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## Neurobiological Findings in Post-traumatic Stress Disorder

# 4

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Studies on mass conflict, torture, or natural disasters have shown that survivors may develop a spectrum of clinical symptoms as a consequence of the experienced traumatic stress. Surprisingly, cross-cultural similarities and consistencies greatly outweigh cultural and ethnic differences (Elbert and Schauer 2002). Hence, there must be a common underlying neurobiological basis of post-traumatic stress disorder (PTSD) symptoms. In this chapter, we present a selection of findings on the underlying neurobiology of PTSD and the structure of traumatic memories in particular. The research findings are interpreted within the context of the fear network model, a theoretical model which explains the formation of traumatic memories and has been proven to be helpful to integrate the diverse findings on neurobiological alterations associated with PTSD.

We first summarize the most important risk factors for the formation of strong traumatic memories and the onset of PTSD, which are (1) cumulative trauma exposure as the strongest environmental factor and (2) genetic risk as an individual biological factor. This is supplemented by a section on epigenetic modifications (Sect. 4.3), which result from the interaction of the biological-genetic makeup and the sociocultural conditions. We continue by presenting evidence for structural and functional alterations in the brain of survivors with PTSD (Sect. 4.4), which might be either a consequence of the accumulation of traumatic stress or a predisposing risk factor for the disorder. Furthermore, we explain potential underlying molecular

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mechanisms which might account for the adverse health consequences and premature aging often observed in PTSD (Sect. 4.5). This chapter concludes with a section on the potential reversibility of the adverse physiological effects of trauma by means of successful treatment with trauma-focused therapy (Sect. 4.6) and an outlook on neurobiological research on other trauma-related mental health disorders (Sect. 4.7).

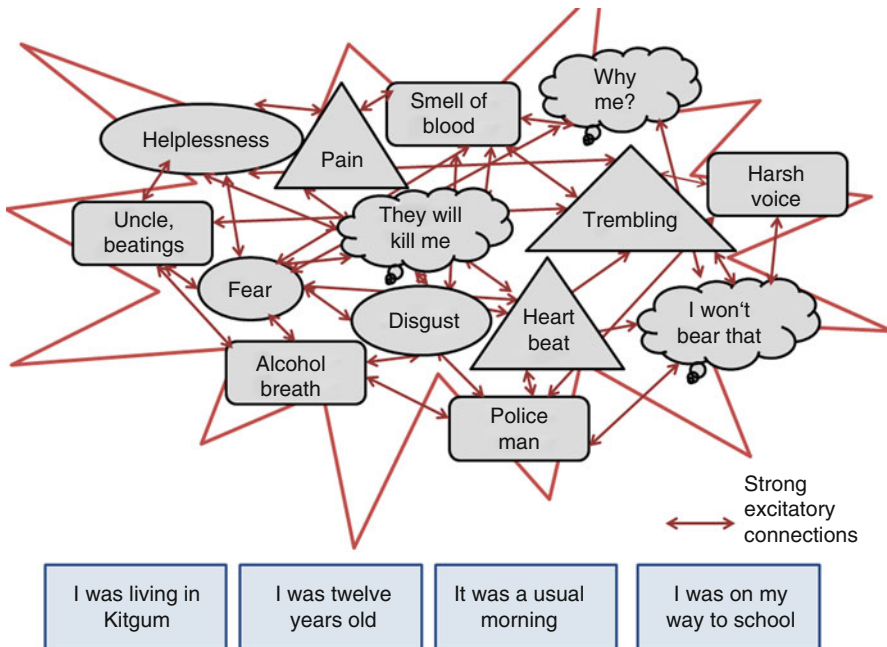
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## 4.1 Cumulative Trauma Exposure Forms Strong Traumatic Memories

Although the vast majority of people experience at least one traumatic event, lifetime prevalence of PTSD in adult Americans is estimated to be limited to 7–12 % (DiGangi et al. 2013; Kessler et al. 1995, 2005; Pace and Heim 2011). However, PTSD lifetime prevalence in populations with greater exposure to traumatic stressors is much higher, with, for instance, up to 58 % after combat exposure (Kessler et al. 1995) and 50 % in Sudanese refugees in Uganda (Neuner et al. 2004). Those numbers show that the development of PTSD is decisively influenced by the cumulative exposure to traumatic stress, which can best be operationalized as the number of different traumatic event types experienced and was termed *traumatic load* (Kolassa et al. 2010a, b; Neuner et al. 2004).

Cumulative trauma affects the severity of major depression and PTSD in a dose-response relationship even a decade after the traumatic event. All symptom categories of depression and PTSD, except for avoidance, correlate highly with cumulative trauma (Mollica et al. 1998). Neuner and colleagues (2004) assessed a sample of 3,371 refugees living in the West Nile region and found a positive correlation between traumatic load and PTSD prevalence as well as severity of PTSD symptoms. PTSD prevalence for participants reporting three or fewer traumatic event types was 23 %, while it reached 100 % for individuals who reported at least 28 events (Neuner et al. 2004). This *building block effect* (Schauer et al. 2003) was replicated and further specified multiple times (Eckart et al. 2009; Kolassa et al. 2010a, b, c). It suggests that there is no ultimate resilience for PTSD (Kolassa and Elbert 2007; Wilker and Kolassa 2013), i.e., any individual will develop PTSD when trauma exposure reaches extreme levels. Furthermore, traumatic load not only influences PTSD risk and severity but also the ability to spontaneously remit from PTSD over time, which means that the individuals which are most affected are those who are least likely to experience spontaneous remission without treatment (Kolassa et al. 2010b).

