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Understanding posttraumatic stress disorder through fear conditioning, extinction and reconsolidation

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ABSTRACT

Careaga MBL, Girardi CEN, Suchecki D. Understanding posttraumatic stress disorder through fear conditioning, extinction and reconsolidation. NEUROSCI BIOBEHAV REV —Posttraumatic stress disorder (PTSD) is a psychopathology characterized by exacerbation of fear response. A dysregulated fear response may be explained by dysfunctional learning and memory, a hypothesis that was proposed decades ago. A key component of PTSD is fear conditioning and the study of this phenomenon in laboratory has expanded the understanding of the underlying neurobiological changes in PTSD. Furthermore, traumatic memories are strongly present even years after the trauma and maintenance of this memory is usually related to behavioral and physiological maladaptive responses. Persistence of traumatic memory may be explained by a dysregulation of two memory processes: extinction and reconsolidation. The former may explain the over-expression of fear responses as an imbalance between traumatic and extinction memory. The latter, in turn, explains the maintenance of fear responses as a result of enhancing trauma-related memories. Thus, this review will discuss the importance of fear conditioning for the establishment of PTSD and how failure in extinction or abnormal reconsolidation may contribute to the maintenance of fear response overtime.

Contents

1. Posttraumatic stress disorder

PTSD is a fear-based disorder that can be induced by exposure to extreme aversive events, such as war, sexual violence or life-threatening accidents (e.g., motor vehicle accidents). These situations usually overcome the individual's coping responses, leading to behavioral and psychological alterations (for review, see Huether, 1996). The last edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) developed by the American Psychiatric Association (APA) reclassified PTSD as a stress or trauma disorder, with the following core features:

– Re-experiencing symptoms of the aversive event, by means of nightmares, flashbacks and intrusive memories.

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– Effort to avoid reminders of the event including places, thoughts and people.
– Hyperarousal symptoms related to physiological manifestations, such as hypervigilance, irritability, impaired concentration, increase in startle response and anger outbreak.

Although not all people exposed to extreme stressful events develop PTSD, this is the fourth most common psychiatric disorder in the USA(Breslau et al., 1991; Kessler et al., 1995). Epidemiological studies in the general population reveal that before the September 11 attacks 5–6% of men and 10–14% of women exhibited lifetime PTSD symptoms (Breslau et al., 1991; Kessler et al., 1995; Resnick et al., 1993). Few months after the attacks, a cross-sectional web-based survey with2273 participants used a PTSD checklist and found a probable PTSD prevalence of 11.2% in New York residents (Schlenger et al., 2002). A subsequent study by Galea (2003) found a decline in PTSD symptoms prevalence in the general population of New York six months after September 11; however, those who were directly involved in the attacks still met PTSD criteria. The deleterious impact of traumatic events is also seen in low and middle-income countries, such as Brazil, Chile and Mexico. The Brazilian population is daily exposed to threatening events, including kidnapping, vehicle accidents and robbery with or without weapon. Ribeiro et al. (2013) conducted a cross-sectional survey with a probabilistic representative sample in São Paulo and Rio de Janeiro, the two largest Brazilian metropolis, and found high lifetime prevalence for traumatic exposure (nearly 90% of the sample) and higher lifetime prevalence estimates of PTSD among women than men in both cities. Moreover, they found an association between psychiatric disorders, such as social phobia, panic disorder and major depression and the three clusters of traumatic events (assaultive violence, other injury, sudden death), suggesting that these events may increase the likelihood of developing mental disorders. Comorbidity is often reported and over 90% of PTSD patients have at least 1 lifetime comorbid psychiatric disorder (Kessler et al., 1995). Major depressive disorder, alcohol abuse and/or dependence and anxiety disorder are commonly diagnosed in PTSD patients (Chilcoat and Breslau, 1998; Raboni et al., 2014).

In the past years, establishment of animal models has been essential to investigate the underlying mechanisms of this disorder. Animal and human studies reveal that the etiology and symptomatology of PTSD involve several brain areas and behavioral systems, some of them related to learning and memory processes. In this regard, we should be aware that some PTSD symptoms are closely linked to associative (e.g., fear conditioning), whereas others are connected to non-associative learning (e.g., sensitization, habituation). Nonetheless, some symptoms are not explained by learning processes, e.g., guilt, shame (for review, see Lissek and van Meurs, 2015). In this review, we will focus our attention on a memory interpretation for PTSD, exploring memory processes that could explain maintenance of some PTSD symptoms, including non-associative and mainly associative learning.

