

Towards an understanding of the molecular basis of Post Traumatic Stress Disorder

Luca Colnaghi
Eric Kandel Laboratory
Columbia University in the City of New York
Department of Neuroscience

Index

1- Post Traumatic Stress Disorder

2- Why study PTSD

3- Definition of PTSD

4- History of the disorder

5- Biology of the disorder

6- How are subjects with PTSD treated?

7- Could we find a better treatment?

1- Post Traumatic Stress Disorder

Post traumatic stress disorder (PTSD), the fourth most common psychiatric diagnosis in the US, is an anxiety disorder that can develop after exposure to a traumatic event that threatens a person's physical integrity, such as natural disasters, violence and combat-related trauma (1). Estimates are that up to 90% of all people in the US will be exposed to a severe traumatic event during their lifetime. However, only 5-10% of them will develop PTSD (2), suggesting that the prevalence of PTSD is relatively low. Yet, the rates of lifetime PTSD are closer to 20–30% in highly exposed trauma populations, such as low-income urban populations, prison inmates, rape victims and soldiers. It is still unclear why some subjects develop PTSD after a traumatic event, but the condition is most likely caused by a complex interaction between environment, genomic background and experiences. Indeed, recent studies have demonstrated a strong correlation between trauma frequency and PTSD development, such that the more traumatic events a person experiences, the greater the likelihood to develop PTSD.

2- Why study PTSD

PTSD is still a poorly understood disorder, with a devastating impact on the life, health, families and jobs of thousands of subjects. Providing additional insights into the molecular mechanisms of PTSD, our research may inform the design of novel diagnostic, prognostic, and pharmacological interventions for the treatment of this condition. With the goal of improving the life of thousands of individuals.

3- Definition of PTSD

Following a life threatening episode, most of the victims and the witnesses develop an acute stress response called Acute Stress Disorder (ASD) that can last from a few days to up to four weeks. The Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association describes the ASR with the following criteria:

1. During or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:
 - 1.1 Sense of numbing, detachment, or absence of emotional responsiveness
 - 1.2 Reduction in awareness of surroundings (e.g., “being in a daze”)
 - 1.3 Derealization
 - 1.4 Depersonalization
 - 1.5 Dissociative amnesia
- 2 The traumatic event is persistently re-experienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event
- 3 Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people)
- 4 Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness)
- 5 The disturbance causes significant distress or impairment
- 6 The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event

- 7 Disturbance is not due to the effects of substance use or medical condition or is not better accounted for by brief psychotic disorder, and is not merely an exacerbation of a preexisting Axis I or II disorder

However, as time goes on, the intensity of ASD and the number of individuals who manifests these symptoms considerably decrease. Yet, a subgroup of trauma survivors will develop PTSD, a chronic stress disorder.

Following studies on Vietnam War veterans during the late '70s, in 1980 PTSD was recognized as a disorder with specific symptoms that could be reliably diagnosed and was added to the American Psychiatric Association's DSM, and the diagnostic criteria are as follow:

1. The traumatic event is persistently re-experienced in at least **one** of the following ways:
 - 1.1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.
 - 1.2. Recurrent distressing dreams of the event.
 - 1.3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated).
 - 1.4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
 - 1.5. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

2. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma)
 - 2.1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
 - 2.2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
 - 2.3. Inability to recall an important aspect of the trauma
 - 2.4. Markedly diminished interest or participation in significant activities
 - 2.5. Feeling of detachment or estrangement from others
 - 2.6. Restricted range of affect (e.g., unable to have loving feelings)
 - 2.7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)
3. Persistent symptoms of increasing arousal (not present before the trauma)
 - 3.1. Difficulty falling or staying asleep
 - 3.2. Irritability or outbursts of anger
 - 3.3. Difficulty concentrating
 - 3.4. Hyper-vigilance
 - 3.5. Exaggerated startle response
4. Duration of the disturbance (symptoms in 1, 2, and 3) is more than one month
5. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The primary differences between ASD and PTSD are:

1- The duration of the symptoms

As mentioned before, ASD refers to symptoms manifested during the period from two days to four weeks post-trauma, whereas PTSD can only be diagnosed from 4 weeks.

