Review

Dysfunctional or Hyperfunctional? The Amygdala in Posttraumatic Stress Disorder Is the Bull in the Evolutionary China Shop

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Our motivation in writing this Review arose not only from the great value in contributing to this special issue of the Journal of Neuroscience Research but also from the desire to express our opinion that the description of the amygdala as “dysfunctional” in posttraumatic stress disorder (PTSD) might not be appropriate. We acknowledge that excessive activation of the amygdala contributes to the cluster of PTSD symptoms, including hypervigilance, intrusive memories, and impaired sleep, that underlies the devastating mental and physical outcomes in trauma victims. The issue that we address is whether the symptoms of PTSD represent an impaired (dysfunctional) or sensitized (hyperfunctional) amygdala status. We propose that the amygdala in PTSD is hyperfunctional rather than dysfunctional in recognition of the fact that the individual has already survived one life-threatening attack and that another may be forthcoming. We therefore consider PTSD to be a state in which the amygdala is functioning optimally if the goal is to ensure a person’s survival. The misery caused by a hyperfunctional amygdala in PTSD is the cost of inheriting an evolutionarily primitive mechanism that considers survival more important than the quality of one’s life.

Key words: PTSD; amygdala; evolution; hippocampus; hyperfunctioning

The editors of this special issue of the Journal of Neuroscience Research have taken on an admirable task in addressing how amygdala dysfunction contributes to psychiatric conditions such as posttraumatic stress disorder (PTSD). Although we applaud their efforts, we question whether the term “dysfunction” is an appropriate description of the status of amygdala functioning in PTSD. We recognize that PTSD is a condition that describes devastating mental and physical outcomes in trauma victims involving unrelenting symptoms that include hypervigilance, intrusive memories, and impaired sleep and cognition. The issue addressed here is whether the brain, specifically the amygdala, should be considered to be dysfunctional in a person who has developed PTSD.

In this Review, we address the issue of amygdala functioning in PTSD at two levels. First, we describe the consensus on the routine use of the descriptor “dysfunctional” in terms of brain structure functioning. It is potentially of benefit to understand the distinction between a dysfunctional and a hyperfunctional state of amygdala activity in PTSD. Second, we speculate on the relevance of amygdala functioning in PTSD in terms of its evolutionary fitness. Our view is that, in people with PTSD, the amygdala is so protective of the individual’s

SIGNIFICANCE:
Posttraumatic stress disorder (PTSD) is a unique psychiatric disorder in which a person has a horrific and potentially life-threatening experience that produces devastating mental and physical outcomes. The issue that we address is whether the symptoms in PTSD reflect an impaired (dysfunctional) amygdala or one that has become overly sensitized (hyperfunctional). Our opinion is that, in PTSD, evolutionarily primitive mechanisms have been activated to produce a hyperfunctional rather than a dysfunctional amygdala. We further suggest that a remittance of symptoms can be accomplished in a person with PTSD with therapy that returns the amygdala to its normative level of functioning.

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survival against all potential threats that it acts in a hyperfunctional albeit self-destructive manner.

WHAT CONDITIONS DESCRIBE A DYSFUNCTIONAL BRAIN STATE?
The first task is to define the term “dysfunctional” in the context of routinely described forms of abnormal physiology and health. A typical example of the use of the term dysfunction in a neurological context is “motor dysfunction,” in which impaired functioning of a brain motor area, as a result of a stroke or disease, interferes with an individual’s ability to make fine or gross movements, control tremors, or initiate voluntary movements (Thobois et al., 2005; Cortes et al., 2012; Ross et al., 2014; Finney, 2015). Another example of dysfunction in common usage is “cognitive dysfunction,” in which impairment of intellectual functions, including processes involved in strategizing, memory storage and recall, and reasoning, is of sufficient severity to interfere with aspects of cognition. Cognitive dysfunction describes various forms of dementia in which brain structures are damaged or diseased, such as in Alzheimer’s disease, aphasia, agnosia, and vascular dementia, all of which are recognized as failures of brain structures to accomplish their functions (Monza et al., 1998; Lanzino et al., 2002; Chen et al., 2013; Neha et al., 2014; Choi and Park, 2015; Schultz et al., 2015). One specific and widely used subset of cognitive dysfunction is “hippocampal dysfunction,” which describes memory impairments that develop as a result of adverse effects on the hippocampus caused by drugs, disease, damage, or stress (Schott, 2008; Roth et al., 2011; Small et al., 2011; Acheson et al., 2012; Pitman et al., 2012; Son et al., 2014; Lucchi et al., 2015; Pirnia et al., 2015).

