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Emotional modulation of multiple memory systems: implications for the neurobiology of post-traumatic stress disorder

Abstract: In lower animals and humans, stress/anxiety can enhance dorsal striatal-dependent habit memory, at the expense of hippocampal-dependent cognitive memory. The present review considers the potential for this 'stress/anxiety-induced habit bias' to explain some aspects of post-traumatic stress disorder (PTSD). In rats, anxiety induced by peripheral or intra-amygdala infusions of anxiogenic drugs can enhance habit memory and impair cognitive memory. In tasks in which both habit and cognitive memory processes may provide a learned solution, stress and drug-induced anxiety favors the use of habit memory. The effect of stress and anxiety on the use of multiple memory systems in rats depends on the functional integrity of the basolateral amygdala. Thus, under robust emotional arousal, amygdala activation can modulate the relative use of memory systems in a manner that favors habit memory. We propose a similar mechanism may underlie the development and persistence of some PTSD symptoms. The traumatic memories of PTSD patients can be deficient in hippocampus-dependent contextual or autobiographical aspects, and enhanced in responding to trauma-related cues, which we suggest may reflect increased involvement of the dorsal striatum. We briefly consider the potential role of a stress/anxiety-induced habit bias with regard to other psychopathologies, including obsessive-compulsive disorder and drug addiction.

Keywords: anxiety; brain; memory; stress; posttraumatic stress disorder.

Introduction

A major goal of the behavioral sciences is to identify the contributing factors in the development and persistence of human psychopathologies. In the context of learning theory, researchers have developed various stimulus–stimulus or stimulus-response (S-R) learning paradigms that putatively generate ‘experimental neuroses’ in lower animals and have suggested that learning in these situations may reflect the development of neuroses in humans as well (Mowrer, 1947; Wolpe, 1952; Eysenck, 1976). Building on these earlier models and considering the modern ‘multiple brain systems’ approach to learning and memory, recent theories have proposed that the development and persistence of some psychopathologies may arise from the differential involvement of neuroanatomically distinct memory systems (e.g., White, 1996; McDonald et al., 2004; Packard, 2009). More specifically, it has been suggested that some psychological disorders, particularly those characterized by strong habit-like behavioral features, may reflect a shift from the use of a hippocampal-dependent ‘cognitive’ memory system towards a dorsal striatal-dependent ‘habit’ memory system.

In ‘dual solution tasks’ that can be solved adequately with either a habit- or cognitive-based learning system, pre-training, post-training or pre-retrieval drug-induced anxiety biases animals towards the use of habit memory (for a review, see Packard, 2009). This anxiety-induced habit bias may be mediated by a dynamic interplay among the amygdala, hippocampus and dorsal striatum (Packard and Wingard, 2004; Elliot and Packard, 2008; Wingard and Packard, 2008; Packard and Gabriele, 2009). Specifically, in some learning situations that occur under high levels of emotional arousal, activation of the amygdala can modulate memory in a manner that favors the use of dorsal striatal-dependent habit memory over hippocampal-dependent cognitive memory. Considering both the potential role of anxiety and S-R learning in post-traumatic stress disorder (PTSD), it is possible that interactions among the amygdala, hippocampus, and dorsal striatum may under-
lie some aspects of the disorder (Packard, 2009). In the present review, we further examine the stress-induced habit bias as a potential model for the development, persistence and expression of some PTSD symptoms.

We begin by considering the literature on the emotional modulation of multiple memory systems in lower animals, describing research indicating that stress/anxiety can facilitate dorsal striatal-dependent habit memory, and that this effect depends on a modulatory influence of the basolateral amygdala (BLA). In some learning situations, the stress/anxiety-induced bias towards the use of habit memory may arise via an impairing effect on hippocampal-dependent memory. Recent evidence indicating that the stress-induced habit bias observed in lower animals may also exist in humans is briefly discussed. The symptomatology and diagnostic criteria for PTSD are summarized, and various models of PTSD that implicate multiple memory systems are described. Considering both the animal literature and the symptomatic features of PTSD, we propose that the stress/anxiety-induced habit bias observed in lower animals may underlie some PTSD symptoms, namely the acquisition and expression of maladaptive behavioral responses to trauma-related cues. In this context, we review findings from relevant human behavioral and neuroimaging experiments. It is important to note that a wide variety of brain structures have been implicated in PTSD (for a recent review, see Hughes and Shin, 2011) and that this review will focus selectively on the potential roles of the amygdala, hippocampus and dorsal striatum in PTSD. Finally, whether the stress/anxiety-induced habit bias may influence the neurobiological and behavioral aspects of other human psychopathologies (e.g., drug addiction and relapse, obsessive-compulsive disorder, etc.) is briefly considered.

