Symposium

Social Origins of Developmental Risk for Mental and Physical Illness

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Adversity in early childhood exerts an enduring impact on mental and physical health, academic achievement, lifetime productivity, and the probability of interfacing with the criminal justice system. More science is needed to understand how the brain is affected by early life stress (ELS), which produces excessive activation of stress response systems broadly throughout the child's body (toxic stress). Our research examines the importance of sex, timing and type of stress exposure, and critical periods for intervention in various brain systems across species. Neglect (the absence of sensitive and responsive caregiving) or disrupted interaction with offspring induces robust, lasting consequences in mice, monkeys, and humans. Complementary assessment of internalizing disorders and brain imaging in children suggests that early adversity can interfere with white matter development in key brain regions, which may increase risk for emotional difficulties in the long term. Neural circuits that are most plastic during ELS exposure in monkeys sustain the greatest change in gene expression, offering a mechanism whereby stress timing might lead to markedly different long-term behaviors. Rodent models reveal that disrupted maternal-infant interactions yield metabolic and behavioral outcomes often differing by sex. Moreover, ELS may further accelerate or delay critical periods of development, which reflect GABA circuit maturation, BDNF, and circadian *Clock* genes. Such factors are associated with several mental disorders and may contribute to a premature closure of plastic windows for intervention following ELS. Together, complementary cross-species studies are elucidating principles of adaptation to adversity in early childhood with molecular, cellular, and whole organism resolution.

Key words: **EEG; foster care; limbic; neglect; parvalbumin; sex-dependent**

Introduction

Decades of basic, developmental, clinical, and epidemiological research demonstrate that adverse childhood experiences contribute to increased risk of poor outcomes in cognitive, social, and emotional functioning, as well as poor physical health in childhood, adolescence, and adulthood (Felitti et al., 1998; Edwards et al., 2003; Anda et al., 2006; Nelson et al., 2014). Yet, data from both cross-sectional and longitudinal studies of human participants are for the most part descriptive and correlational, often including retrospective reporting of adverse life events (Nelson et al., 2016; McEwen and McEwen, 2017).

Evidence from studies of human children now suggests that different types of adversity may have different effects on brain and behavior (Sheridan and McLaughlin, 2014). For example, those exposed to violence or harsh punishment show distinct changes in brain development and stress reactivity compared with those exposed to neglect (Hart and Rubia, 2012). It appears that neglect or deprivation is associated with reductions in cortical thickness, particularly in prefrontal areas involved in complex problem solving, whereas exposure to threat and violence is associated with perturbations in hippocampus and circuits (amygdala-PFC) involved in fear learning. Specific timing of adverse events further impacts the nature of brain development and behavior.

The Bucharest Early Intervention Project represents the first and only randomized controlled trial of a foster care intervention for infants and young children who were exposed to early psychosocial adversity (Zeanah et al., 2003). The study began with an assessment of a large group of young children living in institutions across Bucharest Romania under conditions of neglect. Half of these children were randomized to placement in families living in Bucharest (the Foster Care Group; Smyke et al., 2009); the other half remained in the institutions in which they were living (Care as Usual). Both groups were followed prospectively across childhood and adolescence. The intervention, which included both psychological and material support to the foster families, began at randomization (mean age 22 months) and ended when