A stark contrast to conditions of cognitive dysfunction is hypernesia, which is the enhancement of memory produced by repetition or emotion (Lanza, 1881; Stratton, 1919; Roediger and Payne, 1982; Mulligan, 2005; Hurlemann, 2006; Otani et al., 2008), as well as hyperthymesia, which is the abnormal and extraordinary capacity of some individuals to exhibit great accuracy in the retrieval of their autobiographical memories (Parker et al., 2006; Leport et al., 2012; Ally et al., 2013; Patihis et al., 2013). In one case in which memory testing and brain imaging were conducted for a person with hyperthymesia, the only brain structure with increased volume was the amygdala (Ally et al., 2013). Moreover, in the subject with hyperthymesia, the amygdala displayed significantly greater connectivity with the hippocampus than was found in controls. The authors conjectured that, in this individual, the amygdala “…is hyperactive, resulting in emotionally benign information being processed in a self-relevant affective manner.” Thus, evidence of an abnormally strong memory and a greater linkage between the amygdala and the hippocampus was interpreted as a form of amygdala hyperfunction that produced extraordinarily accurate retrieval of autobiographical memories.

It is worth noting that enhanced memory processing by individuals with hyperthymesia or hyperhyphasia has never been characterized as a form of dysfunctional brain processing. Across studies, evidence of greater than normal functioning of a brain structure is routinely referred to as a hyperactive or hyperfunctional state. By contrast, the term “dysfunctional” is routinely used to describe a condition or disease in which a brain structure fails to perform its function.

WHAT IS AMYGDALA FUNCTION AND DYSFUNCTION?
We can now summarize the normative function of the amygdala within the context of the routinely used characterizations of hyperfunction and dysfunction described previously. Decades of research with humans and animals have thoroughly described amygdala functioning under control (i.e., imaging) and experimental (i.e., localized damage) conditions as well as in brain disease states. In general, the amygdala is described as being an essential brain structure for the formation of emotional memories, particularly in the processing of fear-provoking experiences (Fanselow and Gale, 2003; Rauch et al., 2003; McGaugh, 2004; Phelps and LeDoux, 2005; Sigurdsson et al., 2007; Kim et al., 2011; Pare and Duvarci, 2012). More broadly, the amygdala is a central component of a brain pathway devoted to predator-based (instinctual, life-threatening) responses and conditioned fear (LeDoux, 1998; Rosen, 2004; Rosen et al., 2008; Canteras et al., 2012). Thus, the amygdala is critically involved in different forms of instinctual and learned fear and in modulating attention to fear-related stimuli as well as fear recognition and perception. Although the scope of information that is processed by the amygdala is not limited to fear-provoking cues (Burgdorf and Panksepp, 2006; Berridge et al., 2010; Pessoa, 2010; Markowitsch and Staniloiu, 2011; Chau and Galvez, 2012; Fernando et al., 2013; Hermans et al., 2014), extensive research suggests that fear-provoking stimuli are prominently featured in the domain of amygdala functioning (Phillips et al., 1998; Phelps and LeDoux, 2005; Johansen et al., 2012).

In addition to research on fear conditioning, primarily in rodents with amygdala damage or inactivation (Fanselow and Gale, 2003; Maren, 2008; Chau and Galvez, 2012; Johansen et al., 2012; Hermans et al., 2014), naturalistic disease conditions have provided insight into the consequences of a failure of the amygdala to function properly (i.e., dysfunction). Research on people with Urbach–Wiethe disease, in which there is a selective atrophy of the amygdala, has provided strong evidence that the loss of amygdala functioning leads to impaired fear responses and emotional memory processing (Markowitsch et al., 1994; Cahill et al., 1995; Hurlemann et al., 2007; Klumpers et al., 2014). It is notable that emotion per se can be experienced by individuals with atrophy of their amygdala (Markowitsch and Staniloiu, 2011). Indeed, people with Urbach–Wiethe disease can express enjoyment and even a thrill at experiencing stimuli that
would be viewed as terrifying by amygdala-intact people (Feinstein et al., 2011). For example, the person with Urbach-Wiethe disease described by Feinstein et al. (2011) was so fearless that she put herself in harm’s way by approaching live venomous snakes and spiders. Therefore, we suggest that a core feature of amygdala function is to activate a fear-based sensory and cognitive system that enhances one’s survival by hindering an individual from engaging in unnecessary exposure to life-threatening stimuli.