The fear network model established by the work group of Elbert (Elbert and Schauer 2002) as an extension of Lang (1979) and Foa and Kozak (1986) explains how the accumulation of traumatic stress can lead to intense fear memories. This model proposes that memories of traumatic events, similar to other memories, are stored in propositional networks which are configured by new learning experiences. When exposed to a traumatic stressor, sensory and perceptual information (e.g., the sight of blood, the sound of cries, the smell of fire) together with the cognitive (e.g., the thought “I will die”), affective (e.g., feelings of fear, horror, anger, disgust), and



**Fig. 4.1** The fear network in PTSD: sensory (*rectangles*), emotional (*circles*), cognitive (thought *bubbles*), and interoceptive (*triangles*) elements of the network are highly interconnected, as opposed to the autobiographical context information (*rectangles* below) which is stored separately (From Wilker and Kolassa (2013), reprinted with permission)

physiological responses (e.g., increase or decrease in heart rate, sweating, tense or weak legs) is stored in memory during a highly aroused state (cf. Fig. 4.1). The physiological response during a traumatic event prepares the individual for survival and can take the form of an alarm response: mind and body become extremely aroused and are braced for actions such as hiding, fighting, or escape. Another type of adaptive defensive responding, if fight or flight is not possible, is tonic or flaccid immobility including fainting (Schauer and Elbert 2010). Following the terminology first introduced by Metcalfe and Jacobs (1996), these sensory-perceptual, cognitive, affective, and physiological elements of the resulting memory network are termed “hot memories” and opposed to “cold memories,” which store the context information (time and space) of a particular event.

Evidence not only from cognitive psychology but also from neuroscience confirms distinct neural bases to the abstract, flexible, contextualized representations (cold memory) and to the inflexible, sensory-bound representations (Brewin et al. 2010; Kolassa and Elbert 2007). The latter, part of the hot memory system, is thought to be supported primarily by areas of the brain directly involved in perception (e.g., representational cortex, amygdala, insula) rather than in higher-order cognitive control. By contrast, cold memories require the involvement of the hippocampus and surrounding medial temporal lobe structures (Brewin et al. 1996,

2010). For emotional experiences within the normal range, hot and cold information are well integrated and stored together in autobiographical memory. Yet, if PTSD develops after trauma exposure, these two forms of memory become dissociated for two reasons: first, the extreme state of emotional arousal during a traumatic event, accompanied by the release of stress hormones, affects hippocampal functioning, which could explain the reduced consolidation of declarative memories in PTSD (Elzinga and Bremner 2002). Second, the experience of several traumatic experiences, which generally precedes the onset of PTSD, leads to the activation of the same fear memory structure, since different traumatic experiences share common elements (e.g., fear, screams, and blood). Hence, the hot memories for several traumatic experiences merge in one fear network and strengthen the associative interconnections of its elements. This makes it increasingly difficult to disentangle the different traumatic experiences and, particularly, to recall the adequate corresponding context information. Following principles of associative learning, an interconnected fear network thus encompasses sensory, cognitive, physiological, and emotional experiences and includes the action disposition related to the experience (sensory representation, hot memory) but is detached from the autobiographical context information. Furthermore, the strength of the interconnections of the fear network, as well as the number of elements integrated in the network, increases with accumulating trauma exposure, which explains the aforementioned dose-response effect of traumatic load. Environmental stimuli (e.g., a smell or noise) and internal cues (e.g., a thought), usually in combination, can later activate this network at any given time. The ignition of only a few elements in the network is sufficient for activating the whole structure and leads to strong involuntary memories (intrusive symptoms). This may express itself as a flashback, a perception that one is back in the traumatic situation with its sounds of the harsh voice, smells of blood, feelings of fear, and thoughts of dying (cf. Fig. 4.1). Since the activation of the fear network serves as a frightening and painful recollection, many people suffering from trauma-related experiences learn to avoid cues that act as reminders of the traumatic event. They try to avoid thinking about any part represented in the fear/trauma network, not to talk about it, and to stay away from people and places that remind them of the frightening event.

The fear network model corresponds well with results of structural and functional alterations in the brain of trauma survivors with PTSD (see Sect. 4.4 in this chapter) and provides not only a neurobiological explanation of the development of PTSD symptoms in the aftermath of traumatic stress but also a rationale for trauma-focused therapy approaches (Kolassa and Elbert 2007). The reactivation of consolidated memories turns them into a labile state in which modification is possible (Nadel et al. 2012). Hence, the activation of the fear network during treatment allows the modification of the present memory structure through habituation and extinction learning (Ehlers et al. 2010). One example of such an exposure-based treatment is *Narrative Exposure Therapy* (NET; Schauer et al. 2011 see also Chap. 12 of this book) – a short-term treatment for traumatic stress disorders. By connecting the “hot” sensory, emotional, cognitive, and interoceptive memories of the trauma to the “cold” autobiographical memories, an activation of the fear network

disconnected from context can be prevented and the client can achieve control over the distressing memories. The therapist further supports the client to work through the experienced traumatic experiences in a chronological order, which helps to disentangle the traumatic events which merge in the fear network. The effectiveness of NET supports the concept of a fear network in PTSD (see Robjant and Fazel 2010 for a review on evidence for the effectiveness of NET).

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## 4.2 Genetic Factors in the Etiology, Symptomatology, and Treatment of PTSD

As summarized above, traumatic load increases the risk to develop PTSD in a dose-dependent manner. Yet, individual risk factors are known to interact with traumatic load and influence the likelihood of subsequent PTSD development. From a biological perspective, it is hence crucial to look at genetic and epigenetic risk factors for PTSD.

### 4.2.1 Heritability of PTSD

Family studies examining biological relatives of patients diagnosed with PTSD first indicated genetic risk factors in disorder etiology. For example, children of PTSD patients from different contexts (Holocaust survivors, Cambodian refugees) were found to be at greater risk for PTSD following trauma exposure (Sack et al. 1995; Yehuda et al. 2001). Given that families share genetic and environmental influences (e.g., observational learning and parental distress), twin studies are needed to examine the heritability of PTSD more closely. Comparing PTSD in identical or monozygotic (MZ) twin pairs with those in fraternal or dizygotic (DZ) twin pairs results in heritability estimates of PTSD around 30–40 % (Stein et al. 2002; True et al. 1993), a figure which corresponds with estimates for anxiety disorders (Hettema et al. 2003). However, caution is needed, as identical twins may share a more similar exposure to stressful experiences in comparison to fraternal twins.