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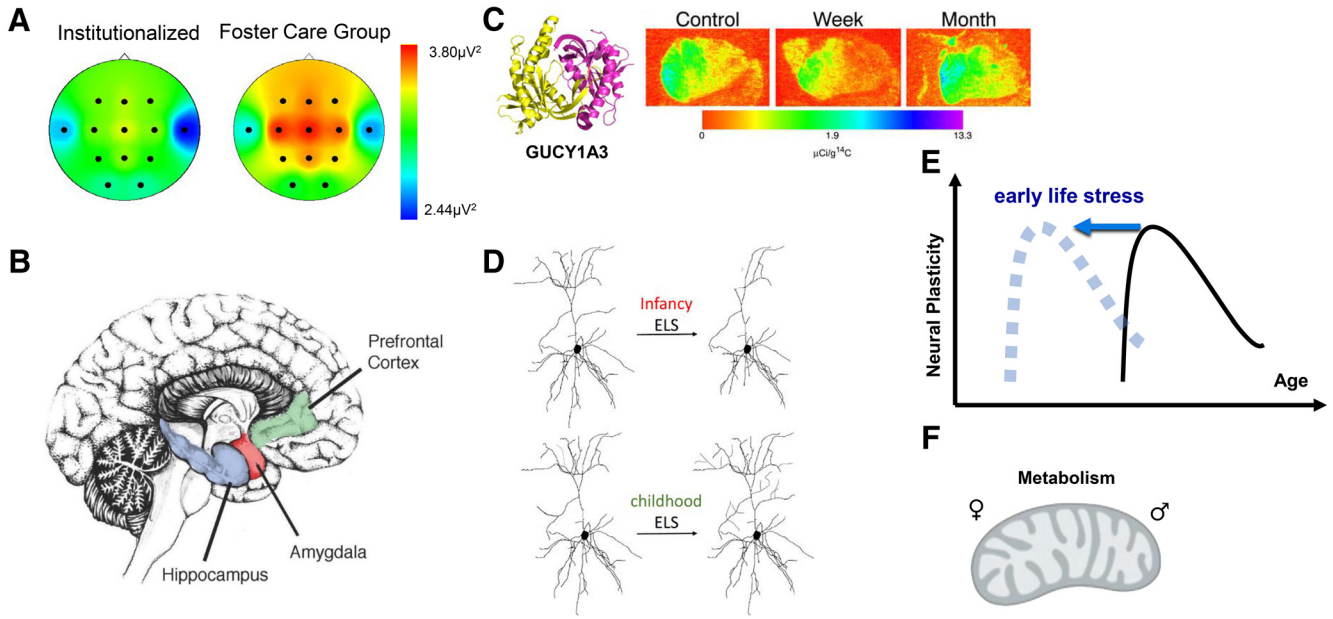

Figure 1. Impact of early life stress across species. ***A***, Analysis of EEG in children randomized for Foster Care, or Care as Usual in the Bucharest Early Intervention Study. There is significant reduction in alpha power in children randomized to Care as Usual in the institution, which reflects a disruption of normal developmental increases in information processing in frontal and central cortical regions (Marshall et al., 2004; Vanderwert et al., 2010). These effects are largely corrected only if foster care begins younger than 24 months of age. ***B***, Limbic structures, which are particularly sensitive to ELS. ***C***, 3D structure of GUCY1A3, and representative pseudocolored images depicting regional amygdala expression of GUCY1A3 mRNA in 3 animals: a control, maternally raised monkey, a week, 1 week separated monkey, and a month, 1 month separated monkey (Sabatini et al., 2007). ***D***, Stress experienced at different developmental stages results in distinct changes in neuronal morphology. Depicted are dendritic arbors of neurons in prefrontal cortex. Early adversity in the form of disrupting infant-maternal interactions results in reduced arbors, whereas disruption later in development generates a paradoxical increase in dendritic growth (Bock et al., 2005; Xie et al., 2013). ***E***, ELS in the first postnatal week results in an accelerated timing of a critical period for limbic circuit plasticity (Callaghan and Richardson, 2011; Bath et al., 2016). ***F***, ELS in the first postnatal week in mice, followed by discovery-based comparative proteomics, yields both increased and decreased expression of specific mitochondrial proteins that are involved in respiration and cellular metabolism. These changes in the hippocampus differ by sex.

a child reached 54 months. At multiple time points, children were assessed across a number of different domains, including cognitive functioning, socio-emotional responses, brain activity (measured with EEG), brain structure and connectivity (measured with MRI), and psychiatric status.

