The Hyperactive HPA Axis:

A Neurobiological Link Between Childhood Trauma and Psychopathology

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Introduction

The debate between nature and nurture is an endlessly controversial topic in the field of developmental psychology. Nonetheless, studies of childhood trauma and neglect have demonstrated the long-lasting and detrimental effects of the environment on the developmental trajectory. The development of the immature brain proves to be a fascinating process characterised by dynamic stages of plasticity as well as complex biological and environmental integration. Yet, while flexibility acts as the primary strength of the immature brain, it also acts as the Achilles' heel. On one hand, the capability of early experiences to shape and consistently alter the function of the brain gives rise to vital developmental competencies such as language, however, on the other, this effect allows adverse exposures like trauma to cause maladaptive developmental trajectories. In this manner, maladaptive structures become consolidated biological characteristics that are tuned to stressful stimuli. Naturally, stress-orientated organisation likely creates a vulnerability to an array of psychological issues later in life. A burgeoning number of studies have demonstrated this, showing that early traumatic experiences have persistent and detrimental effects on psychological well-being in adulthood. Similarly, the prevalence of psychopathologies like major depressive disorder (MDD), post-traumatic stress disorder (PTSD) and psychosis in people with childhood trauma also demonstrate this issue. Moreover, in this paper, I hypothesise that the link between childhood trauma and these various psychopathologies is a result of a hyperactive stress response system, more specifically, the hypothalamic-pituitary-adrenal axis (HPA). The HPA axis is a system that, like any other system during development, is vulnerable to the effects of environmental stimuli. It underlies the mechanisms of trauma as well as the mechanisms of psychopathology, therefore, giving a reason to suggest that it plays a role in this complex relationship. Furthermore, I investigate how early life trauma causes sensitisation of the HPA axis to mild stress in adulthood and its contribution to psychopathological vulnerability.

This paper is divided into three main parts, the first two sections comprise an interdisciplinary literature review, whereas the last comprises an experiment proposal. In the first section, I demonstrate the important mechanisms of organisation at play in the brain of a developing child along with how adverse environmental stimuli become biologically incorporated into the structure and function of the adult brain. This section forms the basis for the hypothesis that early life trauma causes sensitisation of the HPA axis to stress in adulthood. In the following section, I discuss a plethora of evidence that suggests that the sensitisation of the HPA axis leads to a vulnerability to psychopathology. This section focuses on the sensitisation of the HPA axis as a mechanism of vulnerability for the development of various psychopathologies supported by various neuroanatomical and experimental evidence. The final section consists of an experiment that proposes a longitudinal study to investigate if early life stress causes sensitisation of the HPA axis to stress in adulthood and vulnerability to psychopathology as a result.

Chapter 1: Trauma & Sensitisation

The Neurosequential Model, Developmental windows & Plasticity

According to Perry (2002), the neurosequential model proposes that brain development occurs sequentially and hierarchically. This means that the more complex and unessential a system is to immediate survival, the later it develops. For instance, the brainstem is a structure that is fully functional at birth because it is needed to regulate vital functions of the heart and respiratory system. In contrast, cortical areas responsible for cognition and emotion take longer to fully develop, usually later into childhood. These systems are less of a priority in the immediate stages of development and, therefore, develop at a later stage. Moreover, the neurosequential model shows that different areas of the brain are scheduled to develop at different times based on their necessity at that given point. Because the systems of the brain have different neurodevelopmental trajectories (e.g. myelination, migration and differentiation), the systems that are in the process of being developed are more dynamic than others undergoing little neural change. This means that a system that is actively fluctuating and constructing itself is more susceptible to change as it has more elements that can be changed. Moreover, in the case of development, environmental stimuli are the key contributors to change within dynamic biological systems and can have crucial implications for the trajectory of the system.

As demonstrated by the neurosequential model, throughout human development, there are periods when certain biological systems are more plastic in response to environmental stimuli. These periods are often referred to as ‘critical’ or ‘sensitive’ periods because the exposure to stimuli that occurs during these phases is significant to how the system matures. There is, however, a notable distinction between these two types of developmental periods. A critical period is the time frame when a specific stimulus is necessary for the system to develop in a certain way. The sensory stimuli, or lack of, experienced during these periods largely determines the physical and behavioural capacities of the biological system (Levelt & Hübener, 2012, p. 310), however, they do not have an effect before or after the onset. An experiment famously performed by Hubbel and Weisel (1970) demonstrated how during a critical period, the absence of light in the eyes of kittens caused an unusual development of the visual cortex. This showed that certain stimuli, or in this case the absence of stimuli, have to be present to allow for the correct development of associated brain systems, in this case, the visual cortex. Sensitive periods, on the other hand, are the time frames when a system is vulnerable to certain stimuli but the impact is not vital to the trajectory of the system e.g. Language learning (Perry, 2002). Despite being more ambiguous than critical periods, periods of sensitivity are much more of interest in this investigation into trauma. This is simply because pinpointing the exact moment in which a stimulus has an effect is a lot more difficult than identifying a *period* in which a system is vulnerable. In addition to this, the general concepts of how a period becomes sensitive are well versed in contrast to limited knowledge about critical periods.

