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## Overlapping neurobiology of learned helplessness and conditioned defeat: Implications for PTSD and mood disorders

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### Abstract

Exposure to traumatic events can increase the risk for major depressive disorder (MDD) as well as posttraumatic stress disorder (PTSD), and pharmacological treatments for these disorders often involve the modulation of serotonergic (5-HT) systems. Several behavioral paradigms in rodents produce changes in behavior that resemble symptoms of MDD and these behavioral changes are sensitive to antidepressant treatments. Here we review two animal models in which MDD-like behavioral changes are elicited by exposure to an acute traumatic event during adulthood, learned helplessness (LH) and conditioned defeat. In LH, exposure of rats to inescapable, but not escapable, tailshock produces a constellation of behavioral changes that include deficits in fight/flight responding and enhanced anxiety-like behavior. In conditioned defeat, exposure of Syrian hamsters to a social defeat by a more aggressive animal leads to a loss of territorial aggression and an increase in submissive and defensive behaviors in subsequent encounters with non-aggressive conspecifics. Investigations into the neural substrates that control LH and conditioned defeat revealed that increased 5-HT activity in the dorsal raphe nucleus (DRN) is critical for both models. Other key brain regions that regulate the acquisition and/or expression of behavior in these two paradigms include the basolateral amygdala (BLA), central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST). In this review, we compare and contrast the role of each of these neural structures in mediating LH and conditioned defeat, and discuss the relevance of these data in developing a better understanding of the mechanisms underlying trauma-related depression.

### Keywords

Learned Helplessness; Conditioned Defeat; Serotonin; Corticotropin-Releasing Hormone; Dorsal Raphe Nucleus; Bed Nucleus of the Stria Terminalis; Amygdala; Social Defeat; Fear; Anxiety; Stress

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Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are highly comorbid psychopathologies, such that, depending on the study, more than 50% of subjects meeting criteria for PTSD also meet criteria for MDD at the time of diagnoses, and 95% of those with PTSD will be diagnosed with MDD in their lifetime (Bleich et al., 1997) (see (Shalev et al., 1998) for review). Multiple factors have been proposed to explain the high levels of comorbidity between these two diagnoses, including the similarity in the symptoms required for diagnosis as well as similar etiologies for both disorders. Exposure to stressors has been recognized as a contributing factor in the onset of both PTSD and MDD. In fact, diagnostic criteria for PTSD require exposure to a traumatic event or events that are

typically characterized by actual or threatened death, serious injury, or a threat to the physical integrity of the individual or someone close to the individual (American et al., 2000). Notably, PTSD can be diagnosed following exposure to acute or chronic trauma, such as an assault or a life-threatening accident or following exposure to child abuse or domestic violence (see (Vieweg et al., 2006)). While stressor exposure has also been recognized as an important factor in the etiology of MDD, the stressor characteristics that influence risk for MDD are less clear. Exposure to traumatic events, such as those that can produce PTSD, also increase the risk for MDD (Goodyer et al., 2000; Heim et al., 2000; Kohn et al., 2001; Mayou et al., 2001; Shalev et al., 1998); however, risk for MDD might also been linked to a variety of negative life events or adversities that do not meet the criteria for trauma as described above (Kohn et al., 2001). It has also been proposed that these negative life events may alter the response of an individual to a subsequent traumatic experience increasing the likelihood that latter trauma will lead to PTSD or MDD (Yehuda et al., 2004).

Pharmacological treatments for PTSD and MDD also suggest that these disorders share similar causal mechanisms. Selective serotonin reuptake inhibitors (SSRIs) are typically the first class of pharmacotherapies used to treat PTSD or MDD, and are effective in the treatment of both disorders (see (Vaswani et al., 2003)). Also, the disruption of central serotonin (5-HT) systems has been argued to be a critical component of the etiologies for both disorders (Drevets et al., 2007; Neumeister et al., 2004).

While many similarities exist between PTSD and MDD regarding their symptomology, treatment, and etiology, there are notable differences between these disorders. For example, subjects meeting criteria for PTSD have been shown to have disruptions in the function of their hypothalamic-pituitary-adrenal axis (HPA axis), exhibiting reduced basal cortisol levels (Boscarino, 1996; Goenjian et al., 1996) and enhanced cortisol suppression in response to dexamethasone (DEX, (Goenjian et al., 1996; Yehuda et al., 1993), but see (Meewisse et al., 2007) for a critical review). In contrast, MDD is associated with elevated basal cortisol and reduced DEX suppression (Nemeroff et al., 1984). The differences in HPA function between these two disorders may reflect different central mechanisms; however, these differences may also reflect different environmental factors, such as the severity of the traumatic experience, a history of repeated trauma, or whether trauma was experienced in childhood or adulthood (Yehuda et al., 2004).

## Animal Models

Multiple animal paradigms have been argued to model both PTSD and MDD, which may reflect that these disorders share similar symptoms and/or have a similar biological basis. Animal models of depression have often been evaluated on the basis of several criteria: whether they produce behavioral changes that are similar to those observed in depression, whether these changes can be objectively measured, and whether these changes can be reversed by treatments used to treat depression (McKinney and Bunney, 1969). Based on these criteria, several strategies have been utilized to study the neural changes associated with depression-like behavior in animals, including olfactory bulbectomy (Leonard, 1984), genetic alteration and/or breeding for desired behaviors (King et al., 2001; Overstreet et al., 2005), chronic social defeat or subordination in social groups (Blanchard et al., 2002; Blanchard et al., 1995; Fuchs, 2005; Fuchs and Flugge, 2002; Heinrichs et al., 1992), acute exposure to stressful stimuli early in development ((Arborelius et al., 1999; Heim et al., 2004), but see (Schmidt et al., 2011)), and acute exposure to stressful stimuli in adulthood (Maier, 1984). Of these, models that use acute stressors have also been argued to represent PTSD ((Foa et al., 1992), but see (Yehuda and Antelman, 1993)). Hence, in most cases, animal models of MDD (and PTSD) require exposure to a stressor either early in

development, in adulthood, or both. The effects of early life stressors on depression- and anxiety-like behavior in adulthood have been reviewed previously (Heim et al., 2004), as have studies of chronic social stress in group-living animals (Blanchard et al., 2002; Fuchs and Flugge, 2002). The scope of the current review focuses on changes within neural circuits that mediate anxiety-like and depression-like behavior that occur as a consequence of exposure to a traumatic stressful experience during adulthood.

The exposure of adult rodents to stressors can produce lasting behavioral changes that resemble symptoms of MDD such as increased behavioral immobility (Anisman et al., 1978; Rittenhouse et al., 2002), disrupted circadian rhythms (Meerlo et al., 2002), and changes in feeding and body weight (Bartolomucci et al., 2004; Maier, 1984). Furthermore, similar neurochemical mediators seem to be involved in mediating depression-like behavior in rodents and in clinical populations with MDD. Similar to the treatment of MDD within clinical populations, MDD-like behavioral changes within animal models can also be prevented by antidepressant treatment (Berton and Nestler, 2006; Sherman et al., 1982). Exposure to inescapable shock leads to dysfunction of the HPA-axis resembling MDD such as elevated basal levels of glucocorticoids and reduced DEX suppression (Maier et al., 1986; O'Connor et al., 2003). Similarly, a single social defeat produces robust activation of the HPA axis (Huhman et al., 1991; Koolhaas et al., 1997). The effects of repeated social defeat are more complex, as chronic social defeat has been shown to elevate basal glucocorticoid levels (Berton et al., 1998; Miczek et al., 1990), whereas chronic subordination in a group of rats leads to a blunted glucocorticoid response to a subsequent stressor in a subset of subordinates (Blanchard et al., 1995). Because of these behavioral and neuroendocrine changes, the behavioral paradigms described below have been argued to model MDD in humans. In addition, the use of acute traumatic stressful events in these paradigms reflects the similarities between MDD and other types of stress-related mental illness such as PTSD.