In a very different but complementary approach, researchers examined the effects of *Toxoplasma gondii* on the brain, with an emphasis on assessing amygdala functioning and behavior in infected rats and people (Berendeiterova et al., 2011; Mitra et al., 2013; Hari Dass and Vyas, 2014). This protozoan parasite forms cysts in the brains of warm-blooded animals, including rodents and humans (Innes, 2010). Extensive research has demonstrated that rodents infected with *T. gondii* show a reduction in their innate aversion of cats and their odors. Moreover, *T. gondii*-induced changes in behavior appear to be specific to the loss of fear of a predator, such as a cat, because fear responses and memory for nonpredator forms of aversive cues (e.g., paw shock) remain intact (Vyas et al., 2007). It is intriguing that *T. gondii* not only suppresses predator-based fear responses but also appears to increase the appeal of the predator to the rat (Berdo et al., 2000; House et al., 2011). The basis of the shift from fear expressed in response to a predator to an appetitive (i.e., sexual) response by a rat to a cat appears to involve the targeting of the amygdala by *T. gondii* (Berendeiterova et al., 2011; House et al., 2011; Mitra et al., 2013; Hari Dass and Vyas, 2014). Thus, there is strong evidence that *T. gondii* produces a dysfunctional response in the amygdala that is manifested as an increase in the likelihood that a rat will be killed by a cat.

The evolutionary basis for the “rewiring” of the brains of infected hosts is that *T. gondii* has a life cycle that includes reproducing asexually within any warm-blooded animal, but it must return to the digestive system of the cat to undergo sexual reproduction (Carruthers and Suzuki, 2007; Flegr and Markos, 2014). Infection from the cat is transmitted to a host (e.g., a rodent or human) that ingests cysts in undercooked meat or in oocysts in cat feces, which results in the formation of cysts in the brain (and other organs) of the host. Hence, when *T. gondii* reduces a rat’s fear of a cat, it increases rat predation rates, thereby facilitating the completion of the life cycle of *T. gondii* because the cysts in the rat tissue return to the digestive system of the cat (Carruthers and Suzuki, 2007; Innes, 2010; Flegr and Markos, 2014).

There is strong evidence that the effects of *T. gondii* that have been described in rats are present in infected humans as well. In perhaps the clearest translational evidence of *T. gondii* infection effects on behavior and brain, Flegr et al. (2011) reported that infected men found the odor of cat urine significantly more pleasant than uninfected men. Related work has shown that people who test positive for *T. gondii* in serological assays exhibit personality characteristics different from noninfected individuals, including higher reactive aggression and impulsive sensation seeking (Carruthers and Suzuki, 2007; Cook et al., 2015). In a real-life assay of the consequences of *T. gondii* infection on human behavior, numerous studies have shown that people who have been infected with *T. gondii* are as much as six times more likely to have had a traffic accident than those who were uninfected (Flegr et al., 2002, 2009; Yereli et al., 2006; Galvan-Ramirez et al., 2013). One implication of this finding is that *T. gondii* infection increases a person’s recklessness or at least the ability to respond efficiently in a life-threatening situation. Overall, the *T. gondii* findings from rodent and human subjects support the hypothesis that amygdala dysfunction (i.e., failure to respond appropriately in a life-threatening situation) results in behaviors that put an individual in greater peril of loss of life.

The three examples of amygdala dysfunction described here (i.e., damage or suppression of amygdala activity in animal fear conditioning research, Urbach-Wiethe disease, and infection by *T. gondii*) are all comparable in terms of the consequences of their effects on cognitive and behavioral responses to life-threatening stimuli. In all three cases, affected individuals exhibit insufficient amygdala activation in conjunction with reduced innate (and life-protective) fear responses as well as impaired memory for these experiences. Thus, one component of the normative functioning of the amygdala can be seen as exhibiting a level of activity that optimizes the interplay between curiosity and exploratory behavior to obtain appetitive reward (e.g., foraging for food) and the avoidance of situations that can potentially cause harm and the necessary maintenance of a memory trace for the experience. The optimal functioning of the amygdala in this balance between curiosity and fear has been summarized by Choi and Kim (2010), who postulated that the amygdala “… regulates predation risk–foraging behavior in a dynamic fear environment. Without the amygdala and consequently devoid of fear, the animal’s foraging behavior becomes perilously maladaptive.”