To demonstrate the importance of sensitive periods it is first important to understand

how they operate. A sensitive period is triggered by intense neural activity initiated by experience or developmental progression (Zhou, Tao & Poo, 2003). This phenomenon can be characterised as the ‘opening’ of a sensitive period, a point from which the developing system is receptive to environmental stimuli. In contrast, Johnson (2005) describes how the termination of a sensitive period is characterised by a significant decline in plasticity and has three categories of explanation: The first describes how endogenous factors are altered by either biological maturation or environmental triggers. An interpretation of this is that these triggers (maturational or environmental) cause neurochemical changes in certain areas of the brain. In turn, this increases synaptic pruning and neural patterns in these areas become permanently connected, therefore, indicating the end of a sensitive period. The second category illustrates learning as a self-terminating structure. Inspired by computational models, this perspective highlights how systems that have not specialised have a high level of plasticity meaning that the connections within these systems are sensitive and adaptable to error signals. Further, as the system specialises and changes in response to these signals, it becomes rigid and less sensitive as a result. An example of this is language learning; it is more difficult to learn a second language as an adult as the primary language has already been learnt. Essentially, what this means is that learning in one particular way obstructs learning in another and, therefore, reduces plasticity. The third and final explanatory category describes how the constraints of plasticity become stable and plasticity itself does not reduce. For instance, as the distance between an infant's eyes changes, the information received by areas in the visual cortex changes. To keep up with these changes, the cortical areas of the brain must be plastic. However, plasticity does not decline once growth stops rather it becomes constrained once the eyes become fixed. What this means is that plasticity does not cease to exist rather it becomes ‘hidden’ by the factors that constrain it.

Despite the variability between these explanations, all three indicate a reduction of the synaptic plasticity as an endogenous mechanism. In other words, a sensitive period is characterised by its plasticity; so how does plasticity make a period vulnerable? Since many neural circuits are undifferentiated in early life, they must rely on environmental stimuli to sculpt and structure them, a process known as activity-dependent organisation (Perry & Pollard, 1998). Activity-dependent organisation means that the circuits adapt and structure themselves depending on experiences that activate them. The plasticity of the circuits allows them to be sensitive to stimuli and, therefore, transform based on these experiences. These architectural transformations are guided by three mechanisms of activity-dependent organisation: The first is axonal elaboration; the scope of the axon grows and creates new connections (Niell & Smith, 2004). The second is synaptic elimination; the density of dendritic spines decreases, eliminating redundant or weak connections (Antonini & Stryker, 1993). Finally, the last process is synaptic consolidation; This occurs when the synapse and postsynaptic neuron are repeatedly activated. This strengthens the fundamental structure of the synapse, preventing it from being eliminated (Benson, Schnapp, Shapiro & Huntley, 2000).

The Mechanism of Trauma in Children

Plasticity is an imperative function that allows organisms to carry out important functions like language learning, however, it is important to note that because the structure of neural networks is based on experience, it can be sculpted just as easily by negative experiences. To highlight this, the following section focuses on the mechanisms of trauma in children and how they become integrated into the brain. This demonstrates how the human brain organises itself in an activity-dependent manner as well as how trauma can cause vulnerability to stress later in life.

According to Perry, Pollard, Blakley, Baker, & Vigilante (1995), the mechanism of trauma is composed of two main response systems: The stress response, referred to as hyperarousal, and the dissociative response, referred to as dissociation. The first mechanism, hyperarousal, is mediated by the sympathetic nervous system causing symptoms such as increased blood pressure, heart rate, respiration, hypervigilance or crying and screaming in children. While hyperarousal or the 'fight or flight' response is a very adaptive mechanism in adults, it is not as useful for children and infants who lack the physical capabilities to flee or defend themselves. Instead, the main purpose of this response in children is to attract a primary caregiver who can protect or remove them from the situation, hence the presentation of crying or screaming (p. 279). Brunson, Avishai-Eliner, Hatalski & Baram (2001) identified the main neurobiological processes of hyperarousal in both immature and adult animal models (rodent and primate), demonstrating that the stress response occurs in a few major circuits. The first system is the HPA axis. This system is regulated by corticotropin-releasing hormone (CRH), an important hormone that is released immediately after the presentation of stressful stimuli. CRH causes the secretion of adrenocorticotropic hormone (ACTH) in the anterior pituitary further causing the secretion of glucocorticoids from the adrenal cortex. The second major stress response system of the body resides in the limbic system. The limbic system refers to a variety of interconnected regions of the brain, however, one of the most important structures in this system is the amygdala. The amygdala, more specifically the central nucleus of the amygdala, plays an important role in the regulation of the stress response by triggering the sympathetic and endocrine responses of the HPA axis in response to threatening stimuli. As well as this, the amygdala, along with other limbic structures like the hippocampus, contain CRH receptors (Yan, Toth, Schultz, Ribak & Baram, 1998; Gray & Bingaman, 1996). This indicates that CRH plays a role in the activation of these limbic structures in the presence of stressful stimuli.