Whereas twin studies are useful to estimate the heritability of a disorder or trait, association studies are needed to identify which genes and, hence, physiological mechanisms are involved in the etiology of a certain disorder. Candidate gene association studies compare the genotype frequencies of polymorphic regions of certain candidate genes between affected individuals and healthy controls. Polymorphic regions of the genome are defined as regions that vary naturally between individuals. The most commonly studied polymorphisms are single nucleotide polymorphisms (SNPs; variation in a single base pair) and variable number of tandem repeat polymorphisms (VNTRs; the number of repeats and, hence, the length of a repetitive region of the genome differ). As a consequence, both polymorphisms can lead to functional differences in the gene-expression product.

Since PTSD requires exposure to an environmental stressor to manifest, the standard case-control design is not adequate for PTSD research, since controls might

also carry genetic risk factors which never had an impact because the individual was not sufficiently exposed to traumatic stressors. Therefore, to understand genetic susceptibility of PTSD, it is crucial to carefully assess traumatic load and include it in the subsequent genetic analyses (Cornelis et al. 2010; Wilker and Kolassa 2013).

## 4.2.2 Genetics of the Fear Network

According to the fear network model detailed above (Elbert and Schauer 2002; Kolassa and Elbert 2007), strongly interconnected, highly accessible emotional-sensory fear memories, which are detached from the corresponding autobiographical context information, lead to intrusive PTSD symptoms (Wilker and Kolassa 2013).

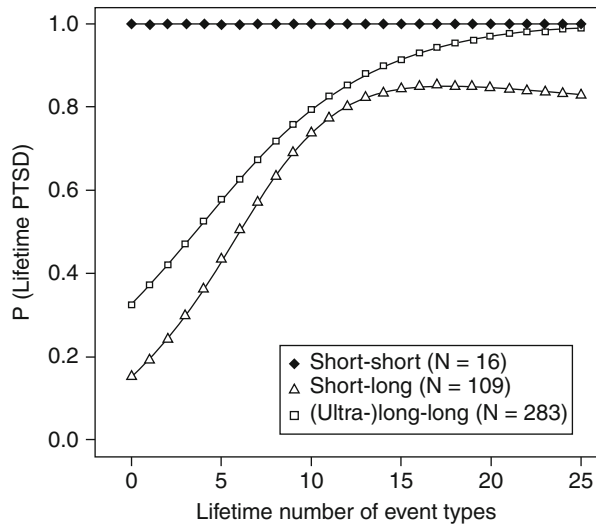
Accordingly, fear memory formation, and fear conditioning in particular, has been widely used as a model for PTSD development. Fear conditioning is a prominent paradigm in PTSD research, since it can be easily studied in animals and provides a sound explanation on how previously neutral stimuli (e.g., a policeman) can become triggers of fear due to a traumatic experience. The hippocampus, the medial prefrontal cortex (mPFC), and the amygdala (together termed *limbic-frontal neuro-circuitry of fear*) were identified as the main areas involved in the acquisition and regulation of conditioned fear in animal studies. The interplay of these areas during (traumatic) stress is influenced by the neuromodulatory actions of neurotransmitters, such as serotonin, dopamine, and norepinephrine, as well as hormones, such as glucocorticoids (for reviews see, e.g., Ressler and Nemeroff 2000; Rodrigues et al. 2009; Shin and Liberzon 2009). Therefore, these systems have been targeted by candidate gene association studies on PTSD.

Whereas studies only comparing the prevalence of genetic risk alleles in PTSD patients and controls have yielded conflicting results, research which accounts for the aforementioned building block effect and, hence, investigates gene  $\times$  environment interactions has brought converging evidence for several genetic risk factors which will be summarized in the following.

### 4.2.2.1 Modulators of the Serotonergic System

The neurotransmitter serotonin is known to influence emotional learning and memory through its inhibitory action on the amygdala (cf. Meneses and Liy-Salmeron 2012; Ressler and Nemeroff 2000). The serotonin transporter is responsible for the active clearance of serotonin from the synaptic cleft. Among candidate genes encoding proteins involved in the serotonergic system, there is convergent evidence indicating an influence of the serotonin transporter gene on the risk to develop PTSD subsequent to traumatic stress. A length polymorphism within the promoter region of the serotonin transporter gene (termed serotonin transporter gene-linked polymorphic region; 5-HTTLPR) influences its activity: in contrast to the long (l) allele, the short (s) allele is associated with lower gene transcription and, hence, lower serotonin transporter activity, higher amygdala reactivity to emotional stimulation, and enhanced fear conditioning (Greenberg et al. 1999; Heils et al. 1996; Lonsdorf et al. 2009; Munafò et al. 2008). Studies investigating gene  $\times$  environment

**Fig. 4.2** Fitted values of probability for lifetime PTSD plotted against the number of traumatic event types for different genotypes (From Kolassa et al. (2010a), reprinted with permission)



interactions consistently show that the short variant enhances PTSD susceptibility subsequent to traumatic stress (Kilpatrick et al. 2007; Kolassa et al. 2010a; Mercer 2012; Pietrzak et al. 2013; Xie et al. 2009, 2012). To give an example, in a sample of Rwandan genocide survivors, carriers of the long variant of the serotonin transporter polymorphism showed the typical building block effect: the more traumatic events experienced, the higher the prevalence of PTSD. Yet, this cumulative effect was not seen in individuals carrying two copies of the short alleles, who already developed PTSD at relatively low traumatic load (Kolassa et al. 2010a; cf. Fig. 4.2).

