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The Formation of a Neural Fear Network in Posttraumatic Stress Disorder: Insights From Molecular Genetics

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Abstract
Individuals differ strongly in their vulnerability to develop posttraumatic stress disorder (PTSD) in the aftermath of traumatic stress. This review on genetic risk factors in PTSD etiology employs the perspective of a psychobiological model, which proposes that intrusive memories, the core PTSD symptom, result from the formation of an associative neural fear network, which stores sensory-perceptual representations of traumatic memories. The current state of research on the genetics of PTSD, as well as common challenges, is presented in light of this framework. Because cumulative trauma exposure increases the fear memory strength, a standardized assessment of traumatic load and the investigation of Gene × Environment interactions are recommended. The investigation of genes involved in long-term memory formation, genome-wide association studies, pathway analyses, and the interplay of genetic and epigenetic factors could contribute to a deeper understanding of the molecular pathways involved in the formation and modification of the fear network.

Keywords
posttraumatic stress disorder, genetics, memory, risk factor, epidemiology, genome-wide association study, epigenetics, fear network

The large impact of traumatic events is illustrated by daily newspapers, which mention atrocities such as terror, torture, war, child abuse, or rape. The majority of people experience at least one traumatic event in their lifetime; however, this prevalence is even higher in areas of war and conflict. Some individuals display resilience in the face of traumatic experiences; others, however, develop a characteristic symptom pattern termed posttraumatic stress disorder (PTSD), which consists of reexperiencing the traumatic event(s), avoidance, emotional numbing, and hyperarousal (American Psychiatric Association, 2000). PTSD is further associated with detrimental consequences for psychological and physical well-being (McFarlane, 2010), is often transmitted to the next generation (Yehuda, Bell, Bierer, & Schmeidler, 2008), and prevents healing and reconciliation in war-torn societies (Bayer, Klasen, & Adam, 2007).

This review critically summarizes the state of research on genetic risk factors involved in PTSD etiology. We first present evidence for a genetic contribution to PTSD. This is followed by an introduction of the fear network model, which explains the etiology of pathological memories in PTSD, and associated molecular pathways involved in fear memory consolidation. This memory-centered perspective is employed to review the literature on the genetics of PTSD and to stress common challenges in this field. We conclude that investigations on genes involved in the memory consolidation cascade are needed to better understand the development of a pathological memory in PTSD. Future perspectives, such as the analyses of epistasis, genome-wide association studies, pathway analyses, and epigenetics, as well as possible consequences from the genetics literature for the further development of the fear network model, are summarized in the outlook.

PTSD Risk Is Heritable

The presence of a strong environmental stressor is a necessary condition for the diagnosis of PTSD. Therefore, the notion that PTSD risk is heritable is counterintuitive at first. An initial hint of a genetic contribution to PTSD was

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Table 1. Glossary

Term	Definition
Traumatic load	Number of traumatic event types experienced.
Gene-environment correlation	The genotype of an individual influences the individual risk of certain environmental exposure.
Gene × Environment interaction	The genotype of an individual interacts with environmental influences to predict individual risk.
Long-term potentiation	Refers to the effect that the synaptic strength between two neurons enhances after synchronous activation.
Fear conditioning	A conditioned stimulus (CS; typically, a tone) is paired with an aversive unconditioned stimulus (US; e.g., a foot shock), which elicits an unconditioned fear response. Subsequent to training, the CS becomes potent to initiate the fear response, even if presented alone.
Consolidation	The transformation of a short-term memory trace into long-term memory.
Reconsolidation	Upon recall, previously consolidated memories turn into a labile state and have to be actively reconsolidated to be stored. Thereby, existing long-term memories can be modified.
Extinction	In extinction training, the CS is repeatedly presented without the US. Therefore, the organism learns to inhibit the fear response subsequent to CS presentation. Extinction is a form of new learning and does not erase the fear memory, which can be reactivated.

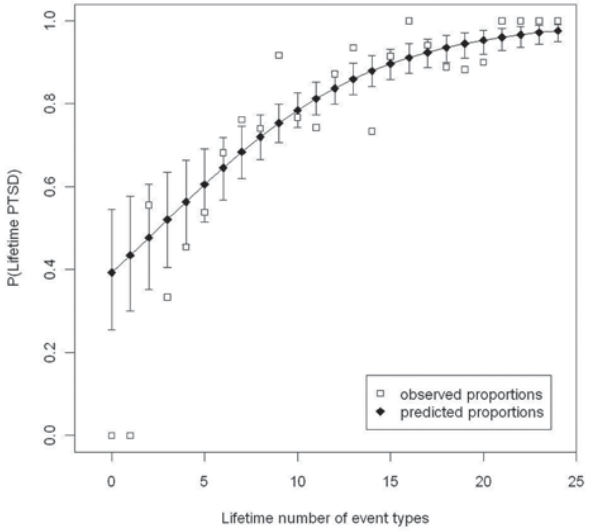

Fig. 1. Dose-dependent effect of traumatic load in posttraumatic stress disorder. The probability of lifetime PTSD is predicted depending on the number of traumatic event types experienced (Kolassa, Ertl, Eckart, Kolassa, et al., 2010). Spontaneous remission from PTSD depends on the number of traumatic event types experienced. *Psychological Trauma: Theory, Research, Practice, and Policy, 2*(3), 169–174, September 2010, American Psychiatric Association, reprinted with permission.

the finding that only few individuals develop PTSD subsequent to a single trauma (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), whereas almost everyone develops PTSD at extraordinarily high levels of *traumatic load* (see Table 1). More precisely, trauma exposure adds to PTSD risk in a dose-dependent manner (Kolassa, Ertl, Eckart, Kolassa, et al., 2010; see Fig. 1), and genetic factors exert a considerable influence at lower levels of traumatic load (Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Kolassa, Ertl, Eckart, Glöckner, et al., 2010).

Sound evidence for a genetic influence on PTSD development stems from twin studies. Earlier studies investigating male Vietnam veterans (True et al., 1993) and a gender-mixed civilian sample (Stein, Jang, Taylor, Vernon, & Livesley, 2002) converged at heritability estimates of 30% to 40%. A multigenerational family study estimated similar PTSD heritability (42%). Intriguingly, the highest heritability (75%) was found for memory-related intrusion symptoms (Bailey et al., 2010). Lately, in a female-only sample, heritability of PTSD was estimated to be as high as 72% (Sartor et al., 2011). Whereas the origin of inconsistent estimates still needs to be systematically studied, a genetic contribution to PTSD is evident.

