The downside of strong emotional memories: How human memory-related genes influence the risk for posttraumatic stress disorder – A selective review

Sarah Wilker,a,⇑ Thomas Elbertb, Iris-Tatjana Kolassaa

aClinical & Biological Psychology, Institute of Psychology & Education, University of Ulm, Albert-Einstein-Allee 47, 89069 Ulm, Germany
bClinical Psychology & Neuropsychology, University of Konstanz, Universitätstr. 10, 78457 Konstanz, Germany

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ABSTRACT

A good memory for emotionally arousing experiences may be intrinsically adaptive, as it helps the organisms to predict safety and danger and to choose appropriate responses to prevent potential harm. However, under conditions of repeated exposure to traumatic stressors, strong emotional memories of these experiences can lead to the development of trauma related disorders such as posttraumatic stress disorder (PTSD). This syndrome is characterized by distressing intrusive memories that can be so intense that the survivor is unable to discriminate past from present experiences.

This selective review on the role of memory related genes in PTSD etiology is divided in three sections. First, we summarize studies indicating that the likelihood to develop PTSD depends on the cumulative exposure to traumatic stressors and on individual predisposing risk factors, including a substantial genetic contribution to PTSD risk. Second, we focus on memory processes supposed to be involved in PTSD etiology and present evidence for PTSD associated alterations in both implicit (fear conditioning, fear extinction) and explicit memory for emotional material. This is supplemented by a brief description of structural and functional alterations in memory relevant brain regions in PTSD. Finally, we summarize a selection of studies indicating that genetic variations found to be associated with enhanced fear conditioning, reduced fear extinction or better episodic memory in human experimental studies can have clinical implications in the case of trauma exposure and influence the risk of PTSD development. Here, we focus on genes involved in noradrenergic (ADRA2B), serotonergic (SLC6A4), and dopaminergic signaling (COMT) as well as in the molecular cascades of memory formation (PRKCA and WWC1). This is supplemented by initial evidence that such memory related genes might also influence the response rates of exposure based psychotherapy or pharmacological treatment of PTSD, which underscores the relevance of basic memory research for disorders of altered memory functioning such as PTSD.

1. Introduction

Traumatic stressors such as natural disasters, terror attacks, war experiences, torture, violent assaults or rape can lead to severe mental health disorders, most prominently posttraumatic stress disorder (PTSD). Whereas some individuals develop PTSD after few traumatic experiences, others show remarkable resilience even in the face of multiple traumatization (Kolassa et al., 2010b). Similarly, individuals differ strongly in their response to trauma focused psychotherapeutic treatments (Bradley, Greene, Russ, Dutra, & Westen, 2005). A better understanding of individual risk and resilience factors could hence contribute to a better understanding of PTSD etiology and the improvement of psychological and pharmacological treatment approaches.

This selective review will focus on genetic liability to PTSD development. Since PTSD has been conceptualized as a disorder of memory impairment, we will show how insights from basic memory research can lead to advancements in the understanding of genetic risk factors of PTSD. Throughout the review, we will discuss potential clinical implications of the presented findings.

2. Traumatic stress and genetic risk elevate the likelihood of PTSD development

PTSD is unique among the disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) since its diagnosis requires the presence of an etiological risk factor, namely a traumatic stressor. According to DSM IV, PTSD has been defined by the...
following three symptom clusters (1) intrusive re-experiencing of the traumatic event in the form of recurrent dreams, thoughts, sensations or flashbacks related to the trauma, (2) avoidance of any potential trauma reminders or emotional numbing as an attempt to prevent the distressing recollections of the trauma, and (3) a persistent state of increased alertness and arousal (American Psychiatric Association, 2000). In the newly released DSM 5, one major change is the division of the previous symptom cluster of avoid ance into two categories: active avoidance of thoughts or activities on one side, and loss of interest, emotional numbing as well as persistent negative emotional states and beliefs on the other side (American Psychiatric Association, 2013).

2.1. PTSD, traumatic load and the building block effect

Studies of survivors of mass conflict, terror or war investigate populations which have encountered various types of traumatic stressors. These studies repeatedly showed that the number of different traumatic events experienced (defining traumatic load) increases the likelihood to develop PTSD and the severity of PTSD symptoms in a dose dependent manner (Kolassa, Ertl, Kolassa, et al., 2010a; Mollica, McInnes, Poole, & Tor, 1998; Neugebauer et al., 2009; Neuner et al., 2004). Furthermore, there is no ultimate resistance towards the development of PTSD; with increasing trauma load, the prevalence of PTSD approaches 100% (Kolassa et al., 2010a; Neugebauer et al., 2009; Neuner et al., 2004). Despite this strong so called building block effect (Schauer et al., 2003), there exists substantial inter individual variability in the susceptibility to develop PTSD, especially at lower levels of traumatic load (Fig. 1; Kolassa et al., 2010a). Therefore, predisposing risk factors are likely to influence the individual ‘critical dose’ of traumatic experiences leading to subsequent PTSD development.

2.2. The role of genetic risk in PTSD etiology

An initial indicator of a genetic contribution to PTSD was the observation that PTSD clusters in families, e.g. children of holocaust survivors with PTSD were found to be at a greater risk to develop PTSD in their life (Yehuda, Schneiderl, Wainberg, Binder Brynes, & Duvedevani, 1998). A clearer picture of the heritability of PTSD can be derived from twin studies. Heritability estimates derived from a male sample of Vietnam veterans (True et al., 1993) and a mixed civilian sample (Stein, Jang, Taylor, Vernon, & Livesley, 2002), converge at values around 30-40% which are comparable to those obtained for other anxiety disorders (Hettema, Neale, & Kendler, 2001).

Genetic vulnerability factors are likely to interact with cumulative trauma exposure throughout the entire lifespan and do not necessarily lead to the manifestation of PTSD at the time of investigation. Therefore, it was recommended to assess lifetime PTSD diagnosis in addition to current symptomatology (Cornelis, Nugent, Amstadter, & Koenen, 2010).

3. The development of PTSD as the formation of pathological memories

The presence of vivid intrusive traumatic memories with here and now quality, often accompanied by a failure to adequately remember the corresponding contextual information, is a basis for many psychological and neurobiological theories of PTSD development.