Interestingly, the short allele was also associated with higher risk of PTSD symptom relapse 6 months after the completion of an 8-week trauma-focused cognitive behavior therapy (Bryant et al. 2010), suggesting more persistent fear memories in carriers of this risk genotype. Furthermore, PTSD patients who were homozygous for the long allele showed higher responsiveness to a pharmacological PTSD treatment with sertraline as well as a lower dropout rate (Mushtaq et al. 2012). Whereas there are only few studies investigating the influence of genetic polymorphisms on PTSD treatment success, this first evidence might indicate the need of personalized treatments depending on individual biological risk factors.

#### 4.2.2.2 Modulators of the Dopaminergic System

Dopamine is another neuromodulator of the neurocircuitry of fear. More precisely, dopaminergic influx in the amygdala is important for the consolidation of fear memories (Guarraci et al. 2000). Dopaminergic activity is modulated by the enzyme catechol-O-methyltransferase (COMT), which degrades and thereby deactivates dopamine and other catecholamines. A SNP in the *COMT* gene results in the integration of the amino acid methionine (Met) instead of valine (Val) in the resulting protein (*COMT* Val158Met polymorphism). On the functional level, the Met allele is associated with lower COMT enzyme activity and, therefore, higher extracellular

dopamine levels (Lachman et al. 1996), as well as impaired fear extinction learning (Lonsdorf et al. 2009). Similarly, the Met allele has been found to interact with traumatic load to predict higher risk for the development of PTSD (Boscarino et al. 2011; Kolassa et al. 2010c). Furthermore, there is initial evidence that this polymorphism might influence therapeutic treatment success. To date, only one study has investigated the influence of *COMT* genotype on psychotherapeutic outcome in a sample of panic disorder patients and found that Met/Met carriers benefited less from the exposure-based elements of the treatment (Lonsdorf et al. 2010). Since effective PTSD treatments also require exposure to the traumatic experiences, it would be interesting to investigate whether these findings translate to PTSD.

#### 4.2.2.3 Modulators of the Biological Stress Responses

During a stressful or traumatic experience, the body's alarm response is initiated by two major stress axes, the hypothalamus-pituitary-adrenal (HPA) axis and the locus coeruleus noradrenergic (LCNA) system. Their joint activity prepares the body for survival, e.g., by mobilizing glucose, increasing the heart rate and blood pressure, and enhancing muscle tension.

The HPA axis activation consists of three steps: initially, corticotropin-releasing hormone is released from the hypothalamus. This stimulates the pituitary gland to secrete adrenocorticotrophic hormone, which leads to the release of cortisol from the adrenal glands. Whereas this stress response is initially adaptive, a prolonged HPA axis activity can lead to adverse health consequences. In order to avoid chronic HPA axis activation, the binding of cortisol to glucocorticoid receptors exerts negative feedback on the release of further corticotropin-releasing hormone and adrenocorticotrophic hormone from the hypothalamus and pituitary, respectively. Elevated cortisol levels have been further found to increase the memorization of emotional experiences, rendering the glucocorticoid system an interesting target for candidate gene association studies on PTSD (see, e.g., Wolf 2009 for a review). Yet, studies investigating glucocorticoid receptor polymorphisms have yielded inconsistent results (Bachmann et al. 2005; Hauer et al. 2011). Another interesting candidate in the glucocorticoid system is the gene encoding co-chaperone FK506-binding protein 51 (*FKBP5*), which regulates cortisol-binding affinity of the glucocorticoid receptor. More precisely, when *FKBP5* binds to co-chaperone FK506, the resulting receptor complex decreases the binding capacity for cortisol (Binder 2009), resulting in reduced negative feedback and, hence, a prolonged stress reaction. So far, research consistently points towards an interaction of *FKBP5* risk alleles and adult or childhood trauma exposure in the risk to develop PTSD (Binder et al. 2008; Boscarino et al. 2011, 2012; Xie et al. 2010).

Stress or emotional arousal leads to the release of noradrenaline from the basolateral amygdala, and this noradrenergic neurotransmission is required to form memories of emotional experiences (e.g., McGaugh and Roozendaal 2002). PTSD is associated with both central and peripheral noradrenergic hyperactivity (Heim and Nemeroff 2009), yet few studies investigated genes involved in the noradrenergic system. One interesting exception is the work of de Quervain and coworkers (2007), who investigated a deletion variant in the gene *ADRA2B*, coding the



alpha-2B-adrenergic receptor, which was associated with enhanced memory for emotionally arousing material in healthy volunteers and more pronounced intrusive memories in survivors of the Rwandan genocide (de Quervain et al. 2007).

In sum, reliable genetic associations were found with genes involved in the development of pathological memories. Understanding genetic risk factors relevant to the formation of intense fear memories is especially important, since those biological systems present a promising target for modifications through future treatment opportunities, especially on a pharmacological level.

Yet, despite increasing efforts and technological advances, only a small proportion of the estimated PTSD heritability can be explained by the identified genetic risk factors. Explanations for this “missing heritability” (Manolio et al. 2009) include the presence of complex multigene interactions and interactions between the individual environmental exposure with the genetic makeup of a person. Furthermore, research in the last decades has elucidated that environmental exposure can shape gene expression through epigenetic modification (Zhang and Meaney 2010). The next section will hence illuminate epigenetic mechanisms, which are essential to obtain a full understanding of the interaction of nature and nurture in PTSD etiology.

