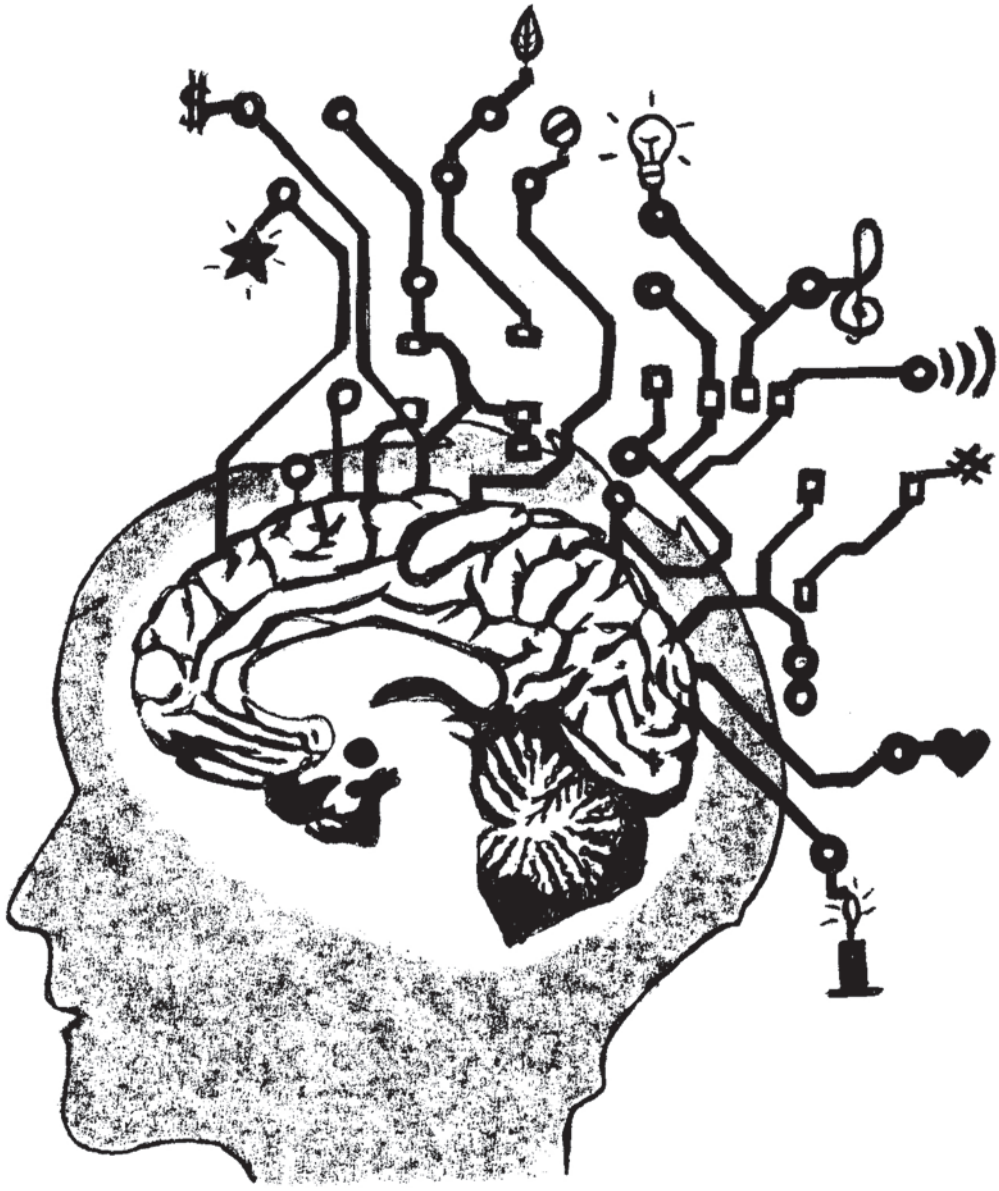

HIPPOCAMPAL DYSFUNCTION AND CONTEXTUAL MEMORY: NEW PERSPECTIVES FOR UNDERSTANDING THE ETIOLOGY OF POST-TRAUMATIC STRESS DISORDER

Disfunción Hipocampal y Memoria Contextual: Nuevas Perspectivas para Comprender la Etiología del Trastorno por Estrés Postraumático

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* Artículo de reflexión.