Initial results revealed significant impacts on all domains of functioning in young children who were living in Bucharest institutions. They were significantly delayed in intellect (IQ) (Smyke et al., 2007), had abnormal attachment-like behaviors toward caregivers (Zeanah et al., 2005), displayed significantly reduced EEG alpha power (Marshall et al., 2004) (Fig. 1*A*), and had multiple abnormal psychological behaviors, including stereotypies and aggressive behaviors (Zeanah et al., 2009). EEG alpha power reflects synchronous neural activity that is associated with visual attention and alertness. Low EEG power is consistent with dampened brain metabolism (Buzsaki et al., 2007). This pattern of findings is consonant with a long history of reports regarding effects of institutionalization on infant brain and behavioral development (Nelson et al., 2016).

Postrandomization, children were followed up at 30, 42 and 54 months, as well as at 8 and 12 years of age. Regarding cognitive functioning, children randomized to Foster Care displayed higher IQ scores compared with those remaining in Care as Usual at each of the assessment points. Interestingly, at the early assessments (30, 42, and 54 months), there appeared to be a critical period for the impact of the intervention. Those children placed before 24 months were more likely to have higher scores compared with those randomized thereafter (Nelson et al., 2007). This pattern of intervention and timing effects held true not only for IQ but also for attachment behavior (Smyke et al., 2010) and EEG alpha activity (Fig. 1*A*) (Vanderwert et al., 2010).

At age 12, intervention effects for IQ and EEG alpha activity persisted, but the timing effects were lost (Almas et al., 2016; Vanderwert et al., 2016). Some domains, such as white matter development, psychiatric status, and socio-emotional responding, exhibited intervention effects across assessment points without evidence of timing effects (Humphreys et al., 2015; Bick et al., 2015). Other domains, such as measures of gray matter volume (Sheridan et al., 2012), executive function (Bos et al., 2009), or attention deficit hyperactivity disorder symptoms (Humphreys et al., 2015), showed no signs of an intervention effect. In these latter domains, all children with a history of institutionalization had less gray matter volume, poor executive skills, and heightened symptoms of attention deficit hyperactivity disorder.

Attachment held particular importance for understanding psychiatric outcomes. Children placed into foster homes who established secure attachments with their foster caregivers were less likely to develop such symptoms compared with those who did not. In girls with a history of neglect and internalizing disorders, the development of secure attachments at 42 months fully mediated the effects of intervention (McLaughlin et al., 2012). Subsequently, we determined that caregiving quality (the degree of sensitivity and responsiveness of the caregiver to the child) predicted psychiatric symptoms and degree of psychiatric impairment at 54 months of age. Security of attachment at 42 months was a mediator of this association with a path through secure attachment to reductions in psychopathology at 54 months of age (McGoron et al., 2012).

One overarching mechanism by which early adversity might affect brain and behavior is through the stress response system, influencing at least some aspects of human development. Extensive evidence suggests that caregivers play a critical role in regu-

lating responses to stress in young children. Early regulation, or lack thereof, may have a lasting effect upon stress response system development. To examine this possibility, the stress systems of children in the Bucharest Early Intervention Project were challenged (at age 12) with the Trier Social Stress Test. Those who were randomized to Care as Usual displayed a blunted stress response as measured both by autonomic and hypothalamic-pituitary-adrenal axis reactivity. A blunted stress response is also observed in postinstitutionalized children adopted into United States homes (Gunnar et al., 2009). Instead, children randomized to the Foster Care intervention had more normative responses, and those randomized before 24 months of age were no different from typical community controls of that age (McLaughlin et al., 2015).

This work illustrates the need to understand the effects of early adversity on developmental outcomes, the importance of intervention early in life, and the long-term perturbations by adversity on brain and behavioral development.

