Chapter 12

Amygdala, Childhood Adversity and Psychiatric Disorders

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Additional information is available at the end of the chapter

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1. Introduction

Above 10% of children in the U.S. are subjected to some form of maltreatment (Table 1) [1]. Childhood adversity can take the form of abuse, neglect, or loss, with examples including but not limited to: sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying. Childhood adversity has been shown to have lifelong impact on the victim's physical and mental well-being (Table 2).

Figure 1. Childhood adversity is prevalent and has pervasive and long term impact on mental and physical health.

In many scientific studies invovling animal or human subjects, childhood trauma has been associated with low resting cortisol levels, altered stress response, increased inflammatory markers, and cognitive impairment [2]. In particular, childhood maltreatment has been linked to a variety of changes in stress-responsive neurobiological systems including brain structure and function [3]. Studies have shown that childhood maltreatment represents a strong risk factor for the development of depression and anxiety disorders in later life [3 - 5].

A presumed mechanism for such association is the persistent sensitization of central nervous system (CNS) circuits, in particular the amygdala, as a consequence of early life stress, which leads to the higher vulnerability to these psychiatric disorders [6].

Childhood abuse	Total N=17,337
Emotional abuse (Did a parent or other adult in the household ...) 1. Often or very often swear at you, insult you, or put you down? 2. Sometimes, often, or very often act in a way that made you fear that you might be physically hurt?	10.6%
Physical abuse (Did a parent or other adult in the household ...) 1. Often or very often push, grab, slap or throw something at you? 2. Often or very often hit you so hard that you had marks or were injured?	28.3%

Table 1. Adverse childhood experience (ACE) score definition and prevalence statistics [1].

2. Childhood adversity and psychiatric vulnerability: Epidemiology studies

It has been shown for a long time that early life adversity significantly increases psychiatric vulnerability in adulthood [7]; such an effect has been replicated in many large sample studies [8,9]. High risk psychiatric conditions include depression [10], anxiety [11], substance abuse [12], as well as psychosis related disorders such as schizophrenia [13,14]. A very large sample (N = 9377) 45-year prospective epidemiologic study has confirmed that such an impact is persistent throughout a person's lifecourse [15]. It has been identified that amygdala hyperactivity and morphological abnoramlity, together with structural and functional abnormality of other brain regions such as the anterior cingulate and prefrontal cortex, could have significant contribution to such heightened risk [16].

		Mental Health Disturbances			
ACE	N	Panic reactions	Depressed affect	Anxiety	Hallucination
0	(6255)	8.3%	18.4%	7.8%	1.3%
1	(4514)	10.9%	25.2%	9.1%	1.5
2	(2758)	13.6%	34.1%	12.4%	2.3%

Table 2. Relationship of the ACE scores (see Table 1 for definition of ACE) to the prevalence of mental health disturbances [1].

What further complicates the picture is the pattern of family risk for psychiatric disorders [17], which goes into a vicious circle, i.e., parents with psychiatric disorders tend to maltreat their children, which increases the psychiatric risk of their children, and such a vicious circle goes on for generations and generations. There are certainly genetic factors in addition to

the family enviromental factor in this vicious cycle. Research in recent years are paying more attention on the epi-genetic mechanisms modified by identifiable patterns of childhood maltreatment [18]. Epigenetic mechanisms are mechanisms that regulate gene expression without altering the DNA sequence but rather through changing the biochemical environment of nucleotides. DNA methylation, histone modification, and chromatin remodeling are common epi-genetic mechnisms. However, it should be noted that although epigenetic mechanisms do not involve changing the DNA sequence, they are still inheritable. It is said that every sperm and every egg has a different epigenetic environment, and such differences are maintained during cell divisions for the remainder of the cell's life and may also last for multiple generations. Studies have shown that prenatal maternal stress, postnatal maternal care, and infant neglect/abuse can lead to epigenetic variation, which may have long-term effects on stress responsivity, neuronal plasticity, and behavior [18]. The remainder of this chapter will not elucidate the exact epigenetic mechanisms invovled in the lifelong impact of childhood adversity, since that is an area of research that is still being explored in heavy mist. Instead, we are going to focus our discussion on the neurobiological phenotypes, in particular, the impact of childhood adversity on the structure and functionality of the amygdala, which in turn serves as a significnat risk factor for developing psychiatric disorders in adulthood.

3. Amygdala abnormality due to early life adversity

The amygdala is critically involved in activation of the hypothalamic-pituitary-adrenal (HPA) axis in the face of emotional challenges and threat [19]. The HPA axis is a complex set of interactions in the neuroendocrine system, which controls stress related reactions as well as many other physiological regulations. The amygdala contains a large amount of neurons that produce corticotropin releasing hormone (CRH), as well as endogenous CRH receptors. Stress can increase CRH levels and upregulate CRH receptors in the amygdala so as to initiate fear responses (with behavioral characteristics including *fight, flee or freeze*). Such an effect has been observed in both adult [20] and developing rodents [21]. The critical role of the amygdala in this process has been confirmed by studies on cases with amygdala lesions, in which elevated glucocorticoid levels were absent during stressful situations [22,23]. Furthermore, external infusion of CRH to the amygdala significantly increases typical anxious behaviors [24]; the same effect can also be caused by electrophysiological stimulation of the amygdala [25], and of course, psychobiological stress such as seizure and chronic psychological stress [26,27].

Although stress-induced amygdala abnormality can happen any time in life, developmental studies have found that the amygdala is particularly sensitive to stress in early life such as during infancy and early childhood. Experiencing childhood adversity produces long lasting structural and functional changes in the amygdala during the dynamic processes of endogenous CRH production and regulation. As a behavioral result, the victim's threshold of emotional reaction is lowered, resulting in heightened excitability of the neural system for emotional response, which puts the individual at risk of general anxiety and anxiety-related psychiatric disorders [28]. Such an effect has been observed in many experiments as

summarized in Table 3. The rest of this section will discuss these experimental evidences from behavioral neuroscience research with animal models as well as neuroimaging research with humans. At the end of this section, the complex interaction between the amygdala and other brain regions in the context of stress-related neural responses will also be discussed.

