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How Early Life Adversity Influences Defensive Circuitry

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Abstract

Childhood maltreatment increases the likelihood of developing anxiety disorders in humans. Early life adversity (ELA) paradigms in rodents produce lasting increases in avoidant and inhibitory responses to both immediate and nonspecific threats, collectively referred to as defensive behaviors. This approach provides an opportunity to thoroughly investigate the underlying mechanisms, an effort that is currently under way. In this review, we consider the growing literature indicating that ELA alters the rhythmic firing of neurons in brain regions associated with defensive behavior, as well as potential neuronal, glial, and extracellular matrix contributions to functional changes in this circuitry. We also consider how ELA studies in rodents may inform us about both susceptible and resilient outcomes in humans.

Prolonged Postnatal Development in Humans Renders Neural Circuitry Sensitive to ELA

Human brain development is protracted, with considerable maturation occurring for years after birth. Substantial amounts of neurogenesis, synaptogenesis, and gliogenesis, all of which begin during fetal life, continue throughout the postnatal period, as do dendritic and glial process growth and myelination. In addition, cellular events that fine-tune the brain, like cell death, dendritic pruning, and synapse elimination, dominate during postnatal life. The dramatic structural change that characterizes the postnatal period provides opportunities for sculpting brain development to suit the environment and there are many examples of how experience affects development in a positive way. Even seemingly deleterious conditions experienced during early life can have a beneficial effect in terms of preparing the individual for challenging circumstances in the future. For example, some studies have shown that ELA can produce increased resistance to negative outcomes of stress later in life, findings that support the ‘stress inoculation’ hypothesis [1].

It is, however, well known that adverse early life experiences, including abuse and neglect, can predispose individuals to develop neuropsychiatric disease in adulthood [2,3]. Because of this well-established relationship, researchers have sought to investigate the neural circuitry affected by ELA in experimental animals and to investigate which changes are responsible for lasting detrimental effects. Although some animal models of ELA focus on non-human primates [4], the vast majority of studies in this domain use rats and mice (Box 1). Similar to humans, laboratory rats and mice are altricial, undergoing a large amount of

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brain development after birth and thus they are useful models for studying the impact of ELA on brain networks. This review considers how ELA affects the brain and behavior in experimental rodents, taking a top-down approach focused on specific circuitry first, then further discussing neuronal, glial, and some molecular effects that may influence the microcircuitry and contribute to changes in overall network dynamics and defensive behavior.

Brain Circuitry Affected by ELA

Many studies have explored how neural circuitry is affected by ELA in humans using fMRI [5]. The vast majority of related studies in experimental animals have used a region-of-interest approach, with a particular focus on pathways supporting functions believed to be relevant to ELA-induced neuropsychiatric problems in humans. These include circuits involved in rodent laboratory behaviors originally designed to measure ‘anxiety’ and ‘fear’, ‘mood’, and ‘cognition’, given the known links between childhood maltreatment and anxiety disorders, major depressive disorder, and cognitive dysfunction [2,3], respectively, in humans. Because other recent reviews have focused attention on how ELA alters circuitry potentially relevant to depression and cognitive dysfunction [6,7], in this section we review the recent literature about how brain regions involved in behaviors potentially relevant to anxiety regulation in humans are affected.

ELA has been shown to affect behaviors thought to reflect anxiety levels in experimental animals (Box 2). Of the published studies on this topic, the majority have shown that ELA increases anxiety-like behavior [8–10], although some studies have reported contradictory effects. The exact reasons for these discrepancies are, for the most part, unknown, and possibilities have been discussed in a recent commentary [11]. Likewise, studies investigating the effects of ELA on ‘fear/threat’ responses as well as on fear-related learning have shown mostly accelerated development and enhancement of these responses [12–14], but contradictory findings have also been reported [15]. In this section, we review the effects of ELA on the circuitry underlying these behaviors using the umbrella term ‘defensive behaviors’ [16], with the important stipulation that individual behavioral measures under this heading are supported by different microcircuits within the larger network.

Circuits Mediating Defensive Behavior

Connections among the hippocampus, amygdala, and medial prefrontal cortex are known to be activated under reported conditions of anxiety and fear in humans, as well as when defensive behaviors are increased in experimental animals [16]. Since most studies on ELA investigating these brain areas in rodents have not examined connectivity between different areas, we first consider findings from the individual components of this circuitry. Although not typically considered part of this specific circuitry, the anterior cingulate cortex has connections with the amygdala and hippocampus and has been implicated in defensive behaviors thought to reflect ‘anxiety’, like inhibition to enter an illuminated compartment or feeding in a novel environment [17,18], as well as in those thought to reflect both innate and learned aspects of ‘fear’, like freezing in response to a predator odor or after observing a conspecific receiving a shock [19,20]. Thus, we consider the effects of ELA on this structure

as well as the limited information about how connections with other relevant brain regions may be affected (Figure 1). It should be emphasized that focusing on these regions is an oversimplification, as there are numerous connections from other afferent and efferent populations that are likely to play a role, but these have not yet been investigated (to our knowledge) in the context of ELA-associated changes in defensive behavior.