Biological impact dependent upon stress timing, neural development state, and poststress parental interaction

Nonhuman primate models have long been used to undertake mechanistic studies of how early life stress (ELS) impacts behavior and brain development, in part because they exhibit many behavioral and physiological characteristics comparable with those of children experiencing ELS. These include increased anxious behaviors, aberrant attachment patterns, and changes in central neurotransmitter levels, including serotonin, norepinephrine, and dopamine, adrenal axis regulation, and social behavior and brain structure in the long term (Harlow and Zimmerman, 1959; Harlow and Suomi, 1974; Suomi et al., 1975; Coplan et al., 1998; Sánchez et al., 2001; Winslow, 2005; Knudsen et al., 2006; O'Connor and Cameron, 2006; Sabatini et al., 2007; Spinelli et al., 2009, 2010; de Campo et al., 2017). We focus here on limbic circuitry (Fig. 1*B*), which is particularly sensitive to ELS.

Impact of the timing of exposure on brain and behavioral responses to stress was explored in a series of studies with monkeys (Knudsen et al., 2006; O'Connor and Cameron, 2006; Sabatini et al., 2007; de Campo et al., 2017). Rhesus macaques were reared from 1 week of age with their mothers in social housing with penmates of various ages and both sexes. The social stress was removal of their mother from the pen environment at either 1 week, 1 month, 3 months, or 6 months of age. Monkeys whose mothers were removed from the social group at 1 week of age initially showed self-comforting behaviors, such as rocking and thumb-sucking, and decreases in social interaction with other monkeys. They later continued to have low levels of social contact and displayed increases in anxious behavior.

In contrast, monkeys whose mothers were removed from the social group at 1 month of age initially showed social withdrawal but soon thereafter exhibited a large increase in seeking social interaction which remained apparent throughout development into adulthood. They showed increased levels of vigilance in response to social cues. Monkeys whose mothers were removed from the social group at 3 months of age showed no significant differences in social behavior from the control group, whose mothers were removed at 6 months of age, an age when female monkeys typically leave their offspring to form consortships with males in the next breeding season. For 1 week and 1 month separated monkeys, behavioral differences persisted stably into adulthood (Knudsen et al., 2006; O'Connor and Cameron, 2006).

We further examined the brains of a second group of monkeys at 3 months of age after separation at 1 week or 1 month of age as described above. Gene microarrays were used to look for differences in transcript expression in the amygdala (Sabatini et al., 2007). This structure is established as having a clear role in social, anxious, and depressive behaviors in the nonhuman primate (Baron-Cohen et al., 2000; Emery et al., 2001; Drevets et al., 2002; Amaral, 2003; Bauman et al., 2004; Etkin et al., 2004; Lorberbaum et al., 2004). Comparing gene expression in the same monkeys in which behavior was carefully characterized throughout development enables a genes-to-behavior approach to directly examine linkages (Nelson et al., 2002).

Guanylate cyclase 1α3 (*GUCY1A3*), the gene that was most differentially expressed between 1 week and 1 or 6 month separated monkeys (Sabatini et al., 2007), showed a strong positive correlation to normal social behaviors, along with a negative correlation to self-comforting behaviors (Fig. 1*C*). Notably in the mouse, knockdown of *GUCY1A3* in the amygdala is associated with increased anxiety (Werner et al., 2004) and also disrupts migration and neurite outgrowth of developing inhibitory neurons (Mandal et al., 2013), key determinants of critical periods of brain plasticity (see below).

Follow-up studies were performed in the para-laminar nucleus of the amygdala, which develops later and would therefore be likely to show altered neuronal maturation genes in response to stress. Indeed, selective downregulation was found there for *tbr1* (de Campo et al., 2017), a transcription factor directing neuroblasts to differentiate into glutamatergic neurons (Hodge et al., 2012). Thus, maternal separation has differential effects on amygdala gene expression reflecting specific trajectories of brain maturation, reinforcing the concept that a circuit's developmental stage contributes essentially to its response to ELS.