Article	N	Subjects	Adversity	Findings
Tottenham *et al*. (2010) [29]	62	Human children	Adverse caregiving	Larger amygdala volume in previously institutionalized group.
Mehta et al. (2009) [30]	25	Human children	Adverse caregiving	Larger amygdala volume in previously institutionalized group.
Bremner et al. (1997) [31]	34	Human adult	Chronic child abuse	Smaller hippocampus and unchanged amygdala volume in PTSD patients
Cohen et al. (2006) [32]	250	Human adult	Various early-life stressors	Differences in hippocampal volume were marginally significant and amygdala were nonsignificant between groups
Driessen et al. (2000) [33]	42	Human adults	Childhood trauma/ BPD	Patients had 16% smaller hippocampal and 8% smaller amygdala volume
Schmahl et al. (2003) [34]	33	Human adult	Childhood trauma/ BPD	Patients had smaller amygdala (~22%) and hippocampal (~14%) volumes
Plotsky et al. (2005) [35]	20	rat	Maternal separation	Elevated CRH mRNA in amygdala
Tsoory et al. (2008) [36]	104	rat	Various	Increased neural cell adhesion molecule in basolateral amygdala
Ono et al. (2008) [37]	148	mice	Early weaning	Precocious development of amygdala at 5 weeks of age
Kikusui et al. (2009)[38]	129	mice	Early weaning	Accelerated amygdala development
Salzberg et al. (2007) [39]	29	rats	Maternal Separation	Amygdala sensitization following maternal separation
Becker et al. (2007) [40]	20	rat	Separation	Higher CRF neuron levels in basolateral with lower levels in central amygdala
Vazquez et al. (2006) [41]	300	rat	Maternal separation	Higher basal CRH gene expression in amygdala than hippocampus.
Moriceau et al. (2004) [42]	108	rat	Predator odor	Exogenously administered cortisol increased amygdala activation
Hatalski et al. (1998) [21]	20	rat	Cold	Increased CRF-mRNA in the central nucleus of the amygdala
Sabatini et al. (2007) [43]	12	rat	Maternal separation	Early separation (more than later), decreased amygdala gene expression

Table 3. Summary of studies about the impact of early life adversity on amygdala. Abbreviation: CRF: corticotropin releasing factor, CRH: Corticotropin-releasing hormone, BPD, borderline personality disorder.

3.1. Evidence from behavioral neuroscience studies

In labaoratory rodents, similar to the case in humans, rodent pups (e.g., baby rats) that experience early life stress also exhibit altered adult behavioral and behavioral responses to stress. There are many ways to introduce early life stress in animal experiments, the most common ones include frequent handling, early weaning, and maternal separation. Chateracteristics of maternal behavior are also commonly used as variables for evaluating early life stress. These characteristics are usually quantified in terms of the frequencies of licking, grooming, arch-back nursing, etc. of the dams (e.g., mom rats) (Figure 2).

Figure 2. Maternal care patterns have important impact on the mental health of offsprings. In animal models with rats or mice, licking and grooming frequencies of the dam to the pups are common behavioral characteristics of maternal care [44]. This figure depicts rat maternal behavior, in comparison with that of human as represented in an artful sculpture.

By manipulating the caregiving conditions of infant rodents with the above methods, behavioral neuroscience experiments found that early life maltreatment could accelerate amygdala development [38,45,46] in terms of accelerated growth of dendrites, early myelination [37], increases in the amount of CRH-containing neurons [40] (Table 3), and functional sensitization [39]. In the central nucleus of the amygdala, decreased levels of benzodiazepine receptor binding, which plays an important role in inhibition of neuron activity, were observed among rats that received worse maternal care during infancy (Figure 4), and these rats also demonstrated higher anxiety levels behaviorally. The earlier such effects occur, the more devastating they are behaviorally [26], which could include socio-emotional deficits [43]. Experiments have elucidated that the most vulnerable time is the early postnatal period [47]. Compared to exposure to stress in adulthood, it might take 200 times less CRH in the early postnatal period to produce similar behavioral effects [48].

Functionally, accelerated amygdala maturation by early life adversity [49] promotes „aversive learning“ (one of the major functions the amygdala is involved in [50]), which can be essential for survival in harsh conditions if seen from an ecological perspective. More importantly, a few studies have shown that amygdala abnormality as a result of adversity

may be irreversible, i.e., amygdala cellular growth in response to stress failed to recover even in reversed environment [51,52]. It is possible that during evolution an "over-cautious" mechanism has been adapted to ensure the organism to be prepared for future adversity in an environment that is known to be threatening.

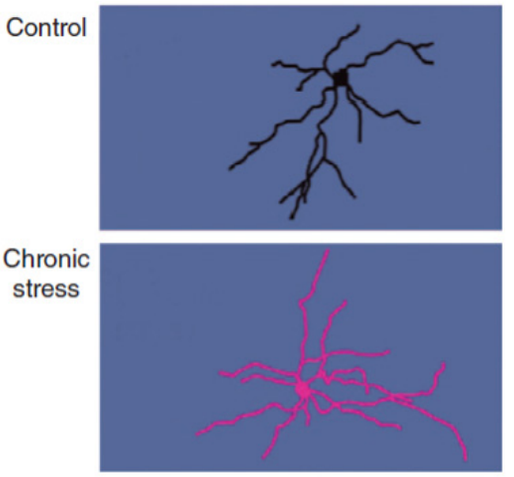

Figure 3. Accelerated amygdala neural growth as a consequence of early life adversity. As illustrated, chronic stress causes increased growth of dendrites (lower pannel compared to the upper panel) in the basolateral amygdala [46].

