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Stress modulation of cognitive and affective processes

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Abstract

This review summarizes the major discussion points of a symposium on stress modulation of cognitive and affective processes, which was held during the 2010 workshop on the neurobiology of stress (Boulder, CO, USA). The four discussants addressed a number of specific cognitive and affective factors that are modulated by exposure to acute or repeated stress. Dr David Morilak discussed the effects of various repeated stress situations on cognitive flexibility, as assessed with a rodent model of attentional set-shifting task, and how performance on slightly different aspects of this test is modulated by different prefrontal regions through monoaminergic neurotransmission. Dr Serge Campeau summarized the findings of several studies exploring a number of factors and brain regions that regulate habituation of various autonomic and neuroendocrine responses to repeated audiogenic stress exposures. Dr Kerry Ressler discussed a body of work exploring the modulation and extinction of fear memories in rodents and humans, especially focusing on the role of key neurotransmitter systems including excitatory amino acids and brain-derived neurotrophic factor. Dr Israel Liberzon presented recent results on human decision-making processes in response to exogenous glucocorticoid hormone administration. Overall, these discussions are casting a wider framework on the cognitive/affective processes that are distinctly regulated by the experience of stress and some of the brain regions and neurotransmitter systems associated with these effects.

Keywords

Cognitive flexibility; prefrontal cortex; decision making; habituation; extinction; fear conditioning

Introduction

This review provides a synopsis of the major discussion points presented during the session on ‘Stress modulation of cognitive and affective processes’ that took place as part of the 2010 workshop on the neurobiology of stress held in Boulder, CO, USA, on 15–17 June 2010. Drs David Morilak and Serge Campeau focused on different aspects of the effects of repeated stress exposures on specific cognitive functions and habituation in rats, while Dr Kerry Ressler focused on the modulation of rat and human aversive memories, and Dr Israel Liberzon presented recent results on human decision-making processes in response to

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exogenous glucocorticoid hormone administration. As the title implied, the emphasis of this session was on how stress modulates a number of cognitive and affective processes, often long after the precipitating episode(s). Improved knowledge of the exact cognitive/affective processes influenced by various stressful experiences is already leading to a refinement of understanding of the brain circuits and local neural mechanisms affected, and is guiding new or enhanced treatment avenues for stress-related disorders. In addition, it is becoming increasingly clear that acute or chronic stress situations simultaneously initiate a number of changes across several cognitive/affective functions, which are likely to depend on the specific stress situations, and unfold with varying temporal characteristics. The following synopsis generally describes each presentation and the major points that were raised in several of the presentations on the modulation of cognitive and affective processes by acute or repeated stress exposures.

Chronic stress and monoaminergic modulatory influence in prefrontal cortex functions (David Morilak, PhD, University of Texas Health Science Center, San Antonio, TX)

The association of stress with a number of mood disorders, including, but not limited to, posttraumatic stress disorder, clinical depression, and other anxiety disorders is well established (Kendler et al. 1999; Chrousos 2000; Tafet and Bernardini 2003). In turn, frontal cortical dysfunctions have been repeatedly reported in patients afflicted with such stress-related psychiatric disorders [see Drevets et al. (1997), Bremner (2002), Anisman and Matheson (2005) for reviews]. Many examples of these cognitive dysfunctions have been observed with the Wisconsin Card Sorting task, used extensively to test cognitive flexibility and executive functions in human subjects (Merriam et al. 1999; Fossati et al. 2002). Indeed, deficits of cognitive flexibility leading to emotionally biased cognitive processing have been suggested to underlie the mood symptoms of depression (see Beck 2005). Given the extensive association of the prefrontal cortex with the expression of behavioral and cognitive flexibility and executive functions on one hand (Ragozzino et al. 1999; Dalley et al. 2004; Ghahremani et al. 2010), and the abnormal prefrontal cortical activity noted in stress-related clinical disorders on the other hand (with a preponderance indicating hypoactivity; Austin et al. 2001; Davidson et al. 2002; Rogers et al. 2004), an important question is how stress, and particularly chronic stress, might modify or predispose organisms to dysfunctional prefrontal cortical activity, and how this dysregulation might be remedied.

There is indeed accumulating evidence that chronic stress in laboratory animals has a negative impact on cognitive flexibility, the process by which feedback from the environment is used to modify previously learnt or prepotent behavioral patterns. A test to assess various aspects of cognitive flexibility has been developed specifically for rodents, the attentional set-shifting test (AST; Birrell and Brown 2000). In the AST, rats are trained to dig for a food reward in small pots filled with material such as sawdust and styrofoam beads and scented with fragrant oils. Thus, the pots are identified by cues along two different stimulus dimensions (digging medium and odor), and the rats must learn which of these dimensions signals reward and which is irrelevant. After successfully learning a given contingency, the rules are changed, similar to several human neuropsychological tests of cognitive flexibility, such as the Wisconsin Card Sort Test. For instance, in the first discrimination, one odor (e.g. lemon) may signal the location of the reward and the other odor (e.g. mint) is explicitly not associated with the reward. Thus, odor is the salient dimension, lemon is the positive cue, and digging medium is the distracting or irrelevant dimension. Then, once this is mastered, the first odor may become negative and the previously negative odor becomes the positive cue, a stimulus reversal (*R*). Then, all new stimuli may be introduced in a new acquisition task, also called an intra-dimensional (ID) set-shift because an entirely new contingency must be learnt, but the salient dimension is the

same (in this example, odor). After several tasks in which the salient dimension remains constant, rats develop what is called a cognitive set, or a 'rule about the rules', in which they have learnt which stimulus dimension will be informative when the rules are changed. Then, the extra-dimensional (ED) set-shift task is a new acquisition in which the salient dimension is also changed, forcing the animals to shift their cognitive set, and abandon the previously learnt higher-order executive rule, a very challenging test of cognitive flexibility that depends on the functional integrity of the medial prefrontal cortex (mPFC; Birrell and Brown 2000; Lapiz and Morilak 2006). By proceeding through this series of increasingly difficult discriminations, from simple to compound discriminations, reversals, ID and ED set-shifts, the AST allows one to study mechanisms underlying distinct aspects of attention, cognitive flexibility, and executive function in rats.

Using this test (see Figure 1), 2 weeks of chronic intermittent cold (CIC) stress induced a selective impairment in one form of cognitive flexibility, reversal learning, without affecting ED cognitive set-shifting (Lapiz-Bluhm et al. 2009; Lapiz-Bluhm and Morilak 2010). In contrast to ED set-shifting, reversal learning is associated more with the functional integrity of the orbitofrontal cortex (Schoenbaum et al. 2002; McAlonan and Brown 2003; Kim and Ragozzino 2005). Thus, this chronic physiologic stressor appeared to impact the orbitofrontal subregion of prefrontal cortex to a greater extent than it did the mPFC. In contrast, also shown in Figure 1, a 2-week regimen of chronic unpredictable stress (CUS), which is a robust psychological stressor, more reliably disrupted ED cognitive set-shifting (Bondi et al. 2008, 2010), similar to the effect reported after chronic intermittent restraint (Liston et al. 2006). Thus, chronic stressors with a substantive psychological component affect cognitive set-shifting, and are thus likely to involve subregions of mPFC (prelimbic and infralimbic cortices) which have been more specifically linked to this process (Ragozzino et al. 1999; Birrell and Brown 2000; Chudasama and Robbins 2003; Lapiz et al. 2007).