Likewise, the ability of an intervention (adoption by an attentive mother) to remediate aberrant behaviors resulting from ELS is also dependent upon the timing of the intervention (Knudsen et al., 2006; O'Connor and Cameron, 2006). One week separated monkeys paired with an experienced mother at 25 d of age displayed completely normal social behavior as they grew up, whereas pairing at 35 d of age only partially restored normal social behavior and those paired at 45 d showed virtually no restoration of normal social behavior (Knudsen et al., 2006; O'Connor and Cameron, 2006). These studies in the monkey provide clear evidence that the timing of stress exposure, or the interventions to remediate it, is a significant factor in determining the long-term consequences of ELS.

Neurobiological signatures of windows of vulnerability

Multiple rodent models have addressed short- or long-term behavioral and neuronal structural changes due to ELS (Walker et al., 2017). Most have focused in adults on changes in emotion regulation, cognition, risk for obesity, immune dysregulation, cardiovascular disease, or cancer. Specific cellular and molecular mechanisms through which ELS influences health remain relatively elementary, with the physiological consequences defined as allostatic load (Ellis and Boyce, 2011; Danese and McEwen, 2012; McEwen et al., 2015). In the brain, region-specific "critical periods" in infancy and childhood are developmental windows of opportunity/vulnerability characterized by high rates of synaptogenesis and synaptic plasticity (Hensch, 2004; Marín, 2016). In both human and animal species, such circuit rewiring occurring early in life imposes long-term effects that persist into adulthood. Ultimately, the proper timing and sequence of these critical periods across brain regions orchestrate the emergence of higher cognitive functions, such as language or sensory integration.

Synaptic pruning is a hallmark of critical period plasticity. This can be quantified physiologically, and anatomically at the

ultrastructural level or by counting dendritic spines on excitatory pyramidal cells of the cerebral cortex. Importantly, the extent and direction of experience-induced synaptic changes in cortical areas correlate with time windows of neuronal as well as endocrine development (Mataga et al., 2004; Elston et al., 2009). Repeated brief maternal separation in newborn rats before a stress hyporesponsive period of the hypothalamic-pituitary-adrenal axis significantly reduces dendritic spine density in layer II/III pyramidal neurons of the prefrontal cortex (Fig. 1*D*). Instead, separation during this hyporesponsive period has no effect and, after this period in young rats, results in spine increase (Fig. 1*D*). In contrast, spine densities in adolescent somatosensory cortex are enhanced independent of the time of separation (Bock et al., 2005), then become persistently unstable due to potentially increased microglial motility (Takatsuru et al., 2009, 2015). Thus, ELS alters the synaptic balance in limbic and sensory cortices in a region-specific manner reflecting maturational stage of endocrine and neuronal systems.

Maternal separation in rodents, however, yields inconsistent results on behavior, which may reflect differences in strain, sex, or reunion response (Moore and Morelli, 1979; Millstein and Holmes, 2007; Mehta and Schmauss, 2011; Savignac et al., 2011). To address this, an alternative limited-bedding paradigm was initially developed in rats (Gilles et al., 1996), obviating the requirement for overt separation of pups and dams typically used in rodent ELS models (Rice et al., 2008; Walker et al., 2017). This paradigm induces inconsistent and fragmented maternal care (Heun-Johnson and Levitt, 2016), which has since been validated and adopted for use with mice by multiple laboratories (Rice et al., 2008; Wang et al., 2011, 2012, 2013; Gunn et al., 2013; Malter Cohen et al., 2013; Liao et al., 2014; Kohl et al., 2015; Naninck et al., 2015; Yang et al., 2015; Arp et al., 2016; Bath et al., 2016, 2017; Liu et al., 2016; McIlwrick et al., 2016, 2017; Yam et al., 2017). The paradigm provides an ethologically relevant framework for addressing heritability of risk-, sex-, and developmentally dependent influences that determine outcomes following ELS. As we detailed by video analyses, changes in both maternal care and pup responses to this environment are complex, with both likely contributing to enduring alterations in brain function (Heun-Johnson and Levitt, 2016).

