2008; Loman et al., 2009; Rutter et al., 2004; van den Dries et al., 2010). Importantly, in a groundbreaking controlled randomized study, Nelson et al. (2007), followed up by Cohen et al. (2008), and van den Dries 2010, found that institutionalized children who went into foster care before their second birthday had better cognitive development compared to children that remained longer in institutional care (Nelson et al., 2007; Cohen et al., 2008; van den Dries et al., 2010). Notably, whereas earlier reports of cognitive decline in middle age of individuals exposed to ELA have not been substantiated, a lower cognitive capacity over the adult life in individuals with ELA history is linked to late-life dementia (Brunson et al., 2005; Tani et al., 2020; Donley et al., 2018). Therefore, ELA does associate with dementia in the aged, providing impetus for identifying the mechanisms that may mediate this association.

As is apparent from the paragraph above, the timing of both ELA and the measured outcomes matter (Hensch, 2004; Takesian and Hensch, 2013; Vanderwert et al., 2010; Farooq et al., 2024). During sensitive prenatal and early postnatal developmental periods (Takesian and Hensch, 2013; Fagiolini and Hensch, 2000; Barkat et al., 2011; Takesian et al., 2018; Birnie and Baram, 2022), environmental signals to the developing brain are either filtered or conveyed by the mother (prenatally) or caregivers and proximate family environment (postnatally) (Gee and Cohodes, 2021; Frosch et al., 2021; Gee et al., 2013). Thus, a significant proportion of ELA derives from aberrant valence and patterns of parental interactions, which can range from a lack of sensitivity to neglect, abuse and inconsistent and unpredictable care (Glynn and Baram, 2019; Davis et al., 2017, 2022). Indeed, a mother (or parent)'s behavior will also be influenced by their environment, and they may convey environmental stressors to the developing brain of the infant and child. Therefore, we propose that in addition to the established physical and emotional early life stressors that can affect cognitive development, an additional dimension, fragmented and unpredictable patterns of care from the caregiver and the environment, significantly contributes to cognitive deficits (Glynn and Baram, 2019; Molet et al., 2016b). Whereas the complete absence of maternal care has catastrophic consequences for cognitive and emotional development (Nelson et al., 2007; Bos et al., 2011; Mehta et al., 2010; Degnan et al., 2011), more recent studies indicate that unpredictable, inconsistent sensory signals (auditory, tactile and visual) from mother to her infant and child impact neurodevelopment (Sheridan and McLaughlin, 2014; Davis et al., 2017, 2022; Molet et al., 2016b; Spadoni et al., 2022), with emphasis on later cognitive performance (Davis et al., 2017, 2022; Ivy et al., 2008, 2010).

2. Memory deficits after early-life stress/adversity in experimental models

Models of ELA in rodents allow for the delineation of mechanisms that mediate cognitive deficits. Indeed, there are a variety of models that seek to understand how specific stress modalities lead to long term detrimental effects on neural circuit function (Murthy and Gould, 2018; Walker et al., 2017; George et al., 2010; Tractenberg et al., 2016; Levine et al., 1957). Focusing on mother-pup interactions, models routinely used include maternal separation/deprivation (MS/MD) (Teissier et al., 2020; Arborelius and Eklund, 2007; Caldji et al., 2000; Grassi-Oliveira et al., 2016; Ganguly et al., 2019), early social isolation (ESI) (Heidbreder et al., 2000; McCool and Chappell, 2009; Lopez et al., 2011; Gong et al., 2018), and simulated poverty via limiting bedding and nesting materials in the cage (LBN) (Molet et al., 2014; Ivy et al., 2008; Rice et al., 2008; Goodwill et al., 2018). Using these models, investigators have studied the short-term and long-term molecular, physiological, and behavioral effects of early life experiences (Goodwill et al., 2018; Levine, 1967; Plotsky and Meaney, 1993; Nieves et al., 2020; Francis et al., 1999). For instance, MS routinely results in anxiety-like behavior manifesting in adolescence and persisting throughout adulthood (Kalinichev et al., 2002; Kikusui et al., 2004; Zeng et al., 2020). In contrast, cognitive deficits and anhedonia-like behaviors, but not anxiety-like behaviors are observed in adolescent and adult rodents reared in the LBN paradigm (Ivy et al., 2010; Birnie et al., 2023a; Gallo et al., 2019; Dalle Molle et al., 2012; Wang et al., 2012). These findings suggest that distinct models of ELA (together with the diverse developmental periods during which they are imposed) contribute differently to the repertoire of neurodevelopmental impacts of ELA on adult motivated behaviors (Ivy et al., 2010; Grassi-Oliveira et al., 2016; Bolton et al., 2018; Kangas et al., 2021; Levis et al., 2022; Naninck et al., 2015; Loi et al., 2017; Janetsian-Fritz et al., 2018; Reshetnikov et al., 2020).

