Social Defeat as an Animal Model for Depression

Fiona Hollis and Mohamed Kabbaj

Abstract

Depression is one of the most disabling medical conditions in the world today, yet its etiologies remain unclear and current treatments are not wholly effective. Animal models are a powerful tool to investigate possible causes and treatments for human diseases. We describe an animal model of social defeat as a possible model for human depression. We discuss the paradigm, behavioral correlates to depression, and potential underlying neurobiological mechanisms with an eye toward possible future therapies.

Key Words: animal models; depression; social defeat; stress

Introduction

Neuropsychiatric diseases, such as anxiety, schizophrenia, autism, and depression are characterized as some of the most disabling medical conditions in the world today. In a recent study of global disease, depression alone was ranked as the second leading contributor to global disease burden (Ferrari et al. 2013b). This statistic highlights a growing prevalence in depression because previous studies ranked depression as the fourth contributor to disease burden (Moussavi et al. 2007). Depression is a serious illness that can occur as early as 3 years of age (Ferrari et al. 2013a) and have devastating consequences for the affected individuals, their family, and friends. Indeed, in the United States alone, nearly 10% of the population is classified as having depression (Kessler et al. 2005). Although the majority of these cases were considered mild, 14% of cases were classified as serious (Kessler et al. 2005). Furthermore, less than half of depression patients receiving treatment enter lasting remission (Nestler et al. 2002), pointing to a large population of individuals suffering from depression.

Unfortunately, despite the prevalence of this disease, much of the etiology and therefore preventative and treatment measures remain unknown. This is, in part, because of the complex nature of depression. Patients can exhibit a variety of symptoms that vary in severity and origin between individuals. Furthermore, a variety of these symptoms have a subjective component that the affected individual either dismisses or is incapable of recognizing. Thus many of these individuals do not receive the proper treatment (Katon and Schulberg 1992; Wells and Marken 1989), and worse, a significant portion of cases are resistant to treatment for reasons that remain unknown (Trivedi et al. 2006). Although twin studies have identified a large genetic component in the cause of depression (Fava and Kendler 2000; Kendler and Prescott 1999), specific genes that confer vulnerability, as well as the remaining nongenetic factors, have yet to be fully elucidated (Lewis et al. 2010; Muglia et al. 2010; Sullivan et al. 2009). Although considerable progress has been made in terms of noninvasive human studies of brain structure and function, such studies are still severely limited in their ability to investigate and conclude causal roles in the physiology and molecular biology of the depressed brain. This has resulted in a demand for animal models of depression that can better tease apart the details of the inner workings of the brain (Nestler and Hyman 2010).

Animal research has been used, often in conjunction with clinical studies, to test a number of hypotheses regarding the etiology of depression and its related behaviors. One such candidate, stress, has long been linked with neuropsychiatric disease, including depression (Barden 2004). Previous epidemiological studies identified a strong correlation between stressful life events and depressive episodes, although, because genetic risks for stressful events are positively associated with a predisposition to depression, this correlation is considered noncausal (Caspi et al. 2003; Kendler et al. 1999). Early human studies found significant differences in glucocorticoid levels between depressed patients and age-matched control patients (de Kloet et al. 2005; Sachar and Baron 1979) that were reversible with antidepressant treatment (Holsboer 2001), pointing to a role for dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis as a root cause of depression. Subsequent studies in rodents have since identified that exposure to stressors in both early life or adulthood greatly increases the risk of developing depression (reviewed in Lupien 2009). Many of these protocols used

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repeated, unpredictable exposure to physical stresses (e.g., footshock, restraint, loud noises, cold temperatures) over a chronic period of time (reviewed in Hill et al. 2012; Hollis et al. 2013). Tests of the animals at the end of this period found evidence for both HPA axis dysregulation (reviewed in Hill et al. 2012) and the development of depressive-like symptoms, which were reversible after chronic, but not acute, traditional antidepressant treatment (Willner 2005). Although highly informative in solidifying the link between stress and depression, such stressors are often criticized as artificial and not representative of the true nature of stress exposure in humans, which is most commonly social in nature (Almeida et al. 2002; Bjorkqvist 2001; Kessler 1997). Thus alternative animal models of depression have begun to focus more on exposure to social stressors. Although there are several different models of social stress (for review, please see Blanchard et al. 2001; Koolhaas, De Boer, et al. 1997; Miczek et al. 2008), this review will focus solely on the role of one particular stressor, social defeat, as a model for depression.

In this review, we describe the social defeat model and summarize the current state of knowledge regarding its associated behavioral and physiological effects related to depression. We then examine the contribution of social defeat to the understanding of several current hypotheses regarding the neurobiology of depression and molecular mechanisms of action. We finally evaluate the appropriateness of social defeat to serve as an animal model for depression and discuss potential avenues for new therapies.