Hippocampus—Humans with a history of childhood maltreatment exhibit reduced activation of the hippocampus in adulthood [5]. The majority of ELA studies using electrophysiological measures of activity in the rodent hippocampus have focused on the examination of synaptic plasticity [i.e., long-term potentiation (LTP) and long-term depression (LTD)]. Studies examining young-adult and aged rodents suggest that ELA results in a decrease in hippocampal LTP [15,21,22]. Hippocampal neuronal oscillations in the theta-frequency range have been linked to self-reported threat/anxiety in adult humans [23] as well as to increased avoidance of the open arms in an elevated plus maze in adult mice [24]. A few studies have looked at the effects of ELA on neuronal oscillations in the hippocampus, including our recent work showing that postnatal stress enhances the power of theta-frequency oscillations in the ventral hippocampus (Figure 1) of awake behaving adult mice in a novel environment [10]. ELA has also been shown to increase theta power in the hippocampus of adult mice during rapid eye movement (REM) sleep [12]. The difference in theta oscillations observed in the adult hippocampus after ELA is not observable around the time of weaning [25], suggesting that this effect becomes evident only after development is complete. These findings point to the existence of lag times in the emergence of the effects of ELA, raising the importance of examining multiple ages to assess ELA's effects on developmental trajectories. Taken together, existing synaptic plasticity and neuronal oscillation findings raise the possibility that ELA may dampen the ability of hippocampal circuits to respond flexibly to changing conditions, while entrenching neuronal populations to fire in synchrony.

Amygdala—Most fMRI studies of adults with a history of childhood maltreatment have shown heightened amygdala reactivity to emotional cues [26,27]. Related findings have been observed in mice using immediate early gene expression as a proxy for neuronal activation; these studies have shown that ELA increases the stress-induced activation of basolateral amygdala neurons during development and in adulthood [28,29]. Electrophysiological studies in rats subjected to ELA have shown that synaptic plasticity (both LTP and LTD) is reduced in the lateral amygdala [30] while neuronal oscillations in the gamma-frequency range have been reported to be increased in awake developing rat pups [31]. Additionally, theta-frequency-range oscillations are increased in the basolateral amygdala of adult rats (Figure 1) while awake [8], as well as during REM sleep [12]. Taken together, these findings raise the possibility that, as suggested above for the hippocampus, ELA may dampen the ability of circuits to respond flexibly to changing conditions, while increasing the probability of neuronal populations firing synchronously.

Medial Prefrontal Cortex—Studies in humans with a history of childhood maltreatment provide an inconsistent picture of how activation of the medial prefrontal cortex is affected, with some reporting hypoactivation [32] and others reporting hyperactivation, particularly

when people are challenged with emotionally charged stimuli [33]. This latter finding is supported by immediate early gene studies in stressexposed adult rats previously subjected to ELA [34]. Studies have reported that ELA impairs synaptic plasticity in the medial prefrontal cortex [35,36], including one that showed a relationship between impaired LTP in the medial prefrontal cortex and failed extinction of a learned contextual defensive behavior [37] and another that showed such a relationship with spontaneous recovery of an extinguished contextual defensive behavior [38]. ELA has also been shown to impair the development of neuronal oscillations in both the theta- and the beta-frequency range (Figure 1) in juvenile rats [25]. The lack of information on how ELA affects neuronal oscillations in the medial prefrontal cortex of adult rodents makes it difficult to draw any firm conclusions. The available data, however, suggest that this brain region shows a slightly different profile than what is observed with ELA effects on the hippocampus and amygdala in that both plasticity measures, like LTP, as well as neuronal oscillations may be diminished.

Hippocampus-Amygdala-Prefrontal Connections—Relatively few studies have looked at the effects of ELA on connections within this circuitry but those that have clearly highlight the need for additional work in this domain. For example, while studies examining synaptic plasticity in the hippocampus, amygdala, and prefrontal cortex have all demonstrated that ELA diminishes synaptic plasticity (LTP and, in some cases, LTD), the few that have looked at connections among these areas have found the opposite. One study found that ELA enhances synaptic plasticity (both LTP and LTD) in the pathway from the amygdala to the dentate gyrus [39] and another found it enhances LTP alone in afferents from the ventral hippocampus to the prefrontal cortex [40]. A few studies have examined ELA effects on resting-state activity under anesthesia (using fMRI) in rodents. One found that connectivity between the basolateral amygdala and the prefrontal cortex is diminished [14], while another reported ‘hyperconnectivity’ among the hippocampus, amygdala, and prefrontal cortex [41]. A recent study demonstrated accelerated development of connectivity in female rats subjected to ELA but no change in males [42]. The exact reasons for these differing findings are unknown but it may be relevant that different paradigms of ELA and different species were examined; the former study used the limited bedding/limited nesting (LB/LN) model during the first two postnatal weeks in rats [14] while the latter two studies used different durations and timings of maternal separation (MS) in mice and rats, respectively [41,42]. Another potentially important difference among these studies is that one examined the entire amygdala [41] while the other two examined the basolateral portion [14,42]. Notwithstanding these differences, examining resting state connectivity under anesthesia and/or conscious restraint has obvious limitations in attempts to understand how circuitry responds to experience. Given evidence from human fMRI studies, as well as from rodent immediate early gene studies, it is highly likely that activity in this circuit differs depending on the stress level at the time of recording. Unfortunately, studies using simultaneous electrophysiological recordings of these brain regions in awake behaving animals after ELA are scarce. One study showed that cross-frequency coupling between the hippocampus and prefrontal cortex is diminished in juvenile rats previously subjected to ELA [25]. Since a causal link between theta rhythm in the ventral hippocampus/medial prefrontal cortex pathway and defensive behavior (avoidance of the open arm in an elevated plus maze) has been established in naïve adult mice using optogenetics [24], it is tempting to