An integral aspect of the above series of studies examining the detrimental impact of chronic stress on cognitive flexibility was based on the fact that monoaminergic neurotransmission in prefrontal cortical regions has been linked both to stress and to modulation of several cognitive functions (Devauges and Sara 1990; Cole and Robbins 1992; Page and Lucki 2002; Ramos and Arnsten 2007). In addition, these neurotransmitter systems remain the leading targets of therapeutic interventions in treating stress-related mood disorders (Schatzberg and Schildkraut 1995; Ressler and Nemeroff 2000; Morilak and Frazer 2004). In view of the above results demonstrating subtle but different cognitive functional alterations with different chronic stress modalities, the question of putative neurotransmitter specificity could also be addressed. Of interest, Morilak and collaborators showed that serotonergic depletion with PCPA (4-chloro-DL-phenylalanine) selectively disrupted reversal learning in rats to levels comparable to that obtained following chronic cold stress, and acute treatment with the serotonin specific reuptake blocker citalopram blocked the chronic cold stress-induced reversal learning deficit (Lapiz-Bluhm et al. 2009). This effect was specific to the serotonin system because desipramine treatment (a norepinephrine reuptake blocker) did not reduce the chronic cold stress-induced reversal deficit (Lapiz-Bluhm and Morilak 2010), supporting prior findings of serotonin-specific modulation of reversal learning in the orbitofrontal cortex (Clarke et al. 2005, 2007). On the other hand, chronic treatments with either the norepinephrine reuptake blocker desipramine (see Figure 2) or the selective serotonin reuptake blocker escitalopram prevented the deficit in ED cognitive set-shifting induced by the psychogenic stressor, CUS (Bondi et al. 2008, 2010). Furthermore, at least for the noradrenergic system, activation of post-synaptic α_1-adrenergic receptors at the level of the prefrontal cortex during the cognitive task is necessary for the effects of chronic desipramine in blocking the CUS-induced deficit in cognitive set-shifting (Bondi et al. 2010). Moreover, acute elevations of norepinephrine by an α_2-adrenergic autoreceptor

antagonist (atipamezole) can facilitate ED set-shifting (Lapiz and Morilak 2006), a facilitation that was observed even after a deficit had been induced by CUS treatment (Bondi et al. 2010).

Together, the above studies suggest that with different stressor modalities, different modulatory neurotransmitter systems can have distinguishable effects on specific cognitive functions in different sub-regions of prefrontal cortex. It is also becoming clear that these same prefrontal cortical regions and their associated cognitive functions can be differentially altered by chronic stress. Monoamine neurotransmission can facilitate cognitive flexibility even in the presence of stress-induced prefrontal cortical dysfunction, providing one specific mechanism via which stress-related cognitive dysfunctions can be improved by pharmacotherapy, but not necessarily cured. This is perhaps consistent with recent findings that antidepressant treatment in depressed patients can rapidly ameliorate some symptoms, including cognitive dysfunction, while producing no immediate effects on ratings of mood or anxiety (Harmer et al. 2009). Although these modulatory systems are likely to be both activated and altered by chronic stress exposure impacting cognitive flexibility, it would appear that the disruption of monoaminergic neurotransmission itself does not represent the primary pathology underlying the cognitive dysfunction that is associated with stress-related psychiatric disorders.

Given the increasing refinements of our understanding of the functional cognitive modulation by stress and monoaminergic transmission, the work of Morilak and collaborators has recently shifted to a similarly refined analysis in animals undergoing early life stress, as one possible factor responsible for later vulnerability to stress-induced cognitive dysfunctions in adulthood. Additional tasks, including the extinction of conditioned fear, are being assessed as possible cognitive functions also modulated by stress, and particularly early life stress. A promising new line of research under investigation by this group, which has to date been little explored, is the possibility that cognitive training of rodents on tasks such as the attentional set-shifting paradigm at some critical developmental stages might protect against the negative effects of later chronic stress. The mechanisms whereby such protection might be conferred could provide novel targets for behavioral or pharmacotherapy, before or after chronic stress.

Learning to live with stress: Modulation of stress responses by prior stress (Serge Campeau, PhD, University of Colorado, Boulder, CO)

The previous section introduced some of the effects of stress chronicity on specific cognitive responses. Although CUS was reported to modulate cognitive functions, the same situations (cold or restraint) experienced repeatedly were also found to alter cognitive functions, albeit with some differences as to the specific cognitive processes and neurotransmitter systems involved. There are a number of additional effects induced by repeated or chronic stress exposures that are known to either increase or decrease the unconditioned or prepotent responses elicited directly by stressful situations. An example is the reduction of behavioral, autonomic, and neuroendocrine responses to the repeated intermittent exposures to the same stressful situation (homotypic stress), a phenomenon defined as stress habituation (Marti and Armario 1998). Reduction of stress responses through prior experience with the same stressor has been studied for many years [see Grissom and Bhatnagar (2008), for a review]. However, with few exceptions (Cole et al. 2000; Bhatnagar et al. 2002; Jaferi et al. 2003), the brain regions and neuroplastic mechanisms subserving this process have remained surprisingly elusive. This presentation discussed the results of several studies aimed at further defining the putative processes and brain regions associated with stress habituation.

For many years, loud noise (audiogenic stress) has been employed as an effective stimulus to activate a number of responses traditionally associated with stressor exposure, including

the neuroendocrine hypothalamo–pituitary–adrenocortical (HPA) axis [as indexed by the release of glucocorticoids and adrenocorticotropin hormone (ACTH; Henkin and Knigge 1963; Borrell et al. 1980; Segal et al. 1989; Campeau and Watson 1997)], the autonomic system [as indexed by peripheral catecholamine release, heart rate, blood pressure, or core body temperature measurements (De Boer et al. 1989; Overton et al. 1991; Gamallo et al. 1992; Saha et al. 1996; Bao et al. 1999; Masini et al. 2008)], and various behavioral responses [measured with locomotor activity, or inhibition of feeding and drinking (Irwin et al. 1989; Segal et al. 1989; Britton et al. 1992; Campeau and Watson 1997; Masini et al. 2008)]. Importantly, most of the above responses to acute loud noise exposure are significantly and robustly reduced upon repeated exposures to the same loud noise (Armario et al. 1984; De Boer et al. 1988; van Raaij et al. 1997; Campeau et al. 2002; Masini et al. 2008). At the intensities and durations employed, habituation to repeated loud noise exposures is not a simple process of progressive sensory hearing loss because loud noise habituated rats display no deficits in acoustic thresholds, as measured with auditory-evoked brainstem potentials, the acoustic startle reflex, or prepulse inhibition or facilitation of the acoustic startle reflex (Campeau et al. 2002; Masini et al. 2008).

