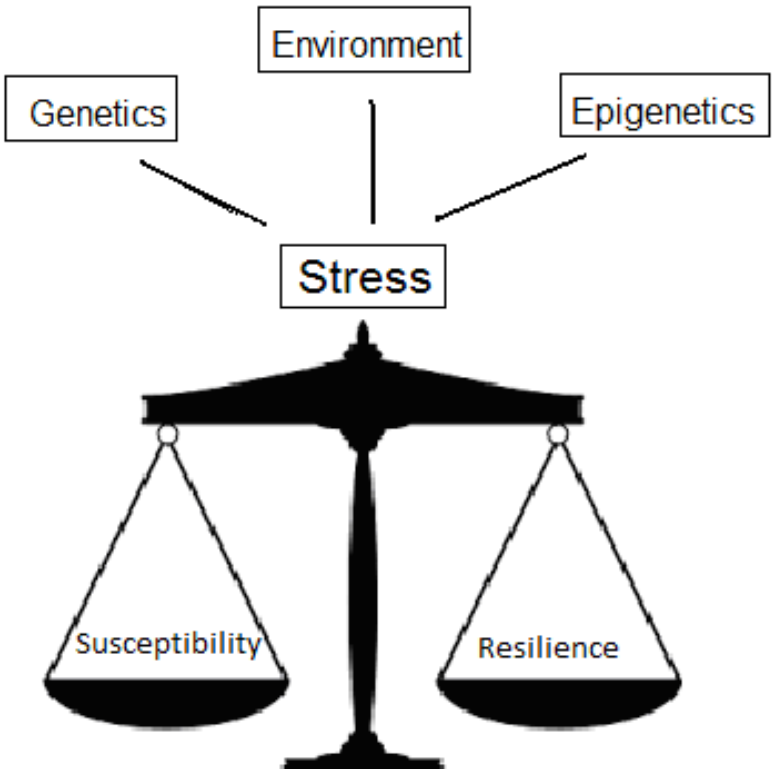
Unravelling stress susceptibility and resilience:
factors contributing to HPA-axis functioning



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Abstract

Since the discovery of the HPA-axis (1936) it has become increasingly more clear that the HPA-axis plays a defining role in stress phenotypes, determining (partially) wether someone is stress susceptible or resilient. The aim of this review is to investigate which aspects of the HPA-axis contribute to these stress phenotypes and can account for the differences between stress susceptibility and resilience.
Genetic polymorphism, influencing corticotrophin releasing hormone receptor (CRHR), mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) functions, have been identified to contribute to both stress susceptibility and resilience. Further research suggested that environmental stressors could play a significant role in influencing stress phenotypes. In certain time frames (prenatal, early life and adolescent), environmental stress is thought to have the greatest impact on a permanent stress phenotype. These environmental stressors have been shown to alter epigenetic factors regulating HPA-axis activity.
There is a delicate balance between the stress susceptible and resilient phenotype. A complex interaction between genotype, environmental factors and epigenetics determine whether an individual becomes more stress susceptible or resilient. Future research should focus on inducing a stress resilient phenotype using this knowledge.

Introduction

During life, every individual experiences stressful events. Stress is classically defined as a condition that seriously perturbs the physiological and psychological state of mind of an individual. In some individuals, events lead to psychiatric diseases like anxiety disorder, depression and post-traumatic stress disorder (PTSD). In others, it does not.
One of the key players in stress-related behavior is the limbic system. The term 'limbic system' was developed by Paul Broca (1824–1880). He described some cortical areas, which form a ring around the brain stem. He used the Latin word 'border', limbus, to call this circle of brain areas the 'limbic lobe'. It comprises broadly of the cingulate cortex, the temporal lobe cortex and the hippocampus. This system was discovered to be involved in emotions by Papez. He linked the cortex with the hypothalamus and this circuitry was called the 'Papez circuit'. Later, the importance of the amygdala in stress-related behavior was acknowledged (Klüver et al., 1939).
When stress research began, stress was thought to have merely an endocrine component (Martin, 1990). When research progressed, it became clear that in addition to physiological components psychological factors played an important role. It was discovered that psychological stimuli are strong activators of the endocrine system (Martin, 1990). In addition, evidence was growing proving stress hormones, like adrenocorticotropin (ACTH), influences brain excitability (Martin, 1990). These discoveries lead to the formation of a hypothesis in which a stress response is a physiological adaptation influenced by psychological processes.
The first to define stress in such a way was Hans Selye (Selye, 1936). He stated that stress was the nonspecific response of the body to any demand upon it (Selye, 1936). The primary experiments confirming this hypothesis were performed on rats, which were injected with different tissue extracts as stressors (Selye, 1936, Selye et al., 1936). Animals developed a pathological reaction, with enlargement of the adrenal glands (Selye et al., 1936). In addition, alteration of lymphatic nodes and gastric erosions were determined (Selye et al., 1936). This research was the foundation for the formulation of the Hypothalamic-pituitary-adrenal axis (HPA-axis) hypothesis, which proved to be the main stress system in the body. In 1950, the basis of the HPA-axis was discovered due to the notion that stress-induced ACTH secretion involved neural control via the hypothalamus and pituitary (Harris, 1950). Biochemical support for this hypothesis was found when the existence of hypothalamic factors elicited ACTH from the pituitary was proved (Guillemin et al., 1955). The name corticotropin releasing factor (CRF) was designed and defined as a factor which has the ability to stimulate ACTH release (Guillemin et al., 1955, Saffran et al., 1955). Due to these discoveries, the neuroendocrine basis of the stress response was founded.
There are physiological stressors as well as psychological stressors. The body responds differently to each of these stressors. Due to these different reactions, Herman et al., proposed an hypothesis in which two stress pathways were determined; a 'systemic' and a 'processive' pathway (Herman et al., 1997). The systemic pathway was represented by respiratory, cardiovascular or immune stimuli and required immediate reactions for survival but no for further interpretation from higher-order brain structures. Processive stressors however, were defined as multimodal stimuli resulting from psychological challenges and are in need of cortical processing (Herman et al., 1997). After cortical processing, the information can, when necessary, be assembled in limbic structures to induce neuroendocrine- and behavioral responses (Herman et al.,1997).