speculate that ELA enhances defensive behavior by altering mechanisms underlying oscillatory coupling in this pathway. More research is needed to determine how network dynamics among the hippocampus, amygdala, and medial prefrontal cortex differ under changing environmental conditions and whether these changes play a causal role in altering defensive behaviors after ELA.

Anterior Cingulate Cortex—Adult humans with a history of early maltreatment show altered resting-state connectivity between the amygdala and anterior cingulate cortex [43–45]. In adult rats, electrophysiology studies have shown that ELA decreases the power of theta in the anterior cingulate (Figure 1) simultaneous with increases in theta power in the amygdala [8], such that coherence between the two brain regions is disrupted. These results are intriguing, particularly because they were obtained from behaviorally characterized rats under awake behaving conditions, and more studies of this sort are needed to fully explore the impact of ELA on the overall circuitry mediating defensive behaviors.

Locus Coeruleus—Tonic activity in the locus coeruleus has been associated with increased anxiety-like behavior, such as increased avoidance of the center of an illuminated open field [46], and increased coherence with the medial prefrontal cortex, which shows increased theta rhythm [47]. Evidence of ELA effects on locus coeruleus activity is limited, but one study reported an increase in tonic activity after MS in adolescent rats [48]. Additional work should clarify whether this effect persists into adulthood and, if so, whether the relationship between locus coeruleus activity and neuronal oscillations in target regions related to defensive behavior is disrupted.

Cellular Factors Influenced by ELA

Numerous studies have examined how ELA impacts brain regions in the above-described circuitry in terms of effects on cells, biochemistry, and gene expression. In this section, we review recent studies investigating ELA's effects on neuronal architecture, both during development and in adulthood, as well as effects on the extracellular matrix and glial cells. A burgeoning literature has been devoted to investigating how ELA influences gene expression in defensive circuitry (Box 3). Epigenetic effects of ELA are likely to contribute to both circuit and cellular effects, but for the most part, the former findings have not been causally linked to changes in defensive behaviors and are not considered extensively in this review.

Neuronal Architecture: Structural Development and Plasticity

In humans, childhood maltreatment has been associated with decreases in the volume or thickness of several regions, including the hippocampus [49], the amygdala [49], the medial prefrontal cortex [50], and the anterior cingulate [51]. In rats and mice, ELA has similar diminishing effects on the volume of the hippocampus, amygdala, prefrontal cortex, and anterior cingulate [52,53].

Studies examining the dendritic architecture after ELA have shown decreased dendritic complexity, length, and/or spines in pyramidal and granule cells in the hippocampus as well as pyramidal cells of the medial prefrontal cortex and anterior cingulate (Figure 2)

[34,35,54-56], consistent with reduced volume of these areas, as is persistently reduced postnatal neurogenesis in the adolescent and adult hippocampus ([57,58] but see [10]).

The impact of ELA on the production of new granule cells in the adult hippocampus has been investigated, with some studies showing continual suppression [59] and others showing no change in cell proliferation and/or the survival of new neurons [10,60]. Despite these contradictory findings, which may result from the use of different species (rat versus mouse) and different paradigms of ELA, it remains possible that alterations in this ongoing form of plasticity represent a mechanism by which developmental stress influences hippocampal function throughout life. Studies have shown that adult neurogenesis is highly sensitive to experience, including stress, with the potential to alter not just the numbers of new neurons but also their connectivity and hence the microcircuitry of the hippocampus [61]. New neurons have been shown to influence hippocampal function, including behaviors that would fall into the realm of defensive [62,63]. Moreover, adult-generated neurons have been shown to influence neuronal oscillations in that they seem to contribute to theta power [64,65] and keep gamma oscillations in check [66]. Taken together, these findings raise the possibility that persistently atypical connections between adult-generated neurons and their targets in the hippocampus may contribute to ELA-induced changes in neuronal oscillations and defensive behavior. This possibility awaits further investigation.

By contrast, studies have reported ELA-induced increases in structural measures that may reflect excessive growth and/or reduced elimination of cells, dendrites, and axons, such as increased dendritic complexity and increased numbers of dendritic spines on pyramidal cells in the basolateral amygdala [14,67], increased numbers of neurons in the medial prefrontal cortex [68], and increased numbers of vasopressinergic fibers in the locus coeruleus [69]. The extent to which ELA-induced changes in dendritic spines and dendritic complexity play a causal role in altered neuronal oscillations and defensive behavior remains unexplored. Despite the lack of evidence linking dendritic structural change to altered neuronal oscillations, some studies have shown that dendritic components, including spines, play important roles in certain types of rhythmic firing in the hippocampus [70,71], raising the possibility that ELA alters defensive behavior through its actions on dendritic structure.