One of the factors, which has received very limited attention, was the question of whether interstimulus interval between stressor presentations was an important variable that might modulate the development of habituated responses to repeated stress exposures. This question appeared to be unresolved with regard to endocrine and autonomic responses to repeated stressful exposures, even if it had led to an important distinction between short- and long-term behavioral response habituation and their associated neural mechanisms (Hinde 1954; Davis 1970; Carew et al. 1972; Menzel et al. 2001; Rose and Rankin 2001). Indeed, this phenomenon might be related to the distributed/spaced and massed training/practice in more traditional learning paradigms, in which longer interstimulus intervals (distributed/spaced) are correlated with better retention or performance on memory tasks or tests with increasing (longer-term) retention intervals (Cepeda et al. 2006). Using loud noise stress, it was determined that 24 h (1 day) intervals between six repeated exposures led to reliable habituation of ACTH and corticosterone release in rats, compared to the initial acute noise exposure (Masini et al. 2008). Importantly, the same six 30-min noise exposures given 60 min apart on the same day led to a very similar reduction of HPA axis activity on the last exposure (short-term test), comparable to the 24 h interstressor condition described above (see Figure 3). However, 2 days after the last (6th) stressor exposure (longer-term test), an additional acute noise exposure revealed that habituation was moderately reversed, but only in the 60-min interstressor interval group. Furthermore, the same pattern of results was obtained in different rats instrumented for measurements of heart rate, core body temperature, and locomotor activity, indicating that the above neuroendorine results were not simply due to short-term feedback effects of corticosterone in the 60-min interstressor interval groups (Masini et al. 2008). These results strongly suggested that there exist distinct neural processes responsible for short- and long-term habituation to stress, similar to the effects of distributed vs. massed practice effects in various other learning conditions (Cepeda et al. 2006). The exact neural bases of these distinct processes are currently unknown.

Another question relating to stress habituation is the extent to which this process is associative. Indeed, an influential associative learning model accounting for habituation to repeated stimulus exposures argues that contextual cues become associated with the repeated stimulus, such that exposure to the contextual cues alone gradually primes the retrieval from the memory of the repeatedly experienced stimulus (Wagner 1978, 1979, 1981). Importantly, for this associative model, the primed memory of a stimulus is suggested to inhibit the elicitation of prepotent responses normally triggered by exposure to the stimulus, thereby providing the basis for the reduction of responses defined as habituation. Some of

the main predictions of this habituation model generally have been supported, especially through contextual manipulations modifying habituation of behavioral responses in predicted ways (Jordan et al. 2000). With regard to the habituation of neuroendocrine responses, some findings have suggested that a change in contextual cues following the acquisition of habituation can restore habituated neuroendocrine responses (Dobrakovova et al. 1993; Grissom et al. 2007). In these studies, however, the situations employed to modify contextual cues were confounded with their familiarity, so it was unclear whether the observed response recovery was a more general response to novelty rather than a reflection of the associative role of contextual cues. In a recent series of studies (Nyhuis et al. 2010), traditional contextual manipulations known to modulate habituation of behavioral responses were tested while measuring HPA axis responses to repeated loud noise exposures. An initial study demonstrated that habituated ACTH and corticosterone release display very modest, if any, spontaneous recovery up to 4 weeks after seven daily repeated loud noise exposures. A classical extinction procedure involving exposure to the contextual cues daily for 14 days after habituation training, in the absence of the loud noise, provided no evidence of ACTH or corticosterone response recovery on a post-extinction loud noise test day. Importantly, it was shown that modifying the contextual cues can restore habituated ACTH and corticosterone responses, but only when the cues are novel, as shown in Figure 4; if the context was made familiar prior to exposure to the loud noise exposures, no response recovery was observed (Nyhuis et al. 2010). The lack of contextual control over habituation to repeated loud noise exposure was not due to a lack of context discrimination, as an additional experiment demonstrated that 11 daily preexposures to contextual cues specifically reduced acute loud noise-induced ACTH and corticosterone responses (Figure 4). This also provided one of the first demonstrations that prior experience with contextual stimuli significantly modifies acute stress responses, akin to the latent inhibition effect described for Pavlovian fear conditioning (Lubow and Moore 1959). A recent study also employing repeated restraint stress failed to demonstrate a link between contextual manipulations and neuroendocrine response habituation (Rabasa et al. 2011). These results highlight the importance of controlling for overall experimental familiarity, given the known role of environmental novelty in inducing stress responses (Bassett et al. 1973; Hennessy et al. 1977; Pfister 1979). Although these studies do not provide support for an associative role of contextual stimuli in stress habituation, they do not rule out the possibility that such stimuli may influence habituation to stress under some conditions. It is conceivable that the very characteristics of some of the stress situations often employed in stress studies (continuous and relatively long-lasting exposures to loud noise, restraining/immobilizing situations, etc.) simply over-ride the need to rely on static contextual cues, which become redundant when the stress stimuli themselves predict the situation, similar to the overshadowing effect reported in Pavlovian fear conditioning paradigms (Kamin 1969). Additional studies will be essential to answer questions regarding context-dependent vs. context-independent forms of habituation to stress and whether these are supported by distinct neural mechanisms.

An analysis of the putative brain regions associated with HPA axis habituation to repeated loud noise exposures was begun using a systematic approach capitalizing on the well-defined sensory pathways mediating responsiveness to acoustic stimuli. An initial study of regional brain activation, as measured by induction of the immediate-early gene c-*fos* mRNA, indicated very slight, if any, reduction in lower brainstem auditory nuclei such as the cochlear nuclei, the nuclei of the trapezoid bodies, superior olivary complex, or lateral lemniscus, or various inferior colliculus nuclei (Campeau et al. 2002). However, a broad regional reduction in c-*fos* mRNA induction in habituated compared to acutely noise-exposed rats was observed, including auditory thalamic and cortical levels. This pattern of c-*fos* mRNA induction was similar to that obtained following complete bilateral auditory thalamic lesions, which specifically blocked acute loud-noise-induced HPA axis responses

(Campeau et al. 1997). These findings strongly suggest that the neuroplasticity associated with HPA axis habituation to loud noise takes place at auditory thalamic levels or some of its targets (Campeau and Watson 2000). To more precisely test the hypothesis that the auditory thalamus is a necessary component of the circuit mediating habituation to repeated loud noise exposures, bilateral reversible inactivation of the auditory thalamus using muscimol was performed daily during the first two of three repeated noise exposures (Day et al. 2009). This reversible inactivation of the auditory thalamus, unlike the permanent lesions of the prior study, allowed a final test of the repeatedly presented loud noise with a functional thalamus. As shown in Figure 5, this study revealed the necessity of this region for HPA axis habituation to repeated loud noise exposures.

Of special significance, preliminary results obtained following large temporal (auditory) cortex lesions either before or after HPA axis habituation to repeated loud noise exposures produced no disruption of acute or habituated ACTH and corticosterone responses to loud noises (C.V. Masini and S. Campeau, unpublished observations). Additional targets of the auditory thalamus, including the amygdaloid complex, and some hypothalamic regions need to be tested to establish their putative role, or that of the auditory thalamus itself, in HPA axis habituation to repeated loud noise exposures.

Overall, the above studies are continuing to more precisely define the conditions under which stress habituation takes place, and are honing in on some of the brain regions mediating these response reductions. Some pressing questions revolve around defining more precisely the multiple processes required for the development of habituation to stressful stimuli, including the possibility that redundant neural mechanisms are responsible for habituation to repeated stress, which might explain the difficulty to pinpoint specific mechanisms associated with this important function. The existence of interstressor interval and other temporal effects (Jordan et al. 2000) suggests the possibility of multiple neural mechanisms, but conclusive evidence is yet to be obtained.