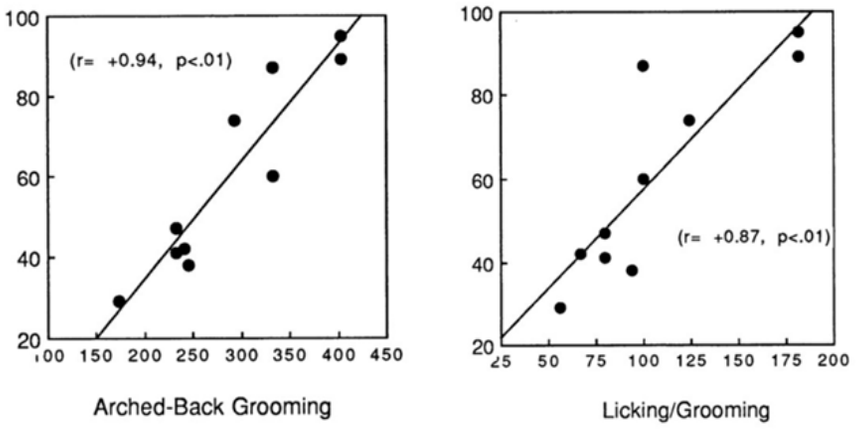

Figure 4. Significant correlations between maternal care characteristics (x-axis) and the level of benzodiazepine receptor binding (y-axis) in the central nucleus of the amygdala [53]. Lower frequencies of maternal care behaviors are associated with lower level of benzodiazepine receptor binding in the central nucleus of the amygdala, indicating less inhibition on neuron activity in the amygdala.

3.2. Amygdala abnormality in human: Neuroimaging studies

Neuroimaging techniques have made it possible to study amygdala morphometric and functional changes *in vivo* in human subjects. Many neuroimaging studies have shown that amygdala is structurally and functionally altered by psychosocial stress. It is usually difficult to study causality from human subjects, yet studies from animal models reviewed above have confirmed that amygdala abnormality follows stress exposure, rather than the

other way round (i.e., inborn amygdala abnormality serving as a risk factor for adversity exposure) [54]. Such a conclusion from animal literature is partially applicable to humans.

As a consequence of early life adversity, accelerated amygdala maturation in the form of increased amount of neurons and dendrites can be demonstrated as increased amygdala gross volumes, which is a measure often used in human neuroimaging literature (Table 3). Neuroimaging studies have been conducted on children adopted from orphanages. These studies found increased amygdala volumes [30,48], and children adopted later tend to have larger amygdala (Figure 5). The fact that these children were adopted by families of very high socio-economic status further supported the view that amygdala abnormality as a result of early life adversity may be irreversible.

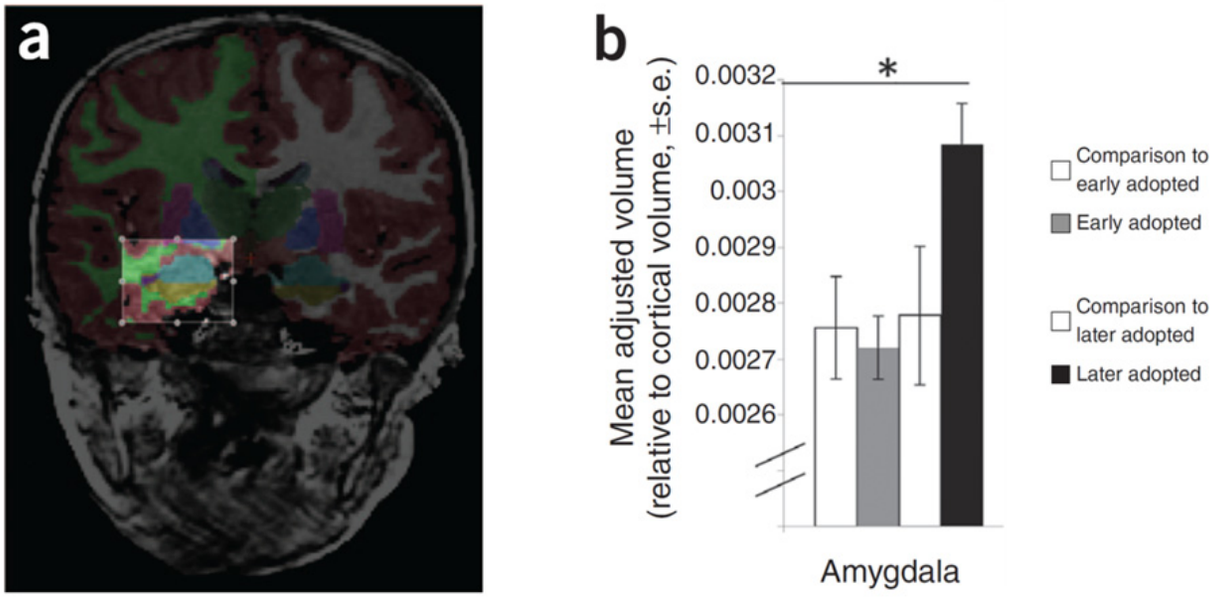

Figure 5. (a) Illustration of amygdala volumetric study with anatomical MRI. In the study presented in (b), it was found that later-adopted post-institutionalized children had larger amygdala volume compared with early adopted and typically developing controls [46].