## Learned Helplessness

In humans, trauma requires the experience or witnessing an actual or threatened death, serious injury or threat to the physical integrity of self or others, and the response to this event must involve intense fear, helplessness or horror (APA, 2000). While it is not possible to determine how animals interpret laboratory stressors, behavioral correlates of fear can be assessed, and the controllability of laboratory stressors can be manipulated to produce situations in which animals are made “helpless.” Exposure to inescapable, but not equivalent escapable, shock produces a constellation of behavioral changes that have been called learned helplessness (LH, (Maier and Seligman, 1976)) or behavioral depression (Weiss and Simson, 1985). Importantly, the behavioral changes associated with LH are mediated by the inescapable/uncontrollable nature of the shock, *and not the shock itself*, and include increases in fear- and anxiety-like behavior, reductions in fight/flight responding, disrupted sleep patterns, disrupted food and water intake, and the subsequent failure to learn to escape aversive stimuli in subsequent tasks where escape is possible (for review, see (Maier, 1984)). Because these changes mimic symptoms of mood disorders in humans, LH has been reviewed extensively as a powerful animal model of several human disorders, including MDD and PTSD ((Foa et al., 1992; Maier, 1984), but see (Yehuda and Antelman, 1993)). Moreover, many treatments effective in treating these disorders in humans such as electroconvulsive shock therapy (Sherman et al., 1982), benzodiazepines (Short and Maier, 1993), and chronic antidepressant administration (Sherman et al., 1982), are also effective in blocking LH in animals.

One criticism of LH is the short duration of LH-associated behavioral changes. The behavioral consequences of LH have been observed 24–48 hr after the inescapable shock session, but typically dissipate within 72-hr, and this timecourse does not resemble the

sustained changes in mood characteristic of PTSD or MDD. However, the behavioral consequences associated with LH have been shown to be prolonged simply by re-exposing organisms to the original stressor environment; that is, the subsequent presentation of contextual cues associated with the original experience of inescapability can prolong the behavioral consequences of LH, even if shock is not delivered during these “reminders” (Maier, 2001).

Recently, Maier and colleagues have argued that LH models the pathological changes induced when environmental stressors are severe and uncontrollable, which may be associated with *multiple* mood disorders in humans (Maier and Watkins, 2005); hence, Maier and colleagues posit that (1) the perception that stress is uncontrollable underlies the etiology of multiple mood disorders, and (2) the mechanisms that mediate LH are activated in mood disorders associated with uncontrollable stress. Notably, exposure to inescapable shock activates the HPA-axis and elevates basal levels of circulating glucocorticoids, which is consistent with the elevated basal glucocorticoid levels observed in MDD; however, these glucocorticoid elevations are also observed after escapable shock (unlike the behavioral consequences of LH), and are not true LH effects, since they do not depend on the escapability of the stressor.

### The Dorsal Raphe Nucleus (DRN)

While glucocorticoid release is necessary, but not sufficient, to produce LH, the behavioral changes associated with LH are critically dependent on the activation of serotonin (5-HT) cells in the caudal aspect of the dorsal raphe nucleus (DRN). The DRN is the primary 5-HT source to the forebrain and has been argued to be topographically organized such that the activation of different DRN subregions mediate different functions (Lowry et al., 2005), with the caudal aspect mediating anxiety-associated behavioral states. Inescapable, relative to escapable, shock activates 5-HT neurons in the caudal region of the DRN (Grahn et al., 1999), and this activation is associated with a significant increase in 5-HT release both in the DRN and its projection regions (Amat et al., 1998a, b). The attenuation of DRN 5-HT activity via intra-DRN infusion of benzodiazepines (Maier et al., 1994), or the 5-HT<sub>1A</sub> autoreceptor agonist 8-OH-DPAT, blocks both the development and expression of LH (Maier et al., 1995b). Also, pharmacologically activating 5-HT neurons in the caudal, but not rostral, DRN produces LH-like behavioral changes 24-hr later (Hammack et al., 2002). Based on these data, Maier and colleagues (2005) have suggested that elevated 5-HT sensitizes the caudal DRN for a period of time after treatment, and that caudal DRN 5-HT sensitization mediates the behavioral effects of LH (Maier and Watkins, 2005). While substantial evidence suggests caudal DRN 5-HT activation mediates LH, the input(s) that activate the DRN during inescapable shock are not well understood.

The data described above suggesting that increased 5-HT release mediates the behavioral consequences of LH appear inconsistent with the therapeutic effects of SSRI treatment, which are also associated with increased levels of central 5-HT. Notably, effective SSRI treatment typically requires several weeks of administration, and the acute effects of these drugs are often associated with increased anxiety and depressive behavior in humans and animals (Bagdy et al., 2001; Burghardt et al., 2004), consistent with the behavioral effects of 5-HT activation observed in LH. We and others have argued that the efficacy of long-term SSRI treatment depends on changes in the function of pre- and/or post-synaptic receptors in brain regions that mediate emotional behavior; hence, the response to 5-HT release after long-term SSRI treatment may be dramatically altered, and these same mechanisms may mediate the efficacy of these drugs in preventing LH ((Berendsen, 1995; Hammack et al., 2009b; Stahl, 1994; Strome et al., 2005; Yatham et al., 1999), see below).

Corticotropin-releasing hormone (CRH) has been heavily studied for its role in initiating peripheral stress responses and emotional behavior (see (Koob and Heinrichs, 1999; Owens and Nemeroff, 1993) for review). While CRH-positive cell bodies can be found throughout the brain, they are dense in regions associated with both stressor responding and emotional behavior, including the paraventricular nucleus of the hypothalamus (PVN), central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST). Generally, the activation of CRH neurons in these regions has been associated with behavioral phenotypes resembling stress, fear and/or anxiety.

CRH receptors are found in the DRN, with the CRH type 2 receptor more highly expressed than the CRH type 1 receptor (Chalmers et al., 1995; Day et al., 2004). CRH type 1 receptors are expressed at low levels throughout the rostral-caudal axis of the DRN, whereas the CRH type 2 is expressed predominantly by 5-HT neurons at mid-levels and on both 5-HT neurons and gamma amino butyric acid (GABA)-expressing neurons at caudal levels (Day et al., 2004). Several reports have suggested that CRH inhibits DRN 5-HT activity in rostral DRN regions (Kirby et al., 2000; Price et al., 1998), likely via activation of CRH type 1 receptors. In contrast, CRH may selectively excite DRN 5-HT neuronal activity only in the middle-to-caudal regions of the DRN, the very same neuronal population activated by inescapable, but not escapable, shock (Lowry et al., 2000). Moreover, while systemic administration of a CRH type 1 receptor antagonist systemically (Deak et al., 1999), or directly into the DRN (Hammack et al., 2003b) does not alter LH, DRN CRH type 2 receptor blockade during inescapable shock blocks the development of LH (Hammack et al., 2003b). Also, CRH 2 receptor activation directly into the caudal, but not rostral, DRN activates middle-to-caudal DRN 5-HT neurons (Abrams et al., 2004; Amat et al., 2004; Forster et al., 2008; Kirby et al., 2008; Staub et al., 2005), and produces LH-like behavioral changes 24-hours later in the absence of shock (Hammack et al., 2003b). Hence, CRH type 2 receptor activation in the DRN is both necessary and sufficient to produce LH (see (Maier and Watkins, 2005) for review). Notably, DRN CRH release is critical for the development of LH, but does not mediate the expression of LH-associated behaviors after the inescapable shock session (Hammack et al., 2002).