It is also important to note in this context that some people diagnosed with PTSD appear to exhibit insufficient activation (perhaps even an active suppression) of the amygdala at the time of trauma as well as during symptom expression. Specifically, some traumatized people are impaired at managing their emotional control in response to trauma, exhibiting alternating periods of hyperarousal with emotional numbness, which, in its extreme form, is referred to as “dissociation” (Feeny et al., 2000; Frewen and Lanius, 2006). The dissociative subtype of PTSD (American Psychiatric Association, 2013) involves the fragmentation of consciousness, memory, identity, body awareness, and perception and is characterized by blunted emotional and physiological responses to trauma-related stimuli (Lanius et al., 2010; Wolf et al., 2012; Armour et al., 2014b). Whereas subjects with the hyperarousal subtype of PTSD tend to exhibit increased amygdala activity (Rauch et al., 2000, 2003; Pissiota et al., 2002; Shin et al., 2006; Pitman et al.,
than pathology residing solely in the amygdala. Nevertheless, individuals with the dissociative subtype of PTSD exhibit exaggerated features of amygdala hyperactivity, including heightened symptoms of depression, hostility, and sleeping difficulties (Armour et al., 2014a). The dissociative subtype of PTSD has been theorized to involve the excessive activation (overmodulation) by the prefrontal cortex to inhibit transiently the amygdala’s response to traumatic stress and its reminders (Hopper et al., 2007; Lanius et al., 2010). The observation of an overly inhibited amygdala during emotional numbing or dissociation is consistent with the hypothesis that trauma-induced psychopathology is produced by an imbalance between amygdala and frontal cortex activity rather than pathology residing solely in the amygdala.

CONSEQUENCES OF A HYPERFUNCTIONAL AMYGDALA IN PTSD

PTSD is commonly induced by a horrific, life-threatening experience (Hou et al., 2005; Bar-Haim et al., 2010; Wald et al., 2011; Edmondson, 2014). The amygdala bears much of the responsibility for ensuring that an individual survives the life-threatening attack as well as preparing for future attacks. Therefore, in those individuals who develop PTSD, amygdala functioning becomes maximally activated (sensitized) to increase the likelihood of surviving future threats. The amygdala accomplishes this task with two different strategies that we will discuss in turn.

First, as we have discussed previously, the amygdala orchestrates the formation of memories of fear-provoking experiences. Thus, plasticity intrinsic to the amygdala (Sears et al., 2014) as well as amygdala-mediated enhancement of memory-related plasticity in other brain structures (Roozenendaal and McGaugh, 2011) generates memories of life-threatening experiences that can last for a lifetime. The great value of having a structure that provides a readily accessible reference system for life-threatening events with a rapid reactivation in case of re-exposure to related cues is obvious; one’s future survival, even decades later, may depend on the rapid recognition of cues that have been associated with a prior life-threatening event.

An adverse consequence of a hyperactive amygdala that overconsolidates the trauma memory is a pathologically intense and intrusive memory. It is notable that there are features of the intrusive memory in common with the memories described by individuals with hyperthymesia. Hyperthymesia is ordinarily considered to be a beneficial state of amygdala (and hippocampus) hyperfunctioning because the memories that are probed are typically neutral or positive (Parker et al., 2006; Leport et al., 2012; Ally et al., 2013). We suggest, therefore, that enhanced autobiographical memories in nontraumatized and traumatized people share the common feature that they both involve a hyperfunctional state of the amygdala that forms an abnormally strong linkage to the hippocampus (Diamond et al., 2007).

It is important to point out that, in PTSD, the memories are intrusive, pathologically intense, and typically composed of fragmented sensory features of the ordeal that may be accompanied by impaired retrieval of key aspects of the trauma experience (Van der Kolk and Van der Hart, 1991; Van der Kolk, 1994; Brewin and Holmes, 2003; Diamond et al., 2007; for discussion of the amnesia issue see Berntsen and Rubin, 2014). In previous work, we theorized that the fragmented features of traumatic memories are based on a hyperactive state of the amygdala in conjunction with brief but intense synaptic plasticity in the hippocampus during the traumatic experience (Diamond et al., 2007). We proposed that the hyperconsolidation of fragments of the memory by the hippocampus and amygdala focusing primarily on isolated cue-based features of traumatic experiences (Huff and Rudy, 2004; Marschner et al., 2008; Lipka et al., 2011) would explain why avoidance of all cues associated with the trauma and the panic that develop from trauma reminders is a hallmark feature of PTSD symptoms.

Related research on memory and PTSD has demonstrated that the dreams in people with PTSD are different from dreams in nontraumatized people. Ordinarily, dreams are in the form of stories that are not accurate portrayals of daily events. That is, neutral episodic memories “are almost never replayed veridically in dreams,” but, in those with PTSD, “traumatic episodic memories are repetitively (and accurately) replayed in sleep” (Stickgold, 2002). van der Kolk et al. (1984) provided similar observations of people with PTSD, noting that their dreams were aberrant and disturbing because they were exact replicas of the actual (traumatic) events. Thus, under non-trauma conditions, dreams appear to integrate episodic experiences into a more global categorical (semantic, neocortical) network. In the process of categorizing information, however, the accuracy of the episodic experience can be compromised (Hardt et al., 2013; Lane et al., 2015). In theory, the hyperfunctioning amygdala in PTSD interferes with the semantic categorization of the trauma memory, even in sleep, to maximize the veracity of the memory of a life-threatening experience.

