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# Animal Models of Depression: Molecular Perspectives

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## Abstract

Much of the current understanding about the pathogenesis of altered mood, impaired concentration and neurovegetative symptoms in major depression has come from animal models. However, because of the unique and complex features of human depression, the generation of valid and insightful depression models has been less straightforward than modeling other disabling diseases like cancer or autoimmune conditions. Today's popular depression models creatively merge ethologically valid behavioral assays with the latest technological advances in molecular biology and automated video-tracking. This chapter reviews depression assays involving acute stress (e.g., forced swim test), models consisting of prolonged physical or social stress (e.g., social defeat), models of secondary depression, genetic models, and experiments designed to elucidate the mechanisms of antidepressant action. These paradigms are critically evaluated in relation to their ease, validity and replicability, the molecular insights that they have provided, and their capacity to offer the next generation of therapeutics for depression.

### Keywords

Animal models; Antidepressants; Behavioral testing; Depression Resilience; Stress; Vulnerability

## 1 Introduction

Major depressive disorder (MDD) or *depression* is a heritable neuropsychiatric syndrome characterized by relatively subtle cellular and molecular alterations distributed across a circuit of neural substrates (Krishnan and Nestler 2008). This disease claims a malignant toll on health: a 2007 World Health Organization study of over 200,000 adults across the world showed that depression produces the greatest decrement in health when compared with chronic diseases like diabetes and arthritis (Moussavi et al. 2007). In spite of a large variety of available antidepressant medications and alternative therapeutic modalities including several forms of psychotherapy (e.g., cognitive behavioral therapy) and several other approaches such as yoga, exercise, and sleep deprivation, depression suffers a huge treatment gap worldwide, whereby large numbers of individuals who require care do not receive treatment (Kohn et al. 2004). Depressive disorders cause morbidity across the entire age spectrum (Kessler et al. 2005): they can be difficult to diagnose and treat in the pediatric and adolescent period (Prager 2009), complicate the course of patients with chronic illness (Evans et al. 2005), and increase overall medical burden in the elderly (Lyness et al. 2006).



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Over and above this alarming public health problem, shortfalls in treatment pose a grave concern. Even if major depression is accurately diagnosed and treated in all individuals with perfect treatment compliance, the best remission rates with standard antidepressants are only *30–40%* (Rapaport et al. 2003; Trivedi et al. 2006). This is in stark contrast with other chronic disorders such as diabetes mellitus (Krishnan and Nestler 2008), where the correct combination of medications ultimately *can* ensure normoglycemia and prevent diabetic complications in a large majority of patients. Several explanations have been put forth for this discrepancy between the treatment of depression and other chronic disabling conditions. First, the diagnosis of depressive episodes is made when patients display a certain number of vaguely defined clinical symptoms (e.g., depressed mood, anhedonia, sleep changes, appetite changes, guilt, etc.) for a 2-week period. In the absence of more objective diagnostics such as neuroimaging, genetic variations, biomarkers, or biopsies, this rudimentary "symptom-counting" approach creates obvious limitations for the development of animal models, clinical trials, and neuropathological investigations (Krishnan and Nestler 2008). While the symptomatic heterogeneity of depression (*atypical* vs. *melancholic* vs. *psychotic*, etc.) is well recognized (Rush 2007), little insight has been gained into the etiological and pathophysiological distinctions between these subtypes. Drug efficacy trials are seldom conducted on subtype-segregated groups, thereby increasing the chance of abandoning therapies that may be subtype-specific. Since all available pharmacological treatments for depression work through altering monoaminergic transmission (Berton and Nestler 2006), it is possible that only one type of depression is being treated ("*monoamine-responsive*"). Due to high placebo response rates (Brunoni et al. 2009) and side effect concerns, monoamine-based agents still constitute a significant proportion of "new" antidepressants being tested in clinical trials (Mathew et al. 2008). And finally, given that genetic, neuroimaging, postmortem analyses and laboratory investigations (e.g., markers in serum or cerebrospinal fluid) have yielded limited insight into the neurobiology underlying depression (Krishnan and Nestler 2008), most current theories of depression are based largely on animal models of the disease, which are also inherently limited.

## 2 Can Depression Be Modeled in Laboratory Animals?

If the full psychiatric syndrome of depression cannot be recapitulated in rodents or nonhuman primates, then is it worthwhile to infer anything at all from animal models of depression? While symptoms such as guilt, suicidality and sad mood are likely to be purely human features, other aspects of the depressive syndrome have been replicated in laboratory animals, and in several instances ameliorated with antidepressant treatment. These include measures of helplessness, anhedonia, behavioral despair and other neurovegetative changes such as alterations in sleep and appetite patterns. From an evolutionary perspective, depression has been proposed to be an analog of the *involuntary defeat strategy* (IDS), which is triggered when an animal perceives defeat in a hierarchical struggle for resources (Sloman 2008). Features of psychomotor retardation, hyperarousal, anhedonia and sleep disturbances in the setting of losing such a struggle are postulated to have an adaptive advantage in that they serve to protect losers from further attack and focus cognitive assets on planning ways out of complex social problems (Nesse 2000; Watson and Andrews 2002). Most, if not all, animal models of depression aim to quantitatively assay some form of experimentally induced *defeat* or *despair*, even though this aspect of mammalian behavior is likely *physiological* (i.e., adaptive) rather than *pathological*. In addition, while despair behavior is often extrapolated as being *depression-like*, the application of stress to rodents also produces *anxiety-like* changes that are manifestations of the *fight* or *flight* response (reduced exploration, freezing, stress-induced hyperthermia, etc.). Just as anxiety and depression often overlap clinically, the distinction between stress-induced *depression-like* and *anxiety-like* behaviors is difficult to ascertain, particularly since both types of behaviors respond to antidepressants. Thus, an important challenge of the field has been to produce a

long-lasting state of depressive pathology in laboratory animals, which has seldom been achieved.