Twin studies revealed three further important findings. First, not only the risk of PTSD but also trauma exposure is moderately heritable (Lyons et al., 1993; Stein et al., 2002), an effect named *gene-environment correlation* (Plomin, DeFries, & Loehlin, 1977). An early investigation of Lyons and coworkers (1993) studied combat exposure in male twins from the Vietnam Era Twin registry and derived heritability estimates of around 40% for different measures of trauma exposure, considering both self-reports and military records. A second twin study, by Stein et al. (2002), focused on civilian trauma and revealed a heritability estimate of 20% for assaultive trauma (e.g., sexual assault, robbery) but no genetic influence on non-assaultive trauma (e.g., sudden family death, natural disaster). Most important, this study found a significant overlap between genetic susceptibility to assaultive trauma and that to PTSD. This is most likely due to genetically influenced personality factors that predispose to trauma exposure and a higher risk for PTSD development (Jang, Stein, Taylor, Asmundson, & Livesley, 2003; Stein et al., 2002). For instance, personality traits that are associated with the experience of higher emotional arousal could increase the probability of getting involved in violent fights and, at

the same time, increase the consolidation of the memories for that experience. This underscores the need to include traumatic load in association studies on PTSD and to carefully investigate whether the identified variants predispose rather to trauma exposure or to PTSD. Second, there exists a considerable overlap between genetic risk factors for PTSD and other, often comorbid, mental disorders, most prominently depression (Koenen et al., 2008). Finally, cot-win studies help to differentiate whether a correlate of PTSD is likely to constitute a vulnerability factor for PTSD or a consequence of the disorder. In this design, trauma-exposed twins with and without PTSD are compared to their unexposed cot-wins. In the case of a genetic vulnerability, an attribute should be more pronounced in individuals with PTSD and their unexposed cot-wins, as opposed to trauma-exposed individuals without PTSD and their cot-wins. Captivatingly, cot-win research indicates that memory distortions (Gilbertson et al., 2006) and reduced hippocampal volume (Gilbertson et al., 2002) are putative genetic risk factors for PTSD development (see Kremen, Koenen, Afari, & Lyons, 2012, for a review). The central role of memory processes in the development of PTSD is further reviewed in the following paragraph.

PTSD: A Disorder of Pathological Memory

PTSD symptoms appear relatively invariant all over the globe, which favors the hypothesis of a shared physiological origin (Elbert & Schauer, 2002). Because the core feature of PTSD is a strong but defragmented traumatic memory that torments the patient in the form of intrusive recollections, the development of a pathological memory structure seems to be the cause of PTSD (Brewin, 2011). We term this memory structure, which stores all elements (emotional, sensory, perceptual, and cognitive) that have been associated with the trauma, a *fear network* (Fig. 2; Elbert & Schauer, 2002; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010). Due to its associative nature, a trauma-associated stimulus can activate the entire fear memory structure, including the emotional, behavioral, and physiological reactions.

But how is such a pathological fear memory formed? Important knowledge stems from translational neuroscience. Although *fear conditioning* (FC) in animals cannot fully capture the complexity of human PTSD (Brewin, 2008), it serves as a convenient model to explain how a previously neutral stimulus can become associated with fear and which neurobiological pathways are involved in this process (Johnson, McGuire, Lazarus, & Palmer, 2012; Lonsdorf & Kalisch, 2011; Rodrigues, LeDoux, & Sapolsky, 2009). A comprehensive description of the neuronal circuits of FC can be found elsewhere (Johnson et al., 2012; Maren, 2001; Rodrigues et al., 2009; Shin & Liberzon, 2010); for a summary, see Figure 3. As a result of convergent stimulus input in the lateral amygdala, new associative connections emerge, mainly as a consequence of *long-term potentiation*. Those new connections serve to easily recall cues that predict danger (Johnson et al., 2012; Rodrigues et al., 2009).

But how can fear learning, which is intrinsically adaptive, become harmful and lead to PTSD? Fear memory

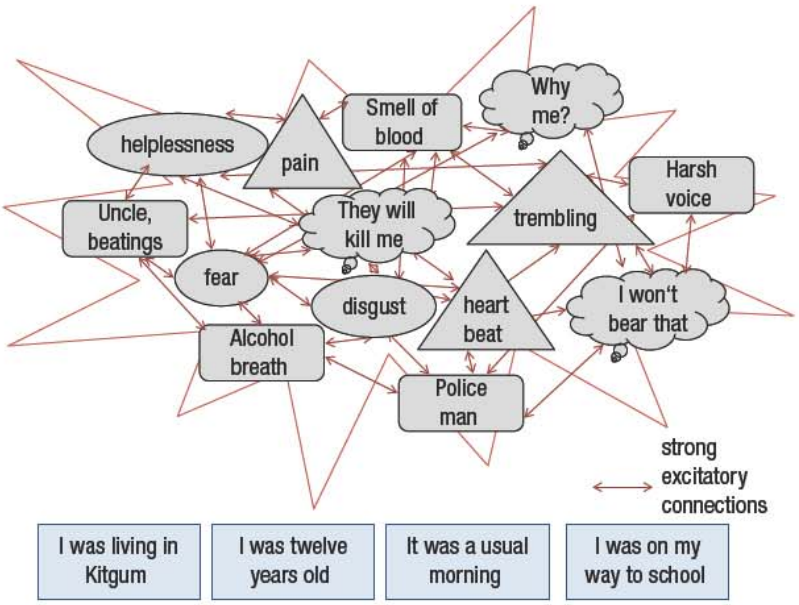

Fig. 2. Structure of an associative fear network in posttraumatic stress disorder. The fear network contains highly interconnected elements: sensory (represented by rectangles), emotional (circles), cognitive (thought bubbles), and interoceptive (triangles). In contrast, autobiographical context information is disconnected from the network.

formation follows several stages. An initial acquisition period is followed by the *consolidation* of the fear memory. However, memory storage is a dynamic process. Upon retrieval, the memory trace turns labile, a phenomenon termed *reconsolidation* (Nadel, Hupbach, Gomez, & Newman-Smith, 2012). Likewise, an emerging fear memory structure can be altered each time it is activated. The fear network model assumes that every new trauma activates the same memory structure, given that different traumatic experiences share important elements (e.g., life threat, strong heartbeat). Therefore, sensory-perceptional elements of new traumatic experiences are added, and the interconnections of the emerging fear network strengthen. At the same time, the network becomes associated with conflicting context information from different events. Hence, the memory for context weakens with increasing traumatic load, and the individual struggles to locate the experiences in time and space; the typical intrusive symptoms emerge (Elbert & Schauer, 2002; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010). The dissociation between vivid sensory-perceptual representations of the trauma and defragmented contextual memories is a common clinical observation also reflected in other prominent theories of PTSD (Brewin, Dalgleish, & Joseph, 1996; Ehlers & Clark, 2000). Accordingly, effective PTSD treatments reactivate the fear memory structure to enable modification through mechanisms of *extinction learning* and higher-order cognitive processes, such as integration of episodic context information and reappraisal of traumatic memories (Ehlers et al., 2010).