Cellular analyses in the limited-bedding model to date have focused primarily on neuronal architecture and function. Except for two studies, which report altered astrocyte glutamate transporter function in the hypothalamus (Gunn et al., 2013) and a premature increase in myelin basic protein in the hippocampus (Bath et al., 2016), the involvement of non-neuronal cells has not been studied. Based on their central roles in regulating neuronal development and function, including synaptogenesis (Hong and Stevens, 2016), disruption of non-neuronal cells likely contributes to the long-term effects of ELS on neuronal function and behavioral outcomes. Moreover, recent studies reinforce the concept that the maturational state of neural circuits during development is likely to determine ELS responses.

For example, reduced expression of the *Met* receptor tyrosine kinase, which results in advanced maturation of hippocampal circuits (Qiu et al., 2014; Peng et al., 2016), when combined with ELS, results in hippocampal structural changes that parallel those observed when ELS is administered later in development (H. Heun-Johnson and P.L., unpublished observations). These and other data place an emphasis on measurements that include assessment of developmental trajectories of specific phenotypes after ELS, not simply "end state" outcomes. This experimental approach is valid for brain, behavior, and peripheral organ functions that reflect states of health.

Inhibitory circuit impact and reversibility of early life adversity

Pioneering work in sensory systems has revealed inhibitory interneuron function to be essential for normal critical period timing (Hensch, 2005). When glutamic acid decarboxylase (GAD65), which is responsible for GABA synthesis at axon terminals, is deleted from mice, critical period plasticity for vision (ocular dominance) (Hensch et al., 1998), hearing (tonotopy) (Barkat et al., 2011), or multisensory integration (insula) (Gogolla et al., 2014) is prevented until inhibition is restored, such as by the benzodiazepine agonist, diazepam. Maturation of a specific, local inhibitory network composed of parvalbumin-positive (PV^+) large basket cells derived from the medial ganglionic eminence drives critical period onset (Takesian and Hensch, 2013). Indeed, manipulations of excitatory/inhibitory balance are so powerful that a brain region may be before, during, or past its critical period regardless of chronological age. This finely tuned excitatory/inhibitory balance is highly susceptible to alteration and pathology in cognitive disorders, such as autism and schizophrenia, leading to subsequent mistiming of plastic windows that derail development (Leblanc and Fagiolini, 2011; Do et al., 2015; Marín, 2012).

Fast-spiking PV^+ large basket cells mature at different rates in different brain regions (del Rio et al., 1994; Conde et al., 1996), thereby playing a central role in the proper sequential timing of critical periods (Hensch, 2005). These cells exert temporal control over the information flow to the pyramidal neurons and are gradually surrounded by perineuronal nets (PNNs), which encapsulate the maturing PV-cell body and its proximal neurites. Chondroitin sulfate proteoglycans in the PNN and myelin factors, produced by oligodendrocytes, bind to the Nogo receptor (Dickendesher et al., 2012), which acts in a complex with immune genes to restrict plasticity beyond a critical period (Atwal et al., 2008; Bochner et al., 2014). The best evidence that disruption of the development of PV^+ interneurons and maintenance of their PNNs are pathophysiological targets comes from studies of schizophrenia (Lewis et al., 2012; Do et al., 2015; Marín, 2016).

A key feature of fast-spiking PV^+ cells is their high metabolic demand (Buzsaki et al., 2007), which generates abundant reactive oxygen species. The PNNs serve to protect PV^+ cells from this oxidative stress (Cabungcal et al., 2013). But they can eventually succumb to the damage themselves, resulting in PNN loss and transiently prolonged critical period plasticity (Morishita et al., 2015) that may contribute to circuit instability in the etiology of mental illness (Do et al., 2015). Maternal and perinatal immune challenge (Meyer et al., 2008; Jenkins et al., 2009), parental separation (Brenhouse and Andersen, 2011), and social isolation (Harte et al., 2007; Schiavone et al., 2009) have all been shown to lead to anomalies in hippocampal and/or prefrontal PV^+ circuits.