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SÍNTESIS:
Recientemente, varios estudios indican que la disfunción del hipocampo juega un rol importante en la etiología del Trastorno por Estrés Postraumático (TEPT). Específicamente, se ha sugerido que la disfunción del hipocampo altera la habilidad para codificar y recuperar información contextual necesaria para generar memorias conjuntivas (holísticas) de los diferentes elementos del contexto o ambiente en el cual el trauma ocurrió. Por el contrario, los pacientes que padecen TEPT codifican asociaciones independientes entre elementos individuales del contexto y el evento traumático. Así, en los pacientes que padecen TEPT un elemento individual por sí mismo es capaz de activar una memoria traumática.

DESCRIPTORES:
Trastorno por Estrés Postraumático, Memoria contextual, hipocampo, memoria de miedo, extinción del miedo

ABSTRACT:
Recently, several studies indicate that hippocampal dysfunction play an important role in the etiology of Post-traumatic Stress Disorder (PTSD). Specifically, it has been suggested that dysfunction of the hippocampus impairs the ability to encode and retrieve contextual information necessary to generate a conjunctive memory (holistic) of the different elements of the context or environment in which trauma occurred. Instead, PTSD patients encoded independent associations between individual elements of the context and the traumatic event. Thus, in PTSD an individual element by itself may be able to activate a traumatic memory.

DESCRIPTORS:
PTSD, contextual memory, hippocampus, fear memory, fear extinction

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Introducción

Fear is a human emotional state that serves an adaptive function and, in most cases, it promotes the survival of individuals. When humans are exposed to traumatic events usually have a set of responses that include avoidance, re-experiencing and hyperarousal. In most people exposed to traumatic events, this set of responses extinguish over time. However, in a small number of people these responses persist over time, and become the symptoms of PTSD (Rothbaum et al., 2003; Rauch et al., 2006; Milliken et al., 2007; Gillespie et al., 2009). Recently, a new body of research in both animals and humans has showed conclusive evidence that impairment in processing contextual information is a key component in the etiology of PTSD. Indeed, the used of contextual fear paradigm have provided important insight into the potential mechanism linking PTSD, hippocampus and contextual memory. In this article I review some studies that supports such linking.

Pavlovian fear conditioning and PTSD

Pavlovian fear conditioning has become a fundamental model for the development of hypotheses that try to explain the pathophysiology of PTSD. In this behavioral paradigm the organisms learn that one or more stimuli in the environment predict an aversive event (LeDoux, 2002; Sullivan et al., 2003; Charney, 2004). According to this paradigm, an aversive unconditioned stimulus (US) is paired with a neutral conditioned stimulus (cue fear conditioning) or with a particular neutral context (contextual fear conditioning). After several trials, the conditioned stimulus (CS) has the capacity to induce conditioned fear responses (CRs), such as skin conductance responses (SCRs) in humans and freezing responses in rodents. Recurrently presenting the CS without the US extinguishes the CR (Ledoux, 2000; Orr et al., 2000; Rudy, 2009). Several studies indicate that extinction does not erase the association between CS and US; instead, extinction is a new memory that exists in parallel with CS/US memory and has the capacity to inhibit the expression of the conditioned responses (Quirk 2002; Rescorla 2001; Bouton, 2004).This assumption is supported by the observation, that during re-exposure to the extinguished CS in the extinction context the CR is minimal. However, conditioned fear response to a CS is renewed when the animal is place in a context different from the one in which it was extinguished (Bouton, 2004). From this perspective, in PTSD, the trauma serves as an unconditioned stimulus, which is associated to the environmental cues where the traumatic event happened (sounds, sights and smells) or CSs. Posterior re-exposure to cues associated with the trauma (CSs) evokes inappropriate fear responses. A series of studies have utilized fear conditioning paradigm in PTSD patients to evaluate fear extinction. These studies have reported deficits in either extinction

