The Effects of Early Life Stress on Brain Development: Implications for Psychopathology

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The Effects of Early Life Stress on Brain Development: Implications for Psychopathology

Submitted by Katarina Salander to the University of Skövde as a final year project towards the degree of B.Sc. in the School of Humanities and Informatics. The project has been supervised by Monica Bergman.

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I hereby certify that all material in this final year project which is not my own work has been identified and that no work is included for which a degree has already been conferred on me.

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Abstract

Several studies have shown that children who grow up under adverse care giving conditions are prone to develop a broad spectrum of different problems, ranging from mild depression to severe psychosomatic pathology later in life. A carefully treated child develops a different attachment strategy and biochemical response than a maltreated child. Early adverse events seem to program the stress response to become either over or under reactive which in turn have the potential to alter brain development. Major consequences include reduced plasticity and abnormal frontal lobe activity. This review further investigates the emotional and cognitive development in children exposed to early life abuse or neglect, trying to get a comprehensive picture of different symptoms that might contribute to later psychopathology.

Keywords: Stress, Brain development, HPA axis, Maltreatment, Psychopathology, The self
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## Glossary

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<th>Concept</th>
<th>Abbreviation</th>
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<tr>
<td>Adrenocorticotrophin hormone</td>
<td>ACTH</td>
<td>Hormone produced by the pituitary gland in response to stress which regulates the secretion of certain hormones by the adrenal glands.</td>
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<tr>
<td>Brain derived neurotrophic factor</td>
<td>BDNF</td>
<td>Protein found in the central nervous system and the peripheral nervous system that influence brain growth by supporting survival of existing neurons and promote growth and differentiation of new neurons and synapses.</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>CORT</td>
<td>The primary glucocorticoids in rodents that regulates the stress response.</td>
</tr>
<tr>
<td>Corticotrophin releasing hormone</td>
<td>CRH</td>
<td>Hormone and a neurotransmitter released by the hypothalamus in response to stress.</td>
</tr>
<tr>
<td>Electroencephalography</td>
<td>EEG</td>
<td>A method to register the electrical activity of the brain.</td>
</tr>
<tr>
<td>Glucocorticoid receptors</td>
<td>GR</td>
<td>Receptors in the brain that glucocorticoids bind to with low affinity.</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>GC</td>
<td>A class of steroid hormones that is produced in the adrenal gland. Cortisol is the major glucocorticoids in humans.</td>
</tr>
<tr>
<td>Hypothalamus/pituitary/adrenal axis</td>
<td>HPA axis</td>
<td>A complex interaction/feedback between the hypothalamus, the pituitary and the adrenal glands that regulates the reaction to stress.</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>MRI</td>
<td>An imaging technique to visualize the structure of an organ.</td>
</tr>
<tr>
<td>Mineralocorticoid receptors</td>
<td>MR</td>
<td>Receptors in the brain that glucocorticoids bind to with high affinity.</td>
</tr>
<tr>
<td>Nerve growth factor</td>
<td>NGF</td>
<td>A protein that is required for development of certain neurons, axon growth and for initiating new connections between the neurons.</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>OT</td>
<td>A hormone that is stored and secreted by the pituitary gland. It is released by bodily contact and promotes the development of the brain, especially in infants.</td>
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<tr>
<td>Term</td>
<td>Abbreviation</td>
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</tr>
<tr>
<td>Prefrontal cortex</td>
<td>PFC</td>
<td>The frontal part of the brain that takes care of the higher aspects of motor control and the planning and execution of behavior, especially tasks that require the integration of information over time and thus working memory mechanisms.</td>
</tr>
<tr>
<td>Representations of interactions that have been generalized</td>
<td>RIGS</td>
<td>A concept created by Daniel Stern that refers to internal cognitive working models which represents an individual’s early experiences and serve as a guiding function in future situations. They are formed during early childhood and are active throughout life.</td>
</tr>
<tr>
<td>Stress-hyporesponsive period</td>
<td>SHRP</td>
<td>A certain time window in rodents where a quiescence of the stress system is crucial for a normal development of the brain circuitry and where prolonged stress response activation is only restored to under severe stress.</td>
</tr>
<tr>
<td>Sympathetic nervous system</td>
<td>SNS</td>
<td>Part of the autonomic nervous system that becomes activated during times of stress to facilitate the fight and flight response.</td>
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1. Introduction

For a long time it has been observed that several individuals showing signs of a wide range of different psychopathologies or deviating social behaviors have experienced a past history of childhood maltreatment including neglect, physical abuse or sexual abuse. More specifically, child neglect and abuse are correlated with increased prevalence of public health problems, violence, delinquency, mental health disorders, substance abuse, obesity, suicide and teen pregnancy (Hagele, 2005). The apparent link between child maltreatment and later morbidity or deviant negative behaviors is important to unravel for various reasons. To begin with the perpetrators of neglect and abuse are profoundly damaged people who themselves have been neglected or abused. Thus with a greater insight of how the different outcomes arise, the bad circle of past on negative behaviors could finally come to an end. Further it could be hypothesized that maltreatment and its consequences substantially consumes the society’s resources. In addition to healthcare costs, reside large expenses across for example educational support, delinquency and criminal justice (Hagele, 2005). With better knowledge of how mental or behavioral disturbances in connection to adverse care come about it is possible to develop prevention programs, therapies or medicines directed towards the children and their families at an early stage and thus promote healthy mental and physical development. These strategies could thus lead to decreased costs for the society in the long run. Last but not least, progress within this area of research would make it possible to prevent or diminish the suffering and pain for those children and adults that have been exposed to an adverse childhood.