Animal research identified the amygdala, the medial prefrontal cortex, and the hippocampus (the so-called limbofrontal neurocircuitry of fear) as the key regions involved in the acquisition, regulation, and extinction of conditioned fear (Fig. 3), and structural and functional alterations have been observed in these areas in PTSD (Kolassa & Elbert, 2007; Rauch, Shin, & Phelps, 2006; Shin, Rauch, & Pitman, 2006), which might be partly heritable (Kremen et al., 2012). Furthermore, alterations in the two major stress systems, the hypothalamic-pituitary-adrenal (HPA) axis and the locus coeruleus noradrenergic system, have been observed in PTSD (Heim & Nemeroff, 2009). Both systems are activated by the central nucleus of the amygdala in FC but also feed back to the limbofrontal neurocircuitry of fear. Although initial research identified these key players involved in the acquisition of

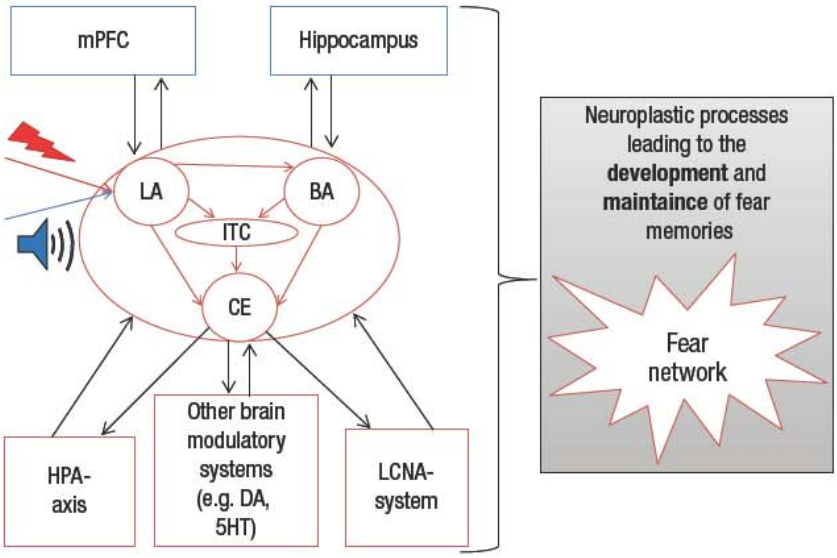

Fig. 3. Brain neurocircuitry involved in fear learning. The amygdala, a limbic structure that consists of several distinct nuclei, is central to fear conditioning. During fear acquisition, information about the conditioned stimulus and the unconditioned stimulus converge in the lateral amygdala (LA). This convergent input is crucial for neuroplasticity to occur. The LA projects directly, and indirectly via the basal nucleus (BA) and the intercalated region (ITC), to the central nucleus of the amygdala (CE). The CE is the major output region of the amygdala and controls the initiation of central and peripheral responses to the stressor via the hypothalamic-pituitary-adrenal (HPA) axis and the locus coeruleus noradrenergic (LCNA) system, as well as modulatory systems such as dopamine and serotonin. These neuroendocrinological modulators in turn influence the functioning of the amygdala, the hippocampus, and the medial prefrontal cortex (mPFC). Context information of fearful situations is passed on to the amygdala by the hippocampus. The mPFC regulates fear expression by projecting to the LA, BA, and ITC. In fear extinction learning, increased mPFC firing to the BA stimulates GABAergic ITC neurons to inhibit the fear response from the CE (Johnson et al., 2012; Rodrigues et al., 2009).

conditioned fear, recent investigations focused on the molecular mechanisms involved in the consolidation, stabilization, and maintenance of fear memories (Johansen, Cain, Ostroff, & LeDoux, 2011; Pape & Pare, 2010). These findings are crucial for PTSD research, given that not the development of fear memories as such, but their strength and longevity, are pathological (Brewin, 2008). Unfortunately, only a few genetic investigations into PTSD have focused on the underlying molecular pathways of long-term memory.

Molecular Genetics of PTSD

Since the 1990s, an increasing number of candidate gene association studies have investigated the influence of small DNA variations, single nucleotide polymorphisms (SNPs), or variable number of tandem repeats on PTSD risk, but sound knowledge is still sparse. The identification of candidates that enter association studies crucially relies on previously published knowledge on biological underpinnings of PTSD. The following paragraphs review the state of the art on candidate gene association studies on PTSD, divided by the biological system investigated, including their strengths and limitations. From the reviewed literature, it will become evident that many studies have focused on genes involved in the regulation of the limbocortical neurocircuitry of fear, the HPA axis, and the locus coeruleus noradrenergic system, crucial for the initial fear response, whereas few investigations have focused on candidates explicitly related to the molecular processes that influence the consolidation and strength of the emerging fear network.

Limbofrontal neurocircuitry of fear

Elevated amygdala responsiveness accompanied by insufficient inhibitory influences of the medial prefrontal cortex, as well as impaired hippocampus functioning, is supposed to be involved in the acquisition of pathological fear in PTSD (Rauch et al., 2006; Shin & Liberzon, 2010). The interplay of these three structures is influenced by the action of several modulatory systems, such as serotonin and dopamine (Fig. 3).

Serotonin. Genes encoding transporters or receptors that modulate the serotonergic system have been investigated because stress responsive alterations in serotonergic transmission occur in the amygdala and medial prefrontal cortex (Krystal & Neumeister, 2009). Furthermore, serotonin exerts anxiolytic effects, probably via its inhibitory action on the amygdala. Interestingly, there is initial evidence of reduced serotonin transporter binding in the amygdala in PTSD (Murrough et al., 2011). To date, 13 studies have investigated variations in the serotonergic system (cf. Table S1, available online at http://cpx.sagepub.com/content/by/supplemental-data), of which 12 analyzed the serotonin-transporter-linked polymorphic region (5-HTTLPR). The short "s" variant promotes reduced serotonin transporter activity, which enhances fear learning (Lonsdorf & Kalisch, 2011). Six studies solely focused on genetic main effects and reported inconsistent results. Two studies reported an association of the s-allele with PTSD (Lee et al., 2005; Z. Wang et al., 2011); two showed negative results (Mellman et al., 2009; Valente, Vallada, Cordeiro, Miguita, et al., 2011); one study found an association only for certain symptom subscores (Sayin et al., 2010); and yet another reported an association of the l-allele with PTSD chronification (Thakur, Joober, & Brunet, 2009). More consistent results stem from the six investigations that modeled potential Gene × Environment interaction effects (G × E). Although these studies investigated different environmental stressors, all of them reported associations of PTSD risk with both 5-HTTLPR genotype and environmental stress level (Grabe et al., 2009; Kilpatrick et al., 2007; Koenen et al., 2009; Kolassa, Ertl, Eckart, Glöckner, et al., 2010; Mercer et al., 2012; Xie et al., 2009). Two further studies investigated the serotonin receptor 2A (5HTR2A) and reported an association with PTSD in females only (Lee, Kwak, Paik, Kang, & Lee, 2007) and in the whole sample (Mellman et al., 2009), respectively.