Second, the amygdala is intimately connected with cortical and subcortical structures that allow it to be sensitive to sensory cues as well as to cognitive features of fear to activate the fight, flight, or freeze (FFF) response (Mobbs et al., 2015). The FFF response is evolutionarily adapted to optimize survival in advance of or in response to an attack. There are multiple levels of the FFF response that are relevant to amygdala functioning and, ultimately, to PTSD. Activation of the amygdala in response to a real or potential threat enhances long-term memory processing (discussed above) and, furthermore, produces a rapid mobilization of energy, including an increase in blood glucose and cardiovascular activity (increased heart rate and blood pressure; Stock et al., 1981; Seto et al., 1983; al Maskati and Zbrozyna, 1989; Oht a et al., 1991) and an
increase in platelet aggregation and immune activation (Shandra and Glukhov, 1992; Von Kanel et al., 2001; Raison and Miller, 2003). All of these stress responses are adaptive from an evolutionary perspective because they allow an animal under attack to mobilize the necessary cognitive and physiological resources to respond to the threat as well as to prepare for hemorrhage, tissue damage, and pathogen invasion in case a wound is inflicted (Sapolsky, 1994).

These adaptive responses to trauma, which include enhanced attention, sensory, and cognitive processing in conjunction with activation of the FFF response, have great adaptive value if one truly is at risk for a life-threatening attack at any moment. In PTSD, however, the repeated unbidden activation of intrusive memories and the FFF response underlies brain and somatic pathology, including amygdala hypertrophy and impaired hippocampal and prefrontal cortex functioning (McEwen, 2007; Zoladz and Diamond, 2013) as well as an increased incidence of cardiovascular, metabolic, and immunological disorders (Altemus et al., 2006; Violanti et al., 2006; Boscarno, 2008; Gill et al., 2009; Brudet et al., 2015; Williamson et al., 2015). Thus, amygdala-mediated heightened vigilance in PTSD maximizes the likelihood that a traumatized person will not be caught off guard by a predator; however, the loss of sleep, intrusive memories, traumatic nightmares, impaired cognition, and increased susceptibility to a multitude of diseases are devastating to quality of life. The misery caused by a hyperfunctional amygdala in PTSD is the cost of inheriting an evolutionarily primitive mechanism that considers survival more important than the quality of one’s life.

CONCLUSION: THE AMYGDALA IN PTSD IS A BULL IN THE EVOLUTIONARY CHINA SHOP

We consider the metaphor of the bull in a china shop to be of heuristic value in understanding the hyperfunctional status of the amygdala in PTSD. A raging bull confined within a china shop can cause immense destruction as it attempts to escape, but we do not consider the bull or its behavior to be dysfunctional. The collateral damage that the bull causes is incidental to its attempt to achieve the primary goal of escaping from a threatening environment. Similarly, we propose that the amygdala in PTSD is excessively protective (i.e., hyperfunctional) in recognition of the fact that the individual has already survived one life-threatening attack and another may be forthcoming. From the amygdala’s perspective, a state of hypervigilance is justified because the traumatized person appears to be living in an unpredictable, hostile, and threatening world.

Just as a raging bull wreaking havoc in a china shop is acting in an adaptive manner, we consider that the amygdala and overall brain function in PTSD are responding to trauma in an evolutionarily adaptive manner as well. What is abnormal in PTSD are intrusive, pathologically intense, trauma memories acting on a background of insufficient control from the prefrontal cortex and parasympathetic nervous system over a hyperactive amygdala and sympathetic nervous system (Hamner et al., 1999; Semple et al., 2000; Shin et al., 2006; Morris and Rao, 2013; Zoladz and Diamond, 2013). In theory, recovery of normative brain function may be accomplished in a person with PTSD in response to therapy that restores an appropriate level of prefrontal cortex control over amygdala hyperactivity (Levin et al., 1999; Osuch et al., 2009; Novakovic et al., 2011; King et al., 2013; Kip et al., 2013a,b; Bornmann et al., 2014; Marin et al., 2014). Successful therapy for PTSD, therefore, is analogous to calming the bull in the china shop and bringing it to an environment it perceives as safe, thereby allowing balance among brain structures and hormonal systems to be restored.

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