**Multiple memory systems in the mammalian brain**

The hypothesis that memory is organized in multiple systems in the mammalian brain is supported by extensive evidence from studies in lower animals and humans (for reviews, see White and McDonald, 2002; Squire, 2004). Numerous theories describing the psychological operating principles that may distinguish different forms of memory have been proposed (e.g., Hirsh, 1974; O’Keefe and Nadel, 1978; Mishkin and Petri, 1984; for a review, see Kesner, 1998). Several of these theories typically draw a distinction between a ‘Tolmanian’ (Tolman, 1932) or cognitive form of learning and memory mediated by a brain system that includes the hippocampus as a critical component, and a ‘Hullian’ (Hull, 1943) or S-R habit form of learning mediated by a non-hippocampal-based memory system. Subsequent neurobiological studies employing dissociation methodology provide evidence that the hippocampus and dorsal striatum mediate ‘cognitive’ and ‘S-R habit’ forms of memory, respectively. For example, in rats, lesions of the hippocampal system selectively impair the acquisition of cognitive tasks that require learning relationships among multiple stimuli in both spatial (for a review, see O’Keefe and Nadel, 1978) and non-spatial (Bunsey and Eichenbaum, 1996) domains. In contrast, lesions of the caudate-putamen (i.e., dorsal striatum) selectively impair the acquisition of several S-R or habit-learning tasks (for a review, see Packard and Knowlton, 2002).

An early experiment in rats demonstrating a double dissociation between the mnemonic functions of the hippocampal system and dorsal striatum used two versions of a radial maze task. In the win-shift or cognitive version of the task (Olton and Samuelson, 1976), each maze arm is baited once during a daily session and rats learn to forage among the various spatial locations and to not return to those maze arms in which food has already been acquired. Acquisition of this task is severely impaired by lesions of the hippocampal system (Olton et al., 1979), but not by lesions of the dorsal striatum (Packard et al., 1989; McDonald and White, 1994). In a win-stay or S-R habit version of the task, rats are reinforced for learning to selectively approach illuminated maze arms. Acquisition of this task is severely impaired by lesions of the dorsal striatum, but not by lesions of the hippocampal system (Packard et al., 1989). Similarly, in a dual-solution plus-maze task that can be acquired using either Tolmanian ‘place’ or Hullian ‘response’ learning, neural inactivation of the dorsal hippocampus selectively blocks the use of place learning, whereas neural inactivation of the dorsolateral striatum selectively blocks the use of response learning (Packard and McGaugh, 1996).

Double dissociations between the roles of the hippocampus and dorsal striatum in cognitive and habit memory are also observed following post-training intracerebral drug injections (e.g., Packard and White, 1991; Packard et al., 1994; Packard and Teather, 1997, 1998). Thus, post-training intra-hippocampal injections of dopaminergic agonists selectively facilitate memory in the win-shift radial maze task described above, whereas similar injections into the dorsal striatum selectively facilitate memory in the win-stay radial maze task (Packard and White, 1991).
Important, when considered across studies, double dissociations between the mnemonic functions of the hippocampus and the dorsal striatum in cognitive and habit memory have also been demonstrated in other mammalian species, including monkeys and humans (for a review, see Packard, 2010).

Emotional arousal and the relative use of multiple memory systems

In view of the evidence that the hippocampus and dorsal striatum mediate cognitive and habit memory respectively, studies have begun to focus on factors that can influence the ‘relative’ use of these two memory systems in various learning situations. In our laboratory we have investigated the hypothesis that robust emotional arousal induced by stress or anxiety can influence the use of multiple memory systems in rats. The results of several studies now indicate that in learning situations in which both the hippocampal and dorsal striatal memory systems can provide an adequate learned solution, acute stress or drug-induced anxiety can bias animals towards the use of dorsal striatal-dependent habit memory. In one study (Packard and Wingard, 2004) rats were trained in a ‘dual-solution’ water plus-maze task to swim from the same start position on each trial (i.e., the south arm), and reach a hidden escape platform that was always located in the same location (i.e., the west arm). In this task, making the same body turn response and approaching the same spatial location is suggested by evidence that the BLA is involved in mammalian emotional behavior, including the ability of various drugs to produce anxiety (e.g., Kluver and Bucy, 1939; Nagy et al., 1979; Scheel-Kruger and Petersen, 1982; Sanders and Shekhar, 1991). In addition, the BLA exerts a modulatory influence on memory processes occurring in several other brain structures, including the hippocampus and dorsal striatum (Packard et al., 1994, 1996; Packard and Teather 1998; Roozendaal and McGaugh, 1996, 1997). In an experiment investigating the effect of pre-training injections of RS 79948–197 directly into the BLA, we observed that this treatment was sufficient to produce the same bias towards the use of response learning in a dual-solution plus-maze task that is produced by peripheral injections of the drug (Packard and Wingard, 2004). Thus, in a task in which both hippocampal-dependent place learning and dorsal striatal-dependent response learning can provide an adequate solution, peripheral or intra-BLA injections of an anxiogenic dose of RS 79948–197 ‘favors’ a facilitated use of response learning.

