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

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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

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following three symptom clusters (1) intrusive re experiencing of the traumatic event in the form of recurrent dreams, thoughts, sen sations 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 Psy chiatric Association, 2000). In the lately 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 per sistent 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 dif ferent traumatic events experienced (defining *traumatic load*) in creases 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 resilience towards the development of PTSD; with increasing trau ma 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 ex ists 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, Schmeidler, Wainberg, Binder Brynes, & Duvdevani, 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 disor ders (Hettema, Neale, & Kendler, 2001).

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

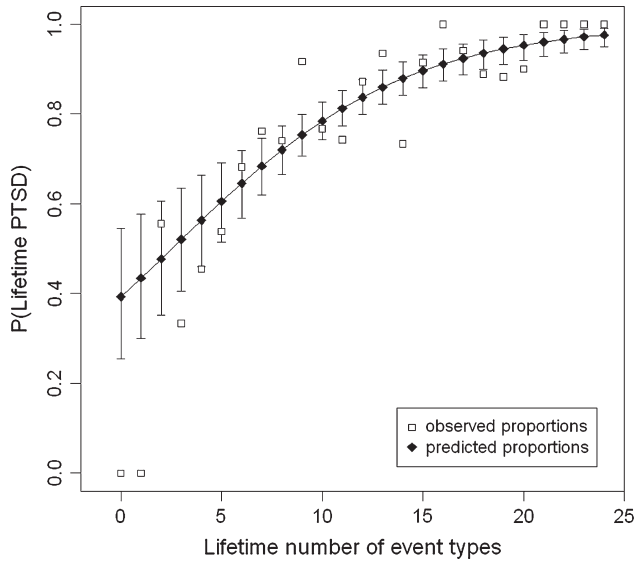

Fig. 1. Predicted and observed proportions of lifetime posttraumatic stress disorder (PTSD) as a function of trauma exposure in a sample of $N = 444$ Rwandan genocide survivors. Bars represent bootstrapped pointwise 95% confidence intervals of the predicted values. With increasing traumatic load, the probability of a lifetime diagnoses 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.

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

3.1. Theoretical perspectives

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) differenti ates between low level, sensory based representations (S reps), which are mainly mediated by early sensory cortical and subcorti cal areas, namely the amygdala and insula, and more abstract, con text 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 cor responding 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 mem ory. 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 forma tion 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 be tween intrinsically neutral stimuli, which have been temporarily associated with the trauma, and the traumatic material. This phe nomenon, 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 men tion that both mechanisms can be intrinsically adaptive, since they aim at early detection and prevention of further life threat.

Finally, the *fear network model*, as formulated by Elbert and col leagues (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 pro poses 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 ter minology proposed by Metcalfe and Jacob (1996). Hot memories comprise the sensory (e.g. hearing screams, smelling blood), emo tional (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 connec tions 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 differ ences in memory performance could constitute a useful endophe notype 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 intercon nections between the traumatic event and stimuli that were tem porarily associated with the trauma. Since fear conditioning leads to the establishment of new stimulus stimulus and stimulus reac tion associations, it was assumed that PTSD clients might display higher conditionability towards novel aversive stimuli (Orr et al., 2000). These authors found that PTSD patients displayed stronger physiological responses (i.e. skin conductance response, fear potentiated startle and heart rate) to the reinforced stimulus in a differential fear conditioning paradigm. At the same time, the fail ure to extinguish the established connections seems to be crucial to the chronification of PTSD. Likewise, impairments in extinction learning have been proposed as a core feature of PTSD vulnerability (Jovanovic & Norrholm, 2011; Jovanovic & Ressler, 2010). Indeed, patients with PTSD display deficits in extinction learning and dis crimination of safety cues (fear inhibition) when compared to trau ma exposed controls without PTSD (Norrholm 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). Prospec tive studies indicate that impaired fear extinction constitutes a risk factor for PTSD rather than a result of the disorder. In two investi gations of firemen (Guthrie & Bryant, 2006) and Dutch soldiers (Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013), pre trauma fear extinction performance predicted 31% and 23% respectively of the variance of subsequent PTSD symptom develop ment 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 con ditioning (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003). Moreover, the aforementioned processes have direct clinical impli cations for the treatment of PTSD, since exposure based treat ments, 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 func tional imaging studies showing enhanced amygdala activation dur ing fear conditioning (LeDoux, 2000; Pape & Pare, 2010; Phelps & LeDoux, 2005; Sehlmeyer 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 mem ory performance in humans (Milad et al., 2005). Finally, the hippo campus 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 arous ing information (de Quervain, Aerni, Schelling, & Roozendaal, 2009). Similar to fear conditioning, episodic memory performance is substantially heritable, with heritability estimates derived from twin studies varying between 30% and 60% (Papassotiropoulos & 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 periph eral 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 develop ment. 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) dis tinguish 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 & Krikorian, 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.