Some neuroimaging studies might be occluding the picture with results seemingly contradictory with those from animal research. For example, many studies on trauma-exposed adults have demonstrated smaller and hyperactive amygdala [33,34]. Decreased amygdala volumes were also observed in subjects with childhood adversity comorbid with current borderline personality disorder (BPD) (Table 3, [33,34]). It should be noted that the above studies, which used adult subjects, might have been confounded by the effect of aging-related neural atrophy. Given that stress induces acceleration of amygdala development, it is possible a continuation of this effect into late adulthood would be demonstrated as "accelerated aging". This hypothesis is reasonable, given that amygdala hyperactivity has been consistently observed in almost all studies. Besides hyper-responsivity to threatening stimuli has been reported in previous literature [55 - 59], a recent study found amygdala hyperactivity even at *resting state* among individuals with unsuccessful stress coping (Figure 10). Such prolonged hyperactivity is likely to result in

cellular atrophy and/or death, as has been seen in terms of reduced brain volumes in MRI studies [60]. Results from some neuroimaging studies also seem to support this hypothesis, in which depression patients showed enlarged amygdala volume at the initial depressive episode [61,62], but decreased amygdala volume after living with depression for extended periods of time [63,64].

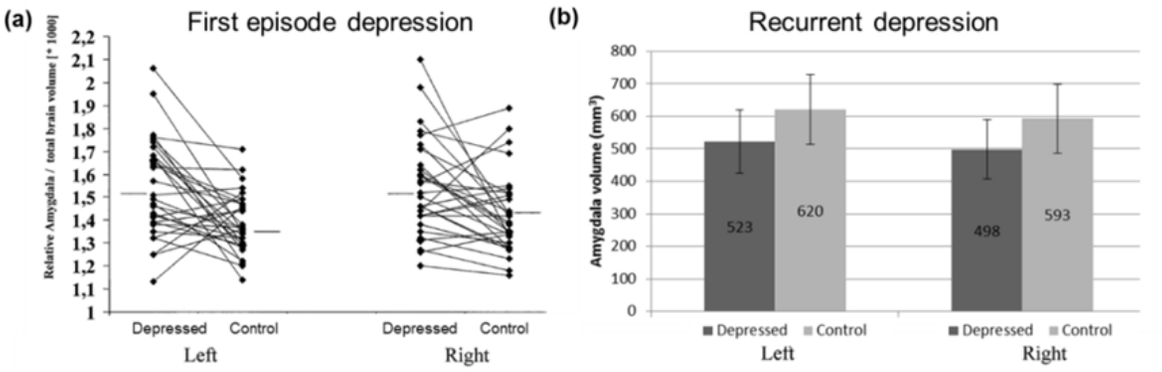

Figure 6. Enlarged versus reduced amygdala volumes in early-state (a) [61] or late stage (b) [63] depression. Note: *p* values are 0.002 (left amygdala) and 0.024 (right amygdala) in (a) with 30 subjects in each group, and 0.001 (left amygdala) and 0.002 (right amygdala) in (b) with 20 subjects in each group.

Thus it is important to identify the time sensitivity of stress impact on amygdala, which seems to have a dichotomy in early life and late life. It is very difficult to identify specific critical time points in humans, because there are rarely isolated stressors in human life and researchers have limited options to manipulate these stressors compared to what we can do with animals. Nonetheless, identifying the turning time points can be helpful for designing timely intervention programs as demonstrated in section 7. Unlike the case in animal literature [63,64], we might be able to reverse the toxic impact on amygdala through appropriate behavioral intervention programs.

4. Amygdala in the neural network

It is important to keep in mind that amygdala should not be considered in isolation since it is interconnected with other brain regions in a complicated neural network. The amygdala has a large number of connections with a wide range of other brain regions (Figure 7). It sends excitatory signals to the HPA axis through periventricular neurons as well as to other limbic structures (such as the anterior cingulate) and the brain stem. It also receives inhibitory signals from the ventral striatum and frontal cortex (Figure 7).

Due to the complicated network formed by the interactions between the above-mentioned structures, aversive influence from early life stress rarely affects the amygdala alone. Many other structures are also impacted, with the most common ones including the hippocampus, the anterior cingulate cortex, the frontal cortex (especially the ventral medial prefrontal cortex, the orbital frontal cortex as well as inferior frontal gyrus), as well as the right anterior insula. For example, numerous studies have demonstrated reduced volumes of the hippocampus [2,30,33,34,38,48,62,65,66] and anterior cingulate cortex [65,67] as a result of

early life stress. Generally speaking, as a consequence of early life adversity, brain regions typically involved in emotional response including the amygdala, anterior cingulate cortex, ventral medial prefrontal cortex, inferior frontal cortex, orbital frontal cortex, as well as the right anterior insula (Figure 8), tend to be *hyperactive*. In the meantime, brain regions typically involved in emotion inhibition and emotion regulation tend to be *hypoactive*, including the dorsal medial prefrontal cortex, the dorsal lateral prefrontal cortex, the posterior cingulate cortex, and the precuneus (Figure 8), which results in reduced inhibition on the amygdala, eventually leading to behavioral patterns demonstrating anxiety. In neuroimaging psychiatric literature, both kinds of brain regions are frequently reported to be associated with anxiety-related psychiatric conditions. Thus, it takes both a *hyperactive* amygdala and a *hypoactive* emotion regulation system to give rise to anxiety-related behaviors.