Emotional modulation of cognitive and habit memory: role of the basolateral amygdala

We have recently investigated the BLA as a potential neural site of action that mediates the modulatory influence of drug-induced anxiety on the relative use of multiple memory systems. A possible role for this brain region is suggested by evidence that the BLA is involved in lower animals involving exposure to acute stress or drug-induced anxiety suggest that in some learning situations, robust levels of emotional arousal can bias the brain towards the use of a habit memory system.
One possible explanation for this modulatory influence of anxiogenic drugs in the dual-solution plus maze task is that the drug activates BLA efferent projections and directly enhances dorsal striatal-dependent memory processes. Alternatively, it is possible that the drug activates BLA efferents in a manner that impairs hippocampal-dependent memory processes, effectively allowing the dorsal striatum to guide the expression of learned behavior. In order to examine these two possibilities, rats were trained in ‘single-solution’ plus-maze tasks that required animals to employ either response or place learning. In the single-solution water plus-maze tasks, the start points varied across trials between north and south. For the place task, rats learned to approach the same spatial location to reach the escape platform (i.e., the west arm), and the body turn response at the choice point (i.e., the left or right) was equally reinforced across trials. Thus, response learning could not provide an adequate solution. For the response task, rats were required to always make the same body turn response (i.e., left) at the choice point to reach the escape platform, and the spatial location of the platform varied equally across trials. Post-training intra-BLA injections of an anxiogenic dose of RS 79948–197 enhanced acquisition of the response learning task and impaired acquisition of the place learning task (Wingard and Packard, 2008). Interestingly, the same pattern of results in these two tasks was observed following post-training neural inactivation of the dorsal hippocampus (Schroeder et al., 2002). Therefore, the bias towards the use of response learning produced by intra-BLA injections of RS 79948–197 was effectively mimicked by a reversible lesion of the hippocampus. Taken together, these findings suggest that intra-BLA administration of this anxiogenic drug impairs the modulatory influence on hippocampal-dependent cognitive memory, resulting in a reliance on dorsal striatal-dependent habit memory. Consistent with this suggestion, neural inactivation of the BLA blocks both the impairing and enhancing memory modulatory effects of peripheral injections of RS 79948–197 on response and place learning, respectively (Packard and Gabriele, 2009).

Emotional arousal and multiple memory systems in humans

Recent research suggests that the effects of emotional arousal on multiple memory systems observed in lower animals may also exist in humans. Specifically, in some learning situations, acute or chronic stress can bias humans towards the use of a S-R habit-learning strategy, at the expense of a more cognitive learning strategy. For example, when trained to locate a ‘win-card’ in a three-dimensional model of a room, humans exposed to an acute stressor (i.e., public speaking) were more likely to associate a proximal cue with the location of the win-card (i.e., a S-R strategy), as opposed to integrating the contextual elements of the room to locate the card (i.e., a spatial strategy; Schwabe et al., 2007). Subjects with higher scores on a chronic stress questionnaire were also more likely to be S-R learners, as opposed to spatial learners, in a two-dimensional version of the win-card task (Schwabe et al., 2008). Thus, consistent with the lower animal findings described earlier, both acute and chronic stress may shift humans towards the use of habit learning in dual solution tasks.

Consistent with these findings, emotional arousal at the time of encoding enhances retention in a probabilistic classification ‘weather prediction’ task (Steidl et al., 2006, 2011). In addition, human subjects exposed to the socially-evaluated cold pressor test were more likely to engage in habitual behavior as opposed to goal-directed behavior in a food-devaluation paradigm (Schwabe and Wolf, 2009). Importantly, learning in the weather prediction task and habitual behavior in the food-devaluation paradigm depend, in part, upon the dorsal striatum (Knowlton et al., 1996; Poldrack et al., 1999; Tricomi et al., 2009).

As suggested in lower animals, the stress/anxiety-induced facilitation of habit memory in humans may also stem from an impairment of hippocampal-dependent memory. Several studies in humans indicate that high levels of stress at the time of encoding or retrieval impair learning in hippocampal-dependent memory tasks (Schwabe et al., 2009; Merz et al., 2010; Schwabe and Wolf, 2010; Thomas et al., 2010). Interestingly, subjects with lower scores in episodic memory tasks were more likely to be response learners in a dual-solution virtual maze task (Bobbot et al., 2011). The observation that impaired hippocampal-dependent memory may result in a greater use of an S-R strategy suggests that the stress-induced facilitation of habit memory may arise indirectly, i.e., through stress-induced impairments of the hippocampal-dependent memory system. Consistent with this interpretation, stressful life events have been associated with reduced gray matter volume of the hippocampus in humans (Papagni et al., 2011), and lower gray matter volume of the hippocampus has been associated with the use of an S-R strategy in a dual-solution virtual maze (Bobbot et al., 2011).

Taken together, findings from investigating the effects of emotional arousal on multiple memory systems in
humans reflect the lower animal literature. In humans and lower animals, acute or chronic stress can produce a bias towards the use of striatal-dependent habit memory, at the expense of hippocampal-dependent cognitive memory. The existence of a stress/anxiety-induced habit bias in humans provides further reason for considering the phenomenon as a potential mechanism underlying some human psychopathologies.