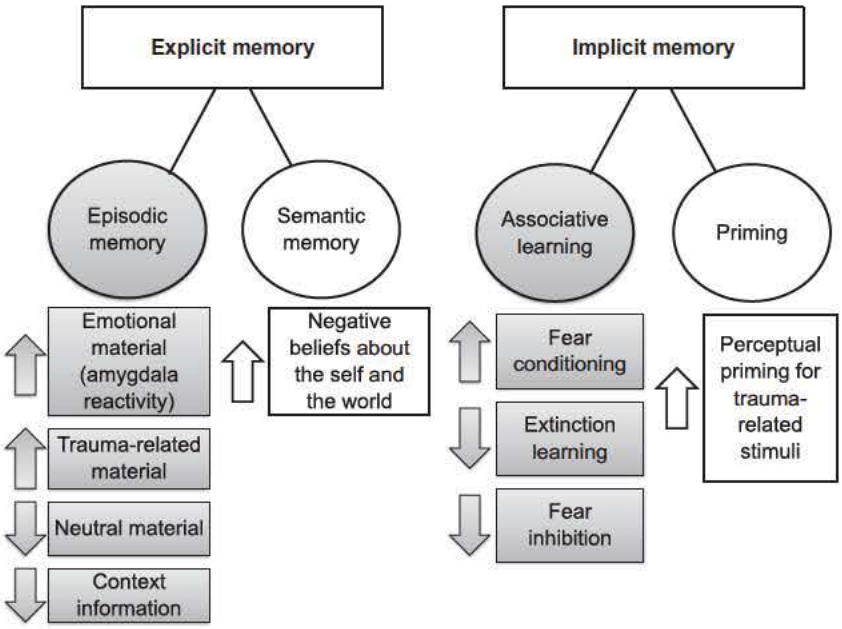

Fig. 2. Memory mechanisms supposed to be altered in posttraumatic stress disorder (PTSD). Memory paradigms central to this review are shaded in grey, and arrows indicate the direction of the alterations.

The 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 attentional 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 (Golier, 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 that 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, 2007). 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 neurophysiological 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 Vietnam veterans and their stay at home identical twins and found that reduced hippocampal volume was not only present in

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, & Mikedis, 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 display 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 heritable. 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, Norrholm, 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, 1999). 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 (Cousijn et al., 2010), indicating a higher amygdala responsivity to emotional material and stress which leads to better memory consolidation in carriers of the

Table 1
Overview of human experimental studies on memory formation and clinical studies on PTSD risk and treatment.

