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Review

Response Variation following Trauma: A Translational Neuroscience Approach to Understanding PTSD

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Exposure to traumatic stress is a requirement for the development of posttraumatic stress disorder (PTSD). However, because the majority of trauma-exposed persons do not develop PTSD, examination of the typical effects of a stressor will not identify the critical components of PTSD risk or pathogenesis. Rather, PTSD represents a specific phenotype associated with a failure to recover from the normal effects of trauma. Thus, research must focus on identifying pre- and posttraumatic risk factors that explain the development of the disorder and the failure to reinstate physiological homeostasis. In this review, we summarize what is known about the clinical and biological characteristics of PTSD and articulate some of the gaps in knowledge that can be addressed by basic neuroscience research. We emphasize how knowledge about individual differences related to genetic and epigenetic factors in behavioral and brain responses to stress offers the hope of a deeper understanding of PTSD.

The Relationship between Traumatic Stress Exposure and PTSD

The theoretical link between exposure to extreme stress and the development of PTSD (APA, 1980) provided the rationale for early hypotheses that PTSD-related biological alterations would be similar in direction to those observed acutely in animals exposed to stressors. When subsequent findings indicated that only a minority of trauma-exposed individuals develop PTSD (Kessler et al., 1995), an alternative hypothesis was generated proposing that PTSD involves a failure of mechanisms involved in recovery and restitution of physiological homeostasis, possibly resulting from individualistic predisposition (Yehuda and McFarlane, 1995). It has been challenging to interpret the extent to which biological alterations that are consistent with normative consequences of stress exposure in PTSD reflect pathogenesis. In this review, we suggest that the clinical syndrome of PTSD may describe several biological phenotypes (e.g., some characterized by exaggerated responses, some by inadequate recovery mechanisms) that reflect individual variation originating from pretraumatic risk factors and review the supporting evidence for this from animal and human studies.

Definition and Description of PTSD

PTSD can occur in persons who experience fear, helplessness, or horror following threat of injury or death. It is characterized by the presence of three distinct, but co-occurring, symptom clusters. *Reexperiencing symptoms* describe spontaneous, often insuppressible intrusions of the traumatic memory in the form of images or nightmares that are accompanied by intense physiological distress. *Avoidance symptoms* involve restricting thoughts and distancing oneself from reminders of the event, as well as more generalized emotional and social withdrawal. *Hyperarousal symptoms* reflect more overt physiological manifestations, such as insomnia, irritability, impaired concentration, hypervigilance, and increased startle responses. These symptoms must be severe enough to impair social, occupational, or interpersonal function and co-occur for at least 1 month. The impairment from PTSD is amplified by poor coping strategies, substance abuse, co-occurring mood and anxiety disorders, lack of social support, and the accelerated development of stress-related medical conditions (Yehuda, 2002a).

Prevalence and Longitudinal Course of PTSD

Approximately 6.8% of persons in the United States develop PTSD at some time in their lives (Kessler et al., 2005), yet estimates of the prevalence of trauma exposure suggests that more than 75% are exposed to at least one traumatic event (Breslau and Kessler, 2001). Experiences that most often give rise to PTSD include rape, assault, and combat, whereas natural disasters or man-made accidents result in PTSD far less frequently. The symptoms of PTSD are present in almost all people in the days and weeks following trauma exposure and are considered reflections of a universal response (McFarlane, 2000). Even among those who develop PTSD (defined by sustained symptoms for more than 1 month following exposure), the most common trajectory is spontaneous remission, with the most dramatic decline in symptoms occurring by 3 months posttrauma (Kessler et al., 1995). Thus, PTSD is best described as a condition in which the process of recovery from trauma is impeded. Approximately

5% of persons follow a different trajectory in that they do not develop PTSD symptoms immediately (Adams and Boscarino, 2006). Whether the underlying mechanism of *delayed PTSD* is similar to that in people who fail to recover from early trauma is unknown. Moreover, those who recover from PTSD can often experience a recrudescence, usually triggered by an adverse life event or traumatic reminder, implying the involvement of mechanisms of biological sensitization in the maintenance or initiation of PTSD symptoms.

Risk Factors for PTSD

The relative rareness of PTSD in trauma-exposed people has prompted an interest in identifying risk factors for this disorder (Yehuda, 2004). These include event characteristics (e.g., severity of trauma) and individual differences (e.g., preexisting traits, pre- or posttraumatic life events). These two domains are theoretically different from one another, but may be linked in practice. For example, the greater prevalence of PTSD following exposure to interpersonal violence as compared to accidents suggests that the former are more potent stressors, and accordingly increase one's risk by providing an increased "dosage" of trauma. Yet, because exposure to interpersonal violence occurs less randomly in populations than accidents, the link between such exposures and PTSD may reflect demographic, socioeconomic, or even genetic predictors of event exposure. One study demonstrated a higher concordance between monozygotic than dizygotic twins for exposure to interpersonal violence as well as for PTSD, implying shared genetic risk factors for exposure and PTSD (Stein et al., 2002). These findings raise the possibility of distinct biological subtypes of PTSD based on trauma type, though such subtypes have not been formally characterized.

Other risk factors for PTSD include a family history of psychopathology, cognitive factors (such as lower IQ), childhood adversity, preexisting avoidant personality or behavioral problems, and poor social support (Bromet et al., 1998; Yehuda et al., 2006). It is not currently known how these risk factors interact or even whether they individually or collectively reflect a genetic diatheses or response to an even earlier life experience. Even factors associated with stable preexposure heritable parental characteristics may increase risk for PTSD by increasing exposure to neglect or abuse. Information about risk factors for PTSD has also been constrained by the fact that most factors have been identified retrospectively, based on comparing people with and without PTSD on many parameters, some of which might have been influenced by posttraumatic factors. Regardless of our incomplete knowledge about the etiology of risk factors, their presence constitutes important sources of individual variation in stress responses and may underlie different biological phenotypes of PTSD.

Peripheral Markers of Stress and PTSD

The physiological changes associated with acute exposure to a stressor have been very well characterized and include increases in sympathetic, and decreases in parasympathetic, tone and the release of ACTH, cortisol, and catecholamines from the pituitary, adrenal cortex, and adrenal medulla, respectively. These and related physiological adjustments of autonomic nervous system (ANS) end organs (i.e., changes in heart rate, blood pressure, respiration, skin conductance) represent adaptive responses, as they help the body accommodate to an immediate demand. A critical feature of the stress response is the autoregulation initiated by cortisol negative-feedback inhibition that restores stress-related reactions to baseline after the termination of the acute stressor (Munck et al., 1984). In contrast, initial descriptions of combat veterans suggested a chronic and sustained physiological hyperarousal (Kardiner, 1941). Subsequent studies confirmed that veterans with chronic PTSD showed increases in peripheral catecholamine levels (Yehuda et al., 1998a) and other autonomic measures compared to controls under baseline conditions and in response to traumatic triggers (O'Donnell et al., 2004). Insofar as the actual stressor (e.g., combat) was no longer occurring in reality, it was not clear why physiological homeostasis had not been achieved in trauma survivors with PTSD.

In 1986, Mason and colleagues reported that although combat veterans with PTSD demonstrated sustained elevations in urinary catecholamine levels, cortisol levels were significantly lower in veterans with PTSD than those with other psychiatric disorders (Mason et al., 1986). These observations were later confirmed by carefully controlled studies of plasma cortisol release over the diurnal cycle (Yehuda et al., 1996a; Bremner et al., 2007). Cortisol levels were lower in combat veterans with PTSD than controls, despite evidence for increased hypothalamic CRF release (Yehuda et al., 1996b). Furthermore, PTSD was associated with an enhanced cortisol negative-feedback inhibition that seemed to result from increased responsiveness of GR (reviewed in Yehuda, 2002b, 2005). The profile of neuroendocrine alterations was different from that observed in animal models of ongoing, chronic stress and also from observations in depressed patients, in which elevated CRF resulted in increased cortisol levels, decreased GR responsiveness, and weaker cortisol negative-feedback inhibition (Holsboer, 2003). Rather, the neuroendocrine altertations observed in PTSD suggested an increased sympathetic and central CRF activation in the face of reduced cortisol signaling.

Implicit in the model of risk for PTSD is that the disorder develops because of factors that interfere with posttrauma recovery. Though cross-sectional studies of chronic PTSD could not address the mechanisms underlying the neuroendocrine findings, results from prospective, longitudinal studies of trauma survivors strongly suggested that cortisol-related alterations in PTSD reflected preexisting vulnerability factors. In rape victims, lower plasma cortisol levels (Resnick et al., 1995) but higher levels of plasma MHPG were associated with the risk factor of prior traumatization (Yehuda et al., 1998b). Studies of motor vehicle accidents demonstrated that persons who subsequently

developed PTSD had lower cortisol levels within hours after the accident than those who did not (Yehuda et al., 1998c; Delahanty et al., 2003). In parallel studies of persons at risk for PTSD, lower cortisol and enhanced cortisol suppression following DEX were noted in the adult offspring of Holocaust survivors with, compared to those without, parental PTSD (Yehuda et al., 2007a, 2007b). Parental PTSD is a risk factor for PTSD because it produces a substantial increase in the prevalence of PTSD that is not attributable to higher rates of trauma exposure in offspring (Yehuda et al., 2001). Lower cortisol levels were also observed in the infant offspring of mothers who developed PTSD following exposure, while pregnant, to the WTC attacks on 9/11, compared to those of mothers who did not develop PTSD (Yehuda et al., 2005). In both of these "at risk" cohorts, neuroendocrine measures associated with severity of parental PTSD symptoms. This was true in the adult offspring of Holocaust survivors even after controlling for mood and anxiety in the offspring. That low cortisol is associated with PTSD risk may also explain why not all persons with PTSD show identical neuroendocrine abnormalities.