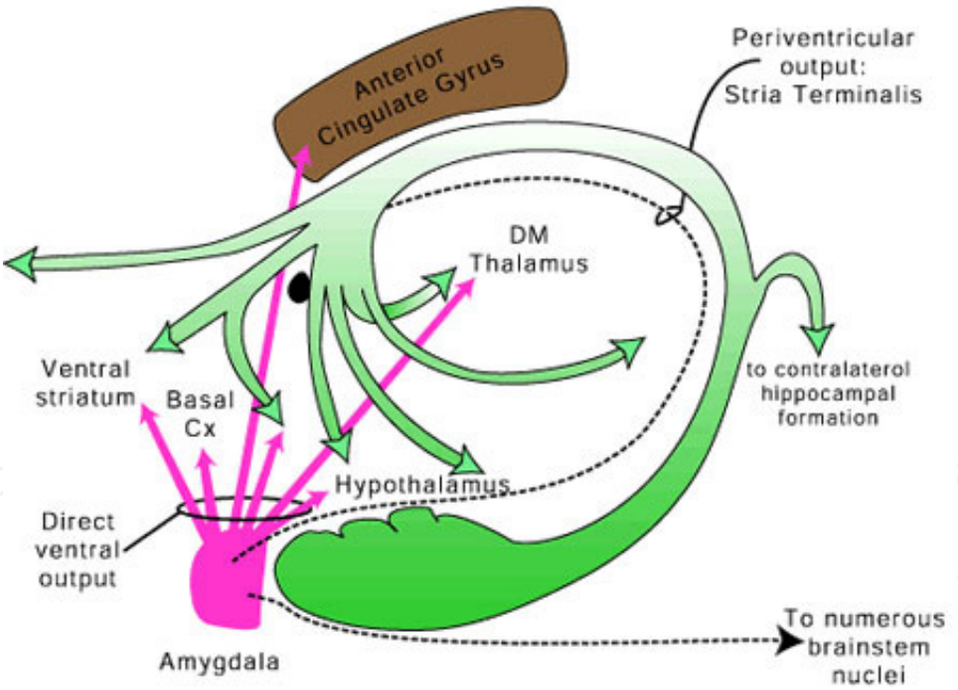

Figure 7. Projections to and from amygdala nuclei to other regions of the brain. Abbreviations: Cx: cortex, DM: dorsal medial.

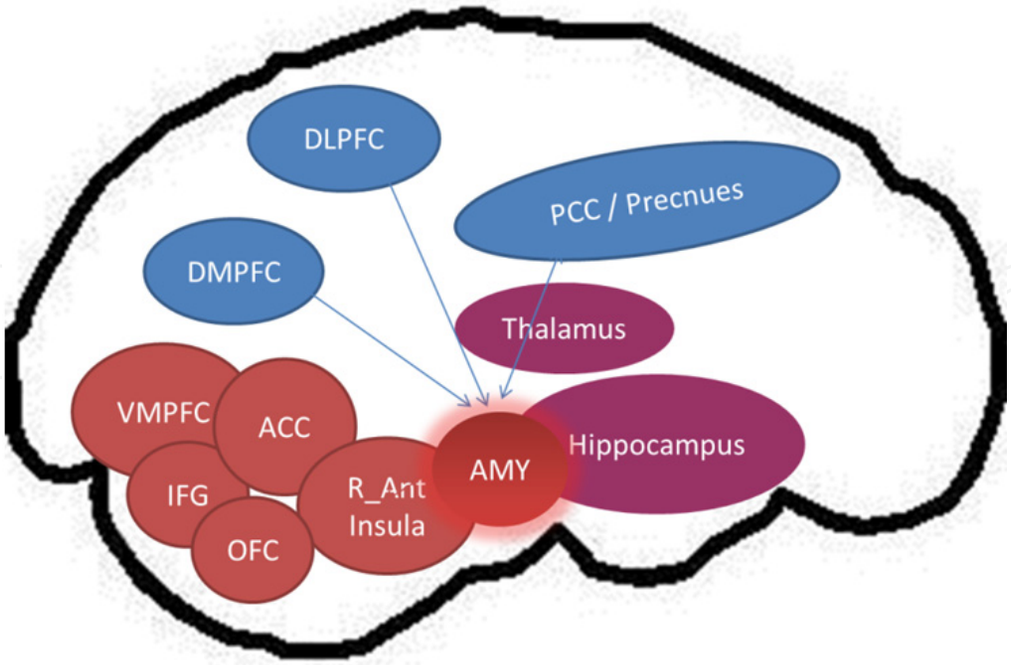

Figure 8. Association of amygdala with brain regions that are actively involved in emotional processing (red) and brain regions that are typically involved in emotion inhibition and regulation (blue), as well as other regions involved in emotional responses (purple). Abnormal morphometry and activity of these brain regions are frequently reported in stress-related psychiatric conditions. Abbreviations: ACC: anterior cingulate cortex, VMPFC: ventral medial prefrontal cortex, IFG: inferior frontal cortex, OFC: orbital frontal cortex, R_Ant_Insula: right anterior insula, DMPFC: dorsal medial prefrontal cortex, DLPFC: dorsal lateral prefrontal cortex, PCC: posterior cingulate cortex.

5. Amygdala abnormality and psychiatric disorders

Amygdala abnormality has been reported in many psychiatric disorders both in pediatric and adult patient population. Most of these disorders are associated with anxiety, such as general anxiety disorder (GAD), panic disorder, posttraumatic stress disorder (PTSD), bipolar disorder and depression. In particular, amygdala abnormality seems to be specifically responsible for the anxiety symptoms, although in the context of comorbid psychiatric disorders, such specificity could be confounded by other comorbid symptoms.

5.1. Amygdala abnormality in pediatric psychiatric disorders

Children with anxiety disorders showed an exaggerated amygdala response to fearful faces compared to healthy children, whereas depressed children showed a blunted amygdala response to these faces [68]. In addition, the magnitude of the amygdala's signal change between fearful and neutral faces was positively correlated with the severity of everyday anxiety symptoms [68]. Figure 9 demonstrates a recent study about the association between childhood maltreatment and amygdala responsiveness to negative facial expressions [69], in which the amount of childhood trauma was positively correlated with the degree of amygdala activity. Such an effect is frequently reported in literature.