The impact of ELS on these critical period "triggers" and "brakes" is then of great interest. Factors that may accelerate or delay GABA circuit maturation, such as BDNF (Huang et al., 1999; Bath et al., 2013), *Clock* gene expression (Kobayashi et al., 2015; Marco et al., 2016), Otx2 (Sugiyama et al., 2008; Pena et al., 2017), or the *GUCY1A3* mentioned above (Sabatini et al., 2007), may be vulnerable to ELS, predicting a shift in developmental timing. Indeed, limbic circuits underlying fear extinction are particularly sensitive to ELS (Fig. 1*B*). Both rats (Callaghan and Richardson, 2011) and mice (Bath et al., 2016) after ELS show an accelerated

transition to mature fear memories that are more enduring (Fig. 1*E*). This transition normally reflects in part the emergence of PNNs in the basolateral amygdala (Gogolla et al., 2009), suggesting that an earlier biochemical maturation of PV^+ circuits may underlie the effects of ELS. Thus, not only does ELS deprive the pups of vital caregiver interactions early in life, it may also prematurely limit the extent of critical period windows of opportunity to potentially correct their derailed circuitry.

Sex- and timing-based vulnerabilities of the biological impact of ELS

Emerging evidence points to neurodevelopmental origins of most psychiatric disorders, spanning internalizing and externalizing behaviors (Leonardo and Hen, 2008; Pechtel and Pizzagalli, 2011). Epidemiological data in humans reveal significant differences between females and males in the incidence of psychiatric disorders. In particular, internalizing disorders, such as posttraumatic stress disorder (Kessler et al., 1995), panic disorder, generalized anxiety, and major depressive disorder (Somers et al., 2006; Eaton et al., 2012) are more prevalent in women, whereas men have a higher risk for externalizing disorders, such as attention deficit hyperactivity disorder, substance abuse, autism, and schizophrenia (for review, see Cover et al., 2014). It is likely that ELS will predispose neuronal circuits to internalizing or externalizing disorders in a stress type- and sex-dependent manner (Keyes et al., 2012).

The Virginia twin study of adolescent (age 8–16 years) behavioral development confirmed that girls are more affected by emotional disorders, and boys more in behavioral disorders (Eaves et al., 1997; Simonoff et al., 1997). This suggests a sex-environment interaction in the development of psychiatric disorders. For example, sex differences in anxiety emerge from adolescence, with females more susceptible especially if they have experienced ELS (for review, see Bale and Epperson, 2015). Likewise, we found that ELS in mice predisposes to internalizing or externalizing behaviors in a sex-dependent manner, which may reflect differentially wired inhibitory circuitry in their prefrontal cortex (Z.Y., H.S.K., C.J., and T.K.H., unpublished observations; Holland et al., 2014).

There is considerable evidence that many sex-dependent outcomes to prenatal stressors are mediated by sex-dependent effects on the placenta (Mueller and Bale, 2007, 2008; Goel and Bale, 2009; Bale, 2011; Bronson and Bale, 2014; Howerton and Bale, 2014; Bronson et al., 2017). Recent studies indicate that, even in the absence of placental effects, the early postnatal period represents a distinct developmental window for sex-dependent responses to early life stressors (Kawakami et al., 2007; Coutellier and Würbel, 2009; Kikusui and Mori, 2009; Gross et al., 2012; Kawakami et al., 2013; Naninck et al., 2015; Arp et al., 2016; Fuentes et al., 2016; Lerch et al., 2016; Bath et al., 2017; de Azeredo et al., 2017; Yam et al., 2017). For the most part, the mechanisms underlying sex-dependent outcomes in response to exposure to stressors during this later period are poorly understood.