If the release of cortisol facilitates the containment of the SNS response to stress, reduced cortisol signaling could impede the reinstatement of physiologic homeostasis. Because the release of adrenaline facilitates consolidation of the threat memory (McGaugh and Roozendaal, 2002), failure to contain the SNS response might lead to more strongly encoded, hence more subjectively distressing, memories of the event. If low cortisol levels represent a preexisting characteristic, reenforced by "overconsolidation" at the time of the trauma, then failing to properly contain the SNS response to traumatic reminders could perpetuate the intrusive and hyperarousal symptoms of PTSD, leading to the elaboration of avoidance symptoms that commonly occurs in the disorder.

Searching for Brain Mechanisms of PTSD: Early Focus on the Hippocampus

The hippocampus was examined as a region of central importance in PTSD due to its prominent role in both the neuroendocrine stress response and memory alterations (McEwen et al., 1992), similar to those that have been observed in PTSD (Golier et al., 2006). Many studies have demonstrated smaller hippocampal volumes in PTSD (for review see Rauch et al., 2006; Bremner, 2007). However, it has been difficult to attribute these findings to glucocorticoid toxicity resulting from extreme trauma exposure, or even trauma exposure itself, as cortisol levels were not found to be elevated in either the acute or chronic aftermath of trauma nor demonstrated in association with hippocampal alterations (Neylan et al., 2003; Yehuda et al., 2006). Furthermore, prospective, longitudinal studies failed to show change in hippocampal volume over time in persons followed in the acute aftermath of trauma and longitudinally (Bonne et al., 2001). This led investigators to consider that smaller hippocampal volume represented a preexisting marker of vulnerability to PTSD.

The best evidence for this possibility is the strong association between hippocampal volume and identical twins discordant for Vietnam combat exposure (Gilbertson et al., 2002; Pitman et al., 2006). The risk hypothesis was also supported by the demonstration of smaller hippocampal volume in veterans who developed PTSD following their first traumatic exposure compared to those who only developed PTSD in response to a subsequent event (Yehuda et al., 2006). When all PTSD subjects were compared to similarly exposed veterans without PTSD, no changes in hippocampal volume were observed in the PTSD group. Smaller hippocampal volume is correlated with other constitutional factors, such as low IQ (Gurvits et al., 1996; Gilbertson et al., 2001), that have also been associated with increasing risk for the development of PTSD in combat veterans (Macklin et al., 1998), but not necessarily in other traumatized groups. If so, this would explain why Holocaust survivors, who were certainly exposed to severe and chronic trauma but had different risk factors for their traumatic exposures, did not show smaller hippocampal volumes relative to nonexposed subjects (Golier et al., 2005).

If reduced hippocampal volume is related to cognitive capacity or even cognitive deficits associated with PTSD (Vasterling et al., 2001), it might confer risk by making it more difficult for persons to contextualize and reinterpret the experience of trauma in a way that can facilitate recovery. A more limited cognitive flexibility could impede posttraumatic recovery even in the absence of prior experience. Risk factors associated with reduced cortisol signaling may be distinct from these (Yehuda and Flory, 2007), as they might result from early experience and confer risk by interfering with the neurochemical response to environmental stress and impeding reinstatement of physiological homeostasis. Yet, persons with both risk factors may be even more vulnerable to PTSD than those with only one.

Searching for Brain Mechanisms of PTSD: Fear Conditioning and the Amygdala

As noted above, one of the limitations of stress theory was that it could not explain the persistence of biological and psychological fear responses in PTSD well after the end of trauma. One idea that arose was that PTSD might reflect strong associative learning akin to Pavlovian fear conditioning (e.g., Pitman, 1989; Charney and Deutch, 1996). In fear conditioning, a neutral conditioned stimulus (CS) comes to elicit conditioned fear responses (CRs) after being associated with an unconditioned stressful stimulus (US), such as a footshock, that elicits unconditioned stress responses (URs) (e.g., Bolles and Fanselow, 1980; LeDoux, 1996). Translating to PTSD, individuals initially react to a traumatic event (US) with arousal and fear (UCR) and then continue to show arousal (CR) when confronted with trauma-related cues (CS), long after the trauma.

Part of the attraction of fear conditioning was that much was concurrently being learned about the neurobiology of this behavioral paradigm from animal studies (LeDoux,

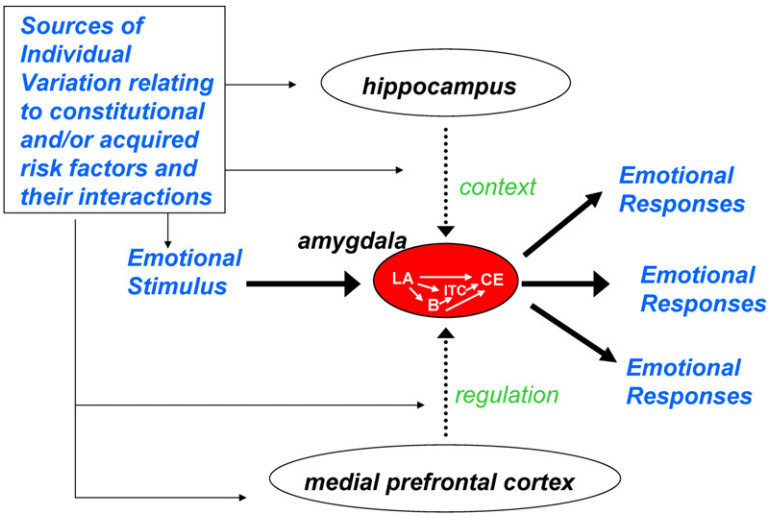

Figure 1. The Amygdala's Ability to Control Fear Responses to Threatening Stimuli Is Regulated by the Hippocampus and Medial Prefrontal Cortex

The hippocampus adds contextual regulation, allowing you to distinguish the difference in threat level posed by a snake in the woods versus in a zoo. The medial prefrontal cortex regulates the degree to which the amygdala expresses fear responses, including the regulation that occurs during extinction of fear. Alterations in information processing by these three areas might account for symptoms in anxiety disorders. However, possibly of greater relevance are the sources of individual variation, either constitutional or environmental, that can affect one of these target areas and lead to different phenotypes with respect to fear-related behavior or biological responses.

1996; Maren, 2001). In brief, fear conditioning occurs as a result of the convergence of information from the CS and US pathways in the lateral nucleus of the amygdala (LA), where synaptic plasticity occurs. When the individual is later exposed to the CS, activity in LA is then transmitted to the central amygdala (directly and through indirect pathways within the amygdala). The latter region then connects to hypothalamic and brainstem areas that control behavioral, ANS, hormonal, and central arousal responses that help the organism cope with the threat. Threat processing by the amygdala is the key step in the circuitry through which catecholamines, ACTH, and cortisol are released into the circulation.

In the 1990s, studies of the human brain began to show a key role for the amygdala in fear conditioning as well (reviewed in Phelps, 2006; Buchel and Dolan, 2000). Thus, damage to the amygdala in humans prevented fear conditioning, and exposure to conditioned fear stimuli led to functional activation of the amygdala, as measured by fMRI. The amygdala is also activated by unlearned threat stimuli, such as fearful or angry faces, in healthy volunteers (Phelps, 2006). For both conditioned and unconditioned threats, it is not necessary to consciously process the stimulus in order to react to it with physiological responses (Dolan and Vuilleumier, 2003).

Consistent with the hypothesis based on animal data regarding fear neurocircuitry, studies of PTSD patients have generally demonstrated increased activation in the amygdala compared to controls, including nontrauma controls and trauma-exposed people who did not develop PTSD, in response to threat stimuli (Rauch et al., 2006; Protopopescu et al., 2005; Bremner, 2007). The fact that in healthy persons threats elicit physiological responses when processed unconsciously makes persons with a hyperactive amygdala, as in PTSD, vulnerable to threats in ways that are difficult for them to protect against. It is not known, at this point, whether a hyperactive amygdala response to threats preexisted and predisposed the development of PTSD or whether it was a consequence of the disorder.

Extinction and PTSD

Conditioned fear responses can be reduced or extinguished by repeatedly presenting the CS without the US. Extinction is an active process, often involving new learning (Myers and Davis, 2007; Sotres-Bayon et al., 2004). In rodents, damage to the medial prefrontal cortex (mPFC) interferes with extinction, as does pharmacological disruption of memory storage in the mPFC or amygdala (Quirk and Beer, 2006; Sotres-Bayon et al., 2007; Myers and Davis, 2007). Fear extinction in the human brain has also been recently shown to involve regions of mPFC and the amygdala (Phelps and LeDoux, 2005), and the size of mPFC areas is related to extinction facility in humans (Milad et al., 2005). Collectively, the animal and human studies suggest that fear disorders may be related to a malfunction of the mPFC that makes it difficult to extinguish or otherwise regulate fears that have been acquired (Morgan et al., 1993; Morgan and LeDoux, 1995; LeDoux, 1996; Quirk and Beer, 2006). These relationships are schematically portrayed in Figure 1. Recent studies in rodents have shown that prolonged stress alters mPFC and amygdala circuits, causing dendritic hypertrophy in mPFC (Radley et al., 2004) and hypertrophy in amygdala (Vyas et al., 2002). Thus, chronic exposures, in particularly, can lead to both a hyperactive amygdala-mediated fear response to threats and a weakened ability of mPFC to regulate these responses. Alternatively, however, persons with a hyperactive amygdala may be more likely to process neutral, unconscious, or implicit threats, which would serve to even further weaken the ability of mPFC to regulate these responses. Indeed, even healthy persons elicit physiological responses to threatening stimuli that are processed unconsciously. As discussed further below, it is not known, at this point, whether a hyperactive amygdala response to threats preexisted and predisposed the development of PTSD, or whether it was a consequence of the disorder.