learning (Orr et al., 2000; Peri et al., 2000) or extinction retention (Milad et al., 2008), and It has therefore proposed that the difficulty in the extinction of conditioned fear response could play an important role in the etiology of PTSD (Morgan et al., 1993; Rothbaum y Davis, 2003; Milad et al., 2006; Rauch et al., 2006; Wessa and Flor, 2007).

The neural basis of extinction of conditioned fear

Evidence suggests that the hippocampus, the medial prefrontal cortex (mPFC) and amygdala play an important role in extinction of conditioned fear responses. mPFC was one the first structures associated to extinction learning. Morgan and coworkers observed that lesion of ventromedial prefrontal cortex (vmPFC) do not affect the acquisition of CR, but impaired extinction of conditioned fear responses (Morgan et al., 1993). Other work has revealed that electrical stimulation of infralimbic (IL) subregion of vmPFC facilitates fear extinction (Milad et al., 2004). Recent studies have shown that pharmacological inactivation of GABAergic neurons of infralimbic vmPFC impairs consolidation and retrieval of fear extinction (Laurent and Westbrook., 2009; Sierra-Mercado et al., 2011). In addition to vmPFC there is considerable evidence that hippocampus is also involved in fear extinction. Corcoran and coworkers have found that selective inactivation of GABAergic neurons of the dorsal hippocampus impairs both acquisition and consolidation of fear extinction (Corcoran et al., 2005). Other study has showed that inhibition of protein synthesis in CA1 subregion of hippocampus impair the acquisition of extinction (Vianna et al., 2001). Likewise, Tronson and coworkers reported that the extracellular signal-regulated kinase (Erk) in hippocampal CA1 neurons is an important mediator of fear extinction (Tronson et al., 2009). Recent studies suggest that amygdala is also involved in de acquisition of extinction memories. For instance, pharmacological inhibition of NMDA receptors in basolateral complex of the amygdala (BLA) impairs the acquisition of extinction (Zimmerman and Maren, 2010). Consequently, evidence suggests that the coordinate action of the amygdala, the hippocampus and vmPFC is essential to extinction of conditioned fear responses. Interestingly, a recent study showed that the inhibitory interneurons of the intercalated cell masses (ITC) subregion of amygdala and IL neurons of vmPFC were active when an extinguished CS was presented in the extinction context. On the contrary, neurons in prelimbic division (PL) of the medial prefrontal cortex, lateral nucleus of the amygdala (LA) and medial division of the central nucleus of the amygdala (CEm) were active when the extinguished CS was presented outside the extinction context. Hippocampal neurons, which project to both the vmPFC and BLA, were active in both conditions, independent of the valence of that memory (Knapska and Maren, 2009). In addition, Herry and coworkers reported that there are specific pools of neurons in the BLA that respond selectively to an extinguished CS presented either in the extinction context or in a new context. Extinction context neurons in BLA are modulated by an afferent input of the vmPFC, whereas new context neurons are activated by electrical stimulation of the ventral hippocampus (Herry et al., 2008). Collectively, these data suggest that hippocampus and vmPFC are crucial for the processing of contextual information necessary to acquisition and consolidation of extinction memories and regulation of fear memories encoding by the amygdala.

