EARLY LIFE STRESS LEADING TO OPPOSITIONAL BEHAVIOUR VIA THE AMYGDALA-PREFRONTAL CIRCUIT

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Insights

There is no standard and correct way to raise a child. Even when you try your best to give them all the care they need, there are many uncontrollable aspects that could affect a child's upbringing, ultimately affecting adulthood. These aspects range from their genetic background to environmental challenges, such as a traumatising event. Researchers have found that children who are exposed to these high stressors are more likely to become aggressive. Interestingly, this is not just due to the emotional effect of the event. It has been described in literature that a structural change in the brain due to exposure to stress could also lead to oppositional behaviour. This article will dive more into detail on what is known about the effect of exposure to high stressors in childhood on the brain, resulting in different types of aggressive behaviour.

Introduction

Early life stress (ELS) can be identified as child maltreatment or chronic poverty with behavioural problems [1]. Exposure to ELS could lead to long-lasting emotional difficulties and aggressive behaviour in adulthood [2]. Besides, it has become evident that ELS is associated with a higher incidence of mental health problems across the lifespan [2]. This oppositional behaviour is caused by compromised brain development due to ELS [3]. It is therefore crucial to investigate the possible neurobiological mechanisms that are involved in this increased risk for psychopathology. Important regions involved in emotion regulation, threat-reactivity and aggression are the prefrontal cortex (PFC), hippocampus and amygdala [1]. While the amygdala and hippocampus are directly associated with this regulation of emotions, the PFC is thought to regulate the activity of the amygdala creating an amygdala-PFC circuitry [4]. Studies suggest that a change in this amygdala-PFC circuitry could affect oppositional behaviour [2]. Therefore, in this paper the effect of ELS on the amygdala-PFC circuitry resulting in different types of aggression will be discussed. Besides focussing on the environmental aspect, we will also elucidate the genetic contribution to this phenomenon.

Amygdala and the PFC in ELS and aggression

Before studying the connectivity between brain regions, it is essential to understand the involvement of the separate brain structures in ELS and aggression. The amygdala is crucial for the modulation of emotion-related behaviour. Therefore, to understand the effect of ELS on the onset of behavioural problems, it is important to first understand more about this small region in the temporal lobe [5].

Considering that the amygdala plays a key role in processing emotions, it was suggested to be an area that causes aggression. Interestingly, a change in amygdala activity can result in two different types of aggressive behaviour, of which one is associated with increased amygdala activity, and the other one with decreased activity [6]. When an individual has increased responsiveness of the basic threat circuit, they will respond to a threat in a more reactive manner, which includes unplanned, enraged attacks on the source of threat or frustration (reactive aggression) [7]. On the other hand, decreased amygdala responsiveness is associated with psychopathic traits, such as deficits in emotional empathy and a reduction in the processing of distressing factors [8]. Such an individual is more likely to harm others in order to achieve their goals (proactive aggression). Therefore, when talking about the effect of the amygdala on aggression, a distinction must be made between these two different types.

Multiple retrospective studies found that people exposed to ELS have a heightened amygdala reactivity to emotional cues, suggesting that the amygdala reactivity increases with stress-related signals [9-13]. Moreover, a number of different types of ELS, such as sexual, physical and domestic violence, were linked to a volume expansion of both left and right amygdala alongside increased glucocorticoid levels [14, 15]. Ultimately, this increased amygdala reactivity was also associated with more reactive aggressive behaviour [16].

Besides the amygdala, the PFC also plays a crucial role in the modulation of aggression. A meta-analysis revealed that prefrontal and structural impairments significantly resulted in antisocial behaviour [17]. Furthermore, people subjected to ELS had an accelerated amygdala-PFC connectivity development, resulting in a significantly early shift to the mature amygdala-PFC connectivity [18]. This could lead to more oppositional behaviour, since the PFC has less control over the amygdala responsiveness, due to the loss of connectivity (Figure 1).