Perry et al. (1995) refer to the second stage of trauma, dissociation, as a reaction to further stressful situations. As mentioned, vocalisation is the initial response of a child in the hyperarousal state, however, it is only functional as long as it is met with aid from a caregiver (p. 279). Therefore, if there is an absence of substantial responses from the caregiver over time, the child will likely progress down a path of dissociative behaviours varying from 'freezing' (allows the child to analyse the environment and assess how to respond) to full dissociation. Dissociation acts as a mechanism of last resort to trauma that is consistent and without relief, causing the child to retreat inwards becoming numb, compliant and avoidant or even depersonalised. Moreover, children that are unable to utilise their 'fight or flight' response

effectively will fall back on their dissociative response mechanisms. The parasympathetic nervous system instigates this dissociative reaction by increasing the circulation of opioids that reduce pain and mobility (Fanselow, 1986) as well as elevated levels of the behaviour inhibitor, cortisol. These effects instigated by the parasympathetic nervous system are the opposite to that of the sympathetic nervous system in the sense that the intention is to conserve energy rather than expend energy. This means that the child can maintain homeostasis in the presence of sympathetic arousal, however, it is important to remember that both the sympathetic and parasympathetic nervous systems of the child are overactivated.

As explained previously, the immature neural structures in young children are plastic and organise in an activity-dependent fashion. This means that the neural circuits that are most commonly activated will become strengthened since they are the most 'used' systems. In the context of trauma, children who are exposed to adverse experiences repeatedly will likely consolidate the certain states of being that they experience the most, in this case, hyperarousal and dissociation. Therefore, because these traumatic states are 'used' the most, they are the default setting of these circuits which can turn into enduring attributes of the mature brain. An example of how early traumatic experiences influence activity-dependent organisation can be demonstrated by attachment theory. In essence, attachment theory categorises how infants learn to cope with stress based on their relationship with their caregiver. In a study by Main & Solomon (1986), the vast majority of infants that were maltreated were characterised by a category called disorganised/disoriented attachment. These same children were found to be the least able to deal with situations of acute stress compared to the other attachment types, measured by their reaction to the situation as well as heart rate and cortisol levels. Similarly, the children of this categorisation also exhibited freezing behaviours, becoming dazed and disorientated indicating an overactivation of the parasympathetic nervous system. These behaviours resemble both hyperarousal and dissociation, the two states of trauma. Because these attachment styles are differentiated at an early age, it is likely that the early brain systems involved in this process are highly sensitive and, therefore, adapt to the surrounding experiences. Research investigating patterns of glucose metabolism in the brains of newborns uncovered that the second-highest levels of activity were in limbic areas associated with emotion, such as the hypothalamus, amygdala and basal ganglia. According to the neurosequential model, this research shows that the systems governing emotion must be of high importance for infant survival (Chugani, 1998). Therefore, because these systems are organised in an activity-dependent manner during a period of sensitivity, maladaptive organisation occurs, in turn, creating a disorganised/disoriented attachment style.

Hazan and Shaver (1987) showed how infant attachment styles are associated with certain outcomes in romantic relationships and demonstrated how individual's conceptual models of the self and relationships are related to that of their attachment style. This highlights how early experiences can have long-term developmental effects. Much like attachment styles, traumatic states also likely extend into adulthood. As mentioned previously, synaptic pathways consolidate and prune throughout childhood meaning that those who have developed hyperactive and dissociative responses to stress as children will likely retain them into matures. Consequently, the adults who have been exposed to traumatic states will likely be the least equipped to deal with stress and are vulnerable to developing psychopathology as a result. In

short, those who experience trauma during early stages of neural plasticity develop a stress response that is dysregulated and, therefore, sensitive to stress. While I believe that both hyperarousal and dissociation are important mechanisms that are involved in the development of various psychopathologies, I have chosen to focus solely on the state of hyperarousal because of its overt and well-researched implications. Furthermore, in the next section, I will demonstrate literature that links the sensitisation of the HPA axis to psychopathological vulnerability.

Chapter 2: Sensitisation & Vulnerability to Psychopathology

As established previously, the limbic system activates the sympathetic nervous system which, in turn, stimulates various neuroendocrine structures such as the HPA axis. These systems are shown to be some of the primary structures that instigate the effects of stress as well as regulate them. In the context of childhood trauma, these systems often become overactive, allowing activity-dependent organisation to incorporate and maintain these atypical conditions into adulthood. Because of this, the brain is organised in a manner that it is more sensitive to stressful stimuli, creating a disposition for a variety of psychopathology to develop. Moreover, in this section, I demonstrate how trauma-induced states of hyperarousal influence the development of the associated systems and how that creates a disposition for psychopathological conditions.

