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Research Paper

# Neurobiological correlates of post-traumatic stress disorder: A focus on cerebellum role

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## ABSTRACT

Post-traumatic stress disorder (PTSD) is a mental disorder that can develop after a person is exposed to a stressful life event, that involved real or symbolic survive treat. It is characterized by an emotional alteration that not recover spontaneously. This disorder is mainly conceived within the fear conditioning model, where the fear conditioned response fails to extinguish. The current hypothesis on PTSD is a learned incapacity of top-down structures as prefrontal cortex in inhibition of an “hyper-reactive” amygdala. The aim of this review is to consider all cerebral structures involved in PTSD and to suggest an alternative hypothesis on PTSD, in a bottom-up frame. Hyper-reactivity of amygdala could be linked to prefrontal deficits but also to the functioning of others cerebral structures as cerebellum. In fact both amygdala and cerebellum are crucial sites in fear conditioning and extinction models.

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Post-traumatic stress disorder (PTSD) occurs after exposure to life threatening episodes and is characterized by intense reliving of the traumatic event through disruptive memories and nightmares, avoidance of reminders of the event, hypervigilance toward potential threats in the environment, negative alterations in cognitions and mood, and in some cases persistent or recurrent depersonalization and derealization symptoms (American Psychiatric Association, 2013).

Therefore, the symptoms of PTSD seem to reflect a persistent, abnormal adaptation of neurobiological systems to the stress of the experienced trauma.

Over the last two decades, a great deal of research has been directed towards understanding the etiology, psychophysiology, clinical characteristics and treatments in PTSD field (Nemeroff et al., 2006). Neuroimaging research has opened up a new window to uncover the mechanisms behind PTSD (Francati, Vermetten, & Bremner, 2007; Hayes, Hayes, & Mikedis, 2012). However, some core psychological and neurobiological processes underlying PTSD have yet to be clarified (Liberzon & Sripada, 2008; Shin, Rauch, & Pitman, 2006).

Neurobiological systems that regulate stress responses include specific endocrine and neuro-transmitter pathways, as well as a

network of brain regions known to regulate the fear response at both conscious and unconscious levels (Sherin & Nemeroff, 2011).

Over 25 years of psychophysiological research on PTSD have revealed the presence in this disorder of an abnormal emotional response to elements recalling the trauma, an exaggerated startle response, and an inability of extinction (Pole, 2007).

One of the first and most replicated result was the increased response of the autonomic nervous system, in terms of increased heart rate and skin conductance, both toward sounds recalling the trauma (Keane et al., 1998) both towards internal mental images about the event (Pitman, Orr, Fergue, de Jong, & Claiborn, 1987). In addition, noradrenergic hyper-reactivity, along with altered function of the hypothalamic-pituitary adrenal (HPA) axis, was another reliable replicated findings in PTSD (Liberzon & Abelson, 2016; Pitman et al., 2012).

Moreover, numerous studies have investigated the anatomical and functional changes in specific areas of the brain associated with PTSD symptoms.

Amygdala, medial prefrontal cortex (mPFC), and hippocampus are those brain regions that primarily appear to be pathologically involved in PTSD (Martin, Ressler, Binder, & Nemeroff, 2009; Shin et al., 2006; Wager, Lindquist, & Kaplan, 2007; Yehuda & LeDoux, 2007).

Amygdala is centrally involved in the interpretation of the emotional valence of the incoming information and plays a pivotal role in the response mechanism to fear and to ambiguous and

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uncertain stimuli (Herry et al., 2007; Sander, Grafman, & Zalla, 2003). Several studies have found an increased amygdala activation pattern in patients with PTSD compared to healthy controls (for review see Francati et al., 2007; Patel, Spreng, Shin, & Girard, 2012). This hyperactivation is thought to account for the failure of the extinction to fearful stimuli, a common component of the clinical presentation of PTSD.

mPFC is implicated in the processing of emotional materials generated internally and in the regulation of arousal. A common finding in PTSD studies is the hypoactivation and a decreased volume of the mPFC (Shin et al., 2006). This hypoactivation of the mPFC may contribute to a loss of top-down regulation of emotional systems (Nicholson et al., 2017; Patel et al., 2012). In other words, the diminished responsivity of the mPFC could be linked to a partial failure in the appropriate functional inhibition of the activity of the amygdala (Etkin & Wager, 2007). This dysregulation is thought to account for a number of problematic neurocognitive processes in PTSD, such as fear conditioning, fear extinction, cognitive–emotional interactions and emotional processing.

Hippocampus is a brain region that is crucial for contextual learning and spatial and episodic memory (Burgess et al., 2002). Evidence of decreased hippocampal volume and neuronal integrity as well as impaired hippocampal function are associated with explicit memory impairment and also with altered contextual processing (Liberzon & Abelson, 2016; Liberzon & Sripada, 2008). Moreover, the decrease in hippocampal functioning is associated with an increased activity of the parahippocampal gyrus, and the latter may be linked to flashbacks and intrusive thoughts, typical symptoms of PTSD (Francati et al., 2007).

Decades of neuroimaging studies also showed other regions that have been identified as involved in PTSD, such as insula, Broca's area, retrosplenial cortex, and thalamus (Doruyter, Stein, & Warwick, 2014; Francati et al., 2007; Gilboa, 2015; Sartory et al., 2013).

