Early life adversity
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Early life adversity: Lasting consequences for emotional learning

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ABSTRACT

The early postnatal period is a highly sensitive time period for the developing brain, both in humans and rodents. During this time window, exposure to adverse experiences can lasting impact cognitive and emotional development. In this review, we briefly discuss human and rodent studies investigating how exposure to adverse early life conditions – mainly related to quality of parental care – affects brain activity, brain structure, cognition and emotional responses later in life. We discuss the evidence that early life adversity hampers later hippocampal and prefrontal cortex functions, while increasing amygdala activity, and the sensitivity to stressors and emotional behavior later in life. Exposure to early life stress may thus on the one hand promote behavioral adaptation to potentially threatening conditions later in life – at the cost of contextual memory formation in less threatening situations- but may on the other hand also increase the sensitivity to develop stress-related and anxiety disorders in vulnerable individuals.

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1. Introduction

Development of the human brain starts during gestation when large numbers of neural progenitor cells undergo neuronal differentiation (Andersen, 2003; Stiles and Jernigan, 2010). Human brain development continues into adolescence, depending on gender and on the brain region studied (Mills et al., 2014; Giedd et al., 1996; Chung et al., 2002) and alterations in neuronal function and neuronal connectivity further continue throughout life (Stiles and Jernigan, 2010; Arain et al., 2013; Toga et al., 2006; Gogtay et al., 2004). During the early postnatal developmental period, the connectivity in the brain is larger than in adults (Innocenti and Price, 2005; Stiles and Jernigan, 2010; Lopez-Larson et al., 2011) which is later fine-tuned via pruning processes (Stiles and Jernigan, 2010).

The postnatal period is a particularly important and sensitive developmental window. Adverse events during this period — such as physical, sexual or emotional abuse - or being raised in an environment with a low socioeconomic status have been associated with an increased disease probability later in life (Hackman et al., 2010; Carroll et al., 2013). For example, low parental income has been associated with increases in the incidence of early-adult hypertension and arthritis (Ziol-Guest et al., 2012). Similarly, childhood maltreatment and being exposed to bullying is a risk factor for inflammatory disorders later in life (Danese et al., 2007; Copeland et al., 2014; Shirtcliff et al., 2009).

Adverse early life experiences can also have long-lasting effects on brain function, cognitive and emotional development (Teicher and Samson, 2016) and can influence the risk to develop stress-related psychopathology later in life (Kendler et al., 2000). For instance, studies on children raised in orphanages - which were lacking proper social and maternal support — report lasting adverse effects on cognitive function and increased risk for psychiatric disorders (Rutter et al., 2010; Bakermans-Kranenburg et al., 2008; Nelson et al., 2007; Zeanah et al., 2009).

Development of the brain and brain function is therefore not only determined by genetic factors but also by environmental experiences, which can interact via epigenetic programming (Bagot and Meaney, 2010). Long-term effects of these environmental factors are most pronounced when they occur during sensitive developmental periods (Meaney and Ferguson-Smith, 2010). Together, the dynamic nature of the brain’s postnatal development — that is moderated by genetic and environmental factors - enables an individual to optimally adapt to environmental changes, but also renders the brain potentially sensitive to adverse environmental influences.

In this review we briefly discuss human and animal studies that investigated how adverse early life experiences determine brain development, cognition and emotional regulation. We focus on the brain regions that are critical for emotional regulation, such as the prefrontal cortex, amygdala and hippocampus (Izquierdo et al., 2016).

2. Early life adversity and human brain development

Humans grow up in a given socio-economic setting and during this early life period, they are influenced by many factors such as the extent and quality of parental care, cognitive stimulation, nutrition and social and financial status. These factors can interact and affect neurocognitive development (Hackman et al., 2010; Noble et al., 2007). Although results from various studies on how early life environment determines brain structure and brain function are sometimes variable (which may be due to the different developmental trajectories or mediating factors that were investigated; for review see Teicher and Samson, 2016), there is evidence from human studies that early life adversity can affect hippocampal, amygdala and prefrontal cortex volumes and their function (Teicher and Samson, 2016; Teicher et al., 2016).