For instance, the dual representation theory (Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010) differentiates between low level, sensory based representations (S reps), which are mainly mediated by early sensory cortical and subcortical areas, namely the amygdala and insula, and more abstract, context bound representations (C reps), mediated by the hippocampus and surrounding medial temporal lobe structures. While the former comprise representations of sensory impressions (e.g., pictures, sounds, or smells) and peri traumatic emotional responding (e.g., fear, disgust or anger), the latter provide the corresponding contextual information and are indispensable for an appropriate allocation of the experience in time and space. In healthy individuals, S reps and C reps are well integrated, which allows voluntary (top down) retrieval of sensory emotional and contextual information associated with an autobiographical memory. This is a necessary condition for replaying an event in mind without losing connection to the here and now. By contrast, the occurrence of an extremely stressful event can lead to the formation of strong and enduring S reps which lack contextualization by appropriate integration of corresponding C reps. Hence, sensory cues can activate the S reps (bottom up) without activating the corresponding higher order contextual information, and thereby lead to flashbacks or other intense intrusions.

Correspondingly the cognitive model of PTSD (Ehlers & Clark, 2000) states that trauma memories in PTSD are characterized by a weak elaboration and contextualization of the respective events. Additionally, implicit memory mechanisms are supposed to rein force the impact of traumatic memories. First, extremely stressful events are thought to elucidate strong associative connections between intrinsically neutral stimuli, which have been temporarily associated with the trauma, and the traumatic material. This phenomenon, termed fear conditioning, renders previously neutral stimuli to potent triggers of intrusive memories and associated fear reactions. Second, the model assumes strong perceptual priming for stimuli that have been present during the trauma, i.e. those stimuli have an increased likelihood to be noticed by the trauma survivor and hence trigger PTSD symptoms. It is important to mention that both mechanisms can be intrinsically adaptive, since they aim at early detection and prevention of further life threat.

Fig. 1. Predicted and observed proportions of lifetime posttraumatic stress disorder (PTSD) as a function of trauma exposure in a sample of N = 444 Rwandan genocide survivors. Bars represent bootstrapped pointwise 95% confidence intervals of the predicted values. With increasing traumatic load, the probability of a lifetime diagnosis of PTSD approximates 100%, and the interindividual variability in PTSD susceptibility decreases. From Kolassa, Ertl, Eckart, Kolassa, et al. (2010). Spontaneous remission from PTSD depends on the number of traumatic event types experienced. *Psychological Trauma: Theory, Research, Practice, and Policy, 2*(3), 169-174, September 2010, American Psychiatric Association, reprinted with permission.
Finally, the fear network model, as formulated by Elbert and colleagues (Elbert & Schauer, 2002; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010; Schauer, Neuner, & Elbert, 2011) as an extension of Lang (1979) and Foa and Kozak (1986), is unique in the sense that it especially accounts for the aforementioned dose dependent influence of multiple traumatization which is frequently occurring in the context of armed conflict. This neurobiological model proposes that traumatic memories (like any other information) are stored in propositional networks, which can be shaped by new experiences through neuroplasticity. Similar to the categorization of S reps and C reps (Brewin et al., 2010), the fear network model distinguishes between ‘hot’ and ‘cold’ memories, following the terminology proposed by Metcalfe and Jacob (1996). Hot memories comprise the sensory (e.g. hearing screams, smelling blood), emotional (fear, horror, disgust), cognitive (e.g. the thought “I will die”) and interoceptive (e.g. the feeling of a strong heart beat) elements of an event. By contrast, cold memories represent the autobio graphical context information (i.e., time and space). Whereas hot and cold elements are well integrated in healthy memory, they are thought to become dissociated if PTSD develops. Once a fear network is established, subsequent traumatic events activate and remodel the existing structure, strengthen the associative connections between its elements, and add further nodes to the network. With a growing number of traumatic events that merge in the fear network, it becomes increasingly difficult to recall the appropriate contextual information of a particular event. Furthermore, due to the strong associative interconnections of the network, one single trauma reminder is potent enough to activate the entire structure and evoke intrusive symptoms and intense fear reactions.

3.2. PTSD and memory practical perspectives

The present article considers the influence of genetic risk factors for PTSD susceptibility. Given the central role of memory processes for PTSD development reviewed earlier, we propose that differences in memory performance could constitute a useful endophenotype for the study of PTSD. More precisely, we suggest the study of memory on healthy volunteers as a valuable inspiration for PTSD research. In the following, we will present two common emotional memory paradigms which can be easily studied in the lab, and are relevant to the memory processes leading to PTSD development. Fig. 2 summarizes memory alterations in PTSD.

3.2.1. Fear conditioning and extinction learning

The cognitive model of PTSD (Ehlers & Clark, 2000) and the fear network model (Elbert & Schauer, 2002; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010) stress the importance of strong interconnections between the traumatic event and stimuli that were temporarily associated with the trauma. Since fear conditioning leads to the establishment of new stimulus stimuli and stimulus reaction associations, it was assumed that PTSD clients might display higher conditionability towards novel aversive stimuli (Orr et al., 1997). Indeed, patients with PTSD display deficits in extinction learning and discrimination of safety cues (fear inhibition) when compared to trauma exposed controls without PTSD (Norholm et al., 2011; Peri, Ben Shakhar, Orr, & Shalev, 2000; Wessa & Flor, 2007). A further line of evidence suggests that memory capacity for extinction learning (i.e. the ability to recall that a certain stimulus no longer predicts danger) is impaired in PTSD (Milad et al., 2009). Prospective studies indicate that impaired fear extinction constitutes a risk factor for PTSD rather than a result of the disorder. In two investigations of firemen (Guthrie & Bryant, 2006) and Dutch soldiers (Lommen, Engelhard, Sijbrendij, van den Hout, & Hermans, 2013), pre trauma fear extinction performance predicted 31% and 23% respectively of the variance of subsequent PTSD symptom development after trauma exposure. Importantly, the individual variation in the acquisition and extinction of fear responses in the laboratory is substantially heritable, with heritability estimates of a twin study ranging from 35% to 45% for the different phases of fear conditioning (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003). Moreover, the aforementioned processes have direct clinical implications for the treatment of PTSD, since exposure based treatments, which have been shown to be effective in treating PTSD, rely on processes of extinction learning (Ehlers et al., 2010).