Rodents, particularly mice and rats, are widely used models in

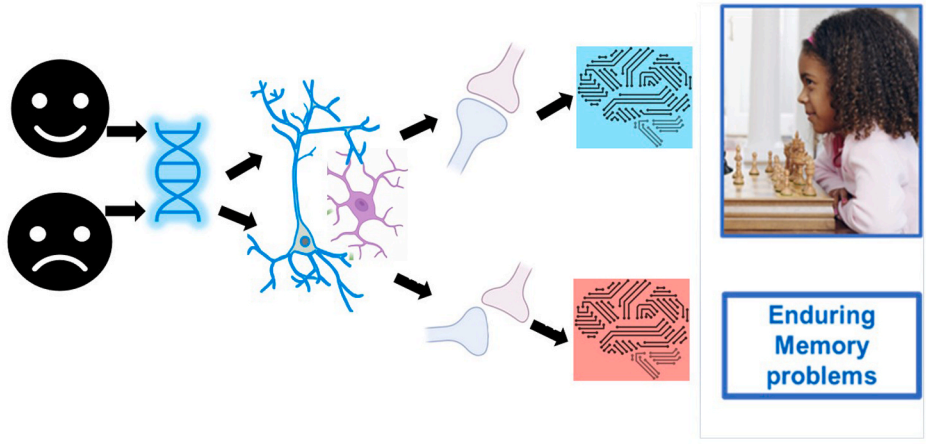

Fig. 1. Cartoon depiction of potential mechanisms by which early-life adversity (ELA) leads to cognitive problems.
Early-life experiences, positive or negative (shown as smiley or crying faces) influence long-term cognitive function. The mechanisms include epigenomics (schematized as the DNA double helix), as well as disrupted circuit maturation. The latter involves aberrant synapse strengthening or pruning (shown as a stylized neuron), executed, in part, by microglia (shown in pink) which may be impacted by ELA. Synaptic connections govern optimal (in blue) or impaired (in red) circuit maturation, which underlie, respectively excellent or impaired memory, executive control and related cognitive functioning. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cognitive behavioral studies (Dalley et al., 2004; Lezak et al., 2017; Hölter et al., 2015). Cognition itself is a broad concept, encompassing components such as short-term and long-term memory. Cognitive deficits are a core feature of several neuropsychiatric and neurological disorders (Millan et al., 2012), therefore assessing how deficits in cognition arise following early life stress is important. Commonly, memory tasks used in mice and rats are the Morris water maze (MWM) (Morris et al., 1982; Vorhees and Williams, 2006), Barnes maze (Barnes, 1979; Harrison et al., 2006), novel object location (NOL) and recognition (NOR) (Dix and Aggleton, 1999; Antunes and Biala, 2012), as well as the Y-maze (Conrad et al., 1996). Indeed, several groups have reported cognitive deficits in adult rodents that were exposed to ELA (Ivy et al., 2010; Xu et al., 2022; Reincke and Hanganu-Opatz, 2017; Bachiller et al., 2020). However, as mentioned above, the term 'ELA' is broad, and diverse outcomes of cognitive function have been described, perhaps in part due to differences in ELA modality, the timing of the postnatal stress, as well as the potential 'second-hit' stressor that may arise when using MWM (Harrison et al., 2009), and other procedures that are stressful in themselves. Using the MS model (which can vary from 3 h–24 h separations, and from postnatal day 1–14) investigators have reported deficits in spatial memory (using the NOL and MWM tasks) (Oomen et al., 2010; Maghami et al., 2018; Shin and Lee, 2023) and recognition memory (NOR) (Reincke and Hanganu-Opatz, 2017; Shin and Lee, 2023). Notably, the difficulty and the hippocampus-dependence of a task will determine the presence and timing of apparent deficits: for example, after rearing in LBN cages, spatial memory, a difficult and hippocampus-dependent task, is impaired from a young age (Ivy et al., 2010; Rice et al., 2008; Xu et al., 2022; Kanatsou et al., 2017). In contrast, recognition memory is only impaired later in life (Molet et al., 2016a; Rice et al., 2008), but the deficit can be unmasked by a 'second-hit' stress (Molet et al., 2016a). These findings suggest that ELA may lead to latent cognitive deficits, which are unmasked by using more difficult tests (e.g., temporal order or episodic memory tasks) or by a second challenge. The behavioral deficits, such as those described for the LBN model, provide a framework to probe underlying mechanisms: multiple groups found deficits in a wide array of cognitive behaviors across the lifespan, and these deficits have been associated with impaired activity-dependent synaptic transmission and the destruction of neuronal arborization and synapses (Brunson et al., 2005; Xu et al., 2022, 2023).