Although the relationship between changes in brain structure and those in neuronal activity remains unknown, these findings provide further evidence for the sensitivity of these circuits to ELA. Future work will be needed to search for both correlational and causal evidence of structural changes influencing circuit-level activity as well as behavioral output.

Studies examining inhibitory interneurons in these regions after ELA have used immunolabeling for interneuron-specific proteins and found evidence for decreased numbers of overall interneurons or of specific interneuron subtypes in the hippocampus, amygdala, and medial prefrontal cortex [10,72–75]. It remains unclear, however, whether these findings represent actual differences in the numbers of these cells or differences in the expression of proteins used to label interneurons (e.g., see [10]). While these results are intriguing, they are far from complete and given that inhibitory interneurons, particularly parvalbumin fast-spiking interneurons, have been linked to the generation of neuronal oscillations [76], further

investigations focused on how ELA changes the structure, biochemistry, and function of these neurons seems warranted.

Extracellular Matrix: Perineuronal Nets

The extracellular matrix has been shown to influence synaptic signaling. In particular, perineuronal nets – specialized extracellular matrix structures that surround specific classes of neurons, mostly inhibitory – have been implicated in neuronal plasticity [77]. ELA reduces perineuronal net formation around inhibitory neurons of the amygdala (Figure 2), reduces inhibitory synapses onto pyramidal neurons, and increases defensive behavior (i.e., avoidance of predator odor) in weanling rats [74]. Furthermore, a causal link between reduced perineuronal net expression in the basolateral amygdala and increased defensive behavior was supported by showing that enzymatic degradation of perineuronal nets in normally reared rats mimicked the effects of ELA [74]. By contrast, ELA has been shown to have an enhancing effect on perineuronal nets surrounding parvalbumin-positive (PV^+) interneurons in the ventral hippocampus (Figure 2) of adult mice [10]. In this case, ELA enhanced defensive behaviors (i.e., behavioral inhibition on the elevated plus maze) and increased perineuronal net intensity, an effect that correlated with increased neuronal oscillations in the theta-frequency range [10]. Given that perineuronal nets may play a role in oscillatory network activity [78], it seems likely that ELA's effects on perineuronal nets, parvalbumin-expressing interneurons, neuronal oscillations, and defensive behavior are causally linked.

In the hippocampus, perineuronal nets surround primarily inhibitory interneurons, which are major targets for dentate gyrus granule cells [79], raising the possibility that ELA-induced increases in perineuronal nets around PV^+ cells [10] reflect altered connectivity between adult-generated granule cells and inhibitory interneurons. Since inhibitory interneurons [76], perineuronal nets [78,80], and adult-generated granule cells [79] have been shown to participate in neuronal oscillations and defensive behavior associated with the hippocampus, altered perineuronal nets may be responsible for important changes in microcircuitry that underlie these effects.

Glial Alterations

Glia participate in neuronal function beyond their role as support cells [81]. In addition to modulating neural transmission through the release of neuroactive molecules by astrocytes and microglia, as well as facilitating neural conduction through the production of myelin by oligodendrocytes, all three major glial cell types have been shown to participate in neuronal oscillations [82–84]. It may be particularly noteworthy that synchronous theta rhythm in the hippocampus and prefrontal cortex seems to require normally functioning astrocytes [85]. Although none of these studies have investigated ELA effects, the links between glia and neuronal oscillations, as well as between neuronal oscillations and defensive behavior, are intriguing. Thus, attempts to gain a comprehensive understanding of how ELA influences neural circuitry requires investigation of its impact on glia. Several studies have done so and although the findings are far from complete, the available evidence suggests that, perhaps unsurprisingly, ELA exerts a differential influence over astrocytes, microglia, and oligodendrocytes (Figure 2). ELA has been shown to decrease astrocyte numbers in the

hippocampus, medial prefrontal cortex, and anterior cingulate [86,87]. By contrast, increases in both the numbers of microglia and the activation of microglia have been observed in the hippocampus and anterior cingulate after ELA [87]. Some evidence suggests that these changes are set in motion during development [86], and given the role of glia not only in regulating synaptic function but also in the development of neural circuits, these changes may be early steps in a cascade of events that lead to functional changes at the circuit level in adulthood. While no studies to date (to our knowledge) have examined changes in astrocytes and microglia after childhood maltreatment in humans, studies have examined effects on measures of white matter integrity and connectivity, and found reductions throughout the brain [88,89] as well as specifically in the prefrontal cortex [90]. Similarly, in rodents, ELA reduces myelination in the medial prefrontal cortex [91], a finding that is likely to be related to ELA-induced accelerated maturation and, consequently, depletion of the oligodendrocyte progenitor pool [92]. These effects on oligodendrocyte development can be mimicked by dampening of neuronal activity in the medial prefrontal cortex of control animals and reversed by enhancing neuronal activity after ELA [92], suggesting that changes in glia and neurons may reciprocally interact to drive changes in neuronal activity within and between brain regions.