Gene (Variation)	Authors	Phenotype	Sample		Main finding
			N (%male)	Ethnicity	
ADRA2B (inframe deletion)	de Quervain et al. (2007)	Emotional Memory	435 (26)	Caucasian (Switzerland)	Increased memory advantage for emotional information in deletion carriers ($d = .4$, $p = .0005$)
ADRA2B (inframe deletion)	Rasch et al. (2009)	Emotional Memory, Amygdala Activity (fMRI)	57 (28)	Caucasian (Switzerland)	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 ($p_{SVC} < .05$)
ADRA2B (inframe deletion)	de Quervain et al. (2007)	Intrusive Symptoms	202 (50)	African (Rwanda)	Deletion carriers had higher intrusive memory symptoms per traumatic event type ($p = .003$)
SLC6A4 (5-HTTLPR)	Garpenstrand et al. (2001)	Fear Conditioning (SCR)	40 (35)	Caucasian (Sweden)	Stronger SCR reactivity to the CS^+ during fear conditioning acquisition in short-allele carriers ($p = .002$)
SLC6A4 (5-HTTLPR)	Crisan et al. (2009)	Fear Conditioning (SCR)	32(28)	Probably Caucasian (Romania)	Stronger SCR reactivity to the CS^+ in the test phase of an observational fear conditioning paradigm in short-allele carriers ($p < .0001$). In comparison to women, men displayed decreased SCR to the CS+
SLC6A4 (5-HTTLPR)	Lonsdorf et al. (2009)	Fear Conditioning (FPS & SCR)	48 (52)	Caucasian (Sweden)	Enhanced startle potentiation to the CS^+ during acquisition ($p = .01$) and extinction ($p < .001$) in short-allele carriers, no genotype-dependent effect was found for SCR
SLC6A4 (5-HTTLPR)	Agren et al. (2012)	Fear Reactivation	33[a] (~42)	Caucasian (Sweden)	Higher fear reacquisition in short-allele carriers following an extinction training which took place outside a reconsolidation window ($p < .001$)
SLC6A4 (5-HTTLPR)	Kilpatrick et al. (2007)	Current PTSD	589 (37)	Mainly Caucasian (USA)	Enhanced PTSD risk for short-allele carriers under conditions of low social support and high hurricane exposure ($p_{interaction} < .03$)
SLC6A4 (5-HTTLPR)	Grabe et al. (2009)	Lifetime PTSD	1,663 (50)	Caucasian (Germany)	Enhanced PTSD risk for long-allele carriers, especially under conditions of high trauma exposure ($p_{interaction} < .05$)
SLC6A4 (5-HTTLPR)	Xie et al. (2009)	Lifetime PTSD	1,252 (52)	Caucasian and African American (USA)	Enhanced PTSD risk for short-allele carriers who face both childhood and adult trauma exposure ($p_{interaction} < .001$, effect was present in both ethnicities investigated)
SLC6A4 (5-HTTLPR)	Kolassa et al. (2010a)	Lifetime PTSD	408 (53)	African (Rwanda)	Enhanced PTSD risk for short-allele carriers across all levels of trauma exposure ($p = .008$)
SLC6A4 (5-HTTLPR)	Mercer et al. (2012)	Acute Stress Disorder Symptoms	123[b] (0)	Caucasian (USA)	More pronounced acute stress disorder symptoms in short-allele carriers when accounting for the levels of shooting exposure ($p = .007$)
SLC6A4 (5-HTTLPR)	Xie et al. (2012)	Lifetime PTSD	5,178 (56)	Caucasian and African American (USA)	Enhanced PTSD risk in short-allele carriers who face childhood trauma exposure only found in Caucasian subsample ($p_{interaction} = .018$)
SLC6A4 (5-HTTLPR)	Pietrzak et al. (2013)	Current PTSD Symptom Severity	149 (41)	Mainly Caucasian (USA)	In a model accounting for sex, age and ancestry, higher PTSD symptoms were observed in short-allele carriers facing high hurricane exposure ($p_{interaction} < .001$)
SLC6A4 (5-HTTLPR)	Bryant et al. (2010)	Current PTSD Symptom Severity	42[c] (~67)	Caucasian (Australia)	Short-allele carriers showed reduced long-term benefits 6 months after trauma-focused cognitive behavioral therapy ($p < .01$)
SLC6A4 (5-HTTLPR)	Mushtaq et al. (2012)	Current PTSD Symptom Severity	226[d] (45)	Asian (India)	Short-allele carriers showed reduced benefits from sertraline treatment ($p < .001$). If response is defined as a 30% reduction in PTSD symptoms, the response rate in short-allele carriers was 0%
COMT ($Val^{158}Met$)	Lonsdorf et al. (2009)	Fear Conditioning (FPS & SCR)	48 (52)	Caucasian (Sweden)	Stronger CS^+ startle potentiation in Met-allele carriers during extinction ($p = .005$), no effect of genotype on fear acquisition. No COMT genotype effects on SCR
COMT ($Val^{158}Met$)	Raczka et al. (2011)	Fear Conditioning (SCR and fear ratings)	69 (100)	Caucasian (Germany)	No effect of COMT genotype on SCR or fear rating during fear acquisition, extinction or reconsolidation
COMT ($Val^{158}Met$)	Norrholm et al. (2013)	Fear Conditioing (FPS)	270 (37)	Mainly African American (USA)	Met homozygous individuals show higher FPS to the CS (i.e., impaired fear inhibition, $p = .006$) and reduced fear extinction learning ($p < .05$). Yet, these effects were mainly carried by Met/Met individuals with PTSD
COMT ($Val^{158}Met$)	Agren et al. (2012)	Fear Reactivation	33[a] (~42)	Caucasian	Higher fear reacquisition in Val/Val homozygous following an extinction training which took place outside a reconsolidation window ($p = .02$)
COMT ($Val^{158}Met$)	Kolassa et al. (2010b)	Lifetime PTSD	424 (53)	African (Rwanda)	While PTSD risk gradually augmented with trauma load in Val-allele carriers, Met homozygous individuals had a constantly higher risk ($p_{interaction} = .04$)
COMT ($Val^{158}Met$)	Boscarino et al. (2011)	Lifetime PTSD	502 (not reported)	Caucasian (USA)	The Met allele was associated with higher PTSD risk in a model including childhood adversity and adult trauma exposure ($p < .05$)
COMT ($Val^{158}Met$)	Valente et al. (2011)	Current PTSD	434 (not reported for whole sample)	Mixed ethnicity (Brazil)	Higher Met allele frequency in PTSD cases compared to trauma exposed controls ($p = .06$) as well as compared to a larger general community sample not selected for trauma exposure ($p < .01$)
PRKCA (rs4790904)	de Quervain et al. (2012)	Emotional Memory	Initial: 723 (34)	Caucasian (Switzerland)	Enhanced memory performance for negative pictures in rs4790904 A-allele carriers ($p = .000002$), and to a lesser extend also for positive and neutral pictures