2.1. Hippocampus

Luby et al. (2013) reported that childhood poverty is associated with smaller hippocampal volumes, which may be moderated by the extent of support from caregivers. The same group reported recently that early maternal support was positively associated with hippocampal volumes (Luby et al., 2016). Smaller hippocampal volumes have been reported in children who suffered from early life stress (Hanson et al., 2015) or after childhood maltreatment (Teicher et al., 2012; Teicher and Samson, 2016). Not only hippocampal structure is sensitive to early life adversity. Liberzon et al. (2015) reported a reduced hippocampal activation following stress exposure in children who were raised in poverty.

2.2. Prefrontal cortex

Early childhood stress and childhood emotional maltreatment have also been related to smaller volumes of the prefrontal cortex (Hanson et al., 2015) and, more specifically, the dorsal medial prefrontal cortex (van Harmelen et al., 2010). In addition, childhood emotional maltreatment is related to enhanced activity in the dorsal medial prefrontal cortex in response to social exclusion (van Harmelen et al., 2014a). Hypo-activation of the medial prefrontal cortex has further been reported during encoding and recognition of words (Van Harmelen et al., 2014b), while less dorsolateral prefrontal activation was found during the processing of emotional faces (Fonzo et al., 2016). Early life adversity has also been correlated with reductions in executive function (Hostinar et al., 2012), and childhood poverty, but not current income, was found to negatively correlate with ventrolateral and dorsolateral prefrontal activity (Kim et al., 2013; Liberzon et al., 2015). Moreover, working memory (Evans and Schamborg, 2009) and individual differences in prefrontal cortex volumes after early life stress have been associated with decreased executive (spatial working memory) function (Hanson et al., 2015).

2.3. Amygdala

Compared to the hippocampus and prefrontal cortex, the amygdala may often respond in an opposite direction; larger amygdala volumes have e.g. been found in children who were raised by mothers who suffered from depressive symptoms (Lupien et al., 2011). By contrast, smaller amygdala volumes were recently found in children raised under conditions of early life stress (Hanson et al., 2015) and in patients suffering from posttraumatic stress-disorder with a history of early life trauma (Veer et al., 2015) and it remains unclear what explains these structural differences.

More consistent findings have been reported when activation of the amygdala is studied after early life adversity. Childhood emotional maltreatment enhances amygdala reactivity in response to emotional faces (Van Harmelen et al., 2013) and during processes of fear and anger, a greater activity of the amygdala has been associated with anxiety symptoms (Fonzo et al., 2016), whereas a failure to suppress amygdala activity has been found during negative emotions (Kim et al., 2013). Finally, enhanced amygdala activation has been found after caregiver deprivation (Maheu et al., 2010; Tottenham et al., 2011) and in conditions of family violence (McCrory et al., 2011).

2.4. Early life adversity: enhanced emotional function in humans

In addition to these structural and functional changes,
3.1. Natural variations in maternal care

When compared to adult offspring from H-LG mothers, adult offspring from L-LG mothers has less complex cells in the hippocampal CA1 area and dentate gyrus (Champagne et al., 2008; Bagot et al., 2009). The dendrites of these cells show fewer spines and the expression of hippocampal synaptic proteins is reduced (Liu et al., 2000). In addition, neurogenesis in the dentate gyrus is affected in these animals. When compared to offspring of H-LG animals, offspring of low-licking grooming animals exhibits reduced survival of newly born cells (Bredy et al., 2003). Functionally, synaptic plasticity in the dorsal part of the dentate gyrus and CA1 area is reduced in L-LG offspring when compared to H-LG offspring (Champagne et al., 2008; Bagot et al., 2009). Even within a litter there are variations in the amount of maternal care that the pups receive and this correlates positively with dendritic complexity and dorsal hippocampal synaptic plasticity later in life (van Hasselt et al., 2012a,b). Less care within a litter is related to less dendritic complexity and reduced synaptic plasticity, at least in males. In line with these structural observations, behavioral studies show that offspring of L-LG mothers displays reduced spatial memory when compared to H-LG offspring (Liu et al., 2000).

Yet, in the ventral hippocampus - the (~20%) part of the hippocampus that has been linked to emotional behavior - neuronal excitability and synaptic potentiation is enhanced in L-LG animals when compared to H-LG animals (Nguyen et al., 2015). Also, when neurons in the dorsal hippocampus of L-LG animals are exposed to stress hormones, synaptic plasticity is enhanced, indicating that these neurons do have the ability to express synaptic plasticity, in particular under conditions that mimic stressful conditions (Champagne et al., 2008; Bagot et al., 2009, 2012). When compared to H-LG animals, learning under stressful conditions such as contextual fear learning (Champagne et al., 2008) is enhanced in L-LG animals and these animals display increased anxiety levels (Weaver et al., 2006; van Hasselt et al., 2012c).