Modulation and extinction of aversive memories: from rodents to humans (Kerry Ressler, M.D., PhD, Emory University, Atlanta, GA)

A common theme of discussion thus far has been that stress is robustly associated with a number of mood disorders. From the multiple symptom clusters associated with different mood and anxiety disorders, it is now recognized that enhanced fear or an inability to suppress fear responses is common across several disorders (Kessler et al. 1995; Breslau et al. 2000; Lissek et al. 2005). Although these observations often blur clear distinctions, and stoke debates, about the existence of separate clinical categories, a trend gaining momentum is to focus on specific symptoms as putative biomarkers in the hope that such fine grained analysis could discriminate between currently closely related disorders. Phenotypic differences associated with fear responses in various psychiatric populations have been at the center of several recent studies, indicating that fear processing represents a target function discriminating between some mood disorders, and offering new preclinically driven strategies in their treatments. An example of this emerging trend is the recent discovery that the acoustic startle or its potentiation by fear-related stimuli is enhanced in various mood and anxiety disorder populations (Butler et al. 1990; Grillon et al. 1993, 1994, 1998a,b; Morgan et al. 1995; Grillon and Morgan 1999; Lissek et al. 2010). Notably, the use of more precise discrimination tasks indicates that patients with post-traumatic stress disorder (PTSD) or panic disorder fail to suppress fear to safety signals. Figure 6 demonstrates that control subjects and subjects with major depression show much more physiological fear to the danger cue (AX +) than they do to safety cues (BX − and AB). In contrast, those with PTSD are unable to perform this emotional discrimination task (see Figure 6), an impairment that is not observed in major depression or generalized anxiety (Lissek et al. 2009, 2010; Jovanovic et al. 2010a,b). An additional possible phenotypic discriminator

between PTSD and panic disorder may involve the normal conscious and appropriate expectancy of danger and safety signals by PTSD patients (Jovanovic et al. 2009), which appears disrupted in panic disorder patients (Lissek et al. 2009).

Modulation of the HPA axis is also a hallmark of several mood disorders, and one of the distinguishing characteristics of trauma-related disorders, including PTSD, is the exaggerated suppression of HPA-induced hormone release in the dexamethasone suppression test (Yehuda et al. 2002, 2004a,b; de Kloet et al. 2007). To determine if HPA axis and fear abnormalities interact in PTSD, as described above, traumatized patients with and without PTSD were given a fear-potentiated startle test under control or dexamethasone suppression conditions. As reported previously, PTSD patients had no HPA hormone differences at baseline, but had reliably more suppressed cortisol levels than non-PTSD traumatized controls following dexamethasone (Jovanovic et al. 2010b). Compared with the non-PTSD traumatized controls, the PTSD patients again displayed an inability to suppress fear on the safe trials, and this was significantly correlated with both cortisol and ACTH at baseline and following dexamethasone treatment. In addition, the lack of differences at baseline between diagnostic groups but the correlation with physiological fear suggests that fear physiology may be an intermediate phenotype that is more closely related to HPA axis functioning than is the diagnosis of PTSD per se.

The high degree of correlations observed between HPA axis and fear reactivity abnormalities may suggest that this link results from a common underlying neural dysfunction in this disorder. Indeed, recent genetic and environmental studies of PTSD-related risk factors indicate that the strong association of child and adult trauma with PTSD (Bremner et al. 1993; Widom 1999; Heim and Nemeroff 2001; Lang et al. 2006; Stovall-McClough and Cloitre 2006) interacts significantly with specific allelic genotypes of the FKBP5 protein (see Figure 7), a modulator of glucocorticoid receptor sensitivity (Binder et al. 2008; Yehuda et al. 2009; Xie et al. 2010). These studies are therefore beginning to offer rational explanations for the large individual variations observed with regard to trauma-related disorders, with vulnerability determined by a combination of developmental/environmental (social support, traumatic events, etc.) and genetic factors (FKBP5 and other recently noted genes), together with improving predictive power for individual risk, and a chance to develop better intervention approaches to mitigate the effects of existing susceptibilities.

Besides abnormalities in suppressing fear to safety signals, deficits in the extinction of fear responses to fear stimuli or situations, even when no longer associated with aversive outcomes, are frequently reported in PTSD populations (Rothbaum and Davis 2003; Bremner et al. 2005; Gillespie and Ressler 2005; Wessa and Flor 2007). Most recently, we have further examined this phenomenon in a large group ($N = 127$) of all-traumatized individuals with and without PTSD (Norrholm et al. 2011). During fear extinction, the PTSD group showed elevated fear-potentiated startle responses to the previously reinforced CS + during the early and middle stages of extinction. During the acquisition and extinction phases, PTSD participants with higher levels of re-experiencing symptoms exhibited greater potentiated startle responses to the CS + compared to PTSD participants with lower re-experiencing symptoms. These results suggest that PTSD is associated with enhanced fear learning and diminished fear extinction, in part due to a greater ‘fear load’ to extinguish after conditioned fear is acquired.

Several animal studies have focused on neural mechanisms mediating fear extinction in the prefrontal cortex, amygdaloid complex, and hippocampal formation (Milad et al. 2006; Chang et al. 2009), regions that are also of primary interest in mood disorders, including PTSD (Liberzon and Sripada 2008). Initial work provided evidence for the role of the brain-

derived neurotrophic factor (BDNF) system in the acquisition (Rattiner et al. 2004), and extinction of fear memories (Chhatwal et al. 2006). For instance, injection of a lentiviral vector coding a truncated copy of the relatively BDNF-specific tyrosine kinase receptor B (TrkB) neurotrophin receptor in the amygdala significantly retards extinction of fear-potentiated startle in rats (Chhatwal et al. 2006). Additional preclinical studies also suggest a role of the hippocampal BDNF system in fear extinction, but not its acquisition (Heldt et al. 2007). Recent results in humans generally support the animal studies whereby a polymorphism of the human BDNF gene (Val66Met single nucleotide polymorphism—SNP) confers, through reduced BDNF signaling, a retarded fear extinction phenotype in human heterozygote and homozygote Met carriers, as it does in knock-in mice with analogous genotypes (Soliman et al. 2010). The potential role of BDNF in mood disorders is further supported by associations with anxiogenic phenotypes in normal and anxious/depressed patients (Lau et al. 2010; Montag et al. 2010), leading to hyperresponsive hippocampal and amygdala functional magnetic resonance imaging (fMRI) responses to aversive stimulation. Given this association with a specific *bdnf* SNP, an intriguing remediation possibility would be to 'rescue' these deficits by providing TrkB stimulation directly. This possibility is currently being tested using a recently discovered TrkB receptor agonist that crosses the blood–brain barrier, 7-8-dihydroxyflavone (Jang et al. 2010), and has been shown to rescue the deficits induced in a region-specific BDNF knock-out mice (Choi et al. 2010). Recent demonstrations in enhancing fear extinction (see Figure 8), and restoration of extinction-like behaviors in an animal model of stress-induced extinction deficits (Andero et al. 2011), could quickly translate to human trials similarly investigating the possibility of enhancing fear extinction in PTSD, and other mood disorders. It is important to note that any cognitive enhancer strategy to enhance fear extinction would need to also carefully take into account the possible effects on non-emotional memories as well. Only giving a TrkB agonist acutely in a limited fashion, at the time of extinction-based exposure therapy, and not in a chronic, or ongoing fashion, might be one way to circumvent these potential concerns.