		394 (39)	Caucasian (Switzerland)	Replication of enhanced memory for negative pictures (p = .03) and positive pictures (p = .005) in the independent sample
	PTSD risk and PTSD symptoms	347 (47)	African (Rwanda)	Stronger re-experiencing symptoms (traumatic memories; p = .03), avoidance symptoms (p = .04) and higher PTSD risk (p = .009) as a function of A allele frequency
WWC1 (rs17070145)	Papassotiropoulos et al. (2006) Episodic memory	351 (32)	Caucasian (Switzerland)	Enhanced free recall performance 5 min (p = .000004) and 24 h (p = .0008) after word list presentation in T-allele carriers
		256 (33)	Mainly Caucasian (USA)	T-allele carriers show better episodic memory performance in two paradigms (AVLT, p = .004; SRT, p = .00005)
		424 (25)	Caucasian (Switzerland)	T-allele carriers recalled more pictures in visual episodic memory task (p = .006)
WWC1 (rs17070145)	Milnik et al. (2012) Episodic Memory (Meta-Analysis)	8.908	Mainly Caucasian samples	Support for association of T-allele with enhanced episodic memory performance in meta-analysis summarizing results from 17 different samples (p = .001)
WWC1 (rs10038727, rs4576167)	Wilker et al. (2013) Lifetime PTSD, Current PTSD, PTSD Symptoms	392 (51)	African (Rwanda)	Reduced lifetime (p = .00008) and current (p = .02) PTSD risk as well as reduced intrusive memory and avoidance symptoms (p < .05)in minor allele carriers in a model accounting for trauma exposure
		399 (47)	African (Uganda)	Replication of the association of the minor allele with lifetime (p < .05) and current (p < .05) PTSD, as well as with intrusive symptoms after removal of one outlier (p < .05)