As in rodents exposed to reminders of fear-producing stimuli, humans with PTSD show an attenuated activation

of mPFC (especially the subgenual ACC) in response to personalized trauma scripts or combat sounds (Bremner et al., 1999; Shin et al., 1999) and show reduced activation, compared to controls, to more generalized negative stimuli in this region (Lanius et al., 2003). Particularly important is that PTSD patients also show a negative correlation between amygdala and mPFC activation in response to fearful versus happy faces, suggesting a disconnect in the normal modulation of amygdala by mPFC (Shin et al., 2005). Thus, in PTSD, there is an increased activation of the amygdala in response to fear-related triggers that is accompanied by an abnormally low response in the brain regions that generally inhibit the amygdala.

The above findings from rodents and humans are consistent in demonstrating alterations in brain regions thought to be important to fear acquisition and recovery. Because PTSD is a clinical syndrome in which an initial fear response does not abate, the neuroimaging findings showing exaggerated amygdala responses recapitulate, but do not explain, the nature of the brain disturbance in PTSD. Indeed, as with stress findings, a limitation of the standard fear conditioning model, and its emphasis on interactions between the amydgala and mPFC, is that it does not address why only some persons exposed to fear develop the abnormality. A modified version of fear conditioning focused on phenotypic differences in fear in a population of subjects (rats or humans) offers a solution, as described below.

Is Altered Fear Processing and Regulation a Consequence of Trauma or Another Risk Factor for PTSD?

One of the challenges of translating information about normal responses to fear and mental disorders in which the emotion of fear may be expressed is that it becomes too difficult to determine whether a noted biological change is, in fact, an aspect of disease physiology. A hyperactive amygdala or hypoactive mPFC may be part of a pathophysiological process that causes or sustains PTSD symptoms (e.g., involving difficulty in mobilizing brain regions that dampen the fear response) or an adaptive one (e.g., "permitting" the amygdala to attend to the stimulus as dangerous because, previously, this was a dangerous stimulus). The cross-sectional nature of most studies does not allow a differentiation between whether findings reflect a response to the focal trauma that initially produced PTSD, an ongoing adaptation to chronic symptoms, or a predisposing risk factor.

The fact that similar observations regarding the exaggerated amygdala activity have also been made in other anxiety disorders, such as panic, specific phobia, and generalized anxiety disorder (Rauch et al., 2003), implies that enhanced activation of the amygdala in response to provocation may be a general consequence of experiencing fear or anxiety regardless of whether the anxiety is anticipatory, based on a real threat, or the product of a disorder.

Particularly important will be studies that compare activation patterns in patients with different disorders using the same behavioral paradigms. For example, exaggerated fear in PTSD and panic disorder may both involve heightened amygdala activity and weakened mPFC regulation, but different responses of the hippocampus or other areas (decreased hippocampal function in PTSD may make PTSD patients insensitive to the context in which fear-arousing triggers occur, while heightened hippocampal function in panic disorder may render them overly sensitive to context and result in extreme avoidance of potentially threatening situations). This notion is based on animal studies showing that the amygdala is regulated by the context of a fear-related stimulus (LeDoux, 1996; Maren, 2001), presumably via projections from the hippocampal formation. A failure of hippocampal contextual processing in distinguishing safe from dangerous contexts could in part explain why patients with PTSD have exaggerated responses to trauma-related triggers. Although the degree to which such deficits in hippocampal processing are linked to hippocampal volume and/or baseline cognitive abilities is unknown, such mediation is certainly possible. Moreover, hippocampally mediated actions relevant to cognitive flexibility (and specifically, the ability to form new associations) may be relevant to recovery from trauma and may similarly provide regulatory influences that help contain excessive amygdala activation. Similarly, preexisting neuroendocrine alterations may underlie differences in responses to traumatic stimuli (Figure 1).

An important point is that the empirical finding of low cortisol in PTSD is seemingly inconsistent with the hypothesis that elevated stress-induced glucocorticoid release mediates the impairment of mPFC and enhancement of amygdala function that occur in stress and that are believed to be mediated by glucocorticoids. At the same time, reduced exposure to glucocorticoids in the amygdala in PTSD could explain in part the failure to adapt to trauma, because glucocorticoid action in the amygdala promotes adaptive cognitive functions such as arousal, attention, and memory formation, thus enhancing survival in threatening situations (Bohus and de Kloet, 1981; McGaugh and Roozendaal, 2002).

Another important issue is the possibility that increased amygdala activation and/or deactivation of the mPFC and/or hippocampus themselves represent preexisting risk factors. This possibility is supported by findings of individual variation in the activation of the amygdala and mPFC based on the extent to which they can deliberately regulate negative emotion in the laboratory, by findings showing that the size of mPFC is related to fear extinction, and to the finding that natural variation in monoamine transporter gene variants is related to fMRI-measured amygdala responses to threatening faces (Hariri et al., 2003). Deliberate emotion regulation skill is a measurable trait associated with an ability to manipulate emotional responses through a conscious cognitive transformation of emotional experience (Urry et al., 2006). Through instruction,

persons can reappraise emotional situations and increase activity in prefrontal areas and decreased activity in the amygdala (Phelps, 2006; Ochsner and Gross, 2005). Thus, persons who have difficulty in emotional regulation may be particularly vulnerable in highly stressful situations and may acquire stronger fear responses or be impaired at recovering from fear through normal homeostatic processes, implicit regulation (as in extinction), or explicit regulation (as in reappraisal).

Adapting Basic Neuroscience Approaches to Achieve Maximal Translational Utility: Searching for Phenotypic Differences Rather than Typical Responses to Stress

In addition to the fear conditioning model already discussed, a number of animal models of PTSD, based on responses to threats and other stressors, have been proposed (Miller and McEwen, 2006; Cohen and Zohar, 2004; Adamec et al., 2006; Mechiel Korte and De Boer, 2003; Rau et al., 2005; Rittenhouse et al., 1992; Richter-Levin, 1998; Cohen et al., 2004). Like fear conditioning, these are potentially very useful because of their ability to identify brain regions that may underpin PTSD symptoms. However, for the most part, animal models, including fear conditioning models, have examined the effects of stressors on "normal" animals. As noted above, a major limitation, and translational gap, in the basic science approaches is that they have emphasized the normative biological consequences of trauma exposure. Because a critical question for PTSD is why only some people develop the disorder, animal models that examine individual differences, or phenotypic differences between subgroups in the population, in response to stressors might be especially informative.

Like humans, outbred rat strains exhibit stable individual differences in a wide range of emotional behaviors (Garcia and Armario, 2001), including fear or anxiety-related responses (Cools et al., 1990; Cure and Rolinat, 1992). Studies of fear conditioning could also delineate the range of responses to a uniform provocation rather than collect information about the "prototypic" animal or human by combining observations from groups assumed to be homogeneous.

There are only a few examples of attempts to develop animal models for PTSD based on the premise of examining individual differences to a uniform provocation that yields long-term biobehavioral consequences analogous to those in PTSD, though criteria for establishing animal models for PTSD were delineated a decade earlier (Yehuda and Antelman, 1993). One example involves exposure of rats to the scent of a predator (cat) and, subsequently, of reminders (Cohen et al., 2006a). This study established behavioral cut-off criteria based on both fearful/avoidant behavior and hypervigilant/hyperalert responses, paralleling aspects of PTSD symptoms in humans, allowing for group differences to the same provocation. This model established proof of concept for several biological correlates of PTSD (Cohen and Zohar, 2004) and also demonstrated reliable biological and behavioral differences in these measures across strains. For example, Lewis rats had a greater susceptibility to negative consequences of the experimental stress paradigm, associated with low cortisol responses to stress, than Fischer rats (Cohen et al., 2006b). However, exogenous administration of cortisol to Lewis rats before applying the stressor decreased the behavioral consequences of fear conditioning (Matar et al., 2006). Furthermore, by manipulating conditions such as timing of the stressors as well as features of early environment prior to stress, this model yielded information demonstrating that rats exposed to trauma as juveniles were more vulnerable to adverse effects of fear conditioning, thus providing a platform by which to compare effects of "early" versus "later" exposures in rats (Cohen et al., 2007a).

A slightly different approach attempted to distinguish between two fundamentally important memory processes in PTSD that seem to involve different neurobiological substrates (Siegmund and Wotjak, 2006). This was achieved by exposing animals to a single stressor but distinguishing between behavioral responses in response to contextual reminders (associative fear, relevant to reexperiencing and avoidance) and sensitization (nonassociative fear, relevant to hyperarousal). Recent studies using this paradigm have yielded face validity, in that the behavioral "symptoms" of PTSD can be produced in a dose-dependent manner by even a single exposure, persist for a considerable length of time, include behaviors from a wide range of domains associated with PTSD, and show individual variation. The model has predictive validity in that the core features of the phenotype respond to common pharmacological interventions, such as SSRI, and also utility, because the stressor can be varied in intensity without inducing habituation (Siegmund and Wotjak, 2007).