Today's depression models are often evaluated by fulfilling three main criteria (a) *face validity* (the requirement for a reasonable degree of symptomatic homology), (b) *construct* (or *etiological*) validity (the requirement for similar causative factors), and (c) *pharmacological validity* (which requires the reversal of depressive symptoms by available antidepressants). These criteria serve as guides to compare models against each other, but each criterion suffers basic flaws (Nestler and Hyman 2010). For instance, in the olfactory bulbectomy model of depression, surgically bulbectomized adult rats display increased locomotor activity, increased aggression, and spatial memory impairments that are all reversed by the chronic administration of a diverse array of antidepressants (Song and Leonard 2005). While this model may appear to be weak in construct and face validity, its pharmacological validity is excellent: virtually all classes of available antidepressants reverse these behavioral changes with a therapeutic delay. Of course, people with depression do not have olfactory lesions. Nevertheless, our assessment of poor construct validity is of limited value, since the etiology of depression is incompletely understood. Strict applications of face validity pose the risk of excessive anthropomorphization, particularly when assessing rodents such as mice, rats or tree shrews, which each have their own distinct behavioral repertoires (Crawley 2000). Since candidate models of depression are often assessed for reversibility with known monoamine-based antidepressants, there exists the alarming possibility that the most popular models of depression may, by design, be insensitive to the antidepressant effects of nonmonoamine-based agents (Berton and Nestler 2006). A potential fourth criterion is *pathological* validity, whereby animal models are validated by their recapitulation of known postmortem pathological or serological changes found in human depressed patients. Given our current state of knowledge, this is a very difficult requirement, but with increasing efforts in this field stemming from more widespread access to human postmortem tissue, the elucidation of pathological validity criteria may potentially eliminate the circular arguments that lie at the core of modeling depression.

This chapter evaluates the current status of animal models in depression and highlights certain novel neurobiological insights which have been generated using these models. Given the emphasis on molecular perspectives, we focus on data from rodent studies. Preclinical studies in nonhuman primates have largely focused on the behavioral and endocrinological impacts of early life stress (Gilmer and McKinney 2003) and, while this is clearly a critical research avenue, this field has been limited by a variety of factors which restrict nonhuman primate research. Instead of attempting to be comprehensive, this review highlights key methodological strengths and limitations and provides recommendations for further experimentation. The reader is referred elsewhere for a recent systematic and concise description of the neurobiology of depression (Krishnan and Nestler 2010).

## 3 Animal Models of Depression and Molecular Insights

### 3.1 Models of Acute Stress

**3.1.1 Forced Swim Test and Tail Suspension Test—**The forced swim test (FST) and tail suspension test (TST) are the most widely used tests of antidepressant action and are also used to infer "depression-like" behavior. In the *Porsolt* test (Porsolt et al. 1977), also known as the FST test, a mouse or rat is placed in an inescapable cylinder of water and, following an initial period of struggling, swimming and climbing, the animal eventually displays a floating or immobile posture. In the TST, immobility is scored while mice are suspended by their tails. Since water is not required, the TST is not confounded by challenges to thermoregulation (Cryan and Mombereau 2004). FST or TST immobility has

been interpreted as an expression of *behavioral despair* or *entrapment* (Cryan et al. 2005; Lucki et al. 2001), and is reversed by the acute administration of almost all available antidepressants. This poses a problem for the model, since antidepressants restore mood in depressed humans only after many weeks of administration. Numerous agents that act independently of monoamine signaling have also been shown to reduce immobility time, such as recombinant ghrelin (Lutter et al. 2008), ketamine (Maeng et al. 2008), and estradiol (Dhir and Kulkarni 2008), to name a few. The foremost strength of these models is their ability to rapidly screen novel agents and phenotype genetically manipulated mice, and both paradigms have been successfully automated to reduce errors in subjective scoring. As shown in Fig. 1, a large number of mutant mice have been screened through the FST or TST. There appear to be a much larger number of "antidepressant-like" knockouts (KO), i.e., those mice that exhibit reduced immobility, compared with the number of KOs that exhibit increased immobility, but this may reflect a constraint of the model since it was originally designed to capture antidepressant effects. These studies illustrate the number and diversity of genes that may play a role in regulating stress-induced immobility, including transcription factors, growth factors, endocrine hormones, immune signaling molecules, and numerous genes encoding proteins required for synaptic neurotransmission.

Since the majority of mutants phenotyped thus far are constitutive KOs, their phenotype could be confounded by developmental compensatory effects, e.g., biochemical and anatomical alterations which are secondary to the loss of the gene of interest [see also Gondo et al. (2011); O'Tuathaigh et al. (2011) for further discussion]. These compensatory effects may, nevertheless, be relevant to the study of depression. For example, the profound antidepressant-like phenotype of TREK1 (*Twik-related K Channel 1*) KO mice is associated with markedly altered $5HT_{1A}$-receptor-mediated excitation in the hippocampus (Heurteaux et al. 2006), a change that is also observed following chronic treatment with a variety of antidepressants (Haddjeri et al. 1998). Performance on the FST and TST is also dependent on the background strain of the animals used: systematic comparisons of inbred mice reveal greater than a tenfold range of immobility (Liu and Gershenfeld 2003; Lucki et al. 2001; see also Gondo et al. 2011; O'Tuathaigh et al. 2011 for further discussion). While the effects of background strain tend to complicate phenotypic analysis of mutant mice, such variation has been exploited for QTL (*quantitative trait loci*) analyses, which have implicated genes in certain broad chromosomal regions in this type of behavioral response (Jacobson and Cryan 2007; Tomida et al. 2009).

The complexities of "simple" immobility testing are exemplified by data from serotonin transporter (SERT) KO mice. Since SERT is inhibited by many available antidepressants, one might expect SERT KO mice to display a robust antidepressant-like phenotype. However, they display increased FST immobility and decreased TST immobility on a *129S6* or 129S6/SvEV mixed background, have increased TST immobility on a *CD1* background, and yet have no phenotype on a *C57BL/6J* background (Alexandre et al. 2006; Holmes et al. 2002; Lira et al. 2003). Subsequently, a SERT KO rat has been generated through random ENU (*N*-ethyl-*N*-nitrosurea) mutagenesis, which displays increased immobility on the FST (Olivier et al. 2008). Thus, while SERT inhibition is required for the antidepressant effects of SSRIs (selective serotonin-reuptake inhibitors) (Holmes et al. 2002), it appears that the developmental loss of SERT produces a complex phenotype that is clearly dependent on background strain. While the precise mechanistic details remain unclear, the observed pro-depressant-like phenotypes may be related to pathologically elevated synaptic serotonin levels during development causing a decrease in the number and firing rate of serotonergic neurons (Lira et al. 2003) as well as disorganized limbic cortical development (Olivier et al. 2008).