Cognitive neuroscience is an extensive scientific field seeking to understand how the brain and the mind work. The progress of brain imaging techniques within this field have unraveled puzzles of the amazing formable brain and how it produces behavior.
Research on the association between childhood maltreatment and brain development is a relatively new area of inquiry. What has been found is that the brain is exceedingly influenced by the external environment especially during development when the first connections between the neurons are made. It has also been shown that there exists an abundance of neuronal connections already at birth. Only the connections that will be used are maintained whereas the remaining connections become distinguished, a process referred to as synaptic pruning.

How the long-term effect of early adversity occurs is not fully known yet but accumulating evidence indicates that the influence of stress hormones is an important determinant (De Kloet, Sibug, Helmerhorst & Schmidt, 2005). Studies have found that changes in the activity of the stress response and the deleterious effects of prolonged exposure to stress hormones are associated with diseased states and deviant behaviors. Emotional stress experienced in early childhood can give rise to severe changes in the developing central nervous system to such a degree that it’s considered increasing the risk for developing different psychopathologies.

This review will seek to comprehend how childhood maltreatment can affect the child’s developing brain, emotion and cognition which further has the potential to lead to diverse symptoms common in different psychopathologies. The focus has been put on the post-natal development in order to limit the extent of the essay even though it is well known that also during the pregnancy the fetus’s brain is influenced by the stress hormone levels of the mother which also have the potential to affect the brain, attachment development and later behavior. Further the review will mainly focus on underlying fundamental biological mechanisms of how the morbidity and deviant behavior occurs.

To make the text easier to understand a glossary with the utilized abbreviations has been established in the beginning of the essay.
This review will begin with elucidating how important the early family environment, mainly constituted by the closest relationships, and in particular the mother is for the developing infant. A carefully treated infant develop a different attachment strategy and biochemical responses than a maltreated infant. Early adverse events seem to program the stress response to become either over or under reactive which in turn has the potential to alter brain structure and function. Further the underlying mechanism mediating this alteration of the stress response will be examined. The second part summarizes some of the most fundamental effects the stress hormones have on the developing brain. This includes different structural changes in important brain areas that also control different emotional and cognitive processes. Early stress also seem to alter brain functioning. Abnormal electrical activity in the right frontal lobe is a common discovery in children and adults with a history of maltreatment. Further analysis of the underlying mechanism for how the structural and functional alterations come about is undertaken. The last part of the review examines the behavior that deprived children present. Stress hormones are able to form implicit emotional memories through fear conditioning which may influence the individual later in life. Whereas stress seems to enhance the emotional memory other memory domains are impaired. The review is summed up by a discussion containing conclusions and additional reflections around the topic and suggestions for further research.

2. The early family environment

Plasticity refers to the brains lifelong ability to undergo structural and functional adjustments to change in the external or internal milieu (Cirulli, Barry & Alleva, 2003). The brain shows the greatest plasticity during early development when the connections are made for the first time. Neuronal connections are created, strengthened and maintained during experience (Cirulli et al., 2003). There are many aspects of the early environment that can
influence the development of the infant’s brain and one of the most important one’s is the early social interaction, especially with the mother but also with the closest caregivers since they provide a rich source for different experiences.

The mother or primary caregiver plays a crucial role in an infant’s neurobiological, emotional and psychological development. One person known to have emphasized and hypothesized about this important role is John Bowlby. During the 1950’s he started to develop what would later become the acknowledged attachment theory (Bowlby, 1969). Simply explained attachment theory implies that infants are biologically prepared to attach to their primary care givers, usually the parents since this serves the evolutionary function by protecting the infant from danger and promote survival. In the beginning the infant is socially promiscuous but after a couple of months develops certain preferences to its primary care givers. Around the age of one the child has established a specific attachment behavior to them. It seems like the child seeks the parents presence when they get stressed and use them as “safe havens” when they explore new environments. Depending of what kind of circumstances for example maltreatment, long separations or loss of an attachment figure the infant can develop an insecure attachment which will continue to influence the child´s interpersonal orientation throughout life (Bowlby, 1969).

Further Mary Ainsworth, advanced Bowlby´s attachment theory by distinguishing between different attachments strategies. She identified them as secure attachment, insecure/ambivalent attachment and insecure/avoidant attachment and those where depending on the child’s behavior towards the parent by the age of one during exposure to a mild stressor, the so called strange situation (Ainsworth, 1969). Ainsworth (1969) also showed that the attachment style was related to the parent’s sensitivity and responsiveness to the child’s signals during the first year of life.
The secure and insecure attachments seem to be mediated by two different neurobiological responsive systems. The secure attachment which emanates from a sensitive and responsive mother appears in part to be mediated by the oxytocin response system (Uvnäs-Moberg, 1998). However if the mother are hostile or for the most part neglectful towards the child an insecure attachment arise which mainly have shown to be mediated by the stress response system. This chapter shall further immerse in how these two response systems work and are implemented. The stress response is explained in detail to clarify how the stress reaction affects the body and in particular the central nervous system. Early prolonged stress seems to program the stress response to become either over or under reactive which in turn has become a biological marker for psychopathologies. Further investigation of how this alteration of the stress response might come about is elucidated.