The two examples above are singled out because of the care taken to model critical aspects of the disorder. However, little is known about the underlying brain mechanisms involved in these animal models. In contrast, recent studies of fear conditioning, especially cued fear conditioning (as opposed to contextual fear conditioning, which is less understood neurobiologically), offer a model in which phenotypic differences in fear can be related to specific brain circuits and cellular, synaptic, molecular, and genetic mechanisms. Bush et al. (2007) examined conditioned fear reactivity in a group of outbred rats (Figure 2). When tested 48 hr after conditioning, individual differences in fear reactivity conformed roughly to a Gaussian distribution. A typical study would focus on the middle of this distribution (the average response). By comparing animals in the middle, upper, and lower ends of the distribution, it is possible to study not just the average fear response, but also individuals that are highly reactive (possibly PTSD prone) and weakly reactive (possibly resilient). However, as noted above, PTSD might reflect a failure to recover from normal fear learning. An additional study therefore focused on rats that were highly reactive and then subjected to extinction. Two additional phenotypes emerged, one that recovered (extinguished fear)

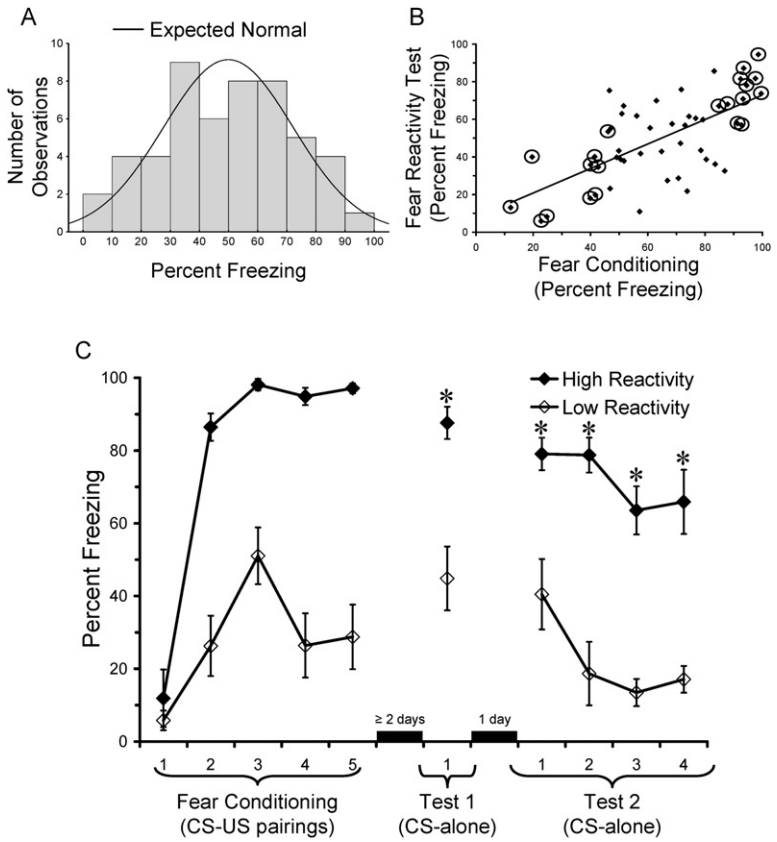

Figure 2. Phenotypic Differences in Fear Reactivity

(A) Frequency histogram showing the distribution of fear reactivity test scores (n = 51). Data are from the average percent freezing responses to the CS-alone presentations across both tests.

(B) Scatterplot showing the correlation between average freezing scores obtained during fear conditioning (x axis, criterion data) and average freezing scores obtained during testing (y axis, test data). Circled data points indicate rats that formed the high and low fear reactivity groups. The trend line indicates the correlation between the criterion and test scores.

(C) Line graph shows that the phenotypic differences in freezing (mean ± SEM) identified during conditioning are stable across the conditioning and two testing sessions (* indicates significant difference between high/low fear reactivity phenotypes, $p < 0.01$).

Reproduced from data in Bush et al. (2007).

quickly and one that was significantly slower to recover (Figure 3). The latter might be particularly useful as a model of PTSD. Thus, examination of phenotypic variation in the response to fear conditioning will yield more relevant information to PTSD, as it addresses the essential question of why some persons demonstrate intense and prolonged reactions to fear-provoking events (i.e., as in PTSD), while others show more attenuated responses or easily recover from them.

With distinct phenotypes established, gene function in relevant brain circuits can be examined with microarray analysis in order to identify relevant molecular processes and/or identify genes that can be subsequently genotyped, in the servie of explaining individual differences in fear. That at least some differences in fear reactivity are heritable is supported by observations in both people (Kagan, 1994; Cohen et al., 2007b) and animals (Gray, 1987). On the other hand, recent studies in monkeys using stress inoculation training have suggested that differences in amygdala/mPFC correlations can be modified by early environment (Parker et al., 2005). The possibility offered by capturing constitutional and acquired factors that explain variation in amygdala and mPFC responses, and testing their relevance to PTSD, represents important directions for the future. As argued above, the fear conditioning model in rodents offers many advantages for such work.

Genetic and Nongenetic Contributions to PTSD Risk

The most compelling evidence for an association between genetic factors and PTSD has been findings of an increased prevalence of PTSD among twins who are discordant with respect to traumatic environmental exposures (Stein et al., 2002; True et al., 1993; Koenen et al., 2002). However, to date, very few genes for PTSD have been identified. Significant associations were found with a variable number tandem repeat (*VNTR*) polymorphism in an untranslated region of the dopamine (DA) transporter gene (Segman and Shalev, 2003) in 93 PTSD patients compared with 95 non-PTSD trauma survivors. No association was found between two GR polymorphisms (*N363S* and *BclI*) and the diagnosis of PTSD in 118 PTSD patients compared with 42 unaffected control subjects, though PTSD patients homozygous for the *BclI* GG genotype tended to show enhanced GR and displayed more severe PTSD symptoms (Bachmann et al., 2005).

The limited number of gene-related findings in PTSD may reflect the complexity of executing research in this area. Alternatively, it may suggest that the enduring pretraumatic changes are not associated with specific genetic polymorphisms, but rather with gene-related differences resulting from epigenetic alterations. Epigenetics refers to a transgenerationally transmissible

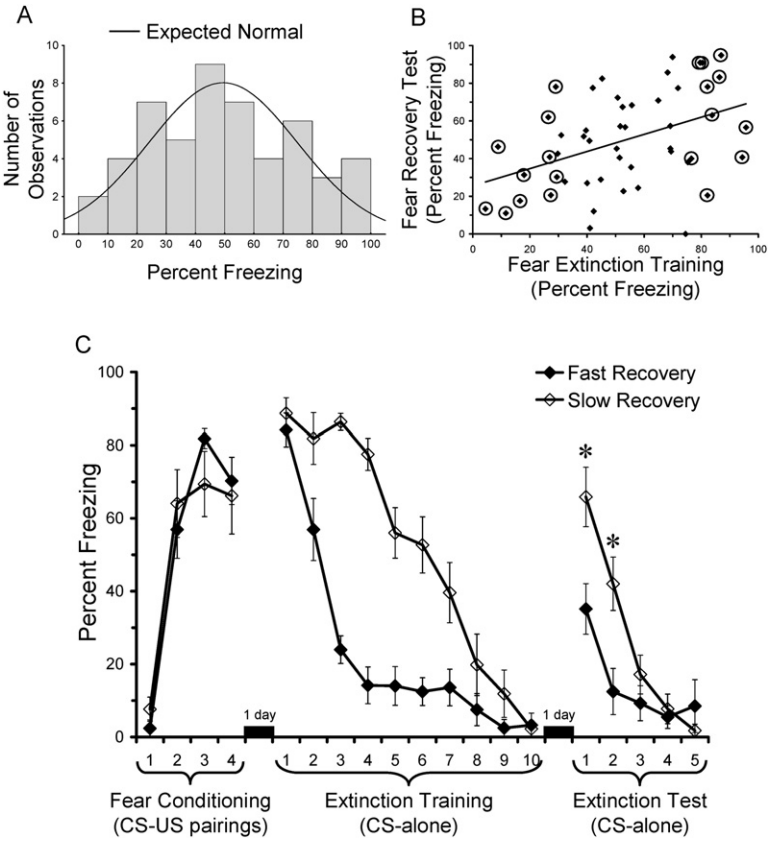

Figure 3. Phenotypic Differences in Fear Recovery

(A) Frequency histogram showing the distribution of fear recovery test scores (n = 51). Data are from the average percent freezing responses to the first two CS-alone presentations during the extinction retrieval test.

(B) Scatterplot showing the correlation between average freezing scores obtained during the early phase (trials 5 to 7) of fear extinction training (x axis, criterion data) and average freezing scores obtained during the first two trials of the extinction test (y axis, test data). Circled data points indicate rats that formed the fast and slow fear reactivity groups. The trend line indicates the correlation between the criterion and test scores.