In many of the reports that found CRH inhibitory effects on DRN 5-HT activity, the inhibitory effects were localized to the rostral DRN and attenuated at high CRH doses. These data suggest that low doses of CRH inhibit DRN 5-HT activity whereas high doses of CRH excite DRN 5-HT activity. If the behavioral consequences of LH depend on caudal DRN 5-HT activation, then low CRH doses might be expected to block LH, whereas high CRH doses should produce LH-like behavioral changes, and indeed this prediction has been confirmed (Hammack et al., 2003a).

As described above, DRN CRH receptor subtypes are organized topographically, so that CRH type 2 receptors are highly expressed only in the middle-to-caudal DRN. Hence, the release of CRH can selectively activate *only this DRN subregion*, which is the same subregion selectively activated by inescapable shock. While many DRN inputs tightly regulate DRN 5-HT activity, to date only the CRH system has been shown to selectively activate the anxiety-associated middle-to-caudal region.

The sources of DRN CRH during inescapable shock are unknown. A small percentage of DRN neurons coexpress CRH (Commons et al., 2003), and we have found that DRN CRH mRNA is upregulated following an acute stressor (unpublished data). Moreover, CRH analogues, such as the urocortin family of peptides, may preferentially activate DRN CRH type 2 receptors to produce LH, and are capable of producing LH-like behavioral changes at low doses (Hammack et al., 2003b). However, for reasons discussed below, DRN-projecting

CRH neurons in the BNST likely contribute to the development of LH following inescapable shock.

### The Bed Nucleus of the Stria Terminalis (BNST)

The extended amygdala has been implicated in emotional responses, with separate extended amygdala subregions mediating fear- and anxiety-like behaviors. A consideration of the paradigms sensitive to manipulations of the CeA and BNST led Walker et al. to argue that the CeA mediates responding when both the fear-eliciting stimulus and the behavioral response are short in duration, whereas the BNST mediates responding when both the stimulus and response have a long duration (Walker and Davis, 2008; Walker et al., 2009; Walker et al., 2003). They have further argued that CeA-mediated responding resembles “fear”, and is anatomically and phenomenologically dissociable from BNST-mediated responding, which they argue more resembles “anxiety.” Consistent with this argument, Waddell et al. (2006), showed that the BNST mediates responding to a 10-min tone that was previously paired with shock, but not a 1-min tone, and argued that anxiety was conditioned to the 10-min tone that was dissociable from the fear state conditioned to the shorter tone (Waddell et al., 2006). In sum, the BNST has been argued to mediate anxiety-like responding to stimuli that are of long duration.

Importantly, the BNST has also been implicated in behavioral changes associated with *depression*. BNST CRH activity has been correlated with anhedonic behavior after chronic mild stress (Stout et al., 2000), inescapable shock activates and sensitizes anterior BNST neurons (Greenwood et al., 2005) and BNST lesions block the development of LH (Hammack et al., 2004). While BNST lesions blocked the *exaggerated* fear conditioning observed 24 hours after inescapable shock such that fear conditioning in inescapably shocked rats did not differ from fear conditioning in control rats, BNST lesioned rats still displayed normal fear conditioning. Notably, BNST lesions blocked more than just the increased fear conditioning observed after inescapable shock, also blocking the escape deficits normally associated with LH. Hence, BNST activity appears necessary for the development of several behavioral consequences of LH, and not just LH effects that are associated with fear and anxiety. In support, we have found that local infusion of pituitary-adenylate cyclase activating polypeptide (PACAP) into the BNST can mimic LH-like increases in anxiety-like behavior as well as escape deficits, likely by activating BNST CRH neurons (Figure 1), and suggesting that BNST activity is both necessary and sufficient to produce LH. Moreover, the over-expression of CRH in the BNST using a lentiviral based system for site-specific CRH-expression increased depressive behaviors on the forced swim and tail-suspension tests (Regev et al.). *Hence, these data implicate the BNST as critical for depressive behaviors in addition to anxiety.* In contrast to these studies, which suggest that BNST activity promotes depressive behavior, BNST lesions have also been shown to aggravate behavioral despair on the forced-swim test in male and female rats (Pezuk et al., 2008; Pezuk et al., 2006). Notably, in these studies BNST lesions extended through the entire rostral-caudal extent of the BNST. Choi et al (Choi et al., 2007) have shown that posterior regions of the BNST may inhibit, while anterior BNST regions excite, stressor responding. Hence, the anterior aspects of the BNST, which contain BNST subregions that highly express CRH, may promote anxiety- and depression-like behavior while posterior regions of the BNST may reduce it, although this has yet to be tested.

CRH afferents from the BNST may modulate DRN 5-HT neuronal activity during LH. As described above, the brain regions exhibiting the highest expression of CRH include the PVN, CeA, and BNST. Notably, PVN CRH expression and glucocorticoid release are not sensitive to shock escapability (Helmreich et al., 1999; Maier et al., 1986), and large electrolytic lesions of the CeA do not block the development/expression of LH (Maier et al., 1993), suggesting that neither the PVN nor the CeA mediate LH. We have found DRN

afferents originating in CRH-rich areas of the BNST (unpublished data), and as noted above, excitotoxic BNST lesions blocked both the increases in anxiety-like behavior and escape deficits associated with LH (Hammack et al., 2004). Hence, exposure to inescapable shock activates BNST neurons (Greenwood et al., 2005), likely leading to the release of CRH in the caudal DRN. Substantial caudal DRN CRH release activates 5-HT neurons and produces the behavioral consequences of LH (Figure 2A).

Notably, the BNST also receives 5-HT projections from the caudal DRN (Commons et al., 2003; Phelix et al., 1992), contains multiple inhibitory and excitatory 5-HT receptor subtypes, and we have shown that 5-HT release in the BNST can both inhibit and excite BNST neuronal activity (see (Hammack et al., 2009b) for review). Because multiple inhibitory and excitatory 5-HT receptor subtypes can be expressed by single BNST neurons, we have argued that treatments that shift the balance of these receptor subtypes towards excitation may produce an anxiogenic and/or depression-like phenotype, whereas treatments that shift the balance of these receptor subtypes towards inhibition may be protective and/or therapeutic (Hammack et al., 2009b).

### **The central nucleus of the amygdala (CeA)**

Because of their many similarities, neurons in the anterolateral BNST and CeA have been argued to form the rostral and caudal extensions of the central extended amygdala (Alheid, 2003). Substantial data has implicated the CeA in mediating the expression of learned fear (see (Davis et al., 1993; LeDoux, 1993) for review), and the CeA highly expresses CRH (Cummings et al., 1983) and projects to and receives input from the DRN (Rizvi et al., 1991). However, while large electrolytic lesions of the amygdala completely blocked the expression of learned fear in a LH paradigm, they did not attenuate the inescapable shock-induced escape deficits (Maier et al., 1993). These data are in contrast to BNST lesions which only attenuated the exaggerated fear conditioning normally observed after inescapable shock to levels observed in controls (Hammack et al., 2004). Hence, while the CeA is critical for fear expression in many paradigms, CeA activity does not appear to be necessary for LH.