stress response differs between individuals (Wood et al., 2010). Stress exposure can lead to severe stress-related disorders for those who are susceptible to stress. Susceptibility is defined as being prone to the effects of stress (Wood et al., 2010). It causes a poor adaptation to stressors and inappropriate stress responses are expressed. However, some individuals seem to cope significantly better with stressors compared to others (Wood et al., 2010). These individuals are called resilient, in which resilience is defined as the ability to withstand the effects of stress or the ability to adapt successfully to acute stress, trauma or chronic forms of adversity (Masten et al., 2001, Wood et al., 2010). These individuals adapt well to stressors and experience an appropriate stress response (Del Giudice et al., 2011). Exposure to adversities cause an adaptive psychological and physiological stress response, which continuous to demonstrate these behaviors. This is called psychobiological allostasis (McEwen, 2003, Charney, 2004).

Why do stress susceptible individuals poorly adapt to stressors whereas stress resilient individuals do not? (Del Giudice et al., 2011). This is a question which has been fascinating researchers for years (Rutter, 2006). Resilience research started in the 1970s, when a group of scientists investigated the children's functioning after significant amounts of stress (Masten, 2001). After this pioneering research, many years of research followed. Gradually, it was proven that many factors like genetic, environmental and neural adaptation, play a role in developing a stress phenotype, displaying stress susceptible or stress resilient behavior. Also, psychosocial determinants influencing the stress phenotype such as positive emotions, self-regulation and social competence, were determined to play significant roles (Masten et al,. 1998, Masten 2001). When technological advances were made, more attention was payed to the biological processes (Hastler et al., 2004). The neurochemical and neuroendocrine systems were determined, clarifying a part of the unknown biological basis of stress phenotypes (Hastler et al., 2004). In addition, animal studies were developed to search for biological determinants of susceptibility and resilience (Southwick et al., 2005, Krishnan, 2008). Animal models were also used to identify neural circuits and molecular pathways mediating the stress phenotypes (Southwick et al., 2005, Krishnan 2008).

It has become increasingly more clear that the HPA-axis plays a significant role in defining the stress phenotypes, influencing wether someone is generally more stress susceptible or resilient (Southwick et al.,2005, Krishnan 2008). Research investigating reciprocity between HPA-axis and stress phenotypes has expended tremendously over the past years (Soutwick et al., 2005, Krishnan 2008). However, it is still not clear which factors contribute to a stress susceptible or resilient phenotype. The aim of this review is to investigate which aspects of the HPA-axis contribute to these stress phenotypes and can account for the differences between stress susceptibility and resilience. This was performed by implanting a broad literary research.

Stress and the neuroendocrine basis: the HPA-axis

After research of Selye, Harris and Giullemin, research investigating the HPA-axis progressed more and the entre pathway was determined (Selye et al., 1936, Harris 1950, Guillemin et al., 1955). It was established that the HPA-axis is one of the most important stress systems in the body and that it is used to describe the complex interplay between the hypothalamus, pituitary and adrenal gland, comprising of a partial stimulating and partial negative feedback system (Coleman, 2010). In response to stress, the Paraventicular part (PVN) of the hypothalamus produces, Vasopressin (AVP) and Corticotrophin releasing hormone (CRH) (figure 1)(Taché et al.,2008, Coleman, 2010). CRH regulates the activity of the pituitary gland by stimulation of the anterior part of the pituitary gland. In response, the pituitary gland secrets ACTH (Taché et al., 2008). ACTH in its turn acts on the adrenal cortex and stimulates it to produce glucocorticoid hormones. The most important glucocorticoid is cortisol. Cortisol exerts an inhibitory effect on the hypothalamus, thereby inhibiting the production of CRH and Vasopressin, resulting in inhibition of the feedback loop (Taché et al., 2008). A secondary function of cortisol is cleavage of the substance Pro-opiomelanocortin (POMC). POMC is normally cleaved into ACTH and beta-endorphins, thereby stimulating the stress response (Taché et al., 2008). These actions are mediated by a high affinity brain receptor, the mineralocorticoid receptor (MR) and a low affinity glucocorticoid receptor (GR) (Taché et al., 2008). The GR is widely expressed. The MR however is predominantly present in limbic brain areas. The MR receptor is mostly activated by basal, pulsatile cortisol deliverance and can have an inhibitory effect on the HPA-axis. The GR however, becomes activated when cortisol levels rise (van Leeuwen et al., 2011). When the negative feedback system is activated and cleavage of POMC is inhibited, the stress response is stopped and the stress system returns to baseline.

Stress reactions are functional (Terburg et al., 2009). Besides the effects of cortisol mentioned above, cortisol exerts many effects on the body. For example, an increase in blood pressure and blood sugar. These functions are evolutionary conserved and prepare the body for fighting or fleeing (Terburg et al., 2009).

However, when a stress reaction is excessive and out of proportion the negative feedback system does not operate in its usual manner. Instead of activation of the negative feedback system, a positive feedback system arises, in which CRH keeps stimulating the pituitary to produce ACTH, which keeps stimulating the adrenal gland to produce cortisol.

This results in a stress response that is excessive and out of control.