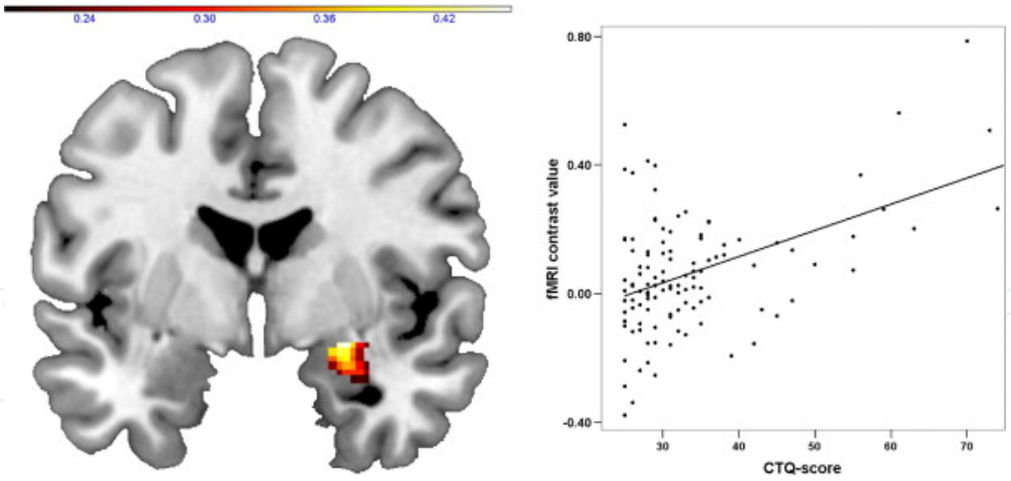

Figure 9. Childhood maltreatment (Childhood Trauma Questionnaire [CTQ] scores) is positively correlated with right amygdala responsiveness to negative facial expressions among 114 adult subjects [69]. The *y* axis stands for the among of fMRI signal change in response to negative facial expressions compared to the control condition.

Amygdala morphmetric changes in pediatric psychiatry literature is more complicated than its functional changes. Children with general anxiety disorder are reported to have enlarged right amygdala volumes [70] (Figure 10). But when anxiety symptoms comorbid with other symptoms, the story gets more complicated. For example, depressed children are reported to have significant reductions of amygdala volumes compared with healthy subjects [71]. Another study found that pediatric depression patients had significantly larger amygdala/hippocampal volume ratios than controls [72]; these increased ratios being associated with increased severity of anxiety but not increased severity of depression or duration of illness [72], suggest that amygdala abnorality was specific to the anxiety symptoms. Patients with a history of childhood trauma and current BPD also have smaller amygdala volumes (Table 3) [33,34]. Such complexity might arise from the timing issue of stress impact on amygdala as discussed in section 3.2, but it may also arise from complicated geneitc and epigenetic variations underlying these comorbid psychiatric disorders.

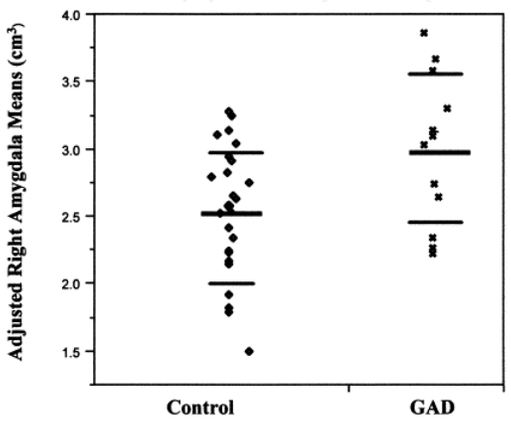

Figure 10. Children with general anxiety disorder (GAD) have an enlarged right amygdala volume compared to healthy developing controls [70]. The *y* axis is the right amygdala volume adjusted for intracranial volume. The horizontal lines stand for group means and standard deviations.

5.2. Amygdala abnormality in adult psychiatric disorders

Amygdala abnoramlity is also frequently reported from studies on adults with stress related psychiatric disorders [73], such as depression, anxiety, BPD, PTSD, etc. Amygdala volume is generally reduced in adult patients, an effect observed with PTSD [74], depression [63] and BPD [33,34]. It is also reported that schizophrenia patients had a left-greater-than-right amygdala asymmetry [75]. Exaggerated amygdala responsivity to threat-related stimuli is also a prevalent effect associated with various kinds of stress-related disorders, such as depression [68,76,77], PTSD [78,79], anxiety [68],etc. A recent study on PTSD using the novel resting state fMRI approach reported that amygdala was hyperactive even in *resting state*, i.e., a state without any prescribed cogntive tasks nor any external stimuli (Figure 11), and it also had reduced functional connectivity with middle frontal cortex, suggesting that amygdala can be constantly hyperactive even without external stimuli, and this is coming along with reduced inhibition from the frontal cortex.

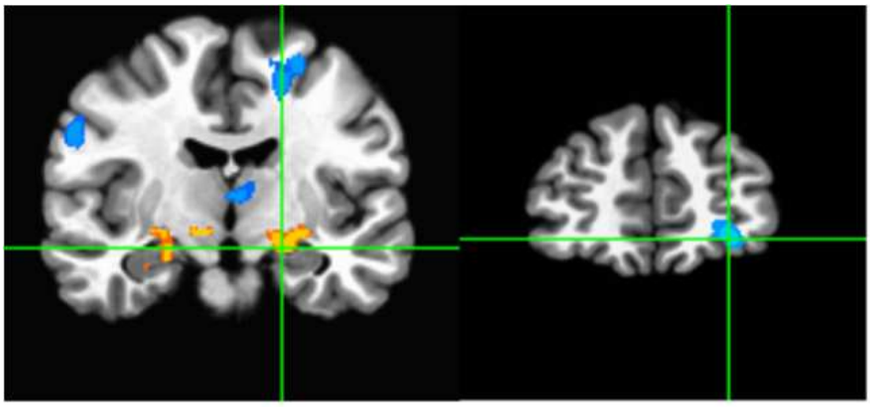

Figure 11. Resting state fMRI revealed higher amygdala spontaneous activity (left) with weaker functional connectivity with middle frontal cortex (right) in PTSD patients.