Dopamine. Animal studies indicate that dopaminergic influx into the amygdala is highly stress responsive (Inglis & Moghaddam, 1999), important for fear memory development (Guarraci, Frohardt, Falls, & Kapp, 2000), and influenced by the genetically shaped functioning of dopamine receptors and transporters. Six studies (cf. Table S1) focused on a polymorphism known as *dopamine receptor D2* (DRD2) TaqIA, a variation hypothesized to be involved in dopamine receptor density (Bailey et al., 2010; Comings et al., 1991; Comings, Muhleman, & Gysin, 1996; Gelernter et al., 1999; Voisey et al., 2009; Young et al., 2002). These studies revealed inconsistent results, with three out of six reporting an association with the A1 allele of TaqIA (Comings et al., 1991; Comings et al., 1996; Young et al., 2002) and one reporting an association with another variant (rs6277) within DRD2 (Voisey et al., 2009). All studies searched for main effects of genotype without considering G × E with traumatic load, and some employed control groups not selected for trauma exposure. Moreover, it was recently discovered that the TaqIA polymorphism is located downstream of DRD2 in a different gene (ankyrin repeat and kinase domain containing [ANKK1] gene), which is involved in signal transduction (Neville, Johnstone, & Walton, 2004), rendering the initial interpretations of TaqIA polymorphism and PTSD questionable. Four studies investigated a dopamine transporter gene (DAT1) variable number of

tandem repeat, and three of them reported increased PTSD susceptibility for 9-repeat-allele carriers (Drury, Theall, Keats, & Scheeringa, 2009; Segman et al., 2002; Valente, Vallada, Cordeiro, Miguita, et al., 2011), whereas another study (Bailey et al., 2010) could not confirm this finding. Importantly, all these studies recruited trauma-exposed control groups but did not yet model G × E. A further study investigated a variable number of tandem repeat in the dopamine receptor D4 gene (DRD4) and modeled G × E with trauma severity. The authors failed to find G × E effects but reported a significant main effect of the "long" allele on PTSD symptom severity (Dragan & Oniszczenko, 2009). Furthermore, the Val^{158}Met polymorphism in the gene encoding catechol-O-methyltransferase (COMT), responsible for the enzymatic inactivation of catecholamines, has been investigated because the low-activity Met-allele is associated with higher dopamine availability. Kolassa and coworkers reported a significant G × E: Whereas traumatic load added to the probability of lifetime PTSD in a dose-dependent manner in Val-allele carriers, Met-homozygous individuals were at constantly higher risk of developing PTSD (Kolassa, Kolassa, et al., 2010). This higher risk for Met-allele carriers was confirmed twice (Boscarino, Erlich, Hoffman, Rukstalis, & Stewart, 2011; Valente, Vallada, Cordeiro, Bressan, et al., 2011). Finally, a dysbindin gene (DNTB1) polymorphism, possibly involved in dopaminergic or glutaminergic functioning, was associated with PTSD when compared to an unselected control group (Voisey et al., 2010).

Other systems. Gamma aminobutyric acid (GABA) exhibits strong anxiolytic effects. The inhibitory action of GABAergic neurons seems to be required to restrain the central amygdala and express fear extinction (Likhtik, Popa, Apergis-Schoute, Fidacaro, & Paré, 2008). A G×E with childhood trauma exposure of four SNPs in considerable linkage disequilibrium in the GABA receptor α2 gene (GABRA2) was reported (Nelson et al., 2009). The apolipoprotein E gene (APOE) ε4 allele is associated with Alzheimer's disease, cognitive decline, and hippocampal atrophy. In contrast, higher reexperiencing symptoms accompanied by poorer memory performance were found in APOE ε2 carriers (Freeman, Roca, Guggenheim, Kimbrell, & Griffin, 2005). These findings have been supported by a recent animal study: Whereas APOE ε2 mice showed acquisition of conditioned fear, they displayed significant extinction deficits compared to APOE ε3, APOE ε4, and wild-type mice. Therefore, extinction deficits might be one mechanism by which APOE ε2 genotype increases PTSD risk (Olsen, Agam, Davis, & Raber, 2012). Additionally, studies accounting for traumatic load reported associations with PTSD for the regulator of G-protein signaling 2 gene (RGS2; Amstadter et al., 2009) and a member of the neuronal nicotinergic receptor family (CHRNA5; Boscarino et al., 2011), respectively.

HPA axis

The HPA axis initiates its stress response by the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, stimulating the pituitary to secrete adrenocorticotropic hormone, which in turn triggers cortisol release from the adrenal glands. Cortisol exhibits negative feedback on both adrenocorticotropic hormone and CRH secretion via binding to glucocorticoid receptors to contain the stress response. The HPA axis serves to mobilize energy resources for survival and to suppress other costly activities, such as recovery or reproduction. Though intrinsically adaptive, chronic HPA activity can lead to detrimental health consequences. Despite inconsistent findings, research points toward elevated CRH levels in the liquor, reduced peripheral cortisol levels, and enhanced glucocorticoid sensitivity in PTSD (Heim & Nemeroff, 2009), which stimulated research interest in genetic variability in this system (cf. Table S2). One study examined genetic variations in the gene encoding CRH receptor 1 and found an association with higher initial stress symptoms but a steeper decline of symptoms over time (Amstadter et al., 2011). Studies examining the glucocorticoid receptor (GCCR), crucially involved in HPA axis feedback regulation, are inconclusive, with one study reporting positive results (Hauer et al., 2011) and one reporting negative (Bachmann et al., 2005). Interestingly, Hauer and coworkers reported an association of a GCCR-SNP with acute stress after heart surgery and increased number of surgery-related traumatic memories. Further studies investigated modulators of the HPA axis, such as the opioid receptor mu 1 gene (OPRM1), the cannabinoid receptor gene (CNR1), and the adenylate cyclase-activating peptide type 1 receptor gene (ADCYAP1R1). An association with diminished symptoms was reported for an OPRM1 variant (Nugent, Lally, Brown, Knopik, & McGeary, 2011); however, the evidence for an involvement of CNR1 (Lu et al., 2008) and ADCYAP1R1 (Chang, Xie, et al., 2012; Ressler et al., 2011) was mixed. The co-chaperone FK506 binding protein 5 (FKBP5) regulates the cortisol binding affinity of the GCCR. The three studies that investigated FKBP5 genotype interactions with adult or childhood trauma exposure consistently reported significant effects (Binder et al., 2008; Boscarino et al., 2011; Xie et al., 2010).

Locus coeruleus noradrenergic system

Noradrenergic activity is crucially involved in stress response, for example, by moderating arousal, attention, and emotional memories (Southwick et al., 1999). Brain noradrenaline further interacts with CRH to enhance FC in the limbofrontal neurocircuitry of fear, which can be inhibited by glucocorticoid feedback. In PTSD, central and peripheral noradrenergic hyperactivity was repeatedly observed (Heim & Nemeroff, 2009); however, candidate

gene investigations on this system are sparse (cf. Table S3). Dopamine-β-Hydroxylase (DβH) enzymatically converts dopamine into noradrenaline, and DβH levels are highly heritable. Two studies investigated a SNP within the gene encoding DβH (DBH) but failed to find any association (Mustapić et al., 2007; Tang et al., 2010). In both studies, control groups faced trauma; however, traumatic load was not included in the analyses. Neuropeptide Y, which is cotransmitted with noradrenaline, was hypothesized to influence PTSD risk. Only one study examined a SNP in the gene encoding neuropeptide Y (NPY; Lappalainen et al., 2002); however, the study lacked a trauma-exposed control group. Hence, despite nonsignificant results, a contribution of NPY in PTSD etiology cannot be excluded. Finally, de Quervain and coworkers (2007) found an association of a deletion variant of the ADRA2B adrenergic receptor and enhanced emotional memory performance, which was mirrored by higher intrusive symptoms in Rwandan genocide survivors.

