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Neurobiological Mechanisms Supporting Experience-Dependent Resistance to Social Stress

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Abstract

Humans and other animals show a remarkable capacity for resilience following traumatic, stressful events. Resilience is thought to be an active process related to coping with stress, although the cellular and molecular mechanisms that support active coping and stress resistance remain poorly understood. In this review, we focus on the neurobiological mechanisms by which environmental and social experiences promote stress resistance. In male Syrian hamsters, exposure to a brief social defeat stressor leads to increased avoidance of novel opponents, which we call conditioned defeat. Also, hamsters that have achieved dominant social status show reduced conditioned defeat as well as cellular and molecular changes in the neural circuits controlling the conditioned defeat response. We propose that experience-dependent neural plasticity occurs in the prelimbic (PL) cortex, infralimbic (IL) cortex, and ventral medial amygdala (vMeA) during the maintenance of dominance relationships, and that adaptions in these neural circuits support stress resistance in dominant individuals. Overall, behavioral treatments that promote success in competitive interactions may represent valuable interventions for instilling resilience.

Keywords

Amygdala; Dominance Relationships; Infralimbic Cortex; Medial Prefrontal Cortex; Resilience; Social Defeat

INTRODUCTION

Stressors often generate adaptive behavioral and physiological responses that restore internal homeostasis. However, when stressors are perceived as uncontrollable, prolonged, or especially severe, they can lead to several negative health consequences, including major

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depression, panic disorder, and post-traumatic stress disorder (PTSD) (Abelson et al., 2007, Meewisse et al., 2007, Heim et al., 2008). Only a portion of individuals exposed to stressful life events develop stress-related psychopathology, suggesting that a great deal of individual variation exists in vulnerability to the negative consequences of stress. More than two-thirds of people in the general population experience a traumatic event at some point in their lifetime, but only 10–20% develop PTSD (Galea et al., 2005, Thomas et al., 2010). Similarly, only 20–25% of individuals exposed to major stressful events develop major depression (Cohen et al., 2007). Understanding the neural circuits and cellular mechanisms that control stress vulnerability is an important step towards identifying novel targets for the prevention and treatment of stress-related psychopathology.

Resilience refers to an individual's capacity to cope with stress and adversity so that they avoid the negative psychological and biological consequences that would otherwise impair physical and psychological well-being (Luthar et al., 2006). Resilience may be demonstrated by resistance to the negative effects of stress or by recovery to a normal state of functioning more quickly than expected following traumatic stress. It is important to distinguish between resistance to and recovery from stressful events, as these processes might involve separate brain regions, neurochemicals, and identifying biomarkers (Yehuda et al., 2006). In animal models, the distinction is not always clear, and resilience usually refers to a decrease in stress-induced changes in future behavior. This body of work indicates that resilience is not simply a passive response involving a failure to display the neuroendocrine, cellular, and molecular changes characteristic of susceptible individuals, but is also an active response that involves distinct neural circuits and cellular mechanisms (Russo et al., 2012).

In this review, we focus on neurobiological mechanisms controlling active processes that characterize resilient individuals. Several animal models of stress resilience focus on mechanisms underlying individual differences that are likely related to genetic and epigenetic factors. We briefly review literature on individual differences in stress vulnerability, although several excellent reviews have recently addressed this topic (Coppens et al., 2010, Russo et al., 2012, Wu et al., 2013). Here, we instead emphasize animal models that investigate mechanisms controlling experience-dependent forms of stress resistance with a focus on resistance to social defeat in Syrian hamsters. In cases of experience-dependent stress resilience, individuals exposed to specific environmental or social stimuli show a reduction in the effects of stress. We maintain that understanding the neurobiological mechanisms controlling the development of resilience should provide the foundation for future evidence-based interventions targeting those at risk for stress-related psychopathology.

INDIVIDUAL DIFFERENCES IN RESILIENCE

It is well recognized that only a subset of people develop mental health problems following exposure to traumatic and/or stressful events. Likewise, animals exhibit considerable variability in behavioral and physiological responses to stress, and the mechanisms underlying these individual differences have been explicitly studied to better understand the biological basis of resilience.

Coping Styles

Individual differences in stress responses that are consistent over time and across contexts are referred to as coping styles (Koolhaas et al., 1999). Individual variation in aggressive behavior is associated with how rodents responded to a variety of challenging situations, with individuals employing either proactive or reactive coping styles. Proactive rats exhibit high levels of offensive aggression in a resident-intruder paradigm, active burying of a shock-probe in a defensive burying test, and high amounts of swimming during a forced swim test. In contrast, reactive rats exhibit low levels of offensive aggression, avoidance of a shock-probe, and high levels of floating (Koolhaas et al., 2007). Several neuroendocrine and neurochemical markers differentiate proactive and reactive individuals. Proactive rats display greater sympathetic nervous system reactivity but no difference in stress-induced plasma glucocorticoids compared to rats with a reactive coping style (Koolhaas et al., 2010). Also, proactive rats show increased sensitivity of 5-HT1a and 5-HT1b autoreceptors compared to reactive rats, indicating that they have enhanced tonic inhibitory control of the serotonin (5-HT) system (de Boer and Koolhaas, 2005).

Proactive and reactive coping styles have also been investigated in feral house mice bred for a bimodal distribution of attack latencies in a resident-intruder test. Mice bred for a long attack latency (LAL) are more vulnerable to the effects of chronic social defeat compared to mice bred for a short attack latency (SAL). Specifically, LAL mice showed a longer lasting body weight loss, a greater increase in corticosterone, and increased anxiety- and depression-like behavior following chronic social defeat compared to SAL mice (Veenema et al., 2003). The LAL mice also exhibited a lower hippocampal mineralocorticoid to glucocorticoid receptor ratio, which is characteristic of the hypothalamic-pituitary-adrenal (HPA) axis dysregulation often found in human depression (Veenema et al., 2003). The coping styles of LAL and SAL mice are also associated with differences in 5-HT signaling. In response to forced swim stress, SAL mice show decreased 5-HT concentrations in the frontal cortex, striatum, lateral septum, hippocampus, amygdala, and brain stem compared to LAL mice (Veenema et al., 2005). Consistent with proactive rats, SAL mice are characterized by enhanced somatodendritic 5-HT1a autoreceptor activity (de Boer et al., 2009). In another animal model of coping styles, Wistar rats have also been bred for high (HAB) or low (LAB) anxiety-related behavior. LAB rats are characterized by increased inter-male aggression, reduced HPA axis activity to nonsocial stressors, and changes in 5-HT neurotransmission (Veenema and Neumann, 2007). Thus, high aggression phenotypes are often associated with changes in the regulation of stress hormones and the 5-HT system that support a proactive coping style.