2.1 Oxytocin response system

Positive social relationships and support have frequently been associated with health (Reblin & Uchino, 2008). The neuropeptide Oxytocin (OT) also have strong connections to positive social behaviors, and it is likely that the protective effects of social bonds might in part be mediated through the physiological actions of this chemical compound (Uvnäs-Moberg, 1998). Several aspects of the mother-infant interaction can influence OT and its receptors during development. Such experiences have the potential to reorganize brain function and behavior. When an infant is gently held, touched, made eye contact with or breast-fed, behaviors that have been described as mediating a secure attachment, secretion of OT is induced in the infant as well as the mother (Uvnäs-Moberg, 1998). Secretion of OT promotes the brain’s growth especially when it comes to young children. OT has a host of functions in the human body and the potential to influence several systems, including the cardiovascular, immune and reproductive systems (Uvnäs-Moberg, 1998). In addition it is
also possible that OT might dampen the stress activity. For instance rats that are centrally injected with OT dampen their stress activity and anxiety behavior to stressors (Windle, Shanks, Lightman & Ingram, 1997) and women who receive intravenous infusion of OT during childbirth significantly decreases their stress hormones concentrations (Izzo et al., 1999).

Early experience of high levels of maternal stimulation such as maternal licking and grooming might up regulate OT gene expression in rats and thus be important for both later behavior and stress reactivity (Champagne, Diorio, Sharma & Meaney, 2001).

In sum it seems like the activation of the OT response system has many favorable consequences for the child as it produces long-term changes in the brain and behavior. The mother is an important source of regulation of the OT response system and by gentle and active behavior towards the child she can enhance the secretion of this neuropeptide. By activation of the OT system at an early age, increases the brain´s ability to produce and absorb this neuropeptide later in life and thus also increase the ability to cope with stress later in life. However if the mother are not able to produce this response in the child by being responsive and caring it could lead to that the child´s stress system will be activated instead.

2.2. The stress response system

The stress response in organisms has for several decades been monitored by measuring the activity in the sympathetic nervous system (SNS) and the hypothalamic/pituitary/adrenal (HPA) axis (de Kloet et al., 2005). Both SNS and the HPA axis are organized by hypothalamus (Lupien, Maheu, Tu, Fiocco & Schramek, 2007). When an organism is exposed to a stressor hypothalamus sends neural impulses via SNS which activates various organs and smooth muscles. The stimulation of SNS further signals the adrenal medulla to release adrenaline into the bloodstream. Adrenaline affects the brain through the vagus nerve
since it is difficult for adrenaline to cross the blood-brain barrier. The most important structure containing the most adrenergic receptors is amygdala.

The HPA axis reacts somewhat slower than SNS. Hypothalamus releases the chemical compound corticotrophin releasing hormone (CRH) into the bloodstream at the same time as the organism is exposed to a stressor. On reaching the pituitary gland also located in the brain, CRH triggers a subsequent secretion of another hormone called adrenocorticotrophin (ACTH). ACTH travels with the blood and reaches the adrenal glands located above the kidneys and initiates the secretion of glucocorticoids (GC), among them is the hormone cortisol in humans and non-human primates and corticosterone (CORT) in rodents.

The combined effect of the various stress hormones carried via the blood stream and the neural activity in the SNS alters the physiology of the body by for example increasing heart rate, breath frequency, muscle tension and blood pressure. These physiological changes form the basic conditions for the organism to effectively act by solving, fighting or fleeing demanding or dangerous situations.

GC have a variety of effects on different systems in the organism which taken together can be summarized as aiming to increase the availability of energy substrates and allow for optimal adaptations to changing conditions in the environment (Lupien et al., 2007). Activation of the HPA axis can be regarded as a basic adaptive mechanism in response to change but prolonged exposure of stress hormones has shown to strain several biological systems in the body and exert deleterious effects especially on the CNS (McEwen, 1998). GC can cross the blood-brain barrier and affect the brain by binding to receptors. The three most important brain areas containing GC receptors are hippocampus, amygdala and prefrontal cortex (PFC) which are brain structures playing an important role in mood, cognition and behavior (Lupien et al., 2007).
The brain also holds a negative feedback system to avoid the negative effect by GC that works at several levels of the HPA axis (Susman, 2006). When GC secretion reaches a certain level hypothalamus and the pituitary reduce their production of CRH and ACTH so that the system can return to a homeostatic state. The set point for the inhibiting effect on GC varies between individuals and may be too high resulting in absence of a rapid termination of the stress response or low resulting in prevention of activation in threatening situations (Susman, 2006).

2.2.1 Stress shapes the stress response

The pioneering work of Levin (1957) has clearly demonstrated that stimulation during infancy have long-term effects on the neuroendocrine system. Handled rodents, which signify a brief daily removal of the pup until weaning from the dam during infancy show when tested as adults higher levels of GC and a more rapid return to basal levels in contrast to pups that continuously have spent their time with the mothers, completely undisturbed, also referred to as non handled subjects, which show a much slower rise and a higher peak of the stress hormones when exposed to stressors as adults (Levine, 1957). The majority of studies have used the non handled subjects as controls in their experiments but it is still under debate whether this condition actually represents the proper control. Today there is more common to use the handled subjects as controls. This might in part explain the diverging evidence that have originated from this field of research. Looking at the outcome of the handling paradigm have even caused some researchers’ to suggest that mild stressors acts as a physiological stimulation and are necessary for normal neural development (Fumagalli, Molteni, Racagni & Riva, 2007). However there exists one important difference between those factors. Handling leads to an alteration in the maternal behavior. Mothers of handled pups show significant more time licking the offspring and performing arched back nursing compared to non
handled animals (Pryce, Bettchen & Feldon, 2001). Further, if animals get exposed to 3 hours daily separations from the dam during their first 3 weeks of life, thus a prolonged maternal separation, a significant increased HPA axis activity have been observed (Aisa, Tordera, Lasheras, Del Rio & Ramirez, 2007). Thus it seems like the dam has a buffering effect on the pups stress response. This experimental setup represents a laboratory model for neglect.