Finally, fear conditioning and extinction have the advantage that the underlying neurocircuitry is well described. Lesion studies in animals revealed that the amygdala (particularly the basolateral amygdala) is essential for the acquisition, storage and expression of conditioned fear, a finding which was supported by human functional imaging studies showing enhanced amygdala activation during fear conditioning (LeDoux, 2000; Pape & Pare, 2010; Phelps & LeDoux, 2005; Selh Meyer et al., 2009). Extinction learning, and particularly extinction memory retention, depends on the medial prefrontal cortex, which regulates fear expression via inhibitory projections to the amygdala (Milad & Quirk, 2002; Quirk, Garcia, & Gonzalez Lima, 2006). Moreover, cortical thickness of the medial prefrontal cortex was found to be associated with extinction memory performance in humans (Milad et al., 2005). Finally, the hippocampus is required to form configural representations of the context in which fear learning occurred (Maren, Phan, & Liberzon, 2013).

3.2.2. Episodic memory

A second memory paradigm relevant to PTSD is the study of episodic memory performance, particularly for emotionally arousing information (de Quervain, Aerni, Schelling, & Rozendaal, 2009). Similar to fear conditioning, episodic memory performance is substantially heritable, with heritability estimates derived from twin studies varying between 30% and 60% (Papassotiriopoulos & de Quervain, 2011). While episodic memory primarily depends on the hippocampus, heightened emotional arousal augments the consolidation of autobiographical events, an effect mediated by the basolateral amygdala (McGaugh, 2004, 2006). It was further suggested that the amygdala promotes memories for the central elements of an event, at the cost of decreased memories for peripheral details (Adolphs, Denburg, & Tranel, 2001; Adolphs, Tranel, & Buchanan, 2005). This memory enhancing effect of emotional arousal is intrinsically adaptive, since it facilitates the recall of the gist of potentially advantageous or dangerous situations and hence promotes optimal decisions for survival. However, intense memories for emotional situations could turn maladaptive in the case of trauma exposure and lead to subsequent PTSD development. Both the fear network model (Elbert & Schauer, 2002; Kolas sa & Elbert, 2007; Rockstroh & Elbert, 2010) and the dual representation theory (Brewin et al., 1996; Brewin et al., 2010) distinguish between amygdala mediated sensory emotional (hot) and contextual (cold) information and stress the dissociation of these two forms of memory in PTSD, a phenomenon that cannot be merely accounted for by processes of fear conditioning (Layton & Krrkian, 2002). Hence, an augmented memory advantage for extremely emotional arousing material accompanied by a poorer memorization of contextual details or neutral information could lead to more pronounced PTSD symptoms according to both models.
The effect of emotional arousal on episodic memory performance can be tested in human experimental studies by presenting words, pictures or stories which are systematically varied in terms of the emotionality (Todd, Palombo, Levine, & Anderson, 2011). Such investigations are frequently designed as functional imaging studies in order to assess the corresponding amygdala activation. Overall, there is congruent evidence that individuals with PTSD show a memory advantage for trauma related information. For instance, in a study comparing crime victims with acute PTSD and healthy controls, PTSD cases showed an attention bias towards trauma related and positive emotional stimuli, but higher explicit memory performance for trauma related stimuli only (Paunovic, Lundh, & Ost, 2002). Likewise, Holocaust survivors with PTSD showed general deficits in explicit memory, but a memory advantage for trauma relevant words when compared to survivors without PTSD and non exposed controls (Goller, Yehuda, Lupien, & Harvey, 2003). This is opposed by a memory deficit for non emotional information in PTSD. A recent meta analysis summarized the results of 27 studies on PTSD and memory function and reported a robust effect of poorer memory performance for emotionally neutral material in PTSD patients compared to non trauma exposed as well as to trauma exposed control groups (Brewin, Kleiner, Vasterling, & Field, 2007). However, a general advantage for trauma unrelated aversive information is not evident, with different studies displaying conflicting results (e.g. Brohawn, Offringa, Pfaff, Hughes, & Shin, 2010; Moradi, Taghavi, Neshat Doost, Yule, & Dalgleish, 2000). By contrast, a large body of research has indicated increased amygdala reactivity towards aversive or fearful trauma unrelated stimuli in PTSD (Armony, Corbo, Clement, & Brunet, 2005; Brohawn et al., 2010; Bryant, Kemp, et al., 2008; Dickie, Brunet, Akerib, & Armony, 2008; Francati, Vermetten, & Bremner, 2010). Furthermore, enhanced amygdala activation was associated with recall performance of aversive stimuli and PTSD symptom severity (Dickie et al., 2008). Hence, while there is no clear pattern of enhanced memory for trauma unrelated negative material in PTSD, there is strong evidence for enhanced amygdala reactivity in response to those stimuli. The clinical significance of this effect is illustrated by investigations suggesting that decreased amygdala reactivity might be protective for PTSD development in the aftermath of trauma (Britton, Phan, Taylor, Fig, & Liberzon, 2005; Osuch et al., 2008), and is associated with treatment success of cognitive behavioral therapy for PTSD (Bryant, Felmingham, et al, 2008).

### 3.3. Structural and functional alterations in the brain of trauma survivors with PTSD

Whereas a comprehensive overview of the structural and functional cerebral alterations observed in PTSD is beyond the scope of this review and can be found elsewhere (Rauch, Shin, & Phelps, 2006; Shin, Rauch, & Pitman, 2006), it is noteworthy to mention that alterations in PTSD correspond well with the relevant regions implicated in fear conditioning and (emotional) episodic memory formation. However, it is important to note that a challenge in interpreting neuroimaging data acquired in patients with PTSD is to disentangle whether neuroanatomical or neurofunctional abnormalities reflect an underlying causal factor or a consequence of the disorder.