A proactive coping style, however, is not always beneficial. Coping styles may differ in behavioral flexibility insofar as animals with a reactive coping style appear more guided by environmental stimuli while animals with a proactive coping style seem more likely to develop routines. For example, in pigs proactive individuals have far more difficulty switching responses in a T-maze reversal learning test compared to reactive individuals (Bolhuis et al., 2004). Similarly, high-aggression hamsters show increased impulsivity compared to low-aggression hamsters as the former repeatedly bar press for immediate, small rewards, whereas the latter will delay responding for large rewards (Cervantes and

Delville, 2009). Overall, the neurochemical and neuroendocrine changes that support a proactive coping style may promote stress resilience and appear adaptive in some context but lead to behavioral inflexibility and impulsivity in others. Interestingly, in some cases a flexible coping strategy may be advantageous compared to a consistent active or passive coping strategy. Rats can be categorized as active or passive copers based on whether they exhibit many or few escape attempts during a series of supine restraint tests, respectively. Further, rats that are categorized as active in one trial and passive in another trail are categorized as flexibility copers. When active, passive, and flexible copers are tested in an effort-based reward model in which rats are trained for four weeks to adjust foraging strategies to maximize rewards, flexible copers exhibit improved performance on a spatial learning task and changes in floating duration on a forced swim test compared to active and passive copers (Bardi et al., 2012, Lambert et al., 2014). Also, rats with a flexible coping style exhibit an increased dehydroepiandrosterone (DHEA) / corticosterone ratio, elevated neuropeptide Y immunoreactivity in the CA1 layer of the hippocampus, and a greater number of immature neurons in the dentate gyrus following effort-based reward training compared to active and passive copers (Bardi et al., 2012, Lambert et al., 2014). In sum, a proactive coping style may produce context-dependent advantages, although individuals with a flexible coping style may show more adaptive responses to contingency training.

Chronic Social Defeat

Chronic social defeat in mice is another model system for investigating individual differences in coping with stress. In this model, C57 mice are exposed to social defeat for 5–10 min on 10 consecutive days and are rotated to a new opponent's cage daily where they maintain sensory contact via a perforated divider (Golden et al., 2011). This protocol leads to an array of long-lasting stress-induced changes in behavior, although about one-third of mice fail to show the full range of behavioral changes and are categorized as resilient (Berton et al., 2006). Mice that are susceptible to the effects of chronic social defeat exhibit increased social avoidance, decreased sucrose preference, increased cocaine-conditioned place preference, decreased circadian amplitude of body temperature, social hyperthermia, and weight loss, whereas resilient mice do not (Krishnan et al., 2007). It is important to note that resilient mice are not devoid of stress-related symptoms as both resilient and susceptible mice exhibit anxiety-like behavior on an elevated plus maze, stress-induced polydipsia, and stress-induced elevation of corticosterone (Krishnan et al., 2007). The neural circuitry regulating responses to chronic social defeat has been well-characterized, including cellular and molecular adaptations in the mesolimbic dopamine system. Following chronic social defeat, susceptible mice show increased brain-derived neurotrophic factor (BDNF) expression in the nucleus accumbens (NAc) compared to resilient mice, and local knockdown of BDNF in dopaminergic neurons from the ventral tegmental area blocks defeat-induced social avoidance (Berton et al., 2006). Susceptible mice also show increased firing rates of dopamine cells in the ventral tegmental area, whereas resilient mice exhibit an up-regulation of K+ channels which normalizes firing within the mesolimbic dopamine system (Krishnan et al., 2007). Similarly, resilience in mice is associated with increased expression of a glutamate AMPA receptor subunit that reduces calcium influx and overall conductance of AMPA channels within medium spiny neurons in the NAc (Vialou et al., 2010). Finally, optogenetic stimulation of ventral tegmental neurons projecting to the NAc

induces a susceptible phenotype in mice previously resistant to the effects of chronic social defeat, and optogenetic inhibition of this pathway induces resilience (Chaudhury et al., 2013).

Other brain regions, such as the ventral medial prefrontal cortex (vmPFC), regulate certain aspects of susceptibility to the effects of chronic social defeat. Optogenetic stimulation of the vmPFC reduces depression-like behavior, but not anxiety-like behavior, in susceptible mice (Covington et al., 2010). vmPFC activity likely regulates resistance to the depressive effects of chronic social defeat by providing top-down inhibition to several limbic and brain stem targets. Optogenetic stimulation of vmPFC terminals within the dorsal raphe nucleus (DRN) has been shown to decrease defeat-induced social avoidance (Challis et al., 2014). In addition, following chronic social defeat, resilient mice show increased firing rates in the vmPFC and suppression of amygdala oscillatory activity at social interaction testing (Kumar et al., 2014). Likewise, vmPFC projections to the NAc regulate stress-induced depressive-like behavior as well as motivation for drugs of abuse (Britt et al., 2012, Vialou et al., 2014). Recently, cholecystokinin (CCK) activity in the vmPFC was shown to mimic the increased anxiety-like and depression-like behavior characteristic of chronic social defeat. Optogenetic stimulation of vmPFC projections to the basolateral amygdala (BLA) blocked the anxiogenic effect on the elevated-plus maze of CCK administration into the vmPFC, whereas stimulation of vmPFC-NAc projections blocked CCK-induced social avoidance and sucrose preference deficits, but not anxiety-like behavior (Vialou et al., 2014). These findings indicate that separate axonal projections from the vmPFC regulate the various behavioral consequences of chronic social defeat. Also, because vmPFC-NAc projections appear to control stress-induced social avoidance in mice, this behavior may reflect a decreased motivation for social behavior rather than increased social anxiety.

Whether resilient mice have a proactive coping style as described above is unknown, but it seems likely that a resilient phenotype represents a tradeoff in which adaptive responses occur in some domains but not others. In a mouse model of acute social defeat, resilient mice show behavioral deficits not observed in susceptible mice. In this model, mice are exposed to four brief social defeat episodes on two consecutive days and resilient mice, which are characterized by reduced social avoidance, exhibit enhanced conditioned fear and severe deficits in fear extinction (Meduri et al., 2013). Overall, individual differences in behavioral and physiological responses to stress indicate that resilience is a stable trait controlled by specific neurobiological mechanisms that are dependent on interactions with the environment.

EXPERIENCE-DEPENDENT RESILIENCE

While a great deal of research indicates that adverse experiences increase vulnerability to the effects of future stress, past experience can also promote resilience. Here, we discuss several environmental factors that have been shown to generate resistance to the deleterious effects of subsequent stressors, including stressor controllability (Maier and Watkins, 2010), environmental enrichment (van Praag et al., 2000), brief maternal separation (Lyons et al., 2010), voluntary exercise (Greenwood and Fleshner, 2011) and social dominance (Morrison et al., 2012). Several of these models have identified the vmPFC as a key neural substrate

underlying stress resilience, and there is a large literature indicating that the vmPFC modulates behavioral and physiological responses to stressors. In many mammalian species, including humans, the vmPFC sends axonal projections to several limbic and brain stem structures (Ongur and Price, 2000, Vertes, 2006). These projections provide top-down control over stress-related cognitive and emotional behavior as well as the neuroendocrine stress response. For example, the vmPFC regulates the acquisition and extinction of conditioned fear via projections to both the BLA and the intercalated cells within the amygdala (Herry et al., 2010, Amir et al., 2011, Cho et al., 2013). Also, the vmPFC projects to anterior portions of the bed nucleus of the stria terminalis (BNST) where activation of GABAergic cells projecting to the paraventricular nucleus of the hypothalamus inhibit the neuroendocrine stress response (Radley and Sawchenko, 2011). It is important to note, however, that the mechanisms by which the vmPFC regulates stress resilience likely dependent on the type of stressor, the behavioral and physiological responses, and type of environmental factors that induce resilience.