We now consider the hypothesis that a stress-induced bias towards the use of dorsal striatal-dependent habit memory may underlie some of the symptomatology of PTSD. We begin with a review of PTSD symptomatology and a description of multiple memory systems theories of PTSD. Subsequently, we briefly review evidence from human neuroimaging studies indicating a role for the amygdala, hippocampus and dorsal striatum in PTSD symptoms. Finally, we consider the converging evidence indicating a stress-induced bias towards the use of habit memory and its implications for PTSD.

Introduction to PTSD symptomatology

The Diagnostic and Statistical Manual of Mental Disorders text revision (DSM IV-TR; American Psychiatric Association, 2000) classifies PTSD as an anxiety disorder that may develop after experiencing a traumatic event. According to the DSM IV-TR, the traumatic episode itself must have included actual or anticipated threats of death or serious injury to oneself or others, and the traumatic episode must have instilled within the patient intense feelings of fear, helplessness or horror. In addition, the patient must persistently re-experience the traumatic episode. This re-experiencing may occur through intrusive recollections of the event (taking the form of mental images, thoughts, or perceptions), a sense that the traumatic event is actually recurring, emotional or physiological reactivity to internal or external cues that somehow represent the traumatic event, or recurrent nightmares of the event. Importantly, these recollections often arise involuntarily. In fact, in many cases, a patient’s ability to recall the event voluntarily proves to be impaired. When considering the PTSD symptoms that relate to memory processes, an interesting paradox emerges. Specifically, the DSM IV-TR suggests that PTSD patients may potentially exhibit both enhanced and impaired memory of the traumatic event. Enhancements of the traumatic memory become evident through the exceptionally vivid and involuntary re-experiencing, or ‘flashbacks’, of the event. Such flashbacks are characterized as being triggered by trauma-related internal cues (e.g., anxiety) or external cues (e.g., loud noises) and as containing vivid perceptual features from the event, such as sounds, smells, and images. Importantly, when a patient experiences a flashback, he or she feels the event is actually recurring, as if it were part of the present instead of the past. These observations suggest that the version of the traumatic memory that is readily and involuntarily invoked by cues fails to acknowledge the spatial or temporal context in which the event originally took place. This lack of contextual content may be viewed as one of the many impairments commonly observed in traumatic memories. Other impairments in traumatic memory become evident through the patient’s inability to recall certain aspects of the event. Thus, amnesia, memory gaps and fragmentary recall of the traumatic event are relatively common features in PTSD (van der Kolk and Fisler, 1995; Koss et al., 1996; Shalev et al., 1996; Tichenor et al., 1996; Mechanic et al., 1998; Yovell et al., 2003). Although a concomitant enhancement and impairment of traumatic memory may be difficult to explain via a unitary model of memory, these seemingly antagonistic effects may be explained more readily through a multiple memory systems approach.

Multiple memory systems in PTSD

In view of the evidence reviewed earlier indicating that the mammalian brain contains multiple memory systems, the enhancement and impairment of traumatic memory in PTSD may be explained by hypothesizing differential involvement of distinct memory systems. Thus, one memory system may be highly active and lead to biased encoding of certain features, and another memory system may be relatively inactive and fail to encode other features of the traumatic event. Interestingly, evidence that more than one memory system encode traumatic memories in PTSD arises from case studies involving traumatic brain injury (TBI). TBI occurring during a traumatic event may produce both anterograde and retrograde amnesia for the event. However, in some cases patients with TBI-induced
amnesia may also develop PTSD-like symptoms, and these symptoms may prove sufficient for making a full (or at least partial) diagnosis of PTSD (Horton and Barrett, 1991; McMillan, 1991; Layton and Wardi-Zonna, 1995; Bryant, 1996; McMillan, 1996; King, 1997; McGrath, 1997; Warden et al., 1997; Krikorian and Layton, 1998; Podoll et al., 2000a,b; Creamer et al., 2005; Bryant et al., 2009). Although TBI may prevent conscious recall of the traumatic event, a patient may re-experience the trauma through recurrent nightmares or through emotional and physiological reactivity to cues that in some manner represent the trauma. For example, in one case study, a 19-year-old male developed PTSD symptoms after a motor vehicle accident that caused TBI and consequent amnesia of the event (see Podoll et al., 2000a). Despite having no memory of the accident, the patient experienced recurrent nightmares involving ‘two lights appearing like the headlights of an approaching motor vehicle’ and ‘the feeling of a shock or concussion going through the whole body’. The patient would also experience intense psychological distress when driving past the location of the accident or when seeing another accident on the road, and he avoided riding in vehicles of the same make and model as the one he was driving during the crash. The patient displayed all these symptoms without having any conscious memory of the accident. Case studies such as this suggest that although a traumatic memory may not be stored or recalled at a conscious level, some remnants of the event may be preserved at a comparatively less conscious level. This view is consistent with the idea of at least two distinct memory systems: one mediating conscious memory of the event (a cognitive, declarative, explicit system) and another mediating latent memory of the event (a habit, non-declarative, implicit system). Thus, TBI may impair the ability of the cognitive system to encode and consciously recall the traumatic event, while sparing the non-declarative/habit memory system’s ability to encode and store the memory at a relatively unconscious level (Layton and Wardi-Zonna, 1995). The unimpaired non-declarative/habit system may then in part subserve the avoidance and emotional reactivity to trauma-related cues. Finally, it is also important to note that TBI-induced amnesia resembles the memory impairments observed in PTSD patients without TBI. For example, in both PTSD patients with TBI and PTSD patients without TBI, voluntary recall of certain aspects proves to be impaired, while involuntary re-experiencing remains intact (e.g., Podoll et al., 2000b; Yovell et al., 2003). Therefore, an impairment of the cognitive/declarative memory system and a concomitant preservation of the non-declarative/habit memory system may be relatively common processes underlying traumatic memories in PTSD.