Memory consolidation and stabilization

A comprehensive explanation of the molecular cascades that underlie memory consolidation and stabilization is a topic of its own (reviewed in Johansen et al., 2011; Pape & Pare, 2010). Basically, synaptic plasticity is mediated by coincident binding of glutamate to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors, which lead to an opening of NMDA receptors for calcium. This initiates a postsynaptic increase of intracellular calcium concentration via calcium-influx through NMDA receptors and voltage-gated calcium channels, as well as via the release from intracellular stores, triggered by second messenger systems secondary to activation of metabotropic glutamate receptors (mGluRs). Likewise, both NMDA receptors and mGluRs present crucial initiators and mediators of synaptic plasticity and have been studied in animal models (Pape & Pare, 2010). Given that mGluRs are known to modulate synaptic plasticity and neurotransmission, they are of particular interest and have been proposed as drug targets for anxiety and stress disorders (Swanson et al., 2005). mGluRs can be divided into three groups: Group I mGluRs are predominantly expressed postsynaptically, whereas groups II and III are generally located presynaptically (Swanson et al., 2005). Two recent investigations studied the involvement of mGluR4 (a member of group III mGluRs) in the acquisition and maintenance of fear memories. Mice lacking mGluR4 showed enhanced amygdala-dependent cued FC but unaltered hippocampal-dependent contextual FC (Davis, Haley, Duvoisin, & Raber, 2012). A further experiment of the same group found that pharmacological stimulation of mGluR4 impaired acquisition of cued FC (Davis, Iancu, et al., 2012). This differential effect of mGluR4 on different memory systems might render it an attractive drug target.

The postsynaptic increase of intracellular calcium concentration initiates protein kinase cascades, which involves protein kinase C (PKC), protein kinase A (PKA), Ca2+/calmodulin-dependent protein kinase II (CaMKII), and mitogen-activated protein kinase (MAPK). These cascades can directly induce changes in synaptic plasticity (e.g., by promoting AMPA receptor trafficking to the synapse) and indirectly, by activating transcription factors that initiate de novo protein synthesis. Likewise, they can act on adhesion and cytoskeletal molecules and thus promote synapse remodeling, which stabilizes a state of enduring higher synaptic excitability. cAMP response element-binding protein (CREB) is the most extensively studied transcription factor targeted by these cascades. It was recently shown that amygdala neurons with elevated CREB activity are preferentially recruited into the neural network of a newly encoded fear memory (Han et al., 2007). Furthermore, ablation of CREB-overexpressing neurons selectively erased an established fear memory (Han et al., 2009). Important targets of CREB are neurotrophins, particularly the brain-derived neurotrophic factor (BDNF). Enhanced BDNF protein levels have been observed in the lateral amygdala after FC, and BDNF receptor blockade impairs fear memory consolidation (Ou & Gean, 2006). Another protein kinase, which is targeted by the described pathway, is the brain-specific protein kinase Mζ (PKMζ; for more details on PKMζ activation, see Sacktor, 2011). PKMζ remains autonomously active due to a positive feedback loop. Persistent activation of PKMζ increases postsynaptic AMPA receptor density and leads to enduring long-term synaptic potentiation (Yao et al., 2008). Furthermore, inhibition of PKMζ can erase an already consolidated memory (Serrano et al., 2008), which established PKMζ as a key substrate of long-term memory (Sacktor, 2011). The described molecular cascades (cf. also Fig. 4) provide interesting candidates for association studies on PTSD, yet few have been investigated (cf. Table S4).

Three studies investigated a potential role of the BDNF gene in PTSD etiology but reported negative results (Lee et al., 2006; Valente, Vallada, Cordeiro, Miguita, et al., 2011; H. Zhang et al., 2006). However, because these investigations are restricted by inadequate power and unselected control groups, an association of BDNF and PTSD cannot be ruled out. Recently, our work group and collaborators investigated 2,005 SNPs spanning the genes involved in the aforementioned protein kinase cascade (PKC, PKA, CaMKII, MAPK, and their different isoforms). A variation within PRKCA, the gene encoding PKCα, was strongly associated with memory performance (including memory for aversive information) after correcting for multiple comparisons. Moreover, this SNP was also associated with enhanced reexperiencing symptoms in Rwandan genocide survivors (de Quervain et al., 2012).