Glucocorticoids, Diurnal Rhythms, and Neuronal Oscillations

The role of glucocorticoids in mediating effects of ELA has been considered since the earliest studies of MS in rodents. Although contradictory information exists, studies have shown that ELA paradigms increase corticosterone levels during the ELA exposure time, although the experience occurs during the stress-hyporesponsive period, when there is a high threshold for hypothalamic-pituitary-adrenal (HPA) axis activation [93]. Studies have also shown that the effects of ELA on glucocorticoids extend far beyond the developmental time when pups are being cared for by their mothers. ELA has been shown to alter the diurnal rhythm of glucocorticoids [94] as well as to increase REM sleep duration, and since REM sleep is associated with increased corticosterone levels [12,95], this change is likely to contribute to lasting differences in glucocorticoid exposure. As mentioned above, ELA produces increases in the power of theta rhythm in the hippocampus [10] and amygdala [8] and, although not directly investigated in the context of ELA, stress and glucocorticoids have been shown to increase theta oscillations in the hippocampus in adulthood [95]. Additional evidence suggests that glucocorticoids increase gamma oscillations in the ventral hippocampus [96,97]. Although no available evidence suggests that ELA increases gamma oscillations in the hippocampus, this effect has been observed in the developing amygdala [31]. Furthermore, ELA has been shown to enhance theta-gamma coupling in the ventral hippocampus [10], which may be at least partially related to altered glucocorticoid signaling. It is also worth noting that evidence exists for glucocorticoids influencing other cellular processes affected by ELA, including dendritic architecture [98], postnatal and adult neurogenesis [99,100], and glial morphology and reactivity [101], which may in turn affect neuronal oscillations and defensive behavior.

Concluding Remarks and Future Perspectives

Considerable progress has been made in showing that ELA influences the component brain regions of neural circuitry known to underlie defensive behaviors in experimental animals. Multiple lines of evidence from these studies may be converging on a model whereby heightened defensive behaviors are driven by altered oscillatory activity in relevant brain regions and changes in oscillatory coupling between them. Changes in neuronal oscillations are likely to be undergirded by cellular and molecular mechanisms involving both excitatory and inhibitory neurons, as well as glia. In attempting to understand how ELA affects these circuits fully, the challenge will be to conduct studies that probe the causal role of these mechanisms while simultaneously examining electrophysiological responses in key points of the circuitry in awake behaving animals at multiple life stages (see Outstanding Questions). These types of studies not only have the potential to suggest targets for intervention in humans with a history of childhood maltreatment and suffering from anxiety disorders, but are also likely to increase our understanding of how ELA often produces adaptive responses, which may then guide future studies designed to shift the balance away from dysfunction.

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Box 1.

ELA Paradigms in Rodents

In the USA, the Centers for Disease Control and Prevention defines adverse childhood experiences as traumatic events occurring between the ages of 0 and 17 years, including physical and emotional abuse or neglect, witnessing violence, household instability, and parental separation (https://www.cdc.gov/violenceprevention/childabuseandneglect/). Additional studies have shown that chronic illness in children can produce vulnerability to mental illness similar to what is observed with the abovementioned forms of ELA [102]. In rodents, ELA paradigms involve manipulations that occur prior to weaning, with the most common time period during the first two postnatal weeks. The most frequent approach to inducing ELA involves manipulations in maternal care. One of the earliest developed means to induce ELA is the MS paradigm, which removes the pups from the mother for specific periods of time during the postnatal period. Because researchers using the MS paradigm noted that maternal behavior was altered after reunion with the pups, it was unclear whether any effects on the offspring were the result of the separation or the altered maternal behavior during the intervening periods. In part to address this issue, the LB/LN paradigm was created to induce ELA in the absence of mother-pup separations. It should be noted that the literature using these paradigms is complicated and often contradictory, with MS or LB/LN sometimes producing lasting behavioral effects and other times not [11]. In an attempt to increase the likelihood of observing lasting effects, the MS paradigm has been modified to include early weaning (MSEW) and the MS and LB/LN paradigms have been modified to include exposure to additional stressors later in life [103]. These ‘two-hit’ or ‘multiple-hit’ paradigms have become increasingly popular in research on ELA, as much of this work is targeted toward understanding the link between ELA and behaviors that may be associated with circuitry linked to mental illness in humans. The difficulty in reliably producing lasting detrimental effects with more modest developmental stress exposure may reflect the overwhelming tendency of brains to exhibit adaptive responses to stress. This is particularly true with studies examining ELA effects on female rodents, where negative behavioral changes have been especially difficult to detect. Potential reasons for these sex differences in ELA effects have been discussed in a recent commentary [11]. It is also worth mentioning that because of the aitricial nature of laboratory rats and mice, the first postnatal week of life may be more analogous to late fetal life in humans, raising the possibility that stress manipulations during the second postnatal week and beyond may be a more effective paradigm to model some of the impacts of postnatal adversity exposure in humans [103].

Box 2.