The strategy of enhancing specific functions given the deficits observed in patient populations such as PTSD is gaining support from a different, but similarly preclinically driven approach, surrounding the role of excitatory *N*-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the acquisition (Miserendino et al. 1990; Kim et al. 1991) and extinction (Falls et al. 1992) of learned fear. Whereas interference of NMDA receptor functions systemically or directly at the level of the amygdaloid complex is known to produce fear learning and extinction deficits, enhancement of their functions with the NMDA receptor partial agonist D-cycloserine facilitates fear extinction rates (Walker et al. 2002). Interestingly, in a BDNF Val66Met polymorphic animal model displaying clear signs of extinction deficits following aversion learning, systemic D-cycloserine was effective in normalizing extinction in this model (Yu et al. 2009). These animal studies are serving as the basis for a treatment approach in which exposure therapy, a method of choice clinically employed to reduce or minimize fear reactions to specific situations, could be augmented by adjunct pharmacotherapy (D-cycloserine) during exposure to the fear-eliciting situations under controlled conditions (Davis et al. 2006). Instead of focusing on reducing fear reactions directly with anxiolytics, this strategy focuses on improving the learning and retention of 'safety' conditions, which would subsequently reduce fear reactions in those situations. Several clinical trials have reported statistically significant improvements in subjective and physiological measures following D-cycloserine augmented exposure therapy in phobia (Ressler et al. 2004), social anxiety disorder (Hofmann et al. 2006; Guastella et al. 2008), and obsessive-compulsive disorder (Kushner et al. 2007; Wilhelm et al. 2008). Current trials are underway to determine if D-cycloserine-augmented exposure to virtual reality-based presentations of Iraq war cues will be effective in reducing some of the PTSD symptoms from returning Iraqi war veterans (Gerardi et al. 2008).

These studies reveal the importance of focusing on precise neural functions in the overall approach to detail dysfunctions associated with specific mood and anxiety disorders. The goal of these rationally based novel approaches is to provide a more direct path to cures rather than symptom control. Answers to remaining questions that could potentially move the field forward is the extent to which the two inhibitory functions previously discussed, stimulus safety discrimination and extinction of aversive memories/responses, are related to each other and mediated by unique or multiple underlying neural processes. This is a clear case in which the emerging clinical outcomes suggest specific questions that could now be addressed with animal research. An additional interesting question concerns the extent to which habituation of prepotent responses to aversive stimuli is similar to extinction of learned aversive memories, given the phenomenological similarity of these two forms of aversive response reduction. The emerging field of genetics and environmental interactions certainly indicates a complex overall picture of the antecedent conditions leading to mood and anxiety disorders, but how these interactions modify specific cognitive and emotional functions still has to be clearly defined.

Cortisol effects on human decision making (Israel Liberzon, M.D., University of Michigan and Veterans Administration Medical Center, Ann Arbor, MI)

As discussed in Dr Morilak's and Ressler's sections, stress, frontal dysfunctions, and mood disorders are frequently associated together. An area of active research is related to the way humans select among multiple alternative responses, especially under ambiguous options, which falls in the general category of decision making. Theories based on the concept of utility, a measure of human value, defined by considering the probabilities of reward and punishment magnitudes associated with each option, have generally been employed to explain decision making. However, it was soon noted that people transform probabilities and values of options in complex nonlinear manners, and that these transformations are different for rewards or punishments, as described in a series of observations now embodied in the 'cumulative prospect theory' of decision making (Tversky and Kahneman 1981, 1992). In addition, to the observed overweighting of small probabilities and underweighting of large probabilities, people are much more sensitive to losses than gains, which has led to the identification and mathematical formulation of a loss aversion parameter in the prospect theory. Thus, decision making, as behaviorally defined in the cumulative prospect theory, is a final outcome of multiple processes that contribute to value estimate and probability assessment that are described by three specific functions: loss aversion, reward discriminability, and a decision-weighting function.

In recent years, a number of functional neuroimaging studies have attempted to identify specific regions distinctly associated with overall value representation in the brain and specifically in performing the distinct functions described above in people subjected to uncertainty and potential loss during decision making. For instance, in a study designed to identify brain regions associated with behavioral parameters of loss aversion, the surprising finding was that structures generally associated with aversive responses (amygdala, insular cortex) were not identified (Tom et al. 2007). Instead, the same regions being selectively activated during gain conditions (ventro-mPFC and portions of the dorsal and ventral striatum) displayed decreased activity under loss conditions. Studies focusing on the decision weighting function (probability estimate) have correlated nonlinear neural activity associated with the probability assessment to the anterior cingulate cortex (Paulus and Frank 2006), the dorsolateral prefrontal cortex (Tobler et al. 2008), and the ventral striatum (Hsu et al. 2009). In parallel, decision-making tasks in rodents are also providing a rich pattern of behavioral results (Simon et al. 2009), together with corresponding set of neural substrates mediating choices in these animals (St Onge and Floresco 2010). These initial general

findings are indeed intriguing, but the detailed neurocircuitry involved in the specific components of decision making remains to be further elucidated.

Activity in many of the same regions implicated in decision making has been recently reported to correlate closely with the elaboration of specific stress responses, including activation of the HPA axis, in humans. A number of studies have linked increased activity in the amygdala, insular, dorsal and ventral prefrontal, and anterior cingulate cortices with HPA axis activation (Shin et al. 2001; Tchiteya et al. 2003; Britton et al. 2005; Phan et al. 2006; Urry et al. 2006). However, these original studies did not clearly distinguish the possibility that the correlated neural activities directly influenced HPA axis responses, or that the ensuing cortisol elevations from the activation of the HPA axis could have modified the observed neural activity, due to the lengthy test sessions employed. Some of these limitations were addressed in recent studies using more temporally restricted sampling methods of both the neural cerebral blood flow and the neuroendocrine release, indicating that the dorsal mPFC, the rostral anterior cingulate cortex, and the insular cortex were closely associated with ACTH levels during various stress-inducing conditions (Liberzon et al. 2007). Taking advantage of the finding that some patients show a lack of ACTH release (non-responders) to stress-induced HPA axis activation (in combat-related PTSD patients as well as combat-experienced non-PTSD subjects), it was recently reported (see Figure 9) that although the insular cortex activity increased in both ACTH responders and non-responders, mPFC activity was increased only in non-responders (King et al. 2009), which was associated with deactivation in the amygdala, hippocampus, and temporal pole area. These results suggest that insular activity is associated with HPA axis activation, while mPFC activity dampens downstream brain activity including the HPA axis, as suggested from an increasing number of animal studies (Diorio et al. 1993; Crane et al. 2003; Radley et al. 2006). The effects of glucocorticoids alone (hydrocortisone injections) prior to a psychological challenge have recently been found to moderate amygdaloid activity, which was again related to mPFC activity (Henckens et al. 2010).