Further studies on this topic suggests that there exist a time period around postnatal day 4-14 in rodents when it is very difficult to elicit an adrenocortical response to stimuli which are able to elicit a strong response in the adult animal (Rosenfeld, Suchecki & Levine, 1992). This period of low stress system activity is known as the stress-hyporesponsive period (SHRP) and has also been suggested to be mediated by appropriate levels of maternal care such as feeding, licking and grooming. If the source of regulation, the mother is removed the pup’s HPA axis is not buffered and releases high levels of stress hormones (Rosenfeld et al., 1992).

Whether humans also exhibits such SHRP remains controversial but it has been proposed that a functionally equivalent period gradually may emerge over the first year of life but it is unclear yet however how long it extends (Gunnar & Donzella, 2002). At birth, healthy human infants exhibit a highly reactive adrenocortical response to stressors but by the age of 12-18 months exposure to mild challenges, such as approach by a stranger or novel environments, doesn’t result in elevated cortisol levels even though a behavioral response can be observed (Spangler & Schieche, 1998). Further it has been shown that 18 month olds who withdrew from strange events and sought comfort with their mothers only exhibited an increase of cortisol if the attachment were insecure (Nachmias, Gunnar, Mangelsdorf, Parritz & Buss, 1996). This down regulation from the early elevated stress response in the beginning presumably seems to develop as the child learns to expect that its attachment behaviors and stress reactions will elicit aid from the caregivers. When the child is cared for responsively
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and sensitively, it learns to anticipate that the parents will protect the child and thus that it can cope with the threat. On the other hand when a child is exposed to a moderately less sensitive and responsive care, increased cortisol levels have been observed (Gunnar & Donzella, 2002). Abusive and neglectful care not only fails to support the young child’s attempt to handle the threat but is in itself threatening.

Nevertheless these results with elevated stress hormone levels have not been consistently reported. Several studies in both humans and animals have instead shown an attenuation of the HPA axis activity to stressors (Susman, 2006). The attenuation of arousal has been proposed to be an adaptive strategy to cope with a chaotic environment. If an organism is exposed to stress during an extended time period it will after a while turn off some cortisol receptors in order to reset the equilibrium of the body (Susman, 2006). Down regulation of the stress system enables the organism to regulate the system so as not to continually evoke a chronic emotional, endocrine and cardiovascular response to threatening events. This down regulation avoids chronic arousal and excessive energy loss, which would eventually lead to vulnerability for diseases and early mortality (Susman, 2006).

Taken together, the data from human children and adults suggests that the HPA axis seem to make a transition from an earlier phase characterized by hypercortisolism, likely due to sustained exposure to adversity, to a later phase characterized by hypocortisolism if adversity ceases. Researchers are now trying to further explain why these changes occur and how they are implemented.

2.2.2. The balance between receptors

There is compelling evidence that the quality of parental care or repeated maternal separations impacts the adult rodents HPA axis to become hyper responsive (Aisa et al.,
Details about the molecular mechanisms that mediate this effect are well studied in rodents.

HPA axis activity is regulated by two different types of GC receptors which are mineralocorticoid (MR) and glucocorticoid receptors (GR) (Sanchez, 2006). MR binds with high affinity to GC and is important in the maintenance of HPA axis basal activity and GR binds to GC with low affinity and are responsible for negative feedback during the circadian peak and following an acute stressor. This differentiation of affinity results in a striking variation in occupation of the two receptor types under different conditions and time of day (Lupien et al., 2007). During stress or the circadian peak of GC secretion, MR becomes saturated whereupon an occupation of GR begins to take place and the negative feedback sets in causing a termination in the secretion of the stress hormones. Thus a balance between the two different GC receptors is needed for a normal HPA axis function. Understanding the postnatal changes in the expression these two types of receptors are important since they are regulated by postnatal experiences.

Meaney (2001) revealed that handled rats that hold a more modest response to stress, as adults show decreased CRH expression and content in different brain regions and increased negative feedback sensitivity to GC, which may be related to the increased GC receptor expression in hippocampus and frontal cortex. Opposite changes have been observed following maternal separation. As adults, rats that have been exposed to prolonged repeated maternal separations during their early postnatal life and thus hold an enhanced response to stress show a blunted negative feedback that might be due to reduction of GR binding in hippocampus and enhanced CRH expression (Ladd, Huot, Thrivikraman, Nemeroff & Plotsky, 2004).

In primates, variation in parental care is also believed to result in long-term changes in the neuroendocrine and neurobiological development of the offspring. But the experimental
evidence of this is very limited and very little is known about the mechanisms mediating these changes. In a study on nonhuman primates, abused infants exhibited higher cortisol levels than controls during the first month of life but thereafter lower cortisol levels were found (Sanchez, 2006). In the analysis of the HPA axis, six months after birth, a blunted ACTH response to CRH was found in the maltreated infants in comparison to the controls. These findings reflect a down-regulation of CRH receptors in the pituitary. An explanatory hypothesis for this is that CRH over activity due to emotional and physical stress in the early ages may have led to an adaptive down-regulation of CRH receptors in the pituitary (Sanchez, 2006).

In sum we have seen that early social experiences and in particular aspects of the maternal care exert a large influence on a child’s developing brain. A responsive and careful mother favors an activation of the OT system which has many beneficial effects. However if the child is less attended to, neglected or abused an insecure attachment results, which is reflected in a greater activation of the stress response. Nevertheless it appears that it is necessary that the child’s HPA axis becomes activated so that a normal development of the stress response is established by proper levels of stress hormones and receptors. However it further seems equally important for the mother to be able to regulate her child’s emotional states and thus buffer the stress response. This implies that an overprotective mother could disturb the developing stress response as well.