The application of discovery-based strategies, such as comparative genomic and proteomic profiling of vulnerable circuits, also can guide investigations of mechanisms that underlie how ELS disrupts brain and peripheral organ development and function. Recent application of one such method, isobaric tag for relative and absolute quantitation, on brain tissue isolated at various times in development, inclusive of both sexes, revealed that prominent among a disrupted developmental proteome are proteins involved in ATP production and mitochondrial homeostasis. Although requiring further investigation, the mitochondria-associated protein changes are consistent with temporal and sex influences on cellular responses to ELS during development (Fig. 1*E*) (K.L.E. and P.L., unpublished observations). The findings are aligned with those described by McEwen and colleagues (Picard and McEwen, 2014; Picard et al., 2014, 2015, 2017) following psychosocial stress. Direct measures of mitochondria-associated phenotypes reveal that ELS using the limited bedding paradigm results in sex-dependent adaptations that likely reflect functional short- and longer-term functional changes (K.L.E. and P.L., unpublished observations).

Mitochondrial dysfunction has been associated with a variety of brain-based and peripheral disorders that display a sex bias, including affective disorders (Chang et al., 2015; Klinedinst and Regenold, 2015; Bansal and Kuhad, 2016), diabetes (Koliaki and Roden, 2016; Wanagat and Hevener, 2016), liver disorders (Pessayre, 2007; Serviddio et al., 2008; Grattagliano et al., 2012), and neurodegenerative disorders (Wallace, 1999). Sex differences in mitochondrial function have been reported and are typically associated with levels of circulating gonadal hormones following puberty (Gaignard et al., 2015) and the decline in estrogen and progesterone following menopause (Irwin et al., 2012; Rettberg et al., 2014; Yin et al., 2015).

These may underlie, at least in part, the increased vulnerability of one sex to certain pathological processes. There remains, however, a limited understanding of the developmental origins of sex-dependent mitochondrial dysfunction, which is particularly relevant in the context of neurodevelopmental disorders that manifest before puberty. This is a rich area of investigation in establishing how early adaptive physiological responses to allostatic load result in maladaptive, long-term functions that can have such profound impacts on physical and mental health.

In conclusion, early studies of the long-term effects of ELS or adversity in early childhood, in both animal and human studies, focused primarily on describing a host of behavioral outcomes that were characterized by poorer ability of an individual to adapt to the ever-changing contexts that characterize life, including perturbed attention skills, aggressive behaviors, difficulty with social relationships (i.e., attachment disorders), and difficulty in interpreting the world around them (i.e., increased display of a myriad of anxious and depressive behaviors). The similarity of the behavioral outcomes led to the general belief that experiencing a variety of early life adversities can set an individual on an alternative developmental trajectory that may differ in severity but was characterized by a rather uniform set of behavioral characteristics. However, as science has delved further into mechanistic studies, the specificity of the impact of early life adversities on brain development is becoming apparent. The nature of the adversity, whether it involves abuse, fear, or neglect, matters, and it is likely that as we understand these phenomena better, we will be able to define specific neural circuits that respond to each type of adversity, and differences in sensitivity to long-term alterations in function. The timing of experiencing adversity matters, as neural circuits that are actively developing at the time the stress is experienced are most likely to be affected by the stress. Factors that alter the developmental state of circuits will influence their response to ELS. Periods when neural circuits are plastic and actively developing represent periods of increased sensitivity to the impact of both stress exposure and remediating interventions. The sex of the individual matters. Early life adversities can have sex-specific effects on developing neural circuits. As neuroscience continues to advance in integrating measures across different levels of resolution, we believe that specific outcomes of exposure to early life adversities will become more predictable.

This will provide a clearer understanding of how to effectively intervene to facilitate adaptation that redirects an individual onto a trajectory of more normative development.

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