The Hyperactivation of the HPA Axis

The HPA axis is one of the fundamental systems involved in the body's stress response. Much like many other systems of the body, the HPA axis is also developing throughout early childhood, indicating that its trajectory is vulnerable to change. Because of this, there is a variety of evidence suggesting that maltreatment early in life can disrupt the development of the HPA and this, in turn, is linked to psychopathology. For example, Heim, Mletzko, Purselle, Musselman and Nemeroff (2008) found that men with a history of childhood trauma (moderate to severe physical or sexual abuse) and major depressive disorder (MDD) showed increased ACTH and cortisol responses to a dexamethasone/CRH test (a procedure that asses adrenal function by observing cortisol levels in response to a dexamethasone injection). These responses strongly indicated an overactive HPA axis, especially when compared to the control sample and those without abusive pasts. According to the study, responsiveness to the test was correlated with the duration, severity and age of onset of the abuse (p. 402). This suggests one of three things: firstly, the HPA axis likely endures a period of sensitivity during childhood, possibly beginning from birth and extending into childhood. Secondly, a dysregulated HPA axis may be the result of trauma during a sensitive period of activity-dependent organisation. Thirdly, the dysregulation of the HPA axis can lead to or create sensitivity to psychopathologies such as

depression and PTSD. Furthermore, while the mechanism at play is still unclear, it is evident that there is a relationship between the dysregulation of the HPA axis and the development of psychopathology. To gain greater insight into the link between early trauma and the development of psychopathologies related to the HPA axis, it is necessary to investigate its components.

The Hypersecretion of CRH

A vital element of the HPA axis is the hormone CRH. There is a variety of evidence suggesting that CRH plays a critical role in mediating the relationship between adverse experiences and mood and anxiety disorders (Heit, Owens, Plotsky & Nemeroff, 1997). Since it is the major regulatory hormone of the HPA axis and is widely distributed across the central nervous system (CNS), persistent dysregulation would, intuitively, have unfavourable effects. According to a variety of studies, this seems to be true; dysregulation, mainly hyperactivity of CRH, has been associated strongly with a variety of psychiatric illnesses; mainly mood and anxiety disorders like depression and obsessive-compulsive disorder (OCD) (Banki, Karmacsi, Bissette & Nemeroff, 1992, p. 454-5; Altemus, Swedo, Leonard, Richter, Rubinow, Potter & Rapoport, 1994). As well as being evident in many psychological disorders, CRH also seems to play a role in forming psychopathological predispositions; An experiment using rat models showed that severe stress (characterised by long periods of maternal separation) resulted in greater vulnerability for stress in adulthood (Plotsky & Meaney, 1993, p. 197-9). As CRH is the main regulatory hormone of the HPA axis, hyperactivity indicates excessive CRH production, described as hypersecretion. This study highlights how high levels of stress in early life (thus implying CRH hypersecretion) creates a disposition to stress in adulthood. Similar investigations have been conducted in human studies: An experiment conducted by Heim, Newport, Heit, Graham, Wilcox, Bonsall & Nemeroff (2000) measured the ACTH, cortisol and heart rate responses in women with a history of child abuse and depression, women with a history of child abuse and a control group. The women that had a history of child abuse had elevated autonomic and pituitary-adrenal responses to the standardised test in comparison to the controls. Further, the women that were abused as children *and* suffered from MDD exhibited the greatest stress response. Much like the rat model, this experiment suggests that early adverse experiences induce CRH hypersecretion causing sensitivity to stress and, in turn, forming predisposition to psychopathologies like depression.

A similar study by Heim, Newport, Bonsall, Miller and Nemeroff (2001) measured the plasma ACTH and cortisol responses to CRH as well as the plasma cortisol response to the administration of ACTH in various women. Like the previous study, the experiment used women with MDD and a history of childhood abuse, women with a history of childhood abuse and no MDD and women with MDD but with no history of childhood abuse. The results showed that there were greater ACTH responses in the women with a history of child abuse without MDD whereas there was a blunted ACTH response in the women suffering from MDD both with and without a history of child abuse. The observation of blunted responses in the women with both MDD and childhood abuse seems to be contradictory with the previous evidence, however, this is not the case. Heim et al. demonstrated that this was an adaptive ‘down-regulation’ response

to persistent hypersecretion of CRH due to consistent stressors, resulting in a blunted ACTH response. The women in this study produced either exaggerated or stunted responses to stress indicating that early life trauma creates vulnerability to stress in adulthood regardless of how it is regulated. Furthermore, both of these studies indicate that adverse early life experiences hyperactivate CRH circuits and, therefore, the HPA axis making them sensitive to stressful stimuli. Consequently, this creates a predisposition for the development of psychopathologies in adulthood such as depression.

Brain-Derived Neurotrophic Factor & Sensitivity to Psychosis

While it is readily established that there is a plausible link between trauma, the HPA axis and the development of various anxiety and mood disorders, there is little discussion about the association between a hyperactive HPA axis and psychosis. Leading theories about psychotic disorders tend to use the diathesis model (the interaction between gene expression and environment creates a psychosis) which makes it difficult to untangle the exact environmental mechanisms that contribute to psychosis. However, it is not unreasonable to think that the HPA axis could play a role in this model since there are a burgeoning number of studies that link both childhood trauma and HPA axis hyperactivation to the emergence of psychotic disorders (Lardinois, Lataster, Mengelers, Van Os & Myin-Germeys, 2011; Morrison, Frame & Larkin, 2003; Read, Agar, Argyle & Aderhold, 2003; Larkin & Read, 2008; Sugranyes, Thompson & Corcoran, 2012; Borges, Gayer-Anderson & Mondelli, 2013). Brain-derived neurotrophic factor (BDNF) is a protein that plays a role in neuroplasticity and the release of neurotransmitters especially in the hippocampus (Sahu, Malavade & Jacob, 2016). Low levels of BDNF have been associated with risk of psychosis (Sahu et al., 2016) and thus have been considered a biomarker of psychotic disorders. Interestingly, low levels of BDNF have also been associated with childhood trauma; Theleritis, Fisher, Shäfer, Winters, Stahl, Morgan and Russo (2014) conducted a study investigating levels of BDNF using a sample of first-episode psychosis (FEP) cases. The study concluded that BDNF levels were significantly lower in those that had experienced a traumatic childhood event than those who hadn't, indicating that early stressful experiences create significant biological changes that influence the levels of neurochemical that facilitate neuroplasticity in the brain.