Either an over or under reactive HPA axis could result from a prolonged stress hormone exposure. This change in the HPA axis is a biological marker for different psychiatric problems and deviant behaviors. Further it was explained how it is assumed that this up or/and down regulation of the HPA axis is implemented. It seems like it is important to have a balance between the high affinity MR receptor that is responsible for the activation of the stress response and the low affinity GR receptor that is responsible for the negative feedback.
The expression of these two GC receptors is depending on how often and for how long the stress response is activated.

Exposure of high levels of stress hormones during extended time periods can notably alter the development of the infant’s brain in an abnormal direction. These changes occur on both structural and functional levels. The next chapter shall focus on the most characteristic one’s on each level.

3. The effect of stress on the developing brain

From a sole fertilized egg a human being is constructed, a process which is very intricate and initially controlled by powerful genetic prespecifications. By the time of birth the fetal brain is well developed, showing cortical layers, neural connectivity and myelination but even though the brain is very complex it is far from complete in all its details (Gazzaniga, Ivry & Mangun, 2002). After birth the fetal brain will continue to increase in size and most importantly continue to wire together the billions of neurons, forming complex neural circuits which finally will be activated and give rise to complex cognition, emotion and behavior. The nervous system is tremendously plastic during development. It can change its form, including the type and location of cells and how they are interconnected with one and other (Gazzaniga et al., 2002). The brain continues to change markedly until the late teens when it in most respect resembles the adult brain. During this prolonged postnatal period the brain is markedly influenced by a combination of nature and nurture, genetics and experience.

Prolonged and elevated stress hormone levels could result in devastating effects for the organism (McEwen, 1998). The following chapter shall elucidate the most prominent effects on both a structural and functional level of the developing brain. In addition it has been discovered that neurotrophins might as well play an important role in the implementation of structural changes. Thus is a section devoted to how neurotrophins affect the brain.
These structural and functional changes are important to understand because they might in part reflect the emotional and cognitive consequences that may occur later in life.

3.1 Changes in brain structures and plasticity

In addition to the neurochemical imbalances, structural changes in the developing brain have also frequently been reported among individuals who have experienced childhood maltreatment. Structural changes include volume, dendritic debranching, hypertrophy and synaptic remodeling.

Brain areas that are especially vulnerable to stress hormones are the hippocampus, amygdala and PFC which also are important brain structures for emotion and cognition. Rats that receive a reduced amount of maternal care show a retraction of hippocampal development (Liu et al., 2001). There is also evidence of reduced hippocampal volume in adults with a history of severe childhood stress (Bremner et al., 1997). Hippocampus is a gray matter structure of the limbic system that is involved in explicit, working and episodic memory (Gazzaniga et al., 2003). This means that an abnormal development of hippocampus could lead to different forms of memory problems later in life.

Similar changes to those in hippocampus have also been discovered in PFC. In an anatomical magnetic resonance imaging (MRI) study of children and adolescents with a history of maltreatment suffering from posttraumatic stress disorder showed a reduced PFC, prefrontal cortical white matter, right temporal lobe volume and mid section of corpus callosum and enlargement of the lateral ventricles compared to healthy control subjects. PFC is known for playing a vital role in executive functions and emotional regulation and an attenuation of this area could thus lead to an impairment of inhibiting impulses or poor ability in regulating emotional states (Gazzaniga et al., 2003). However a different structural picture is emerging for amygdala in subjects exposed to early stress.
Several animal studies point toward a contrasting pattern with an increase of dendrites and hypertrophy of neurons in amygdala (Wolf, 2008). Other instances where amygdala hypertrophy or over activity has been observed are in children with generalized anxiety disorder and depression that in turn may reflect a history of early life trauma (De Bellis et al., 2000). Amygdala is considered a key mediator of emotions and fear conditioning and if this structure becomes over stimulated this would lead to enhanced emotional states and implicit emotional learning (Gazzaniga et al., 2003).

In sum it seems like stress hormones have the potential to alter the development of special brain structures in different directions. Hippocampus and PFC have in several studies showed a reduced ability for plasticity and volume whereas amygdala in some cases have shown an increased plasticity and volume in subjects exposed to severe early stress. These alterations are thought to be mediated by a combination of elevated stress hormone levels and changes in neurotrophins. During normal brain development which is characterized by maximal neuronal growth, differentiation and synaptogenesis, neurotrophins and their receptors significantly increases. Therefore they have become interesting targets to study when it comes to the effects of adverse events and changes in brain structures.

3.1.1. Neurotrophins influence on plasticity

Neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) plays an important role in neuronal growth and synaptic plasticity (Poo, 2001). Therefore neurotrophins have become interesting targets to study since changes in their expression represent one of the mechanisms through which developmental manipulation such as stress can alter brain structure and functionality.

Studies performed in rodents have shown that neurotrophins are sensitive to manipulations of the mother-infant relationship and more in general of the rearing
environment (Cirulli, Alleva, Antonelli & Aloe, 2000; Roceri, Cirulli, Pessina, Peretto, Racagni & Riva, 2004).