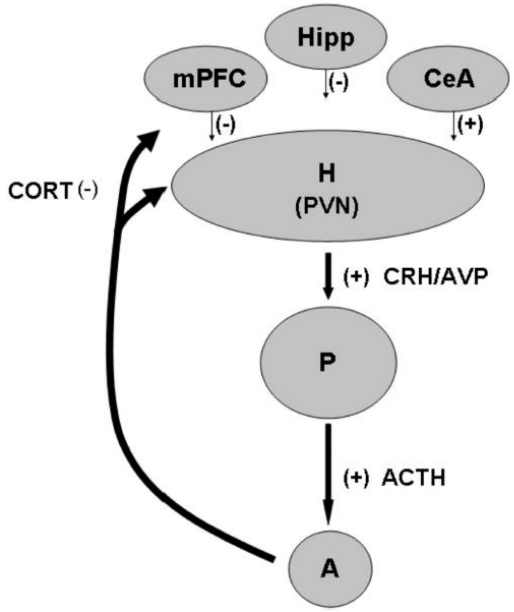

Figure 1: Overview of the HPA-axis response (Romeo et al., 2006)

mPFC = medial prefrontral cortex, Hipp = hippocampus, CeA = central nucleus of the amygdala

H (PVN) = paraventricular nucleus of the hypothalamus , CRH = corticotrophin releasing hormone , AVP = arginine vasopressin

P = pituitary, ACTH = adrenocorticotrophin releasing hormone

A = Adrenal gland, CORT = cortisol

Genes are the basis of every human being and determine our phenotype. A gene is the molecular unit of heredity within a living organism (Pearson, 2006). Genetic variability can account for differences in phenotypes.

The function of the HPA-axis is largely determined by well-regulated gene expression at different levels of the axis (van West et al., 2010). It becomes increasingly more clear that polymorphisms of the HPA-axis genes significantly contribute to stress phenotypes and might even account for the different phenotypes stress susceptibility and resilience (van West et al.,2010). Polymorphisms arise due to point mutation in the DNA sequences, changing the overall sequence and influencing the phenotype. To study the relevance of polymorphisms, single-nucleotide polymorphisms (SNP) maps were developed, organizing all known polymorphisms (van West et al.,2010). SNPs can be found in every intermediate of the HPA-axis stress cascade (van West et al.,2010). A summary of the most important HPA-axis related polymorphisms is displayed below (table 1).

Table 1: An overview of genetic polymorphisms causing susceptibility or resilience

	Susceptibility	Ref	Resilience	Ref
HPA-axis				
CRH	rs110402 rs7209436	Bradley et al.,2008	rs4792887 rs242924 rs7209436 rs110402 rs242924	Bradley et al.,2008 Amstadter et al.,2011
GR	rs9296159 rs3800373 rs1360780 rs9470080	Menke et al.,2013 Ising et al., 2008		
MR			rs2070951	De Rijk et al.,2008

SNPs of the HPA-axis were first determined in CRH. SNPs can cause alterations in functioning of CRH in the HPA-axis, by either a change in CRH production or changes in the receptors sensitivity (Bradley et al.,2008). These changes can cause an altered stress response. A CRH-receptor polymorphism can be caused by alterations in genes encoding the CRH receptor 1 (CRHR1). A study of Bradley et al., reported an interaction between SNPs rs110402, rs7209436 and later life depression in children suffering from child abuse (Bradley et al.,2008). They found that individuals who were genetically predisposed with these SNPs, reacted with increased HPA-axis activity, creating a stress susceptible phenotype (Bradley et al.,2008). Bradley et al suggested that increased HPA-axis activity might be caused by increased CRH concentrations as well as increased CRHR1 mRNA expression, causing increased pituitary activity, resulting in increased cortisol production (Bradley et al.,2008). This causes increased HPA-axis activity, influencing the stress phenotype. In addition, Bradley et al., found that when possessing these genetic polymorphisms, an alteration in behavioral aspects of stress occurs (Bradley et al., 2008). They suggested a stress susceptible related behavioral consequence of these polymorphisms (Bradley et al.,2008). Rs110402 and rs7209436 cause an increased CRH binding in limbic brain regions such as the hypothalamus and amygdala, altering stress-related behavior (Bradley et al.,2008.

Protective SNPs of CRH were also determined, inducing a more stress resilient phenotype (Bradley et al.,2008). Homozygous forms of the short allele of rs110402 and rs7209436 have proven to be stress protective in a dose dependant manner, decreasing CRH binding and preventing increased HPA-axis activity. Other SNPs, like rs4792887 and rs242924 were determined to decrease CRH expression and thereby HPA-axis activity as well, resulting in protective effects against stress-related pathologies, such as depression (Bradley et al.,2008).

SNPs of ACTH also can influence the stress phenotype (de Rijk et al.,2008, Ising et al, 2008, Menke et al., 2013). FKBP5, which is a chaperone protein regulating GR sensitivity can bind the receptor complex. Consequently, cortisol binds with lower affinity and nuclear translocation of the receptor is less efficient, causing activation of the adrenal gland (Ising et

al., 2008). A study of Menke et al., found that there are four SNP's known (rs9296159, rs3800373, rs1360780 and rs9470080) for influencing GR sensitivity. When carrying one of these four SNP's, sensitivity of GR increases (Menke et al., 2013). This causes a more easily triggered HPA-axis, contributing to a stress susceptibility profile. In addition, when carrying one of the four FKBP5 polymorphisms, there is an inefficient recovery of HPA-axis activity after social stress, causing a prolonged stress response (Menke et al.,2013). The study of Binder et al., found that the efficiency of negative feedback of the stress hormone axis decreases when possessing one of these four SNPs (Binder et al., 2009). According to the study of Menke et al., this is a risk factor for clinical elevated cortisol and thereby stress-related psychopathology (Menke et al.,2013). Other studies also proved an insufficient recovery of cortisol activity, contributing to a stress susceptible profile (Ising et al.,2008). MR, The other ACTH receptor, is known to play an important role in the negative feedback system of the HPA-axis. Sensitivity of the MR receptor is influenced by genetic polymorphisms like rs2070951 (de Rijk et al.,2008). This SNP causes a lower threshold for MR activation (de Rijk et al., 2008). Enlarged inhibitory effect on the HPA-axis are the consequence. Carriers of this genetic polymorphism have lower levels of cortisol and are generally more immune to stress (de Rijk et al., 2008).