**3.1.2 The Learned Helplessness Model—**Following an *uncontrollable* and *inescapable* stress such as exposure to inescapable electric shocks, animals develop a state of "helplessness" such that when re-exposed to the same shocks, now with an easy escape route, animals will either display increased escape latency or completely fail to escape (Seligman et al. 1975). Following one or more sessions of inescapable shock, rats have been shown to develop persistent changes including weight loss, alterations in sleep patterns and HPA axis activity and loss of spine synapses in hippocampal regions (Cryan and Mombereau 2004; Haddjeri etal. 1998; Nestler et al. 2002). In mice, the learned helplessness (LH) syndrome appears to be short-lived (2–3 days), and several mutant lines of mice have been phenotyped on the LH assay, with results largely compatible with their corresponding FST data. Like the FST or TST, both mice and rats display a considerable degree of interstrain variation, and escape deficits are reversed by a variety of antidepressants (Henn and Vollmayr 2005).

One distinctive feature of LH is the considerable degree of variability in the expression of helplessness: anywhere from 10 to 80% of animals simply fail to develop escape deficits. While this may be a disadvantage in certain scenarios, this variability has been exploited to devise selective inbreeding strategies to create of helpless and nonhelpless strains of rats which differ across a variety of other indices, including measures of anhedonia, activity and sleep behavior (Henn and Vollmayr 2005). DNA microarray analyses performed on hippocampal tissues reveal that nonhelpless rats activate a distinct pattern of gene expression compared with helpless or stress-naïve rats, suggesting that their passive responsiveness may be due to distinct neurobiological changes (Kohen et al. 2005). In mice, the development of helpless behavior is inversely related to the activation of the transcription factor ΔFosB (a stable splice variant of FosB) in the periaqueductal gray (PAG) of the midbrain. The virally mediated overexpression of ΔFosB in PAG neurons protects against developing an escape deficit partly through the transcriptional repression of *substance P*, a neuropeptide known to modulate the physiology of serotonergic and other neurons (Berton et al. 2007).

Today, these acute stress models make up the first line of behavioral tests utilized to phenotype transgenic mice and are also exploited as tools to rapidly screen putative antidepressant compounds. Even though direct links to human depression may be weak since they use acute stressors and test acute antidepressant responses, these tests have directed the field toward a number of previously unappreciated molecular players (Fig. 1). Of course, to truly implicate these targets in the pathophysiology of depression without false positives and to shed light on complex relationships such as those observed in the case of the SERT KOs, positive hits on these screens require much further validation through a more diverse set of molecular and behavioral assays, ideally in conjunction with postmortem validation (Covington et al. 2009; Hunsberger et al. 2007; Krishnan et al. 2008; Svenningsson et al. 2006). Furthermore, the FST, TST and LH are highly sensitive to manipulations which impair motor function, and the LH model is particularly sensitive to alterations in central and peripheral pain sensitivity (Cryan and Mombereau 2004). Therefore, these screening assays should be followed up with tests of motor function or pain sensitivity.

## 3.2 Models of Secondary or Iatrogenic Depression

**3.2.1 Hormones of the HPA Axis—**The hypothalamic–pituitary–adrenal (HPA) axis is activated by a wide variety of stressful stimuli, and resultant increases in serum glucocorticoids serve an immediate adaptive role through increases in gluconeogenesis and lipolysis. The "cortisol" hypothesis suggests that certain symptoms of depression may be mediated by a persistently overactive HPA axis, brought about through (1) increased

production of hypothalamic corticotropin-releasing factor (CRF) and (2) reduced negative feedback at the level of centrally expressed glucocorticoid receptors (Holsboer and Ising 2009). Clinical studies have demonstrated HPA axis dysregulation in some depressed individuals, mainly those with severe depression and psychotic symptoms (Gold and Chrousos 2002), and these patients may uniquely benefit clinically from pharmacological antagonists of the glucocorticoid receptor (Krishnan and Nestler 2008). In contrast, atypical depression (associated with increased sleep and appetite), posttraumatic stress disorder, chronic fatigue syndrome, and fibromyalgia are associated with reduced circulating glucocorticoid concentrations and heightened negative feedback (Krishnan and Nestler 2008), demonstrating that alterations in HPA axis activity in either direction can result in depressive features. A significant amount of preclinical effort has been devoted to generating animal models of impaired glucocorticoid function. Perhaps the most syndromically accurate model of melancholic depression is the forebrain glucocorticoid receptor (GR) knockout mouse, derived through conditional deletion of the GR allele via *cre-recombinase loxP* technology: these mice display enhanced basal serum glucocorticoid levels, dexamethasone nonsuppression, increased FST and TST immobility, and these changes are all reversible with chronic antidepressants (Boyle et al. 2005). Interestingly, the forebrain *overexpression* of GR leads to an identical behavioral phenotype (Wei et al. 2007), which suggests that the mood altering properties of glucocorticoid signaling are more complex than simple increases or decreases in steroid or receptor levels.

Depression is also commonly observed as an *iatrogenic* side effect of chronic glucocorticoid administration and is a key psychiatric symptom of Cushing's syndrome which is characterized by hypercortisolemia secondary to adrenal or pituitary corticotrophic hyperplasia. Thus, the negative consequences of heightened HPA axis activity are at least partially related to the adverse effects of glucocorticoids themselves (McEwen 2007; Pittenger and Duman 2008). Consistent with this hypothesis, mice exposed to 20 days of corticosterone dissolved in their drinking water to develop decreased responding for food pellets in an operant conditioning task (an anhedonic phenotype) and increased TST immobility, both of which are reversible by chronic amitriptyline (a tricyclic antidepressant) (Gourley et al. 2008). Such corticosterone exposure decreases activation of ERK1/2 (extracellular signal regulated kinase 1/2) in the dentate gyrus, which is itself sufficient to increase FST immobility and antagonize the action of antidepressants (Duman et al. 2007).