Essential Role for the vmPFC

Learned helplessness is a model in which exposure to an uncontrollable stressor leads to exaggerated fear, deficits in escape behavior, and reduced social exploration. However, exposure to escapable tailshock immunizes rats from the development of learned helplessness when they are later exposed to inescapable tailshock (Maier and Watkins, 2010). Pharmacological inactivation of the vmPFC during escapable tailshock blocks its immunizing effect on learned helplessness (Amat et al., 2006), whereas pharmacological activation of the vmPFC during inescapable tailshock promotes an immunizing effect on learned helplessness (Amat et al., 2008). Resistance to learned helplessness strongly depends on the activity of neurons within the prelimbic (PL) cortex that send axonal projections to the DRN. The PL cortex is a subregion of the vmPFC and prior experience with escapable tailshock has been shown to increase stress-induced c-Fos immunoreactivity in DRN-projecting PL neurons (Baratta et al., 2009). These findings are consistent with the framework that PL neurons projecting to the DRN activate GABAergic interneurons and thereby inhibit DRN serotonergic activity (Celada et al., 2001, Varga et al., 2001, Vertes, 2004). Also, prior experience with escapable, but not inescapable, stress increases intrinsic membrane excitability in PL neurons, suggesting that synaptic plasticity within the PL cortex is critical for the immunizing effect of escapable stress exposure (Varela et al., 2012). Similarly, blockade of NMDA receptors and the extracellular signal-regulated kinase (ERK) cascade within the PL prevents the immunizing effect of stressor controllability, suggesting that synaptic plasticity within the PL is necessary for rats to learn this form of stress resistance (Christianson et al., 2014).

Environmental enrichment is another experience known to mitigate the deleterious effects of stress in humans and other animals (Rosenzweig and Bennett, 1996, Salmon, 2001, Francis et al., 2002). Environmental enrichment has been shown to increase neurotrophin expression, dendritic branching, and neurogenesis in the hippocampus (van Praag et al., 2000, Faherty et al., 2003, Lambert et al., 2005). Importantly, three weeks of environmental enrichment reduces social avoidance in mice following chronic social defeat and neural plasticity in the hippocampus is critical for this effect. When transgenic mice with

conditionally suppressed neurogenesis in the dentate gyrus are housed in an enriched environment, they fail to show stress resistance following chronic social defeat and instead exhibit defeat-induced changes in social avoidance, depression-like, and anxiety-like behavior characteristic of mice housed in an impoverished environment (Schloesser et al., 2010). The infralimbic (IL) cortex, which is subregion of the vmPFC, is another neural substrate controlling the ability of environmental enrichment to confer stress resistance (Lehmann and Herkenham, 2011). Although enriched housing leads to increased ΔFosB immunoreactivity in both the PL and IL cortices following chronic social defeat, lesions of the IL, but not the PL, prevent environmental enrichment-induced stress resistance in defeat mice.

Mildly stressful experiences are also able to promote the development of resilience. Experiences that are challenging but not overwhelming in childhood can promote coping skills and reduce stress reactivity in adulthood (Khoshaba and Maddi, 1999, Gunnar et al., 2009). In rodent models, 15 min of maternal separation increases the licking and other affiliative behavior displayed by mothers after reunion with pups. Postnatal handling, which is designed to mimic maternal behavior, has been shown to decrease behavioral and endocrine responses to stress in adulthood (Levine, 1962, Bhatnagar and Meaney, 1995). Rat pups exposed to postnatal handling show increased glucocorticoid receptor expression in the hippocampus and frontal cortex, which enhances sensitivity to glucocorticoid negative feedback (Meaney et al., 1989). Furthermore, handled rat pups show decreased CRF mRNA expression in the paraventricular nucleus of the hypothalamus and central amygdala and also decreased CRF receptor density in the locus coeruleus (Francis et al., 1999). Non-human primate models further support the notion that mild early life stress promotes the development of resilience. Squirrel monkeys exposed to intermittent maternal separation early in life show fewer behavioral indications of anxiety, increased novel object exploration, and diminished stress-induced levels of cortisol and adrenocorticotropic hormone (Parker et al., 2004, Parker et al., 2007). Separated monkeys also exhibit increased grey and white matter in the vmPFC compared to non-separated controls indicating that the process of coping with mild early life stress increases myelination and volume of the vmPFC (Katz et al., 2009). Overall, mild early life stressors and their associated behavioral responses can induce neural plasticity in the limbic system and HPA axis which may inoculate individuals against stressors encountered later in life.

Rats allowed to run voluntarily on home cage running wheels for six weeks fail to develop learned helplessness following inescapable stress (Dishman et al., 1997, Greenwood et al., 2003). A great deal of research has delineated the cellular and molecular mechanisms by which voluntary wheel running promotes resistance to inescapable stress. For instance, voluntary wheel running increases ΔFosB immunoreactivity in the NAc (Greenwood et al., 2011), increases BDNF mRNA expression in the hippocampus and amygdala (Greenwood et al., 2009), increases 5-HT1a autoreceptor mRNA expression in the dorsal raphe nucleus (Greenwood et al., 2005), and decreases 5-HT2c receptor mRNA expression in the amygdala and posterior dorsal medial striatum (Greenwood et al., 2012). Interestingly, lesions of the vmPFC do not eliminate the protective effects of wheel running on the development of learned helplessness (Greenwood et al., 2013). These findings indicate that while voluntary exercise promotes resistance to learned helplessness, this effect is

independent of top-down inhibition from the vmPFC. Rather the protective effects of exercise appear dependent on neural plasticity within the 5-HT system and the desensitization of 5-HT2c receptors appears critical for exercise-induced resilience. Injection of higher doses of a 5-HT2c receptor agonist into either the BLA or dorsal striatum are required to enhance fear and interfere with escape behavior of physically active rats compared to sedentary rats (Greenwood et al., 2012).

In sum, several environmental factors can generate structural and functional plasticity in the vmPFC that supports resistance to the behavioral and physiological effects of stress. However, not all forms of experience-dependent stress resilience require the vmPFC (for a review see Christianson and Greenwood, 2014). In addition to exercise, safety signals mitigate the consequences of uncontrollable stress although they do not require neurotransmission in the vmPFC. Pharmacological inactivation of the vmPFC during uncontrollable tail-shocks accompanied by safety signals fails alter the protective effect of safety signals on subsequent social exploration, whereas bilateral lesions of the posterior insular cortex prevent the protective effect of safety signals (Christianson et al., 2008). Altogether, these findings indicate that the use of multiple animal models with a range of environmental factors will be required to delineate the biological bases of experience-dependent stress resilience.