Interestingly, contemporary psychological theories surrounding PTSD often implicate more than one memory system to explain the development and persistence of PTSD symptoms. For example, the dual representation theory (Brewin et al., 1996) suggests the existence of a ‘verbally accessible memory’ (VAM) system and a ‘situationally accessible memory’ (SAM) system. The VAM system mediates memories that are easily retrieved through voluntary recall. These memories often contain contextual aspects of the event (i.e., time and place) and are usually integrated with other autobiographical memories. However, the VAM system can only encode information that is consciously attended to during the event. Therefore, considering that a person amidst trauma may focus his or her attention selectively on the immediate source of the threat, the VAM system may fail to encode the contextual aspects (i.e., time and place) surrounding the trauma. Unlike the VAM system, the SAM system is postulated to mediate memories that fail to be recalled voluntarily. Memories mediated by the SAM system are instead triggered involuntarily through situational reminders (e.g., internal or external cues). These memories may contain information from lower-level processes (e.g., sights, sounds and smells), the emotions felt during the experience (e.g., fear and helplessness), and the body’s initial responses to the trauma (e.g., a change in heart rate). Therefore, when the SAM memory is later triggered by a situational reminder, the patient re-experiences the perceptions, emotions and bodily responses from the traumatic event. These features recalled through the SAM system culminate into a highly distressing flashback.

Similarly, Ehlers and Clark (2000) propose a cognitive model for PTSD that implicates two distinct systems. The authors suggest that, like other memories, trauma memory may be encoded through either conceptual or data-driven processing. Through conceptual processing, the mind encodes the meaning of the event and organizes the memory within its appropriate context, allowing the memory to be voluntarily retrieved at a later time. According to the author’s hypothesis, trauma victims that use conceptual processing during the event do not develop persistent PTSD. In contrast, through data-driven processing the mind encodes the sensory impressions of the event, priming the individual to later readily respond to cues that resemble these impressions. Trauma victims that had used data-driven processing during the event fail to recall the event voluntarily, yet show enhanced involuntary recall when cued. According to the model, more data-driven processing (relative to conceptual processing) increases the chance that a trauma victim will develop long-lasting PTSD symptoms. Consistent with this inter-
Evidence the amygdala has a role in PTSD

In view of the role of the mammalian amygdala in stimulus-affect learning (for reviews, see Maren, 2001; McGaugh, 2004), it is perhaps not surprising that numerous studies have implicated this brain structure in PTSD symptomatology. Using various neuroimaging techniques, studies have consistently revealed increased activation of the amygdala in PTSD subjects (Hughes and Shin, 2011). For example, amygdala activation is increased in combat veterans with PTSD in response to both combat-related noises (Liberzon et al., 1999) and odors (Vermetten et al., 2007), suggesting that the amygdala may be involved in the discrete-cued recall of the traumatic event. In another study, Vietnam veterans with PTSD listened to a script describing a traumatic event that the subject had actually experienced during the war (Shin et al., 2004). Positron emission tomography scans revealed that the regional cerebral blood flow in the right amygdala maintained a positive correlation with the severity of PTSD symptoms. Using similar techniques, several other studies have established positive correlations between amygdala activation and PTSD symptom severity (Rauch et al., 2000; Pissiota et al., 2002; Armony et al., 2005; Bryant et al., 2005; Protopopescu et al., 2005; Dickie et al., 2008; Brunetti et al., 2010). Conversely, there is evidence that in subjects exposed to trauma, decreased amygdala activation may actually be associated with a failure to develop PTSD (Britton et al., 2005; Osuch et al., 2008). Taken together, the evidence suggests that the amygdala is likely to be involved in the development, and potentially the expression, of PTSD symptoms. As the amygdaloid nuclei project to several brain structures related to different types of learning and memory (McGaugh, 2004), it may also be reasonable to infer that heightened amygdala activation during and after a traumatic event may modulate memory via an interaction with other brain structures as well.