Since there is a conspicuous link between both structures that is affected by impairment, studying the effect of different aspects on this circuitry will contribute to our understanding of ELS and aggression. While ELS is an important risk factor for the development of behavioural problems, this does not mean that it invariably leads to this dysfunction [19]. The different outcomes can be explained partially by the interactions of genetic and environmental factors: a person's mental state is usually healthy when exposed to low environmental stressors. However, it will become impaired when the person has to deal with high stressors. While environmental stress by itself could decrease the normal functioning, the genetic background can make a person more resilient or vulnerable to these environmental stressors [19].

Environmental factors in ELS

In humans, the amygdala-PFC circuitry undergoes age-related changes across childhood, adolescence and young adulthood. Evidence from multiple animal species showed that the amygdala-PFC circuitry is highly sensitive to environmental inputs, especially during the early life of an organism [18]. Examples of environmental inputs, besides age, that could affect the outcome are sex and the type of event.

When one compares the connectivity of previously institutionalised children to typically raised children, apparent differences are found.

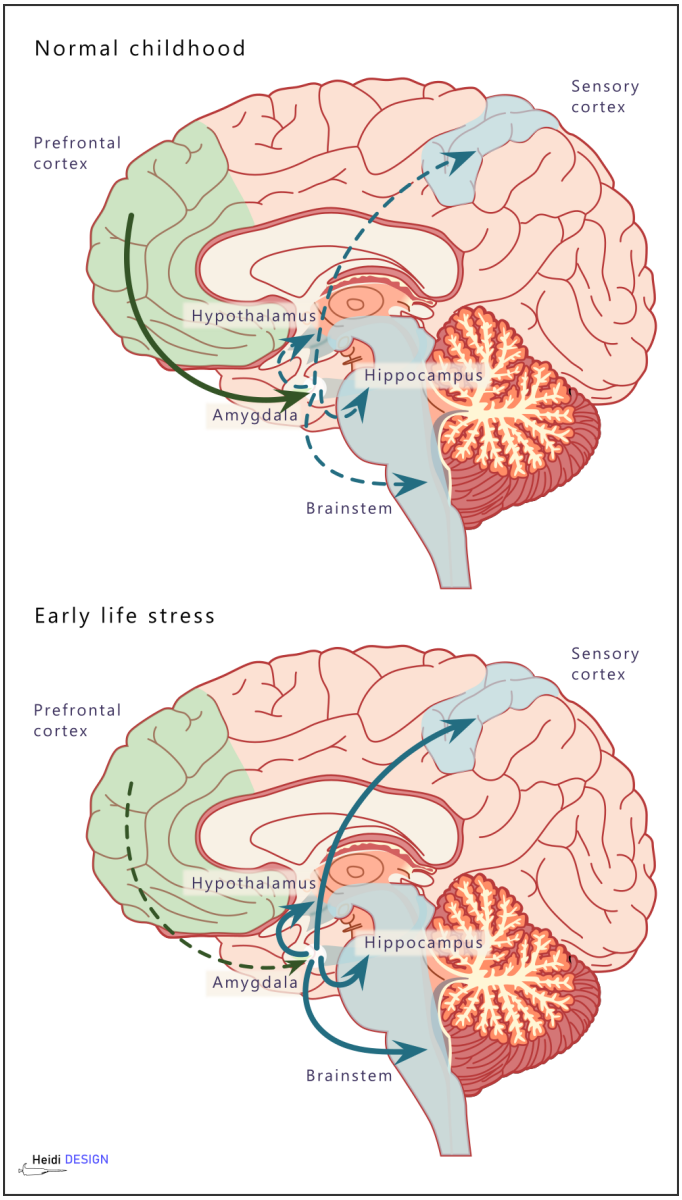

Figure 1: Reduced top-down regulation of amygdala as a result of decreased PFC-amygdala connectivity

Early life stress can decrease the connectivity between the PFC and amygdala. This affects the emotional circuitry, since an important role of the amygdala is to communicate with the hypothalamus, the sensory cortex, the brain stem and the hippocampus. When top-down regulation of the amygdala is reduced, this will ultimately affect the beforementioned structures. This is associated with an increase in oppositional behaviour.