Findings by Walker and DiForio (1997) have shown that schizophrenic patients had higher baseline levels of cortisol, the hormone that is produced by the HPA axis. Similarly, Non-suppression in the dexamethasone suppression test (DST) - a way of assessing the regulatory mechanisms of the HPA - has been associated with the hyperactivation of the HPA axis (Aleem, Kulkarni & Yeragani, 1988) and is now a well-established trait in patients with schizophrenia (Walker & DiForio, 1997). Larger studies have also highlighted the relationship between childhood trauma and psychotic disorders. For instance, a study of 4433 participants investigated the effect of trauma in children up to the age of 17 (Croft, Heron, Teufel, Cannon, Wolke, Thompson, Houtepen & Zammit, 2018). The key findings of this study were that firstly, trauma before the age of 18 significantly increases the chance of psychotic symptoms. Secondly, the exposure to three or more types of trauma before the age of 18 increased the probability of experiencing psychotic symptoms by 4.7 fold. According to this study, any

exposure to trauma causes sensitivity to psychosis and persistent exposure to trauma indicates even greater sensitivity. Moreover, this demonstrates the hypothesis that childhood trauma hyperactivates the HPA axis and makes it more sensitive to environmental stressors. This also demonstrates that the more disruption the HPA axis undergoes during childhood, the more likely one is to develop a psychotic disorder, thus, indicating that there is indeed a relationship between psychotic disorders and a hyperactive HPA axis.

A study by Tienari (1991) investigated the interaction between genetic vulnerability and environment in adopted children whose biological mothers had schizophrenia. The adopted children were placed into adoptive families that were either deemed 'healthy' or 'disturbed' and follow-ups were made on the mental health of the children. The term 'disturbed' in this context is used to describe families that ranged from moderate to severe in domains like conflict resolution, the rigidity of psychological boundaries and inflexibility to change. The results showed that if even one of the two adoptive parents was 'disturbed' the likelihood of a child developing 'severe and psychotic' characteristics increased substantially (p. 462-7). Further, the attributes that constitute a 'disturbed' family overtly indicate a stressful and chaotic environment. This suggests that the adoptees experienced a lot of environmental stressors from an early age and, therefore, had an increased likelihood of developing a hyperactive HPA axis. Further, as demonstrated, dysregulation of the HPA axis can create sensitivity to environmental stressors and, in turn, contribute to the development of psychotic disorders. Furthermore, the HPA axis plays some sort of regulatory role in the prevalence of psychotic disorders such as schizophrenia.

Because of the strong basis for psychotic disorders in genetics and environment, the exact mechanism is unclear. However, the given evidence suggests that traumatic early life experiences increase sensitisation to environmental stimuli, in turn, laying a foundation for psychotic disorders to manifest. Moreover, the research indicates that childhood trauma does indeed have an impact on the development of psychopathological structures in the HPA axis. The compilation of research shows that the main psychopathological structure that presents itself is the dysregulation of the HPA axis. The exact mechanism that is common throughout the studies is that hyperactivity leads to the sensitization to stress of various components of the HPA axis. Consequently, this sensitisation is strongly linked with a variety of different mood, anxiety and psychotic disorders showing that childhood trauma can indeed affect the development of psychopathological structures.

Morphological & Functional Implications in the Limbic System

Another important implication of HPA axis hyperactivity is its effects on the morphological and functional changes that occur in the limbic system, more specifically the hippocampus. The hippocampus is a limbic structure that plays an important role in forming and storing contextual-dependent memory (Fanselow, 2000), however, this is not its only function. It contains a high density of glucocorticoid receptors that have been hypothesised to play a role in the glucocorticoid negative feedback system that moderates the HPA axis (Sapolsky, Armanini, Packan, Sutton & Plotsky, 1990). This indicates that the hippocampus plays some role in the regulatory stress response of the HPA axis, therefore, it's likely that hippocampal anatomy and