In line with the theoretical models supposing reduced memory for context information in PTSD (Brewin et al., 2010, 1996; Elbert & Schauer, 2002; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010), and the empirical evidence for worse performance on emotionally neutral episodic memory tasks in PTSD (Brewin et al., 2007), there is evidence for hippocampal atrophy in PTSD. As illustrated by two recent meta analyses, the majority of studies reported reduced hippocampal volume in PTSD patients when compared to healthy, trauma unexposed controls, and, to a lesser extent, when compared to trauma exposed controls (Karl et al., 2006; Woon, Sood, & Hedges, 2010). The finding that trauma exposed individuals without PTSD also develop structural hippocampus abnormalities, and that the difference in hippocampal volume is strongest in individuals with severe PTSD (Karl et al., 2006), is indicative for the assumption that the building block effect is mirrored in this neuro physiological correlate of PTSD (Kolassa & Elbert, 2007). Yet, a study of Gilbertson et al. (2002) points towards a heritable component of reduced hippocampal volume in PTSD. The authors investigated越南 veterans and their stay at home identical twins and found that reduced hippocampal volume was not only present in

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**Fig. 2.** Memory mechanisms supposed to be altered in posttraumatic stress disorder (PTSD). Memory paradigms central to this review are shaded in grey, and arrows indicate the direction of the alterations.
the trauma exposed PTSD patients, but also in their non exposed siblings. However, it should be considered that childhood adversity is another source of stress that may affect hippocampal development (Andersen & Teicher, 2004) and that exposure to early stress affects hippocampal subfield development (Teicher, Anderson, & Polcari, 2012). It is therefore possible that some of the variance shared by the twins in Gilbertson et al.’s study results in part from a similarity in the developmental stress patterns. There is also evidence for abnormal hippocampal activity in PTSD; however, the direction of the association varies depending on the tasks and methods of the respective studies (see Shin & Liberzon, 2010 for a review).

Since stress can induce amygdala hypertrophy in animal models (Vyas, Bernal, & Chattarji, 2003), and due to the central role of the amygdala in both fear conditioning and emotional episodic memories, research has also focused on PTSD associated alterations in amygdala volumes, but conflicting results and methodological differences (e.g. the comparison of PTSD cases with trauma exposed or non exposed groups, the investigation of adult or pediatric samples) prevent valid conclusions (Karl et al., 2006; Kuo, Kaloupek, & Woodward, 2012; Morey et al., 2012; Woon & Hedges, 2009). However, as reviewed earlier, there is large empirical support for amygdala hyperreactivity in response to aversive stimuli in PTSD (Armony et al., 2005; Brohawn et al., 2010; Bryant, Kemp, et al., 2008; Dickie et al., 2008; Francati et al., 2007).

Finally, the medial prefrontal cortex (mPFC), implicated in extinction learning and retention of extinction memories, has been investigated in PTSD. Albeit with some inconsistent findings, research points towards reduced mPFC volume (Karl et al., 2006; Kuhn & Gallinat, 2013) and hyporesponsivity of the mPFC in response to trauma related and trauma unrelated aversive stimuli (Hayes, Hayes, & Mikkalis, 2012) and during extinction learning (Bremner et al., 2005). Furthermore, an inverse relationship between PTSD symptom severity and mPFC activation was reported (Britton et al., 2005; Dickie et al., 2008).

To sum up, the theoretical frameworks reviewed in this section propose associative learning and altered episodic memory as core mechanisms leading to the onset of PTSD. Indeed, altered memory performance and/or brain activation has been observed in both paradigms when investigating PTSD patients. Furthermore, the cerebral regions involved in fear conditioning, extinction learning, and the formation of episodic memories for emotional events play both morphological and functional alterations in PTSD. Genetic vulnerability seems to play a role in at least some of the observed abnormalities, and both human associative learning and episodic memory are substantially inheritable. This supports the notion of a diathesis stress model which includes the interaction of memory related genes and traumatic stress to predict PTSD vulnerability.

4. Variations in memory-related genes and implications for PTSD

In the following paragraphs, we will review the potential benefits of a translational perspective which utilizes knowledge derived from investigations that focus on genetic variations implied in human associative learning or episodic memory to improve our understanding of PTSD vulnerability. This review will therefore include genetic association studies of biological systems with convergent evidence from both human experimental studies on memory performance and clinical studies on PTSD risk, with a focus on the biological pathways investigated by our work group. For a more complete overview on candidate gene association studies on PTSD, the reader is referred to e.g. Cornelis et al. (2010), Skelton, Ressler, Norholm, Jovanovic, and Bradley Davino (2012) or Wilker and Kolassa (2013).

It was recently shown that pretreatment differences in immediate story recall, a measure of verbal memory, could distinguish responders from non responders (defined as clients with persistent PTSD) to cognitive behavioral therapy for PTSD (Wild & Gur, 2008). The effect remained when controlling for IQ and pretreatment symptom severity. While the study does not disentangle whether the differences in memory performance originate from the trauma or represent pre-existing risk factors, it points towards a clinical relevance of memory processes not only for PTSD etiology, but also for its treatment. We will therefore also review studies investigating how memory related genes influence psychotherapeutic treatment response. Table 1 provides an overview on the human experimental as well as clinical studies reviewed in this chapter.

4.1. Neuroendocrinological modulation of fear memories

The neurocircuitry of emotional memories (i.e., the interplay of the basolateral amygdala, mPFC and hippocampus) is influenced by the neuromodulatory action of neurotransmitters, such as serotonin, dopamine and norepinephrine and hormones, such as glucocorticoids (for reviews see e.g. Ressler & Nemeroff, 2000; Rodrigues, LeDoux, & Sapolsky, 2009). This selective review focuses on genetic variations involved in the regulation of norepinephrine, dopamine and serotonin with joint evidence from human experimental studies on memory performance and clinical studies on PTSD.

4.1.1. Norepinephrine

Memories for emotionally significant events require intact noradrenergic neurotransmission in the basolateral amygdala (e.g. McGaugh & Roozendaal, 2002). More precisely, emotionally arousing experiences lead to the release of norepinephrine in the basolateral amygdala, and pharmacological stimulation or blockage of norepinephrine signaling lead to enhanced or impaired memory consolidation, respectively (Roozendaal & McGaugh, 2011). In a seminal work, Cahill and co workers showed that the memory enhancing effect of emotional arousal vanished, if study participants were treated with propranolol, a β adrenergic antagonist (Cahill, Prins, Weber, & McGaugh, 1994). By contrast, pharmacological treatment with yohimbine, an antagonist of α adrenergic receptors, activates the noradrenergic system and leads to enhanced memory for emotionally arousing items (O’Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1998). Furthermore, a recent investigation also showed that pharmacological stimulation of noradrenergic transmission with yohimbine leads to enhanced associative fear learning in healthy volunteers, which was evidenced by delayed extinction rates (Soeter & Kindt, 2011). Excessive release of norepinephrine in trauma survivors with a hyperresponsive noradrenergic system might hence contribute to the overconsolidation of traumatic memories and the development of PTSD (Southwick et al., 1999).