Natural variations in maternal care also affect prefrontal cortex function. Van Hasselt et al. found that individual variations in maternal care correlate with decision making in the Iowa gambling task, a task that critically depends on (among other regions) the prefrontal cortex (van Hasselt et al., 2012c). In this study, H-LG correlated with more beneficial choices during the last trials of this task.
Together, these studies suggest that lower levels of maternal care received during the first postnatal week are later on accompanied by reduced spatial and executive function, but favor emotional learning processes and enhance anxiety (Fig. 1).

3.2. Maternal deprivation

Maternal deprivation, induced by 24 h removal of the dam from the pups increased neurogenesis in males 21 days of age (Oomen et al., 2009), but reduced proliferation of cells in 2 months’ old male rats, and reduced survival and maturation of newborn cells at an adult age (Oomen et al., 2010). No effects on neurogenesis were found in female rats, while the number of granular cells in the dentate gyrus were reduced after maternal deprivation (Oomen et al., 2011). In addition, maternal deprivation slightly reduced complexity of primary dendrites in the rat dentate gyrus without affecting synaptic plasticity in this area in male rats (Oomen et al., 2010). No effects on plasticity were found in female animals (Oomen et al., 2011).

Behaviorally, Morris water maze learning was also found to be impaired after maternal deprivation (Oitzl et al., 2000; Oomen et al., 2010). As reported for animals in which natural variations in maternal care were compared, synaptic plasticity in slices of maternally deprived animals was affected by stress-hormones. Exposure to corticosterone enhanced synaptic plasticity in maternally deprived rats, suggesting a different response of hippocampal networks during exposure to stress. In line with this, contextual fear conditioning was enhanced in maternally deprived male rats (Oomen et al., 2010) while auditory fear conditioning was enhanced in both male and female rats (Oomen et al., 2011).

Also maternal separation, i.e. separating the pups from the dam repeatedly over the first postnatal days has long-lasting effects. It has been reported to enhance anxiety, reduce hippocampal synaptic plasticity and spatial memory performance (Sousa et al., 2014; Cao et al., 2014), reduce performance in the object temporal order memory task (Baudin et al., 2012; Lejeune et al., 2013) and enhance generalization of fear and fear retention (Sampath et al., 2014).

3.3. Limited bedding and nesting material

Limiting the amount of bedding and nesting material from postnatal days 2 – 9 (LBN) results in fragmented care and impacts cognitive and emotional function later in life (Baram et al., 2012). LBN reduced rat hippocampal CA1 dendritic complexity (Brunson et al., 2005) and also reduced the density of spines in mouse hippocampal CA3 pyramidal cells (Wang et al., 2011b, 2013). Moreover, neurogenesis in the mouse dentate gyrus later in life was found to be affected (Naninck et al., 2015). LBN increased neurogenesis (proliferation and differentiation of newborn cells) at P9, but at the long term (P150) the survival of newborn cells as well as the volume of the dentate gyrus were reduced (Naninck et al., 2015). In line with these findings, synaptic plasticity is reduced after LBN in the hippocampal CA1 and CA3 area of middle-aged rats (Brunson et al., 2005). In slightly younger mice, LBN reduced synaptic plasticity in the adult male mouse hippocampal CA3 area (but not hippocampal CA1 area) (Wang et al., 2011b).

Behaviorally, LBN was shown to reduce spatial learning and object recognition memory (Brunson et al., 2005; Rice et al., 2008; Naninck et al., 2015). Interestingly, these effects strongly correlated with altered levels of neurogenesis (Naninck et al., 2015). While hippocampal dependent learning and memory processes were generally hampered, LBN enhanced freezing in male mice in an auditory-fear conditioning paradigm where repeated tones are presented during retrieval twenty four hours after training (Arp et al., 2016). In particular, ELS enhanced freezing between the presentation of the tones. This suggests that being raised in LBN conditions later in life hampers the ability to discriminate between potentially safe (between the tones) and non-safe (exposure to the tones) episodes.