Given the overlap in regional activations so far noted in response to psychological stress and decision making in humans, an emerging question concerns the way in which stress modifies decision making. Although a number of studies have reported significant neuropsychological effects of stress on decision making (Garvey and Klein 1993; Klein 1996; Preston et al. 2007; Starcke et al. 2008), the neural correlates of this impaired function have not been explored. Studies are currently underway, employing the cumulative prospect theory of decision making to determine how glucocorticoids and stress modify the activity of the neurocircuitry so far associated with different aspects of decision making under risk and uncertainty (Paulus and Frank 2006; Tom et al. 2007; Tobler et al. 2008; Hsu et al. 2009). Preliminary results suggest that hydrocortisone administration modulates neural activity associated with loss aversion and reward processing in insular and extended amygdala regions accordingly, but the signal associated with probability processing of the dorsolateral prefrontal cortex might be blunted. These findings, while preliminary, suggest that a novel role for stress hormones is to alter behavior via modification of the decision-making process through feedback, in a manner adaptive to stressful environment.

The above human studies investigating the psychological and neural decision-making processes are thus beginning to identify specific aspects of this complex function which are coupled to relatively localized brain loci. These findings, combined with the continuing interest in uncovering the influences of stress, and hormones released by stress, during decision making are helping to further define the specific effects that stress and stress hormones exert on critical components of decision making. Exactly how these functions might be altered in stress-related disorders, such as PTSD, is only beginning to be investigated (Sailer et al. 2008).

Conclusion

Analyses of the influence of acute and chronic stress on increasingly basic and well-defined cognitive/affective functions are allowing a more precise description of the brain regions, and in some instances, the associated neurotransmitter systems, mediating these functions. Simultaneously, these studies provide the basis to determine whether and where in the brain stress-related disorders modify these functions. How different functions may be permanently modified by stress, and more importantly, how these modifications could be reversed back to relative normalcy with targeted treatments is obviously a matter of intensive investigations.

The fact that stress influences multiple cognitive/affective functions simultaneously raises some important questions. For instance, are all the functions impacted by stress the result of a unique neural modification at a regional level or do they occur across different regions? In addition, are these stress-related changes occurring via the same underlying mechanism or via independent mechanisms and modifications which are associated with different functions? The development of increasingly sophisticated cognitive tests across multiple functions would provide answers to these questions, and in turn suggest appropriate treatment options. The continuing interplay between basic, preclinical, and clinical research associated with stress and stress-related disorders is also of special importance. For instance, the non-invasive neuroimaging and neuropsychological studies in patient populations under specific cognitive demands are providing increasingly specific regional targets that are so far well recapitulated in animal studies. On the other hand, the increased mechanistic approach afforded by animal research serves as a hypothesis testing ground to determine the role of specific neurotransmitter systems/molecular changes associated with the functional phenotypes. An additional advantage of the interdependency of clinical and preclinical research based on specific cognitive functions is the determination of the validity of specific animal models of disease or dysfunction, which should, at the very least, display similar loss of functions compared to the human clinical condition. These approaches are still in their infancy, but hold promises to improved understanding of stress-related disorders, and novel rational approaches to their treatments.

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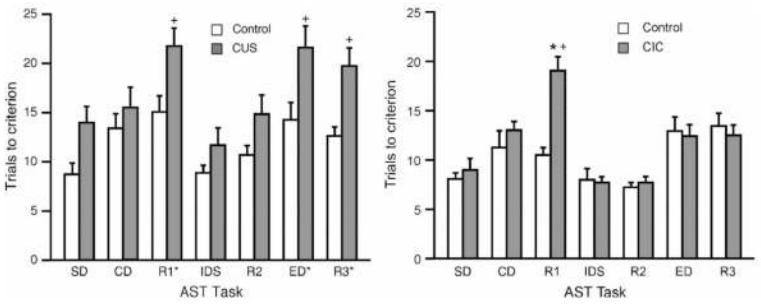

Figure 1.

Left panel: CUS produced a significant deficit in cognitive flexibility on the AST, manifested as a significantly higher number of trials required to reach criterion on the reversal tasks (R1, R3) and the ED cognitive set-shift task; $^{+}p < 0.05$ compared with non-stressed controls on the same stage. White bars: unstressed controls; Gray bars: chronically stressed rats; data expressed as mean ± SEM ($n = 14$/group). Reproduced with permission from Bondi et al. (2008). Right panel: In contrast, CIC stress produced a selective deficit in reversal learning on the AST. Stressed rats required significantly more trials to criterion on the R1 reversal task compared with non-stressed controls ($^{*}p < 0.01$ compared with control rats on the same stage; $^{+}p < 0.05$ compared with other tasks for the same group. White bars: unstressed controls; Gray bars: chronically stressed rats ($n = 12$/group). Reproduced with permission from Lapiz-Bluhm et al. (2009).

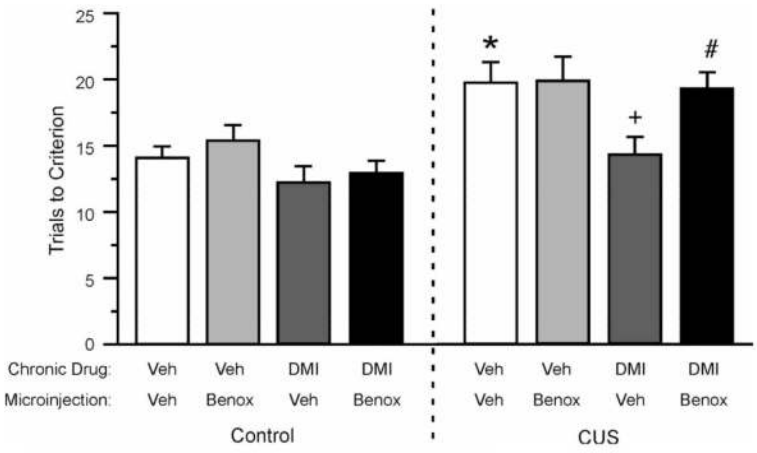

Figure 2.

The beneficial effects of chronic treatment with the NE reuptake blocker and antidepressant drug, desipramine (DMI, 7.5 mg/kg day, given by osmotic minipump), against the detrimental cognitive effects of CUS are mediated by α_1-adrenergic receptors in mPFC. CUS induced a significant set-shifting deficit on the ED task compared with unstressed controls ($^{*}p < 0.001$), which was prevented by chronic DMI treatment ($^{+}p < 0.01$ compared with vehicle-treated, chronically stressed rats). Bilateral microinjections of the α_1-adrenergic receptor antagonist benoxathian (2.0 nM per side), given into mPFC immediately prior to testing on the ED cognitive set-shifting task, significantly blocked the protective effect of chronic DMI treatment against the detrimental effects of CUS ($^{\#}p < 0.024$ compared with CUS-exposed rats that were DMI-treated and vehicle-microinjected). All data expressed as mean ± SEM, $n = 5–8$/group. Reproduced with permission from Bondi et al. (2010).