The Social Defeat Paradigm

Social defeat (also referred to as the resident-intruder test) uses social conflict between members of the same species to generate emotional and psychological stress. Social defeat is initiated when a male rodent is introduced into the home cage of an older, aggressive, dominant male. In some models, the intruder replaces a cohabitating female in the resident cage, whereas others introduce the intruder to a previously isolated resident. In all models, the intruder is quickly attacked and forced into subordination for the remainder of the physical interaction. When flight is barred, the intruder will assume a submissive, supine posture, emitting frequent calls of distress and illustrating freezing behavior (Blanchard and Blanchard 1977). The defeat experience, however, is not only a physical stressor. After a brief physical exposure and attack, intruders are often placed in a protective cage for the remainder of the test, allowing for psychogenic exposure to the resident without physical harm (for a list of different protocols, please see Table 1). Such a paradigm draws its strength from an ethologic and ecologic validity because repeated exposure to social defeat generates persistent emotional stress without habituation (Tidey and Miczek 1997). The lack of habituation is in stark contrast with other common stressors, particularly restraint stress, where animals quickly adapt by the third or fourth presentation (Girotti et al. 2006; Harris et al. 2004; Helmreich et al. 1997). Social defeat induces a number

of profound physiologic and behavioral changes. After encountering a resident rat, the intruder experiences increased heart rate, elevated blood pressure, and increased adrenocorticotropin hormone (ACTH) and corticosterone levels (Tornatzky and Miczek 1993). After the encounter with aggressive rats or mice, intruders already exhibit signs of stress, including elevated glucocorticoid activity, tachycardia, and hyperthermia that take many hours to recover (Tornatzky and Miczek 1993). Even a single defeat experience can elicit a number of profound physiologic changes, such as changes in daily body temperature rhythms (Meerlo, De Boer, et al. 1996), retarded growth, sensitivity to other stressors, and increased anxiety (Meerlo, Overkamp, Daan, et al. 1996; Ruis et al. 1999), with many changes persisting for days after the exposure.

Effects of Chronic Social Defeat on Behavior

It is not surprising then that repeated exposure to social defeat induces long-term changes. After two to four consecutive days of social defeat, rats exhibit significantly decreased locomotor and exploratory activity (Koolhaas, Meerlo, et al. 1997; Meerlo, Overkamp, Daan, et al. 1996; Tidey and Miczek 1997), reduced aggression and sexual behavior (Meerlo, Overkamp, Daan, et al. 1996), and increased submissive behavior and anxiety (Crawford et al. 2013; Ruis et al. 1999). Additionally, a number of depressive-like symptoms are induced by multiple exposures to social defeat. In humans, a diagnosis of depression is made after the display of a number of symptoms, including self-reported depressed mood, guilt, suicidal thoughts, loss of pleasure (anhedonia), social avoidance behavior, hopelessness, sleep disturbances, weight changes, and psychomotor alterations (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision). Of these symptoms, a subset can be objectively studied in animals, including anhedonia, social avoidance, locomotor changes, and metabolic changes. Repeated exposure to social defeat (4–7 consecutive days) induces a number of these symptoms, including reduced mobility in the forced swim test and social avoidance behavior (Berton et al. 1998; Hollis et al. 2010). More chronic presentations (5–10 consecutive days of defeat) produce impairments in thermoregulation, cardiac and autonomic circadian rhythms, and immune function (Hayashida et al. 2010; Sgoifo et al. 2002; Stefanski 2000; Tornatzky and Miczek 1993). After a period of 5 weeks of social defeat, similar behaviors are induced, in addition to anhedonia—a core symptom of depression in humans (Rygula et al. 2005). Some of the effects of chronic social defeat even result in generalized behaviors. For example, mice exposed to 10 days of social defeat or rats exposed to four consecutive defeats actively avoid an unfamiliar caged male (Berton et al. 2006; Hollis et al. 2010; Tsankova et al. 2006). Often these behaviors are quite persistent, lasting at least 4 weeks after the last exposure (Berton et al. 2006; Hollis et al. 2010; Tsankova et al. 2006). Additionally, the behavioral effects of this stressor are reversible, as social avoidance