The mechanisms by which ELA leads to cognitive problems (in humans and rodents) are likely multiple and are not fully understood. Here we discuss molecular changes, aberrant synaptic transmission and plasticity as well as transcriptomic and epigenomic candidate processes.

3. Synaptic and structural mechanisms of memory deficits following chronic early-life adversity

A key challenge in associating ELA to life-long cognitive issues involves uncovering the mechanisms by which a transient exposure to stress results in enduring changes to brain operations. A well-accepted concept suggests that ELA takes place during sensitive (or critical) periods (Hensch, 2004; Takesian and Hensch, 2013), in which the brain machinery that executes cognitive function is particularly vulnerable to environmental and experiential influences. Yet, by itself, the concept of a sensitive period does not explain *how* ELA impacts brain maturation to elicit memory problems. In other words, what molecules, cells and processes are targets of ELA, and how does exposure to ELA alter their fate?

In the 1990s, research groups began to examine the structure of the hippocampus, a key node in memory processes, to identify structural and physiological changes induced by stress in general (Vorhees and Williams, 2006; Antunes and Biala, 2012) and by ELA in particular (reviewed in (McEwen et al., 2016; Chen and Baram, 2016)). As described originally for adult stress, loss—or poor maturation—of dendritic trees of hippocampal pyramidal cells were described in adult rats experiencing ELA in the form of recurrent maternal separation (Lippmann et al., 2007; Huot et al., 2002), in conjunction with memory problems. Similarly, chronic ELA related to cages with resource scarcity imposed on rats and mice during the first two postnatal weeks (typically postnatal days 2–10) leads to robust and selective memory problems. This ELA consists of placing pups and dams in cages with 'simulated poverty', i.e., where bedding and nesting material are limited (LBN paradigm) (Molet et al., 2014, 2016b; Rice et al., 2008). Physical stress and hypothermia are minimal to absent in pups growing up in these cages (Bolton et al., 2019). Instead, the significant chronic stress, which manifests as elevated plasma corticosterone and adrenal hypertrophy (Short et al., 2021; Brunson et al., 2005; Rice et al., 2008), results from 'emotional' stress related to disrupted, fragmented and unpredictable patterns of maternal caring behaviors (Glynn and Baram, 2019; Davis et al., 2017, 2019, 2022; Molet et al., 2016b; Spadoni et al., 2022; Walker et al., 2017). These fragmented unpredictable sequences of maternal behaviors in experimental animals (Molet et al., 2016b; Ivy et al., 2008; Walker et al., 2017), and analogous unpredictable parental and environmental inputs to human infants (Glynn and Baram, 2019; Luby et al., 2020) might also be a direct mechanism for the disrupted maturation of brain circuits involved in memory, via modulation of synaptic strengthening and pruning. This notion is plausible, as it has been demonstrated in other circuits with well-established developmental timelines, such as the auditory and visual systems, in which consistent and repeated patterns of stimuli are required for normal maturation (Birnie and Baram, 2022; Birnie et al., 2020). While not yet substantiated, the idea that unpredictable and fragmented sequences of maternal behaviors would negatively impact the developing hippocampus and result in long-term deficits in hippocampal function is plausible.