Although the functioning of the HPA-axis is largely determined by well-regulated gene expression and variation in gene expression can contribute to a certain stress phenotype, not the entire phenotype is determined by genes (Sullivan et al., 2000, van West et al., 2010). Twin studies have revealed a unique environmental risk in the aetiology of stress disorders (Sullivan et al., 2000). Sullivan et al., investigated the genetic and environmental basis of depression using twin studies (Sullivan et al.,2000). They found that the heritability of stress-related disorders such as depression, is likely to be around 31-42%. Heritability of other stress-related diseases is even lower; the study of Stein et al., concluded that genetic factors can moderately influence the incidence of PTSD up to 20%(Stein et al., 2002). In addition, they concluded that it is more likely that individual differences in personality influence environmental choices, contributing to a stress phenotype (Stein et al.,2002). This study suggests that, although the functioning of the HPA-axis depends on genes, genetic predisposition is, for the majority, not responsible for a certain stress phenotype.

Stress and environment: the critical time period

Stein et al., suggested that environmental influences and choices could play a significant role in influencing stress phenotypes (Stein et al., 2002). What is the influence of these factors on stress phenotypes? And can environmental influences and choices contribute more significantly to a certain stress phenotype compared to genetic polymorphisms?

Stressful events experienced during life can contribute to developing of a certain stress phenotype (McEwen, 2012). There are many events imaginable playing significant dues, however not every stressful life event leads to an altered phenotype. Research has proven that there are certain time frames in which stress is thought to have the greatest impact on a permanent stress phenotype. Studies of Matthews et al., Huizink et al., Welberg et al., Bremne et al., Levine et al., Traslavina et al., and Lyons et al., suggest that stress during the prenatal, early life and adolescent period contribute most to the development of stress resilience or vulnerability (Levine et al.,1956, Bremne et al., 2001, Welberg et al., 2001, Matthews et al., 2002, Huizink et al.,2004, Lyons et al., 2010, Traslavina et al., 2014). An overview of these critical time periods is shown below (figure 2).

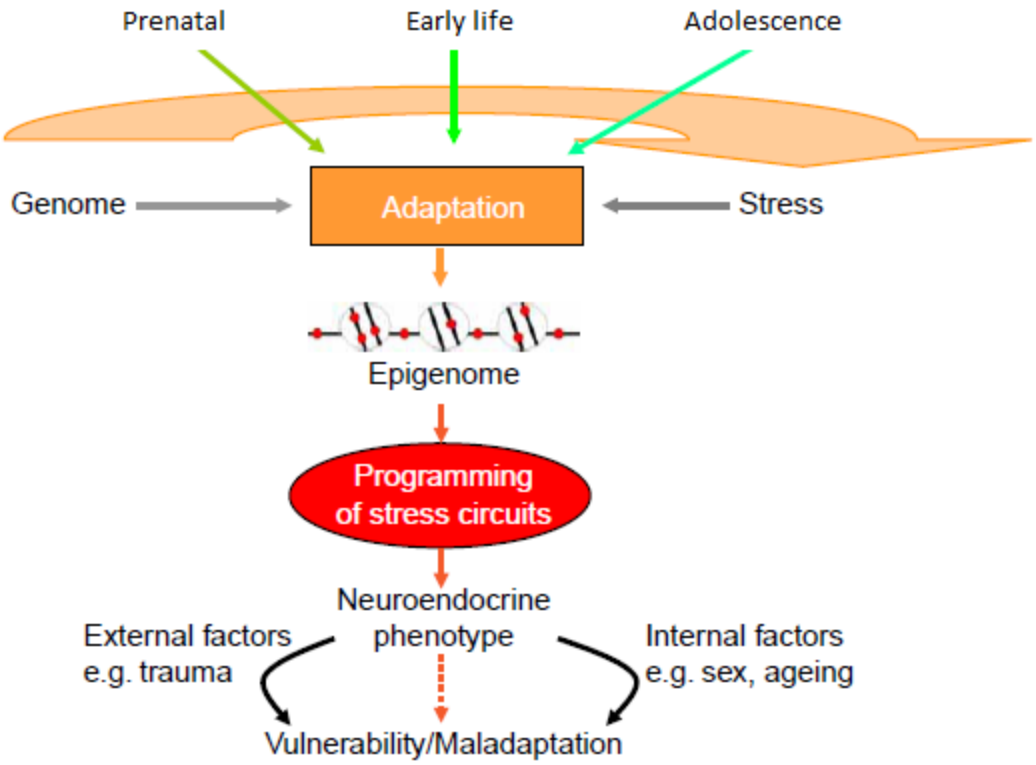

Figure 2: An overview of critical time periods in which environmental stressors have the biggest impact (Murgatroyed et al., 2011)

Prenatal

Many studies have investigated the effects of maternal stress on stress phenotypes of unborn offspring (Blehar et al.,1995, Welberg et al.,2001, Matthews et al.,2002, Huizink et al., 2004, Darnaudery et al.,2007).