Table 1 Social defeat protocols

Reference	Protocol	Duration	Study organism	Behavioral outcome	Biological outcome
Calvo et al. 2011; Duclot and Kabbaj 2013; Duclot et al. 2011; Hollis et al. 2010; Hollis et al. 2011; Kabbaj et al. 2000; Kabbaj et al. 2004	Intruders placed in resident home cage and allowed physical interaction for 5 minutes, followed by 10 minutes of threat[a]	1 (acute) or 4 consecutive days	Male rats/SD	Anhedonia (reduced sucrose preference), social avoidance, increased immobility in the FST, increased contextual fear response	Histone H3 acetylation changes, hippocampal BDNF changes
Tidey and Miczek 1996, 1997	Intruders placed in resident home cage and allowed physical interaction until 4 seconds of submissive behavior observed, followed by 20 minutes of threat	4 consecutive days	Male rats/LE	Increased latency to acquire cocaine self-administration	Increased extracellular dopamine levels in NAc and PFC during threat period
Tornatzky and Miczek 1993	Intruders placed in resident home cage with 10 minutes of threat, followed by 10 minutes of physical interaction, followed by 10 minutes of exposure to resident cage without resident present	5 consecutive days	Male rats/LE	Increased defensive upright posture	Acute tachycardia and hyperthermia, chronic depressed circadian rhythm for heart rate and core body temperature
Berton et al. 2006; Razzoli et al. 2011; Tsankova et al. 2006	Intruders placed in resident home cage for 10 minutes of physical interaction, followed by 24 hours of threat	10 consecutive days	Male Balb/c, C57/bl6 mice (background for transgenic strains)	Social avoidance, hyperphagia,	Increased BDNF protein and sensitized c-fos induction in the NAc, increased VTA DA phasic firing, decreased BDNF mRNA in the HPC, changes in histone methylation and acetylation in the HPC at BDNF promoter regions
Berton et al. 1998	Intruders were placed in resident cages for 30 minutes physical interaction, followed by 24 hours of threat	1 (acute) or 7 consecutive days	Male rats/ Lewis, SHR	Decreased body weight growth and food intake, increased anxiety in the EPM, immobility in the FST, and hypolocomotion in Lewis rats	Increased corticosterone, and adrenal weights, decreased thymus weights, increased serotonin metabolism in the midbrain of Lewis rats, decreased serotonin metabolism in SHR, decreased HPC 5-HT$_{1A}$ receptors in both

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Table 1   Continued

Reference	Protocol	Duration	Study organism	Behavioral outcome	Biological outcome
Tornatzky and Miczek 1994	Intruders placed in resident cage without resident, followed by repeated brief physical interactions until submission, followed by 1 hour threat	Acute defeat with 4-week threat	Male rats/LE	Decreased exploratory and motor behavior, increased defensive behavior, increased USV	Hyperthemia, acute tachycardia within the first exposures
Razzoli et al. 2006; Razzoli et al. 2007; Razzoli et al. 2009	Intruders placed in resident cages for intermittent physical interaction until submission, followed by 30 minutes of threat	1 or 3 consecutive days	Male rats/SD	Social avoidance, increased defensive behaviors, immobility, acute anhedonia, body weight loss, anxiety-like behaviors	Increased corticosterone and ACTH, decreased testosterone, no change in peripheral immune, neurotrophic, or metabolic factors
Holly et al. 2012	Intruders placed in resident cages for 10 minutes of threat, followed by physical exposure until submission for 10 bites or 6 seconds supine or 5 minutes from the first bite, followed by 10 minutes threat	4 exposures every 72 hours	Male and female rats/LE	Enhanced and prolonged cocaine locomotor sensitization in stressed females compared to males, increased SA during cocaine binge in stressed males but not females, longer binge bouts in stressed females	Increased DA after cocaine from baseline in stressed male but not stressed female rats, earlier and prolonged increased DA in stressed female rats after cocaine
Vidal et al. 2011	Intruders placed in resident cages for 10 minutes of physical contact, then returned to home cage	2 consecutive days during adolescent PND 45–46	Males rats/ WTG/W	Increased social avoidance in W rats compared to WTG. No effects of adolescent social defeat on WTG	
Koolhaas et al. 2013	Intruders placed in resident cages for 10 minutes of physical contact and either returned to home cage or cohabitated with separation	1 to many exposures	Male rats/WTG/W	Detailed descriptions of offensive and defensive behaviors displayed by both W and WTG rats	

Abbreviations: ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; DA, dopamine; FST, forced swim test; HPC, hippocampus; LE, Long-Evans; NAc, nucleus accumbens; PFC, prefrontal cortex; PND, postnatal day; SA, self-administration; SD, Sprague-Dawley; SHR, spontaneous hypertensive rat; USV, ultrasonic vocalizations; VTA, ventral tegmental area; W, Wistar; WTG, wild-type Groningen.
[a]Threat indicates a period where the intruder is protected from physical harm by either a wire mesh cage or cage partition but still given full sensory access to the resident.

and anhedonic behaviors can be reversed with chronic, but not acute, antidepressant administration (Berton et al. 2006; Rygula et al. 2006; Tsankova et al. 2006), providing predictive validity as a model for depression in humans. Such predictive validity is in stark contrast with other animal models of depression, such as learned helplessness, where acute antidepressant administration has been found to be effective (reviewed in Nestler et al. 2002).