(C) Line graph shows that phenotypic differences in rate of fear recovery during extinction training (mean ± SEM) predict the sustainability of fear recovery in the extinction retrieval test. Both groups showed comparable levels of fear reactivity prior to extinction training and comparable levels of fear reduction by the end of extinction training (* indicates significant difference between fast/slow fear recovery phenotypes, $p < 0.05$).

Reproduced from data in Bush et al. (2007).

functional change in the genome that can be altered by environmental events and does not involve an alteration of sequence (Novik et al., 2002). Such mechanisms offer the possibility of defining concrete molecular pathways by which environmental risk factors might directly alter the expression of a gene, thus forming a basis for individual differences in a function relating to the gene and, perhaps, vulnerability to disorder (Sutherland and Costa, 2003). These are likely to be relevant to PTSD and might specifically explain the origin of glucocorticoid-related alterations associated with PTSD and PTSD risk.

Indeed, DNA methylation has been demonstrated as a mechanism in programming the activity of genes regulating HPA activity by early life events (i.e., differences in maternal care) (Weaver et al., 2004) paralleling observations that early life events are associated both with the development of PTSD (Nishith et al., 2000; Breslau et al., 1999; Koenen et al., 2007) and the HPA axis alterations (Yehuda, 2002b) described in this condition. Such changes in the rat pups result in permanent changes in hippocampal GR expression and HPA function (Francis et al., 1999) and provide a clear molecular link between early environment and gene expression and function. The alterations observed are in the same direction as those described in PTSD (i.e., increased GR sensitivity, enhanced cortisol to DEX, lower cortisol), offering proof of principle that environmental exposures can result in such changes. Epigenetic contributions to HPA alterations in PTSD would explain the relationship between such alterations and pretrauma risk and may be particularly relevant to transgenerational transmission of risk from mothers to offspring.

Other Challenges for the Translational Research

Also important to translational studies of PTSD is the use of a developmental neurobiological approach, spanning across the entire course of the illness. Symptom severity in PTSD can wax and wane over several decades. Biological alterations reflecting risk rather than pathophysiology may not account for this phenomenon. On the other hand, even putative risk factors such as glucocorticoid responsiveness and hippocampal volume show changes in response to factors such as environmental exposures, duration of illness, comorbidity, and aging. Thus, it is important to understand whether risk factors influence, or are influenced by, other parameters associated with PTSD.

A recent longitudinal studies of PTSD in aging subjects demonstrated that cortisol levels in trauma survivors may influence the longitudinal course of PTSD and/or interactions between PTSD and age-related neuroendocrine alterations (Yehuda et al., 2007c). At a 10 year follow-up, there was a general decline in cortisol levels in Holocaust survivors who maintained their diagnostic status or developed PTSD, but an increase in those who demonstrated remission. Cortisol levels at the initial assessment

predicted remission or relapse, though they themselves showed change over time (Yehuda et al., 2007c).

That risk factors are not immutable but may change over time should be carefully considered in interpreting biological studies in PTSD. For example, smaller hippocampal volumes have been noted more often in younger cohorts with PTSD. However, two investigations of older combat veterans failed to observe this association (Yehuda et al., 2006; Freeman et al., 2006). Because normal aging is associated with hippocampal atrophy, it is possible that smaller hippocampal volumes in PTSD may be particularly evident at a time at which healthy subjects are not manifesting atrophy in this region.

Basic neuroscience research can help anticipate the relevant systems that should be investigated using a developmental perspective. If biological alterations reflecting a superimposition of PTSD and aging diverge from normal patterns associated with either PTSD or aging, such as they do with respect to both cortisol and hippocampal-related alterations, this information will provide important insights for interpreting variables previously associated with risk, pathophysiology of PTSD, and chronic effects of trauma exposure.

Treatment Implications

There have been several recent biological approaches to PTSD prevention based on clinical neuroscience data. The first builds on findings of lower cortisol levels in PTSD as exerting permissive effects to facilitate increased catecholamines in the immediate aftermath of trauma. Accordingly, cortisone has been administered to patients immediately after experiencing acute trauma (usually associated with critical illness) in several randomized clinical trials. Cortisol treatment demonstrated specificity for the prevention of recurring traumatic memories (Schelling et al., 2006; de Quervain, 2006). Animal studies have also confirmed the potential utility of cortisol-related treatments in preventing "PTSD-related" consequences of fear conditioning (Cohen et al., 2006c). In a recently developed paradigm in which rats are exposed to single-prolonged stress, administration of a GR antagonist prior to SPS exposure prevented the normally observed potentiation of fear conditioning in the amygdala, impairment of LTP in the hippocampus, enhanced inhibition of the HPA axis, and increased expression of GR in the hippocampus with this treatment (Kohda et al., 2007). Inactivating GR receptors in the amygdala postretrieval similarly blocked the "traumatic memory" (i.e., behavioral response to conditioning) (Tronel and Alberini, 2007). Given the role of GR receptors in both traumatic memory processing and PTSD pathophysiology, future approaches may include the use of GR blockers, such as mifipristone, in the treatment of PTSD.

A more direct containment of SNS in the immediate aftermath of trauma can be accomplished using catecholaminergic drugs such as propranolol and guanfacine. However, neither has been shown to prevent PTSD (Neylan et al., 2006; Pitman et al., 2002; Vaiva et al., 2003). In one randomized trial, propranolol impeded the development of PTSD-related psychophysiological alterations (Pitman et al., 2002). These approaches are promising, yet the disconnection between what would be predicted based on ameliorative effects on fear conditioning when exposing animals to such drugs (Shinba et al., 2001; Levy et al., 2001) and clinical trials serves as a cautionary note for the increased complexity of humans. Ultimate PTSD prevention with biological mechanisms may require identifying a broader range of factors, including genetic or epigenetic modifications that underlie failure of reinstatement of physiological homeostasis.

On the basis of findings of SNS alterations in PTSD, it might be predicted that catecholaminergic drugs would be effective in treating this condition. Although findings for α2-adrenergic antagonists have been mixed, treatment with the α1-adrenergic antagonist prasozin has been shown to be extremely effective, particularly in reducing nightmares in PTSD (Raskind et al., 2003), with effects confirmed in animal models (Manion et al., 2007). More recently, efficacy has been achieved for chronic PTSD symptoms using glucocorticoids (Aerni et al., 2004). However, the rationale for positive glucocorticoid effects in chronic PTSD appears to be more related to glucocorticoid-induced inhibition of memory retrieval rather than its role in containment of the stress responses (de Quervain, 2006).

Advances in basic and clinical neuroscience studies of fear may in the future prove to be relevant to providing strategies for supplementing psychotherapeutic approaches. One common approach to the clinical treatment of PTSD has focused on the facilitation of fear extinction through cognitive behavioral therapy. However, this approach is often difficult to implement due to high drop-out rates and the need for good adherence among patients. Moreover, even under the best of circumstances, extinction is known to exhibit spontaneous recovery, which means that the fear simply comes back (Myers and Davis, 2007). If the extinction process could be facilitated through some means, such as the acute administration of a drug in connection with the therapeutic session, the success rate might increase. One possible agent is the partial NMDA agonist d-cycloserine (DCS). Administration of this drug facilitated extinction training in rats and then produced a more rapid extinction of phobic fear in anxiety disordered patients (Ressler et al., 2004). A pilot controlled trial found that DCS had some efficacy for the treatment of PTSD (Heresco-Levy et al., 2002). Though promising, more work is needed to evaluate how DCS might be best used in PTSD and how effective it will be.

A different approach emerging from animal studies involves the blockade of memory reconsolidation (Nader et al., 2000; Nader and Wang, 2006). Although much of the initial work in animals involved the use of protein synthesis blockers, later studies in rats showed that the β-adrenergic antagonist propranolol was also effective in blocking memory reconsolidation when given

systemically or directly in the amygdala (Debiec and LeDoux, 2004, 2006; Debiec and Altemus, 2006). Propranolol is believed to mimic the effects of protein synthesis inhibitors by negatively modulating, via protein kinases, protein synthesis. Although propranolol has been reported to be somewhat effective in preventing the development of PTSD (Pitman et al., 2002), the reconsolidation approach is potentially useful in chronic PTSD because it only depends on pairing of the drug with the retrieval of traumatic memory. A pilot study in PTSD patients demonstrated some efficacy (Brunet et al., 2007).

Advances in understanding whether alterations in fear conditioning in PTSD are related to preexisting traits (e.g., ability to activate mPFC or inhibit amygdala in response to negative stimuli) or state may one day provide an elegant tool for helping to predict persons who are most likely to benefit from cognitive behavioral therapies and even persons who might particularly benefit from pharmacological augmentation of psychotherapy. Possibly, patients who respond to cognitive behavioral therapy possess an enhanced ability to modulate activity in relevant brain regions and fear circuits when exposed to tasks involving emotion regulation or cognitive restructuring. Alternatively, studying fear circuits following successful treatment may help confirm that the manipulation of such circuits is the active ingredient of such therapies, designed to promote extinction.

Future Horizons: Delineating the Contribution of Resilience to Individual Differences Associated with Risk and PTSD

The literature regarding the homogeneous effects of stressful or fear-provoking stimuli has allowed the field of clinical neuroscience to define relevant circuits or systems that might be involved in PTSD, but at the same time has fallen short of explaining the mechanisms through which stress exposure directly contributes to PTSD. This is because classic studies using animal models of stress or fear have not explained the variation in phenotypes that might explain why some people develop PTSD while others do not. We have suggested above that identification of neurobiological correlates of PTSD requires an extension of prior translational approaches aimed at examining the contribution of stress exposure to the development of this condition, so as to focus on biological correlates of individual differences.