2- The generalized fear typical of subjects with PTSD, but not with ASD

Although fear memory is an evolutionarily conserved mechanism of self-preservation, when these memories are triggered by irrelevant cues of everyday life they become extremely debilitating. In people affected by PTSD, learned fear (the memory of the trauma) caused by the traumatic event becomes generalized to situations that would normally be considered not threatening.

3- The ASD's emphasis on dissociative reactions to the trauma.

Dissociative symptoms include reduced awareness of one's surroundings, de-realization, de-personalization or emotional numbing.

Although temporally separated, I think ASD and PTSD are more linked than we can currently appreciate. Preceding it, ASD has been described as one of the most significant predictors of PTSD in several studies. Most likely, as also suggested by some preliminary evidence that I will present on Wednesday, in the days after the traumatic event (during ASD), still uncharacterized changes in the structure of brain circuits happen, leading to the development of PTSD.

4- History of the disorder

The study of the human psychological reaction to traumatic events started with the analysis of the soldiers' behavior during and after combat. Some of the first observations

date back to the American Civil War, when physicians reported that a large number of soldiers suffered from generalized weakness, heart palpitations and chest pain. Using terms such as “soldier’s heart” or “irritable heart” to describe what they thought was a biological response to physical stress. It was only in the 20th century that psychiatrists started to link the fatigue, exhaustion and anxiety experienced by soldiers to the threat of death or physical integrity during combat. During War World I, British psychiatrist were the first one to describe symptoms of ASD in soldiers, the symptoms comprised physical and psychological components, including crying, trembling, paralysis, stupor, mutism, deafness, blindness, anxiety attacks, insomnia, confusion, amnesia, hallucinations, nightmares, heart problems, vomiting, and even intestinal disorders. Their observations where the basis for the modern psychological support in military operations. Following those studies, the Americans optimized the psychological support to troops after combat during World War II, the Korean War and the Vietnam War. While during the first two world wars, less than 40-50% of the neuropsychiatric victims returned to battle, during the Korean and Vietnam Wars more than 80% of the soldiers with ASD returned to combat. While psychiatrists did a remarkable job in understanding and successfully treating ASD, I think they were also one of the primary causes of the high percentage of Vietnam and Korean Wars veterans affected by PTSD in later years. It is now clear that continuous exposure to trauma is a leading cause of PTSD, and forcing war veterans to be repeatedly traumatized during several battles could have increased the risk of developing PTSD.

Another leading cause of PTSD in Vietnam veterans could have been the fact that upon returning to the United States they were often reviled instead of celebrated as heroes, likely worsening their neuropsychiatric disabilities.

Just to give you some numbers, between 30 and 50% of Vietnam Veterans

displayed symptoms of PTSD at one time or another (3). Although it is impossible to make any scientific comparison with the PTSD rate of WWI and WWII veterans (due to the lack of epidemiological data), it is believed that the Vietnam Veterans were the one with the highest rate.

5- Biology of the disorder

PTSD is a very complex disorder, where subjects express several symptoms: from anxiety to depression, from generalized fear to hallucinations. This variety makes the condition extremely difficult to study. However, during the past decade there has been great progress in starting to understand the biological roots of the disorder. Scientists have found that the neural structures most altered in PTSD belong to the limbic system, a network of brain regions that regulate emotional processing both in humans and animals, and the tightly connected prefrontal cortex (PFC).