Neurobiology of Defeat-Induced Depressive-like Behaviors

Morphologically, chronic social defeat experience has significant consequences on the rodent brain. Rodents repeatedly exposed to social defeat have decreased volume and cell proliferation in the hippocampus and medial prefrontal cortex that is reversible by chronic antidepressant treatment (Becker et al. 2008; Czeh et al. 2001; Czeh et al. 2007; Van Bokhoven et al. 2011). This reduction in neurogenesis may be transient, however, because a recent study by Lagace and colleagues (2010) found that hippocampal neurogenesis was decreased immediately after 10 days of social defeat, but restored to normal levels 24 hours later. These findings bear similar resemblance to studies of depressed human patients, where significant atrophy of the hippocampus was identified and even correlated with the duration of depressive episode (reviewed in Bremner et al. 2000; Pittenger and Duman 2008; Sheline et al. 1999; Sheline et al. 1996).

Social defeat also has strong effects on dendritic morphology. A recent study found that dendritic morphology after chronic defeat was also significantly altered, with an increased number of stubby spines with small postsynaptic densities and increased frequency of miniature excitatory postsynaptic current in the nucleus accumbens (NAc) highlighting the possibility for altered synaptic connectivity (Christoffel et al. 2011). Such dendritic alterations were accompanied by increased activation of the inhibitor of kappa B (IκB) kinase signaling pathway known for its regulatory role in neuronal morphology (Christoffel et al. 2011). The increase in this pathway within the NAc was found to mediate both the social defeat–induced morphological alterations and the depressive-like behaviors of social avoidance (Christoffel et al. 2011).

Such defeat-induced morphological changes, as well as underlying mechanisms such as the IκB signaling pathway, may require further investigation in terms of their transience and vulnerability to social defeat stress. Less chronic regimes of social defeat, such as four consecutive exposures, failed to induce changes in spine densities in the nucleus accumbens, hippocampus, or medial prefrontal cortex after a 2-week recovery period (Dietz et al. 2008). Whether the lack of observed density change was due to a transient property of dendritic morphological alterations or simply a subthreshold exposure remains an important question to address in future studies.

As previously discussed, HPA axis dysregulation has been implicated in the pathogenesis of major depression in humans, with depressed patients exhibiting significant differences in glucocorticoid levels (de Kloet et al. 2005; Sachar and Baron 1979) that were reversible upon antidepressant treatment (Holsboer 2001). Similarly, studies have found that exposure to social defeat induces significant dysregulation of this axis in rodents. In rats exposed to two or three consecutive social defeats, ACTH (Buwalda et al. 1999) and, in the case of three exposures, corticosterone levels were significantly elevated in the following week (Razzoli et al. 2007). Exposure to the context of social defeat 3 weeks later prompted a hyperactive and maladaptive HPA response not seen in similarly exposed control animals (Razzoli et al. 2007). Such findings reveal long-term regulatory effects on the HPA axis after even a brief period of social stress. Studies in male mice with multiple defeat experiences over the course of several weeks revealed an interesting time course in this dysregulation. Defeated animals exhibited first a short-term adaptation, followed by a maladaptive increased corticosterone response, possibly due to elevated hypothalamic arginine vasopressin levels (Keeney et al. 2006). Repeated exposure (4–5 consecutive days) induced increased thymus, heart, and bladder weights (Calvo et al. 2011; Crawford et al. 2013). Male rats exposed to a chronic regimen of social defeat for 4 consecutive weeks demonstrated hyperactive HPA axis, with increased corticosterone levels and adrenal gland weights that lasted more than 2 weeks from the last stress exposure (Becker et al. 2008).

Such long-lasting imbalances in circulating glucocorticoids have been shown to be detrimental to hippocampal function (Sapolsky et al. 2000) and hippocampal neurogenesis (Cameron and Gould 1994; Gould and Tanapat 1999). A recent study highlighted the functional consequences of HPA axis dysregulation by removing the adrenal glands before social defeat exposure (Lehmann et al. 2013). Adrenalectomized mice exposed to 2 weeks of consecutive social defeat showed enhanced resilience to the development of anxiety- and depressive-like behaviors compared with defeated sham mice (Lehmann et al. 2013). The authors went on to show the importance of HPA dysregulation on neurogenesis, as defeated sham mice had significantly decreased neurogenesis compared with both defeated adrenalectomized mice and control mice (Lehmann et al. 2013). Preventing neurogenesis blocked the preventative effects of adrenalectomy, showing that both neurogenesis and normalized HPA activation are required for stress resilience to depression (Lehmann et al. 2013).