Increases in circulating serum cortisol in depression may also be secondary to increased CRF synthesis and secretion (Nemeroff et al. 1984). Many of CRF's strong effects on behavior occur through centrally mediated processes independent of adrenal function, i.e., are not reversed by adrenalectomy (Muller and Holsboer 2006). To tease out the behavioral significance of brain CRF signaling, numerous transgenic and knockout lines have been generated. While the loss of brain CRF has negligible behavioral consequences, the transient overexpression of CRF during development leads to reduced exploratory behavior (increased anxiety) and FST/ TST immobility during adulthood, and constitutive CRFR1KO mice display increased exploration (anxiolysis) (Kolber et al. 2010; Muller and Holsboer 2006). These data, combined with postmortem evidence of enhanced CRF levels in depression, have encouraged pharmaceutical companies to invest in the development of a safe and effective CRFR1 antagonist to be used in depression and anxiety disorders (Mathew et al. 2008). However, despite decades of study and numerous pharmacological prototypes, this hypothesis remains to be tested effectively in humans. An important challenge in this field has been to selectively antagonize brain CRF signaling without altering natural HPA axis responsiveness.

**3.2.2 Retinoic Acid Derivatives—**Isotretinoin (Accutane ©), a retinoic acid derivative used as a highly effective treatment of severe acne, has been associated with an increased

risk for depression and suicide (Bremner and McCaffery 2008). Mice chronically treated with isotretinoin develop increases in FST and TST immobility which have thus far been correlated with decreased hippocampal metabolism and neuronal proliferation (Crandall et al. 2004; O'Reilly et al. 2006). Isotretinoin is known to bind and activate retinoic acid receptors (RARs) which are widely distributed in the adult brain (Bremner and McCaffery 2008). RARs belong to the nuclear hormone receptor family of transcription factors, and the transcriptional consequences of isotretinoin exposure within limbic brain regions remain unexplored.

**3.2.3 Cytokines and Immune System Dysregulation—**Proinflammatory cytokines such as interferon-α are used in humans to treat several disease states. Many of these recombinantly derived proteins produce clinically significant depression as a side effect (Loftis and Hauser 2004). A large body of preclinical evidence suggests a bidirectional association between immune activation and depressive symptoms: certain cytokines have been shown to induce depression-like behavior in rodents and primates (Dunn et al. 2005; Felger et al. 2007), and several models of chronic stress produce significant changes in immune function (Miller et al. 2009). One such example is IL-1β (interleukin-1β): increases in IL-1β signaling in the hippocampus play a role in mediating the anhedonic and antineurogenic effects of chronic stress through the actions of the transcription factor NFκB (nuclear factor-κB) (Koo and Duman 2008; Koo et al. 2010). A key priority in this field will be to progress from focusing on the *sickness behavior* induced by strong immune stimuli such as LPS (lipopolysaccharide) (O'Connor et al. 2009) to the behavioral consequences of more elegant manipulations of specific cytokine signaling axes, as well as defining the therapeutic relevance of a whole host of antiinflammatory therapeutics popularly prescribed for autoimmune conditions. Clearly, the answer is not simply *decreasing* inflammation. The immunization of rats with an altered version of MBP (myelin basic protein) activates weakly self-reactive T-cells and has been shown to render rats immune to the anhedonic effects of chronic unpredictable stress (CUS) (Lewitus et al. 2009), suggesting that specific activators of immune function may in fact promote stress resilience. Understanding the *immunology of depression* is particularly applicable to autoimmune diseases such as multiple sclerosis (MS) where up to 50% of patients experience clinically significant depression. Murine MS models display depression-like changes such as weight loss, anorexia and reduced social exploration well before the onset of neurologic deficits (Ghaffar and Feinstein 2007; Gold and Irwin 2009), suggesting the presence of shared pathogenic mechanisms.

Depression which is secondary to medical conditions (e.g., stroke, pancreatic cancer, hypothyroidism, hypercortisolemia, etc.) is clinically indistinguishable from so-called *endogenous* or primary depression. Without clear knowledge of the etiology of endogenous depression, models that are designed based on the direct application of clinical observations are positioned to play a critical role due to their strong construct validity. A direct comparison of the molecular changes associated with corticosterone, cytokine and/or isotretinoin exposures versus stress models are likely to provide insight into shared and distinct pathophysiological mechanisms between stress-induced, endogenous, and iatrogenic forms of depression. One obvious path of investigation would be to employ genome-wide transcriptional profiling techniques to look for shared patterns of molecular plasticity in both animal models and patient samples. These "common denominator" patterns could identify potential targets for antidepressant drug discovery, and such agents would likely be active against all forms of depression.

### 3.3 Chronic Stress Models

While acute stress paradigms are used broadly for their ease, automation, and rapid phenotyping abilities, they offer singular readouts that often cannot be unambiguously

interpreted. For instance, increased immobility in the FST is often anthropomorphized as an expression of despair. However, it can also be understood as a successful and adaptive behavioral response that functions to conserve energy. Today's chronic stress models are distinguished by their remarkable ability to simultaneously produce a set of behavioral alterations with strong face validity for depression. However, this enhanced face validity often comes at the cost of low throughput: the precise application of these chronic stress models requires more space and time and greater sample sizes and are consequently significantly more expensive than other models. Thus, fewer laboratories have experienced consistent success. Furthermore, even with their known pharmacological validity, their low throughput makes them poorly suited for the pharmacological validation of novel compounds. In essence, these models are composed of repeated applications of an uncontrollable and unpredictable stress that is coupled with a quantifiable assay of depression-like behavior. They are based on clinical evidence that stressful life events that significantly increase the risk of depressive episodes are generally of a chronic nature (divorce, financial problems, and sexual abuse) (Krishnan and Nestler 2008). As is discussed below, their main strengths lie in their ability to characterize the neuroplasticity associated with chronic stress or antidepressant exposures.

**3.3.1 Chronic Mild Stress—**Chronic mild stress (CMS), better described as CUS, paradigms involve the application of varied intermittent physical stresses applied over a relatively prolonged time period (between 1 and 7 weeks, Fig. 2). Sucrose drinking is the most commonly utilized assay to assess the impact of CUS and CUS-exposed rats or mice show deficits in their motivation to consume a dilute (1–2%) solution of sucrose measured either as total sucrose intake or as a preference against water (Willner 2005). CUS has also been shown to result in a number of other "emotional" changes that are difficult to objectively quantify, such as grooming deficits and changes in aggressive and sexual behavior. Many of these phenotypes are reversed by chronic antidepressants applied either during the stress or as a poststress treatment (Strekalova et al. 2006). This model has been the subject of considerable controversy related to poor reproducibility (Argyropoulos and Nutt 1997; Broekkamp 1997; Willner 2005), and while some groups have had consistent success in repeatedly generating anhedonic mice/rats with a given paradigm, others have not experienced the same reliability. It would appear that this model is particularly sensitive to subtle variations in design (the various permutations of stressors) and numerous other sources of variability endemic to behavioral research (e.g., time of testing, vendor differences, etc.) and has accordingly faded in popularity. While it may not have the pharmacological screening capabilities of the FST, when performed reproducibly and reliably, it has clear potential to generate important molecular insights into depression.