5.3. Amygdala abnormality as a risk factor for adult psychiatric disorders

In the context of lifelong human develoment, pediatric and adult psychiatric conditions are not isolated from each other. Epidemiology studies have shown that early onset depression and anxiety are highly predicative of adult psychiatric disorders [80]. An important scientific question is to test the following causal link: ealry life adversity → amygdala abnormality (and other neural abnormality) → increased risk for developing psychiatric disorders. Responding to this question is a very difficult scientific challenge. To begin with, it is very hard to identify a causal relationship with emprical experiments involving human subjects, because it is difficult to conduct longitudinal studies across the human lifespan. A common appraoch is to use the cross-sectional research paradigm instead of the longitudinal approach. In order to differentiate the influence of genetic and environmental factors on psychiatric conditions, a common approach is to use twin-studies, in which researchers study monozygotic and/or dizygotic twins, particularly those reared seperatly since brith [81 - 84]. PTSD is a particularly good disease model to address this question, because it has a clear onset and an obviously identifiable external stressor (which may still

have complicated interation with other factors in real life). A recent twin study on PTSD identified vulnerability indicators such as smaller hippocampal volumes, low intellectual ability etc, and indicated that higher resting anterior cingulate metabolism could be the consequence rather than a pre-existing risk factor of PTSD [85], although another recent twin study suggest that hyper-responsitivity at dorsal anterior cingulate cortex could be a familial risk factor [86]. However, given the short history of prevelant application of neuroimaging approaches in studies of psychiatric disorders, there has not yet been a neuroimaging study directly establishing the above hypothesized causal link between early life adversity, amygdala abnoramlity and heighted vulnerability to psychiatric disorders in adulthood.

6. The neglected impact of stress from natural environment

Previous studies on childhood adversity have been focused on social stress particularly related to parental relations. However, other factors, such as malnutrition, poverty, crowded housing, urban noise, even industrial pollution and harsh natural environment, can also constitute stress factors during childhood and have equal, if not more, toxic impact on neural substrates including the amygdala, which may in turn have a lifelong influence on mental and physical health. These factors can also induce parental abuse by imposing stress thus elevating the irritability and irrationality of parents. Nonetheless, these factors have been neglected in the literature. In our laboratory, we conducted a series of multi-modal MRI studies on the long term impact of chronic hypoxia on young adults who were born and raised at high altitudes (2500-4000 meters above sea level) regions [87-93]. Our data did not show any effect of hypoxia on the amygdala; however, other regions typically involved in emotion processing such as the insula and hippocampus, were shown to have reduced gray matter volumes and elevated spontaneous activity among the subjects raised at high altitudes compared to control subjects [89]. There is one study that reported smaller amygdala and hippocampal volumes among adult individuals (aged 44-48 years) that suffered from financial hardship during childhood compared to those who did not [94]. These studies suggest a possible impact of factors that constitute childhood adversity on the structure and function of amygdala-related neural circuitry that are not directly linked to parental relationships.

7. What can we do? Neural plasticity and interventions

We hope there are ways to alleviate, if not to reverse, the toxic impact of early life adversity on the amygdala, and eventually, on behavioral patterns. More and more recent studies suggest that neural plasticity can be induced by social, cognitve and behavioral intervention [46]. For example, a study showed that Cognitive Behavioral Therapy (CBT, a common behavioral intervention approach particularly effective for depression) administered to depressive patients, was able to reduce amygdala activity and enhance prefrontal activity [95] (Figure 12). Another study suggested that Mindfulness Based Stress Reduction (MBSR) training (commonly known as “meditation”) induced changes in perceived stress level as

well as in amygdala gray matter density, while larger decreases in perceived stress were associated with larger decreases in amygdala gray matter density [96] (Figure 13).