A natural genetic variation of the α adrenergic receptor 2B (ADRA2B) consists of an inframe deletion leading to the absence of three acidic residues in a large glutaminergic stretch. De Quervain et al. (2007) were the first to show that carriers of the deletion variant show enhanced memories for emotionally arousing compared to emotionally neutral pictures, suggesting that the polymorphism seems to exert loss of function consequences similar to receptor blockage with yohimbine. This effect was confirmed and extended by evidence that deletion carriers show heightened amygdala activity during encoding of emotionally arousing negative pictures (Rasch et al., 2009) as well as in response to acute environmental stress (Coussijn et al., 2010), indicating a higher amygdala responsivity to emotional material and stress which leads to better memory consolidation in carriers of the
Overview of human experimental studies on memory formation and clinical studies on PTSD risk and treatment.

Table 1

<table>
<thead>
<tr>
<th>Gene (Variation)</th>
<th>Authors</th>
<th>Phenotype</th>
<th>Sample</th>
<th>Ethnicity</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRA2B (inframe deletion)</td>
<td>de Quervain et al. (2007)</td>
<td>Emotional Memory</td>
<td>435 (26)</td>
<td>Caucasian (Switzerland)</td>
<td>Increased memory advantage for emotional information in deletion carriers (d = 4, p = 0.0005)</td>
</tr>
<tr>
<td>ADRA2B (inframe deletion)</td>
<td>Rasch et al. (2009)</td>
<td>Emotional Memory, Amygdala Activity (SMB)</td>
<td>57 (28)</td>
<td>Caucasian (Switzerland)</td>
<td>Non-significant trend for an increased emotional memory in deletion carriers (d = 4, p = .14). Higher activation of the right amygdala in deletion carriers during encoding of negative vs. neutral pictures (p = .05)</td>
</tr>
<tr>
<td>ADRA2B (inframe deletion)</td>
<td>de Quervain et al. (2007)</td>
<td>Intrusive Symptoms</td>
<td>202 (50)</td>
<td>African (Rwanda)</td>
<td>Deletion carriers had higher intrusive memory symptoms per traumatic event type (p = .003)</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Carpenter et al. (2001)</td>
<td>Fear Conditioning (SCR)</td>
<td>40 (35)</td>
<td>Caucasian (Sweden)</td>
<td>Stronger SCR reactivity to the CS+ during fear conditioning acquisition in short-allele carriers (p = 0.002)</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Gruen et al. (2009)</td>
<td>Fear Conditioning (SCR)</td>
<td>32 (28)</td>
<td>Probably Caucasian (Romania)</td>
<td>Stronger SCR reactivity to the CS+ in the test phase of an observational fear conditioning paradigm in short-allele carriers (p &lt; 0.001). In comparison to women, men displayed decreased SCR to the CS+</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Lenzner et al. (2005)</td>
<td>Fear Conditioning (PS)</td>
<td>48 (52)</td>
<td>Caucasian (Sweden)</td>
<td>Enhanced startle potentiation to the CS+ during acquisition (p = .01) and extinction (p &lt; .001) in short-allele carriers, no genotype-dependent effect was found for SCR</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Agren et al. (2012)</td>
<td>Fear Reactivation</td>
<td>33 (62)</td>
<td>Caucasian (Sweden)</td>
<td>Higher fear reinstatement in short-allele carriers following an extinction training which took place outside a reconsolidation window (p &lt; .001)</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Kivipelto et al. (2007)</td>
<td>Current PTSD</td>
<td>589 (37)</td>
<td>Mainly Caucasian (USA)</td>
<td>Enhanced PTSD risk for short-allele carriers under conditions of low social support and high hurricane exposure (p_{HTTLPR}&lt;.05)</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Clarke et al. (2009)</td>
<td>Lifetime PTSD</td>
<td>1,663 (50)</td>
<td>Caucasian (Germany)</td>
<td>Enhanced PTSD risk for long-allele carriers, especially under conditions of high trauma exposure (p_{HTTLPR}&lt;.05)</td>
</tr>
<tr>
<td>COMT (HTTFLP)</td>
<td>Sier et al. (2009)</td>
<td>Lifetime PTSD</td>
<td>1,252 (52)</td>
<td>Caucasian and African American (USA)</td>
<td>Enhanced PTSD risk for short-allele carriers who face both childhood and adult trauma exposure (p_{HTTLPR}&lt;.001, effect was present in both ethnicities investigated)</td>
</tr>
<tr>
<td>SLC6A4 (5-HTTLPR)</td>
<td>Kolassa et al. (2010a)</td>
<td>Lifetime PTSD</td>
<td>408 (53)</td>
<td>African (Sweden)</td>
<td>Enhanced PTSD risk for short-allele carriers across all levels of trauma exposure (p = .008)</td>
</tr>
<tr>
<td>SLC6A4 (5-HTTLPR)</td>
<td>Pierer et al. (2012)</td>
<td>Acute Stress Disorder Symptoms</td>
<td>123 (0)</td>
<td>Caucasian (USA)</td>
<td>More pronounced acute stress disorder symptoms in short-allele carriers when accounting for the levels of shooting exposure (p = .007)</td>
</tr>
<tr>
<td>SLC6A4 (5-HTTLPR)</td>
<td>Sier et al. (2011)</td>
<td>Lifetime PTSD</td>
<td>5,178 (56)</td>
<td>Caucasian and African American (USA)</td>
<td>In a model accounting for sex, age and ancestry, higher PTSD symptoms were observed in short-allele carriers facing high hurricane exposure (p_{HTTLPR}&lt;.01)</td>
</tr>
<tr>
<td>SLC6A4 (5-HTTLPR)</td>
<td>Potetzka et al. (2011)</td>
<td>Current PTSD Symptom Severity</td>
<td>140 (41)</td>
<td>Mainly Caucasian (USA)</td>
<td>Mainly Caucasian (USA)</td>
</tr>
<tr>
<td>SLC6A4 (5-HTTLPR)</td>
<td>Nkholok et al. (2012)</td>
<td>Current PTSD Symptom Severity</td>
<td>226 (45)</td>
<td>Asian (India)</td>
<td>Short-allele carriers showed reduced benefits from sertraline treatment (p &lt; .001). If response is defined as a 30% reduction in PTSD symptoms, the response rate in short-allele carriers was .05</td>
</tr>
<tr>
<td>COMT (Val158Met)</td>
<td>Lenzner et al. (2009)</td>
<td>Fear Conditioning (PS)</td>
<td>48 (52)</td>
<td>Caucasian (Sweden)</td>
<td>Stronger CS+ startle potentiation in Met-allele carriers during extinction (p = .05). No effect of genotype on fear acquisition. No COMT genotype effects on SCR</td>
</tr>
<tr>
<td>COMT (Val158Met)</td>
<td>Raczka et al. (2011)</td>
<td>Fear Conditioning (SCR and fear ratings)</td>
<td>60 (100)</td>
<td>Caucasian (Germany)</td>
<td>Met homozygous individuals show higher EPS to the CS (i.e., impaired fear inhibition, p &lt; .001) and reduced fear extinction learning (p &lt; .05). Yet, these effects were mainly carried by Met/Met individuals with PTSD</td>
</tr>
<tr>
<td>COMT (Val158Met)</td>
<td>Kolassa et al. (2013)</td>
<td>Fear Reactivation</td>
<td>270 (37)</td>
<td>Mainly African American (USA)</td>
<td>Caucasian (USA)</td>
</tr>
<tr>
<td>COMT (Val158Met)</td>
<td>Kolassa et al. (2013b)</td>
<td>Lifetime PTSD</td>
<td>434 (50)</td>
<td>African (Sweden)</td>
<td>Increased memory advantage for emotional information in deletion carriers (d = 4, p = .0005)</td>
</tr>
<tr>
<td>COMT (Val158Met)</td>
<td>Boscanino et al. (2011)</td>
<td>Lifetime PTSD</td>
<td>502 (not reported)</td>
<td>Caucasian (USA)</td>
<td>The Met allele was associated with higher PTSD risk in a model including childhood adversity and adult trauma exposure (p &lt; .05)</td>
</tr>
<tr>
<td>COMT (Val158Met)</td>
<td>Valente et al. (2011)</td>
<td>Current PTSD</td>
<td>434 (not reported for whole sample)</td>
<td>Mixed ethnicity (Brazil)</td>
<td>Enhanced memory performance for negative pictures in Val/Val short-allele carriers (p = .000002) and to a lesser extend also for positive and neutral pictures</td>
</tr>
</tbody>
</table>