For simplicity, we have emphasized the distinction between persons with and without PTSD. However, the latter consists of a diverse group who, even though unaffected with PTSD, may nonetheless show a wide range of effects. Indeed, the complexity of the relationship between stress exposure and any psychopathology can be further illustrated by considering that not only does exposure to stressful life events sometimes fail to contribute to psychopathology, but that depending on the timing and intensity of the exposure(s) and/or other individual differences, it may actually be protective or "inoculating." An important direction in translational neuroscience studies concerns an examination of the bidirectional effects of stress, with those at the extreme ends showing not only a lack of a poor outcome, but the presence of a beneficial one. Examples of animal models of stress that might be particularly helpful in this regard include studies of stress-inoculated animals (Parker et al., 2005) that are generated through the presentation of early maternal separations in early development and animals exposed to maternal handling.

If the effects of stress range beyond detrimental to neutral and extend to include beneficial outcomes, this would serve as a basis for understanding both resilience and PTSD. Indeed, if there are preexisting factors that increase vulnerability, there might also be distinct, countervailing resilience-related traits that may either contribute to recovery from stress, being resistant to stress effects, or even using stressful experiences as a means of achieving mastery. What remains unknown is whether the resilient phenotype fails to demonstrate, or shows directionally different changes in the same biological systems that are altered in PTSD, or rather, manifests biological attributes in different systems that serve to regulate, countervail, or otherwise modify the biological responses to stress that impede recovery from trauma. The answers to these questions will undoubtedly yield important insights into prophylaxis and treatment of PTSD. Exploiting new developments in techniques of genotyping, microarray analysis, methylation, molecular biology, and functional neuroimaging will allow for an expansion of relevant biological markers. The opportunity to combine these technological advancements with an approach aimed at elucidating individual differences represents an exciting frontier for translational studies of both stress and PTSD.

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REFERENCES

Adamec, R.E., Blundell, J., and Burton, P. (2006). Relationship of the predatory attack experience to neural plasticity, pCREB expression and neuroendocrine response. Neurosci. Biobehav. Rev. *30*, 356–375.

Adams, R.E., and Boscarino, J.A. (2006). Predictors of PTSD and delayed PTSD after disaster: the impact of exposure and psychosocial resources. J. Nerv. Ment. Dis. *194*, 485–493.

Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A., Nitsch, R.M., Schnyder, U., and de Quervain, D.J. (2004). Low-dose cortisol for symptoms of posttraumatic stress disorder. Am. J. Psychiatry *161*, 1488–1490.

American Psychiatric Association (1980). Diagnostic and Statistical Manual of Mental Disorders, Third Edition (Washington, D.C: American Psychiatric Association).

Bachmann, A.W., Sedgley, T.L., Jackson, R.V., Gibson, J.N., Young, R.M., and Torpy, D.J. (2005). Glucocorticoid receptor polymorphisms

and post-traumatic stress disorder. Psychoneuroendocrinology *30*, 297–306.

Bohus, B., and de Kloet, E.R. (1981). Adrenal steroids and extinction behavior: antagonism by progesterone, deoxycorticosterone and dexamethasone of a specific effect of corticosterone. Life Sci. *28*, 433–440.

Bolles, R.C., and Fanselow, M.S. (1980). A perceptual-defensive-recuperative model of fear and pain. Behav. Brain Sci. *3*, 291–323.

Bonne, O., Brandes, D., Gilboa, A., Gomori, J.M., Shenton, M.E., Pitman, R.K., and Shalev, A.Y. (2001). Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am. J. Psychiatry *158*, 1248–1251.

Bremner, J.D. (2007). Functional neuroimaging in post-traumatic stress disorder. Expert Rev. Neurother. *7*, 393–405.

Bremner, J.D., Staib, L.H., Kaloupek, D., Southwick, S.M., Soufer, R., and Charney, D.S. (1999). Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol. Psychiatry *45*, 806–816.

Bremner, J.D., Vermetten, E., and Kelley, M.E. (2007). Cortisol, dehydroepiandrosterone (DHEA), and estradiol measured over 24 hours in women with childhood sexual abuse-related posttraumatic stress disorder (PTSD). J. Nerv. Ment. Dis., in press.

Breslau, N., and Kessler, R.C. (2001). The stressor criterion in DSM-IV posttraumatic stress disorder: an empirical investigation. Biol. Psychiatry *50*, 699–704.

Breslau, N., Chilcoat, H.D., Kessler, R.C., and Davis, G.C. (1999). Previous exposure to trauma and PTSD effects of subsequent trauma: results from the Detroit Area Survey of Trauma. Am. J. Psychiatry *156*, 902–907.

Bromet, E., Sonnega, A., and Kessler, R.C. (1998). Risk factors for DSM-III-R posttraumatic stress disorder: findings from the National Comorbidity Survey. Am. J. Epidemiol. *147*, 353–361.

Brunet, A., Orr, S.P., Tremblay, J., Robertson, K., Nader, K., and Pitman, R.K. (2007). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. J. Psychiatr. Res., in press. Published online June 22, 2007. 10.1016/j.jpsychires.2007.05.006.

Buchel, C., and Dolan, R.J. (2000). Classical fear conditioning in functional neuroimaging. Curr. Opin. Neurobiol. *10*, 219–223.

Bush, D.E.A., Sortres-Bayon, F., and LeDoux, J.E. (2007). Individual differences in fear: Isolating fear reactivity and fear recovery phenotypes. J. Trauma. Stress *20*, 413–422.

Charney, D.S., and Deutch, A. (1996). A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. Crit. Rev. Neurobiol. *10*, 419–446.

Cohen, H., and Zohar, J. (2004). An animal model of posttraumatic stress disorder: the use of cut-off behavioral criteria. Ann. N Y Acad. Sci. *1032*, 167–178.

Cohen, H., Zohar, J., Matar, M.A., Zeev, K., Loewenthal, U., and Richter-Levin, G. (2004). Setting apart the affected: the use of behavioral criteria in animal models of post traumatic stress disorder. Neuropsychopharmacology *29*, 1962–1970.

Cohen, H., Matar, M.A., Richter-Levin, G., and Zohar, J. (2006a). The contribution of an animal model toward uncovering biological risk factors for PTSD. Ann. N Y Acad. Sci. *1071*, 335–350.

Cohen, H., Zohar, J., Gidron, Y., Matar, M.A., Belkind, D., Loewenthal, U., Kozlovsky, N., and Kaplan, Z. (2006b). Blunted HPA axis response to stress influences susceptibility to posttraumatic stress response in rats. Biol. Psychiatry *59*, 1208–1218.

Cohen, H., Kaplan, Z., Matar, M.A., Loewenthal, U., Kozlovsky, N., and Zohar, J. (2006c). Anisomycin, a protein synthesis inhibitor, disrupts traumatic memory consolidation and attenuates posttraumatic stress response in rats. Biol. Psychiatry *60*, 7–76.

Cohen, H., Kaplan, Z., Matar, M.A., Loewenthal, U., Zohar, J., and Richter-Levin, G. (2007a). Long-lasting behavioral effects of juvenile trauma in an animal model of PTSD associated with a failure of the autonomic nervous system to recover. Eur. Neuropsychopharmacol. *17*, 464–477.

Cohen, H., Geva, A.B., Matar, M.A., Zohar, J., and Kaplan, Z. (2007b). Post-traumatic stress behavioural responses in inbred mouse strains: can genetic predisposition explain phenotypic vulnerability? Int. J. Neuropsychopharmacol., in press. Published online July 27, 2007. 10.1017/S1461145707007912.

Cools, A.R., Brachten, R., Heeren, D., Willemen, A., and Ellenbroek, B. (1990). Search after neurobiological profile of individual-specific features of Wistar rats. Brain Res. Bull. *24*, 49–69.

Cure, M., and Rolinat, J.P. (1992). Behavioral heterogeneity in Sprague-Dawley rats. Physiol. Behav. *51*, 771–774.

de Quervain, D.J. (2006). Glucocorticoid-induced inhibition of memory retrieval: implications for posttraumatic stress disorder. Ann. N Y Acad. Sci. *1071*, 216–220.

Debiec, J., and LeDoux, J.E. (2004). Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. Neuroscience *129*, 267–272.

Debiec, J., and Altemus, M. (2006). Toward a new treatment for traumatic memories. Cerebrum, 2–11.

Debiec, J., and LeDoux, J.E. (2006). Noradrenergic signaling in the amygdala contributes to the reconsolidation of fear memory: treatment implications for PTSD. Ann. N Y Acad. Sci. *1071*, 521–524.

Delahanty, D.L., Raimonde, A.J., Spoonster, E., and Cullado, M. (2003). Injury severity, prior trauma history, urinary cortisol levels, and acute PTSD in motor vehicle accident victims. J. Anxiety Disord. *17*, 149–164.

Dolan, R.J., and Vuilleumier, P. (2003). Amygdala automaticity in emotional processing. Ann. N Y Acad. Sci. *985*, 348–355.

Francis, D.D., Champagne, F.A., Liu, D., and Meaney, M.J. (1999). Maternal care, gene expression, and development of individual differencesin stress reactivity. Ann. N Y Acad. Sci. *896*, 66–84.