In a study where rat pups where exposed to a separation time for up to three hours an increase of NGF expression was shown in the hippocampus, hypothalamus and cerebral cortex at 9 and 16 days of age (Cirulli et al, 2000). A similar profile for BDNF has been found after repeated maternal separation. Roceri and colleagues (2004) found that BDNF expression were increased at postnatal day 17 in the hippocampus and frontal cortex of rats deprived of their mothers from postnatal day 2-14. A proposed hypothesis is that in an early phase the brain might up-regulate the expression of neurotrophic factors as a compensatory mechanism in order to limit the consequences of negative experiences. However these short-term changes of neurotrophins appear to differ from the effects measured later in life were the majority of data shows that early life stressors may reduce neurotrophins (Fumagalli, Molteni, Racagni & Riva, 2007).

Studies in humans have shown that NGF increases in anxiety loaded situations (Aloe, Bracci-Laudiero, Alleva, Lambiase, Micera & Tirassa, 1994) and that low BDNF blood levels are associated with mood disorders (Karege, Bondolfi, Gervasoni, Schwald, Aubry & Bertschy, 2005). It has also been disclosed that antidepressants aiming at increasing BDNF are effective (Karege et al, 2005).

Early life stress does not only affect the structure of the developing brain, functional changes have also been observed, the most prominent observation have been abnormal brain activity in the frontal lobe.

3.2 Abnormal electrical activity

Exposure to early life stress has been associated with functional abnormalities in the brains electrical activity (Diego, Field, Jones, Hernandez-Reif, 2006). For infants one of the
most painful experiences is not to be able to catch the mother’s attention. Maternal depression is characterized by unavailability and neglect towards the infant. Studies within the field of electroencephalography (EEG) changes in infants born to mothers with depression provide a valuable insight of how sensitive the infant brain is to early life stress. The most consistent results have been found in the frontal lobe. As early as 3 months of age, infants of depressed mothers exhibit a distinct physiological profile marked by a greater relative right frontal EEG asymmetry (Diego et al., 2006). This same electrical brain pattern has consistently been noted in adults with depression (Davidson, 2000). Greater relative right frontal activation are associated with more behavioral withdrawal, negative affect, responses to negative stimuli and poor emotion regulation (Diego et al, 2006). On the contrary left frontal EEG activation have been associated with approach emotions such as joy (Fox, 1991) and seen as the more normal pattern.

Right frontal EEG asymmetry in depressed individuals has shown to remain stable across time and continues to be present even when these individuals show an improvement in their behavioral symptoms (Vuga, Fox, Cohn, George, Levenstein & Kovacs, 2006). Perhaps this reflects their diminished ability to experience joy or susceptibility towards experiencing negative emotions.

In sum it has been shown that early stress has the potential to alter different structures in the developing brain. The studies focused on how hippocampus, PFC and amygdala were affected since they are important brain areas associated with emotion and cognition. Studies have also suggested that it may not be stress hormones alone that influence these structural changes but neurotrophins have shown to be an underlying mechanism as well. Abnormal right frontal lobe electrical activity is a characteristic feature in children to depressed mothers. An interesting finding is that this alteration seems to be persistent through time.
In the next chapter the focus shall be turned to the behavioral changes that have been observed in both animals and humans after adverse rearing conditions.

4. Implications for psychopathology

Studies in rodents have shown that prolonged, repeated maternal separations or low parental care results in more anxious and stress reactive offspring as adults (Meaney, 2001). Data on non-human primates suggests that naturally occurring physical abuse from the mother seriously affects the offspring’s socioemotional development, who grow up exhibiting behavioral signs of distress, observed by high rates of tantrums and screams and delayed social development, observed by late independence from the mother as well as less exploration and play (Sanchez, 2006).

Symptoms seen in humans with a history of maltreatment are for instance impaired social competence, emotional regulation and cognition as well as anxiety, mood and addictive disorders (Glaser, 2000).

The psychotherapist Sue Gerhardt has worked for several years with children and attachment problems. In trying to describe the importance of the interplay between children and their parents she uses both her psychological knowledge and the latest research within neuroscience and biochemistry. Her conclusion is that our psychological as well as our physiological systems develops through a positive interaction with other people during childhood. A child that is exposed to inconsistent or repeated negative experiences develops an inability to trust other people (Gerhardt, 2003). This is a belief that is formed at an early stage towards the parents and lasts into adulthood and influence the interaction with other people if the individual never experiences or learn an opposite belief later in life. These individuals often yearn for emotional support and closeness from other people but are at the same time afraid of it. Lack of trust leads to isolation and could thus express itself as an
impaired social competence (Gerhardt, 2003). Children also learn a certain approach to the world at an early age depending on if the early family environment has been hostile or kind. A common subjective experience in children and adults with a history of maltreatment are decreased hedonic capacity characterized by sad mood, anhedonia, loss of interest and lack of pleasure and enjoyment (Gerhardt, 2003).

Further it is very common that these individuals develops negative thinking about the self characterized by negative emotional bias, self-dislike, worthlessness, self-criticism and guilt (Gerhardt, 2003). It has been proposed that the reason why they do this is to be able to exercise control over their environments by denying the destructiveness in their parents and seeing themselves as bad and worthless.

Lack of trust, isolation and negative thinking about the world and self could all lead to a depressed or anguished emotional state. It could further be hypothesized that such emotional state gradually may become unbearable which would make it easier to resort to any drug that could help escape from it. This might explain why addictions disorders may be common among these individuals (Glaser, 2000).

The different physiological and psychological responses to stress could in the beginning be seen as adaptive, aiming at preservation of individual safety and integrity which later can become maladaptive. A maltreated child is forced to respond to environmental threats rather than engaging in activities crucial for the development of complex emotional, behavioral and cognitive functioning. Thus impairment could develop in those areas.