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### 4.3 Epigenetic Alterations Associated with PTSD

The term epigenetics originates from the Greek syllable *epi*, meaning upon, and genetics. The epigenome can be viewed as a “second layer of information” (Zhang and Meaney 2010, p. 447) which consists of chemical modifications altering the accessibility of the DNA, without changing the sequence of nucleotides. More precisely, gene expression depends upon the binding of transcription factors to the promoter region of a gene, and different epigenetic mechanisms dynamically allow or prevent transcription factor binding. These mechanisms are crucial to cell differentiation: since the genome of mostly all cells in a given human individual is the same, the epigenetic profile allows the specialization regarding the cellular function (e.g., heart cell vs. neuron) by determining which genetic sequences are expressed as proteins. Furthermore, and of particular relevance in the context of PTSD, epigenetic alterations allow for the dynamic adaption of gene expression to challenging environmental demands (Zhang and Meaney 2010). In the last years, evidence suggesting that traumatic stress can influence the individual epigenetic profile has accumulated (Malan-Müller et al. 2013). At first, it was supposed that particularly early developmental adversity leads to alteration in the epigenome, which can be associated with higher stress vulnerability later in life. Thereafter, however, it was acknowledged that epigenetic modifications occur during the entire lifespan and are crucial to learning and memory (Zhang and Meaney 2010). Hence, on the one hand, early developmental stress can lead to stable epigenetic alterations which constitute a risk factor for later PTSD development. On the other hand, adult traumatic stress might also lead to epigenetic modifications which could in turn perpetuate the psychological symptoms and biological alterations associated with PTSD.

The three epigenetic mechanisms which may lead to an alteration of the transcriptional accessibility of genes without changing their structure are RNA-associated silencing, histone modification, and most prominently DNA methylation (Egger et al. 2004). The modifications can enhance or decrease gene expression and even “silence” the gene entirely (Sutherland and Costa 2003).

First evidence for the influence of early experiences on the epigenetic profile stems from animal studies which show that low versus high maternal care of rat mothers leads to differential DNA methylation in their offspring (Weaver et al. 2004). More precisely, low maternal care was associated with enhanced methylation of the glucocorticoid receptor gene (*GCCR*) promoter in the hippocampus and, hence, reduced *GCCR* expression. As indicated earlier, the *GCCR* is involved in negative regulatory feedback of the hypothalamic-pituitary-adrenal (HPA) axis. Increased *GCCR* promoter methylation can therefore reduce *GCCR* sensitivity, which might lead to a prolonged HPA activation under stress. Returning to the study by Weaver et al. (2004), these epigenetic changes, which may persist into adulthood, could be prevented by placing the rodents with rat mothers providing them with high maternal care – a finding that is of utmost importance for psychotherapy in the field of psychotrauma.

McGowan et al. (2009) showed comparable findings in humans: they found enhanced methylation in a neuron-specific glucocorticoid receptor gene (*NR3C1*, the human homolog of the site investigated in rats in the Weaver study) promoter in the hippocampi of suicide victims who had experienced childhood abuse, compared to suicide victims with no documented history of childhood abuse. The study implies a common effect of early stress experiences on the epigenetic regulation of hippocampal *GCCR* expression (McGowan et al. 2009). This was confirmed by a recent study (Mehta et al. 2013) comparing DNA methylation and gene expression between a sample of PTSD patients with childhood and adult trauma, a PTSD sample without childhood trauma, and a trauma-exposed control group without PTSD. The authors found distinct gene expression patterns in the two PTSD groups, indicating differential biological pathways involved in PTSD etiology depending on childhood trauma history. Furthermore, only in the childhood trauma group, differences in gene expression overall matched with epigenetic modifications of the corresponding gene loci, suggesting that childhood trauma leads to enduring epigenetic alterations which still influence gene expression in adulthood.

Likewise, Radtke et al. (2011) showed for the first time that prenatal stress – in particular intimate partner violence – experienced by mothers during pregnancy altered the methylation status of the *GCCR* of their offspring (assessed at age 10–19). Hence, this study provides a possible link between prenatal stress and psychopathology later in life (Radtke et al. 2011).

Indeed, recent studies provide initial evidence that epigenetic modifications influence the probability of PTSD development. For instance, Koenen and colleagues showed in a primarily African American sample from the Detroit Neighborhood Health Study that methylation level at the serotonin transporter promoter polymorphisms (5-HTTLPR) and traumatic load interacted to predict PTSD vulnerability (Koenen et al. 2011). Chang and colleagues investigated the

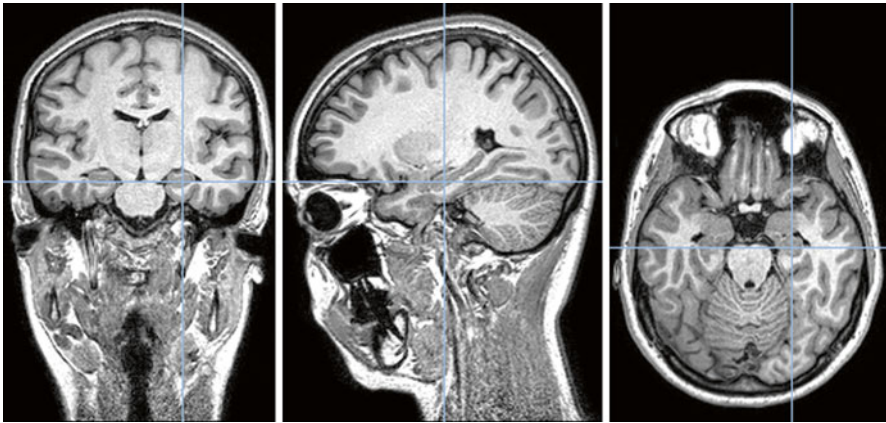
dopamine transporter gene, another genetic locus previously found to be implicated in PTSD vulnerability (Drury et al. 2009; Segman et al. 2002; Valente et al. 2011; but see Bailey et al. 2010). They found the highest PTSD probability in carriers of the high-risk genotype, who also present with higher methylation levels at this locus (Chang et al. 2012). Moreover, it was recently suggested that the combination of an *FKBP5* risk genotype and early adversity leads to demethylation at the *FKBP5* locus, which may be associated with higher FKBP5 responsiveness and an augmented stress response later in life (Klengel et al. 2012). These studies provide first evidence that traumatic experiences, especially if they occur during early developmental windows, can shape the epigenetic profile, which in turn influences the vulnerability for PTSD in the case of subsequent trauma exposure. Furthermore, the work of Klengel and coworkers indicates that epigenetic alterations may be influenced by genotype. Consequently, we are confronted with a complex interaction of genetics, epigenetics, and early and late trauma exposure in the prediction of PTSD.