Finally, LBN also strongly affected development of the prefrontal cortex (Yang et al., 2015). Stress exposure during the first postnatal week hampered the development of dendrites in layers II/III and V pyramidal neurons in various subregions of the prefrontal cortex and reduced performance in the temporal order memory task, which assesses prefrontal cortex function (Yang et al., 2015). In these studies, preventing apical dendritic retraction and spine loss in the prefrontal cortex after LBN also prevented impairments in prefrontal cortex-dependent cognitive tasks.

3.4. Early life adversity: towards emotional learning in rodents

Together, these rodent studies indicate that low levels and a fragmented unpredictable nature of maternal care, as well as maternal deprivation and maternal separation are accompanied in general by impaired hippocampal and prefrontal cortex functions, and by impairments in spatial and executive memory processes, whereas fear learning is enhanced (Fig. 1).

4. Early life adversity and stress-responsiveness

There is substantial evidence that early life adversity enhances activation of the hypothalamus-pituitary-adrenal (HPA)-axis and neuronal sensitivity to stress-hormones in a lasting manner (Caldji et al., 1998, 2000; Francis et al., 1999; Stanton et al., 1988). Activation of the HPA-axis results in the release of corticosteroid hormones from the adrenal glands. These hormones bind in the brain

![Fig. 1. Early life adversity changes the balance towards enhanced cognition. Early life adversity hampers several critical measures for higher cognitive function (such as executive function) while enhancing fear learning and activation of the amygdala.](image-url)
to high-affinity mineralocorticoid receptors (MRs) and lower affinity glucocorticoid receptors (GRs) (de Kloet et al., 2005). Substantial evidence indicates that L-LG when compared to H-LG rats exhibit enhanced stress-responsiveness while hippocampal GR and MR levels are reduced (Liu et al., 1997; Champagne et al., 2008). The effects on GR expression may involve epigenetic (methylation) processes (Weaver et al., 2004, 2006; Radtke et al., 2015).

Methylation of specific genes has also been implicated in regulating stress-responsiveness after childhood trauma in humans (Houtepen et al., 2016) and epigenetic regulation of the GR has been correlated with childhood abuse in suicide victims (McGowan et al., 2009). Early life adversity in humans has been linked to an altered sensitivity of GRs for corticosterone (Touma et al., 2011; Klengel et al., 2013). In addition, in rodents, early life experience determines the response of hippocampal synapses to corticosterone (Oomen et al., 2010; Champagne et al., 2008) since maternal deprivation and low levels of maternal care enhance hippocampal synaptic plasticity in the presence of stress-hormones.

These studies may hint to therapeutic options that could focus on targeting stress-hormones for the treatment or prevention of behavioral phenotypes after early life adversity. In line with this, Arp et al. (2016) reported that in mice that were raised under conditions of fragmented care, the increase in adult freezing behavior in a fear conditioning paradigm could be overcome by targeting GRs at adolescent age, i.e. weeks after the actual exposure to early life adversity but months before the behavioral testing (Arp et al., 2016).

Also Corticotropin Releasing Hormone (CRH) is an important mediator of early life adversity and potential target in this respect. In several studies, genetic deletion of CRH-R1 receptor (CRH-R1), or pharmacologically targeting of CRH-R1, has been reported to prevent the effects of early life adversity (Wang et al., 2011a,b, 2013; Yang et al., 2015).

5. Outstanding questions

5.1. Which neurocircuitry underlies the enhanced emotional behaviors seen after early life adversity?

Early life adversity has been reported to alter functional connectivity between brain areas involved in emotional regulation (Birn et al., 2014; Herrlinga et al., 2013; Gee et al., 2013). Yet, exactly how this connectivity alters over time and whether it contributes to enhanced emotional behavior after early life adversity remains elusive. Optogenetic or chemogenetic tools (e.g. using DREADDs (Designer Receptors Exclusively Activated by Designer Drugs)) are now available an allow highly specific control of the activity of selective neuronal populations and their networks in brain areas. This may help to understand changes in functional connectivity between brain areas in controlling emotional regulation after early life adversity. In such studies, it will be of great interest to investigate effects of early life stress on the ability to discriminate between potentially safe and harmful contexts.