Another major link in the pathogenesis of major depression is altered serotonergic neurotransmission. The link between serotonin and depression originates from the monoamine hypothesis, which suggests that a depletion of monoamines such as serotonin, norepinephrine, and dopamine leads to a depressed state (reviewed in Lee et al. 2010). Clinical observations noted that therapies that enhance the levels of these monoamines alleviated depression symptoms in humans (Heninger et al. 1996). As such, current antidepressant treatments have focused on the elevation of monoamine transmission, either by reuptake inhibitors (selective serotonin reuptake

inhibitors) such as fluoxetine; serotonin-norepinephrine reuptake inhibitors; monoamine oxidase inhibitors such as deprenyl; or tricyclic antidepressants such as imipramine, which serve to both inhibit serotonin-norepinephrine reuptake and partially antagonize serotonergic receptors (Krishnan and Nestler 2008). In rodents, serotonin has been linked with social behaviors such as aggression, social status, and sexual behavior (reviewed in Blanchard et al. 2001). Numerous studies have suggested that social stress exposure enhances serotonergic activity (Berton et al. 1998; Berton et al. 1999; Blanchard et al. 2001; Lopez et al. 1998). Acute or repeatedly defeated rats exhibited increased immediate-early gene activation in serotonergic neurons, indicative of increased activation of the serotonergic system (Paul et al. 2011). Interestingly, in the dorsal and ventral parts of the mid-rostrocaudal dorsal raphe, repeated social defeat, compared with acute defeat, resulted in decreased immediate-early gene expression, which correlated with freezing behavior (Paul et al. 2011). These findings suggest roles for selective serotonergic influence over anxiety and fear-like responses to repeated stress. Additionally, after chronic defeat, tissue concentrations of 5HT and its metabolite 5-hydroxyindole acetic acid were increased in the rat midbrain, suggesting enhanced serotonergic activity (Berton et al. 1998). Recent investigations revealed these increases could be due to modulation of GABAergic transmission in the dorsal raphe (Challis et al. 2013; Crawford et al. 2013). In fact, electrophysiologic recordings from two distinct regions of the dorsal raphe revealed decreased GABAergic inhibition in the ventral medial dorsal raphe but enhanced GABAergic inhibition in the lateral wing of the dorsal raphe, both with functional consequences for serotonin transmission in their respective targeted regions (Crawford et al. 2013). Such enhanced GABAergic inhibition in the lateral wing of the dorsal raphe was found, in a separate optogenetic study, to be required for the acquisition of social avoidance behavior after exposure to social defeat (Challis et al. 2013).

Attention has also been given to the role of neurotrophic factors in the causation of depression. Neurotrophic factors are growth factors that induce the survival, development, and function of neurons (Arevalo and Wu 2006). When comparisons between depressed patients and healthy control subjects found decreased hippocampal and forebrain volumes, it was suggested that declining levels of neurotrophins may be responsible (Duman 2004; Krishnan and Nestler 2008). One neurotrophin in particular has been the focus of numerous studies—namely, brain-derived neurotrophic factor (BDNF). BDNF became an ideal candidate when clinical studies found decreased levels in the hippocampus after stress (Nestler et al., 2002), decreased levels in depression patients, and enhanced levels in patients receiving antidepressant treatment (reviewed in Duman and Monteggia 2006). The role of neurotrophins, particularly BDNF, is not entirely clear, as studies have found region-specific effects with opposing actions. Increased levels of BDNF in the ventral tegmental area (VTA) and NAc have a prodepressant behavioral effect in rats (Eisch et al. 2003), whereas increased levels in the hippocam-