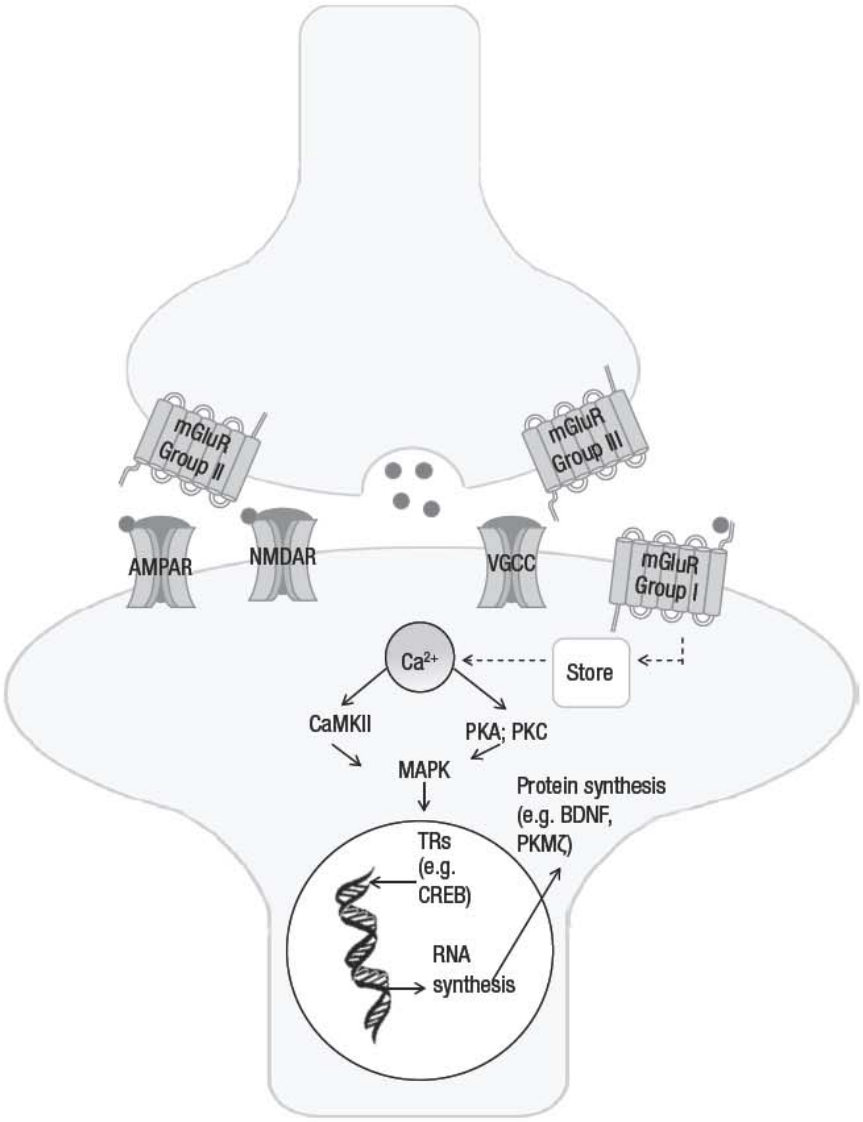

Fig. 4. Incomplete overview of processes involved in fear memory consolidation. Neuronal plasticity is initiated by elevated calcium (Ca^{2+}) concentration in the postsynaptic neuron. This is mediated by the coincident binding of glutamate to AMPA receptors (AMPAR) and NMDA receptors (NMDAR), leading to an opening of NMDARs for Ca^{2+}. Influx through voltage-gated calcium channels (VGCC), as well as Ca^{2+}-release from intracellular stores triggered by second messenger systems activated by postsynaptically located metabotropic glutamate receptors (mGluR), leads to a further increase in the intracellular Ca^{2+} concentration. Presynaptically, mGluRs further regulate neurotransmission and excitability. Ca^{2+} activates Ca^{2+}-dependent protein kinase pathways (CAMKII = Ca2+/calmodulin-dependent protein kinase II; PKA = protein kinase A; PKC = protein kinase C). Inhibition of either of these protein kinases results in deficits in FC. CAMKII, PKA, and PKC pathways lead to the initiation of mitogen-activated protein kinase cascades, leading to the activation of transcription factors, such as the cAMP response element-binding protein (CREB), which increase protein synthesis. Two of the proteins regulated by this pathway are the brain-derived neurotrophic factor (BDNF) and the brain-specific protein kinase M zeta (PKMζ; Johansen et al., 2011; Pape & Pare, 2010).

Summary

Given the divergence and methodological challenges of the reported results, unambiguous conclusions can hardly be drawn. First, studies that employ unselected control groups are difficult to interpret, given that it is unknown whether the healthy controls are carriers of risk alleles that did not exert behavioral effects due to an absence of trauma exposure. Some studies argue that unselected controls are applicable because the majority of individuals

face traumatic experiences at least once in a lifetime (Kessler et al., 1995); however, we know that trauma accumulation increases PTSD vulnerability in a dose-dependent manner (Kolassa, Ertl, Eckart, Kolassa, et al., 2010). Because PTSD forms a unique psychological disorder that requires exposure to an environmental stressor to manifest, it is especially suited for the investigation of G × E. In sum, the probability of reliably detecting genetic factors involved in PTSD would increase if more researchers explored G × E by modeling traumatic load quantitatively. In addition, gene-environment correlation between a genetic risk factor and the probability of trauma exposure cannot be ruled out in most of the studies. Further challenges include inadequate power and the employment of different phenotypic measurements. Moreover, many studies investigated current or chronic as opposed to lifetime PTSD, despite the fact that a genetic predisposition might act throughout the entire lifespan and does not necessarily manifest itself in psychopathology at the time of the investigation. With this in mind, a careful interpretation of the presented results suggests that 5-HTTLPR (serotonergic system), COMT Val^{158}Met (dopaminergic system), and FKBP5 rs9470080 (HPA axis) seem to be robustly associated with PTSD in G × E studies. For other interesting candidates, such as BDNF, the highlighted challenges render conclusions difficult.

Recommendations and Future Perspectives

Candidate gene association studies

Future candidate gene association studies on PTSD should adhere to certain methodological standards to increase the informative content of reported results. In particular, this should include first and foremost adequate phenotyping, which is crucial to obtain valid conclusion from association studies. More precisely, this comprises a valid and reliable assessment of PTSD, which can be only obtained from structured clinical interviews, which are considered to be the gold standard for PTSD, as well as an adequate assessment of the amount of trauma experienced by the survivors. We strongly believe that trauma assessment is just as important as correct PTSD diagnosis because the adequate measurement of the relevant environmental risk factor will substantially improve the explained variance of the statistical model fitted and thereby increase the likelihood of an unbiased identification of genetic risk factors. In the literature reviewed so far, the survivors experienced various forms of trauma, ranging from natural disasters to military combat, civil war, or genocide. Likewise, the conceptualization of trauma or stress load differed among studies: Whereas some studies assessed trauma exposure severity (e.g., severity of earthquake or hurricane exposure), others assessed the number of different traumatic event types experienced. Finally, depending on the study population and research question, studies differed in whether they assessed adult trauma, childhood trauma, or both (cf. Tables S1–S4). So what is the best way to assess trauma in genetic studies on PTSD risk? First, individuals that are interviewed after a recent traumatic event (e.g., a natural disaster) are very likely to have encountered previous traumatic experiences. For example, in a sample of Sri Lankan school-aged children, the majority of the interviewed children experienced multiple traumatic experiences next to the tsunami, such as civil war experiences, family violence, or the loss of family members, adding to the cumulative risk of PTSD development (Catani et al., 2010). Second, even an event that might be considered as one stressor (e.g., a natural disaster) might imply different traumatic event types (the natural disaster as such but also sudden losses of family members or displacement). Therefore, the assessment of different traumatic event types can lead to a more nuanced understanding of the trauma encountered. Finally, considering the aforementioned dose-dependent effect of trauma exposure on PTSD risk (Kolassa, Ertl, Eckart, Kolassa, et al., 2010), genetic risk factors can only increase the vulnerability to develop PTSD at lower levels of traumatic load, whereas almost everyone develops a PTSD at extraordinary high levels of trauma exposure. Therefore, to better disentangle genetic and environmental risk, we strongly endorse the employment of a lifetime traumatic event checklist in genetic investigations on PTSD (as opposed to measuring the severity of a single incident trauma). Some of the commonly used diagnostic instruments to assess the diagnosis of PTSD come along with an event checklist to assess trauma exposure (e.g., Clinician-Administered PTSD Scale [Blake et al., 1995]; Posttraumatic Stress Diagnostic Scale [Foa, 1995]). However, these event checklists might need to be extended to meet the cultural context of the studied population and include all relevant traumatic experiences. Furthermore, given that traumatization is believed to have a stronger impact if it happens during developmental sensitive periods (McLaughlin, Conron, Koenen, & Gilman, 2010; van der Kolk, 2005; Yehuda & Bierer, 2009), we strongly encourage authors to employ a measurement of childhood trauma, as, for instance, the widely used Childhood Trauma Questionnaire (Bernstein et al., 1994) or Early Trauma Inventory (Bremner, Vermetten, & Mazure, 2000). To conclude, we believe that genetic variations can be assessed more reliably if more researchers would assess the number of adult and childhood traumatic experiences, thereby capturing relevant variance in the outcome measure PTSD.