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#### 4.4 Structural and Functional Alterations in the Brain of Trauma Survivors with PTSD

Structural changes associated with PTSD such as hippocampal atrophy could be the cause for functional impairments and dysfunctions associated with PTSD (Sherin and Nemeroff 2011) but were also discussed as risk factors (Gilbertson et al. 2002).

Using brain-imaging methods, PTSD has been implicated with structural changes in the medial prefrontal cortex (mPFC), the amygdala, and the hippocampus (see Liberzon and Sripada 2008 for a review). The mPFC performs inhibitory control over stress responses through its connection to the amygdala, and it plays a major role in fear extinction (Heim and Nemeroff 2009). According to the neurocircuitry model of PTSD, regions of the ventral mPFC, which are supposed to inhibit the amygdala, are dysfunctional in patients suffering from the disorder. At the same time as the amygdala responses are amplified, the hippocampus shows deficits in explicit learning and memory and, therefore, fails to identify safe environments (Rauch et al. 2006). The hippocampus (Fig. 4.3) is especially important in the development of PTSD; it is crucial for controlling stress responses as well as declarative memory, and it plays a major role in contextual aspects of fear conditioning (Heim and Nemeroff 2009). Since this area of the brain is known for its high plasticity, studies investigating structural changes in the brain due to PTSD have mainly focused on volume changes in the hippocampus (Hughes and Shin 2011). Animal studies show that pathological stress can lead to hippocampal size reduction, possibly caused by adverse effects of stress hormones (Sapolsky et al. 1990). Several meta-analyses describe smaller hippocampal volumes in trauma-exposed individuals with and without PTSD, when compared to a non-exposed control group (Smith 2005; Woon et al. 2010), while others find hippocampal volume reduction only in PTSD patients but not in trauma-exposed and non-exposed control groups (Karl et al. 2006; Kitayama et al. 2005).



**Fig. 4.3** Morphological alterations of the hippocampus have been repeatedly found in PTSD and might represent a risk factor or a consequence of the disorder

Gilbertson and colleagues (2002) conducted a study with twins; they compared war veterans with combat exposure to their twins without combat exposure. In accordance with previous studies, they also found smaller hippocampi in PTSD patients. However, the co-twins of the PTSD patients who neither suffered from PTSD nor had been exposed to combat also had smaller hippocampi compared to the non-PTSD control group (Gilbertson et al. 2002). This suggests smaller hippocampal volume to be a risk factor for PTSD rather than a consequence of the disorder. In a further study, configural processing performance was found to be significantly lower in PTSD patients in comparison to trauma-exposed controls. Nevertheless, the co-twins of the PTSD patients showed the same impairments which were related to hippocampal volume, even though they did not suffer from PTSD, nor were they trauma-exposed as adults (Gilbertson et al. 2002). However, a recent study of Teicher et al. (2012), which presents evidence that childhood adversity massively affects hippocampal development, provides an alternative explanation for the results of the Gilbertson work group. It is possible that those twins exposed to adversity during vulnerable childhood periods may have both a reduced hippocampal volume and a greater risk for developing PTSD when exposed to combat. Possibly such altered development of hippocampal organization may reduce contextualizing representations of stressful events and generalize fear. While this brain organization may be adaptive in dangerous environments, it also includes the risk of extending the fear network and eventually the maladaptive formation of PTSD.

Finally, another study found reduced hippocampal volume in current PTSD patients compared to a control group with remitted PTSD. Again, two alternative explanations could account for this finding: on the one hand, lower hippocampus volume could be a risk factor for a chronic pathology of PTSD. On the other hand, smaller hippocampus volume could be a consequence of PTSD, which might be reversible if the disorder remits (Apfel et al. 2011).

To conclude, the current state of research does not clearly support the notion that reduced hippocampus volume is a consequence of traumatic stress or a (genetic) risk factor for PTSD onset. Yet, an association of PTSD with reduced hippocampal volume is evident and corresponds well with the assumption of unreliable autobiographical context information of the fear network model.

Since the amygdala plays a central role in the neurocircuitry of fear in general, and the acquisition and expression of conditioned fear reactions in particular, several studies looked at structural alterations of the amygdala in survivors suffering from PTSD. Yet, in contrast to research on hippocampus volume, results are far from consistent. For instance, a meta-analysis from 2009 which summarized nine studies found no differences in left and right amygdala volume if PTSD patients were compared to trauma-exposed or unexposed control groups (Woon and Hedges 2009). More recent studies continue to provide inconsistent findings. Kuo and colleagues (2012) found enhanced total amygdala volumes in combat veterans with PTSD compared to trauma-exposed veterans without PTSD. Yet, another study also investigating trauma-exposed military veterans found reduced left and right amygdala volume in PTSD (Morey et al. 2012).

Finally, PTSD-associated structural alterations of the PFC, which plays a central role in fear inhibition and extinction learning through its inhibitory influence on the amygdala, have been investigated. A recent meta-analysis summarized the results of nine studies using voxel-based morphometry to assess gray matter volume in PTSD patients opposed to trauma-exposed controls and found significantly reduced volumes in several regions implicated in the neurocircuitry of fear, including the left hippocampus and the ventromedial PFC (Kühn and Gallinat 2013).