Interpreting Rodent Behavior in the Context of ELA

Much of the research on ELA in rodents has been driven by the motivation to understand brain changes associated with anxiety and mood disorders in humans. Rodent behavioral assays have been widely deployed in this endeavor and findings from such studies are often interpreted as reflecting anxiety, fear, and depression. Given the relative lack of progress in using this approach to develop effective therapies to treat people, the field has been re-evaluating assumptions made in these interpretations and is reorienting toward more accurate descriptions of how rodent behavioral measures relate to human mental processes. The emerging consensus is that since ‘anxiety’, ‘fear’, and ‘depression’ in humans are emotional states involving conscious awareness and complex cognitive function, these terms should not be used to describe more automatic defensive and reward responses that are typically measured in animal studies [16]. Behavioral tasks of ‘anxiety’ typically involve measuring a rodent’s willingness to venture into an open arm on an elevated plus maze, into an unprotected center area in the open field task, or into a brightly illuminated area in the light-dark box, or to eat food in a novel environment. While a low score on each of these tasks is often interpreted as high anxiety, a more accurate descriptor for these tasks would be that they measure ‘behavioral inhibition’. Likewise, tasks that have been thought to measure ‘fear’ often involve measuring freezing behavior, which together with the previously mentioned tasks would be perhaps more accurately described as ‘defensive behaviors’ [16]. Behavioral tests of ‘depression’ are typically either measures of ‘anhedonia’, the most common being decreased consumption of a palatable drink or social avoidance, or measures of ‘behavioral despair’, the most common being how quickly a rodent stops struggling movements in an inescapable swim test. The designation of these tests as measures of depression requires anthropomorphic reasoning, with anhedonia being more accurately described as decreased ‘reward seeking’ and behavioral despair more accurately described as altered ‘stress coping’ [104,105]. Decoupling these rodent laboratory behaviors from clinical descriptors should prevent the overinterpretation of findings, as well as provide more rigorous approaches to identify circuits altered by ELA that contribute to substantial behavioral changes. Anxiolytic and antidepressant drugs known to effectively treat some humans also alter many of the rodent behavioral measures in the expected direction [106,107], which may be encouraging, but it remains the case that these behaviors lack critical features of human anxiety and depression. Even with the acknowledgment that these measures do not address the emotional suffering experienced by humans with mental health problems, these approaches have provided and should continue to provide meaningful insight into how ELA affects the brain.

Box 3.

ELA and Gene Expression Changes in Defensive Circuitry

The possibility that ELA exerts lasting effects on circuitry through changes in gene expression has received considerable attention over the past two decades in both the human and the experimental animal literature. Based on findings that ELA produces dysfunction of the HPA axis, many gene expression studies have focused on specific genes involved in glucocorticoid receptor signaling. These include the glucocorticoid receptor gene nuclear receptor subfamily 3 group C member 1 (NR3C1), the glucocorticoid receptor co-chaperone gene FK506-binding protein (Fkbp5), the corticotropin-releasing hormone gene, and the transcriptional repressor neuron restrictive silencing factor (NRSF) gene along the HPA axis, as well as in the hippocampus and prefrontal cortex given their known glucocorticoid sensitivity and their roles in feedback regulation of the HPA axis [108,109]. Studies have also focused on the expression of genes related to trophic factors such as brain-derived neurotrophic factor (BdNF), as well as those related to numerous neurotransmitter systems, and have reported examples of up- or downregulation of genes depending on the brain region as well as the species, sex, and age of the animal. Epigenetic mechanisms (e.g., DNA methylation and histone modifications of transcription factors or specific genes, which are instigated by ELA and exert numerous downstream influences on the expression of the above-mentioned genes) have been identified in the hippocampus, amygdala, and prefrontal cortex [108–111]. The use of approaches for screening genome-wide transcriptional changes after ELA [111] has greatly expanded our knowledge of how these brain regions are changed. Given this information, the next challenge will be to determine which epigenetic and gene expression changes are crucial elements of the sequence of events that lead to persistently aftered activity in neural circuits and increased defensive behavior.

Highlights

Childhood maltreatment predisposes individuals to develop anxiety disorders. Rodent studies have attempted to model this connection and have shown that early life adversity (ELA) increases defensive behaviors, including responses to immediate and nonspecific threats.

ELA diminishes synaptic plasticity and enhances the rhythmic firing of neurons in brain regions involved in defensive circuitry, including the hippocampus, amygdala, and medial prefrontal cortex. Neuronal oscillations have been causally linked to defensive reactions and their enhancement following ELA is likely to contribute to behavioral change.

ELA-induced changes in excitatory and inhibitory neurons, as well as in glia and perineuronal nets (specialized extracellular matrix structures), have been reported in the aforementioned brain regions. Neurons, glia, and perineuronal nets have been linked to neuronal oscillations, so ELA-induced changes in them are likely to contribute to altered defensive behavior.

Outstanding Questions

How does ELA alter communication among brain regions involved in defensive behavior? A growing body of literature has identified electrophysiological changes in defensive circuitry but relatively little of this information has been obtained from awake behaving animals under different experiential conditions. Such information will be critical for understanding how ELA alters neural circuitry related to coping with stress and novelty.

Which ELA-induced changes in neurons and glia contribute to increases in defensive behavior? A large number of changes in excitatory and inhibitory neurons, as well as in astrocytes, microglia, and oligodendrocytes, have been reported in response to ELA; however, most of this work has been correlational. Studies designed to identify the cellular changes causally linked to alterations in defensive behaviors would be particularly useful for devising strategies for intervention.