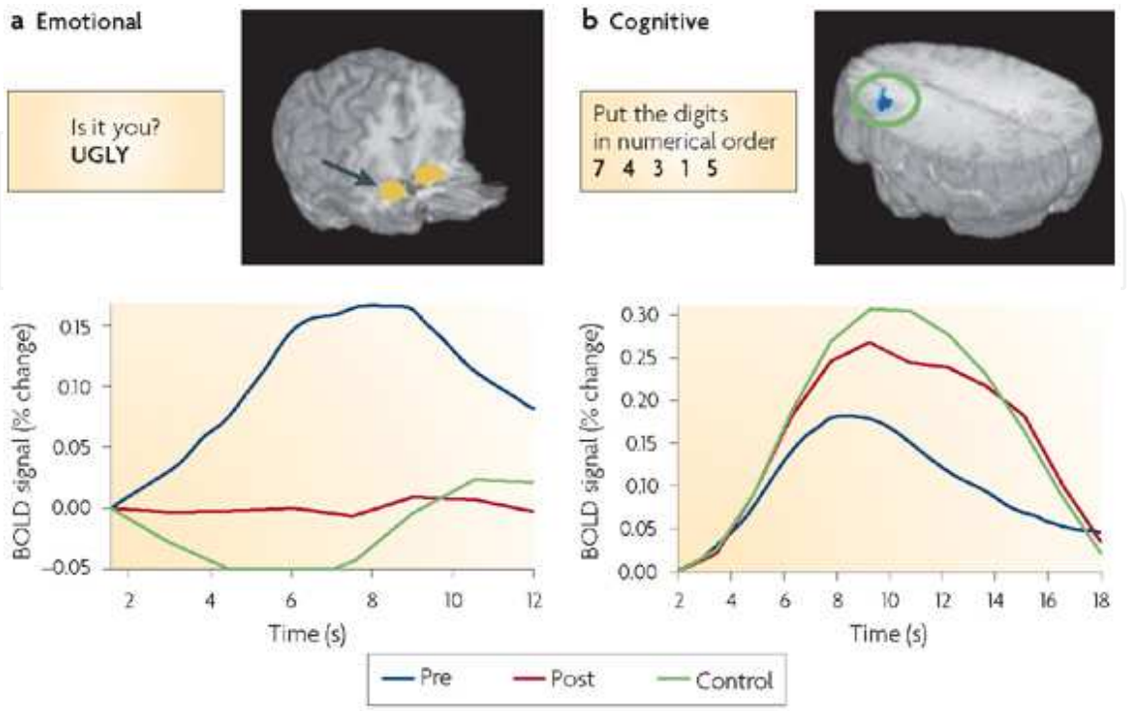

Figure 12. Cognitive behaivoral therapy on depressed patients induced reduced amygdala activity in an emotional task and enhanced prefrontal activity in a cognitive task [95]. Panel (a) represents amygdala response in an emotional task (rating the personal relevance of negative words), panel (b) represents prefrontal cortex response in a cognitive task (arranging digits in numerical order). These experiments were conducted on 9 depressed participants before (*pre*) and after (*post*) they had CBT and 24 control participants. As shown in the response profiles, after depressed patients completed CBT (*post* vs. *pre*) they had reduced amgydala response and increased prefrontal response, with the response profile closer to that of the *control* group.

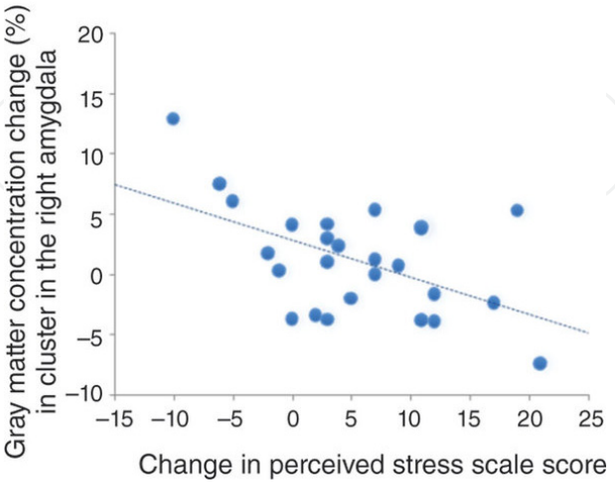

Figure 13. Mindfulness Based Stress Reduction (MBSR) training induced changes in perceived stress level as well as in amygdala gray matter density. Larger decreases in perceived stress were associated with larger decreases in amygdala gray matter density [96].

Other studies indicated that physical exercise was able to modulate aging related neural atrophy [97]. A significant effect was observed at the medial temporal lobe (Figure 14), but there was also a remarkable trend in the amygdala, the volume of which had a significant negative correlation with age in the low-exercise group (r=-0.62, p<0.001) but no significant correlation in the high exercise group (r=-0.21). It is possible that exercise might also help alleviate stress-induced amygdala atrophy, which is a good topic for future study.

In summary, childhood adversity can cause structural and functional changes of the amygdala, which increase the risk of developing psychiatric disorders in adulthood. Nonetheless, some behavioral intervention strategies (Figure 15) might help to promote neural plasticity, thus alleviating the neural toxicity and, thereby, reducing the risk to develop these disorders lately.

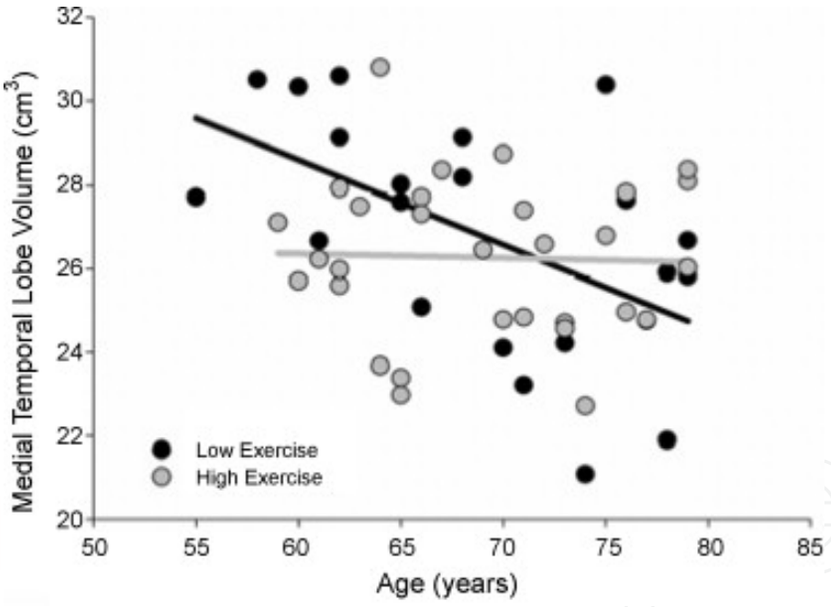

Figure 14. Exercise modulates aging related neural atrophy [97]. There was a significant negative correlation between the medial temporal lobe volume in the low exercise group (r = -0.65, $p < 0.001$), which demonstrates aging related atrophy, but such effect was absent in the high exercise group (r = -0.24). Such effect was also observed in the amygdala.

Figure 15. Behavioral intervention can induce neural platicity to protect the toxicity of early life adveristy on neural substracts such as the amygdala, thus reducing the risk of developing psychiatric disorders in later life. There are many easily implementable behavioral interventions, such as prosocial activity [98], meditation [99] or exercise [100], which have been suggested to be helpful in neuroscience literature [95 - 97].

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8. References

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