### **The basolateral nucleus of the amygdala (BLA)**

Many studies have implicated BLA plasticity as critical for the acquisition of learned fear (see (Davis et al., 1993; LeDoux, 1993)), and the BLA projects to and modulates activity in both the BNST and CeA. However, while BLA activity seems to be critical for mediating the expression of anxiety-like behavior following inescapable shock, BLA activity does not appear necessary for the development of LH. The BLA receives 5-HT input from the DRN, and substantially more 5-HT is released within the BLA following inescapable shock than equivalent escapable shock (Amat et al., 1998a). Moreover, 5-HT release was potentiated in the BLA in rats exposed to a stressor 24 hr after inescapable shock, suggesting that serotonin release is sensitized during IS (Amat et al., 1998a). Lastly, BLA 5-HT<sub>2C</sub> antagonism during testing blocked the anxiogenic effects of prior inescapable shock and BLA 5-HT<sub>2C</sub> agonism mimicks the anxiogenic effects of prior inescapable shock (Christianson et al.). While these data implicate BLA 5-HT<sub>2C</sub> receptors as mediating the expression of the anxiogenic consequences of LH, it is unknown whether BLA 5-HT<sub>2C</sub> receptors mediate *other* behavioral consequences of LH not related to fear or anxiety. Moreover, BLA 5-HT<sub>2C</sub> antagonism prior to inescapable shock had no effect on the development of LH (Christianson et al.). Together, these results suggest that the BLA is efferent to the DRN and critical for mediating the expression of exaggerated fear and anxiety observed following the development of LH. These data stand in contrast to the BNST, whose activity is both necessary and sufficient for LH development.

## Conditioned Defeat

Social defeat is a robust stressor that, like LH, produces an array of behavioral changes including anxiety- and depression-like behavior (Berton et al., 1998; Heinrichs et al., 1992; Keeney et al., 2006; Krishnan et al., 2007; Rodgers and Cole, 1993). In Syrian hamsters, social defeat leads to a loss of species-typical territorial aggression and increased submissive and defensive behavior in subsequent social encounters with smaller non-aggressive intruders. This phenomenon has been called conditioned defeat (Huhman et al., 2003). Like LH, conditioned defeat can be produced by a single treatment session such that a single 15 min social defeat leads to changes in agonistic behavior the next day. On the surface the changes in agonistic behavior that characterize conditioned defeat are reminiscent of LH because defeated hamsters submit to non-threatening conspecifics as if they were helpless. Interestingly, inescapable shock can produce social avoidance as well. Rats that receive inescapable, but not equivalent escapable, shock show reduced social investigation with juvenile conspecifics (Christianson et al., 2008). Although social defeat activates the HPA axis in hamsters (Huhman et al., 1991), blocking glucocorticoid synthesis prior to social defeat does not alter the acquisition of conditioned defeat (Cooper and Huhman, 2010). Thus, consistent with LH glucocorticoids do not appear to be critical for the developmental of conditioned defeat.

While conditioned defeat and LH paradigms have important similarities, there are also some noteworthy differences. Stressor controllability is critical for LH, but may not be critical for conditioned defeat. We have found that hamsters still show conditioned defeat behavior when they are allowed to escape from the aggressor during social defeat training (Figure 3). Also, unlike LH, the changes in agonistic behavior that characterize conditioned defeat can persist for at least a month (Huhman et al., 2003). The consequences of social defeat also may depend on how animals are tested, as defeated hamsters do not avoid novel conspecifics when tested in a Y-maze (Lai et al., 2005). In sum, the LH and conditioned defeat paradigms have some important similarities and in this review we suggest that the neural structures mediating the respective behavioral changes are remarkably similar as well.

As discussed below, many of the brain regions that mediate LH are also important for conditioned defeat; however, a careful examination of the subregions implicated in conditioned defeat in some of these areas (i.e. the DRN) reveal important differences between these two models. The reasons for these differences are provocative, but currently unclear, and will be discussed in the following sections.

### The Dorsal Raphe Nucleus (DRN)

Social defeat has been shown to increase neural activation in the DRN as indexed by c-Fos expression (Kollack-Walker et al., 1997; Martinez et al., 1998). Also, social defeat has been shown to decrease 5-HT<sub>1A</sub> receptor mRNA expression in the DRN (Cooper et al., 2009). Thus, social defeat appears to activate DRN 5-HT neurons and may sensitize them to future stressors as has been proposed for LH. Researchers have also investigated c-Fos expression in separate DRN subregions and found that social defeat activates 5-HT neurons in middle and caudal portions of the DRN (Gardner et al., 2005). These data are consistent with the effects of inescapable shock on caudal DRN activation; however, in hamsters, social defeat selectively increases c-Fos expression in rostral portions of the ventral DRN (Cooper et al., 2009). Similarly, social defeat interacts with maternal separation in rats to increase tryptophan hydroxylase mRNA (Gardner et al., 2009b) and serotonin transporter mRNA (Gardner et al., 2009a) in rostral portions of the ventral DRN. Although the mid and caudal DRN are well-known for reciprocal connections with limbic structures, the rostral DRN may also have connections with the amygdala and BNST (Commons et al., 2003; Imai et al., 1986; Rizvi et al., 1991). Urocortin 1 administration into the rat BLA was shown to increase



c-Fos expression in the rostral DRN (Spiga et al., 2006). However, the BLA does not have major direct projections to the DRN, and a BLA-DRN pathway likely involves other brain regions such as the BNST, central amygdala, or medial prefrontal cortex (Peyron et al., 1998). Glutamatergic projections from the lateral ventral BNST to the rostral-mid DRN have been proposed to contribute to the ability of wheel running to attenuate stress-induced c-Fos expression in DRN 5-HT neurons and prevent LH (Greenwood et al., 2005). The rostral DRN also sends serotonergic projections to brain regions critical for aggressive behavior including the medial preoptic area and anterior hypothalamus (Ferris et al., 1999; Rizvi et al., 1991). Thus, the rostral DRN has the necessary neuroanatomical connections to regulate agonistic behavior in potentially threatening situations.

The role of the DRN in modulating the acquisition and expression of conditioned defeat has been examined using similar strategies to those described for LH. Inhibition of DRN 5-HT neurons via local infusion of a 5-HT<sub>1A</sub> autoreceptor agonist blocks both the development and expression of conditioned defeat (Cooper et al., 2008). Moreover, the activation of DRN 5-HT neurons via 5-HT<sub>1A</sub> autoreceptor antagonism exacerbates conditioned defeat following a suboptimal social defeat experience (Cooper et al., 2008). Notably, the infusion sites in these studies extended throughout the rostral-caudal axis of the DRN, targeting all DRN subregions. Together, these data suggest that, like LH, DRN 5-HT activation is necessary and sufficient to modulate the behavioral consequences of social defeat in Syrian hamsters. The DRN inputs that drive 5-HT activity during the acquisition and expression of conditioned defeat are unknown, although CRH is likely a key factor.

The combined blockade of CRH type 1 and type 2 receptors in the DRN reduces the acquisition and expression of conditioned defeat (Cooper and Huhman, 2007). In contrast, infusion of a selective CRH type 2 receptor antagonist into the DRN reduces the expression, but not acquisition, of conditioned defeat (Cooper and Huhman, 2007). The immunohistochemical and pharmacological data together suggest that, unlike LH, the development of conditioned defeat is likely modulated by neurochemical signaling at CRH type 1 receptors in the rostral DRN. In contrast, CRH type 2, and not type 1, receptors in the forebrain appear to modulate the development of conditioned defeat. Injection of a CRH type 2 receptor antagonist into the lateral ventricle reduces the acquisition of conditioned defeat, whereas injection of a CRH type 1 receptor antagonist does not (Cooper and Huhman, 2010). As discussed below, one potential forebrain region that could mediate the effect of CRH type 2 receptor blockade is the medial amygdala.

### **The Bed Nucleus of the Stria Terminalis (BNST)**

BNST activation is necessary for the expression, but not acquisition, of conditioned defeat. Inhibiting the BNST with local infusion of the GABA(A) receptor agonist muscimol prior to testing blocks the production of conditioned defeat behavior, while infusion prior to social defeat does not disrupt the development of conditioned defeat (Markham et al., 2009). Consistent with this role for the BNST, injection of a CRH type 2 receptor antagonist into the BNST reduces the expression of conditioned defeat, whereas injection of a CRH type 1 receptor antagonist into the lateral ventricle does not (Cooper and Huhman, 2005). These data suggest that CRH type 2 receptors are activated in the BNST at the time of conditioned defeat testing. The CRH or urocortin input to the BNST likely originates in the CeA, because unilateral blockade of CRH receptors in the BNST together with a contralateral CeA lesion also impairs the expression of conditioned defeat (Jasnow et al., 2004).