Aggression and Social Defeat in Syrian Hamsters

Syrian (sometimes called golden) hamsters are sexually monomorphic, solitary, burrow-living rodents native to southern Turkey and northern Syria (Gattermann et al., 2008). Both male and female hamsters are highly aggressive in resident-intruder models in a laboratory setting (Payne, 1973, Floody and Pfaff, 1977). Hamster aggressive behavior is easily quantified and highly ritualized such that animals are rarely wounded in brief aggressive encounters. Hamsters also have excellent individual recognition and form stable dominance relationships in dyadic encounters (Ferris et al., 1987, Bath and Johnston, 2007). For these reasons Syrian hamsters have been an ideal model species for the study of aggression and social conflict (Albers et al., 2002, Huhman, 2006).

Kim Huhman and colleagues first noticed that acute social defeat in Syrian hamsters leads to long-term changes in agonistic behavior. They found that male hamsters exposed to a single social defeat in the home cage of a larger opponent abandon their species-typical territorial aggression and instead produce submissive and defensive behavior even when tested in their own home cage with a non-aggressive intruder. They called this defeat-induced change in agonistic behavior conditioned defeat and hypothesized that it was an ethologically relevant form of conditioned fear (Potegal et al., 1993, Huhman et al., 2003). This hypothesis appears largely correct, and several lines of evidence now indicate that similar cellular and molecular mechanisms in the BLA regulate the acquisition of conditioned defeat and conditioned fear. Viral vector-mediated up-regulation of cAMP response element binding (CREB) protein in the BLA prior to social defeat enhances the acquisition of conditioned defeat (Jasnow et al., 2005). Also, the acquisition of conditioned defeat is disrupted by the pharmacological blockade of either NR2b subunits of NMDA receptors (Day et al., 2011), protein synthesis (Markham and Huhman, 2008), or Trk receptors (Taylor et al., 2011). A

similar set of cellular and molecular mechanisms in the BLA regulate the acquisition of conditioned fear in rats and mice (Schafe and LeDoux, 2000, Josselyn et al., 2001, Rodrigues et al., 2001, Rattiner et al., 2004). However, important differences exist between conditioned defeat and conditioned fear. Social defeat is a multisensory stimulus that is not paired with a conditioned stimulus in a straightforward manner, and the conditioned defeat response appears to combine both fear and anxiety-like behavior (Bader et al., 2014, Clinard et al., 2015). Overall, the complexity of social defeat models, such as conditioned defeat, leads to a great deal of individual variation in behavioral and physiological responses and generates the diversity needed for studies of vulnerability.

The expression of submissive and defensive behavior during conditioned defeat testing requires neural activity in the central nucleus of the amygdala (CeA) and BNST. Injection of the GABAa agonist muscimol into the CeA (Jasnow and Huhman, 2001) or BNST (Markham et al., 2009) reduces the expression of conditioned defeat. Corticotropin-releasing factor (CRF) is a key neurochemical in the CeA-BNST neural circuit promoting the expression of conditioned defeat. Blockade of CRF receptors in the BNST reduces the expression of conditioned defeat (Jasnow et al., 2004). Importantly, unilateral lesions of the CeA and blockade of CRF receptors in the contralateral BNST also reduce the expression of conditioned defeat. The effects of CRF on the expression of conditioned defeat appear to be mediated by CRF type-2 receptors. Systemic blockade of CRF type-1 receptors does not reduce the expression of conditioned defeat (Jasnow et al., 1999), whereas selective blockade of CRF type-2 receptors in the BNST does (Cooper and Huhman, 2005). These results are consistent with data from other models showing that CRF signaling in a CeA-BNST neural circuit regulates stress-induced fear and anxiety (Lee and Davis, 1997, Hammack et al., 2010, Gafford et al., 2012).

The conditioned defeat model has important similarities to, but also some differences with, learned helplessness (Hammack et al., 2011). Similar to learned helplessness, hamsters appear to ‘give up’ unnecessarily following exposure to acute social defeat. However, the conditioned defeat response is not dependent on the controllability of the defeat stressor as animals exposed to escapable or inescapable defeat exhibit similar levels of social avoidance (McCann et al., 2014). Thus, it appears that the psychological aspects of losing generate a physiological stress response and dramatically alter subsequent agonistic behavior (Huhman et al., 1992). A great deal of research indicates that uncontrollable tailshock increases 5-HT activity in the DRN, desensitizes DRN 5-HT1a autoreceptors, and thereby promotes learned helplessness (Maier and Watkins, 2005, Rozeske et al., 2011). Because 5-HT1a autoreceptors provide negative feedback on 5-HT neurons within the DRN, their down-regulation would be expected to elevate 5-HT output and stress-related behavior. We, and others, have shown that acute social defeat increases c-Fos expression in select DRN subregions in both hamsters and rats (Gardner et al., 2005, Cooper et al., 2009, Paul et al., 2011). We have also found that social defeat in hamsters reduces mRNA expression for 5-HT1a autoreceptors in the DRN (Cooper et al., 2009). Furthermore, pharmacological activation of DRN 5-HT1a autoreceptors would be expected to decrease 5-HT output and stress-related behavior, and we found that activation of DRN 5-HT1a receptors either prior to social defeat or prior to conditioned defeat testing reduces the acquisition and expression of conditioned defeat, respectively (Cooper et al., 2008). The role of CRF in the DRN is

another point of contrast between conditioned defeat and learned helplessness. The activation of DRN CRF type-2 receptors promotes the acquisition of learned helplessness (Hammack et al., 2003), whereas the activation of DRN CRF type-1 receptors appears to promote the acquisition of conditioned defeat (Cooper and Huhman, 2007). In sum, both acute social defeat and uncontrollable tail shock appear to sensitize the DRN so that a larger serotonin response is generated when animals are challenged at testing. While much progress has been made understanding the neural circuitry underlying the acquisition and expression of conditioned defeat, our laboratory has begun using this model to examine mechanisms controlling vulnerability and resistance.

Resistance to Conditioned Defeat

We have documented considerable individual variation in the amount of submissive and defensive behavior male hamsters display following acute social defeat. After ruling out several husbandry-related variables, we hypothesized that success in aggressive encounters when hamsters are group-housed as they grow might lead to experience-dependent neural plasticity that reduces conditioned defeat in young adults. This possibility is consistent with research showing that winners and losers display different physiological responses to aggressive encounters. In hamsters, we have shown that dominant individuals have increased vasopressin 1a receptors in the lateral ventromedial hypothalamus (Cooper et al., 2005) and increased 5-HT1a receptor mRNA expression in the DRN compared to subordinates (Cooper et al., 2009). Also, subordinate hamsters show elevated plasma cortisol and reduced plasma testosterone following repeated agonistic encounters, whereas dominant hamsters show a transient increase in testosterone that habituates with repeated encounters (Huhman et al., 1991). Similarly, in a visible burrow system, dominant rats display initial increases in testosterone and corticosterone which diminish over several days, whereas subordinates show a gradual decrease in testosterone and increase in cortisol over several days (Hardy et al., 2002). Finally, dominant Anolis lizards exhibit elevated 5-HT concentrations in the amygdala, whereas subordinates show elevated dopamine concentrations in the amygdala (Ling et al., 2009).