Abbreviations: **ADRA2B** – α-2B-adrenergic receptor gene, **AVLT** - Rey Auditory Verbal Learning Test, **COMT** – catechol-O-methyltransferase gene, **CS** – Conditioned Stimulus, **fMRI** – functional magnetic resonance imaging, **FPS** – fear potentiated startle, **SLC6A4** – serotonin transporter gene, **5-HTTLPR** – serotonin transporter linked polymorphic region, **PRKCA** – protein kinase C alpha gene, **PTSD** – posttraumatic stress disorder, **SCR** – skin conductance response, **SRT**-Buschke's Selective Reminding Test, **SVC** - small volume corrected, **WWC1** – WW, C2, and coiled-coil domain-containing 1.

[a] Sample available for final reacquisition analysis.

[b] Subsample of white participants interviewed 2–4 weeks subsequent to the shooting exposure from which final results were reported.

[c] Sample available at 6-month follow-up measurement.

[d] Individuals who completed treatment. N = 104 dropped out of the study.

loss of function variant. The study of de Quervain et al. (2007) was also the first to investigate the *ADRA2B* deletion variant in relation to clinical implications in PTSD. In a sample of 202 survivors of the Rwandan genocide, the *ADRA2B* deletion variant was associated with more pronounced re experiencing symptoms per traumatic event type. Hence, better memories for emotional arousing events, which are intrinsically adaptive, could have adverse consequences in the case of extremely stressful experiences and render individuals more vulnerable to distressing intrusive memories of such events.

4.1.2. Serotonin

Serotonergic pathways originating from the nucleus raphé pro ject 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. Ressler & 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., 1996). Fur thermore, according to a recent meta analysis, carriers of the s al lele display elevated amygdala activation in response to emotional stimuli (Munafo, Brown, & Hariri, 2008). Finally, and most impor tantly, the s allele has been consistently associated with enhanced fear learning in differential fear conditioning studies investigating healthy volunteers. Two studies reported enhanced skin conduc tance response in s allele carriers in response to the conditioned stimulus (Crisan et al., 2009; Garpenstrand, Annas, Ekblom, Ore land, & 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 (Agren, Furmark, Eriksson, & Fredrikson, 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 investi gated 408 survivors of the Rwandan genocide, of which 81% were diagnosed with a lifetime PTSD as a consequence of the experi enced traumatic events. Importantly, the authors assessed trau matic load quantitatively and found that 5 HTTLPR genotype modified the dose dependent relationship. Whereas the probabil ity 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 consid ered (for reviews see Cornelis et al., 2010; Wilker & Kolassa, 2013), studies including environmental exposure supported an associa tion 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 signifi cantly 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 ther apy 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 (Mushtaq, Ali, Margoob, Murtaza, & Andrade, 2012). To conclude, a polymorphism of the serotonergic system associated with ele vated fear conditioning and higher amygdala responsiveness en hances the susceptibility to the adverse psychological effects of trauma, but also reduces the likelihood of successful psychothera peutic 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 en zyme central to the degradation of extracellular dopamine, is cen tral for the scope of this review, since it has been extensively studied in human memory, fear, and PTSD. A common non synon ymous polymorphism in the *COMT* gene at codon 158 results in a change of valine to methionine (Val^{158}Met 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 learn ing when measuring only skin conductance response (Raczka et al., 2011). Yet, Lonsdorf and co workers also failed to observe an asso ciation 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 pa tients and trauma exposed controls, higher fear to both safety and danger cues in PTSD was captured by measuring fear potenti ated 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 (Norrholm 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 out side a fear reconsolidation window.

