Stress, evolution and Barbra Streisand

A neuroscientific account of PTSD symptomatology

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Introduction

In recent years, a large amount of evidence on posttraumatic stress disorder (PTSD) and the stress system has been published. In this paper we will attempt to analyse and interpret some of the evidence to come to a better understanding of the disorder. First, we will give some insight in the behavioral associated with PTSD. Next, we will consider the stress system from an evolutionary and a cognitive perspective. We will then use the available evidence to create a neuroscientific model of the stress system. Using this model, we attempt to explain the behavior associated with PTSD in terms of deficits in regard to the stress system. Finally, we will propose subsequent research to come to a better understanding of the neural substrates involved in human stress behaviors and PTSD in particular. We will illustrate our findings by applying our model to the case study of Barbra Streisand.

Case study

Approximately 50 years ago, in 1967, the well-known singer and actress Barbra Streisand forgot the lyrics of her song during a concert (Santopietro, 2007). This resulted in an extreme fear to get on stage. She did not perform in front of people for 27 years. Only after extensive research she could perform again. Based on our knowledge of PTSD symptomatology we suggest that Streisand developed and suffered from PTSD.

PTSD symptomatology

PTSD is a mental health condition which is experienced by people who have been traumatised by certain stressful events (Hamblen et al., 2009). In most cases, patients suffer as a result of experiencing warfare, sexual assault, traffic collision or, as with Barbra Streisand, major threats in personal life. A majority of people who are exposed to such traumatic events, are experiencing symptoms such as flashbacks, nightmares, uncontrollable thoughts about the event and severe anxiety (Keane et al., 1995), leading to avoidance behavior. The symptoms are closely linked to the stress system. We will attempt to come to a better understanding of this system by discussing the evolutionary roots.

Evolutionary roots of stress

From an evolutionary standpoint, the stress system is extremely important. Selection pressures presumably promoted the development of stress as an essential feature of our defense system. When our cognitive system interprets a stimulus as threatening, this will often result in avoidance of the stimulus. The stress system, in this respect, is adaptive, as it helps us to cope with potential danger. However, when the stress system becomes hyperactive, this can result in dysfunctionalities in life, as can be represented by the case study of Barbra Streisand.

Cognitive model of stress

We can explain the stress system in the cognitive perspective by dividing it into three components: the threat detection mechanism, the stress response and fear extinction processes. The threat detection mechanism is used to become aware of dangerous events. If a stimulus is considered dangerous, body and brain need to be activated in order to respond appropriately. This process is mediated by fear learning and fear extinction processes.

We learn to associate certain stimuli with danger through fear conditioning (Pavlov et al., 2003). When a neutral stimulus (e.g. performing) gets paired with an unconditioned frightening stimulus that evokes an unconditioned stress response in us (e.g. a feeling of humiliation), we link the neutral stimulus to the unconditioned response. The neutral stimulus will then become a conditioned stimulus, evoking a conditioned response in the absence of the unconditioned stimulus. Ideally, if the conditioned stimulus later turns out to be safe, extinction will set in.

Neural scheme of the stress system

Next, we will try to develop a neural model of the stress system. Of course, it has to be noted that we cannot account for all the different brain regions and interconnections underlying this system. Also, we have to point out that the presented model (fig. 1) is merely our own interpretation of a subset of the evidence on the subject. Still, we will attempt to combine the available data in a systematic manner. We will mainly focus upon the interactions between the amygdala (AM), the locus coeruleus (LC), the medial prefrontal cortex (mPFC) and the hypothalamic–pituitary–adrenal axis (HPA axis).