### **The basolateral and central nuclei of the amygdala**

Several studies indicate that the BLA is a critical brain region for the neural plasticity underlying the formation of conditioned defeat. Selective blockade of the NR2B subunit of

N-methyl-D-aspartate (NMDA) receptors in the BLA by infusion of ifenprodil impairs the acquisition, but not expression, of conditioned defeat (Day et al., in press). Also, inhibition of protein synthesis in the BLA by infusion of anisomycin impairs the acquisition of conditioned defeat (Markham and Huhman, 2008). Furthermore, using a viral vector to over-express cyclic AMP response element binding protein (CREB) in the BLA was shown to enhance the acquisition of conditioned defeat (Jasnow et al., 2005). These findings suggest the neural structures and neurochemical signals that control the formation of conditioned defeat overlap with those that underlie the formation of conditioned fear.

The BLA has significant projections to the CeA and, as mentioned above, CeA activation is critical for the expression of some forms of conditioned fear. Inhibition of protein synthesis in the CeA also has been shown to impair the consolidation of conditioned fear, which suggests that the formation of fear memories may depend on neural plasticity in the CeA as well as the BLA (Wilensky et al., 2006). Inactivation of the CeA with infusion of muscimol reduces both the acquisition and expression of conditioned defeat (Jasnow and Huhman, 2001). Several injections in this study occurred at the border between the CeA and BLA, and therefore it is difficult to know whether muscimol blocked the acquisition of conditioned defeat by diffusing into the BLA. Thus, the precise role the CeA plays in the neural plasticity underlying conditioned defeat remains uncertain.

The BLA receives input from several brain regions important for the development of conditioned defeat including the medial amygdala (MeA) and hippocampus (Coolen and Wood, 1998; Petrovich et al., 2001). The MeA is known to modulate fearful and defensive behavior (Blanchard et al., 2005; Li et al., 2004), and social defeat activates MeA neurons that express CRH type 2 receptor mRNA (Fekete et al., 2009). Pharmacological inactivation of the MeA (Markham and Huhman, 2008) and ventral hippocampus (Markham et al., 2010) prior to social defeat has been shown to disrupt the acquisition of conditioned defeat. However, injection of a protein synthesis inhibitor into the MeA (Markham and Huhman, 2008) and ventral hippocampus (Markham et al., 2010) does not impair the acquisition of conditioned defeat. All together, data on the acquisition of conditioned defeat suggest that several brain regions provide crucial input to the BLA during social defeat training, including the MeA, ventral hippocampus, and DRN. This input likely modulates the critical neural plasticity in the BLA that underlies the formation of conditioned defeat. In conclusion, the neural structures implicated in the development of conditioned defeat are a combination of those known to be critical for the development of LH and conditioned fear (Figure 2B).

## Developing a circuit (BNST-DRN interactions)

A direct comparison of the anatomical and pharmacological similarities and differences of LH and conditioned defeat is described in Table 1. While the neural mechanisms that mediate LH and conditioned defeat are not identical, the similarities should be noted. First, activity in the DRN, BNST, and BLA is critical for the acquisition and/or expression of the behavioral changes associated with both models. Second, the activation of 5-HT neurons in select subregions of the DRN is necessary for both the acquisition and expression of LH and conditioned defeat, and the activation of DRN 5-HT is sufficient to produce LH behavioral changes in the absence of shock (Hammack et al., 2003a; Hammack et al., 2002; Maier et al., 1995a) or exacerbate the effects of defeat (Cooper et al., 2008). Third, the activation of CRH type 2 receptors is critical for the acquisition of learned helplessness and modulates both the acquisition and expression of conditioned defeat.

Repeated stress models extend findings from LH and conditioned defeat, and together suggest that interactions between the serotonergic DRN, BLA, and BNST play a prominent

role in mediating depressive symptoms associated with stressor exposure (Figure 4). The nature of the interaction between these systems may depend in part on characteristics of the stress exposure. For example, when an organism interprets a stressor as uncontrollable, the BNST may be activated prior to BLA activation, whereas following a social defeat, the BLA may be activated prior to the BNST. Likely, frontal brain regions such as the medial prefrontal cortex may coordinate activity in the ventral forebrain and brainstem differently depending on the behavioral paradigm. Notably, when activity in the ventral aspects of the medial prefrontal cortex (mPFC) is suppressed, escapably shocked rats exhibit marked DRN 5-HT activity and develop LH (Amat et al., 2005). These results suggest that the mPFC actively inhibits the neurocircuitry that mediates LH when an organism learns it has control over stress. In addition to its modulation of DRN activity, the mPFC may project to and modulate activity in the BLA, BNST and CeA (McDonald et al., 1999); hence, the expression of depressive behaviors may result from a failure of the mPFC to inhibit activity in these emotional circuits during stressor exposure.

## New Directions

As discussed above, it is likely that the brain regions implicated in LH and conditioned defeat are important targets for current pharmacological approaches in the treatment of MDD and PTSD, and we have previously suggested that changes in the 5-HT response of brain regions like the BNST and DRN mediate the efficacy of some of these treatments ((Hammack et al., 2009b), also see (Berendsen, 1995; Stahl, 1994; Strome et al., 2005; Yatham et al., 1999)). However, the data described above suggest that other mechanisms for modulating these neural circuits may represent novel treatments for trauma-related disorders; some of these are discussed below.

CRH type 2 receptor knockout mice exhibit an anxiogenic profile, suggesting that the expression of the CRH type 2 receptor might be anxiolytic (Bakshi et al., 2002; Takahashi, 2001). Because substantial evidence suggests the opposite role for the CRH type 1 receptors, and CRH type 1 receptors have been shown to mediate the effects of CRH activity on the HPA-axis (see (Takahashi, 2001) for review), considerable interest has focused on the development of CRH type 1 receptor antagonists for the treatment of anxiety disorders and MDD. While results from these studies have been mixed, there likely remains a valuable role for the use of CRH type 1 antagonists in the treatment of these disorders. Interestingly, there has been considerably less interest in the development of CRH type 2 receptor antagonists for the treatment of anxiety disorders or MDD, despite the fact that many pharmacological studies also show a role for CRH type 2 receptors in mediating anxiogenic states. The data reviewed here showing that CRH regulates the development of LH and conditioned defeat indicates a critical role for CRH type 2 receptors. One important consideration for future research on antidepressant treatments is that activation of these receptor subtypes likely depends on the brain region targeted.

Moreover, the action of other therapeutic treatments may be mediated by changes in the neurocircuitry depicted in Figure 4. For example, voluntary exercise has been shown to have many therapeutic benefits on mood in both humans and animals (see (Greenwood and Fleshner, 2008)), and 6 weeks of voluntary wheel running in rodents has been shown to block behavioral consequences of LH (Greenwood et al., 2003). Notably, voluntary exercise upregulated 5-HT<sub>1A</sub> receptors in the DRN, reducing both DRN and BNST activity (Greenwood et al., 2005; Greenwood et al., 2003). We have shown that prior exercise blocks the anxiogenic effects of the 5-HT<sub>2C</sub> agonist m-chloro-phenylpiperazine (mCPP, (Fox et al., 2008)), and we have localized this protective effect of exercise on mCPP-induced anxiety to the BNST (unpublished data). Hence a shift in the BNST response to 5-HT towards

inhibition (via a decrease in function of excitatory 5-HT<sub>2C</sub> receptors) may mediate a behavioral phenotype of resistance to stress.