Aside from being a tool to study the physiological consequences of chronic stress, CUS has been applied recently to phenotype mouse mutants, study gender differences in stress responses, and validate novel antidepressants (Kong et al. 2009; LaPlant et al. 2009; Vitale et al. 2009). Like LH, CUS studies have reported significant individual differences. In one mouse study, decreased sucrose preference (anhedonia) was only observed in 61% of mice and was uniquely associated with increased immobility in the FST. In contrast, all CUS-exposed mice developed changes in locomotor behavior and decreased exploration, suggesting that segregating a subgroup of anhedonic mice identifies a unique susceptible population that displays stress-induced depressive features (Strekalova et al. 2004). A similar degree of variability has been observed in rats and when CUS-sensitive (i.e., vulnerable) rats were treated with antidepressants two distinct populations emerged: antidepressant-sensitive and antidepressant-resistant (Jayatissa et al. 2006). This ability of CUS to model two poorly understood human phenomena, stress resilience and antidepressant resistance has inspired a series of microarray studies aimed at exploring the molecular signatures associated with these phenomena. Resistance to the antidepressant

effects of escitalopram, an SSRI, is associated with the upregulation of proapoptotic genes including APP (amyloid precursor protein) and TNF (tumor necrosis factor) in hippocampus, while vulnerability to CUS-induced anhedonia is associated with reduced expression of genes required for cellular proliferation and differentiation (Bergstrom et al. 2007). Similar experiments have been conducted in other brain regions including the amygdala and cingulate and frontal cortices (Orsetti et al. 2008; Sibille et al. 2009; Surget etal. 2009), each revealing unique region-specific molecular signatures associated with vulnerability to CUS.

At this stage, cellular heterogeneity represents a key limitation in the interpretation of these data: microarray studies performed on mixed samples of neuronal, glial, endothelial and immune cells are likely to result in poor reproducibility and low signal/noise ratio. Two important developments that are likely to address this problem are (1) laser capture microdissection techniques, which allow for precise isolation of limbic nuclei and subnuclei, and (2) mutant mice where subpopulations of neurons or other cell types are fluorescently labeled, allowing precise sorting of cells of interest through fluorescence-mediated techniques (Pollak et al. 2008; Sugino et al. 2006). As technological advances in DNA and protein array analysis allow for the rapid, reliable, and cost-effective genome-wide analysis of transcriptional regulation, these studies set the stage for an understanding of the complex gene network interactions involved in the pathophysiology of depression and antidepressant responsiveness.

**3.3.2 Psychosocial Stress Models—**One caveat with CUS is its questionable construct validity since certain routinely employed CUS stressors are physical (e.g., strobe lights, restraint or swim stress, or abrupt circadian disruptions) and are unlikely to be encountered by rats or mice in the wild. At least in this respect, models of psychosocial stress display their greatest strength since they entirely rely on innate social behavior. The central theme in these models (Fig. 3), whether they are conducted in rats, mice, or tree shrews, is to allow two or more subjects to socially and physically interact (an *agonistic* encounter) such that one achieves dominant status (*alpha*) and the others remain subordinate (*omega*). While some groups identify subordinates between age- and strain-matched pairs of mice or *dyads* (Avgustinovich et al. 2005; Malatynska and Knapp 2005), others employ a “forced subordination” strategy whereby reliably aggressive rodents (usually larger and/or of a more aggressive strain) are employed to consistently subordinate other subjects (Berton et al. 2006; Covington and Miczek 2005). In addition to the intense and unpredictable physical stress during social encounters, several laboratories add on the psychological stress of prolonged “sensory contact” through which subordinate mice are housed in the same cage as their dominant counterparts across a partition that prevents all but sensory interaction (Martinez et al. 1998). Following multiple defeat encounters, rodents display reduced social interaction, decreased exploration and locomotor behavior, anhedonia (e.g., decreased sucrose preference and sexual behavior), increased stress-induced immobility and alterations in HPA axis and autonomic function (Avgustinovich et al. 2005; Krishnan et al. 2007), many of which are reversed by chronic but not acute antidepressant administration (Becker et al. 2008; Rygula et al. 2008). Like CUS, the establishment and validation of such social stress models can be cumbersome and expensive. Reliable expression of aggressive behavior can be easily disrupted by minor procedural variations such as changes in bedding or cage size. In addition, laboratory personnel performing social defeat experiments must attain a sense for the correct “quantity” of aggressive behavior: while excessively injurious physical interactions are both unethical and irrelevant to the study of depression, weakly aggressive encounters pose the risk of producing mild and short-lived phenotypes that may affect molecular analyses.

The decreased sociability following such defeats can be quantifiably assessed with automated tests of social interaction that permit an assessment of individual differences among defeated mice. By combining this type of highly quantitative behavioral analysis with standard molecular and cellular techniques, this model has shed light on a number of mechanistic hypotheses related to variability in stress responsiveness. These include the role of activity-dependent BDNF (brain-derived neurotrophic factor) signaling within the mesolimbic dopamine circuit (Feder et al. 2009; Krishnan and Nestler 2008), endogenous kappa-opioid signaling (McLaughlin et al. 2006), the contribution of adult hippocampal neurogenesis (Lagace et al. 2010) and the role of peripherally derived mediators of energy homeostasis (Chuang et al. 2010). Such significant variability even among age-matched members of an inbred strain suggests that this heterogeneity occurs independently of DNA sequence variations. One possibility is that *epigenetic* modifications of the genome, which occur stochastically during development, may contribute to this variability seen among inbred mice raised in near identical environmental conditions. These epigenetic mechanisms include covalent modifications to histones (e.g., histone acetylation, methylation or phosphorylation) or DNA (e.g., DNA methylation) (Krishnan and Nestler 2008; Bountra et al. 2011).