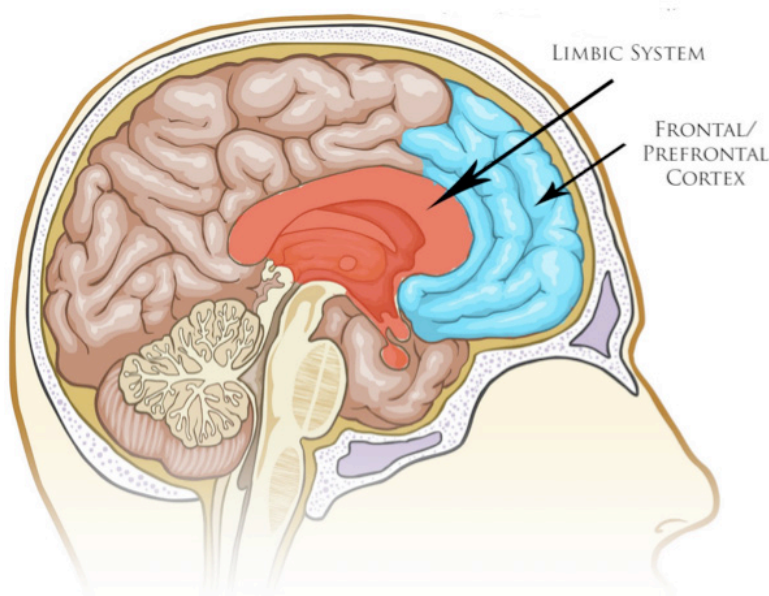


Figure 1. Cartoon showing the position in the brain of the Limbic System and the Prefrontal Cortex.

Specifically, neuroimaging studies reported drastic effects on the amygdala, the hippocampus and the aforementioned PFC.

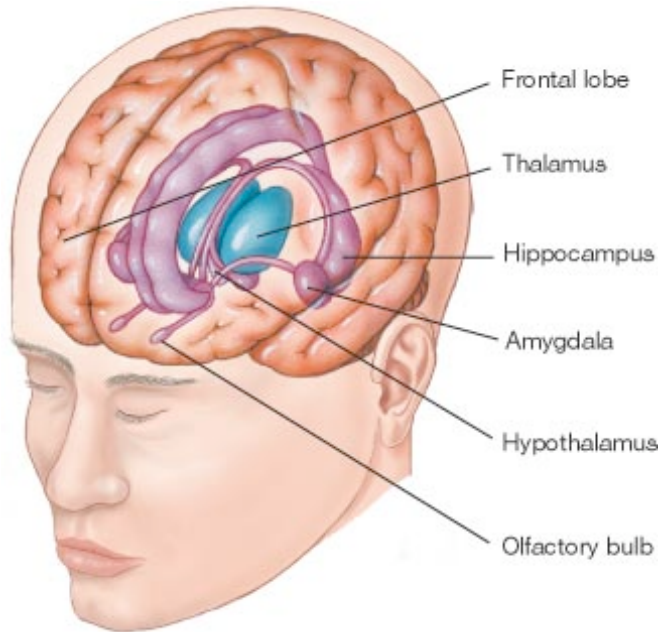


Figure 2. Cartoon showing the components of the Limbic System.

The amygdala is the center of fear learning and storage and most importantly of assessment of threat-related stimuli (7). The PFC is involved in extinction and the retention of fear and it is well connected to the amygdala, while the hippocampus encodes context during fear learning, projecting to the amygdala. Given their roles, it comes as no surprise their involvement in the biology of the syndrome. What scientists have found is that subjects with PTSD show hyper-activity of the amygdala paired to hypo-activity of the prefrontal cortex and likely of the hippocampus (4).