It is well known that people form social bonds under most conditions and avoids the dissolution of existing ones. The need to form and maintain strong, stable interpersonal relationships have in several studies shown to have numerous good and strong effects on emotional patterns and cognitive processes (Baumeister & Leary, 1995). It has further been
shown that ill effects on health and well-being are related to lack of attachment (Baumeister & Leary, 1995).

This chapter will deal with how stress hormones form implicit emotional memories through fear conditioning and how they are able to influence the individual later in life. It will also disclose how important the early close interactions are for the development of the child’s sense of self. Stress does not only influence the emotional memory but have a negative effect on other learning and memory forms. Studies on cognitive impairments are highlighted and an association to the structural brain changes observed in individuals with a history of maltreatment is made.

4.1 Formation of implicit emotional memories

Experimental studies have shown that humans remember emotional information better than neutral information (Wolf, 2008). An emotional picture of a wound is remembered better than neutral one of a house for example. There also seems like emotional arousal, ranging from high to low are more important than emotional valance, ranging from positive to negative. Emotional stimuli are processed in a different way than neutral stimuli (Wolf, 2008). The evolution of such differentiation assures that high priority is given to stimuli that are most relevant for survival.

Amygdala is primarily important for emotional learning and memory. Increasing GC levels and noradrenergic activation of the amygdala via the vagus nerve are crucial for modulating memory consolidation in other brain areas such as the hippocampus (Wolf, 2008). Studies have revealed that a blockade of either GC or noradrenaline activity impair emotional memory (Maheu, Joober, Beaulieu & Lupien, 2004). Thus secretion of the main stress hormones is required for adequate encoding of emotionally relevant information. This function for amygdala in emotional learning affects a number of emotional behaviors related
to implicit learning. Fear conditioning is a classical form of conditioning where the unconditioned stimulus is aversive (Gazzaniga et al., 2002). The role of amygdala in learning to respond to stimuli that have come to represent aversive events through fear conditioning is implicit (Gazzaniga et al., 2002). An example of this is a woman that may not remember that she was sexually abused by her father as a child but may panic when her husband approaches her intimately. A great number of responses can be assessed as the conditioned response in this type of fear learning paradigm.

Immediate responses of the brain to new and potentially threatening events may be adaptive and result in new learning and acquired behavioral strategies for coping, as may be the case in some fear related memories. A poor interaction between the parent and the child has also shown to influence the human intellect and sense of self.

4.1.1 The impaired development of the self

Jean Piaget is considered by many to be the father of modern developmental psychology. By creating and performing different tests he came to the conclusion that human infants and children perceive and comprehend the world differently than adults do (Gazzaniga, 2002). Different cognitive processes develop as the child grows older. Further Piaget believed that newborns were unable to form a concept of self that could distinguish between it and the outside world, and thus the development of self-identity had to begin during this period. The human intellect and sense of self arises from, and emotions are organized through interaction with other people and not in isolation (Fonagy, 2003). A maltreated infant develop different biochemical patterns and expectations than a carefully treated infant. In this way are our emotional states and reactions throughout life not just only based on primitive instincts but are rather patterns from our early emotional experiences with our care givers.
The explicit memory located in hippocampus arises around 18 months of age whereas the implicit memory system, involving limbic processes is available from birth (Gazzaniga et al., 2002). Thus is emotional memories laid down before the human being is able to verbalize them or even explicitly recall them, yet they are able to influence our lives without our awareness (Gazzaniga et al., 2002). The altogether experience from childhood thus becomes unforgettable since it is imprinted into our organisms brain, behaviors and expectations.

Daniel Stern (1985) also emphasizes the importance of the mother and the primary caregivers in the development of the self even though he approaches the topic from a more cognitive point of view. Stern asserts that it is through interaction with the primary caregivers the formation of perceptions about the world and relationships begin to develop in the infant. Stern further coined the term “affect attunement” which refers to the parent’s ability to mediate to the infant that they understands its emotions. When the parents are able to register the infant’s emotional states and then respond appropriately a positive sense of self arises. The repetitive experiences thus become inner cognitive working models for how the world and relationships functions. Stern calls these inner working models for representations of interactions that have been generalized (RIGS). These representations will continue to govern the infant’s thoughts and actions as he or she becomes adult.

According to Damasio is perception dependent on emotions (1994). The rational part of the brain can’t work in isolation but rather works together with the basic body regulated and emotional parts of the brain. Nature seems to have built our ability to reason not just on top on the biological regulation system but rather from and together with it (Damasio, 1994). Cognitive processes are thus able to affect our emotional reactions but can’t exist without them. Neuroscientific evidence has also come to the conclusion that emotion and cognition can’t be considered independently from each other (Gazzaniga et al., 2002). This imply that it
still exists a possibility for maltreated children who suffer from different psychopathologies or deviant behaviors to recover.

It might not come as a surprise that early adverse care does not only influence emotional memory but have the ability to influence other learning and memory forms as well.

4.2 Cognitive impairments

Early stressful adverse life events are also associated with cognitive impairments (Aisa et al, 2007). In a study on rats that had been exposed to 3 hours daily separation from the dam during their 3 first weeks of life where tested as adults in different behavioral and cognitive experiments. The maternally separated rats showed an increased HPA axis activity response to stressors. In the forced swimming test the maternally separated subjects showed a depressive like behavior with greater passivity and immobility compared to the controls. Further maternally separated subjects showed a significant learning and memory impairment in both the Morris water maze and the novel object recognition test.