functions are susceptible to the dysregulation effects of the HPA axis. An indication of this can be demonstrated by morphological changes to the hippocampus as a result of trauma. For example, a study by Stein, Koverola, Hanna, Torchia & McClarty (1997) involving women who were sexually abused as children found that left-hippocampal volume was significantly reduced in the abused women in comparison to the controls. The women that showed diminished hippocampal volume also showed dissociative and other symptoms of PTSD. Similarly, the severity of these symptoms, predominantly the dissociative symptoms, was correlated with the volume of the left-sided hippocampus. This indicates two things: firstly, the hippocampus is a structure that is vulnerable to the hyperactive stress response mediated by the HPA axis, thus it is involved in the stress response. Secondly, the effects of stress can decrease hippocampal volume and pave the way for psychopathologies such as PTSD. As demonstrated earlier in this paper, the dysregulation of the HPA axis is not specific to one single pathology. The same is true for significant reduction of hippocampal volume; it is prevalent in both schizophrenia (Suddath, Christison, Torrey, Casanova & Weinberger, 1990) and depression (Bremner, Narayan, Anderson, Staib, Miller & Charney, 2000) as well. Depression is one of the psychopathologies most commonly linked with diminished hippocampal volume, Bremner et al. (2000) suggest that high levels of glucocorticoids during episodes of depression could cause hippocampal, in turn, reducing volume. This mechanism is, again, associated with the hyperactivation of the HPA axis. Seemingly contradictory results from a longitudinal study researching the hippocampal volumes of adults who survived recent traumas showed that there were no changes to the size of the hippocampus (using MRI) (Bonne, Brandes, Gilboa, Gomori, Shenton, Pitman & Shalev, 2001). However, these findings are not contradictory. They simply indicate that hippocampal volume decreases over a longer period of stress, for instance, child abuse, MDD or fighting in a war. Moreover, the co-occurrence of childhood trauma in morphological abnormalities in the hippocampus seems to show that a persistent dysregulated stress response often associated with childhood trauma likely creates or leads to the formation of morphological abnormalities in the hippocampus. Furthermore, these structures have high comorbidity with the prevalence of psychopathologies such as PTSD, depression and schizophrenia.

Inflammation

Finally, the last structure affected by the HPA axis is the body's inflammatory response. The purpose of the body's inflammatory response is to repair damaged tissues and prevent the intrusion of disease in the body. It is an innate immune response that releases phagocytes and acute phase proteins into the circulatory system that travel to the site of infection. This mechanism is triggered in response to foreign objects/infections in the body, however, it can also be triggered by short or long term psychosocial stress. Psychosocial stress triggers the sympathetic nervous system which initiates the inflammatory response. It is an anticipatory reaction to wounds or disease that are yet to happen rather than the damage that has already occurred. While this mechanism may have once served a greater purpose, the environmental stressors in the modern world are not the same as they once were. However, the mechanism of inflammation is still a topic of interest as it can attack the body if uncontrolled, a process which

has been associated with the development of depression. According to Li & Danese (2018), the mechanism of inflammation is controlled in one of two ways: partly by the parasympathetic nervous system and also by the HPA axis. As mentioned previously the parasympathetic nervous system has the opposite effect on the sympathetic nervous system, by counteracting the consumptive effects with conservative effects. The problem with both of these systems is that those who have hyperactive HPA axes and parasympathetic nervous systems will not be able to exhibit an anti-inflammatory response. This means that children that have experienced trauma will likely have impaired response systems (like the HPA axis and parasympathetic nervous system) that will not be able to protect them from the inflammatory response. Moreover, children that have these impairments are susceptible to autoimmune damage caused by the inflammatory response and, therefore, become vulnerable to developing associated psychopathology like depression (Dantzer, O'Connor, Freund, Johnson & Kelley, 2008; Miller, Maletic & Raison, 2009).

Chapter 3: Experiment proposal

Background

Childhood trauma has been linked to the development of psychopathological physiology in the brain and body. A structure of interest is the HPA axis, a system that often becomes dysregulated as a result of trauma and underlies a variety of psychopathologies. The studies presented in this paper indicate a relationship between childhood trauma and the dysregulation of the HPA axis, however, this data is largely cross-sectional meaning that a causal relationship cannot be established. Thus, the purpose of this study is to provide a longitudinal framework that will identify a cause and effect between these factors. Further, another aim of this study is to evaluate the presence of various psychopathologies between participants and the relationship this has with trauma and HPA regulation. Moreover, this leads to two main hypotheses. Firstly, trauma during early life (regardless of type) will indicate an overactive HPA axis response to mild stress. Secondly, those that have the highest response rates of reactivity will be the most inclined to develop psychopathologies such as anxiety, mood and psychotic disorders.

Aims

This study aims to investigate if early life stress causes sensitisation of the HPA axis to stress in adulthood and vulnerability to psychopathology as a result.

Design

The design of this experiment is longitudinal. The purpose of this is to establish a causal relationship between the independent and dependent variables. The independent variables are childhood trauma and psychopathology. The dependent variable is the peak level of cortisol.

Participants

Communities with the highest risk of victimisation are often those of low socioeconomic status (high instances of poverty, unemployment and violence) (CDC, 2020; WHO, 2020). Therefore, a sample of 'at risk' children should be taken from a neighbourhood that meets these criteria. Participants must have no history of abuse in any form (physical, emotional, sexual etc.). Participants should be between the ages of 8-17 in order to fit the requirements of the screening apparatus to determine their eligibility to take part in the study. Participants are recruited through leaflets in local areas or online through various clinical study websites. Written informed consent is given by all the participants and they are all given a verbal and written explanation of the study. Participants are compensated for their involvement.