The repertoire of memory disruptions elicited in adult rats and mice by a single week of ELA imposed via the LBN cage paradigm is described above. Here we focus on their structural/functional correlates: The loss of hippocampus-dependent memory and commensurate poor synaptic plasticity may take place via several converging mechanisms that act at molecular, cellular and network levels: Anatomical studies relying on neuronal filling and Golgi staining have revealed a loss (or aberrant development) of dendritic arbors and dendritic spines of CA3 and CA1 hippocampal pyramidal cells (Brunson et al., 2005; Ivy et al., 2010). This consequence of ELA is reminiscent of the dendritic and spine loss reported after stress in the adult (Magarinos and McEwen, 1995; Moda-Sava et al., 2019). The impoverishment of apical dendritic branching and resulting loss of synapses appears to be progressive, commencing in area CA3 in 2–4 month old rats and heavily involves CA1 as well at older age (Molet et al., 2016a; Brunson et al., 2005; Ivy et al., 2010) and similar findings have been reported in mice (Xu et al., 2022; Wang et al., 2013). Notably, the reduction of dendritic arborization, which accounts for ~40% of neuronal volume, was detectable on whole brain imaging (Molet et al., 2016a). Indeed, this reduced arborization may account for the reduced hippocampal volume and activity reported in people with a history of ELA (Luby et al., 2013; Rao et al., 2010; Hanson et al., 2015; Teicher et al., 2012; Liberzon et al., 2015; Karten et al., 2005). Support for the physiological significance of the loss of functional synapses that reside on dendritic spines after ELA was evident using in vitro slice electrophysiology (Brunson et al., 2005; Ivy et al., 2010). In essence, CA1 pyramidal cells had electrophysiological features of denervation, related to a paucity of CA3-origin Schaeffer collaterals. Thus, a plausible mechanism for the cognitive problems resulting from ELA may involve aberrant neuronal-synaptic function and specific deficits in circuit organization (Short and Baram, 2019; Kohl et al., 2015).

Notably, while many studies have focused on the impact of ELA on hippocampus dependent memory processes and the underlying mechanisms, others identified problems with working memory in adult rats exposed to maternal separation (Brenhouse and Andersen, 2011). Accordingly, based on the accepted localization of working memory circuits, investigators have searched for cortical biomarkers, predictors

and mechanisms for these deficits (Grassi-Oliveira et al., 2016). Similarly, other groups have contributed to the understanding of the impact of ELA on emotional memories (Nieves et al., 2020; Manzano-Nieves et al., 2018).

However, for all these phenotypes, what might be the underlying mechanisms leading to disruption of synapse stabilization and persistence after ELA? In the next section, we describe a potential role for synaptic pruning by microglia, which are selectively impacted by ELA in specific brain regions.

4. Microglia abutting stress-sensitive neurons may malfunction during ELA

Microglia are the brain's primary neuroimmune cells that regulate brain development (Paolicelli et al., 2011; Schafer et al., 2012; Lenz et al., 2013; Parkhurst et al., 2013; Cunningham et al., 2013; Ueno et al., 2013) and therefore they are particularly sensitive to early life stress (Fanikos et al., 2024; Milbocker et al., 2021). Indeed, microglia are highly responsive to several mediators of stress, including glucocorticoids (Frank et al., 2012) and corticotropin-releasing hormone (CRH) (Stevens et al., 2003; Ock et al., 2006; Kritas et al., 2014; Bolton et al., 2022) via expression of their cognate receptors, glucocorticoid receptors (GRs) (Picard et al., 2021) and CRHRs (Stevens et al., 2003; Wang et al., 2002), respectively. Initial studies of the effects of early postnatal stress on microglia utilized dexamethasone, a potent and highly selective GR agonist, to mimic the stress condition (Kaur et al., 1994; Wu et al., 2001). Similarly, a number of ex vivo investigations looking at microglia following maternal separation have reported various outcomes. Interestingly, although an overall increase in the total number of microglial cells has been reported across the brain, in the hippocampus, it appears subfield specific – with an increase observed in CA1 (Delpech et al., 2016)' (Réus et al., 2019), a decrease in CA3 (Saavedra et al., 2017), or simply no change in the number of microglia cells or expression of the microglial marker Iba-1 (Roque et al., 2016). More recently, using the LBN model of ELA during the early postnatal period, investigators reported an increase in total number, and activation of, microglia in the hippocampus, which was correlated with deficits in spatial memory (Bachiller et al., 2020; Hoeijmakers et al., 2017). Interestingly, this adverse outcome could be rescued with ω-3 and ω-6 long-chain polyunsaturated fatty acid treatment (Yam et al., 2015, 2019) – which has previously been shown to modulate microglial phagocytosis in the early postnatal mouse brain (Madore et al., 2020).