In addition to the identified structural alterations in the neurocircuitry of fear, it is also of interest to understand if the functioning or the interplay of these structures is altered in PTSD patients. A consistent body of research indicates that amygdala reactions to threatening cues are accelerated in PTSD. The common design to investigate amygdala reactivity is to compare brain activity while presenting neutral versus emotional stimuli. For instance, Brohawn and coworkers (2010) found significantly elevated amygdala reactivity in response to negative pictures in PTSD patients compared to trauma-exposed controls. These results were confirmed in numerous studies, revealing higher amygdala activity in response to fearful or aversive stimuli in PTSD patients versus controls (see Hayes et al. 2012 for a recent meta-analysis), as well as a positive correlation between current PTSD symptom severity and amygdala reactivity to these stimuli (Armony et al. 2005; Dickie et al. 2008, 2011). In addition, a recent study found enhanced spontaneous amygdala activity in PTSD, indicating that an increase in amygdala activity in PTSD is not only present during specific experimental provocations but can be a general condition in PTSD (Yan et al. 2013). Heightened amygdala activity is associated with decreased mPFC activity in response to aversive stimuli (Hayes et al. 2012). This is supplemented by recent evidence indicating that trauma survivors with PTSD show reduced functional connectivity between the amygdala and the mPFC in response to fearful stimuli, a finding that can further explain the failure of the mPFC to inhibit exaggerated amygdala responses in PTSD (Stevens et al. 2013).

Somewhat in contrast to the general finding of prefrontal hypoactivity in PTSD, Adenauer and colleagues found enhanced early activation in the right prefrontal cortex in response to aversive pictures in PTSD patients, compared to trauma-exposed individuals not suffering from PTSD and unexposed control subjects (Adenauer et al. 2010). Such early activity might be missed in functional magnetic resonance imaging studies, which have a lower time resolution than the magnetoencephalography (MEG) paradigm implemented in the Adenauer study. This early prefrontal activity might represent an acquired hypersensitivity to threatening stimuli in a traumatized brain, which constitutes one form of expression of a strong fear network that is prepared to rapidly detect danger (Rockstroh and Elbert 2010). This early adaptive activation is most likely followed by subsequent deactivation of prefrontal regions, a vigilance-avoidance pattern that was also described for other anxiety disorders (Adenauer et al. 2010).

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#### **4.5 The Effects of Psychological Trauma on Physical Health: Identifying Potential Molecular Modulators**

PTSD has been associated with poor self-reported health and increased healthcare utilization (Schnurr and Jankowski 1999) but also unfavorable lifestyle factors such as physical inactivity and smoking (Zen et al. 2012). Psychological stress, particularly if it takes extreme (traumatic) forms, has been shown to enhance the risk for cardiovascular, cerebrovascular, respiratory, gastrointestinal, musculoskeletal, inflammatory, and autoimmune diseases, as well as other age-related diseases including even cancer (Boscarino 2004; Felitti et al. 1998; Fuller-Thomson and Brennenstuhl 2009; Glaesmer et al. 2011; Schnurr and Jankowski 1999). For more details, see Chap. 5.

Although traumatic experiences and PTSD have often been related to adverse health outcomes, the precise molecular mechanisms underlying this relationship warrant further investigation. The ongoing stress an individual is exposed to through adverse environments (traumatic stressors) seems to cause the immune system to age prematurely and to alter various molecular pathways. Sommershof et al. (2009) showed a relative reduction in naïve cytotoxic and regulatory T cells in the lymphocytes of PTSD patients as well as a relative increase in memory T cells due to more past infections and a higher wear and tear of the immune system. The reduction in naïve cytotoxic T cells might lead to a compromised immune response, which could then contribute to the enhanced susceptibility for infections. A similar effect is observed in elderly people, where the natural reduction of naïve T lymphocytes leads to a greater risk for diseases associated with aging (Shen et al. 1999). In addition, the reduction of regulatory T cells might put PTSD patients at risk for inflammatory and autoimmune diseases. Indeed, there is a high prevalence of autoimmune and inflammatory diseases in PTSD patients (Boscarino 2004). More interestingly, we observed in this study (Sommershof et al. 2009) and in an extension study (Morath et al. 2014a) that naïve cytotoxic T cells and regulatory T cells were also reduced in trauma-exposed individuals without a diagnosis of PTSD; this group

took an intermediate position between PTSD patients and controls. As traumatized individuals with PTSD usually experienced more traumatic events than traumatized individuals without PTSD, this suggests a cumulative effect of traumatic stress on T-cell distribution independent of the diagnosis of PTSD (Sommershof et al. 2009).

Another potential link connecting PTSD to poor physical health is the increased pro-inflammatory status observed in individuals who experienced traumatic events or suffered from chronic stress. Gola et al. (2013) observed an augmented pro-inflammatory state in PTSD patients: peripheral blood mononuclear cells (PBMCs) exhibited an increased spontaneous secretion of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ). In addition, IL-6 and TNF- $\alpha$  were significantly positively associated with PTSD symptom severity. The enhanced spontaneous production of pro-inflammatory cytokines observed in PTSD patients indicates that traumatic stress leads to a preactivation of PBMCs (Gola et al. 2013). A chronic upregulation of pro-inflammatory cytokines might increase the risk for various physical diseases such as atherosclerosis, myocardial infarction, and stroke (Schnurr and Jankowski 1999). One mechanism by which a chronic inflammatory state leads to adverse health outcomes is the overproduction of free radicals. In low doses, free radicals serve to protect the body against pathogens; however, in higher concentrations, they can have detrimental consequences, including the impairment of functioning of DNA, proteins, and lipids. Together, the adverse consequences of free radical over-concentration are termed oxidative stress (Khansari et al. 2009). Chronic inflammation, and the resulting oxidative stress, has been associated with several types of cancer, pathological aging, and a wide range of age-related diseases such as diabetes, cardiovascular, and autoimmune disease (Hold and El-Omar 2008).

A biomarker that can be interpreted as a measure of physical age is the length of the telomeres of a cell (von Zglinicki and Martin-Ruiz 2005). Telomeres, which cap and protect the end of the chromosomes from damage and uncontrolled fusion with neighboring chromosomes, are essential for chromosome replication and stability. During cell division the telomeres are successively consumed and consequently shorten in length (Chan and Blackburn 2004). A shortening of the telomeres increases the risk for age-related diseases such as cardiovascular diseases but also cancer and cancer mortality (Epel et al. 2008; Willeit et al. 2010). Childhood maltreatment (Tyrka et al. 2010), childhood chronic or serious illness (Kananen et al. 2010), and psychological stress (Epel et al. 2004) have been associated with shorter telomeres. Moreover, Entringer et al. (2011) observed significantly shorter telomeres in the offspring of mothers who had been exposed to psychosocial stress during pregnancy. The study provides initial evidence for a transgenerational transmission of adverse health effects caused by stress exposure during pregnancy (Entringer et al. 2011).