Prenatally stressed adult animals had an enhanced basal HPA-axis activity and fewer GR, resulting in increased HPA-axis activity (Matthews et al.,2002). In addition, these animals

suffered from a prolonged response to stress due to decreased levels of MR and impaired negative HPA-axis feedback system (Matthews, 2002). Maternal stress can thus induce a more stress susceptible phenotype. The study of Matthews is paralleled by findings that document an impact of prenatal exposure to exogenous glucocorticoids (GCs) on HPA axis functioning later in life, also suggesting an increased HPA-axis activity and a more stress susceptible profile (Welberg et al.,2001).
The overall prevalence of mood disorders and stress-related disorders is higher in women compared to man (Blehar et al., 1995). Some studies claim sex-related differences concerning stress susceptibility and resilience (Zuena et al.,2008). A study of Hover et al., found that male Sprague-Dawley rats are more affected by prenatal stress compared to female rats (Blehar et al., 1995). While male rats showed an increase in anxiety and depression related behavior, females showed a more resilient stress reaction pattern, contradicting the current notion in which women are more stress susceptible (Blehar et al., 1995).
Similar results were proven by Zuena et al., who also found that male Spargue-Dawley rats showed a more stress susceptible behavioral phenotype (Zuena et al.,2008).
In addition, Zuena et al., found that prenatally stressed females were less anxious compared to other female offspring, thus creating a form of stress resilience (Zuena et al., 2008).

Early life stress
Traumatic events experienced during development, or early life stress (ELS) can damage neurobiological and neuroendocrine systems, affecting child devolvement, behavior, emotion, social, physical and cognitive aspects (Bremne et al., 2001) ELS can be subdivided into sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect (Bremne et al.,2001).
The notion that ELS could influence later life stress phenotypes is not novel. This hypothesis was formulated many years ago by the famous scientist Freud. He suggested that early life stress contributes to the development of subsequent emotional instability and a more stress susceptible phenotype. However, Levine et al., found that rats being exposed to intermitted foot shocks during infancy, showed signs of subsequent emotional stability in adolescence and adulthood (Levine et al., 1956). Levine et al., therefore concluded that intermitted stress can result in the capacity of an organism to respond more effectively when confronted with novel situations, creating a more stress resilient phenotype (Levine et al.,1956).
Following Levine et al., the study of Lyons et al., investigated the same principle in Squirrel monkeys. They separated infants from mothers for short periods of time and looked at the initial and long-term consequences (Lyons et al., 2010). Although separation resulted in short term increase of cortisol levels, suggesting a more stress susceptible phenotype, long term effects of separation proved resilience (Lyons et al., 2010). In later life, these squirrel monkeys showed less behavioral indications of anxiety, diminished stress levels of cortisol and increased sensitivity to glucocorticoid feedback regulation of the HPA-axis (Lyons et al.,2010). They concluded that controlled stress exposure increases stress resilience suggesting that controlled exposure to stress-related cues can be a key factor of resilience (Lyons et al., 2010). Earlier studies proved comparable results; adult humans tend to cope better with spousal loss, illness and accidents if they had previous experience with stress in childhood (Khoshaba et al., 1999). Early life stress seems to cause a generally more stress resilient phenotype in adulthood.
Not all studies are that conclusive. The study of Bremne et all., suggest ELS involvement in

persistent HPA-axis response changes, creating a hyperactive HPA-axis and increased cortisol production (Bremne et al., 2001). This seemed to cause a more stress susceptible phenotype in later life, with an increased risk of depression (Bremne et al., 2001).

Adolescent stress

Adolescence is being viewed increasingly as a significant period for development of the stress phenotype, especially vulnerabilities to stress (Spear 2000, Andersen 2003, Dahl 2004). Puberty is marked by an increase in susceptibility to various stress-related psychological disorders, such as depression (Conger et al., 1984, Masten 1987).
Studies have identified puberty as an important time period for the development of the stress system (Romeo et al., 2006, Eiland et al., 2013). Many studies found that the stress response differs between adolescent and adult animals (Eiland et al.,2013). It was proven that adolescent animals have a basal and stress-induced ACTH and corticosterone secretion comparable to adult animals. However, pubertal animals have a prolonged ACTH and corticosterone stress response compared to adults, causing a more stress susceptible phenotype when enduring acute stress (Eiland et al.,2013). These effects are different when the amount of stressor time exposure elongates (Romeo et al.,2006). When enduring chronic stress, a higher ACTH and corticosterone response was noticed in pubertal animals, enduring a more intense stress response. However, these values returned to baseline faster compared to adults animals (Romeo et al., 2006). Thereby, the largest risk factor for developing stress susceptibility, prolonged HPA-axis activity, ceases. This suggests chronic stress as protective factor against stress susceptibility (Romeo et al., 2006).
McEwen et al., proved that adolescence is a critical time period for the development of stress-related pathologies (McEwen, 2003). Stressors in adolescence can both lead to the onset and exacerbation of psychological disorders (McEwen, 2003). In response to stress, brain regions like the medial prefrontal cortex (mPFC), hippocampus and amygdala undergo changes in structure and function (McEwen, 2003). Stress-induced alteration in pubertal nervous system may contribute to an individual's stress vulnerability during adolescence, because the mPFC, hippocampus and amygdala play a significant role in regulating emotionality and stress responsiveness (McEwen, 2003). A recent study of Traslavina et al., investigated the stress response in adolescents rats and found gender related-differences (Traslavina et al.,2014). They found that anxiety-like behavior was affected based on a specific stressor for males (Traslavina et al.,2014). Females however, showed different behavioral consequences after different types of stressors (Traslavina et al.,2014). The duration of stressor application had effect on the HPA-axis in adolescent male rats, female adolescent stress was modulated by the nature and the duration of the previous stressor (Traslavina et al.,2014). Regardless of gender, these animals all showed an altered stress phenotype in later life, leaning towards a more stress susceptible phenotype (Traslavina et al., 2014).

Many studies have proven an effect of stress experienced during life, whether this is prenatally, during early life or adolescence. However, only the minority of individuals will develop stress-related disorders or stress resilient phenotypes following environmental stress (Cohen et al., 2007). For example, two third of the general population experiences traumatic events in their lives, but merely 5-10% of them develop PTSD or other stress-related pathologies (20-25%) (Galea et al.,2005, Cohen et al.,2007). The same accounts for resilience, stressful events can also lead to resilience, confirmed by posttraumatic growth (PTG), which is defined as a positive psychological change following exposure to a

challenging life experience (Levine et al.,2008). However, PTG does not occur in every individual enduring environmental stress (Levin et al., 2008).