The control group is derived from the sample group; these participants are characterised by the absence of trauma after the second measurement (Phase 2). The purpose of the control group is to compare HPA axis reactivity in those who have not experienced trauma during early life with those who have. This will indicate the influence of trauma on the HPA axis and the development of various psychopathologies. Deriving the control group from the sample also helps to control for various environmental and cultural factors that would otherwise need to be controlled for statistically. The sample size is calculated using standard measurements seen across a variety of similar studies: a confidence level of 95%, a margin of error at 5%, a population proportion of 50% and an unlimited population size. Using an online calculation tool and these parameters, the minimum sample size necessary to obtain a significant result is 385. Taking into consideration that this study takes place over a long period, it is vital to recruit more participants than this number as the likelihood of having many dropouts is very high. Therefore, recruiting at least 500 participants or more is suggested to make sure this study produces significant results.

Procedures

This experiment is longitudinal and follows participants over the span of 10 years utilising children of the ages of 8-10 and again at the ages of 18-20. The purpose of this is to observe changes in the HPA axis that occur as a result of childhood trauma, thus it is necessary to observe children pre-trauma and adults post-trauma. Based on theories such as the neurosequential model, activity-dependent organisation and plasticity it is likely that traumatic experiences have a greater effect when experienced at a younger age than in comparison to late adolescence. This means that it would be ideal to measure trauma from a younger age, however, this is a costly and time-consuming process. Similarly, there are little trauma scales that measure from an age younger than 8. This means that there would have to be some level of involvement from parents of which there are some studies investigating the effects of physical abuse in young children where parental involvement was successful. However, this does not seem to be the case with both sexual and emotional abuse. Therefore, this experiment provides a more economic and realistic alternative to investigate causal relationships between various types of trauma.

The study is broken down into two phases: the first investigates HPA activity of participants (as children) who have not experienced trauma. The second phase investigates the HPA activity of participants (as adults) who have and have not experienced trauma.

Phase 1

The experimental group of children are assessed using the Juvenile Victimisation Questionnaire (JVQ), a tool that screens for victimisation in both degree and nature. The JVQ test can be implemented as a clinical interview (for younger participants) or in written form. The purpose of this test is to eliminate any children that have been abused prior to the study and thus help to isolate trauma as a causal factor of an overactive HPA axis.

After the interview, the children are asked to perform the Trier Social Stress Test for Children (TSST-C). The TSST-C is a standardised psychosocial procedure used to activate the HPA axis. It is economical, effective (Kirschbaum, Pirke & Hellhammer, 1993) and less invasive than the dexamethasone/CRH test. Firstly demonstrated by Buske-Kirschbaum, Jobst, Wustmans, Kirschbaum, Rauh and Hellhammer (1997), the TSST-C is adapted to the abilities of the child in comparison to the standard TSST. The test involves an endocrine and autonomic stress response through a 5-minute (increased to 10-minutes for adults) participation/anticipation followed by a 5-minute (increased to 10-minutes for adults) public speaking and arithmetic task in front of an audience. The standard protocol for the TSST is to take blood samples to measure cortisol and ACTH, which, as a procedure, requires multiple intensive and invasive blood collections. Frankly, this is an unsuitable way to measure HPA activity in children so alternatively, cortisol concentration can be derived from salivary samples. As observed in previous experiments, cortisol is tightly linked with the regulation of the HPA axis and has been demonstrated as an effective method to evaluate HPA function (Törnhage Carl-Johan, 2009). Therefore, salivary concentration tests are optimal for this experiment as they are fast, simple, suitable for all ages and provide accurate results that can be used to interpret the function of the HPA axis. On average, previous experiments investigating salivary cortisol show that concentrations seem to peak around 10-minutes after a stressful event (Petrowski, Herold, Joraschky, Wittchen & Kirschbaum, 2010; Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009; Rimmele, Seiler, Marti, Wirtz, Ehlert & Heinrichs, 2009), however, there is also evidence to suggest that concentrations peak at 5 and 20 minutes after exposure (Childs, Vicini, & De Wit, 2006; Rohleder, Schommer, Hellhammer, Engel & Kirschbaum, 2001).

Based on this information, I propose a total of six saliva tests at 10-minute intervals: the first test should be administered 10 minutes before the TSST. The first and second tests should be used to provide a baseline off of which the following tests can be compared. Tests 3-6 should be used to observe the peak of cortisol in the participants.

Kalman and Grahn (2004) demonstrate a cost-effective and accurate methodology for saliva collection. Firstly, a cotton ball is placed into the mouth of the participant until saturated in salvia. Then the contents of the cotton ball are squeezed into a microfuge tube using protective gloves until about 200µl of saliva are extracted. The saliva sample is then frozen as soon as possible to prevent mould. The second stage is the salivary cortisol assay, this procedure can be carried out using a widely available enzyme-linked immunosorbent assay (ELISA) kit. The results of this procedure are recorded.

Phase 2

The second phase is repeated ten years later when the participants are legal adults (18-20 years old) and have endured puberty.

The reactivity of the HPA axis is also tested again using the same test (TSST) but this time with anticipation, public speaking and arithmetic tasks increased to 10-minutes. Saliva is measured in the same fashion as described in phase 1.