Second, many studies did not investigate whether the identified risk alleles predispose to PTSD, trauma exposure, or both. Potential gene-environment correlation effects, as indicated by a significant association between

genotype and trauma load, should be hence investigated and reported. Finally and most important, potential G × E effects should be investigated to better understand how a risk genotype interacts with the amount of trauma exposure to predict the clinical outcome. Our research repeatedly indicated that the effect of traumatic load on PTSD susceptibility is much larger than the effect of a single risk allele. Furthermore, we consistently observed G × E effects in PTSD etiology: Whereas carriers of low-risk genotypes displayed the typical dose-dependent relationship of trauma load on PTSD risk, carriers of risk variants were at considerable higher risk of PTSD independent of traumatic load (Kolassa, Kolassa, et al., 2010; Kolassa, Ertl, Eckart, Glöckner, et al., 2010). For several biological systems already investigated, we therefore recommend a second analysis including G × E, which might explain reported inconsistencies.

From the memory-centered perspective illustrated in this review, a further central recommendation can be derived. As reviewed earlier, studies so far have mainly focused on the neurotransmitter systems involved in the initial fear response. However, the investigation of the molecular cascades that underlie the long-term consolidation, strength, and maintenance of the developing fear memory (Fig. 4) could contribute significantly to our understanding of PTSD etiology. For instance, metabotropic glutamate receptors and NMDA receptors are key mediators in the initiation of synaptic plasticity. Furthermore, both the transcription factor CREB and the atypical protein kinase PKMζ were shown to be required for the maintenance of fear memories. However, so far, the genes encoding these interesting players in memory formation have not yet been targeted in candidate gene association studies on PTSD.

Genome-wide association studies: Potential, limitations, and future strategies

A further important constraint of candidate gene association studies is their dependence on the present knowledge of the neurobiology of PTSD or related comorbid disorders. Because our understanding of the biological underpinning of PTSD is still relatively sparse, this limits the investigations to a very small number of genes and polymorphisms. Genome-wide association studies (GWAS) became feasible with advances in high-density genotyping platforms and an increasing knowledge on human genetic variations. Employing array-based chip-genotyping, GWAS can simultaneously investigate millions of SNPs to capture most common variation in the genome in a hypothesis-free manner. Therefore, this approach might help to discover new biological variations associated with PTSD development. The classical GWAS design investigates associations of all assessed SNPs with the trait of interest in an additive, main effect approach. However, the high number of genetic variations investigated implies a substantial multiple testing burden (Teo, 2008). Hence, GWAS require large sample sizes (in the order of thousands of individuals) to be adequately powered to detect the small effect sizes of single genetic variations.

Very recently, the first GWAS on PTSD was published, which constitutes a milestone for behavioral genetic research on PTSD (Logue et al., 2012). Despite a moderate sample size and no inclusion of traumatic load in the initial genome-wide scan of the discovery sample, the authors observed a strong association for the gene encoding the retinoid-related orphan receptor alpha (RORA). This gene has not yet been known to be involved in PTSD etiology and hence illustrates the potential of GWAS to uncover novel genes related to PTSD. However, previous GWAS identified RORA, which is known to exert neuroprotective functions, as a risk factor for various psychiatric disorders. Therefore, the authors propose that variations in RORA might influence the neuronal ability to cope with biochemical stress induced by trauma, and thereby alter PTSD vulnerability.

Whereas GWAS constitute a powerful tool to uncover novel genetic variants, for the majority of complex traits and disorders, the method fell short of expectations. Despite a very large number of GWAS conducted for complex traits and disorders, the proportion of the explained variance by all uncovered variants constitutes only a small fragment of the estimated heritability by twin studies—a phenomenon termed *missing heritability* (Manolio et al., 2009). Many explanations have been provided for this phenomenon, which include small power to detect genetic variants with small effect sizes, a higher significance of low frequent and rare variations (which are not tagged by common SNP arrays) on common diseases than initially thought, and the existence of complex Gene × Gene and Gene × Environment interaction effects, which complicate the discovery of genetic variations in GWAS (Cordell, 2009; Juran & Lazaridis, 2011; Thomas, 2010). How can these challenges best be addressed in future genetic investigation on PTSD? This is briefly addressed in the next section.

Joining forces. The existence of only one GWAS on PTSD might reflect the inability to detect genome-wide significant findings in relatively small samples of PTSD cases and controls. This could be surmounted if different research groups would join forces to recruit large samples or combine existing samples. The latter might however be complicated by the fact that existing study populations differ in genetic ancestry, phenotypic measures, trauma exposure, and PTSD rates, which could introduce multiple biases.

Investigating epistasis effects. The fact that carriers of a genetic risk variant do not display a uniform behavioral outcome is not only due to G × E but also to interactions with other genetic variants, a phenomenon termed *epistasis* (Lehner, 2011). Hence, one explanation of the missing heritability phenomenon might be the neglect of potential epistasis effects in the classical GWAS design (Cordell, 2009; Ritchie, 2011). There are emerging approaches to investigate statistical epistasis in human genetic associations studies (i.e., statistical interaction effects among genetic loci; for recent reviews, see Cordell, 2009; Ritchie, 2011; van Steen, 2012), and evidence from model organisms suggests that epistasis detected via statistical techniques could be biologically relevant (Ritchie, 2011). Furthermore, a recent investigation by Heck and coworkers (2011), who scanned SNPs in memory-related genes for two-way interactions, illustrates the feasibility and importance of the investigation of nonadditive genetic effects for complex traits: This study revealed a large epistasis effect between two SNPs mapping on two different potassium voltage-gated ion channels on episodic memory performance and brain activity the parahippocampal gyrus in an fMRI experiment. Epistasis effects might hence also contribute to a better understanding of genetic effects in PTSD susceptibility, but, to our best knowledge, no such investigation has been conducted to date. For genome-wide investigations, however, the investigation of epistasis effects would exponentially increase the multiple testing burden (Cordell, 2009; Ritchie, 2011).

Scanning for genome-wide G × E effects. From the crucial role of traumatic load in PTSD etiology reviewed so far, it becomes evident that the investigation of G × E would be also desirable in genome-wide approaches. However, a high interest in the study of genome-wide G × E effects is not confined to PTSD. Arguments to investigate these effects include the hope to better understand the biological mechanisms of identified genetic risk factors, to identify novel genes that do not show marginal effects but only act through interactions with environmental risk factors, to understand differential effects of environmental exposure, and to optimize and individualize treatment approaches accordingly (Aschard et al., 2012; Thomas, 2010). However, similar as for the investigation of epistasis, the majority of investigations lack power to investigate genome-wide G × E effects.

Inclusion of prior biological knowledge in genome-wide approaches. GWAS on PTSD, which might seek to include epistasis or G × E effects, share the common challenge of low power due to high multiple testing burden. One option to increase both power and interpretability of GWAS is to include prior biological knowledge to prioritize results (Cantor, Lange, & Sinsheimer, 2010; Ritchie, 2011). A straightforward analysis method to include biological knowledge is pathway analysis. This approach aggregates the test statistics for a group of related genes that are known to be part of a pathway or molecular network (K. Wang, Li, & Hakonarson, 2010) using publically available databases such as Gene Ontology (Ashburner et al., 2000) or the Kyoto Encyclopedia of Genes and Genomes (Kanehisa, Goto, Sato, Furumichi, & Tanabe, 2012). In light of the memory-centered perspective employed in the present review, this approach could substantially increase the power to look for genetic risk factors involved in the formation of a pathological fear memory. However, the shortfall of this methodology is that it relies—albeit to a lesser extent than candidate gene association studies—on previous biological knowledge and might hence limit the potential to discover complete new biology. Still, the possibility to investigate complex epistasis and G × E effects with traumatic load with adequate power render this method especially suitable for PTSD research.