Evidence the hippocampus has a role in PTSD

As mentioned previously, several studies report impairments in the traumatic memories of PTSD patients (e.g., van der Kolk and Fisler, 1995; Koss et al., 1996; Shalev et al., 1998). As mentioned previously, several studies report impairments in the traumatic memories of PTSD patients (e.g., van der Kolk and Fisler, 1995; Koss et al., 1996; Shalev et al., 1998).
et al., 1996; Tichenor et al., 1996; Mechanic et al., 1998; Yovell et al., 2003). These impairments include a lack of temporal or spatial context, failure to integrate the event into autobiographical memory, inability to intentionally recall important aspects of the traumatic event, and fragmented or disorganized recall of the traumatic memory. Also, relative to healthy controls, PTSD patients tend to perform poorly on declarative memory tasks (for a brief review, see Bremner, 2006). Considering their characteristics, these memory impairments may reflect a functional decline of hippocampal-dependent cognitive memory processes in PTSD (Bremner, 2006). There are several lines of research in support of this idea that indicate abnormalities of the hippocampus in PTSD patients. For example, several neuroimaging studies suggest that patients with PTSD have a reduced hippocampal volume (for a review, see Bremner, 2007; and also Bonne et al., 2001; Carrion et al., 2001; De Bellis et al., 2001; Fennema-Notestine et al., 2002; Pederson et al., 2004; Golier et al., 2005). Moreover, neuroimaging studies have established a negative correlation between hippocampal volume and the severity of PTSD symptoms (Gilbertson et al., 2002; Villarreal et al., 2002; Bremner et al., 2003).

In view of extensive evidence that behavioral stressors and stress hormones can be detrimental to hippocampal structure and morphology (Watanabe et al., 1992; Gould et al., 1998; Kim and Diamond, 2002), it is possible that the traumatic event and the distress it may engender reduces the volume of the hippocampus. However, there is also evidence that a prior reduction in hippocampal volume may serve as a risk factor for developing PTSD (e.g., Pitman et al., 2006). Indeed, whether the reduction in hippocampal volume precedes or follows the traumatic event and the development of PTSD symptoms remains debatable (Bremner, 2001; Pitman, 2001). Results in favor of the latter view (i.e., that traumatic stress reduces hippocampal volume) came from one study that measured hippocampal gray matter volume in healthy human subjects at two different time points, separated by a three-month interval (Papagni et al., 2011). The number of stressful life events that a participant experienced during the three-month interval was positively correlated with a reduction in gray matter volume of the right hippocampus, suggesting that the stressful life events preceded and contributed to the reduction in hippocampal volume. Experiments in animals yield potentially similar results (Kim and Diamond, 2002). For example, rats subjected to 21 days of chronic restraint stress showed a 3% reduction in hippocampal gray matter volume relative to non-stressed controls (Lee et al., 2009).

In addition to reduced hippocampal volume, neuroimaging studies reveal decreased activation of the hippocampus in patients with PTSD (for reviews, see Francati et al., 2007; Hughes and Shin, 2011). Typically, these experiments measure hippocampal activation while the subject performs a hippocampal-dependent memory task. For example, researchers trained individuals with PTSD and healthy individuals who had not been exposed to trauma on a virtual version of the Morris water maze (Astur et al., 2006). While performing the task, the PTSD group showed no significant activation in the hippocampus, whereas individuals without PTSD showed a robust increase in hippocampal activation. Moreover, a negative correlation between hippocampal activation and severity of PTSD symptoms was observed (Astur et al., 2006). It should be noted that, although reduced hippocampal activation is often observed, some studies have reported increases in hippocampal activation in PTSD patients (Werner et al., 2008; Whalley et al., 2009). The reason for this discrepancy remains uncertain, but it may depend on the features of the particular learning task or the analyses used for the scans (Francati et al., 2007; Hughes and Shin, 2011).

Evidence the dorsal striatum has a role in PTSD

As described earlier, there is extensive evidence from studies in lower animals and humans indicating that the dorsal striatum has a selective role in S-R/habit learning and memory. In PTSD, the learning of behavioral responses to trauma-related cues may be a form of S-R learning. PTSD patients may learn in part to associate discrete stimuli/cues surrounding the trauma (e.g., loud noises) with the trauma itself and have subsequently learned to respond to the cues as if the cues themselves posed a serious threat. This automatic/habitual responding to cues without regard to the spatial or temporal context in which they occur is characteristic of both PTSD symptomatology and S-R (or habit) learning. Indeed, the idea that S-R learning may be associated with PTSD pathology is not a new concept. In the 1980s, drawing from Mowrer’s earlier (1960) two-factor learning theory, researchers attempted to describe the development of PTSD as involving two distinct learning phases, one characterized by classical conditioning and the other by instrumental learning (for a review, see Foa et al., 1989). In the initial phase, a trauma victim learns to associate spatially or temporally proximal sounds,
Evidence the noradrenergic system has a role in PTSD