Whereas in the hippocampus ELA leads to persistent and perhaps progressive losses of synapses on hippocampal principal cells (Brunson et al., 2005; Ivy et al., 2010; Xu et al., 2022), the story differs in the hypothalamus. Hypothalamic neurons expressing the stress-sensitive peptide corticotropin releasing hormone (CRH) have an augmented density of excitatory synapses following ELA (Gunn et al., 2013), whereas augmented maternal care behaviors reduces this density (Korosi et al., 2010; Singh-Taylor et al., 2018). Neuroanatomical studies using traditional methods as well as transgenic mouse lines and live two-photon imaging have identified an increased number of excitatory synapses onto CRH-expressing cells in the hypothalamic paraventricular nucleus (PVN) (Bolton et al., 2022). Remarkably, this synaptic exuberance was confined to CRH cells and absent from other hypothalamic or neighboring region neurons. Electrophysiological studies confirmed aberrant excitatory input onto these CRH cells Bolton et al., 2022, Gunn et al., 2013, and mechanistic studies demonstrated that the 'excess' glutamatergic synapses result from a failure of synaptic pruning by microglia residing in close proximity to these neurons (Bolton et al., 2022). Microglial process excursions were slower in surveying CRH neurons, and therefore synaptic ingestion was reduced. Importantly, artificial activation of microglia with chronic DREADD manipulation during ELA restored normal synaptic pruning and prevented the aberrant stress responses in adult mice experiencing ELA (Bolton et al., 2022).

Whereas the functions of microglia abutting hippocampal pyramidal cells have not yet been studied, it is tempting to speculate that ELA might also impact microglial activity in the developing hippocampus. Here, we would predict that microglia are "hyperactive", and over-prune synapses.

5. Potential molecular mechanisms of the influence of ELA on memory

It is well established that ELA leads to chronic elevation of plasma glucocorticoid levels during the ELA period (Brunson et al., 2005; Ivy et al., 2008; Rice et al., 2008), which normalize by adulthood (Davis et al., 2022; Xu et al., 2022). Glucocorticoids penetrate the brain and have innumerable effects on neuronal viability, structure, and function, acting via GRs and mineralocorticoid receptors (MRs) (Reul and Kloet, 1985; Reul and de Kloet, 1986; Pooley et al., 2017; Chao et al., 1989; Birnie et al., 2023b). Accordingly, studies looking at gene expression changes in adult hippocampus of ELA and control rats identified an enrichment of differentially expressed genes that are targets of GR, a receptor that acts as a transcription factor (Pooley et al., 2017; Birnie et al., 2023b; Flynn et al., 2021; Bolton et al., 2020; Stavreva et al., 2009). Therefore, it is logical to ascribe some of the neuroanatomical and electrophysiological changes and cognitive deficits to elevated levels of glucocorticoids that target the GR-rich hippocampus (Reul and Kloet, 1985; Reul and de Kloet, 1986; McEwen, 1999; McEwen et al., 2015). For example, elevated glucocorticoids secreted as a result of ELA will bind to the GR and MR to negatively impact neurogenesis (Huot et al., 2002; Magarinos and McEwen, 1995; Birnie et al., 2023b; Sapolsky, 1996, 2001). However, the studies described in the next section suggest that other transcription factors, in addition to GR, are activated by ELA to influence structural and functional effects of ELA on hippocampus.