Stress and hippocampal abnormalities

A large body of evidence indicates that chronic exposure to stress induces the activation of several hormonal and neurotransmitter systems which can drive morphological and functional changes in amygdala, hippocampus and mPFC. For instance, Roozendaal and coworkers show that high doses of glucocorticoids in mPFC impair working memory in rats, and this effect is dependent of BLA activity (Roozendaal et al., 2004). Other study showed that BLA activation enhances the dentate gyrus long-term potentiation, and both norepinephrine and corticosterone enabled this effect (Arikav and Richter-Levin, 2002). In addition, some studies suggest that corticosterone and glutamate release in BLA neurons in response to chronic stress can lead changes in synaptic plasticity in the amygdala and other brain regions. Specifically, Mitra and coworkers reported that chronic and acute immobilization stress induces spinogenesis in the BLA (Mitra et al., 2005). On the contrary, chronic exposure to stress and repeated corticosterone treatment lead atrophy in both mPFC and prelimbic cortex layer II/III neurons (Wellman, 2001; Cook and Wellman, 2004). Similarly, exposure to stress induces dendritic atrophy in hippocampal CA1 pyramidal cells (Conrad et al., 199; Vyas et al., 2002). In consonance with these results, many neuroimaging studies in PTSD patients have reported reduction in both hippocampal and mPFC volumes compared to either trauma-exposed control subjects or trauma-unexposed healthy subjects (Gurvits et al., 1996; Bremner, 2002; Gilbertson et al., 2002; Yamasue et al., 2003; Woodward et al., 2006). Additionally, both hippocampal volumes and mPFC activation have been inversely correlated with PTSD symptom severity (Gilberston et al 2002; Shin et al., 2004). Interestingly, the CA1 /DG are the areas of hippocampus that reveal the most prominent volume reduction in PTSD patients, and these subregions are strongly related with context memory (McHugh and Tonegawa, 2009; Wang et al., 2010). In sum, these data indicate that PTSD is characterized by morphological and functional alterations in brain structures necessary for the processing of contextual information.

Hippocampal dysfunction and conjunctive memories

Taking into account the above, there is considerable evidence that PTSD involve functional and structural hippocampal and mPFC abnormalities, which have been linked with the difficulty in extinction of fear responses observed in PTSD patients (Morgan et al., 1993; Rothbaum y Davis, 2003; Milad et al., 2006; Rauch et al., 2006; Wessa and Flor, 2007). Interestingly, extinction of fear responses is a process strongly dependent of the context. An extinguished CR remain extinct only in the context in which they was acquired (Bouton, 2004; Kalisch et al., 2006; Maren, 2011). Consequently, the ability to process contextual information is essential to acquire and consolidate extinction memories. Particularly, it has been suggested that dysfunction of the hippocampus impairs the ability to encode and retrieve contextual information necessary to generate a conjunctive representation (holistic) of the different elements of the context or environment in which trauma occurred. Instead, PTSD patients encoded independent associations between individual elements of the context and the traumatic event (Rudy et al., 2004; Rudy, 2009; Brewin et al.,2007; Acheson et al., 2012). Several studies suggest that hippocampus is necessary for encoding memories in which contextual stimulus are

holistically associate with aversive events (Fanselow, 2000; Rudy et al., 2004; Rudy 2009;). Early studies reported that hippocampal lesions impaired contextual fear memories, while cue fear memories remain intact (Kim and Fancelow, 1992; Young et al., 1994). Recently, Iordanova and coworkers, using a rodent paradigm of episodic memory, have shown that pharmacological inactivation of hippocampus impairs the ability to retrieve conjunctive memories that include; visual, auditory and temporal cues. Conversely, disruption of hippocampal function does not impair the formation of elementary associations between individual elements of the context (Iordanova et al., 2009).

Conclusions

In essence, there is sufficient evidence to support the role of hippocampus in the encoding and retrieval of conjunctive memories associate to aversive events. These finding suggest that in PTSD hippocampal dysfunction can interrupt the associating between the threat and the context as a whole; instead, PTSD patients would generate independent associations between individual elements of the context and the traumatic event. Thus, in PTSD an individual element by itself may be able to activate a fear memory. Despite the fundamental role of hippocampus in the processing of contextual information, experimental data on the relationship between PTSD, hippocampus and contextual memory is still limited.

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