The recent finding that PACAP may mediate behavioral changes associated with LH as well as those associated with repeated stress (Hammack et al., 2009a) suggests that this peptidergic system may represent a promising new target for the development of therapeutic drugs in the treatment of disorders associated with stressor exposure. To date most of the literature investigating the physiology of PACAP-related peptides has focused on the neuroprotective and neurotrophic actions of these molecules (see (Shioda et al., 2006)); however, accumulating evidence is suggesting a role for PACAP in mediating the physiological response to stress exposure (see (Hammack et al.)), and elevated PACAP levels and alterations in PAC1 receptor expression and methylation were recently shown to predict PTSD symptoms and diagnosis in women (Ressler et al., 2011). More studies are necessary to determine the potential benefits of targeting this system in the treatment of anxiety disorders and MDD.

## Conclusions

The LH and conditioned defeat paradigms produce behavioral changes that may be associated with the symptomology of trauma-related depression. A consideration of the neural circuitry underlying each of these behavioral paradigms suggests that the DRN, BNST, BLA, and CeA play a critical role in the acquisition and expression of these behavioral changes, although the precise role of these structures may differ depending on the behavioral paradigm studied. Based on these studies, it seems clear that interactions between the serotonergic DRN and emotion-related brain regions such as subregions of the amygdala and BNST play a key role in the development and/or expression of LH and conditioned defeat. Hence the efficacy of treatments for mental disorders associated with traumatic stress will likely depend on a modulation of activity in this neural circuit.

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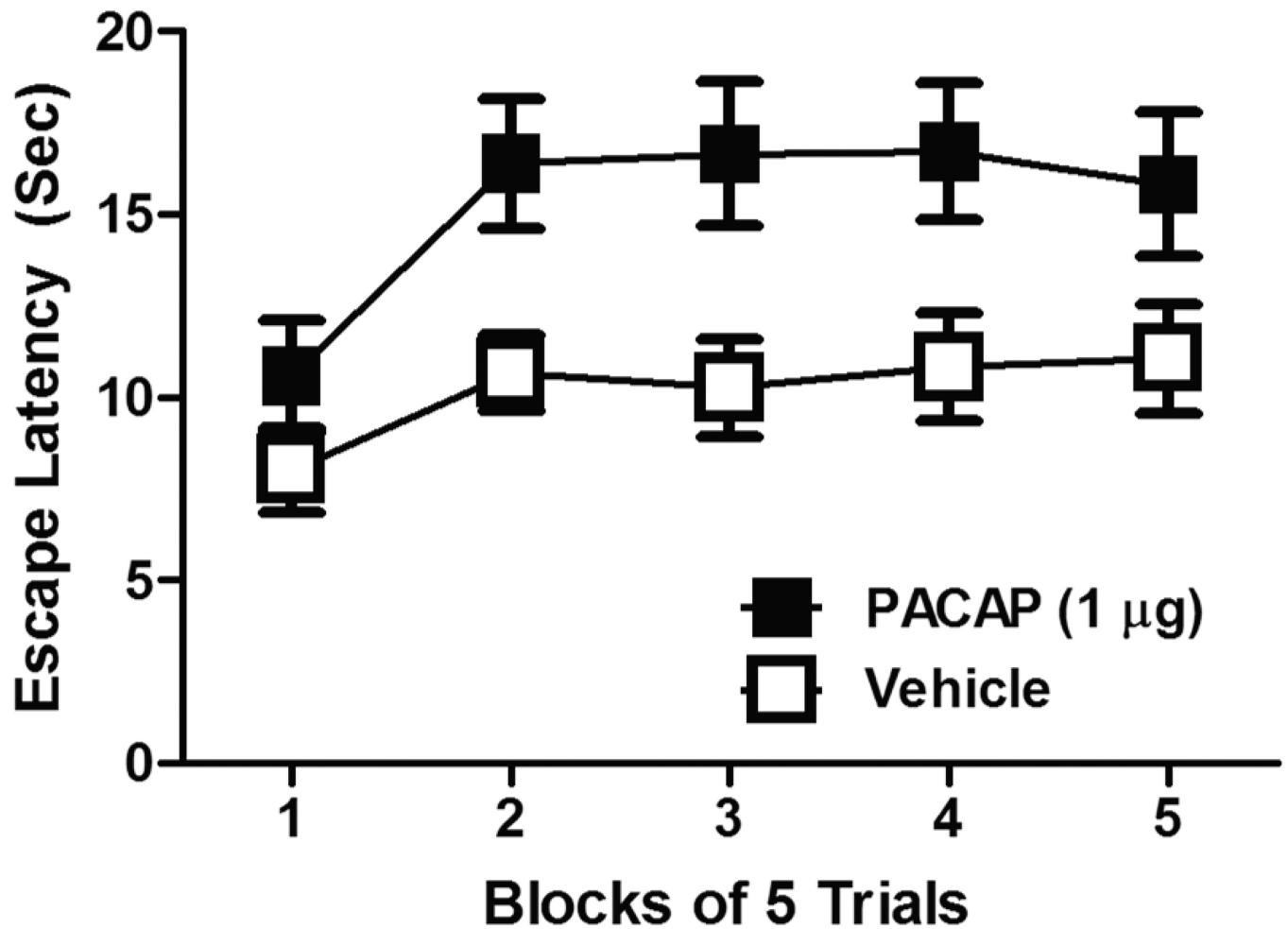