Considering the above it can be concluded that neither genetic predispositions nor stressful life events can by itself explain stress susceptibility or resilience. In addition, studies investigating the effects of environmental stress during certain life-periods on the phenotype, do not explain how the environment causes stress phenotypes.
The effects of environmental studies have to be long-term, otherwise they cannot occur prenatally, during early life or adolescence and be persistent in adult life. In addition, environmental stressors need to have effect on significant parts influencing the phenotype, otherwise the effect of the environmental stressors cannot be perceived.
The only way how such environmental factors can persist over a long period of time and influence the phenotype, is through exerting an effect on genetics. The first one to suggest such an interaction was Charles Weddington (1905-1975). He thought of the term 'epigenetic' in 1942, which he defined as the interaction between epigenesis and genetics (van Speybroeck, 2002). He was the first to think of an interaction between environmental influences and the genetic basis (van Speybroeck, 2002). His pioneering idea was followed by studying environmental and genetic interaction in every biological field imaginable, hoping to elucidate unexplainable mysteries (van Speybroeck, 2002). Among these fields belongs the field of comprehending the stress phenotype, in which researchers tried to untravel the composition of stress resilience and susceptibility (Franklin et al., 2010, Metha et al., 2013, Niwa et al., 2013). Epigenetics offered a window in which genes, the unalterable basis of the HPA-axis, can be influenced by a variable factor, the environment. This comprises that although genetic sequences do not change during life, the function exerted by these genes can. This offers an explanation for the correlations seen above.

Stress and epigenetics: the critical time period

Epigenetic is the study of changes in gene expression, caused by alterations in DNA accessibility but not by sequence. Consequences of these alterations are that certain genes are (re)activated or suppressed (Zannas et al., 2014).
Broadly, epigenetic changes are caused by posttranslational modifications. The most common one is methylation. DNA methylation is a epigenetic modification achieved though addition of a methyl group to cytosine within the DNA sequence (Turner, 2001). Methylation depends on enzymatic function of DNA methyltransferase, such as DNMT1, DNMT3a and DNMT3b (Turner 2001). Other posttranslational modifications such as acetylation, methylation, phosphorylation and ubiquitinilation are made on the N-terminus of the histone (Peterson et al.,2004). DNA methylation is usually associated with a decreased transcription, whereas processes like acetylation usually enhance transcription. Across species it is evident that epigenetic effects can be induced by a variety of experiences, such as exposure to stressors (Gudsnuk et al., 2012). These developmental effects can be transmitted across generations, leading to neurobiological and behavioral changes that persist (Franklin et al.,2010). Epigenetics are therefore the integration of life-time experiences into the genetic basis, the fusion between genetic- and environmental factors. Stressors are one of the many environmental factors that can change epigenetic patterns in the brain. Various stress paradigms have been shown to decrease methylation of multiple gene encoding intermediates of the HPA axis (Zannas et al.,2014). An overview of these stress-related epigenetic effects on the stress phenotypes is shown below (table 2).

Table 2: A overview of epigenetic effects on stress susceptibility and resilience, classified according to time period

ELS = Early Life Stress

	Susceptibility	ref	Resilience	ref
Prenatal	**CRF methylation** ↓	Gudsnuk et al., 2012		
	Nr3c1 methylation ↑	Gudsnuk et al., 2012		
	DNMT1 ↑	Mueller et al., 2008		
ELS	**AVP methylation** ↓	Murgatroyd et al., 2009	**Nr3c1 Methylation** ↓	Weaver et al., 2004
	DNMT1 ↑	Zhang et al., 2010	**MeCP2 phosphorylation** ↑	Cohen et al., 2011
	FKBP5 ↓	Klengel et al., 2013		
Adolescent	**CRF methylation** ↓	Elliot et al., 2010	**CRF methylation (unchanged)**	Elliot et al., 2010

Prenatal
Prenatal stress caused by maternal stress, is one of the environmental factors altering epigenetics and influencing the stress phenotype. (Gudsnuk et al. 2012). Especially DNA methylation and histone modifications have been observed in offspring enduring prenatal stress (Gudsnuk et al.,2012). Chronic stress experienced by pregnant females induces long-term effects on the HPA-axis. In mice, stress during the first week of pregnancy has been found to induce significant increases in CRF gene expression, still present in adulthood

(Mueller et al.,2008). Mueller et al., proved that these changes occur due to reduction of CRF gene methylation in the promoter region (Mueller et al.,2008).
In the Nr3c1 gene, encoding GR, there is an increase in DNA methylation in response to premature stress (Mueller et al.,2008). It is thought that these epigenetic modifications, altering the accessibility of DNA, are passed on from mother to child through the placenta. When investigating mice placenta on the presence of enzymatic DNMTs, elevation of the DNTM1 enzyme was determined, indicating an increase in DNA methylation (Mueller et al.,2008). These epigenetic modifications offer an explanation for perceived stress susceptibility, caused by environmental factors, mentioned above.