The participants will be asked to take a psychopathological evaluation, such as the Minnesota Multiphasic Personality Inventory (MMPI), followed by an Early Trauma Inventory (ETI) test. The purpose of the MMPI test is to later observe which participants developed mental illnesses so as to observe a causal relationship between HPA hyperactivity and the development of various mental illnesses. A structured clinical interview using the DSM-V is also applied to those who require an MDD, FEP and PTSD diagnosis. The Hamilton Rating Scale for Depression was used to quantify the symptoms of depression. The Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS). The Clinically-Administered PTSD Scale (CAPS) is used to assess PTSD (Blake, Weathers, Nagy, Kaloupek, Gusman, Charney & Keane, 1995). The purpose of the ETI is to see which of the participants have suffered from physical, emotional or sexual abuse since the last phase. The ETI consists of a structured interview that scores the different trauma types based on their duration and frequency which contribute to an overall score (Bremner, Vermetten & Mazure, 2000). This test is completed after the TSST as recalling trauma may induce hyperarousal and distort the cortisol levels in saliva.

Measuring peak cortisol levels to indicate HPA axis activity. We take this over 6 samples over an hour during a mild stress test. The test is repeated when the participants are children and then again in adults. The children have not experienced trauma whereas some of the adults will have. The purpose of this is to see how trauma causes the development of HPA hyperactivity. This is then combined with data taken from the participants as adults regarding psychopathologies.

Data Analysis

This experiment is carried out using a 2-way ANOVA, comparing the independent variables of psychopathological vulnerability (characterised by the presence of psychopathology) and trauma to the dependent variable of peak salivary cortisol concentration. One may argue that trauma and psychopathology are dependent variables, however, given the cross-sectional research surrounding this topic, it seems that they are correlated at best. The purpose of this experiment is to show that the HPA axis is the mediator between these two variables meaning that, yes, they are connected, however, they are not dependent on each other. Therefore, in this experiment, trauma and psychopathology will be counted as independent variables. The levels of the group ‘Psychopathological vulnerability’ includes first-episode psychosis (FEP), Major depressive disorder (MDD), post-traumatic stress disorder (PTSD) and the absence of psychopathology. These levels are most prevalent psychopathologies linked to hyperactivity of the HPA axis and, therefore, most of interest. The levels of the group ‘Trauma’ include sexual, physical and emotional abuse as well as the

absence of abuse. The absence of trauma/psychopathology was included in both groups to ensure the presence of a control. The differences (Delta) between peak cortisol levels recorded in phase 1 and phase 2 are calculated allowing for the data of two time points to be combined and analysed as one. The data from the psychopathological test (prevalence/absence of MDD, PTSD or FEP), trauma inventory (prevalence/absence of sexual, physical or emotional abuse) and cortisol measurements are put into the statistics software SPSS. From this, it will be possible to see if psychopathological vulnerability and trauma explain a significant amount of variation in peak salivary cortisol concentrations. The 2-way ANOVA will only show which parameters are significant, therefore, a post-hoc test such as the Tukey's Honestly-Significant-Difference (Tukey HSD) test can be used to see which levels were different from each other.

Results

According to the information put forward in the literature review, the results should indicate that all types of trauma (sexual, physical and emotional) should have a significant effect on the independent variable, salivary cortisol concentration. The same should also be true for the other independent variable psychopathology, however, the effect would likely be the strongest among patients with PTSD and depression according to current literature. Another possible result, highlighted in the previous experiments, could be a blunted cortisol response to the stress test. This was previously described as an 'adaptive response' to highly stressful situations, something researchers should be aware of.

Limitations

While there are many benefits to carrying out a longitudinal study, there are also many disadvantages. Firstly, it is without a doubt that this type of investigation is both expensive and time-consuming. This study is, in fact, rather simple, however, because it spans over 10 years the resources required become increasingly costly. Secondly, because of this period, there will be many drop-outs. This is a limitation that is out of the control of the researchers and the best they can hope for is recruiting enough participants at the beginning of the study to account for those who decide not to participate the second time.

Conclusion

In conclusion, there is a variety of evidence suggesting that hyperactivity in the HPA axis is a characteristic of childhood trauma. Theories about developmental windows, plasticity and activity-dependent organisation demonstrate how adverse early life experiences can become integrated into development. Similarly, many experiments and case studies have shown the underlying role of an overactive HPA axis in the development of psychiatric illness such as depression, PTSD and psychosis. Together, this indicates that early life trauma can cause consistent sensitisation of the HPA axis to mild stress in adulthood and thus contribute to psychopathological vulnerability. Additionally, an important question to ask is what suggestions

can be made with this knowledge? Firstly, further investigations can be made in this area to prevent the negative repercussions of early life trauma. For instance, CRH receptor antagonists are currently being developed as a preventative therapy for individuals exposed to early life stress. Human trials of these antagonists have yet to be carried out, however, this thesis gives support for research in this area. Secondly, investigations into the second stage of trauma (dissociation) could provide a better understanding of the underlying mechanism of psychopathologies, especially dissociative disorders. It was not possible to incorporate both stages of trauma into this thesis yet this is an area for possible research in the future. Lastly, this research highlights the complexity that is development and the importance of protecting children from adverse early experiences. Furthermore, greater investigations need to be made into this area of research in order to establish a causal link between the dysregulation of the HPA axis, trauma and various psychopathologies. The evidence presented in this paper is by no means exhaustive and shows potential for future research in this area.

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