How do ELA-induced changes in perineuronal nets contribute to alterations in neuronal oscillations and related changes in defensive behavior? Recent studies have reported evidence of changes in perineuronal nets resulting from ELA and one of these studies has established a causal link between perineuronal net changes and behavior' however, the mechanisms by which perineuronal nets alter the function of this circuitry remain unknown.

What are the primary mechanisms responsible for promoting a resilient phenotype? Most studies on ELA focus on identifying brain changes associated with increased defensive behavior, but many papers have reported examples of no change or a reduction in such behaviors. The identification of protective mechanisms causally linked to the latter two conditions would shed light on individual differences as well as potential targets for interventions.

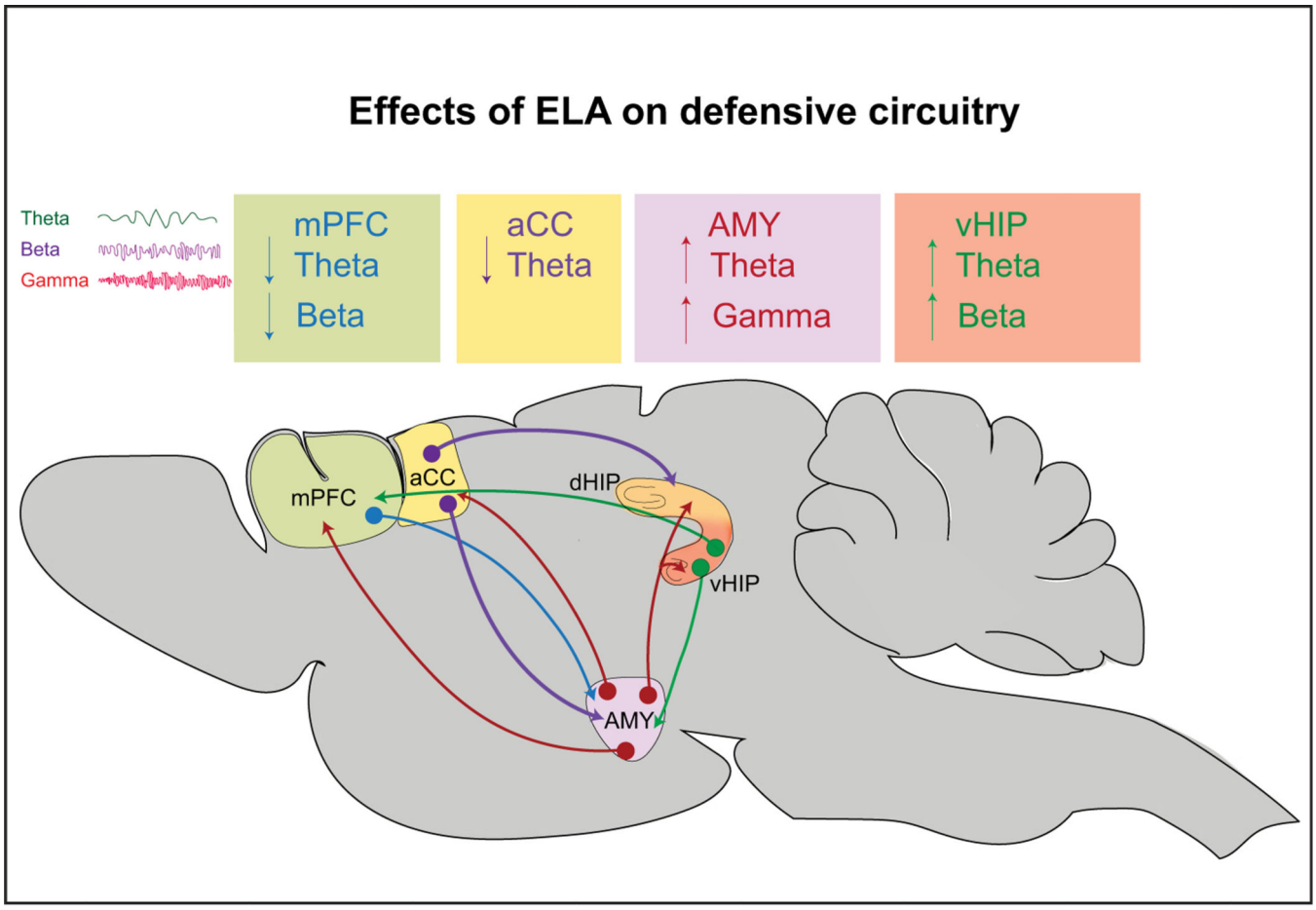

Figure 1. Early Life Adversity (ELA) Alters Neuronal Oscillations in Defensive Circuitry.

Sagittal view of the rodent brain depicting key brain regions in the circuitry underlying behavioral inhibition in response to immediate and nonspecific threats. Arrows depict connections between brain regions. Studies have shown that ELA alters the rhythmic firing of neurons in these areas, with increases in neuronal oscillations in the theta range observed in the ventral hippocampus (vHIP) and amygdala (AMY) and decreases in the anterior cingulate (aCC) and medial prefrontal cortex (mPFC). Theta rhythm has been causally linked to anxious states in humans and avoidance behavior in rodents. While more research is needed, these findings suggest that ELA-induced abnormalities in network activity within as well as between brain regions in this circuitry may be responsible for increased defensive behavior.