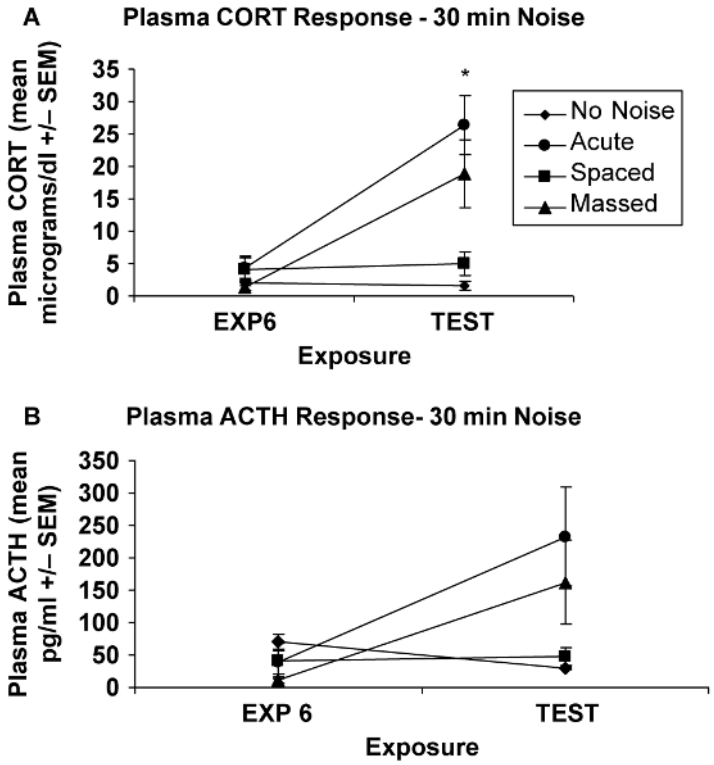

Figure 3.

Mean (±SEM) plasma levels of corticosterone (A) and ACTH (B) immediately following control quiet exposure to the experimental chambers (No noise, Acute, *n*'s = 4), or the 6th (EXP6) loud noise (95 dB) exposure, with either 1-h (massed, $n = 4$) or 24-h (spaced, $n = 4$) interstressor intervals. Note the similar and habituated responses in the two different interstressor interval groups after six loud noise exposures. Each graph also displays mean (±SEM) plasma levels of corticosterone (A) and ACTH (B) 48 h later (TEST) following an additional control chamber exposure (no noise, $n = 8$), acute loud noise ($n = 8$), or the 7th loud noise 30 min, 95 dB) exposure in the spaced ($n = 8$), and massed ($n = 8$) groups. Note that the 1-h interstressor interval massed group displays significant recovery of corticosterone and ACTH levels compared to their levels on the 6th exposure, and compared to the 24-h interval group. *Indicates a significant difference between massed and spaced groups ($p < 0.05$). Reproduced with permission from Masini et al. (2008).

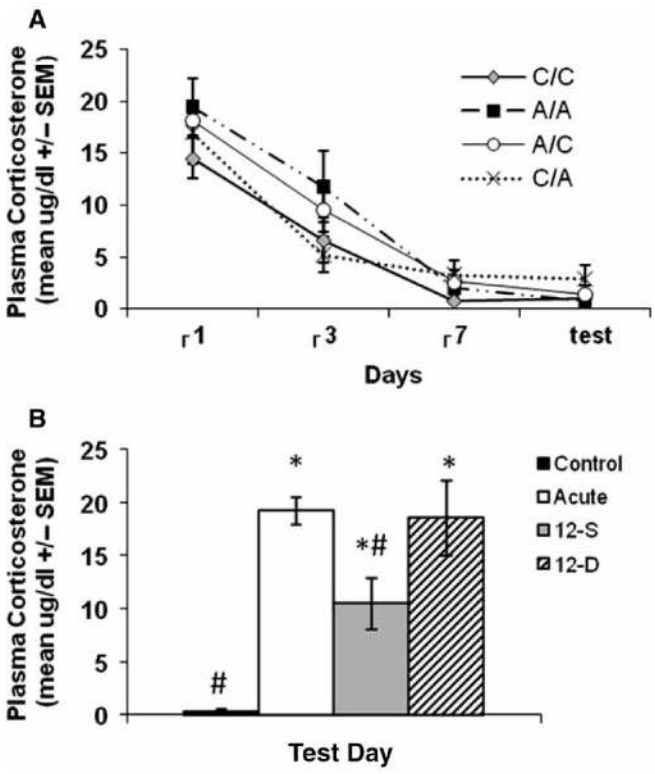

Figure 4.

(A) Mean plasma corticosterone responses (±1 SEM) over the course of seven consecutive loud noise exposures (30 min, 95 dB), and during an additional exposure 48 h later when rats were tested in the same context in which they were habituated (A/A, C/C), or in a different context (A/C, C/A). Corticosterone values did not significantly differ between the groups on Days 1, 3, 7 or the test loud noise exposure, whether rats were tested in the same context or a different context, as long as rats had been equally familiarized in both contexts (*n*'s = 8; ACTH results were similar, but are not shown here). (B) Mean plasma corticosterone responses (±1 SEM) on an acute loud noise exposure (30 min, 95 dB) in contexts A or C, in rats preexposed to the same (12-S) or a different test context (12-D) for 12 consecutive days. The graph shows that only 12 preexposure days (30 min daily exposures) to the same context in which they were tested (12-S) reduced loud noise-induced corticosterone release compared to acute responses without any preexposure (Acute), or preexposure in a different context (12-D).*, A significant difference from Control group; #, a significant difference from both the Acute and 12-D groups (Tukey's HSD; *p*'s < 0.05). Reproduced with permission from Nyhuis et al. (2010).

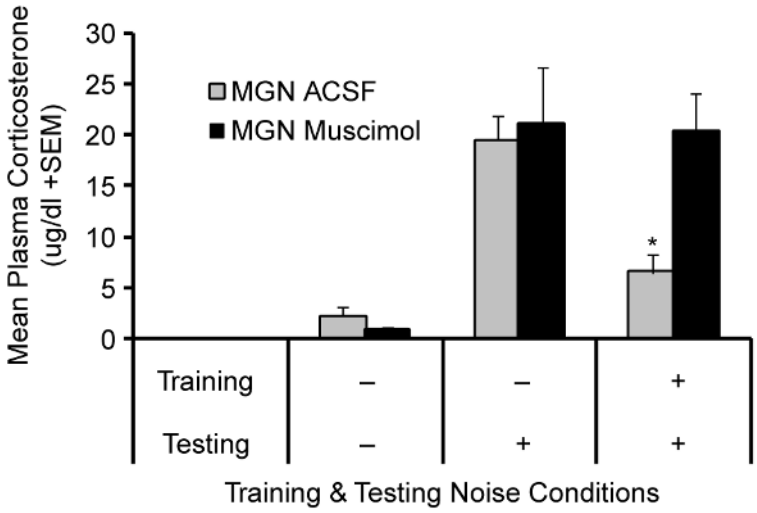

Figure 5.
Mean plasma corticosterone levels (μg/dl + 1 SEM) measured immediately following 30 min loud noise (95 dB, testing +) or quiet chamber (testing −) exposure on the 48 h test, in rats previously injected in the auditory thalamus (medial geniculate nucleus; MGN) with ACSF (gray bars) or muscimol (black bars) and exposed to loud noise (training +) or quiet chambers (training −). Note the significant reduction of corticosterone release in the rats previously treated with intra-MGN ACSF and noise, and tested again with noise, compared to the complete block of this reduction in the rats receiving intra-MGN muscimol. *Statistically different from muscimol-injected group repeatedly exposed to loud noise, $p = 0.003$. Reproduced with permission from Day et al. (2009).