Note: *p* values are indicated by *p* < .001, *p* < .01, *p* < .05, and *p* < .10. No effect of COMT genotype on SCR or fear rating during fear acquisition, extinction or reconsolidation. No effect of COMT genotype on SCR or fear rating during fear acquisition, extinction or reconsolidation.
4.1.2. Serotonin

Serotonergic pathways originating from the nucleus raphé project to almost all brain areas including those central to memory formation. Besides its impact on numerous vegetative processes, a growing body of literature suggests that serotonin influences emotional learning and memory (cf. Meneses & Liy Salmeron, 2012). Furthermore, serotonin exhibits inhibitory influence on the amygdala, promotes tolerance towards aversive stimuli and might hence reduce fear learning (cf. Reissler & Nemeroff, 2000).

The serotonin transporter terminates the action of serotonin by transporting the neurotransmitter from the synaptic cleft back to the presynaptic neuron. The gene encoding this transporter (SLC6A4) contains a polymorphism termed serotonin transporter linked polymorphic region (5 HTTLPR), which consists of a 44 bp insertion/deletion referred to as the long (l) and short (s) allele, respectively (Heils et al., 1996). The s allele has been associated with reduced serotonin transporter activity and hence reduced serotonin reuptake (Greenberg et al., 1999; Heils et al., 1998). Pur thermore, according to a recent meta analysis, carriers of the s allele display elevated amygdala activation in response to emotional stimuli (Munafo, Brown, & Hariri, 2008). Finally, and most importantly, the s allele has been consistently associated with enhanced fear learning in differential fear conditioning studies investigating healthy volunteers. Two studies reported enhanced skin conductance response in s allele carriers in response to the conditioned stimulus (Crisan et al., 2009; Garpenstrand, Annas, Ekblom, Ore, & Fredrikson, 2001), whereas another study found elevated fear potentiated startle in the absence of altered skin conductance response (Lonsdorf et al., 2009). Finally, s allele carriers seem to be more prone to fear reactivation following extinction learning, if the extinction training takes place outside a reconsolidation window (Ager, Furmark, Eriksson, & Fredriksson, 2012).

This evidence for a pivotal role of 5 HTTLPR in human fear memory formation inspired research on its association with the development of PTSD. Kolassa and co workers recently investigated 408 survivors of the Rwandan genocide, of which 81% were diagnosed with a lifetime PTSD as a consequence of the experienced traumatic events. Importantly, the authors assessed trauma load quantitatively and found that 5 HTTLPR genotype modified the dose dependent relationship. Whereas the probability to suffer from lifetime PTSD increased as a function of traumatic load in carriers of the l allele, s homozygous individuals were at continuously elevated risk to develop a lifetime PTSD, which is indicative for a higher responsiveness to environmental stress in carriers of the high risk genotype (Kolassa et al., 2010a). While other candidate gene investigations on 5 HTTLPR and PTSD risk failed to find consistent associations if trauma load was not considered (for reviews see Cornelis et al., 2010; Wilker & Kolassa, 2013), studies including environmental exposure supported an association of the s allele with increased PTSD susceptibility following environmental stress (Kilpatrick et al., 2007; Mercer et al., 2012; Pietrzak, Galea, Southwick, & Gelernter, 2013; Xie, Kranzler, Farrer, & Gelernter, 2012; Xie et al., 2009) with only one study reporting an opposite effect (Grabe et al., 2009). Interestingly, the shape of the reported gene × environment interaction differed across stud
ies. While the influence of genotype was only visible at “lower” levels of trauma load in the sample of highly traumatized Rwandan genocide survivors, the effect of 5 HTTLPR on PTSD risk was most pronounced at “higher” trauma exposure in the majority of the other investigations. This indicates that the total amount of trauma exposure and PTSD rates in the population under study significantly influence the results of genetic association studies, and highlights the importance to quantify traumatic load in order to compare studies investigating different samples.