Epigenetic modifications: A biological manifestation of environmental shaping

A broad understanding of the neurobiological underpinnings of PTSD needs to include the mechanisms involved in the complex interplay of genes and environment that lead to the phenotypic outcome PTSD. This cannot be achieved by merely statistically modeling G × E. Environmental factors can influence gene expression through epigenetic mechanisms, most important, DNA methylation and histone modification, which influence the transcriptional accessibility of DNA without changing its structure. Therefore, a genetic risk factor might exhibit different functional consequences, depending on epigenetic modifications of the relevant DNA segments. For instance, a genetic variant that is associated with high levels of gene expression might be hypermethylated and hence express low transcriptional activity. Therefore, epigenetic modifications most likely constitute a further reason for the aforementioned missing heritability problem. Furthermore, epigenetic modifications vary between cell types and brain regions, which adds to the complexity of environmental-shaped gene-regulation (T.-Y. Zhang & Meaney, 2010).

Initially, epigenetic alterations were thought to mainly occur in early developmental stages and stably alter gene expression (T.-Y. Zhang & Meaney, 2010). Animal research showed that low maternal care leads to elevated GCCR promoter methylation, associated with reduced GCCR expression (Weaver et al., 2004). Similarly, in humans, early life stress constitutes a major risk factor for PTSD, and elevated GCCR methylation has been observed in suicide victims who faced childhood trauma (McGowan et al., 2009). Epigenetic modifications provide a sound

explanation of how early developmental adversity, including prenatal stress, increases stress sensitivity and PTSD risk later in life and how such a risk could be transmitted to the next generation (Yehuda & Bierer, 2009). Increasing evidence shows that epigenetic regulation also constitutes an important mechanism of activity-driven gene regulation in the adult brain (T.-Y. Zhang & Meaney, 2010). Importantly, fear memory consolidation and associated plasticity in the lateral amygdala were found to be regulated by epigenetic modifications (Monsey, Ota, Akingbade, Hong, & Schafe, 2011). Furthermore, developmental adversity might influence the functioning of these activity-driven epigenetic modifications (T.-Y. Zhang & Meaney, 2010). Hence, a growing line of evidence suggests a pivotal role of epigenetic regulation in PTSD etiology. Accordingly, one investigation has already indicated that the dose-dependent effect of traumatic load on PTSD risk is modified by the methylation pattern of the serotonin transporter gene (Koenen et al., 2011), whereas another investigation provided evidence for an interaction of the low-function risk allele and differential methylation at the dopamine transporter gene locus, suggesting that the combination of a low-function genotype with higher methylation levels leads to the highest PTSD risk (Chang, Koenen, et al., 2012). Yet, a further recent investigation demonstrates how the joint effects of genetic risk and developmental trauma lead to differential, allele-specific demethylation at functional glucocorticoid response elements of the FKBP5 locus. The observed demethylation had functional consequences on gene transcription and glucocorticoid receptor sensitivity, suggesting that the observed epigenetic mechanisms constitute an important mediator of genetic and early environmental risk on psychopathology (Klengel et al., 2012). Four further studies reported different methylation patterns of immune-associated genes (Smith et al., 2011; Uddin et al., 2010; Uddin et al., 2011) and genomic repetitive elements, important for DNA stability (Rusiecki et al., 2012) in PTSD. In sum, the findings from the first epigenetic studies on PTSD described altered methylation levels at genomic loci that have been previously identified as genetic risk factors for PTSD (i.e., serotonin transporter, dopamine transporter, and FBBP5 polymorphisms), which provide a further hint for the biological relevance of these candidate genes for PTSD etiology, as well as at genomic sequences encoding immune-associated agents. Whereas these findings seem biological plausible, thus far, no independent replication studies confirmed the initial findings.

Furthermore, because human research is mainly confined to the investigation of epigenetic alterations in peripheral cells, the question of whether findings allow valid conclusions about corresponding patterns in the brain remains controversial (T.-Y. Zhang & Meaney, 2010). Likewise, at the moment, human epigenetic research crucially contributes to our understanding of how environmental stress can be transferred to the enduring alterations in immune cell function observed in PTSD. However, insights on the central epigenetic modifications involved in fear memory formation and consolidation mostly rely on translational research. Rapid advances can be expected in this young research field that will greatly influence our understanding of biological risk in the development of pathological fear memories.

Implications for the fear network model

Whereas there is no ultimate resilience to PTSD (i.e., everyone develops PTSD at sufficient levels of traumatic load [Kolassa, Ertl, Eckart, Glöckner, et al., 2010; Kolassa, Kolassa, et al., 2010]), from the reviewed literature, it becomes evident that individual genetic factors and epigenetic modifications significantly influence the fear memory strength and, hence, PTSD development at lower levels of traumatic load. From the perspective of the fear network model (Elbert & Schauer, 2002; Kolassa & Elbert, 2007; Rockstroh & Elbert, 2010), as well as other prominent theories on PTSD etiology (Brewin et al., 1996; Ehlers & Clark, 2000), the dissociation between strong and interconnected sensory-emotional memories and weak memories for autobiographical context memories leads to the typical intrusive symptoms. Likewise, genetic variations that lead to an enhanced memorization of emotional memories should result in higher reexperiencing symptoms, and indeed, this prediction was confirmed by our group for variations of the ADRA2B receptor (de Quervain et al., 2007). Furthermore, there is initial evidence that good memory performance as such increases the risk for PTSD. An investigation on genes involved in the memory consolidation kinase cascade revealed a strong association among PRKCA, healthy memory performance, and pathological fear memories in PTSD (de Quervain et al., 2012). A careful interpretation could be that individuals with good memory, which is intrinsically adaptive, might be more vulnerable to a strong memorization of the emotional-sensory elements of a trauma in a fear network. However, other studies reported impaired memory performance for neutral information in PTSD patients (Brewin, Kleiner, Vasterling, & Field, 2007). Future studies should directly investigate the influence of genetic risk factors on emotional-sensory as opposed to autobiographical memories in healthy subjects, followed by association studies of the identified genes on PTSD risk, to test the influence of genetic risk on the memory mechanisms described by the fear network model.

To sum up, molecular genetic research on PTSD started two decades ago, with the first studies simply reporting the frequency of risk alleles in PTSD cases as opposed to controls. Important steps consisted of the assessment of trauma exposure, the modulation of G × E and the simultaneous investigation of several candidate genes. The

investigation of G × E in GWAS or pathway analytic approaches and advancements in epigenetics might finally lead to the crossing of the Rubicon and improve our understanding of how genetic risk factors and epigenetic modification interact in the development of PTSD. But most important, the employment of innovative biological techniques will only hold its promise if researchers from neuroscience and clinical psychological science join forces. A mutual scientific exchange between research on genetic risk factors and epigenetic modifications, as well as clinical psychological models on PTSD etiology, could finally lead to the long-awaited deeper understanding of the development of pathological memories in PTSD.

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