ELS

Epigenetic alteration can also be caused by ELS. This has become especially clear in animal models of neglect, abuse and variation in maternal care quality (Gudsnuk et al., 2012). Licking and Grooming (LG) of the pups in Long-Evans rats are a good indication for maternal care. Lactating females display individual differences in amounts of LG during the postnatal period. DNA methylation within the glutamic acid decarboxylase (Gad1) is reduced in high LG compared to low LG and histone acetylase is increased in the Gad1 promoter (Zhang et al.,2010). These effects are thought to be associated with increased methylation of the DNMT1 enzyme, among offspring fostered by low LG females (Zhang et al.,2010).
Childhood trauma in human subjects was found to correlate with reduced methylation of the FKBP5 gene of which the protein chaperones GR (Klengel et al.,2013). Glucocorticoids induce expression of FKBP5, which in turn modulates GR sensitivity via an ultra-short negative feedback loop (Binder et al.,2009). This results in GR resistance and a slower recovery of stress-induced increases in the HPA-axis activity, contributing to a stress susceptible phenotype(Binder et al.,2009).
In mice, maternal separation has been proven to influence the PVN of the hypothalamus (Murgatroyd et al.,2009). Separation causes decreased methylation at several cytosine nucleotides within the promoter region of the AVP gene, causing an increase in transcription (Murgatroyd et al.,2009). Persistent hyperactivity of the HPA-axis is the consequence, contributing to a stress susceptible phenotype (Murgatroyd et al.,2009).
Methyl-CPG binding domain 2 (MeCP2) is a methyl binding domain (MBD) protein (Lyst et al., 2013). Once bound to methylated DNA, MeCP2 can scaffold multiple chromatin regulators, including histone deacetylase and methyltransferase (Lyst et al.,2013). Polymorphisms of MeCP2 can regulate its protein-protein interaction (Ebert et al.,2013). MeCP1 is a target of stimulus-regulated phosphorylation at multiple sites, including Ser80, Ser86, Ser274 and Thr308 (Zhou et al.,2006). The consequences of these phosphorylation events have not been determined yet. However, Ebert et al found that phosphorylation of MeCP2 at Thr308 disrupts the association of MeCP2 with chromatin regulators, reducing DNA-methylated dependant repression (Ebert et al., 2013). Stressors can alter the stress response through MeCP2, following ELS. ELS induces increased mRNA expression of AVP (Murgatroyed et al.,2009). This increase in AVP was associated with a decrease in CpG methylation of intragenic AVP enhancer and decreased association of MeCP2 with this enhancer, conducing to a stress susceptible phenotype (Murgatroyed et al.,2009).
Phosphorylation of MeCP2 at SER421 was elevated in AVP of mice exposed to ELS compared with age matched controls (Cohen et al., 2011). Phosphorylation of MeCP2 at SER421 reduces association with the AVP enhancer, inducing resilience. Similar results were found in other animal studies (Cohen et al., 2011). Cohen et al., also proved that SER421

phosphorylation plays a role in depressive behavior and antidepressant responses, contributing to a stress resilient phenotype(Cohen et al., 2011). Treatment with antidepressants induced SER421 phosphorylation of MeCP2 in parts of the mesolimbic system (Hutchinson et al.,2012).
GR induces expression of FKBP5 via its association with glucocorticoid response elements (GREs), which couples with FKBP5 through a chromatin loop mechanism (Klengel et al., 2013). ELS correlates with reduced methylation of CpG dinucleotides in and around GREs in the FKBP5 gene (Klengel et al.,2013). Decreased methylation of this dinucleotide is associated with higher induction of FKBP5 expression upon GR activation, leading though FKBP5-dependent feedback regulation of GR to increased GR receptor resistance and a higher HPA-axis setpoint (Cohen et al., 2014). This cascade of actions contributes to a more stress resilient phenotype(Cohen et al.,2014).
High or low levels of LG have significant long-term epigenetic effects on offspring (Meaney, 2001). Variation in LG behavior predicts variation in DNA methylation and histone modification: high LG decreases DNA methylation in male offspring in the promoter region of the Nr3c1 gene in the hippocampus (Weaver et al.,2004). This mediates enhanced glucocorticoid feedback, long-term decreased HPA-axis responses and stress-resilient phenotypes during adulthood (Meaney et al., 1985). Expression of mRNA encoding GR is inversely correlated with DNA methylation of CpG residues in the Nr3c1 promoter, which serves as a binding site for transcription factors nerve growth factor inducible protein A (NGFI-A). By expelling demethylation from the Nr3c1 promoter, NGFI-A dependent GR expression is permitted and LG is thought to determine the set-point of HPA-axis responses in adulthood (Weaver et al., 2004). Histone acetylation of the Nr3c1 gene is increased in high LG offspring, improving later life resilience (Weaver et al.,2004). Cross fostering of pups between high and low LG parents has indicated that these epigenetic effects are related to the quality of postnatal care rather than prenatal or genetic factors (Weaver et al.,2004). Comparable results were achieved with human subjects: children exposed to either low- or high maternal care showed similar epigenetic alterations (Zannas et al.,2014).

Adolescent
Initially it was thought that epigenetic alterations were limited to early stages of embryogenesis. However, it becomes increasingly more evident that experiences during life are capable of inducing epigenetic alterations.
La Plant et al., showed that stress from chronic social defeat in mice increased DNMT3a activity (LaPlant et al., 2010). Induced expression of DNMT3a after chronic stress contributes to development of depressive behavior and thus a more stress susceptible phenotype (La Plant et al.,2010). In addition, a different study performed by Elliot et al., found that social defeat stress causes a decrease in DNMT3b activity, causing a decrease in methylation (Elliot et al., 2010). Demethylation of the promoter gene encoding the CRF in the PVN befalled, increasing CRF mRNA expression (Elliot et al., 2010). Demethylation was accompanied by a suppressed methyltransferase activity, which might contribute to stressor-induced changes in promoter methylation status (Elliot et al.,2010). All events contribute to a more stress susceptible phenotype. An overview of the effects of DNMT3 activity is shown below (figure 3).