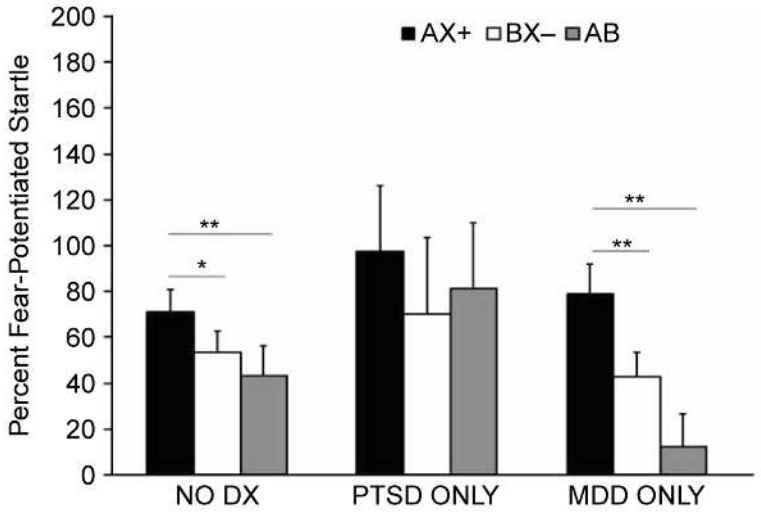

Figure 6.

Different fear responses across traumatized subjects with PTSD vs. depression (MDD). Fear-potentiated startle on AX + (danger), BX − (safety), and AB (transfer) trials across diagnostic groups. The *Y*-axis represents average percent startle potentiation for each trial type. These data show that control and depressed groups show good discrimination with the highest level of startle to the danger cue relative to the safety and transfer tasks. In contrast, those with PTSD have higher fear-potentiated startle to fear and safety cues compared to others, suggesting that they are unable to discriminate these conditioned cues. *, within-subject trial type effect, $p < 0.05$; **, within-subject trial type effect, $p < 0.01$. Reproduced and adapted with permission from Jovanovic et al. (2010a).

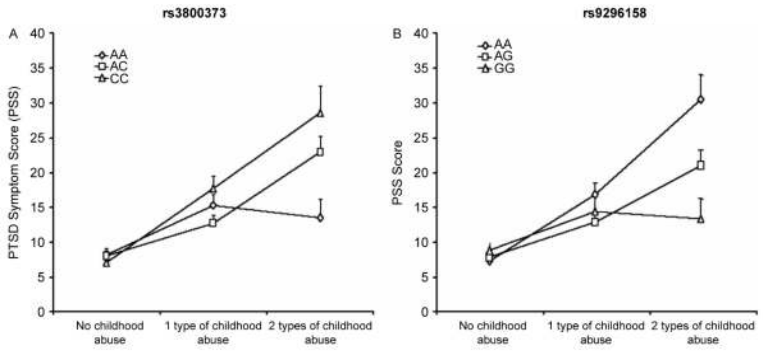

Figure 7.

Gene × environment interactions predict risk for adult PTSD. Interaction of FKBP5 polymorphisms rs3800373 (A) or rs9296158 (B) with level of physical, emotional, or sexual child abuse history (*x*-axis) predicts level of PTSD symptoms (PTSD symptom scale, *y*-axis). Reproduced and adapted with permission from Binder et al. (2008).

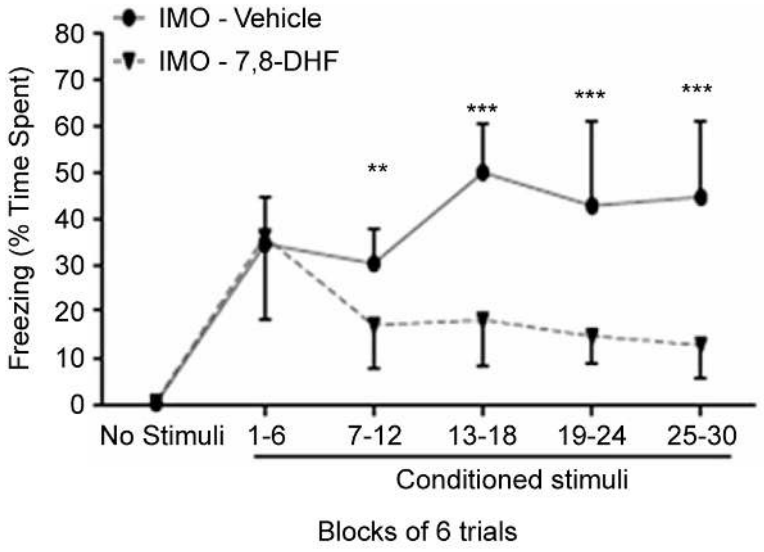

Figure 8.

Effect of a BDNF agonist molecule, 7,8-DHF on extinction of fear in an animal model of PTSD. 7,8-DHF decreased freezing in the within-session extinction trials in mice with a prior history of immobilization. Previously, we have shown that prior immobilization led to deficits in extinction of fear as a model of PTSD. Freezing (average of 6 trials within each bin) is shown during within-extinction session, 1 h after 7,8-DHF or vehicle. (***$p < 0.001$, **$p < 0.01$) Results are expressed as mean + SD. Reproduced and adapted with permission from Andero et al. (2011).

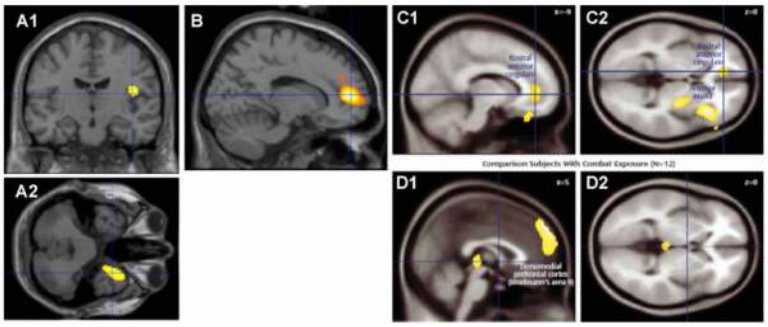

Figure 9.
(A1, A2) Regions of greater activation in 'ACTH responders' vs. 'non-responders' (ACTH responders > nonresponders of regional cerebral blood flow (rCBF) responses to trauma script (trauma script > neutral script contrast), (A1) insula and (A2) temporal pole. $p < 0.005$ uncorrected). (B) Regions of greater activation in 'ACTH non-responders' vs. 'responders' (ACTH nonresponders > responders rCBF responses to trauma script. Rostral anterior cingulate. All combat-exposed subjects ($n = 13$ responders, $n = 12$ ACTH nonresponders). Trauma scripts were participant-specific emotionally arousing autobiographical script-driven imagery. Reproduced and adapted with permission from King et al. (2009). (C, D), Areas of covariation with postscan plasma ACTH responses during 10 emotion–induction scans in combat-PTSD patients and combat-exposed healthy comparison subjects. Regions of covariation in the rostral anterior cingulate (C1), anterior insula (C2) in PTSD patients, and dorsal mPFC (Brodmann's area 9) in healthy combat-exposed controls. Covarying voxels ($p < 0.005$, uncorrected) are projected onto a canonical Montreal Neurological Institute brain. Reproduced and adapted with permission from Liberzon et al. (2007).