The beneficial effects of winning may first occur during adolescence when animals freely switch offensive and defensive roles during social play. In Syrian hamsters, the neural circuitry controlling social play during adolescence matures into the neural circuitry controlling adult aggression (Delville et al., 2003, Cheng et al., 2008). Also, social play is critical for the structural maturation of the prefrontal cortex and necessary for the development of competent social behavior in adulthood. Restricting social play in juvenile rats disrupts species-typical social behavior in adulthood (Hol et al., 1999, van den Berg et al., 1999). Also, restricting social play alters dendritic morphology in brain regions that regulate coping with stress such as the mPFC (Bell et al., 2010). Overall, social play may alter vulnerability to the effects of social stress in adulthood by organizing specific neural circuits that mediate stress-related behavior and coping.

To address whether dominant hamsters show less conditioned defeat than subordinates, we developed a model in which male hamsters are briefly paired with the same individual each day for two weeks so that they develop a stable dominance relationship. After this training,

all animals are exposed to acute social defeat and subsequent conditioned defeat testing. In our initial study, we found that dominants exhibit less submissive and defensive behavior during conditioned defeat testing than do subordinates and controls that lack dominant or subordinate status (Morrison et al., 2011). In subsequent studies, we found that dominants show less conditioned defeat than do subordinates but that controls show an intermediate amount of submissive and defensive behavior and do not differ significantly from either dominants or subordinates (Morrison et al., 2012). Together, these findings suggest that dominants show resistance to conditioned defeat and subordinates show susceptibility. Another feature in this model is that dominant individuals often counter-attack resident aggressors during social defeat exposure while subordinates and controls very rarely counter-attack. While dominant animals may initially attack resident aggressors during social defeat episodes, they invariably lose the fight and then exhibit similar rates of submissive and defensive behavior compared to subordinates. The initial period of fighting back against resident aggressors suggests an active coping style in dominant individuals. In rats, some individuals cope with social defeat stress by actively defending themselves and counter-attacking aggressors, while others exhibit a passive strategy characterized by immobility and low aggression (Koolhaas et al., 2007). Rats that exhibit active coping behavior during social defeat show reduced plasma corticosterone and less c-Fos immunoreactivity in several brain regions compared to rats with passive coping behavior (Walker et al., 2009). These findings suggest that actively coping with a social challenge might reduce neuroendocrine and neurochemical responses to stress and prevent the development of stress-induced fear and anxiety. Consistent with this idea, elevated offensive aggression has been associated with increased struggling during a forced swim test (Veenema et al., 2004), increased shock probe burying (Koolhaas et al., 2010), and increased active avoidance in a shuttle box (Benus et al., 1989). Although coping styles are thought to be stable traits, aggressive experience has been shown to change them. For example, rats that initially respond to acute social defeat with a proactive coping style will shift towards a passive coping style following repeated social defeat (Paul et al., 2011). Whether experience in a dominance relationship produces stable coping styles across behavioral domains has yet to be determined.

The extent of the behavioral changes observed in conditioned defeat does not appear linked to changes in HPA axis activity. We collected blood plasma at several time points after social defeat and found that defeated animals show elevated cortisol levels compared to non-defeated animals. Surprisingly, however, plasma cortisol levels were not significantly different among groups with previous dominant exposure, previous subordinate exposure, or controls (Figure 1). These findings are consistent with other research showing that blocking glucocorticoid synthesis during social defeat does not alter the acquisition of conditioned defeat (Cooper and Huhman, 2010). Although glucocorticoid feedback appears to have a limited role in conditioned defeat, the activation of CRF type-1 and type-2 receptors can alter the acquisition and expression of conditioned defeat as noted earlier. However, changes in the expression of CRF type-1 and type-2 receptors following aggressive interactions do not appear to account for vulnerability or resistance to conditioned defeat. McCann et al. (2013) recently found that dominant, subordinate, and control hamsters do not differ in CRF type-1 and type-2 receptor density in the amygdala, lateral septum, BNST, hypothalamus, or

DRN. These findings, although somewhat preliminary, suggest that the resilience conferred by previous dominant status is not mediated via adaptions in glucocorticoid release or central CRF receptors.

Resistance to conditioned defeat in dominant hamsters is an active process characterized by increased neural activity in a multi-node circuit that includes brain regions associated with aggression and coping. We examined c-Fos immunoreactivity following social defeat and found that dominants showed increased neural activation in several brain regions including the IL cortex, ventral medial amygdala (vMeA), ventral lateral septum, and lateral ventromedial hypothalamus (Morrison et al., 2012). While not quantified in the initial paper, we subsequently analyzed c-Fos immunoreactivity in DRN tissue and found that subordinates showed increased neural activation in ventral portions of the rostral and caudal DRN (Gerhard et al., 2012; Figure 2). Together, these data indicate that reduced conditioned defeat in dominants is associated with elevated defeat-induced neural activity in several regions of the forebrain, including the IL cortex, whereas increased conditioned defeat in subordinates is associated with elevated defeat-induced neural activity in the DRN. Because the vmPFC is critical for other forms of experience-dependent stress resilience, we tested whether neural activity in the vmPFC was necessary for resistance to conditioned defeat in dominants. We found that pharmacological inactivation of the vmPFC prior to social defeat reinstates the full conditioned defeat response in dominants, although it does not increase conditioned defeat in subordinates or social status controls (Morrison et al., 2013). These findings are consistent with previous research showing that injection of a higher dose of muscimol into the vmPFC enhances the acquisition of conditioned defeat (Markham et al., 2012). In this study, however, injection of the protein synthesis inhibitor anisomycin into the vmPFC did not alter the acquisition of conditioned defeat. Collectively, these findings suggest that increased vmPFC neural activity during social defeat may reduce the acquisition of conditioned defeat in dominant hamsters by reducing defeat-induced neural plasticity in vmPFC projection regions.

One limitation of using dominance relationships as an experimental variable is that subjects cannot be randomly assigned to groups, and animals may have pre-existing differences that influence both the formation of dominance relationships and the display of conditioned defeat. To test whether reduced conditioned defeat in dominants is an experience-dependent form of stress resistance, we investigated the time course of changes in c-Fos immunoreactivity and the conditioned defeat response. Dominant hamsters showed less conditioned defeat than did subordinates after 14 days of dominance experience, but dominants and subordinates did not significantly differ in conditioned defeat after 1 or 7 days of interactions (Morrison et al., 2014). Similarly, we found that dominants showed elevated neural activation in the IL, PL, and vMeA after 14 days of dominance experience compared to subordinates and social status controls but not after 1 or 7 days of interactions. Importantly, the time course for the development of conditioned defeat resistance matched the time course for changes in defeat-induced neural activation in key brain regions that we have shown to be critical for social stress-induced changes in behavior. Altogether, our results suggest that the maintenance of dominant social status leads to experience-dependent neural plasticity that supports elevated neural activity in the vmPFC and vMeA during social defeat and that these changes may confer resistance to conditioned defeat.