Finally, the practical relevance of 5 HTTLPR for the treatment of PTSD is underscored by a study examining the influence of 5 HTTLPR on cognitive behavioral therapy for PTSD. A sample of 31 s allele carriers and 14 l allele carriers received 8 sessions of therapy which comprised imaginal and in vivo exposure as well as cog nitive restructuring. Whereas the two groups did not show statistically significant differences in PTSD symptom severity prior to the treatment, or immediately thereafter, the 6 months follow up assessment clearly showed higher PTSD symptoms in s allele carriers, indicating a higher risk of symptom relapse in this group (Bryant et al., 2010). Similarly, carriers of the s allele displayed poorer responses and higher drop out rates to a pharmacological treatment with sertraline, a selective serotonin reuptake inhibitor (Mushkat, Ali, Margoob, Murtaza, & Andrade, 2012). To conclude, a polymorphism of the serotonergic system associated with elevated fear conditioning and higher amygdala responsiveness enhances the susceptibility to the adverse psychological effects of trauma, but also reduces the likelihood of successful psychotherapy or pharmacological treatments. These results emphasize the necessity to adjust interventions for carriers of the high risk allele if exposed to traumatic stress.

4.1.3. Dopamine

Among several interesting candidates involved in dopaminergic neurotransmission, catechol O methyltransferase (COMT), an enzyme central to the degradation of extracellular dopamine, is central for the scope of this review, since it has been extensively studied in human memory, fear, and PTSD. A common non synonymous polymorphism in the COMT gene at codon 158 results in a change of valine to methionine (Val158Met polymorphism). The Met/Met genotype is associated with 3-4 fold lower enzymatic activity compared to the Val/Val genotype (Lachman et al., 1996), resulting in higher levels of extracellular dopamine, particularly in the PFC (for a review see Witte & Floel, 2012), a region central for fear extinction. A functional brain imaging study further showed that the number of Met alleles positively correlated with brain activation in limbic (hippocampus, amygdala) and prefrontal areas when processing aversive, but not positive stimuli (Smolka et al., 2005).

A study by Lonsdorf and co workers reported an association of the low activity Met allele with impaired fear extinction learning one day after fear acquisition in a fear potentiated startle measure ment, however, the effect was absent when measuring the skin conductance response (Lonsdorf et al., 2009). A subsequent study failed to find such an effect of COMT genotype on extinction learning when measuring only skin conductance response (Raczka et al., 2011). Yet, Lonsdorf and co workers also failed to observe an association with the skin conductance response, and it was recently suggested that fear potentiated startle might be the more sensitive measurement of fear responses. In a study investigating PTSD patients and trauma exposed controls, higher fear to both safety and danger cues in PTSD was captured by measuring fear potentiated startle, but not when measuring the skin conductance reaction (Glover et al., 2011). Furthermore, since Raczka and co workers employed an immediate extinction paradigm, the conflicting results could be interpreted in a way that COMT influences long term memory consolidation, leading to different genotype dependent extinction rates only if extinction is tested delayed (Lonsdorf & Kalisch, 2011). An investigation of a large mixed sample of PTSD patients and healthy individuals replicated the effect of the Met genotype on impaired extinction learning; yet, this effect was mainly carried by Met allele carriers with PTSD. Furthermore, reduced fear inhibition to the safety stimulus in the differential fear conditioning paradigm was observed in the Met/Met PTSD+ group (Norholm et al., 2013). By contrast, the previously mentioned study of Agren and co workers (2012) found reduced fear reacquisition in Met allele carriers compared to homozygous Val allele carriers following extinction training outside a fear reconsolidation window.

The first study investigating the association of the COMT Val158Met polymorphism on the risk to develop PTSD was conducted by Kolassa and colleagues in Rwandan genocide survivors (Kolassa, Kolassa, Ertl, Papassotropoulos, & De Quervain, 2010). Data on trauma exposure, lifetime PTSD and COMT genotype was available for 424 study participants. The researchers found evidence for a complex interaction between genotype and traumatic load: Whereas carriers of the Val allele presented with the typical dose response relationship of traumatic load on PTSD risk, the likelihood to develop PTSD did not depend on traumatic load for Met/Met homozygous individuals, who were at continuously elevated risk. The effect of genotype was most pronounced at smaller levels of traumatic load, and vanished at higher levels, were the likelihood of lifetime PTSD approximated 100% for all genotype groups.

A significant gene x environment interaction was also reported by Boccarino, Erlich, Hoffman, Rukstalis, and Stewart (2011) in a sample of chronic pain patients, who found the highest PTSD risk in carriers of the Met allele who reported high levels of trauma exposure and childhood adversity. Furthermore, an elevated risk of the Met allele was again confirmed by Valente et al. (2011), but the authors did not report the investigation of interaction effects with trauma exposure. To date, there is no study investigating effects of COMT Val158Met on the effectiveness of trauma focused psychotherapy. However, if we accept that extinction learning is the common mechanisms to all exposure therapies, evidence suggests reduced benefits from exposure therapy in homozygous Met Allele carriers with panic disorder (Lonsdorf et al., 2010) encourages parallel investigations with PTSD patients.