5.2. What is the cellular and molecular substrate that determines enhanced emotional behavior after early life adversity?

Activity-dependent changes in synaptic connectivity underlie learning and memory processes (Rumpel et al., 2005; Kessels and Malinow, 2009; Nabavi et al., 2014). In order to examine whether such changes underlie altered fear behavior after early life adversity, viral vectors can be used to target synaptic functions in prefrontal cortex, hippocampus and amygdala (Wang et al., 2011a).

Recent studies have demonstrated a role of so-called ‘engram’ cells in emotional memory formation (Liu et al., 2012; Redondo et al., 2014). Capturing these sparsely distributed cells during critical periods of early life adversity and fear learning (acquisition, consolidation, retrieval) will enhance our understanding of how networks and memory traces later in life are modified by early life adversity (Mayford and Reijmers, 2015; Gouty-Colomer et al., 2016). Molecular and electrophysiological tools can then be applied to identify and dissect the molecular, epigenetic and functional profile of these neurons. Using intervention studies, the causal role of these neurons and their properties (e.g. synaptic function, the (epi)genetic factors) in the effects of early life adversity on cognition can be studied.

5.3. Which factors contribute to individual variability?

An important question is why some individuals are sensitive to develop stress-related disorders, while others – which were exposed to similar adverse conditions – appear to be resilient. This requires detailed understanding of interaction between early life experiences and factors that contribute to vulnerability or resilience, such as function of GRs (Klengel et al., 2013) and MRs (Kuningas et al., 2007; Klok et al., 2015; Otte et al., 2015; Kanatsou et al., 2015), but also other genes (Caspi et al., 2003), and how they interact with the circuitry that underlies e.g. fear behavior. Preferably, these investigations are carried out in a (epi)genome-wide unbiased manner (Schraut et al., 2014; Houtepen et al., 2016).

5.4. Understanding gender differences in the effects of early life adversity

Evidence suggest gender differences in the risk to develop stress-related psychopathology. It will therefore be important to understand why – in general – females are more prone to develop pathologies. In an interesting recent paper, Loi et al. (2015) suggested that male and female mice with a history of early life adversity respond comparable in anxiety-related tasks, while hippocampal function is relatively less sensitive to early life adversity in females (Loi et al., 2015). Yet, the nature of gender differences in sensitivity to early life adversity deserves further attention.

5.5. Early life adversity and age-related cognitive alterations

Several studies indicate that stress responsiveness correlates with cognitive decline during aging and the progression of Alzheimer’s pathology (Davis et al., 1986; Masugi et al., 1989). Since the activity of the HPA-axis is determined by early life adversity, it will be important to investigate whether and how early life experience determines the progression of age-related cognitive decline and in particular Alzheimer’s Disease. Preliminary data indicates that this is relevant since early life adversity affects overall survival and amyloid levels in transgenic Alzheimer mice (Lesuis et al., 2016) and may modify inflammatory responses as well (Hoeijmakers et al., 2016).

5.6. Can the effects of early life adversity on cognition and emotional behavior be targeted?

i. Preliminary data suggests that targeting GRs and CRH can be effective in preventing later effects of early life adversity on cognitive function (Arp et al., 2016; Wang et al., 2011a,b, 2013). Future studies will be required to investigate in detail the optimal time windows for such interventions or treatments, and the role of gender.

ii. Raising rodents in enriched environments generally enhances brain function and cognition. Also in humans, cognitive stimulation has beneficial effects on cognition,
which may be related to increasing cognitive reserve (Barulli and Stern, 2013). It will therefore be important to investigate whether increasing cognitive abilities can prevent/or overcome the effects of early life adversity on executive function and emotional behavior.

iii. The notion that emotional memories become labile after retrieval, has stimulated researchers to investigate whether emotional responsiveness can be targeted by interfering with the process of reconsolidation (Nader et al., 2000; Monfils et al., 2009; Kindt et al., 2009; Schiller et al., 2010). It will be important to determine the boundary conditions that are required to reduce enhanced fear expression after early life adversity and interesting to investigate whether this window of “lability” can be used to reduce the expression of fear and

iv. Finally, recent early nutrition based interventions have become of interest as a potential lead to prevent the detrimental consequences of early life adversity (Lucassen et al., 2013; Naninck et al., 2011, 2016; Yam et al., 2015).

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