2. Associative learning and PTSD

Classical conditioning is a form of associative learning in which two or more stimuli are paired, with a change in the salience of the conditioned stimulus. Ivan Petrovich Pavlov (1849–1936) was the first to study this form of learning, when he observed, in dogs, that a neutral stimulus (e.g., sound – known after conditioning as conditioned stimulus – CS) was able to trigger physiological and behavioral changes after being associated to a biological relevant stimulus (food – known as unconditioned stimulus – US). After pairing of both stimuli, CS led to behavioral or physiological changes known as conditioned responses (CR) (for review, see VanElzakker et al., 2014). Classical conditioning can also be established by using aversive stimuli as the US, forming what is known as classical fear conditioning(for review, see Maren, 2001). Currently, in animal studies on fear conditioning, neutral stimuli, such as a tone, light or the environment as a whole are paired with a noxious stimulus, usually, foot shock. As a result of this association, CS acquires aversive properties and induces fear responses that in rodents usually include freezing behavior (Blanchard and Blanchard, 1972), potentiated startle (Hitchcock and Davis, 1986), ultrasonic distress vocalization (Blanchard et al., 1991) and changes in heart and respiratory rates and in blood pressure (Iwata et al., 1986; Kapp et al., 1979).

Classical fear conditioning paradigm is one of the most employed models to study learning and emotional memory and is a powerful tool to reveal the neurobiological underpinnings of psychiatric disorders in which strong emotional memory component is present, such as in PTSD. In this disorder, cues/stimuli present in the environment at the time of the trauma, e.g., loud sounds, objects, are associated with the aversive experience (e.g., assault, kidnap), leading to physiological and behavioral reactions. For this reason, fear conditioning is pointed out as an outstanding memory feature of PTSD that can explain re-experiencing and, in part, avoidance symptoms (for review, see VanElzakker et al., 2014; Yehuda and LeDoux, 2007). In the past years, the neurobiological mechanisms of fear conditioning were extensively studied and some key brain structures were identified. Interestingly, these brain areas have also been implicated in PTSD.

2.1. Key brain structures for fear conditioning and their relation to PTSD

2.1.1. Hippocampus

The hippocampus is located in the temporal lobe and has an important role in the regulation of the neuroendocrine stress response, learning and memory (for review, see Maren, 2001; McEwen et al., 1992). It is involved in certain forms of conditioned fear that depend on contextual processing, such as contextual fear conditioning (Kim et al., 1993; Maren et al., 1997; Phillips and LeDoux, 1992). In rodents, electrolytic lesion of the dorsal hippocampus impairs acquisition and expression of contextual fear memory, whereas tone fear conditioning is spared (Phillips and LeDoux, 1992). This effect is clearly seen when the lesion takes place prior to training in a spatial memory task, but not always when it is done several weeks after the training (Broadbent et al., 2006; Debiec et al., 2002; Maren et al., 1997). Recently, Goshen et al. (2011) assessed the role of the hippocampus on retrieval of remote memories in mice (memories evaluated weeks or months after acquisition) and observed that inhibition of the dorsal hippocampus during the test impaired contextual memory retrieval even nine weeks after training, suggesting that the hippocampus still plays a relevant role in retrieval of older memories. Interestingly, this impairing effect has only been observed with the use of optogenetic tools, which provide a fast inhibition, but not with pharmacological inhibition with tetrodotoxin (TTX), a selective blocker of sodium channels, and CNQX, a glutamate receptor antagonist. The authors suggest that differential effects observed with these manipulations can be explained by compensatory mechanisms that can only be engaged by pharmacological inhibition (Goshen et al., 2011).

The hippocampus plays an important role in the regulation of the hypothalamic- pituitary-adrenal (HPA) axis, participating in the glucocorticoids (GCs) negative feedback loop (Herman et al., 1989; for review, see Jacobson and Sapolsky, 1991). This negative feedback regulation is mainly mediated by type II glucocorticoids receptors present in a high density in this structure (Reul and De Kloet, 1985). It is well established, in animals, that exposure to high GCs levels or chronic stress leads to deleterious changes in the