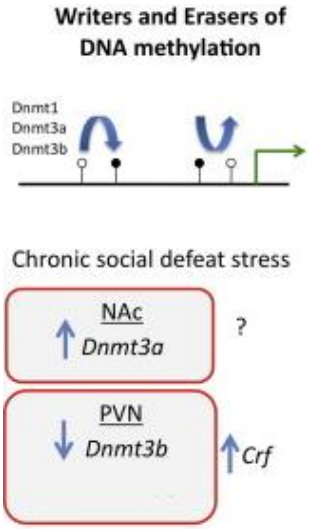

Figure 3: Overview of writers and erasers of DNA methylation (Zannas et al.,2014)

Nac = Nucleus Accumbens, PVN= paraventricular nucleus

The study of Covington et al., found that histone acetylation is transiently decreased right after social defeat, but is long-term increased among socially defeated mice (Covington et al.,2009). This effect might be associated with long-term, stress-induced induced reduction of histone deacetylase levels, decreasing accessibility of the DNA and therefore inducing inhibition (Covington et al.,2009). Long-term effects of stress seem to contribute to a stress susceptible phenotype (Covington et al., 2009). In addition, Covington et al., also found that when inhibiting histone deactylases pharmacologically, behavioral consequences of social defeat diminished, proving the importance of histone deactylase in the stress phenotypes (Covington et al.,2009).

An overview of epigenetic alterations affecting stress susceptibility or resilience is shown below (figure 4).

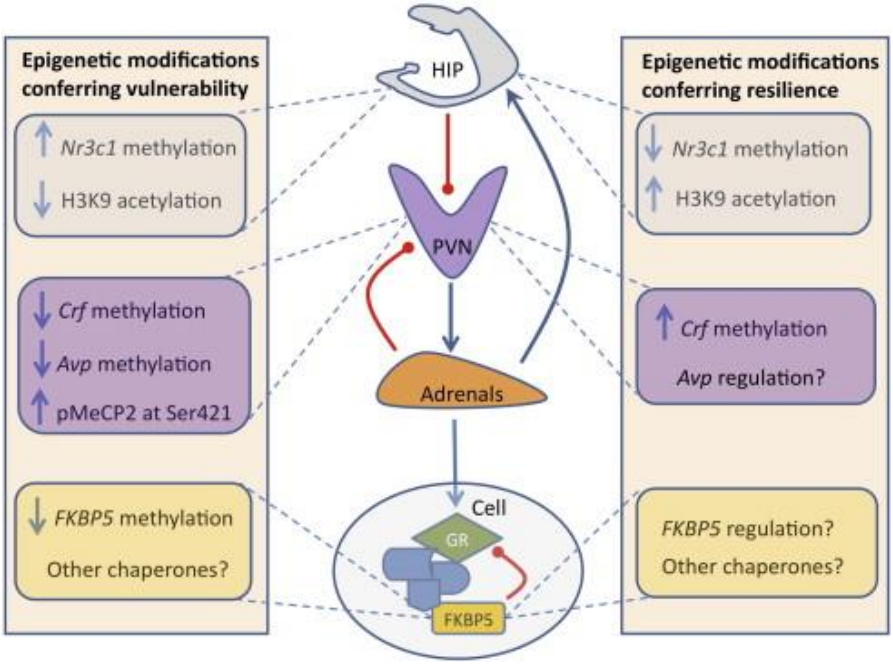

Figure 4: Overview of epigenetic modifications concerning vulnerability and resilience (Zannas et al., 2014)

Stress phenotype: genotype versus epigenetics

Literature proves that social defeat induces long-term effects, either contributing to stress susceptibility or resilience. A part of the animals undergoing the social defeat paradigm showed susceptibility to the stressor, whereas others displayed resilience (Elliot et al.,2010). Elliott et al., found that stress-susceptible mice had increased level of CRF mRNA in the PVN and decreased DNA methylation in the CRF gene (Elliot et al., 2010). Stress-resilient mice however, displayed no changes in CRF levels and DNA methylation (Elliot et al.,2010). Uchida et al., suggested that genotype specific effects might be the cause of this, proving that the combination of genes and environment establishes a certain stress phenotype (Uchida et al.,2011).
Similar results were shown in another study performed by Uchida et al., (Uchida et al., 2011). A different stress paradigm, called the chronic ultra-mild stress (CUMS), uses chronic exposure to a series of mild environmental and socials stressors (such as small cages, paired housing, light exposure)(Uchida et al., 2011). According to the study of Uchida et al., CUMS induces depression-like behavior over time (Uchida et al.,2011). Different genetic strains of mice differ in degree to which CUMS induces depressive-like behavior, suggesting an interplay between genes and environment (Zannas et al., 2014).

Conclusion

There is a delicate balance between the two stress phenotypes susceptibility and resilience. Both phenotypes are determined by differences in HPA-axis activity, in which susceptibility is generally caused by a higher HPA-axis activity and resilience by a lower HPA-axis activity. These differences in activity can be caused by genetic polymorphisms regulating intermediates of the HPA-axis. In addition, it has been proven that environmental stressors can exert significant effects, predominantly when occurring during critical time periods. Epigenetic alterations are the consequence. In conclusion, there is not a unambiguously answer to the question which factors influence HPA-axis functioning. However, from this study it has become clear that a complex interaction between genetic profile, environmental factors during critical time periods and epigenetic factors affect HPA-axis functioning, influencing the stress phenotypes.

Future research

Future research should focus on inducing stress resilience to prevent a stress susceptible phenotype and thereby stress-related pathologies. This review highlights the contribution of the genetic basis. It can be deduced from the information stated above that genetic alteration could contribute to a stress resilient phenotype. Polymorphism conducing to stress susceptible phenotypes could be altered in more stress-resilient polymorphisms. However currently, there are (mostly) ethical objections to genetic alterations. In the future, these objections might diminish or cease to exist.
This review also indicates that exposure to environmental stressors during critical time periods can influence the phenotype. More research investigating the precise epigenetic mechanisms involved in this process is necessary. Exposure to environmental stressors during critical time periods combined with genetic alterations might, in the future, pave the way to eradicate stress-related pathologies.

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