Freeman, T., Kimbrell, T., Booe, L., Myers, M., Cardwell, D., Lindquist, D.M., Hart, J., and Komoroski, R.A. (2006). Evidence of resilience: neuroimaging in former prisoners of war. Psychiatry Res. *146*, 59–64.

Garcia, A., and Armario, A. (2001). Individual differences in the recovery of the hypothalamic-pituitary-adrenal axis after termination of exposure to a severe stressor in outbred male Sprague-Dawley rats. Psychoneuroendocrinology *26*, 363–374.

Gilbertson, M.W., Gurvits, T.V., Lasko, N.B., Orr, S.P., and Pitman, R.K. (2001). Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. J. Trauma. Stress *14*, 413–432.

Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., and Pitman, R.K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat. Neurosci. *5*, 1242–1247.

Golier, J.A., Yehuda, R., De Santi, S., Segal, S., Dolan, S., and de Leon, M.J. (2005). Absence of hippocampal volume differences in survivors of the Nazi Holocaust with and without PTSD. Psychiatry Res. *139*, 53–64.

Golier, J.A., Harvey, P.D., Legge, J., and Yehuda, R. (2006). Memory performance in older trauma survivors: implications for the longitudinal course of PTSD. Ann. N Y Acad. Sci. *1071*, 54–66.

Gray, J.A. (1987). The Psychology of Fear and Stress (New York: Cambridge University Press).

Gurvits, T.V., Shenton, M.E., Hokama, H., Ohta, H., Lasko, N.B., Gilbertson, M.W., Orr, S.P., Kikinis, R., Jolesz, F.A., McCarley, R.W., and Pitman, R.K. (1996). Magnetic resonance imaging study of

hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol. Psychiatry *40*, 1091–1099.

Hariri, A.R., Mattay, V.S., Tessitore, A., Fera, F., and Weinberger, D.R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. Biol. Psychiatry *53*, 494–501.

Heresco-Levy, U., Kremer, I., Javitt, D.C., Goichman, R., Reshef, A., Blanaru, M., and Cohen, T. (2002). Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. Int. J. Neuropsychopharmacol. *5*, 301–307.

Holsboer, F. (2003). Corticotropin-releasing hormone modulators and depression. Curr. Opin. Investig. Drugs *4*, 46–50.

Kagan, J. (1994). Galen's Prophecy: Temperament in Human Nature (New York: Basic Books).

Kardiner, A. (1941). The Traumatic Neuroses of War (New York: Hoeber).

Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., and Nelson, C.B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. Arch. Gen. Psychiatry *52*, 1048–1060.

Kessler, R.C., Chiu, W.T., Demler, O., and Walters, E.E. (2005). Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Arch. Gen. Psychiatry *62*, 617–627.

Koenen, K.C., Harley, R., Lyons, M.J., Wolfe, J., Simpson, J.C., Goldberg, J., Eisen, S.A., and Tsuang, M. (2002). A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. J. Nerv. Ment. Dis. *190*, 209–218.

Koenen, K.C., Moffitt, T.E., Poulton, R., Martin, J., and Caspi, A. (2007). Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort. Psychol. Med. *37*, 181–192.

Kohda, K., Harada, K., Kato, K., Hoshino, A., Motohashi, J., Yamaji, T., Morinobu, S., Matsuoka, N., and Kato, N. (2007). Glucocorticoid receptor activation is involved in producing abnormal phenotypes of single-prolonged stress rats: A putative post-traumatic stress disorder model. Neuroscience *148*, 22–33.

Lanius, R.A., Williamson, P.C., Hopper, J., Densmore, M., Boksman, K., Gupta, M.A., Neufeld, R.W., Gati, J.S., and Menon, R.S. (2003). Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. Biol. Psychiatry *53*, 204–210.

LeDoux, J.E. (1996). The Emotional Brain (New York: Simon and Schuster).

Levy, A., Kadar, T., and Dachir, S. (2001). An animal model for studying therapeutic drugs against post-traumatic stress disorder. Mil. Med. ***166***(12, Suppl), 74–75.

Macklin, M.L., Metzger, L.J., Litz, B.T., McNally, R.J., Lasko, N.B., Orr, S.P., and Pitman, R.K. (1998). Lower precombat intelligence is a risk factor for posttraumatic stress disorder. J. Consult. Clin. Psychol. *66*, 323–326.

Manion, S.T., Gamble, E.H., and Li, H. (2007). Prazosin administered prior to inescapable stressor blocks subsequent exaggeration of acoustic startle response in rats. Pharmacol. Biochem. Behav. *86*, 559–565.

Maren, S. (2001). Neurobiology of Pavlovian fear conditioning. Annu. Rev. Neurosci. *24*, 897–931.

Mason, J.W., Giller, E.L., Kosten, T.R., Ostroff, R.B., and Podd, L. (1986). Urinary free-cortisol levels in posttraumatic stress disorder patients. J. Nerv. Ment. Dis. *174*, 145–149.

Matar, M.A., Cohen, H., Kaplan, Z., and Zohar, J. (2006). The effect of early poststressor intervention with sertraline on behavioral responses in an animal model of post-traumatic stress disorder. Neuropsychopharmacology *31*, 2610–2618.

McEwen, B.S., Gould, E.A., and Sakai, R.R. (1992). The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. Br. J. Psychiatry Suppl. *15*, 18–23.

McFarlane, A.C. (2000). Posttraumatic stress disorder: a model of the longitudinal courseand the role of risk factors. J. Clin. Psychiatry *61* (*Suppl 5*), 15–20.

McGaugh, J.L., and Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. Curr. Opin. Neurobiol. *12*, 205–210.

Mechiel Korte, S., and De Boer, S.F. (2003). A robust animal model of state anxiety: fear-potentiated behaviour in the elevated plus-maze. Eur. J. Pharmacol. *463*, 163–175.

Milad, M.R., Quinn, B.T., Pitman, R.K., Orr, S.P., Fischl, B., and Rauch, S.L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proc. Natl. Acad. Sci. USA *102*, 10706–10711.

Miller, M.M., and McEwen, B.S. (2006). Establishing an agenda for translational research on PTSD. Ann. N Y Acad. Sci. *1071*, 294–312.

Morgan, M.A., and LeDoux, J.E. (1995). Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behav. Neurosci. *109*, 681–688.

Morgan, M.A., Romanski, L.M., and LeDoux, J.E. (1993). Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci. Lett. *163*, 109–113.

Munck, A., Guyre, P.M., and Holbrook, N.J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr. Rev. *5*, 25–44.

Myers, K.M., and Davis, M. (2007). Mechanisms of fear extinction. Mol. Psychiatry *12*, 120–150.

Nader, K., and Wang, S.H. (2006). Fading in. Learn. Mem. *13*, 530–535.

Nader, K., Schafe, G.E., and LeDoux, J.E. (2000). The labile nature of consolidation theory. Nat. Rev. Neurosci. *1*, 216–219.

Neylan, T.C., Schuff, N., Lenoci, M., Yehuda, R., Weiner, M.W., and Marmar, C.R. (2003). Cortisol levels are positively correlated with hippocampal N-acetylaspartate. Biol. Psychiatry *54*, 1118–1121.

Neylan, T.C., Lenoci, M., Samuelson, K.W., Metzler, T.J., Henn-Haase, C., Hierholzer, R.W., Lindley, S.E., Otte, C., Schoenfeld, F.B., Yesavage, J.A., and Marmar, C.R. (2006). No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. Am. J. Psychiatry *163*, 2186–2188.

Nishith, P., Mechanic, M.B., and Resick, P.A. (2000). Prior interpersonal trauma: The contribution to current PTSD symptoms in female rape victims. J. Abnorm. Psychol. *109*, 20–25.

Novik, K.L., Nimmrich, I., Genc, B., Maier, S., Piepenbrock, C., Olek, A., and Beck, S. (2002). Epigenomics: genome-wide study of methylation phenomena. Curr. Issues Mol. Biol. *4*, 111–128.

Ochsner, K.N., and Gross, J.J. (2005). The cognitive control of emotion. Trends Cogn. Sci. *9*, 242–249.

O'Donnell, T., Hegadoren, K.M., and Coupland, N.C. (2004). Noradrenergic mechanisms in the pathophysiology of post-traumatic stress disorder. Neuropsychobiology *50*, 273–283.

Parker, K.J., Buckmaster, C.L., Justus, K.R., Schatzberg, A.F., and Lyons, D.M. (2005). Mild early life stress enhances prefrontal-dependent response inhibition in monkeys. Biol. Psychiatry *57*, 848–855.

Phelps, E.A. (2006). Emotion and cognition: insights from studies of the human amygdala. Annu. Rev. Psychol. *57*, 27–53.

Phelps, E.A., and LeDoux, J.E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron *48*, 175–187.

Pitman, R.K. (1989). Post-traumatic stress disorder, hormones, and memory. Biol. Psychiatry *26*, 221–223.

Pitman, R.K., Sanders, K.M., Zusman, R.M., Healy, A.R., Cheema, F., Lasko, N.B., Cahill, L., and Orr, S.P. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol. Psychiatry *51*, 189–192.

Pitman, R.K., Gilbertson, M.W., Gurvits, T.V., May, F.S., Lasko, N.B., Metzger, L.J., Shenton, M.E., Yehuda, R., Orr, S.P., and Harvard/VA PTSD Twin Study Investigators. (2006). Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. Ann. N Y Acad. Sci. *1071*, 242–254.