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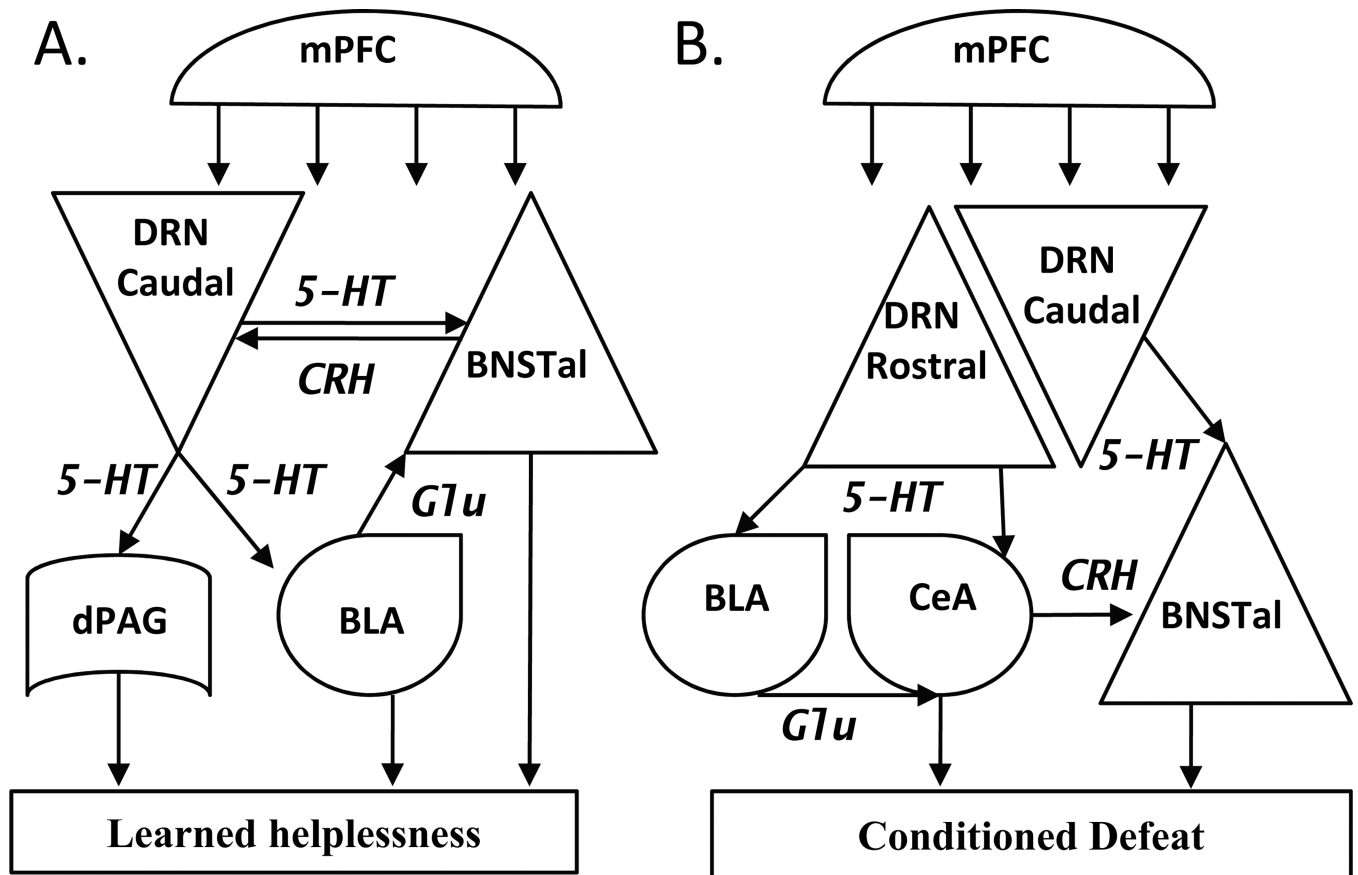
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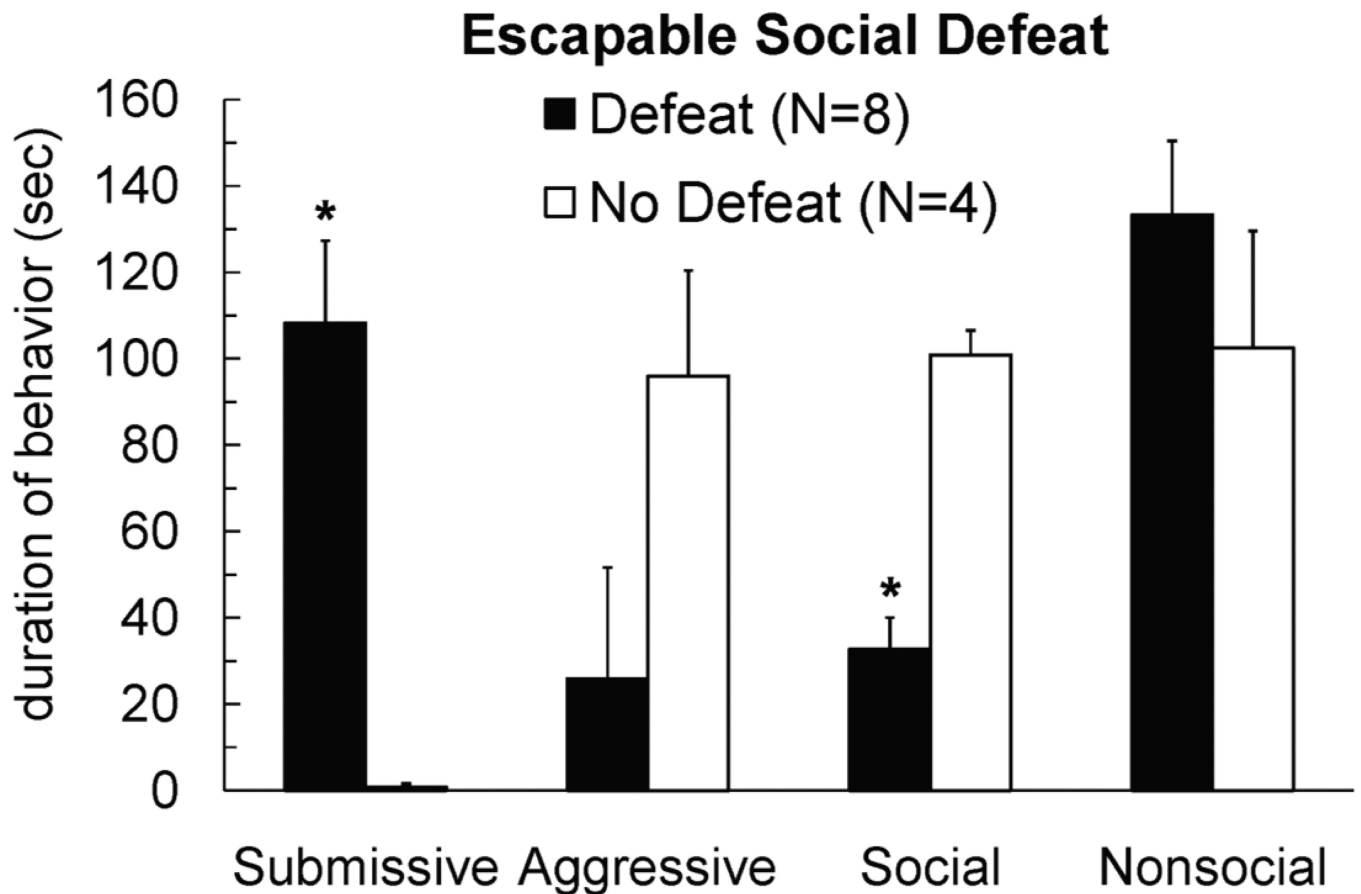


**Figure 1.**

Rats were infused into the BNST with 1 µg PACAP or equivolume (0.5 µg) vehicle. 24-hr later, rats were tested in a shuttlebox escape task for the latency to escape footshock (FR-2 schedule). Prior BNST PACAP infusion produced a learned-helplessness like behavioral phenotype; 2-way analysis of variance revealed a main effect of drug  $F(4,132) = 8.588$ ,  $p < 0.05$ , and time  $F(4,132) = 8.046$ ,  $p < 0.05$ .