Another biomarker measuring physiological aging is the N-glycan profile. N-glycosylation is the enzymatic attachment of a sugar molecule to a lipid or protein. N-glycans are secondary gene products which are not directly regulated by the genome and can be influenced by environmental stress (Varki 2008). The concentration of the nine different N-glycan structures in human plasma varies as a function of age. Particularly, N-glycan peak 1 increases with age, whereas N-glycan peak 6

decreases. The logarithmized ratio of the concentration of these two N-glycan structures has been established as a biomarker of physiological aging and was termed GlycoAgeTest. The test may even be used as a marker for general health in humans (Vanhooren et al. 2010).

Moreno-Villanueva et al. (2013) found significant alterations in the GlycoAgeTest for individuals with PTSD and trauma-exposed subjects in contrast to a low-stress control group. This alteration in N-glycosylation was equal to an acceleration of physiological aging by 15 years. The trauma-exposed subjects were positioned between the PTSD and the low-stress exposure group. In addition, a significant positive correlation of traumatic load with the GlycoAgeTest was observed, i.e., the more traumatic stress a person had experienced, the higher the GlycoAgeTest score and, therefore, the higher the person's physiological age (Moreno-Villanueva et al. 2013). In sum, the N-glycosylation profile strengthens the concept that traumatic stress causes an acceleration of physiological aging which might be mediated by a state of low-grade inflammation.

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## 4.6 Reversibility of Immunological and Molecular Alterations in PTSD Through Psychotherapy

As described above (Sect. 4.5), experiencing traumatic stress can cause severe biological alterations. Fortunately, at least some of these biological modifications seem to be reversible through psychotherapy.

Morath et al. (2014a) showed in a recent study that the initial reduction of regulatory T cells in PTSD patients could be reversed to some extent through a treatment with Narrative Exposure Therapy (NET) in a 1-year follow-up. The positive effect on the patients' immunological level was not observed in the waiting list control group. Unfortunately, some of the alterations in the immunological profile could not be reversed by psychotherapy, in particular, the reduction of naïve and memory T lymphocytes (Morath et al. 2014a).

Furthermore, Morath et al. (2014b) found that basal DNA strand breaks were increased in PTSD patients when compared to a control group. Interestingly, treatment with NET led to a decrease in DNA strand breaks together with a PTSD symptom reduction (Morath et al. 2014b).

Moreover, treatment with trauma-focused cognitive-behavioral therapy (TF-CBT) was found to be correlated with reduced stress symptoms on the biological level, including a declined heart rate, blood pressure, and electromyogram (EMG) reactivity. Implying that TF-CBT leads to those alterations in physiological reactivity, these findings can explain the modified stress response achieved through psychotherapy (for a review see Zantvoord et al. 2013).

Correspondingly, Adenauer et al. (2011) found not only decreased PTSD and depressive symptom severity after treatment with NET but also enhanced parietal and occipital activity in the brains of trauma survivors when exposed to adverse, threatening stimuli. Those activity changes point towards a cortical top-down regulation of attention which may be caused by NET and enable the patient to reevaluate



threatening stimuli detached from their original trauma (Adenauer et al. 2011). Hence, this study demonstrates that the modification of a fear memory network through effective trauma-focused therapy is associated with corresponding changes in cortical activity.

These initial findings show that psychotherapy, in this case NET, can be effective even on a molecular level and is able to reverse some of the severe biological changes in individuals suffering from trauma-associated psychopathology. Consequently, those studies underscore the importance of adequate psychological treatment for trauma survivors.

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## 4.7 Future Promising Directions of Neurobiological Research in Trauma-Related Disorders

This chapter focused on neurobiological findings in PTSD, one of the most commonly observed psychological disorders in the aftermath of trauma exposure. Yet, the psychological impact of trauma is not limited to the onset of PTSD but may also lead to profound alterations of the survivor's personality. As LeDoux (2003) indicates in his concept of the "synaptic self," personality is formed by an interaction of genetic makeup and environmental experiences which manifest in the formation of memories (i.e., the establishment of new synaptic connections). Emotional arousal enhances the consolidation of memories, which explains the detrimental influence of traumatic experiences. Furthermore, if strong emotional experiences occur during sensitive developmental periods, their impact on personality building is even higher, explaining the strong impact of childhood abuse and maltreatment (LeDoux 2003). There are several concepts which try to acknowledge the long-lasting impact of (early) traumatization on individual development. These concepts include the suggested new diagnoses "developmental trauma disorder" (van der Kolk 2005) as well as "complex PTSD" (Maercker et al. 2013).

The literature on epigenetic alterations in response to early adversity reviewed earlier further highlights the high impact of childhood experiences on neurobiological development and hence the establishment of the synaptic self. For instance, Klengel and colleagues showed that childhood but not adult trauma exposure was associated with allele-specific demethylation at the *FKBP5* locus which may lead to enduring alterations of the stress system (Klengel et al. 2012). While research on the influence of early adversity on neurobiological alterations (especially epigenetics) is accumulating, the literature on distinct neurobiological signatures of complex PTSD or developmental trauma disorder is still relatively sparse. In the future, it would be interesting to investigate whether these diagnostic categories are at least partly reflected by distinct underlying biomolecular processes (cf. Miller 2010). Recent technological advances enable the assessment and computational analysis of large biological data sets with high coverage in the fields of genetics, epigenetics, or proteomics (Patti et al. 2012) and may hence allow identifying both distinct and shared biological pathways of trauma-related psychological disorders. Once the identification of distinct neurobiological signatures of the aforementioned

trauma-related disorders becomes possible, this may point to novel treatment opportunities directed at these more complex reactions to trauma.

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