In lower animals, the effect of anxiety on the relative use of memory systems can be produced by drugs that increase norepinephrine release and hence can activate adrenergic receptors in the BLA (Packard, 2009). Consistent with the hypothesis that this anxiety-mediated habit bias may underlie some PTSD symptoms, converging evidence indicates that PTSD patients have increased basal norepinephrine levels and show exaggerated noradrenergic responses to trauma-related stimuli (for reviews, see Pitman and Delahanty, 2005; Strawn and Geraci, 2008). Pitman (1989) advanced a pathophysiological model of PTSD suggesting that stress hormones released during and after a traumatic event may lead to an ‘overconsolidation’ of the traumatic memory, precipitating the intrusive recollections and conditioned emotional responses observed in PTSD. Aside from the consolidation of traumatic experiences, it has also been suggested that the retrieval of traumatic memories may depend on noradrenergic mechanisms (Pitman, 1989; Pitman and Delahanty, 2005). Considering the putative role of the noradrenergic system in PTSD, several studies have investigated the treatment efficacy of antiadrenergic agents (for reviews, see Pitman et al., 2006; Stein, 2006; Strawn and Geraci, 2008). For example, treatment with the β-adrenoreceptor blocker propranolol in the acute aftermath of trauma or after the development of the disorder has been shown to reduce PTSD symptoms (Famularo et al., 1988; Pitman et al., 2002; Vaiva et al., 2003; Brunet et al., 2008; Krauseneck et al., 2010). Considering the effects of norepinephrine on the relative use of memory systems (Packard, 2009), it is tempting to speculate that exaggerated norepinephrine release during and after a traumatic event may increase amygdala activation, thus mobilizing a shift from a hippocampal-dependent memory system towards a dorsal striatal-dependent system. Disrupting the noradrenergic system with drugs like propranolol may prevent or reverse this shift to habit memory.

The stress-induced habit bias: implications for PTSD

Research in lower animals described earlier indicates that anxiety-induced impairment of the hippocampal-dependent memory system enhances dorsolateral striatal-dependent habit memory and that this enhancement depends on the integrity of the basolateral amygdala. We
propose that a similar mechanism may in part underlie the development, persistence and expression of some PTSD symptoms. More specifically, we suggest that during a traumatic event the amygdala becomes highly active and modulates memory of the experience by impairing modulatory influence on the hippocampus, essentially allowing the dorsal striatum to play a prominent role in encoding and consolidating trauma-related cues. The prominence of the dorsal striatal-dependent S-R learning system may manifest in part as enhanced learning of maladaptive avoidance behaviors in response to these cues. In addition, considering that pre-test anxiety also induces a habit bias in lower animals (Elliot and Packard, 2008), we suggest that the anxiety-driven retrieval of traumatic memory may similarly engage the dorsal striatum to guide the automatic-like avoidance behaviors observed in PTSD patients. Support for these ideas comes from human neuroimaging research and neurobehavioral studies in lower animals suggesting potential roles for the amygdala, hippocampus and dorsal striatum in PTSD symptomatology.

As described previously, a recurrent finding among PTSD patients is an impaired hippocampus. The hippocampal impairments commonly observed in PTSD include reductions in volume, lower activation levels and relatively poor performance in hippocampal-dependent memory tasks. Likewise, common deficits observed in traumatic memory may reflect hippocampal impairment. Although the mechanism underlying these impairments remains uncertain, contributing factors may include the high levels of stress experienced both during and after the traumatic episode (Bremner, 2001). Interestingly, in lower animals, stress-induced impairments of hippocampal long-term potentiation or neurogenesis have been associated with the use of an S-R strategy in dual solution tasks (Kim et al., 2001; Ferragud et al., 2010). Similarly, in healthy human subjects, lower hippocampal volume and poor performance in episodic memory tasks have been associated with an S-R strategy in a dual solution virtual maze (Bohbot et al., 2007, 2011). With this evidence, it is tempting to speculate that trauma-induced impairments in hippocampal structure and function may promote a habit bias in PTSD patients.

The recent neuroimaging evidence we have summarized indicates that the dorsal striatum may have a role in PTSD symptoms. Further evidence such a role exists may be gleaned from fear conditioning experiments in lower animals. It should be noted that auditory fear conditioning fails to mimic all the symptoms of PTSD (e.g., emotional numbness, memory impairment, recurrent nightmares, etc.). In addition, we might speculate that this model fails to replicate the hippocampal memory impairment commonly observed in PTSD, because footshock treatment may not elicit the same high levels of stress or the prolonged nature of traumatic experiences. Despite these inefficiencies, auditory fear conditioning may nevertheless serve as a useful model for understanding other major PTSD symptoms, in particular the learning of emotional and behavioral responses to trauma-related cues (Foa et al., 1992; Rasmussen and Charney, 1997; Siegmund and Wotjak, 2006; for a recent review of PTSD animal models, see Berardi et al., 2012). Consistent with the dorsal striatum having a role in PTSD, pre-training or post-training lesions delivered to the dorsal striatum in rats impaired conditioned freezing behavior in response to an auditory cue, while having no effect on freezing behavior in response to the context (Ferreira et al., 2003, 2008). Thus, dorsal striatal lesions selectively impaired learning to freeze in response to a discrete cue (i.e., S-R learning). Post-training amphetamine infused directly into the dorsal striatum enhanced freezing in both auditory and contextual versions of the task (White and Salinas, 2003). Interestingly, it has been demonstrated more recently that an amygdala-dorsal striatum system is necessary for auditory fear conditioning (Ferreira et al., 2008). A pre-training unilateral lesion to the central amygdaloid nucleus and contralateral lesion to the dorsal striatum impaired conditioned freezing, while ipsilateral lesions had no effect. Lastly, the contralateral lesions did not affect conditioned freezing in a contextual version of the task, suggesting that the amygdala-dorsal striatum system may mediate conditioned freezing selectively to discrete cues (i.e., stimulus-response learning). Taken together, these experiments suggest that the acquisition of behavioral responses to fear-conditioned cues may depend on an indirect pathway from the amygdala to the dorsal striatum (Ferreira et al., 2008). Considering the parallels between auditory fear conditioning and some PTSD symptomatology, we might also speculate that the development of avoidance behaviors to trauma-related cues in PTSD may depend on an amygdala-dorsal striatum system.