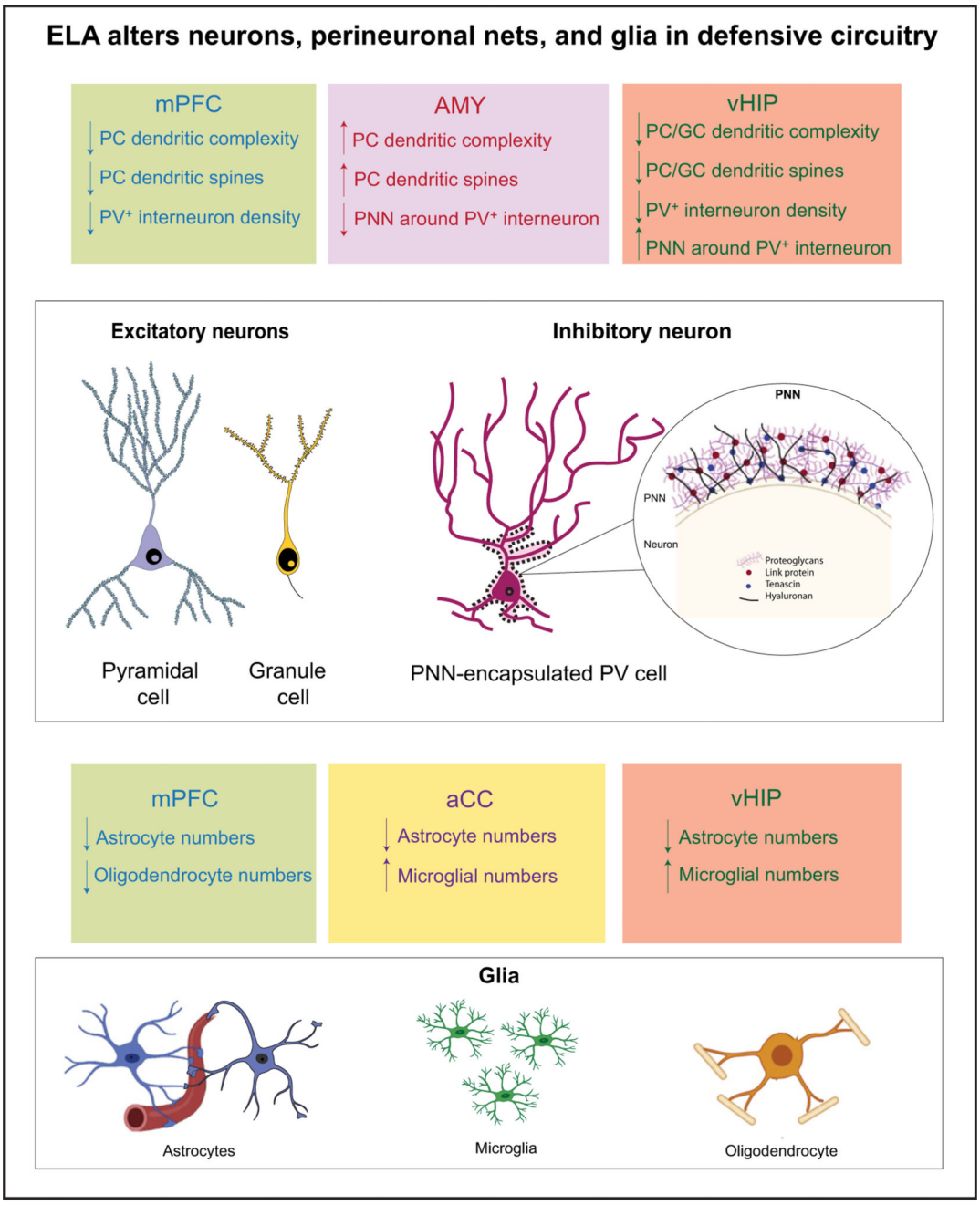

Figure 2. Early Life Adversity (ELA) Alters Neurons, Perineuronal Nets (PNNs), and Glia in Defensive Circuitry.

Summary of region-specific ELA-induced changes in neuronal architecture, PNNs, and glia in brain regions associated with defensive behavior. ELA reduces dendritic complexity and dendritic spines on pyramidal neurons of the medial prefrontal cortex (mPFC) and ventral hippocampus (vHIP) as well as on granule neurons of the latter structure. ELA also reduces parvalbumin-positive (PV^+) interneuron density in the mPFC and vHIP and increases the presence of PNNs surrounding PV^+ interneurons in the vHIP. By contrast, ELA increases dendritic complexity and dendritic spines on pyramidal cells (PCs) of the amygdala (AMY)

while reducing PNNs surrounding PV^+ interneurons in this structure. ELA reduces the numbers of astrocytes and oligodendrocytes in the mPFC and astrocytes in the anterior cingulate cortex (aCC) and vHIP, as well as increasing microglia numbers and microglial reactivity in the aCC and vHIP. Since dendritic spines, PV^+ interneurons, PNNs, astrocytes, microglia, and oligodendrocytes have been linked to neuronal oscillations, each of these elements represents a potential causal link between ELA and altered defensive behavior. Abbreviation: GC, granule cell.