The hippocampus is endowed with a large population of cells expressing an endogenous stress-mediator, corticotropin-releasing hormone (CRH) (Bale and Vale, 2004; Chen et al., 2004a, 2012, 2015). CRH-expressing hippocampal neurons are GABAergic interneurons that regulate excitability during stress (Gunn et al., 2017, 2019). CRH cells appear prior to birth and migrate to the pyramidal cell layers during the first weeks of life (Chen et al., 2001, 2004a, 2004b). ELA increases the expression of hippocampal CRH (Ivy et al., 2010), leading to an apparent increase in the number of immunocytochemically visible neurons in both CA3 and CA1 hippocampal subfields (Chen et al., 2004a). CRH has been shown to contribute to dendritic and synapse loss in the hippocampus (Chen et al., 2008, 2012), acting via its cognate receptor, CRHR1, that resides in dendritic spines (Chen et al., 2013; Andres et al., 2013). Mechanistic studies have demonstrated that activation of CRHR1 disrupts spine integrity via and NMDA-receptor dependent activation of the enzyme calpain [189.] Further work demonstrated that CRH perturbs the signaling of the RhoA pathway, one of the several small GTPases that control the integrity of the spine's actin cytoskeleton (Chen et al., 2012). Indeed, activation of both CRHR1 and GR inflicts synergistic effects on RhoA: CRHR1 leads to calpain-mediated destruction of RhoA, and GR activation seems to prevent RhoA phosphorylation/activation (Chen et al., 2016).

Previously, Ivy et al., sought to prevent the cognitive effects of ELA by chronically blocking CRHR1 activity during the week immediately following ELA (Ivy et al., 2010). The effort successfully prevented several of the memory deficits that follow ELA, providing strong support for the role of CRH signaling in mediating these adverse outcomes. In parallel, Wang et al. used conditional knockouts of CRHR1 to demonstrate that this protected ELA mice from memory deficits (Wang et al., 2011). Notably, whereas blocking the receptor genetically or pharmacologically early in life was effective at rescuing mice and rats from the effects of ELA, intraventricular infusion of the CRHR1 receptor antagonist, NBI30775, in adulthood could only partially recover hippocampal-dependent memory (Short et al., 2020), consistent with a

relative 'sensitive period' for both the induction and amelioration of ELA-induced memory problems (Fagiolini and Hensch, 2000; Barkat et al., 2011; Birnie and Baram, 2022; Sun et al., 2018).

6. Converting a transient ELA into life-long memory deficits: Epigenetic mechanisms

The previous sections centered on the enduring, life-long and potentially progressive consequences of ELA on memory function. We discussed structural changes related to microglia and the actions of stress hormones which accompany and potentially mediate cognitive deficits. However, whether the structural changes and loss of synapses result from transient vulnerabilities during sensitive periods of ELA involve persistent changes in neuronal properties is unresolved. Transcriptomic studies of adult hippocampus (Bolton et al., 2020; Kos et al., 2023; Reemst et al., 2022) and other brain regions (Short et al., 2021; Peña et al., 2019; Bennett et al., 2024; Parel et al., 2023; Deckers et al., 2024) in rodents experiencing ELA have begun to shed light on these questions, identifying numerous differentially expressed genes following ELA. Probing of upstream 'master regulators' of these persistent changes identified GR as a driving transcription factor (Lambert et al., 2013; Lesuis et al., 2018), as expected, but also a second potent transcription factor, neuronal restrictive silencing factor, (NRSF or REST) (Singh-Taylor et al., 2018; Bolton et al., 2020). Indeed, blocking the binding of NRSF to the chromatin rescued ELA rats from the cognitive deficits caused by early stress (Bolton et al., 2020).