The stress-induced habit bias: implications for other psychopathologies

In addition to PTSD, other human psychopathologies may similarly reflect a stress-induced facilitation of the dorsal striatal-dependent habit memory system. Considering both the role of anxiety and the habit-like nature of compulsions in obsessive-compulsive disorder (American
Psychiatric Association, 2000), the stress-mediated habit bias observed in lower animals may also underlie at least some symptoms of the disorder (McDonald et al., 2004). More specifically, the anxiety arising from obsessions or stressful/traumatic life events may lead to the compulsive behavior observed in obsessive-compulsive disorder patients, and this process may depend on an interaction between the amygdala, hippocampus and dorsal striatum. When exposed to distressing life events or obsessions, the amygdala may become highly active and, through its inputs to different learning and memory structures, modulate which behavioral strategy becomes employed to relieve the anxiety. In this situation, a highly active amygdala may favor the use of a habit learning strategy mediated by the dorsal striatum, as opposed to a more cognitive strategy, which would be mediated in part by the hippocampus. In a recent study, researchers trained obsessive-compulsive disorder patients on a set of instrumental learning tasks and found that relative to healthy individuals they demonstrated deficient knowledge of action-outcome relationships and were more likely to rely on habit-like responses to the stimuli (Gillan et al., 2011). These results may represent the impairment of a cognitive, goal-directed learning system and consequent reliance on the habit memory system in obsessive-compulsive disorder. In addition, a number of studies report that environmental factors contributing to the development and persistence of obsessive-compulsive disorder symptoms may include stressful or traumatic life events (Happle, 2005; Sasson et al., 2005; Cromer et al., 2007a,b; Tolin et al., 2010; Landau et al., 2011). Lastly, several neuroimaging studies have provided evidence of abnormal structure and function of the amygdala, hippocampus and regions of the dorsal striatum in obsessive-compulsive disorder patients (for recent reviews, see Del Casale et al., 2011; Milad and Rauch, 2012).

In drug abuse, the acquisition and subsequent relapse of drug-seeking behaviors may be attributed to aberrant or maladaptive functioning of different memory systems (White, 1996; Di Chiara, 1999; Everitt and Robbins, 2005; Schwabe et al., 2011). Whereas the initial acquisition of drug-taking behavior may depend on a hippocampal-dependent memory system, extended drug use may shift the control of drug-taking behavior to a dorsal striatal-dependent system, increasing the rigid and habit-like nature of these behaviors (White, 1996). In a similar hypothesis, initial drug-taking behavior may depend on a goal-directed learning system mediated by the dorsomedial region of the striatum and gradually shift to a habit-learning system mediated by the dorsolateral striatum (Everitt and Robbins, 2005; Schwabe et al., 2011). Consistent with the stress-induced habit bias observed in lower animals, emotional arousal or stress may facilitate a shift to the use of the habit memory system in drug addicts or reinstate drug cravings in rehabilitated users (Packard and Wingard, 2004; Schwabe et al., 2011).

In humans, major stressful life events have been associated with increased drug abuse (Newcomb and Bentler, 1988; Kaplan and Johnson, 1992; Harrison et al., 1997; Chilcoat and Breslau, 1998). Acute stressors can also increase alcohol consumption (Higgins and Marlatt, 1975). Drug abusers often report that stress and negative affective states are common factors contributing to their relapse (Marlatt and Gordon, 1980; Wallace, 1989), and successfully coping with stress is associated with the prevention of relapse in abstinent drug-users (Marlatt and Gordon, 1980; Shiffman, 1982).

Thus, although the present review has focused on emotional modulation of multiple memory systems in PTSD, a stress-induced bias towards the use of habit memory may have implications for the neurobiology of several psychopathologies.

Conclusion

The effect of stress/anxiety on the relative use of memory systems in the mammalian brain is partly characterized by greater dorsolateral striatal-dependent habit learning, to the detriment of hippocampus-dependent memory. Moreover, this stress/anxiety-induced habit bias appears to depend on a functionally-intact basolateral amygdala. The idea that a similar mechanism in part underlies the development, persistence and expression of avoidance behaviors in PTSD receives some support from neuroimaging and fear conditioning experiments. Future research should investigate the exact role of the dorsal striatum in PTSD symptomatology, in particular its potential role in the learning of avoidance behaviors in response to trauma-related cues.

Received May 14, 2012; accepted July 5, 2012

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