Usually, untraumatised children show a positive connectivity between the amygdala and PFC, which switches to a more adult-like phenotype around ten years of age. This results in a negative connectivity in adolescence. Interestingly, the previously institutionalised children already showed this negative connectivity in their early life. This early shift results in a change of the amygdala and PFC structure compared to typical children [20].

Another study observed that the age of the child and the type of abuse is important for the amygdala sensitivity later in life and the functional connectivity with the PFC [21]. Peer emotional abuse of 15-year-olds is associated with a reduced amygdala volume and increased activation, resulting in reactive aggression. In contrast, parental physical abuse is a primary risk factor around the age of four, resulting in enhanced amygdala volume (proactive aggression) [21]. This suggests that there are developmental differences after maltreatment concerning the amygdala, the PFC connectivity and the type of aggression when looking at age and the type of abuse.

Besides age, the activation of the PFC after ELS is also moderated by sex in early adolescence [19]. Colich *et al.* showed that compared to males, females had an increased association between ELS and PFC activity. However, when studying the PFC-amygdala connectivity, no significant difference was found between sexes, as they both showed a negative correlation between connectivity and ELS severity (more ELS results in less connectivity) [22]. Another study showed that females in their childhood have higher cortisol levels, which will lead to more negative connectivity compared to males. However, the causal relationship between these factors remains unknown [23].

Genetic factors in amygdala-PFC connectivity

Genetic factors also have an important effect on our behaviour. Extensive research found that genetic variations in the serotonin transporter (*5-HTTLPR* polymorphism) and monoamine oxidase A (*MAOA*) are able to modulate amygdala functioning and its connectivity with the PFC. These variants were found to predispose the increased aggression [24]. In rhesus monkeys, the common polymorphism of *5-HTTLPR* is associated with an increase of amygdala activation and an increase in aggressive behaviour [25].

A common polymorphism in the *MAOA* gene that is also associated with aggression is the *MAOA-L* variant, the variable-number tandem repeat in the upstream region of the gene. The low expression variant of *MAOA* predicted limbic volume reductions and a hyperresponsive amygdala compared to the high expression allele [26]. A study by Buckholtz *et al.* suggests that there is a strong influence of sex on these genetic effects, showing a neurobiological susceptibility of the effect of the low expression variant in men [27].

Discussion

From this overview can be concluded that there is a neurodevelopmental mechanism by which ELS in childhood can affect the amygdala-PFC connectivity resulting in different behavioural problems. A decreased connectivity results in a reduced top-down regulation of the PFC on the amygdala, resulting in more aggressive behaviour. As discussed, age, sex, the type of abuse and common polymorphisms in itself are important modulators for the connectivity and ultimately the type of aggression. Interestingly, the combination of the aforementioned factors also has a strong influence on the susceptibility. Therefore, we can conclude that the risk of onset of aggression after exposure to ELS is affected by a strong interaction of both environmental and genetic factors.

However, a lot still remains unknown about the exact influence of these interactions on the connectivity between the amygdala and the PFC. These knowledge gaps leave room for interesting studies that could still be conducted. First, it would be of interest to study whether the amygdala-PFC connectivity could be used as a possible biomarker to treat people with oppositional behaviour in an early stage. Furthermore, since it was found that age, sex and the type of abuse are important modulators, studying whether adjustment of treatment schemes would be beneficial to fit the sensitive periods for males and females at certain types of abuse at certain ages is a promising step forward.

Acknowledgements

RAMS would like to thank Danique Smeijers, PhD, Pompestichting, Nijmegen, the Netherlands, for providing the author of this article with feedback.

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