NRSF is a universal transcriptional repressor that silences neuronal genes in non-neuronal cells, and is thus typically enriched in these cells. During embryogenesis it plays an important role in cell differentiation (Chong et al., 1995; Schoenherr and Anderson, 1995; Schoenherr et al., 1996). Later, it binds to the repressor element 1/neuron-restrictive silencer element (RE1/NRSE) site on the DNA and represses preferentially neuronal genes (Bruce et al., 2004; McGann et al., 2021). Hence, NRSF acts via epigenetic mechanisms to silence neuron-specific genes involved in synaptogenesis, synaptic plasticity, and structural remodeling (Singh-Taylor et al., 2018; Paquette et al., 2000; Zhao et al., 2017; Lepagnol-Bestel et al., 2007; Buffolo et al., 2021). In the brain, NRSF levels are low, except early during neuronal differentiation. Interestingly, augmented levels and function of NRSF have been reported after several brain insults during development as well as in the adult (McClelland et al., 2014; Navarrete-Modesto et al., 2019; Carminati et al., 2020; Natali et al., 2023). The findings linking NRSF to the effects of ELA suggest that, similar to the role of NRSF in early-life seizures and adult stroke, this transcriptional repressor might persistently regulate hippocampal gene expression after ELA.

What might be the evolutionary benefit of augmented NRSF actions? Neurons are a high-energy demanding cell type (Vergara et al., 2019) because maintaining a polarized membrane potential as well as cell firing activity are energy costly (Pissadaki and Bolam, 2013; Castrillon et al., 2023; Laughlin et al., 1998). During periods of stress, nutrient deficits, or excessive energy demand (e.g., seizures) (Castrillon et al., 2023; Kagias et al., 2012), cells may choose to reduce the probability of catastrophic energy depletion and death by repressing neuron-specific genes and maintaining cell viability at the cost of loss of function, including of cognitive function (Singh-Taylor et al., 2018; Vergara et al., 2019).

While the authors highlight here their work on specific epigenetic processes, including the role of NRSF, there are clearly additional epigenetic processes including changes in methylation and alteration of glucocorticoid receptor transcriptional functions (Pillai et al., 2018; Daskalakis et al., 2015) that play important roles. Other molecular cascades triggered by ELA may contribute to its effects on memory and other complex brain operations (Peña et al., 2017). Metabolic changes, including micronutrients have also been suggested as a mechanism for the cognitive consequences of ELA (Yam et al., 2015, 2019), as have other factors and processes.

Finally, whereas a majority of studies have focused on the effects of an individual's ELA on cognitive and emotional functions later in life, several groups have tested, both in humans (Duffy et al., 2024; Jawaid et al., 2021) and in experimental animals–the possibility that ELA of one generation might influence cognition and emotion of the subsequent generations, and explored potential underlying mechanisms (Short et al., 2016; Bale, 2015; Bohacek and Mansuy, 2015; Yeshurun et al., 2017; Gapp et al., 2017).

In summary, ELA affects the majority of the world's children, and is associated with lifelong cognitive problems including deficits in learning and memory. However, the causal relation of ELA to poorer memory functions, and the potential mechanisms by which ELA might lead to such problems are very difficult to study in humans. Here, we focus on the use of experimental animals in which ELA can be imposed in a controlled manner, and delineate several of the learning and memory problems directly caused by ELA. We then discuss potential mechanisms for the effects of ELA on the complex maturational processes of the brain. We review structural and functional changes, cognizant of their interactions: e.g., reduction in synaptic activity may influence synaptic developmental and strengthening and vice versa. Similarly, changes in gene expression will influence neuronal activity and, in turn, neuronal activity governs gene expression (Bading et al., 1993). We consider ELA-induced changes at molecular, neuronal and circuit levels, and discuss the emerging roles of non-neuronal cells, including microglia. Notably, many issues remain unresolved: how does ELA interact with the immense genetic diversity? How important is the type of ELA (e.g., McLaughlin & Sheridan (Sheridan and McLaughlin, 2014)), what precisely are sensitive periods to vulnerability and mitigation of the effects of ELA? How do they translate across sex and species (Birnie et al., 2020; Avishai-Eliner et al., 2002), and especially, what is the basis of individual differences that govern vulnerability vs resilience to ELA? These and other remaining questions await research using state-of the art methodologies, to enable a full understanding of the impact of ELA and how to counteract or mitigate its enduring consequences.

CRediT authorship contribution statement

Tallie Z. Baram: Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Matthew T. Birnie:** Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no conflicts.

Data availability

No data was used for the research described in the article.

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