Because the BLA is the main neural substrate controlling the acquisition of conditioned defeat, we expect that experience-dependent changes in the vmPFC and vMeA are integrated by the BLA (Figure 3). Elevated c-Fos immunoreactivity in the vmPFC of dominant hamsters is consistent with the prefrontal cortex providing inhibitory control over the amygdala, although elevated c-Fos immunoreactivity in the vMeA of dominants is inconsistent with MeA afferents increasing BLA activity. One possibility is that elevated c-Fos immunoreactivity in the vMeA represents activation of local inhibitory GABAergic circuits, while another possibility is that elevated c-Fos immunoreactivity in the vMeA reflects the engagement of neural circuits that do not project directly to the BLA. Ultimately, future research will be needed to identify cellular and molecular signals in the vmPFC and vMeA that change during the 14 day maintenance of dominance relationships and support the development of resistance to conditioned defeat.

Winning and Testosterone

Because dominant individuals gain resistance to conditioned defeat after repeatedly winning aggressive encounters, it is possible that changes in testosterone signaling modulate the development of conditioned defeat resistance. In humans, the experience of personal success, as well as a feeling of dominance in competitive situations, is associated with increased testosterone concentrations (Booth et al., 1989, Schaal et al., 1996, Suay et al., 1999). In numerous other species, winners of competitive interactions and social challenges also exhibit increased plasma testosterone (Wingfield et al., 1987, Cavigelli and Pereira, 2000, Yang and Wilczynski, 2002, Oyegbile and Marler, 2005). The connection between fluctuating levels of testosterone and aggression has been described in the challenge hypothesis, which states that testosterone levels rise and facilitate aggression during challenges that occur in a reproductive context such as territory formation, dominance disputes, and mate guarding (Wingfield et al., 1990, Wingfield et al., 2000). Winning aggressive encounters also increases the probability of winning future aggressive encounters, which is referred to as the winner effect (Dugatkin and Earley, 2004). The winner effect has been demonstrated in a wide variety of species including mammals (Oyegbile and Marler, 2005), fish (Oliveira et al., 2009), reptiles (Schuett et al., 1996), and insects (Moore et al., 1988). California mice are an excellent model species in which to examine both the challenge hypothesis and winner effect. In male California mice, winning multiple agonistic encounters creates a post-victory surge in plasma testosterone (Oyegbile and Marler, 2005), and castration prevents the winner effect (Trainor and Marler, 2001). These findings suggest a winner-challenge effect in which winning an aggressive encounter leads to a transient increase in testosterone that increases the probability of winning future encounters. Also, the winner-challenge effect appears to be mediated by androgen receptors. Testosterone injection after an agonistic encounter increases aggression in future encounters, and inhibition of the aromatase enzyme does not block the effect of testosterone injections (Trainor et al., 2004). Consistent with this idea, winning in an aggressive encounter increases the expression of androgen, but not progestin, receptors in brain regions associated with agonistic behavior (Fuxjager et al., 2010).

Reduced plasma testosterone and androgen receptor activity has been associated with elevated stress-related behavior in humans and other animals. Reduced plasma testosterone

has been associated with major depression in some studies (McHenry et al., 2014), and testosterone supplementation has been shown to decrease symptoms of depression and promote active coping (Pope et al., 2003). Although plasma testosterone does not differ between soldiers with and without PTSD, soldiers with PTSD and comorbid depression or alcohol dependence have lower testosterone compared to those with PTSD without comorbid conditions (Karlovic et al., 2012). Also, a polymorphism in the gene coding for 5α-reductase (SRD5A2), which reduces the conversion of testosterone to dihydrotestosterone, has been associated with the severity of post-traumatic stress symptoms and risk for PTSD diagnosis in men, but not women (Gillespie et al., 2013). In rodents, castration increases anxiety-like behavior compared to intact rats in the open field (Adler et al., 1999), elevated plus-maze (Bitran et al., 1993), and defensive burying task (Frye and Seliga, 2001). Also, testosterone replacement reduces fear and anxiety-like behavior (Bitran et al., 1993, Bouissou and Vandenheede, 1996, Frye and Seliga, 2001). In the conditioned defeat model, castrated male hamsters treated with testosterone or dihydrotestosterone exhibit more aggression and less submission at testing compared to estradiol treated animals, which suggests that chronic androgen treatment decreases conditioned defeat (Solomon et al., 2009).

Animals that actively cope with stressful events and exhibit less stress-related fear and anxiety may have greater activation of androgen receptors. For example, rats that exhibit an active coping strategy on the defensive burying test show elevated plasma testosterone and a larger number of androgen receptor immune-positive cells in the MeA and BNST (Linfoot et al., 2009). Likewise, male rats carrying a feminizing mutation of the androgen receptor show increased anxiety on the elevated plus maze and open field (Zuloaga et al., 2011, Hamson et al., 2014). Several recent studies also indicate that androgens may promote structural plasticity in brain regions such as the hippocampus and mPFC. Androgens increase the survival of newborn neurons in the hippocampus of adult male rats by acting directly through nuclear androgen receptors (Spritzer and Galea, 2007, Hamson et al., 2013). Also, gonadal hormones act on androgen, as well as estrogen, receptors to increase spine synapse formation in the mPFC (Hajszan et al., 2007, Hajszan et al., 2008). Altogether, these findings suggest that testosterone may act on androgen receptors in select brain regions to generate the structural neural plasticity that supports a reduction in stress-induced changes in behavior. In our model of conditioned defeat resistance, we propose that the maintenance of dominance relationships increases plasmatestosterone, sensitizes androgen receptors in select brain regions, and thereby reduces the conditioned defeat response.

CONCLUSIONS

There is no universal neurobiological mechanism or neural circuit controlling stress resilience. The neurochemical and neuroendocrine signals that promote proactive coping styles support adaptive responses in some environmental context but not others. Several animal models indicate that the vmPFC is a key node within a neural circuit underlying stress resilience, although the activity of the vmPFC is not essential for all types of resilience. Experience-dependent neural plasticity within the vmPFC appears dependent on the environmental factors that promote stress resistance. Also, the role of specific efferent projections from the vmPFC likely depends on the type of stressor, as well as the behavioral

and physiological response. Consequently, a wide variety of research using an array of animal models, theoretical perspectives, and technical approaches is needed to build a comprehensive understanding of the biological bases of resilience.