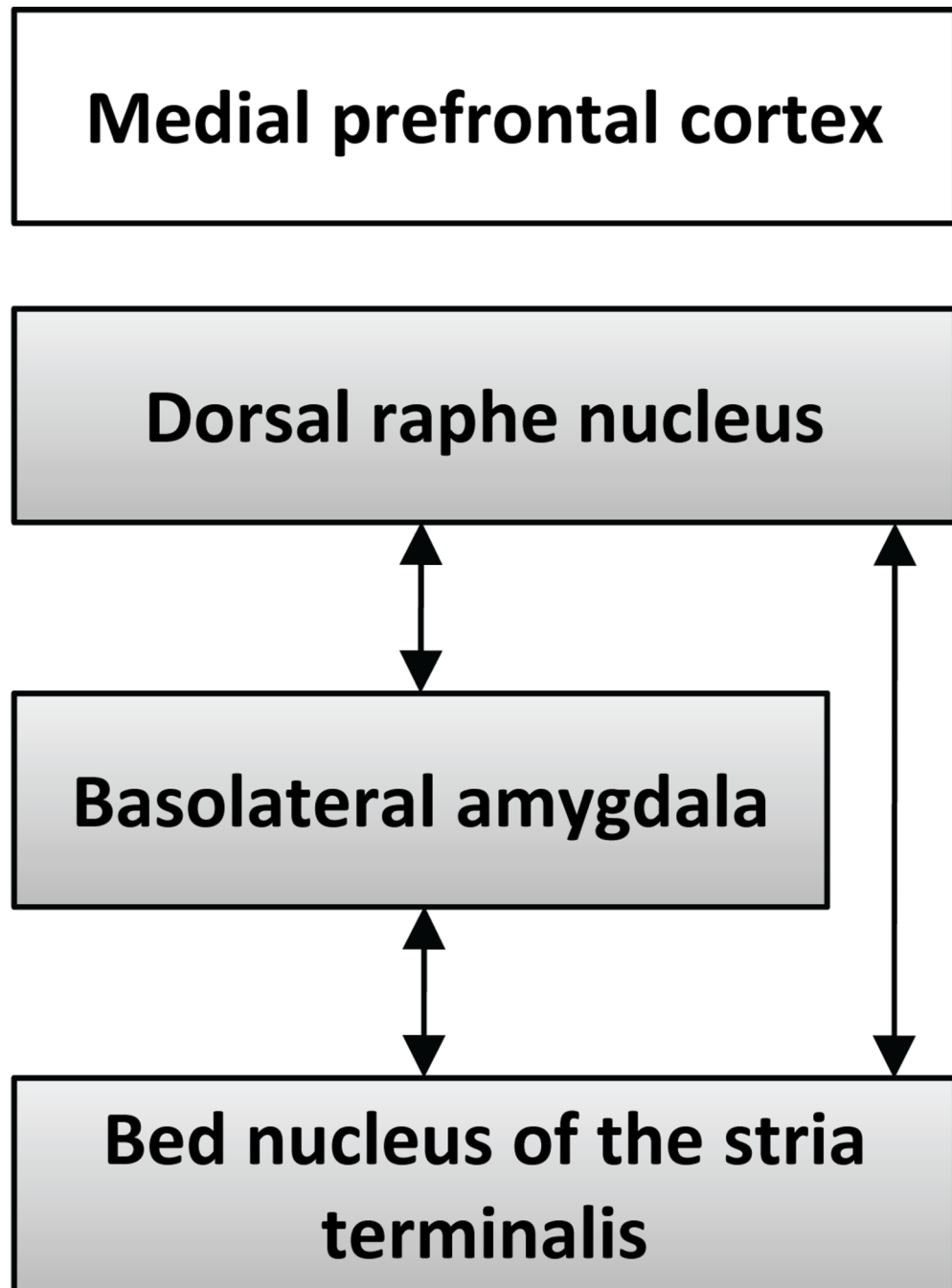


**Figure 2.** Hypothesized circuits for A. Learned helplessness and B. Conditioned defeat. Abbreviations: 5-HT, serotonin; BLA, basolateral amygdala; BNSTal, anterolateral bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CRH, corticotropin-releasing hormone; dPAG, dorsal periaqueductal gray; DRN, dorsal raphe nucleus; Glu, glutamate; mPFC, medial prefrontal cortex.



**Figure 3.**

Male Syrian hamsters received 3 social defeats in a neutral arena at 3-min intervals. Subjects were able to jump out of the arena during social defeats, and individuals were removed from the arena by the experimenter after 3 failed jumps. Subjects escaped from the arena more quickly during the 2nd and 3rd defeats compared to the 1st (ANOVA,  $p < .05$ ). No defeat controls received corresponding exposure to an empty neutral arena. Subjects were tested for conditioned defeat 24-hours later in a 5-min social encounter with a non-aggressive intruder. \* indicates that defeated subjects showed increased submissive and defensive behavior and reduced social behavior during conditioned defeat testing compared to no defeat controls (t-tests,  $p < .05$ ).



**Figure 4.**

A review of the literature investigating the brain regions that mediate both learned helplessness and conditioned defeat suggest that interactions between the dorsal raphe nucleus, basolateral amygdala and bed nucleus of the stria terminalis are critical for both behavioral paradigms. Activity within this hypothesized circuit is tightly regulated by projections from the medial prefrontal cortex.



Table 1

	Learned Helplessness (LH)	Conditioned Defeat	Manuscript
<b>Basolateral Amygdala (BLA)</b>	-↑ 5-HT within the BLA following IS <sup>1</sup> -BLA 5-HT release is sensitized 24-hr after inescapable shock (IS) <sup>1</sup> -BLA 5-HT <sub>2C</sub> activation mimics the anxiogenic effects of IS <sup>2</sup> -BLA 5-HT <sub>2C</sub> blockade during IS blocks the subsequent anxiogenic effects of IS <sup>2</sup>	-BLA NR2B subunit blockade impairs acquisition but not expression of conditioned defeat <sup>3</sup> -Intra-BLA anisomycin impairs acquisition of conditioned defeat <sup>4</sup> -Intra-BLA CREB over-expression enhances acquisition of defeat <sup>5</sup>	<sup>1</sup> Amat et al., 1998a <sup>2</sup> Christianson et al., in press <sup>3</sup> Day et al., in press <sup>4</sup> Markham & Huhman, 2008 <sup>5</sup> Jasnow et al., 2005
<b>Other Amygdala Subregions</b>	Large electrolytic lesions of the amygdala centered around the central nucleus of the amygdala (CeA) block fear conditioning, but do not block the escape deficits produced by IS <sup>6</sup>	-CeA Muscimol blocks acquisition and expression of conditioned defeat <sup>7</sup> -MeA inactivation impairs acquisition of conditioned defeat <sup>4</sup>	<sup>6</sup> Maier et al., 1993 <sup>7</sup> Jasnow & Huhman, 2001
<b>Bed Nucleus of the Stria Terminalis (BNST)</b>	-Electrolytic lesions block LH <sup>8</sup> -Inescapable shock sensitizes BNST neuronal activity <sup>9</sup> -PACAP infusion produces LH-like behaviors 24-hr later <sup>[unpublished]</sup>	-Muscimol blocks the expression but not acquisition of conditioned defeat <sup>10</sup> -CRHR2 antagonism blocks the expression of conditioned defeat <sup>11</sup>	<sup>8</sup> Hammack et al., 2004 <sup>9</sup> Greenwood et al., 2005 <sup>10</sup> Markham et al., 2009 <sup>11</sup> Cooper & Huhman, 2005
<b>Dorsal Raphe Nucleus (DRN)</b>	-↑ 5-HT release within the DRN and its projection regions following IS <sup>1,12</sup> -Increased 5-HT activity in the middle-caudal DRN regions after IS <sup>13</sup> -5-HT <sub>1A</sub> activation blocks development and expression of LH <sup>14</sup> -Caudal DRN 5-HT activation produces LH-like behaviors 24-hr later <sup>15</sup> -Caudal DRN CRH-R2 blockade blocks development <sup>16</sup> -Caudal DRN CRH-2R activation produces LH-like behaviors 24 hrs later <sup>16</sup>	-5-HT <sub>1A</sub> receptor activation blocks acquisition and expression of conditioned defeat <sup>17</sup> -Decreased 5-HT <sub>1A</sub> receptor mRNA following defeat <sup>18</sup> -Increased activity in rostral ventral DRN following social defeat <sup>18</sup> -Blockade of CRHR1 & R2 reduces acquisition and expression of conditioned defeat <sup>19</sup>	<sup>12</sup> Amat et al., 1998b <sup>13</sup> Grahn et al., 1999 <sup>14</sup> Maier et al., 1995 <sup>15</sup> Hammack et al., 2002 <sup>16</sup> Hammack et al., 2003 <sup>17</sup> Cooper et al., 2008 <sup>18</sup> Cooper et al., 2009 <sup>19</sup> Cooper & Huhman, 2007
<b>Other Areas</b>	Inactivation of ventral medial prefrontal cortex (mPFC) in escapable rats ↑ LH behavior <sup>20</sup>	Inactivation of ventral hippocampus reduces acquisition of conditioned defeat <sup>21</sup>	<sup>20</sup> Christianson et al., 2009 <sup>21</sup> Markham et al. 2010