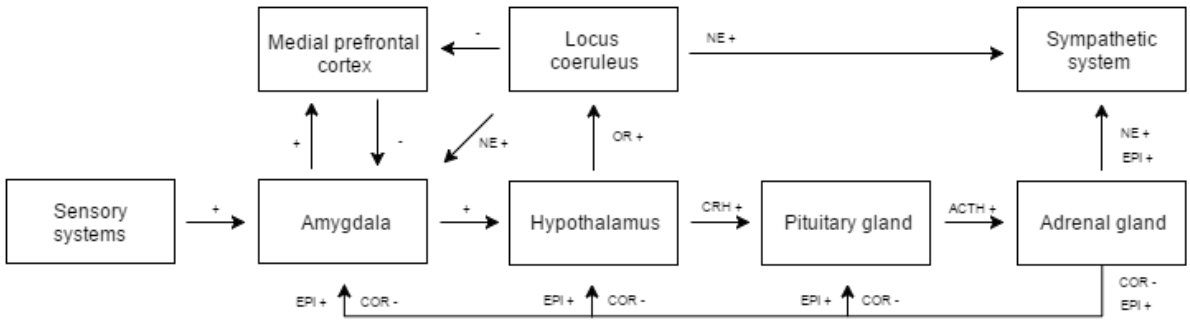

Figure 1. *A schematic overview of our neuroscientific model of the stress system. The model contains the relevant brain regions and connections. Arrows indicate the direction of signaling. A plus indicates an excitatory connection while a minus indicates an inhibitory connection. The letters next to the arrows stand for the chemicals associated with the connections. amygdala (AM) serves as a threat detection mechanism. When a stimulus is perceived to be threatening, the AM outputs to the hypothalamus (HTH). The HTH produces orexin (OR) to project upon the locus coeruleus (LC). The LC immediately excites the cortex and the sympathetic nervous system through noradrenergic (NE) connections. At the same time, the HTH secretes corticotropin releasing hormone (CRH), causing the pituitary gland to secrete adrenocorticotropic hormone (ACTH). The adrenal gland then releases the hormones epinephrine (EPI), NE and cortisol (COR) into the bloodstream. NE and EPI further stimulate bodily responses. Furthermore, EPI further stimulates the hypothalamic-pituitary-adrenal axis (HPA axis) and the AM. Simultaneously, COR acts as a negative feedback mechanism, deactivating the HPA axis and the AM to restore the hormonal balance. Finally, the medial prefrontal cortex (mPFC) is reciprocally connected to the AM, enabling the mPFC to deactivate the AM.*

The AM is hypothesized to be an important factor in threat assessment. Evidence for this claim is found in studies with patient SM, who has bilateral and exclusive AM damage, as caused by Urbach Wiethe Disorder (UWD). In a study by Feinstein et al. (2011), SM was exposed to real spiders and snakes, scary movies and taken to a haunted house. Patient SM never showed any overt fear responses and she reported feeling no more than limited levels of fear.

Some important subdivisions within the AM can be made. The basolateral amygdala (BLA) is hypothesized to be important in fear regulation. This is supported by the finding that BLA lesions due to UWD in South African patients were linked to hypervigilance (Terburg et al., 2012). The regulatory role in fear for the BLA could be linked to serotonergic connections with the central nucleus of the amygdala (CeA) (Christianson et al., 2010), a structure that is thought to be important in fear expression (Pare et al., 2012). Stimulation of cells in the lateral amygdala (LA), paired with an auditory stimulus, resulted in fear responses to the stimulus in absence of the stimulation (Johansen et al., 2010). This may indicate that fear learning involves an activation of the LA by aversive stimuli.

The CeA projects to the hypothalamus (HTH) (Makino et al., 1994), triggering a cascade of subsequent reactions. The HTH excites the LC (Hagan et al., 1999). The LC synthesizes norepinephrine (NE), which activates the sympathetic nervous system, initiating bodily responses such as an acceleration of heart rate, an increase in sweat secretion and a dilation of the pupils (Valentino et al., 1983). Additionally, the LC regulates arousal in the brain (Sara et al., 2012). The LC thus, in our model, lies at the basis of the acute fight-or-flight response, while it is also an import factor in mediating cognitive processes. The LC has noradrenergic connections with the BLA. It was shown in a recent review that NE in the AM is highly involved in memory acquisition. The same review showed that multiple studies found that more arousal due to elevated NE activations leads increased memory consolidation. Furthermore, activation in the AM correlated with the strength of the memory (McIntyre et al., 2012).

Simultaneously, the HTH secretes corticotropin-releasing hormone, activating the pituitary gland (PIT) (Frankenhaeuser et al., 1985). The PIT, in turn, secretes adrenocorticotropic hormone, causing the adrenal gland to secrete epinephrine (EPI), NE and cortisol (COR). EPI and NE are hypothesized to lead to a further stimulation of bodily responses to stress. COR, in turn, serves as a feedback mechanism. When the stressor is removed, COR acts on the glucocorticoid receptor (GR) in the AM, PIT, HTH and the hippocampus, restoring the original hormone levels (Yehuda, 2002). The activity of the LC is also influenced by the sensitivity of the GR. We suggest that an increased sensitivity of the GR leads to lower levels of COR. The inhibition of the HTH would then be reduced, leading to an increase in LC activation.

The mPFC is hypothesized to be important in fear conditioning processes. It is widely accepted that the mPFC stimulates the BLA, that in turn inhibits the CeA (Marek et al., 2013). In a study with rats, by Milad et al. (2004), a conditioned tone was paired with a brief stimulation of the infralimbic region within the mPFC. A flight response, as a result of AM stimulation, was inhibited after a stimulation 0,1 seconds before the onset of the tone, but not for a stimulation 1 second before or after onset of the tone. From this study, we conclude that the mPFC may function as a gating mechanism in fear responses. It is hypothesized that the mPFC helps us to learn new associations when an unconditioned stimulus is presented in the absence of a conditioned stimulus (Quirk et al., 2006). We believe the connections between the mPFC and the AM might have evolved to regulate emotional learning mechanisms. The signalling between the mPFC and the AM might thus underlie fear extinction processes.

Explaining PTSD

The aim of this paper is to explain PTSD symptomatology by elucidating potential dysfunctionalities within the stress system. As we enumerated earlier in this paper, common symptoms are severe anxiety, uncontrollable thoughts, flashbacks and nightmares.