Insula is involved in processing of negative emotions and in the regulation of the autonomic nervous system. Several functional and structural studies have consistently shown the involvement of anterior or posterior insula, or both in PTSD pathophysiology (King et al., 2009; Liberzon, Britton, & Phan, 2003; Lindauer et al., 2008; Nardo et al., 2011; Osuch et al., 2001; Whalley, Rugg, Smith, Dolan, & Brewin, 2009). Posterior insula contains a center of interoception, and a hyperactivation of this part could be related to the activation of somatic representations of the traumatic experience (dissociated memories), which remain non-integrated and fail to reach the declarative memory. This interpretation is in line with a view of PTSD as a memory disorder characterized by the reliving of non-integrated traumatic memories (Van Der Kolk, Burbridge, & Suzuki, 1997).

Anterior insula is a center of emotional awareness, and an increased activity in anterior insula could be connected with the processing of fear or other negative emotional responses to symptom-provoking stimuli, suggesting the existence of a dysfunctional emotional regulation system (Etkin & Wager, 2007).

Broca's area is designated to the creation of semantic representations of personal experiences, in order to translate into communicable language and cognitively restructure them. In patients with PTSD, Broca's area is partially deactivated, and this could explain patients' difficulty in describing and correctly position in their semantic memory their traumatic experience (Hull, 2002; Van Der Kolk et al., 1997).

Retrosplenial cortex role for the establishment and maintenance of traumatic memory was recently pointed out (Sartory et al., 2013). This area could represent the neural basis of intrusive and re-experiencing symptoms, and of the feeling of reliving the traumatic event. In fact, patients with PTSD in comparison with control subjects show a significant activation of retrosplenial cortex and of precuneus in response to stimuli associated with the trauma.

Another frequent finding in functional neuroimaging studies is the involvement of thalamus in patients with PTSD. Thalamus is reciprocally interconnected with several cortical and subcortical areas and it can be considered as a relay center for top-down and bottom-up information processing (Bergmann, 2008). Thalamus is also involved in the transmission of external sensory information to different areas of the cerebral cortex and limbic system. Data from different neuroimaging studies have shown that patients with PTSD have a significant deactivation of the thalamus (Kim et al., 2007; Lanius et al., 2001; Lanius et al., 2004). This reduced thalamic activation is linked to impairments in the functional connectivity of several networks, leading to failures in somato-sensory, cognitive, memory and hemispheric dynamic integration (Bergmann, 2008). Due to its functional nature, a disruption in thalamo-cortical connectivity could lead to the misinterpretation of external stimuli (Francati et al., 2007) and may be implicated in excessive fear recall, failure of expression and maintenance of extinction memory, and heightened traumatic remembrance which cause the characterized symptoms in PTSD (Yin et al., 2011).

In accordance with this findings, recently Liberzon and Abelson (2016) proposed that a context processing deficit based on the dysfunction of a hippocampal-prefrontal-thalamic network is at the core of PTSD pathophysiology. Their model focuses on dysfunction within specific brain circuits governing the critical adaptive function of contextualization – involving hippocampus (Hpc) prefrontal cortex (PFC), thalamic circuits that modulate activity in amygdala, and other limbic and cortical regions, indicating that PTSD could be considered as a context pathology.

Our aim is trying to deepen this model, taking into consideration also the specific role of cerebellum and a bottom-up impaired regulation in this disorder.

Cerebellum is a neural structure responsible for motor control, voluntary movement, balance and associative learning. It is reciprocally interconnected to several parts of the brain such as brain stem, limbic areas, cerebral cortex, and the frontal lobes and it can be considered as an important associative area (Bergmann, 2008).

There is a growing awareness that the cerebellum plays a role in higher cognitive functions such as sensory processing, attention, verbal working memory and emotion (Bergmann, 2000; Schmahmann, 2010).

Recently, some studies have observed altered functioning of the left cerebellar hemisphere (Osuch et al., 2001) and vermis (Anderson, Teicher, Polcari, & Renshaw, 2002; Pissioti et al., 2002) in PTSD patients. Increased activation in the cerebellum was found in PTSD patients exposed to traumatic reminders (Driessen et al., 2004; Fernandez et al., 2001). Another study conducted on pediatric maltreatment-related PTSD subjects (Baldaçara et al., 2011) confirmed the results of previous study on children and adolescent with PTSD (Carrion et al., 2009; De Bellis & Kuchibhatla, 2006) and provided evidence that cerebellar volume is smaller in adult PTSD subjects than in trauma-exposed controls without PTSD. This volume reductions in the left hemisphere and vermis is associated with the magnitude of the PTSD symptoms. Moreover, the study found an association between these cerebellar reductions and early traumatic life experiences, posing the question of whether the changes are a consequence of abnormal neurodevelopmental adaptations in subjects that later develop PTSD.

Other two recent studies using magnetic resonance imaging on rape victims and on soldiers respectively, reported a volumetric increase in the cerebellum (Sui et al., 2010; Sussman, Pang, Jetly, Dunkley, & Taylor, 2016).

The age at exposure to the traumatic event and age of onset of PTSD could account for the discrepancy shown between results of these studies. As underlined by Sussman et al. (2016), in childhood the cerebellum is undergoing a rapid developmental change,

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