4.2. Molecular cascades of memory formation

4.2.1. Protein kinase pathways

It is well established that emotional learning in the amygdala involves the calcium dependent activation of protein kinases, which include Ca2+/calmodulin dependent protein kinase II (CaM KII), protein kinase A (PKA), and protein kinase C (PKC). This protein kinase cascade converges in the mitogen activated protein kinase (MAPK) pathway. The described pathway results in the activation of transcription factors, most importantly cAMP response element binding protein (CREB), which facilitates de novo protein synthesis required for the long term stabilization of emotional memories (Johansen, Cain, Ostrow, & LeDoux, 2011; Rodrigues, Schafe, & LeDoux, 2004). De Quervain et al. (2012) recently investigated a total number of 2005 SNPs spanning the genes encoding CaMKII, PKA, PKC, MAPK, and their various isoforms as to their association with memory for aversive pictures in a sample of 723 healthy Swiss volunteers. Among all variations studied, one SNP (rs4790904, A allele) in the gene encoding PKCalpha (PRKCA) was found to be associated with memory for aversive information subsequent to correction for multiple comparisons. On a nominal level, rs4790904 was also associated with memory for neutral and positive information. Enhanced memory for aversive information in carriers of the rs4790904 A allele was found for both short term
cortex) (Johannsen, Duning, Pavenstadt, Kremerskothen, & Boeckers, 2008). It is further assumed that KIBRA is involved in synaptic plasticity and the organization of the postsynaptic membrane trafficking of AMPA receptors. The same authors reported fear memory performance in adult KIBRA knock out mice (Makuch et al., 2009). Recently, KIBRA was further shown to regulate memory of KIBRA in human memory, Wilker et al. (2013) investigated whether common WWCT1 alleles also predicted the risk to develop strong traumatic memories in survivors of mass conflict. Employing high throughput technology, the authors simultaneously investigated 115 tagged WWCT1 SNPs in two independent samples of survivors of the Rwandan genocide, and the conflict with the rebel group Lord’s Resistance Army in Northern Uganda, respectively. In a model accounting for the influence of genotype and traumatic load, two SNPs in high linkage disequilibrium (rs10038727 and rs4576167, minor allele) were associated with lifetime PTSD sub sequent to correction for multiple comparisons in the Rwandan discovery sample (N = 392). While both genotype groups exhibited large deficits in hippocampal long term potentiation as well as in fear memory performance in adult KIBRA knock out mice (Makuch et al., 2011).

Due to this convergent line of evidence suggesting a pivotal role of KIBRA in human memory, Wilker et al. (2013) investigated whether common WWCT1 alleles also predicted the risk to develop strong traumatic memories in survivors of mass conflict. Employing high throughput technology, the authors simultaneously investigated 115 tagged WWCT1 SNPs in two independent samples of survivors of the Rwandan genocide, and the conflict with the rebel group Lord’s Resistance Army in Northern Uganda, respectively. In a model accounting for the influence of genotype and traumatic load, two SNPs in high linkage disequilibrium (rs10038727 and rs4576167, minor allele) were associated with lifetime PTSD sub sequent to correction for multiple comparisons in the Rwandan discovery sample (N = 392). While both genotype groups exhibited the typical cumulative effect of trauma exposure, minor allele car riers were continuously at a reduced risk to develop PTSD. Further more, a nominal significant effect of reduced risk of current PTSD as well as diminished re experiencing and avoidance symptoms was observed in minor allele carriers in the Rwandan sample. The effects of WWCT1 genotype on lifetime and current PTSD as well as intrusive symptoms could be replicated in the second indepen dent sample from Northern Uganda (N = 399). In line with the work of de Quervain et al. (2012), the results of this study suggest that genes involved in regular memory performance might influence the strength of the resulting fear memories subsequent to intense traumatic stress. Since the two SNPs identified in the study have not been previously described, future studies are necessary to elucidate which memory mechanisms mediate the observed reduced PTSD risk in minor allele carriers.

5. Conclusion

This review summarized studies investigating genetic vulnerability for PTSD from a memory centered perspective. We showed how genetic variations, which lead to normal phenotypic variance in fear conditioning or emotional episodic memory performance in healthy volunteers, can have significant impact on the likelihood to develop PTSD. Furthermore, there is initial evidence that genetic risk variants which are associated with the formation of stronger traumatic memories also render those memories more resistant to extinction and modification through evidence based treatments for PTSD, underscoring the clinical relevance of memory related genes for PTSD etiology and treatment.

With the advancement of genome wide association studies, which enable the simultaneous investigation of millions of SNPs, it was expected to rapidly uncover the genetic underpinnings of many psychiatric disorders. Yet the variance explained by genetic association studies falls far behind the variance estimates derived from twin studies, a phenomenon which was termed missing heritability (Manolio et al., 2009). Reasons include small effects of single genetic polymorphisms, the potential impact of rare variants, complex interactions between genes, and epigenetic modification which influence the expression of the genes under investigation (Cordell, 2009; Juran & Lazaridis, 2011; Manolio et al., 2009; Schmidt, Holsboer, & Rein, 2011; Thomas, 2010). Whereas these aspects, and the development of new analytic approaches which facilitate their investigation, are without doubt crucial to a more complete understanding of genetic variability in PTSD, the focus of this review lies on a different central point. We argue that one option to improve the consistency of genetic association studies on PTSD lies in the quality of assessing the phenotypic data.

First, if we accept that intense memorization of traumatic mate rial is the central element leading to intrusive symptoms and PTSD development, the importance to adequately assess trauma exposure in genetic studies can simply not be underestimated. According to the presented framework (Elbert & Schauer, 2012; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010), the number of traumatic events experienced which merge in the fear memory network strongly influences the strength of the associative connections between its ‘hot’ elements as well as the binding of corresponding ‘cold’ context information. To add on this, several studies reviewed in this article investigated gene × environment interactions in PTSD and revealed that the critical amount of cumulative traumatic experiences which lead to the subsequent onset of PTSD is influenced by genetic risk factors. Furthermore, as especially evident by studies of our work group on highly traumatized individ uals, there is no ultimate resilience to PTSD. Therefore, genetic influences on PTSD risk cannot be detected at extreme levels of traumatic load. We therefore consider the assessment of traumatic load as a central prerequisite for the investigation of genetic liabil ity in PTSD.

Second, we want to highlight the potential of basic memory re search on both implicit (fear conditioning) and explicit emotional memories to inspire PTSD research. Since variations in memory performance were found to be predictive of PTSD development subsequent to traumatic stress (Guthrie & Bryant, 2006; Lommen et al., 2013), such investigations can be extremely useful for the identification of candidate genes for PTSD development as well
as its treatment. Indeed, the presented findings consistently sup
port associations between enhanced emotional memory perfor-
mance in healthy individuals and elevated risk for PTSD
development. Hence, strong emotional memories, which are
intrinsically adaptive since they serve to recall and distinguish
favorable from unfavorable situations, can turn maladaptive in
the case of exposure to extreme stress. This is in line with the
cent suggestion that genetic variations referred to as risk factors
most likely rather represent variants that predict enhanced plastic
ity towards environmental experience and can hence be both
adaptive and maladaptive dependent on the environment (Belsky
et al., 2009).

We believe that technical advances in the field of behavioral
genetics and also in the future of behavioral epigenetics can re-
veal the highest benefits for PTSD research, if combined with psy-
chological theories and evidence concerning memory alterations in
PTSD, as well as with knowledge derived from experimental labo-
atory studies of memory.

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