Social defeat itself has a powerful impact on the epigenome: defeated mice display increases in repressive histone methylation in the hippocampus and nucleus accumbens (Tsankova et al. 2006) and increases in histone acetylation in the NAc (Covington et al. 2009). ChIP–chip techniques (chromatin immunoprecipitation combined with promoter array chips) have allowed for an appreciation of epigenetic profiles associated with the expression of susceptible or resilient behavior and antidepressant exposure (Wilkinson et al. 2009). This latter approach has illustrated a significant degree of overlap in patterns of epigenetic regulation between antidepressant-treated susceptible mice and vehicle-treated resilient mice, suggesting that certain individuals may avoid the deleterious effects of stress by naturally mounting an endogenous antidepressant-like response (Wilkinson et al. 2009). Furthermore, with the advent of pharmacological inhibitors of epigenetic enzymes such as histone deacetylase inhibitors (HDAC inhibitors; see Bountra et al. 2011), one can directly test epigenetic hypotheses in a more precise manner. For example, the antidepressant effects of systemically administered weakly selective HDAC inhibitors such as sodium butyrate and valproic acid (Gundersen and Blendy 2009; Schroeder et al. 2006; Tsankova et al. 2006) can be recapitulated by a localized infusion of more specific and selective drugs in the NAc (Covington et al. 2009). Similar strides have been made in understanding the behavioral impact of DNA methylation (LaPlant et al. 2010). Microarray analyses comparing the effects of systemic fluoxetine and localized HDAC inhibitor infusions reveal significant overlap in patterns of transcriptional activation and repression (Covington et al. 2009). On the other hand, genes influenced by HDAC inhibitors, and not by fluoxetine, may prove even more interesting in terms of identifying truly novel approaches for more effective antidepressant treatments.

Other forms of social stress are worth mentioning. Prolonged social isolation during adulthood results in reduced sucrose drinking and alterations in sexual reward behavior. While this model has received less recent attention, it displays excellent construct validity and requires minimal sophistication (Wallace et al. 2009; Wilkinson et al. 2009). Early life stress, typically applied in the form of maternal separation during early postnatal developmental periods, has been shown to result in cognitive and emotional changes that persist through adulthood. These phenotypes, such as altered HPA axis function, increased immobility, weakened prepulse inhibition, spatial learning deficits, etc., have been linked to a variety of neuropsychiatric syndromes with strong developmental hypotheses including schizophrenia (Fumagalli et al. 2007; Lupien et al. 2009). While studies in this field have traditionally almost exclusively emphasized the role of the HPA axis, more recent ventures

have demonstrated how maternal separation paradigms are quite aptly designed to study epigenetic forms of neuroplasticity (Murgatroyd et al. 2009) as well as mechanisms by which early life stress can in fact promote resiliency during adulthood (Lyons et al. 2009). Since social defeat models rely on differences in intermale aggression, they cannot be directly applied to females. However, females do display depression-like features following other social stressors such as intermittent crowding or isolation (Herzog et al. 2009). Given the twofold preponderance of depression in females, further studies of pathophysiological mechanisms in female rodent models are a very high priority for the field and these psychosocial stress models, in their ability to directly compare across sexes, are ideal candidates for such studies.

## 4 Insights from Models of Antidepressant Action

While the molecular targets of current antidepressant agents are known, there still remain large gaps in understanding their neuroanatomical sites of action and why these agents are associated with a significant therapeutic delay. Most of the current knowledge of these mechanisms has come from animal studies examining neurobiological changes following chronic antidepressant administration, voluntary exercise (through the exposure to a running wheel), or the application of ECT. More recent reports have exploited other strategies in rodents such as repetitive transcranial magnetic stimulation (rTMS) using a noninvasive cortical stimulating device (Vieyra-Reyes et al. 2008) as well as more creative cognitive paradigms such as *learned safety*, where a benign environmental stimulus that signals "safety" produces antidepressant-like effects (Pollak et al. 2008).

The most compelling and reproducible biological findings from these approaches are focused largely on the hippocampus, perhaps due to its well-understood anatomy. These studies have contributed to the development of neurotrophic model of depression, whereby stressful experiences through glucocorticoid signaling and other mechanisms reduce the level of neurotrophic factors such as BDNF in the hippocampus resulting in atrophic morphological changes. Antidepressants, by activating cellular signaling cascades that culminate in the activation of CREB (cyclic-AMP response element binding protein), function to enhance levels of BDNF and other growth factors like VEGF (vascular endothelial growth factor) and VGF (nonacronymic), which promote the proliferation and differentiation of hippocampal progenitors and alter monoaminergic synaptic transmission (Balu and Lucki 2009; Krishnan and Nestler 2008; Pittenger and Duman 2008). Other key molecular mediators have been identified, such as *p11*, a scaffolding protein induced by antidepressants that binds and enhances the surface expression and activity of the serotonin 1B (5-$HT_{1B}$) receptor, promoting an antidepressant-like response in laboratory assays (Svenningsson et al. 2006). p11 also enhances the activity of serotonin receptor type 4 (5-$HT_4$) (Warner-Schmidt et al. 2009), which is of particular significance since 5-$HT_4$ receptor agonists have rapid antidepressant-like activity. In the CUS model, while only 3–4 days of daily injections of RS67333 (a prototypical 5-$HT_4$ receptor agonist) alleviated the reduced sucrose intake in CUS-vulnerable rats: citalopram-treated controls required greater than 14 days of treatment to observe a significant improvement (Lucas et al. 2007). This study illustrates a key point related to pharmacological validity. Even though acute stress models are often criticized for their acute responses to antidepressants, efforts should nevertheless still be devoted to identifying novel agents that do not exhibit a therapeutic delay. The identification of such rapidly acting agents offers hope that antidepressants of the future will no longer be limited by their therapeutic delay. A clinically validated example of one such a rapidly acting agent is ketamine (aan het Rot et al. 2010), and recent preclinical experiments reveal that ketamine's antidepressant effects may be mediated through rapid forms of glutamatergic synaptic plasticity (Li et al. 2010).