Our data indicate that hamsters with previous experience winning fights show increased neural activation in the vmPFC and vMeA during social defeat stress. Neural activity in the vmPFC during social defeat is necessary for the resistance to conditioned defeat found in dominant hamsters. Future research will be needed to determine whether neural projections from the vmPFC to the amygdala reduce the acquisition of conditioned defeat and/or whether vmPFC projections to brain regions such as the BNST or DRN reduce the expression of conditioned defeat. In addition, testosterone is also a good candidate to modulate neural plasticity during establishment and maintenance of dominance relationships and changes in testosterone or testosterone-sensitive signaling may promote stress resistance. Currently, there are no available interventions to promote stress resistance. Our research indicates that behavioral treatments that promote winning and/or personal success would be a viable first step toward instilling resilience to the social stress that is pervasive in our society.

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Abbreviations

BDNF	brain-derived neurotrophic factor
BLA	basolateral amygdala
BNST	bed nucleus of the stria terminalis
CeA	central nucleus of the amygdala
CRF	corticotropin-releasing factor
CREB	cAMP response element binding
DHEA	dehydroepiandrosterone
DRN	dorsal raphe nucleus
ERK	extracellular signal-regulated kinase
HPA	hypothalamic-pituitary-adrenal
HAB	high anxiety-related behavior
IL	infralimbic cortex
LAB	low anxiety-related behavior
LAL	long attack latency
MeA	medial amygdala

NAc	nucleus accumbens
NMDA	N-methyl-$_D$-aspartate
PL	prelimbic cortex
PTSD	post-traumatic stress disorder
SAL	short attack latency
vmPFC	ventral medial prefrontal cortex
5-HT	serotonin;

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Highlights

- Stress resilience is an active process that involves distinct neural circuits
- Experience-dependent neural plasticity in key brain regions supports resilience
- Dominant hamsters show resistance to the effects of social defeat
- Neural plasticity in vmPFC circuits supports stress resistance in dominant hamsters

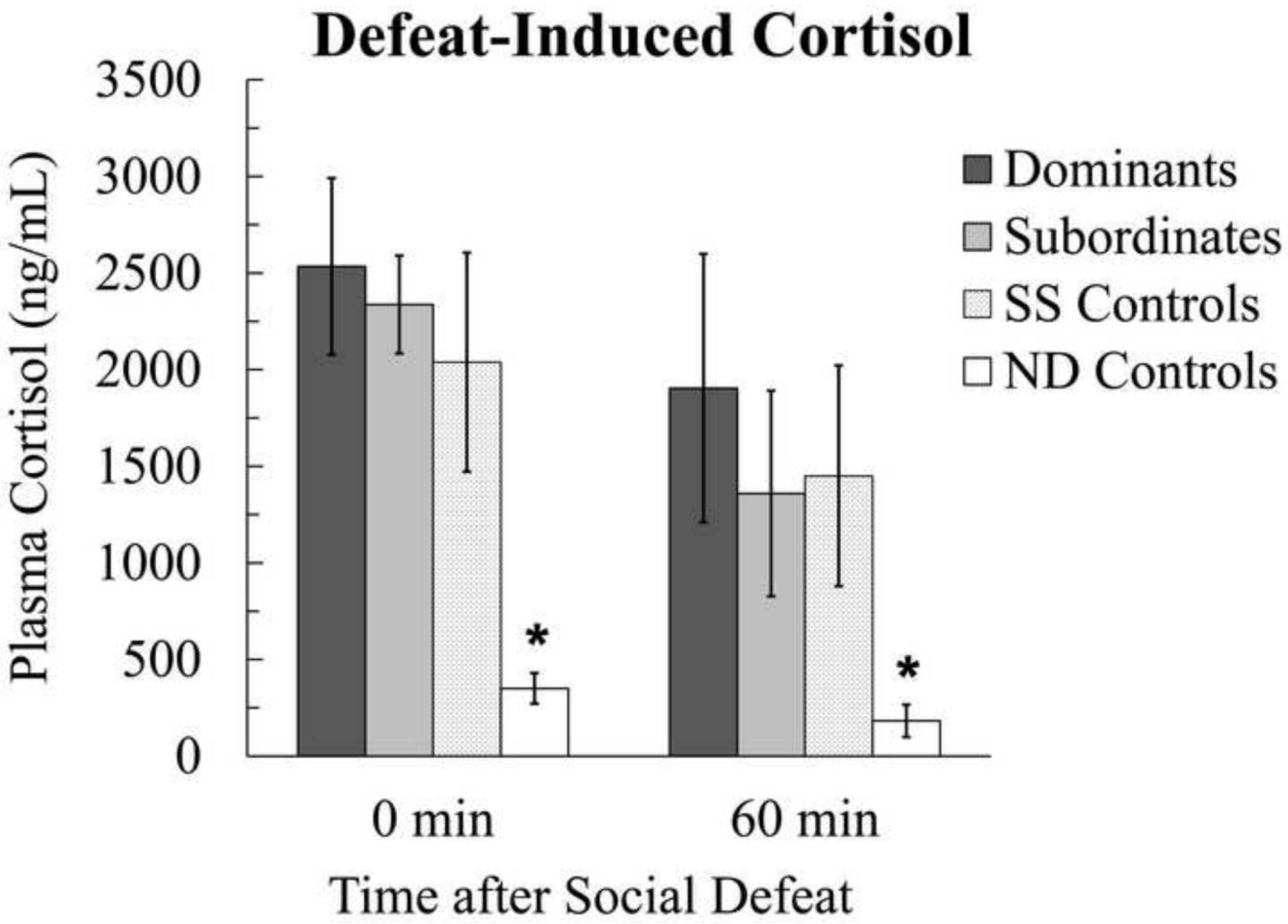

Figure 1.

Plasma cortisol levels are shown for dominant (N = 10), subordinate (N = 10), social status (SS, N = 10), and no-defeat (ND, N = 9) control animals following social defeat. Social defeat, regardless of prior social status, elevated plasma cortisol compared to ND controls ($F_{(3,35)} = 4.95$, $p = .006$). Dominants, subordinates, and SS controls do not significantly differ in cortisol levels at either 0 or 60 min following social defeat. * indicates significantly different compared to all other subjects at the same time point ($p < .05$).