pus elicit antidepressant-like behaviors (Shirayama et al. 2002). Interestingly, social defeat exposure was found to modulate BDNF expression in a number of brain regions. In the hippocampus, chronic exposure to social defeat significantly downregulated BDNF mRNA for at least 4 weeks (Tsankova et al. 2006). Chronic administration of the tricyclic antidepressant imipramine reversed the effects of defeat by increasing BDNF levels to that of saline-treated controls (Tsankova et al. 2006). A recent report found that inactivation of hippocampal BDNF signaling by infusion of a BDNF scavenger induced social avoidance behavior after social defeat, whereas activation of hippocampal BDNF promoted social approach behavior (Duclot and Kabbaj 2013). Meanwhile, the same chronic regimen of defeat stress was found to up-regulate BDNF protein in the NAc at both 24 hours and 4 weeks after the last exposure to social defeat (Berton et al. 2006). Interestingly, increased BDNF signaling in the NAc was found to mediate the susceptibility to the effects of chronic social defeat, not through local transcriptional regulation but through enhanced BDNF release from the VTA (Krishnan et al. 2007). Indeed, local deletion of the BDNF gene in the VTA resulted in a reversal of defeat-induced social avoidance behavior seen in controls (Berton et al. 2006). Furthermore, the optogenetic activation of VTA neurons in socially stressed mice stimulated the release of BDNF from the VTA to the NAc from dopaminergic neurons in a firing pattern–dependent manner (Walsh et al. 2014), implicating a context-dependent role for dopaminergic BDNF release in the development of pathology. Additional study of other limbic regions found increases in BDNF protein and mRNA after repeated social defeat in the prefrontal cortex, amygdala, and substantia nigra (Fanous et al. 2010). These alterations ranged in persistency from 2 hours to 28 days after the last stress exposure (Fanous et al. 2010). These findings highlight a significant and perhaps specific role for BDNF in defeat-induced depressive-like behaviors.

The dynamics of neuronal and behavioral changes after social defeat have suggested the involvement of epigenetic factors. Indeed, a number of recent studies have delineated a role for epigenetics in psychiatric disorders, such as depression (reviewed in Tsankova et al. 2007), as well as in the transmission of anxiety- and depressive-like behaviors from parent to offspring (Dietz et al. 2011). Epigenetic factors promote changes in gene expression without altering the genetic code itself. Many of these changes can occur on a relatively rapid time scale, with dynamic modification of histones that can lead to increased or silenced gene expression (Felsenfeld and Groudine 2003).

A number of animal studies have identified such changes in histone modifications after exposure to social defeat, many of which underlie the neuronal changes discussed in this review. Rats exposed to either acute (one) or repeated (four) defeats exhibited significant alterations in histone H3, but not histone H4, acetylation in the hippocampus and amygdala as early as 30 minutes after the last exposure to social defeat (Hollis et al. 2010). In mice, chronic social defeat imposed a significant downregulation of BDNF in the hippocampus, which was

associated with a robust increase in the repressive histone H3 lysine 27 methylation at BDNF promoter regions (Tsankova et al. 2006). Although decreased BDNF was restored to control levels with chronic imipramine treatment, H3 lysine 27 methylation persisted at least 4 weeks after the last exposure to social defeat (Tsankova et al. 2006). These findings suggest that chronic social defeat is capable of inducing long-lasting repressive markers at specific genes that may not be reversible by antidepressant treatment. Further investigation found that imipramine actually increased BDNF levels through enhanced histone acetylation and histone H3 lysine 4 methylation at the gene's promoter (Tsankova et al. 2006). In fact, hippocampal histone deacetylase5 (HDAC5) mRNA was found to be downregulated by chronic injection of imipramine in chronically defeated mice (Tsankova et al. 2006). Overexpression of HDAC5 in the hippocampus blocked the effects of imipramine in animal models of depression, including social defeat (Tsankova et al. 2006). Finally, administration of HDAC inhibitors had antidepressant effects in animals exposed to social defeat (Covington, Vialou, et al. 2011; Schroeder et al. 2007; Tsankova et al. 2006).

Similar to BDNF findings, histone modifications appear to have region-specific effects. Renthal and colleagues (2007) found that exposure to chronic, but not acute, social defeat reduced HDAC5 levels in the NAc, whereas administration of imipramine significantly increased HDAC5 levels. Additionally, HDAC5 knockout mice exhibited hypersensitive responses to social defeat—namely, an enhanced social avoidance behavior that was significantly increased compared with that in wild-type defeated mice (Renthal et al. 2007). This suggests that HDAC5 is important in moderating the response to chronic social defeat, possibly through deacetylation of genes such as BDNF or those exerting GABAergic control over serotonergic neurons.

Importantly, these histone modifications appear to be highly conserved and can be translated to humans. Similar patterns of histone H3K14 acetylation were found in the NAc between socially defeated mice and postmortem brains of depression patients (Covington et al. 2009). Both defeated mice and depressed patients exhibited increased histone H3 acetylation in the NAc that corresponded with decreased levels of histone deacetylase2 mRNA (Covington et al. 2009). Infusion of specific HDAC inhibitors reversed the effects of chronic social defeat on both behavior and gene expression (Covington et al. 2009). Additionally the repressive histsone H3 lysine 9 dimethylation was also significantly increased in the NAc after chronic social defeat (Covington, Maze, et al. 2011). Such repressive methylation markers appear to actually promote adaptive responses to stressful stimuli. Mice exposed to chronic social defeat that exhibited increased H3 lysine 9 dimethylation and its associated enzymes G9a and G9a-like protein in the NAc actually demonstrated resilience against developing the depressive-like responses (Covington, Maze, et al. 2011), suggesting a positive role for chromatin repression in the lasting effects of social defeat.