The first study investigating the association of the *COMT* Val^{158}Met polymorphism on the risk to develop PTSD was conducted by Kolassa and colleagues in Rwandan genocide survivors (Kolassa, Kolassa, Ertl, Papassotiropoulos, & de Quervain, 2010c). 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 ele vated 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 × environment interaction was also reported by Boscarino, 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 ef fects with trauma exposure. To date, there is no study investigating effects of *COMT* Val^{158}Met on the effectiveness of trauma focused psychotherapy. However, if we accept that extinction learning is the common mechanisms to all exposure therapies, evidence sug gesting 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 Ca^{2+}/calmodulin dependent protein kinase II (CaM KII), protein kinase A (PKA), and protein kinase C (PKC). This pro tein kinase cascade converges in the mitogen activated protein kinase (MAPK) pathway. The described pathway results in the acti vation 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, Ostroff, & LeDoux, 2011; Rodrigues, Schafe, & LeDoux, 2004). De Quervain et al. (2012) recently inves tigated 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 PKCα (*PRKCA*) was found to be associated with memory for aversive information sub sequent to correction for multiple comparisons. On a nominal le vel, 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

(10 min) and long term (24 h) memory and could be replicated in an independent sample. Finally, the authors hypothesized that *PRKCA* rs4790904 would be also associated with strong memories for traumatic experiences and hence investigated the association of this SNP with PTSD risk and symptomatology in a sample of Rwandan genocide survivors. Indeed, the A allele was related to enhanced re experiencing and avoidance symptoms, as well as an elevated general risk to suffer from PTSD. In sum, the results of this study indicate a role of *PRKCA* in the formation of emotional memories, including long lasting traumatic memories, and underscore the potential of the combination of basic memory and PTSD research.

4.2.2. Memory related protein KIBRA

A critical role of the scaffolding protein KIBRA in memory performance has been proposed due to convergent results of human genetic association studies, gene expression analyses, animal experiments, and molecular investigations (Schneider et al., 2010). The gene encoding KIBRA, *WWC1*, was first found to be related to episodic memory in an early genome wide association study investigating verbal delayed recall (Papassotiropoulos et al., 2006). The observed association of rs17070145 (T allele) with enhanced memory performance has been replicated in the majority of studies, albeit with some inconsistencies (see Schneider et al., 2010 for a recent review). Importantly, a robust effect of *WWC1* on human episodic memory has been confirmed by a recent meta analytic investigation, even when including unpublished results to antagonize publication bias (Milnik et al., 2012). Accordingly, it was demonstrated that KIBRA is predominantly expressed in regions central to memory performance (hippocampus, cortex) (Johannsen, Duning, Pavenstadt, Kremerskothen, & Boeckers, 2008). It is further assumed that KIBRA is involved in synaptic plasticity through interaction with its bindings partners (Schneider et al., 2010), which include Synaptopodin and Dendrin, involved in neuronal synaptic plasticity and the organization of the postsynaptic cytoskeleton (Duning et al., 2008; Kremerskothen et al., 2003), as well as Protein Kinase M ζ, a brain specific isoform of PKC ζ, supposed to be involved in long term potentiation (Buther, Plaas, Barnekow, & Kremerskothen, 2004; Yoshihama, Hirai, Ohtsuka, & Chida, 2009). Recently, KIBRA was further shown to regulate membrane trafficking of AMPA receptors. The same authors reported 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 *WWC1* 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 *WWC1* 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 subsequent 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 carriers were continuously at a reduced risk to develop PTSD. Furthermore, 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 *WWC1* genotype on lifetime and current PTSD as well as intrusive symptoms could be replicated in the second independent 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 material 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, 2002; 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 individuals, 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 liability in PTSD.

Second, we want to highlight the potential of basic memory research 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 support associations between enhanced emotional memory performance 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 recent suggestion that genetic variations referred to as risk factors most likely rather represent variants that predict enhanced plasticity 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 reveal the highest benefits for PTSD research, if combined with psychological theories and evidence concerning memory alterations in PTSD, as well as with knowledge derived from experimental laboratory studies of memory.

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