The idea of the Morris water maze is that the rat shall try to find an invisible platform in a tank filled with water. After six training trials the platform is removed and the level of learning and memory is measured by distance swam in the quadrant where the platform used to be. The novel object recognition test where constituted as follows. The animal was put in the middle of two similar objects located in a chamber where it was free to explore for five minutes. It was considered that the animal explored the object when the head was oriented 2 cm from and towards the objects (Aisa et al, 2007). In a second trail one hour later, in which one object was replaced by a different one the exploration was scored for additional 5 minutes. The learning and memory ability was scored as percentage spent with the novel object (Aisa et al, 2007).

In the same experiment is was further shown that if the maternally deprived animals were treated with a GC receptor antagonist before the behavioral and cognitive testing’s a
completely reversed effect was observed as they showed equal mobility in the forced swim test and similar memory capabilities in the novel object recognition test as the control subjects (Aisa et al, 2007). Data from this study further supports the hypothesis that elevated GC levels may be associated with behavioral and cognitive deficits in maternally separated rats.

Natural variations in maternal care can also affect the adult rodents’ cognitive functions (Liu, Diorio, Day, Francis & Meaney, 2000). In an experiment examining spatial learning and memory with help of Morris water maze animals reared by low arched-back nursing, licking and grooming mothers showed a learning impairment compared to offspring’s reared by high arched-back nursing, licking and grooming mothers who also showed a greater hippocampal development. Studies performed in humans seem to support the rodent literature reporting negative effects of GC on hippocampus dependent forms of memory (Lupien et al., 2007).

Thus it seems like early adverse events can lead to impaired spatial memory and working memory. A different story emerges for emotional memories where early stress leads to enhanced performance. These behavioral observations are in accordance with the structural changes which show that cognitive and explicit forms of memory which are mediated by hippocampus and PFC become impaired during chronic stress whereas emotional learning and memory mediated by amygdala becomes enhanced.

Taken together early adversity seem to alter organisms behavior. The stress response is highly adaptive under normal circumstances but becomes maladaptive in the case of adverse care. This might in part explain how negative emotional states or deviant behaviors occur. Further it has been disclosed that early stress may impair the explicit memory and this might be due to the structural changes that have been observed in hippocampus.
5. Discussion

The connection between childhood maltreatment and later psychopathologies is a difficult and a complex topic which is far from being fully understood. Early life experiences have a profound and lasting influence on how an individual will respond during the rest of the life course. Early life stress appears to have lasting structural effects on brain regions such as hippocampus and functional effects with EEG asymmetry in the right PFC. Those alterations in turn have the power to affect mood, cognitive functions as well as behavior. How stress hormones exert these long-lasting changes is an important avenue of investigation at the moment. It has been shown that many individuals that have experienced stress during their postnatal and early childhood develops an over reactive stress response. However these findings are not consistent. Equally often, low stress activation is found in those individuals. As progress has been made within this topic of research several subsequent questions arise. Could it be that different attachment styles leads to the different outcomes or could it be that these children first develop a high reactive HPA axis which later, in order to diminish the strain on the body becomes down regulated. These questions still needs to be answered and are now under investigation.

Different brain structures are sensitive to early stress but also these findings points in different directions and seem to be highly individual. What is interesting however are the EEG studies in infants of depressed mothers where some more stable findings have been reported. These infants seem to develop a greater relative right frontal EEG asymmetry compared to infants of non depressed mothers. The asymmetry seems to be able to develop both postnatally and during pregnancy depending to some degree on when the mother fell into depression. These infants of depressed mothers that show a greater relative EEG asymmetry would be an interesting group to follow-up, to see if they as adults still show this asymmetry and additionally note how they are feeling subjectively.
This review contains many animal studies and an obvious question that should be asked is weather how well these studies can be translated onto humans. Studies on how adverse care giving environments affect the human brain are sparse. Clearly, ethical considerations make it impossible to impose on the developing child the experimental manipulations that are frequently used in animal studies. The studies within humans have also shown to be difficult to interpret since they rely on naturally occurring events which seldom take place in isolation, making the adverse events difficult to identify and quantify. Much of the research on humans also depends on retrospective reports which raise numerous other issues, not least about the reliability of the human memory. However more clinical studies in humans with the help of brain imaging techniques are warranted.

Among all the data I have been going through on this topic it seems like the most fundamental question asked, is how the long-term effects of early maltreatment occur. Additional question that should be asked are whether any studies have been performed on individuals that have had a bad childhood but are feeling well today and if that’s the case, do they also possess an over reactive stress response? Further, can one feel well but still have an elevated HPA axis? And also how is it with people that suffer of a psychiatric disease but have had a good childhood? Answers to these questions could bring a lot of further knowledge to this field of research.

Early adverse events leading to changes in the HPA axis are not associated to a single disease but rather produce different symptoms, suggesting that a complex array of factors must interact to determine the final outcome. Proposed factors playing an important role for the long-term consequences are the infant’s perceived stress, the maternal buffering of the infants stress response, sex and genetic factors that either increase or decrease vulnerability.

Childhood maltreatment and its consequences is perceived as a large problem in the society today, it consume large amounts of the societies resources and produces a great deal
of human suffering. This might be reason enough to why we should try to prevent or at least diminish this phenomenon.

The best thing would be to develop intervention or support programs in the society that could help children and their families at an early stage. Such programs would require engagement and expenditures by the government and the private sector but in the long run they would be a more gainful way of making a difference.

Psychopathology obviously has a neurobiological and a genetic dimension but on a behavioral level it is also the result of internal cognitive working models that have been shaped very early in life. Thus the need of a combination of medicines and specific psychotherapies would enhance the treatment success for several psychiatric conditions. However these suggested interventions can only become implemented if it became an acknowledged fact that the key to certain psychopathologies lies in the early childhood.
References