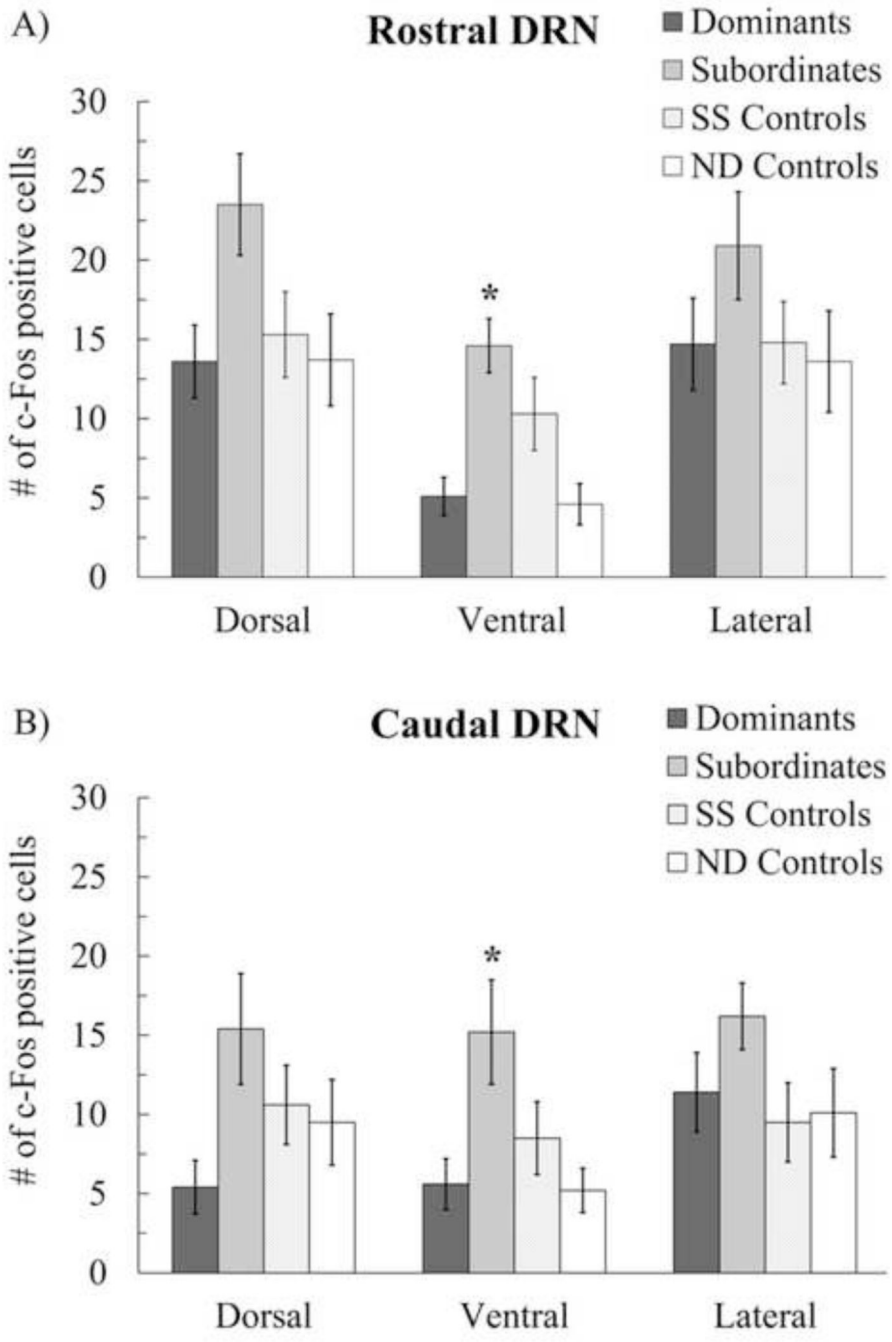

Figure 2.

The number (mean ± SE) of c-Fos immuno-positive cells are shown for dominants (N = 11), subordinates (N = 11), social status (SS, N = 12), and no-defeat (ND, N = 10) control animals in the dorsal raphe nucleus (DRN) 60 min following social defeat. A) In ventral portions of the rostral DRN subordinates show increased c-Fos immunoreactivity compared to dominants and ND controls ($F_{(3,40)} = 7.28$, p = .001). B) In ventral portions of the caudal DRN subordinates show increased c-Fos immunoreactivity compared to dominants and ND controls ($F_{(3,40)} = 4.09$, p = .014). Similar trends were found in dorsal portions of the rostral

and caudal DRN, although the main effects of social status were marginally significant ($p = .06$ and $p = .11$, respectively). * indicates significantly different compared to dominants and ND controls ($p < .05$).

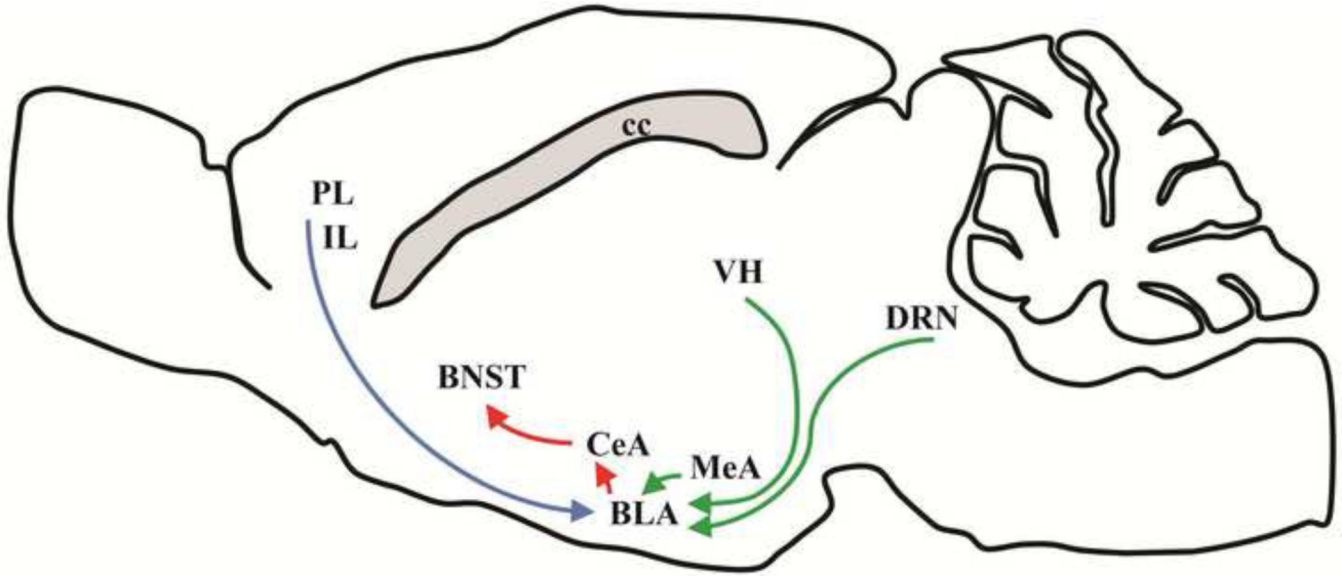

Figure 3.

Brain circuitry implicated in the acquisition and expression of conditioned defeat in Syrian hamsters. We propose that the BLA integrates neural signals from the limbic forebrain and brain stem regarding social defeat stress and signals to downstream structures that regulate behavioral and physiological responses. Also, we propose that experience-dependent changes in neural signals from the PLC, ILC, and MeA regulate resistance to conditioned defeat in dominant hamsters. Green arrows represent neural circuits activated during social defeat that increase the acquisition of conditioned defeat. Blue arrows represent neural circuits activated during social defeat that decrease the acquisition of conditioned defeat. Red arrows represent neural circuits activated during behavioral testing which increase the expression of the conditioned defeat response. BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; cc, corpus callosum; CeA, central amygdala; DRN, dorsal raphe nucleus; IL, infralimbic cortex; MeA, medial amygdala; PL, prelimbic cortex; VH, ventral hippocampus.