Of course, not all repressive epigenetic marks are protective; enhanced DNA methylation from increased DNA meth-

yltransferase 3a in the NAc were linked to depressive-like behaviors after social defeat (LaPlant et al. 2010). The question of how these epigenetic changes are able to mediate such behaviors as social approach and avoidance has been difficult to fully demonstrate. A recent study highlighted the complexity surrounding such interactions, reporting the involvement of HDAC6 in regulating serotonergic neuronal populations through control of the glucocorticoid chaperone complex to act in both glucocorticoid and serotonin signaling to facilitate social avoidance behavior (Espallergues et al. 2012).

Using Social Defeat to Investigate Individual Differences

A further advantage of social defeat is that it can be used to study individual differences in stress responsiveness. It is well known that individuals vary in their responses to both stressful events and treatments for depression. In today's era of genome sequencing, focus has shifted to a more personalized approach to medical treatment, particularly within the realm of psychiatric diseases such as depression. The United States Federal Drug Administration even recommends that patients be genotyped to identify any relevant biomarkers before treatment, including antidepressants (Miller and O'Callaghan 2013). Because no acceptable biomarkers are available for the diagnosis of depression or selection of appropriate antidepressant, rodent studies on the topic of individual differences are relevant for current models of depression.

Our work has focused on examining the effects of social defeat exposure on predefined subsets of the population, with respect to vulnerability to depressive-like behaviors. In humans, individual differences in novelty-seeking behaviors have been identified, where voluntary participation in "risky" activities was associated with a history of manic-depressive episodes and drug-taking behaviors (Zuckerman and Neeb 1979). Such sensation-seeking individuals tend to seek out dangerous situations despite the personal risk involved and tend to have reduced anxiety levels during these activities (Zuckerman and Kuhlman 2000). To gain insight into the neurobiological mechanisms behind sensation-seeking and its potential role in depression, we studied a rat model of individual differences based on novelty-seeking behavior. Previous reports indicate that when experimentally naive rats are exposed to the mild stress of a novel environment, some rats (known as high responders [HRs]) exhibit high rates of exploratory locomotion, whereas others (known as low responders [LRs]) exhibit low rates of locomotor activity (Hooks, Colvin, et al. 1992; Kabbaj and Akil 2001; Piazza et al. 1989; Pierre and Vezina 1997). This locomotor response in a novel environment has vast predictive power for not only subsequent behavioral responses to drugs such as amphetamine and cocaine (Hooks, Jones, et al. 1992; Kabbaj and Akil 2001; Piazza et al. 2000; Pierre and Vezina 1997) but also anxiety-related behavior in these animals (Dellu et al. 1996; Kabbaj et al. 2000). We sought to investigate whether novelty-seeking phenotypes could represent a model for

vulnerability to stress-induced depression. We found that HR rats exposed to 4 consecutive days of social defeat exhibited an increased sensitivity to stress through a heightened emotional state (Duclot et al. 2011; Hollis et al. 2011). Defeated HR rats displayed decreased locomotion in an open field, decreased preference for sucrose solution, reduced body mass gain, increased social avoidance behavior, and a persistent contextual fear response compared with nondefeated HR counterparts (Calvo et al. 2011; Duclot et al. 2011; Hollis et al. 2011). Defeated HR rats also displayed increased immobility in the forced swim test compared with nondefeated HR rats (Calvo et al. 2011). Interestingly, defeated LR rats exhibited no behavioral changes in response to social defeat exposure, suggesting a link between novelty-seeking behavior and stress-related mood disorders such as depression (Calvo et al. 2011; Duclot et al. 2011; Hollis et al. 2011). Such behavioral differences could have underlying neurobiological mechanisms. With rodent studies, we were able to investigate possible candidates underlying the HR vulnerability to stress. HR rats exhibited significantly elevated corticosterone levels during the recovery phase after defeat exposure, suggesting an extended stress response (Calvo et al. 2011). Examination of the ratio of mineralocorticoid to glucocorticoid receptors in the hippocampus found significant decreases after repeated defeat in HR rats only, possibly explaining the extended stress response at the neural level (Calvo et al. 2011). Additional studies by our group identified differential changes in hippocampal gene expression between HR and LR rats exposed to social defeat in key genes such as CAM kinase II, Leptin, and importantly, BDNF, suggesting a neural basis for vulnerability to stress-induced depressive-like disorders (Duclot and Kabbaj 2013; Kabbaj et al. 2004).