The neurotrophic hypothesis described above is consistent with the observation that certain subpopulations of depressed patients display small reductions in total hippocampal volume with consequent ventricular enlargement (Savitz and Drevets 2009). Aside from these correlative data, there is little direct clinical evidence that alterations in hippocampal activity alter mood per se. Functional neuroimaging studies designed specifically to reveal the neuroanatomical substrates of altered emotional processing in depression have indicated roles for the amygdala and frontal cortical regions such as the subgenual cingulate cortex (area cg25), where the application of deep brain stimulation (DBS) produces long-lasting antidepressant effects in treatment-resistant depression (Mayberg 2009). Such profound effects of DBS applied to Cg25 or the NAc (Bewernick et al. 2010) constitute not only an important therapeutic development, but also provide unequivocal evidence regarding neural substrates that participate in improving mood symptoms. Of interest, patients in these studies were noted to have an immediate and intolerable worsening of depressive symptoms when DBS stimulators were turned off (Bewernick et al. 2010), illustrating how the antidepressant effects of nucleus accumbens DBS are profound and yet short-lived. In the future, we can expect refinements in stimulation parameters and localization of DBS thanks to rodent studies which have begun to explore the effects of DBS and optogenetic stimulation (a spatiotemporally precise technique that relies on light-mediated activation of cation or anion channels) on circuit-level neurophysiology and molecular mediators (Gradinaru et al. 2009; McCracken and Grace 2009; Temel et al. 2007). While this approach is still in its infancy, it promises to improve understanding of the dispersed neurocircuitry involved in complex psychiatric symptoms such as anhedonia and may offer insight into how DBS may one day be combined with pharmacological interventions to enhance antidepressant efficacy.

## 5 Conclusions

Sadly, in spite of almost 40 years of research into depression's mechanisms, the newest agents released on to markets today only vary from their predecessors in side-effect profile, with negligible improvements in efficacy. Therefore, in addition to combining pharmacotherapy with psychotherapy, clinicians are often forced to initiate multiple antidepressant medications simultaneously, or rely on adjunct medications like thyroid hormone, antipsychotic agents or psychostimulants to boost the antidepressant response, with each additional medication coming at the expense of new off-target effects. From the examples discussed above, there is a diverse array of useful animal models that can expand our understanding of mechanisms in depression. Rather than advocate for a single "best" model, investigators must realize the relative strengths and limitations of each paradigm and always aim to utilize tools that advance our understanding of the disease. While there are examples of "simple" tests that have provided key molecular insights (Berton et al. 2007; Svenningsson et al. 2006), there have been other instances when more "sophisticated" models have only provided behavioral minutiae (Avgustinovich et al. 2005). To increase the likelihood that these models will provide the next generation of effective antidepressants, the approach to the utilization of animal models must mature.

The overarching goal should be to narrow the gap between basic and clinical fields of investigation, and this can be executed at several different levels. Neuroplastic changes that reliably occur in rodents following stress or antidepressant exposures can be explored in human postmortem samples, with replications providing a further validation and increasing knowledge of biomarkers in depression. When examining genes of interest, instead of focusing on behavioral phenotypes in constitutive knockout mice, efforts should be focused on recapitulating human polymorphisms in those genes, understanding their cellular and physiological consequences and advancing models to tease out more subtle phenotypes. Moreover, given the significance of *gene* × *environment* interactions in the pathogenesis of

virtually all psychiatric disorders (Caspi and Moffitt 2006; see also Lesch 2011), we can gain insight into their neurobiological basis by recapitulating such interactions in animal models (Carola et al. 2008). Rather than emphasizing the more traditional "treatment versus control" approach, focusing on *individual differences* will increase the understanding of biological mechanisms underlying such variability, including a role for epigenetic mechanisms. Finally, while clinicians continue to refine novel experimental treatments for depression such as intravenous ketamine or DBS, basic scientists must complement their efforts by exploring the neurobiological mechanisms underlying those treatments; such *translational* approaches will further narrow the gap between human depression and the theoretical formulations of its mechanisms.

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## Abbreviations

| | |
|---|---|
| **5HT** | 5-Hydroxytryptamine or serotonin |
| **BDNF** | Brain-derived neurotrophic factor |
| **CRF** | Corticotropin-releasing factor |
| **CUS** | Chronic unpredictable stress |
| **DBS** | Deep brain stimulation |
| **DNA** | Deoxyribonucleic acid |
| **ECT** | Electroconvulsive therapy |
| **FST** | Forced swim test |
| **GR** | Glucocorticoid receptor |
| **HPA** | Hypothalamic–pituitary–adrenal |
| **KO** | Knockout |
| **LH** | Learned helplessness |
| **SERT** | Serotonin transporter TST Tail suspension test |

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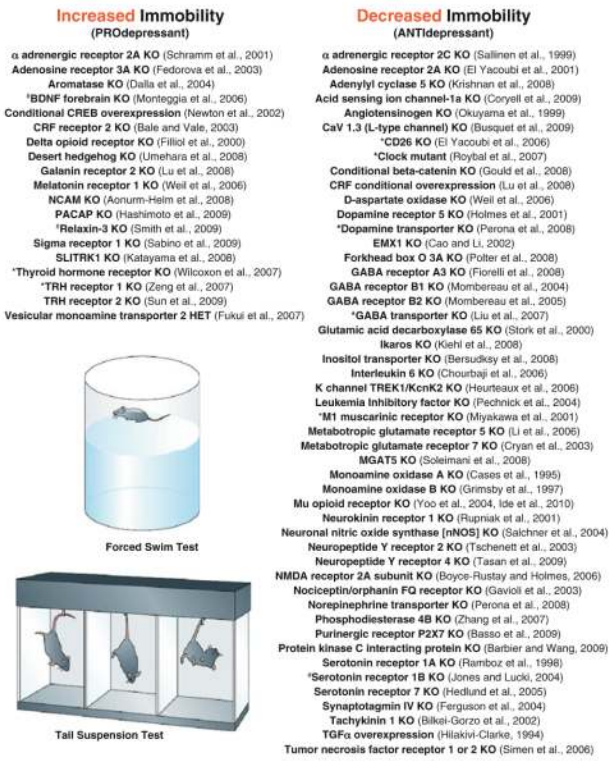