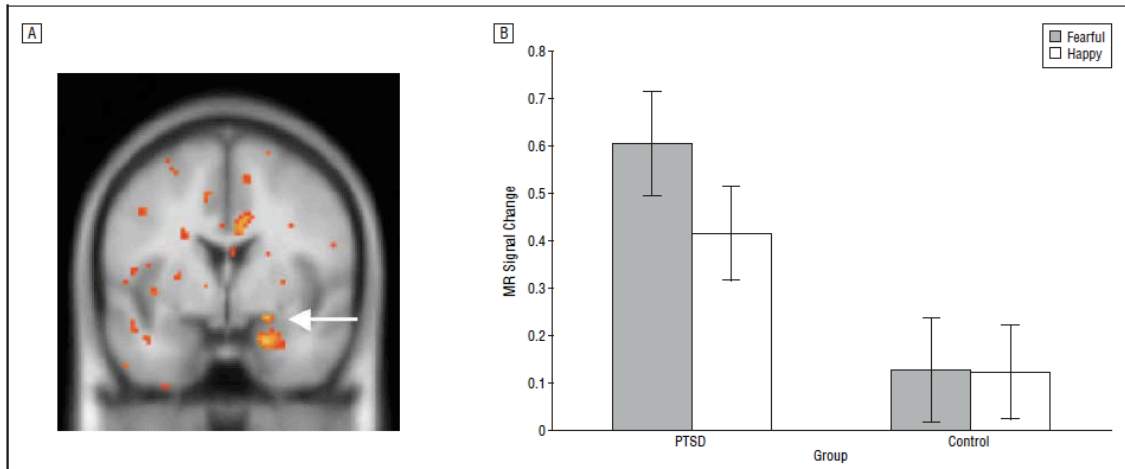


Figure 3. The functional magnetic resonance (MR) image (A) displays activation to fearful vs happy facial expressions in the amygdala. In B the quantification.

While the aberrations in the hippocampus seem a secondary effect of the disorder, the amygdala and the prefrontal cortex are casually involved in the pathogenesis of PTSD. A study on a sample of Vietnam War veterans, who suffered brain injuries and combat-related traumatic events, determined a significant reduction of the prevalence of PTSD among those individuals with lesions in the PFC and, strikingly, absence of PTSD among the ones with amygdala lesions. Furthermore, unilateral lesions of the amygdala are enough to prevent the onset of the disorder. Suggesting the importance and central role of the amygdala and the PFC in the development of PTSD (5).

My research is therefore focused on the amygdala and the PFC.

6- How are subjects with PTSD treated?

Broadly, there are two main approaches to treatment: pharmacotherapy and cognitive or behavioral therapy. And neither one is very effective.

My research focuses on the pharmacological approach to the treatment of the disorder. Serotonin selective reuptake inhibitors (SSRIs) are currently the most recommended pharmacological treatment for PTSD (7). They are a class of antidepressant, among which Prozac, or fluoxetine, is the most popular. However, their therapeutic effects are limited, since patients have been shown to develop resistance to them. Additionally, SSRI treatments in some patients lead to exacerbation of PTSD symptoms, such as depression.

7- Could we find a better treatment?

The fear circuit in the brain is well conserved from mice to humans (6). Could we take advantage of that to learn more about the biology of the syndrome to inform the design of novel diagnostic, prognostic, and pharmacological interventions for the treatment of this condition? Maybe... See you on Wednesday!

8- References

1. Jovanovic, T., and Ressler, K.J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am J Psychiatry* 167, 648-662.
2. Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., and Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62, 593-602.
3. Kulka, R.A., Schlenger, W.A., Fairbanks, J.A., Hough, R.L., Jordan, B.K., Marmar, C.R. and Cranston, A.S. (1990). Trauma and the Vietnam War generation: Report of findings from the National Vietnam Veterans Readjustment Study. New York:

Brunner/Mazel.

4. Shin, L.M., Rauch, S.L., and Pitman, R.K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci* 1071, 67-79.
5. Koenigs, M., Huey, E.D., Raymond, V., Cheon, B., Solomon, J., Wassermann, E.M., and Grafman, J. (2008). Focal brain damage protects against post-traumatic stress disorder in combat veterans. *Nat Neurosci* 11, 232-237.
6. Siegmund, A., and Wotjak, C.T. (2006). Toward an animal model of posttraumatic stress disorder. *Ann N Y Acad Sci* 1071, 324-334.
14. Tye, K.M., Prakash, R., Kim, S.Y., Fenno, L.E., Grosenick, L., Zarabi, H., Thompson, K.R., Gradinaru, V., Ramakrishnan, C., and Deisseroth, K. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature* 471, 358-362.