First, we will briefly consider a cognitive perspective towards PTSD. Patients show an attentional bias towards threat in emotional processing tasks, such as the emotional Stroop task and dot probe tasks involving facial expressions, in comparison to controls (Fani et al, 2012). This finding indicates a state of hypervigilance in PTSD patients. Furthermore, Blechert et al. (2007) showed in a fear conditioning experiment that the extinction of skin conductance responses to a conditioned stimulus is delayed in PTSD patients, when compared to healthy subjects. From this study, we conclude that PTSD may partly result from disrupted fear extinction processes.

Blood samples show lower levels of COR in PTSD patients than in healthy controls (Mouthaan et al., 2014). It has to be noted, however, that not all studies find significant results (Meewisse, Reitsma, De Vries, Gersons & Olff, 2007). Still, it is hypothesized that this reduction is due to an excessive negative feedback mechanism of COR, as a result of an increased sensitivity of the GR (Yehuda, 2002). Since COR levels in PTSD patients are lower, the

inhibition of the HTH is reduced, leading to an increase in HTH activation. This causes the HTH to send stronger excitatory signals to the LC, resulting in elevated NE synthesizing (George et al.,2013). This increase in NE synthesizing may underlie many aspects of the PTSD symptomatology.

As we described earlier, the LC stimulates the AM through noradrenergic signals. This connection is also important to memory acquisition processes. As the synthesizing of NE is elevated, memory consolidation during the acquisition phase might be intensified. This, we suggest, explains the nightmares and flashbacks as experienced by PTSD patients. This view is supported by the finding that prazosin, an antagonist of the α1-adrenergic receptor, is effective in reducing occurrences of nightmares in PTSD patients (Aurora et al., 2010).

High levels of NE may also lead to a decrease in mPFC activation (Arnsten et al., 2015). This finding is consistent with activation patterns in PTSD, as observed during brain imaging studies. A review by Shin et al. (2006) detailed much evidence of reduced mPFC activation in exposure to traumatic narratives and tasks involving emotional processing in PTSD patients relative to controls. Since the mPFC might be involved in fear extinction processes, we suggest that dysfunctionalities in the connectivity between the mPFC and the AM, may lead to hyperactivity in the AM. Multiple studies found relations in PTSD patients between high activity of the AM and the hypervigilant behavior after detecting fearful stimuli (El Khoury-Malhame et al., 2011; Shin et al., 2010). Moreover, the severity of certain anxiety symptoms is proportionally related to activity in the AM (Protopopescu et al., 2005). Hyperactivity in the AM, as a result of increased noradrenergic stimulation through the LC and a decrease in inhibitory signaling from the mPFC, may therefore be an important aspect underlying the severe anxiety and avoidance behavior in PTSD patients.

Conclusion

From an evolutionary standpoint, the stress system is of utmost importance. It enables us to adequately cope with potential danger. If, however, the stress system becomes hyperactive, as is the case in PTSD patients, this may lead to dysfunctionalities in life. The AM is an essential factor in this aspect. Hyperactivity in this area may lead to hypervigilance, which may underlie

many PTSD symptoms, including severe anxiety and avoidance behavior. Furthermore, it is likely that extinction processes are complicated as a result of disrupted connections between the mPFC and the AM. This may also explain the extremely long duration of the symptoms.

This brings us back to the case study of Barbra Streisand. The reason she did not perform for almost thirty years, may very likely be caused by a combination of hypervigilance and disabilities regarding to her fear extinction system. She learned to associate performing in front of people with humiliation. This may have led her to be extremely alert, in order to avoid a similar situation in the future. At the same time, she was unable to disrupt the established associations through fear extinction mechanisms. These factors combined may have led Barbra Streisand to avoid the stage for 27 years.

Discussion

In our paper, we attempted to explain the symptoms of PTSD by developing a neural model of the stress response. Therefore, the validity of our explanations of the PTSD symptomatology depends on the validity of our neuroscientific model. As we pointed out earlier, our model contains a highly simplified view of all the cortical areas and connections involved. Our model, for example, does not account for the fact that imaging studies show declined activations and decreased volumes of the hippocampus in PTSD patients, compared to healthy controls (Shin et al., 2006).

However, the most important mechanism to further investigate is in our view the role of the AM-mPFC coupling in fear extinction. A study from van Wingen et al. (2000) showed that testosterone acts upon this specific interaction. Testosterone might reduce the coupling between the AM and the mPFC. This would reduce the regulatory control of the mPFC over the AM. Furthermore, it is also found that administration of cortisol might have positive effects on fear extinction processing (Dominique et al., 2011). Therefore, we are interested to see future studies hypothesizing negative effects of testosterone administration on fear extinction learning. This hypothesis could be tested by using a classical conditioning paradigm on human phobics. A neutral stimulus, such as a tone, could be linked to an unconditioned fear evoking stimulus, such as a picture of a spider (if the participants are arachnophobes). When this link would be

established, the tone should be presented in the absence of the unconditioned stimulus, and this should be repeated over a few time intervals. Fear responses could be indicated by measuring skin conductance responses. Participants could be divided in two groups. One group should then be administered testosterone, while administering a placebo to the other. It would then be interesting to see if skin conductance responses decline faster in the control group, when compared to the placebo group. If that would be the case, it might be concluded that testosterone has a negative effect on fear extinction learning. While this would be further evidence for our model, such results might also have implications for the treatment of PTSD.

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