**Fig. 1.**

The forced swim test (FST) and tail suspension test (TST) have been utilized to phenotype a large number of genetically manipulated mice, illustrating the sheer diversity of genes and pathways potentially involved in depression-related behavior. Knockout mice ("KO"), transgenic overexpressors or other types of mutants have been segregated into those that display increased immobility in *either* the FST or TST ("pro-depressant"), or reduced immobility (antidepressant-like). *Hash* indicates gender differences in the phenotype; *asterisk* indicates that results may be confounded by locomotor behavior. Shown are examples of genetic mutant mice examined to date; studies utilizing virally mediated gene transfer are not included. Abbreviations: *HET* heterozygote; *BDNF* brain-derived neurotrophic factor; *TRH* thyrotropin-releasing hormone; *CREB* cyclic adenosine monophosphate response element binding protein; *CRF* corticotropin-releasing factor; *NCAM* neuronal cell adhesion molecule; *PACAP* pituitary adenylyl cyclase activating peptide; *SLITRK* slit and NTRK-like family member 1; *GABA* gamma aminobutyric acid; *NMDA N*-methyl D aspartate; *TGF* transforming growth factor; *EMX* empty spiracles homolog; *MGAT* mannosyl glycoprotein acetylglucosaminyl transferase. Images obtained from Cryan and Holmes (2005)

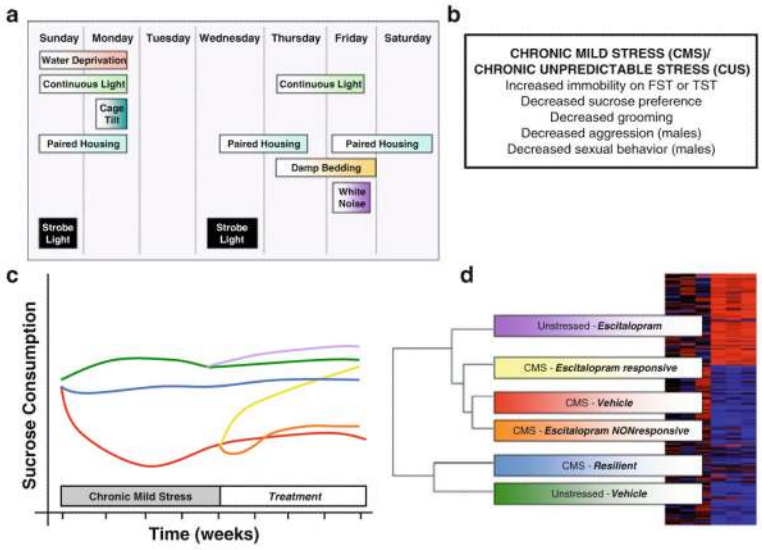


**Fig. 2.**

The chronic mild stress (CMS)/chronic unpredictable stress (CUS) model of depression relies on a series of mostly physical stresses that are presented over 1–6 weeks (Willner 2005). (**a**) One example of a rat CUS protocol (Grippo 2009). (**b**) CUS paradigms in rats and mice produce a variety of behavioral changes. (**c**, **d**) The most popular assay for the effects of CUS is sucrose preference or sucrose intake whereby reductions in the consumption of a palatable sweet solution are interpreted as anhedonia. CUS has been applied to the study of stress resilience (CUS-resilient mice do not display a reduction in sucrose intake) and antidepressant resistance (escitalopram treated mice do not recover impairments in sucrose drinking). The key for the *colored lines* is provided in *Panel d*. DNA microarray technology combined with gene expression cluster analysis can aid in correlating behavioral groups with their gene expression patterns. For example, in this study examining total hippocampal tissue, genes modulated in CUS-resilient and vehicle-treated unstressed control rats were strongly overlapping, and these gene expression patterns were quite *distant* from unstressed rats treated with escitalopram (Bergstrom et al. 2007)

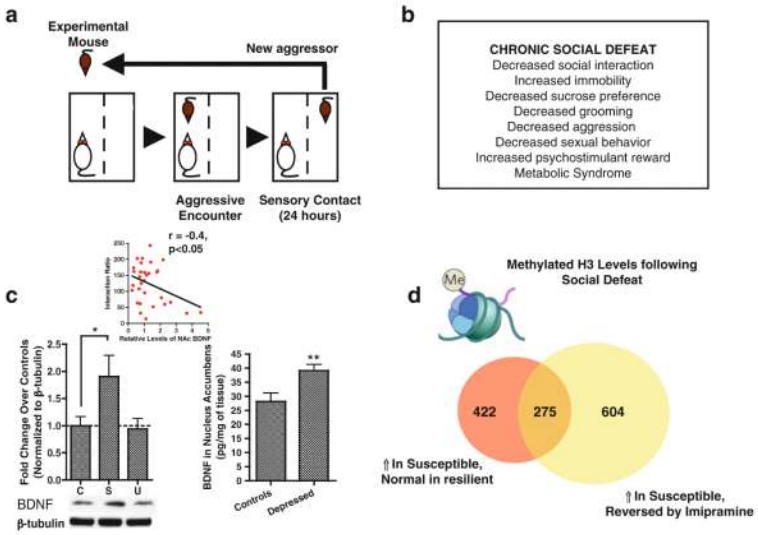


**Fig. 3.**

Psychosocial stress models rely on innate social behavior among pairs or groups of male rodents allowing for the formation of stable dominant/subordinate relationships. (**a**) In the sensory contact adaptation of rodent social defeat, an intruder is periodically subordinated by a territorially aggressive resident mouse and is forced to spend the remainder of the day across a partition that permits sensory contact without fighting. (**b**) The main behavioral consequences of repeated bouts of such social subordination. (**c**) Aside from face, construct, and pharmacological validity, one can further validate animal models by demonstrating the presence of identical molecular changes in human postmortem tissue. Here, 10 days of social defeat in C57Bl/6 mice increases BDNF protein levels (by immunoblot) in the nucleus accumbens such that vulnerable or susceptible mice (S) display the greatest increases in BDNF (*C* controls, *U* unsusceptible), with the inset demonstrating a significant inverse correlation between interaction scores and BDNF levels. This molecular change is also observed in postmortem accumbens samples from male depressed individuals (Krishnan et al. 2007). (**d**) ChIP–chip analyses (chromatin immunoprecipitation followed by DNA promoter arrays) examining genome-wide patterns of a repressive form of histone H3 methylation in the nucleus accumbens. The region of Venn overlap (“275”) corresponds to 275 genes that are upregulated in susceptible animals and that are also reversed by imipramine and not seen in resilient animals (Wilkinson et al. 2009). Some examples of genes that fall within this overlap include CNK1D (casein kinase 1 delta), FGF1 (fibroblast growth factor 1) and HDAC4 (histone deacetylase 4). These results suggest that inhibiting the stress-induced histone methylation at these genes through inhibitors of histone methyltransferases constitutes a potential novel target for antidepressant development