An alternate use of social defeat has focused on using defeat to examine behavioral and molecular responses of individuals that exhibit resilience to chronic stress. In a population of mice exposed to 10 consecutive days of social defeat, a subset never developed the behavioral and metabolic symptoms of their similarly stressed counterparts (Krishnan et al. 2007). Termed "unsusceptible," these mice exhibited signs of chronic stress exposure, such as elevated corticosterone levels and increased anxiety at similar levels to the "susceptible" cohort but never exhibited anhedonia or weight loss typical of susceptible mice exposed to chronic social defeat (Krishnan et al. 2007). Such resiliency was not found to be not simply a lack of vulnerability but rather the result of an increased molecular plasticity within the mesolimbic dopaminergic circuitry—an important circuit for natural reward (Krishnan et al. 2007). Further investigation revealed a role for differential patterns of histone deacetylation and methylation that could underlie such molecular plasticity (Renthal et al. 2007; Wilkinson et al. 2009). Intriguingly, epigenetic regulation within the NAc of defeated unsusceptible mice exhibited overlapping patterns of expression with defeated susceptible mice under chronic antidepressant treatment, highlighting possible avenues for future therapies (Wilkinson et al. 2009). Other models characterized individuals based on differences in their behaviors during the social defeat proce-

dure (Frank et al. 2006; Walker et al. 2009; Wood et al. 2010). Rats that used active coping behaviors, such as fighting and guarding, exhibited smaller corticosterone, corticotropin-releasing factor, and neuronal activation responses to social defeat compared with those that remained passive and became submissive early during the encounter (Walker et al. 2009; Wood et al. 2010). Importantly, rats with passive coping styles were more prone to develop depressive-like behavioral and endocrine profiles, highlighting a possible avenue for preventative therapies.

Social Defeat as a Model for Depression

Animal models of psychiatric disease face a number of challenges, from poor construct validation to low predictive power (reviewed in Nestler and Hyman 2010). With the incidence of depression on the rise, the demand and search for better animal models has increased. Social defeat meets many criteria for such a model. In terms of face validity, chronic social defeat exposure reproduces all of the depressive-like symptoms that are capable of objective measurement in animals. Many of these symptoms are reversible with current antidepressant treatments, whereas others are reversible with the inhibition or activation of new targets that remain to be tested in humans, providing a measure of predictive validity that is not necessarily present in other animal models of depression. Although a single etiology for depression remains unlikely, exposure to stress appears to be a significant contributing factor, providing some measure of construct validity for social defeat.

Social defeat is not without its drawbacks, however. One serious concern is the difficulty in studying female subjects. All of the research discussed in this review has focused entirely on the effects of exposure to social defeat in male subjects. Epidemiologic studies, however, report a higher incidence of depression in women (Ferrari et al. 2013b; Kessler 2003); thus attention must be given to studying the effects of stress on both sexes. In the past, this has proved challenging for models of social defeat, which typically rely on male aggression not readily displayed by female subjects (reviewed in Haller et al. 1999). Recent experiments have performed social defeat on female rats using older, lactating females as residents to elicit aggressive displays to generate stress (Holly et al. 2012; Jacobson-Pick et al. 2013). Interestingly and unsurprisingly, social defeat in female rodents appears to elicit a number of symptoms but only after a delay (Jacobson-Pick et al. 2013). With this in mind, we caution against simply extending the findings of social defeat to both sexes because important sex differences may be at play and reiterate the necessity of continuing to examine female subjects for the same depressive-like behaviors after defeat exposure as male subjects.

Another potential drawback of social defeat is the age during exposure. Social defeat is performed nearly exclusively in adult animals, which provides excellent insight into the development of depression in adulthood. Numerous

studies, however, point to the importance of early-life exposure to stress in programming adult behaviors (reviewed in de Kloet et al. 2005; Hollis et al. 2013). Because the adolescent brain is still undergoing remodeling (Spear 2000), it is difficult to extend the findings of social defeat in adults to juveniles. Indeed, several studies indicate a different response or even lack of response to defeat exposure during adolescence (Buwalda et al. 2011; Vidal et al. 2011). Thus the effects of social defeat discussed herein cannot necessarily make predictions for the development of depression after exposure in young animals. Despite these caveats, we maintain that social defeat is a valuable research tool that has the potential to identify new, personalized avenues for therapy.

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