Protopopescu, X., Pan, H., Altemus, M., Tuescher, O., Polanecsky, M., McEwen, B., Silbersweig, D., and Stern, E. (2005). Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. Proc. Natl. Acad. Sci. USA *102*, 16060–16065.

Quirk, G.J., and Beer, J.S. (2006). Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr. Opin. Neurobiol. *16*, 723–727.

Radley, J.J., Sisti, H.M., Hao, J., Rocher, A.B., McCall, T., Hof, P.R., McEwen, B.S., and Morrison, J.H. (2004). Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience *125*, 1–6.

Raskind, M.A., Peskind, E.R., Kanter, E.D., Petrie, E.C., Radant, A., Thompson, C.E., Dobie, D.J., Hoff, D., Rein, R.J., Straits-Troster, K., et al. (2003). Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am. J. Psychiatry *160*, 371–373.

Rau, V., DeCola, J.P., and Fanselow, M.S. (2005). Stress-induced enhancement of fear learning: an animal model of posttraumatic stress disorder. Neurosci. Biobehav. Rev. *29*, 1207–1223.

Rauch, S.L., Shin, L.M., and Wright, C.I. (2003). Neuroimaging studies of amygdala function in anxiety disorders. Ann. N Y Acad. Sci. *985*, 389–410.

Rauch, S.L., Shin, L.M., and Phelps, E.A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research–past, present, and future. Biol. Psychiatry *60*, 376–382.

Resnick, H.S., Yehuda, R., Pitman, R.K., and Foy, D.W. (1995). Effect of previous trauma on acute plasma cortisol level following rape. Am. J. Psychiatry *152*, 1675–1677.

Ressler, K.J., Rothbaum, B.O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., Hodges, L., and Davis, M. (2004). Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch. Gen. Psychiatry *61*, 1136–1144.

Richter-Levin, G. (1998). Acute and long-term behavioral correlates of underwater trauma–potential relevance to stress and post-stress syndromes. Psychiatry Res. *79*, 73–83.

Rittenhouse, P.A., Bakkum, E.A., O'Connor, P.A., Carnes, M., Bethea, C.L., and van de Kar, L.D. (1992). Comparison of neuroendocrine and behavioral effects of ipsapirone, a 5-HT1A agonist, in three stress paradigms: immobilization, forced swim and conditioned fear. Brain Res. *580*, 205–214.

Schelling, G., Roozendaal, B., Krauseneck, T., Schmoelz, M., de Quervain, D., and Briegel, J. (2006). Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Ann. N Y Acad. Sci. *1071*, 46–53.

Segman, R.H., and Shalev, A.Y. (2003). Genetics of posttraumatic stress disorder. CNS Spectr. *8*, 693–698.

Shin, L.M., McNally, R.J., Kosslyn, S.M., Thompson, W.L., Rauch, S.L., Alpert, N.M., Metzger, L.J., Lasko, N.B., Orr, S.P., and Pitman, R.K. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. Am. J. Psychiatry *156*, 575–584.

Shin, L.M., Wright, C.I., Cannistraro, P.A., Wedig, M.M., McMullin, K., Martis, B., Macklin, M.L., Lasko, N.B., Cavanagh, S.R., Krangel, T.S., et al. (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch. Gen. Psychiatry *62*, 273–281.

Shinba, T., Shinozaki, T., and Mugishima, G. (2001). Clonidine immediately after immobilization stress prevents long-lasting locomotion reduction in the rat. Prog. Neuropsychopharmacol. Biol. Psychiatry *25*, 1629–1640.

Siegmund, A., and Wotjak, C.T. (2006). Toward an animal model of posttraumatic stress disorder. Ann. N. Y. Acad. Sci. *1071*, 324–334.

Siegmund, A., and Wotjak, C.T. (2007). Hyperarousal does not depend on trauma-related contextual memory in an animal model of Posttraumatic Stress Disorder. Physiol. Behav. *90*, 103–107.

Sotres-Bayon, F., Bush, D.E., and LeDoux, J.E. (2004). Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn. Mem. *11*, 525–535.

Sotres-Bayon, F., Bush, D.E., and LeDoux, J.E. (2007). Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. Neuropsychopharmacology *32*, 1929–1940.

Stein, M.B., Jang, K.L., Taylor, S., Vernon, P.A., and Livesley, W.J. (2002). Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. Am. J. Psychiatry *159*, 1675–1681.

Sutherland, J.E., and Costa, M. (2003). Epigenetics and the environment. Ann. N Y Acad. Sci. *983*, 151–160.

Tronel, S., and Alberini, C.M. (2007). Persistent disruption of a traumatic memory by postretrieval inactivation of glucocorticoid receptors in the amygdala. Biol. Psychiatry *62*, 33–39.

True, W.R., Rice, J., Eisen, S.A., Heath, A.C., Goldberg, J., Lyons, M.J., and Nowak, J. (1993). A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch. Gen. Psychiatry *50*, 257–264.

Urry, H.L., van Reekum, C.M., Johnstone, T., Kalin, N.H., Thurow, M.E., Schaefer, H.S., Jackson, C.A., Frye, C.J., Greischar, L.L., Alexander, A.L., and Davidson, R.J. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J. Neurosci. *26*, 4415–4425.

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., and Marmar, C.R. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol. Psychiatry *54*, 947–949.

Vasterling, J.J., Duke, L.M., Brailey, K., Constans, J.I., Allain, A.N., Jr., and Sutker, P.B. (2001). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology *16*, 5–14.

Vyas, A., Mitra, R., Shankaranarayana Rao, B.S., and Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. *22*, 6810–6818.

Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., and Meaney, M.J. (2004). Epigenetic programming by maternal behavior. Nat. Neurosci. *7*, 847–854.

Yehuda, R. (2002a). Post-traumatic stress disorder. N. Engl. J. Med. *346*, 108–114.

Yehuda, R. (2002b). Current status of cortisol findings in post-traumatic stress disorder. Psychiatr. Clin. North Am. *25*, 341–368.

Yehuda, R. (2004). Risk and resilience in posttraumatic stress disorder. J. Clin. Psychiatry *65* (*Suppl 1*), 29–36.

Yehuda, R. (2005). Neuroendocrine aspects of PTSD. Handb. Exp. Pharmacol. *169*, 371–403.

Yehuda, R., and Antelman, S.M. (1993). Criteria for rationally evaluating animal models of posttraumatic stress disorder. Biol. Psychiatry *33*, 479–486.

Yehuda, R., and McFarlane, A.C. (1995). Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. Am. J. Psychiatry *152*, 1705–1713.

Yehuda, R., and Flory, J.D. (2007). Differentiating biological correlates of risk, PTSD, and resilience following trauma exposure. J. Trauma. Stress *20*, 435–447.

Yehuda, R., Levengood, R.A., Schmeidler, J., Wilson, S., Guo, L.S., and Gerber, D. (1996a). Increased pituitary activation following metyrapone administration in post-traumatic stress disorder. Psychoneuroendocrinology *21*, 1–16.

Yehuda, R., Teicher, M.H., Trestman, R.L., Levengood, R.A., and Siever, L.J. (1996b). Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol. Psychiatry *40*, 79–88.

Yehuda, R., Siever, L.J., Teicher, M.H., Levengood, R.A., Gerber, D.K., Schmeidler, J., and Yang, R.K. (1998a). Plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol concentrations and severity of depression in combat posttraumatic stress disorder and major depressive disorder. Biol. Psychiatry *44*, 56–63.

Yehuda, R., Resnick, H.S., Schmeidler, J., Yang, R.K., and Pitman, R.K. (1998b). Predictors of cortisol and 3-methoxy-4-hydroxyphenylglycol responses in the acute aftermath of rape. Biol. Psychiatry *43*, 855–859.

Yehuda, R., McFarlane, A.C., and Shalev, A.Y. (1998c). Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. Biol. Psychiatry *44*, 1305–1313.

Yehuda, R., Halligan, S.L., and Bierer, L.M. (2001). Relationship of parental trauma exposure and PTSD to PTSD, depressive and anxiety disorders in offspring. J. Psychiatr. Res. *35*, 261–270.

Yehuda, R., Engel, S.M., Brand, S.R., Seckl, J., Marcus, S.M., and Berkowitz, G.S. (2005). Transgenerational effects of PTSD in babies of mothers exposed the WTC attacks during pregnancy. J. Clin. Endocrinol. Metab. *90*, 4115–4118.

Yehuda, R., Golier, J.A., Tischler, L., Harvey, P.D., Newmark, R., Yang, R.K., and Buchsbaum, M.S. (2006). Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: Relation to risk and resilience factors. J. Psychiatr. Res. *41*, 435–445.

Yehuda, R., Blair, W., Labinsky, E., and Bierer, L.M. (2007a). Effects of parental PTSD on the cortisol response to dexamethasone administration in their adult offspring. Am. J. Psychiatry *164*, 163–166.

Yehuda, R., Teicher, M.H., Seckl, J.R., Grossman, R.A., Morris, A., and Bierer, L.M. (2007b). Parental posttraumatic stress disorder as a vulnerability factor for low cortisol trait in offspring of holocaust survivors. Arch. Gen. Psychiatry *64*, 1040–1048.

Yehuda, R., Morris, A., Labinsky, E., Zemelman, S., and Schmeidler, J. (2007c). Ten year follow-up study of cortisol levels in aging Holocaust survivors with and without PTSD. J. Trauma. Stress, in press.