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Antidepressant effects of ketamine on depression-related phenotypes and dopamine dysfunction in rodent models of stress

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Abstract

Depression, the most prevalent psychiatric disorder, is characterized by increased negative affect (i.e. depressed mood) and reduced positive affect (i.e. anhedonia). Stress is a risk factor for depression in humans, and animal models of chronic stress are typically used to study neurobehavioral alterations relevant to depression. Common behavioral outcomes in rodent models of chronic stress include anhedonia, social dysfunction and behavioral despair. For example, chronically stressed rodents exhibit reduced reward preference, as measured by a loss of preference for sucrose solutions and time spent interacting with a novel conspecific, while also exhibiting less time struggling against inescapable stressors (e.g. forced swim, tail suspension). In both humans and rodents, anhedonia is associated with dysfunction of the dopamine (DA) system. Unlike traditional antidepressants, which are limited by inadequate efficacy and delayed therapeutic response, acute ketamine administration rapidly alleviates depressive symptoms in humans and reverses stress-induced changes in animal models. These effects are partially mediated via actions on the DA system. This review summarizes the clinical effects of ketamine, the neurobiological underpinnings of depression with a focus on DA dysfunction, as well as antidepressant effects of ketamine on depression-related endophenotypes (i.e. anhedonia, despair) and ventral tegmental area (VTA) activity in rodent models of repeated stress. Moreover, we discuss evidence regarding sex differences in ketamine's antidepressant effects, wherein females appear to be more sensitive to lower dose ketamine, as well as novel findings suggesting that ketamine has prophylactic effects with regard to protection against the neurobehavioral impact of future stressors.

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Keywords

stress; animal models; depression; anhedonia; dopamine; ketamine

Introduction

Major depressive disorder (MDD), also referred to as depression in this review, is the most prevalent psychiatric disorder and one of leading causes of disability worldwide (Collins et al., 2011; Fava and Kendler, 2000; Otte et al., 2016; WHO, 2017). In the United States, the lifetime prevalence of depression is estimated to be ~17–20% (Kessler et al., 2005).

Although depression is characterized by changes in mood (i.e. increase in negative affect, decrease in positive affect) (Gross and Munoz, 1995; Hofmann et al., 2012; Nutt et al., 2007), it is a symptomatically heterogeneous disease spanning cognitive, emotional, motivational and physiological domains and, as such, it is particularly difficult to treat (Otte et al., 2016). First line pharmacotherapies for depression, such as serotonin reuptake inhibitors (SSRIs), target monoaminergic systems but are limited by low response rate (e.g. ~40–60% of patients fail to achieve remission) and slow onset of therapeutic effects in the patients that do respond, in that weeks or even months of treatment are required (Akil et al., 2018; Gaynes et al., 2009; Katz et al., 2004). This delay is particularly concerning given the elevated suicide risk in depressed individuals (Henriksson et al., 1993), and underscores a need for fast-acting antidepressants.

In contrast with the delayed therapeutic effects of existing antidepressants, ketamine rapidly improves depressive symptoms (Berman et al., 2000) and suicidal ideation in depressed individuals (DiazGranados et al., 2010; Price et al., 2009). It is particularly effective in those exhibiting treatment resistant depression (TRD) (Covvey et al., 2012; Zarate et al., 2006), which refers to an inadequate response to at least two different antidepressants administered at adequate doses and duration (Akil et al., 2018). Indeed, clinical studies have shown that a single low-dose ketamine infusion produces rapid antidepressant effects that last up to 7 days (Berman et al., 2000; Zarate et al., 2006), and these findings have been replicated many times (Coyle and Laws, 2015). Importantly, similar antidepressant effects have been observed in animal models of chronic stress, which are used to model depression-like physiological and behavioral changes in rodents and include changes in dopaminergic pathways within the brain's reward system (Belujon and Grace, 2017; Slattery and Cryan, 2017). The ability of ketamine to reverse the effects of stress exposure, and even produce prophylactic effects in certain stress models, provides reverse-translational support for initial clinical results (Hare et al., 2017).

In this review, we provide an overview of mechanisms underlying ketamine's antidepressant actions in humans and animal models of chronic or repeated stress. We focus on animal models of stress due to the known link between stress exposure and depression in the clinical literature (Hammen, 2005; Kendler et al., 1999; Lloyd, 1980), but also because repeated stress has significant adverse consequences on the mesolimbic dopamine (DA) system (Pani et al., 2000), which originates in the ventral tegmental area (VTA) and projects to the prefrontal cortex (PFC) and nucleus accumbens (NAc), among other areas (Ikemoto,

2007). Indeed, stress exposure increases glucocorticoid signaling via elevated corticosterone (CORT) secretion (Holsboer, 2001) to precipitate neuronal degeneration and dysfunction in the hippocampus (Conrad, 2008; Sapolsky, 2000) and medial PFC (Arnsten, 2009; McEwen and Morrison, 2013). These effects have direct influence on DA function, as glucocorticoids modulate firing of DA neurons (Belujon and Grace, 2015), and stress-sensitive regions that suffer glucocorticoid-mediated atrophy (i.e. hippocampus, PFC) (McEwen, 2004) are key regulators of mesolimbic and mesocortical dopaminergic pathways (Belujon and Grace, 2015; Grace et al., 2007). Thus, we review findings indicating that 1) MDD and chronic stress models are associated with compromised DA function, and 2) manipulations of the DA system, particularly VTA DA neuron activity, contribute to the antidepressant actions of ketamine.

Ketamine as a fast-acting antidepressant

Ketamine is a non-competitive antagonist acting at the NMDA glutamate receptor. Although ketamine has been used extensively in anesthesia and pain management (Kurdi et al., 2014), it shows great promise for its antidepressant effects (DeWilde et al., 2015). During the past 20 years, numerous clinical trials have provided strong evidence that a single sub-anesthetic dose of ketamine rapidly and robustly alleviates depressive symptoms in MDD patients (Berman et al., 2000; Coyle and Laws, 2015; Kraus et al., 2017; Murrough et al., 2013a; Phillips et al., 2019; Zarate et al., 2006). Unlike classic antidepressants whose therapeutic effects take weeks to be observed, an acute intravenous (i.v.) injection of ketamine is sufficient to induce quick and long-lasting antidepressant effects. The first clinical study to assess the antidepressant effects of ketamine reported that a low-dose ketamine infusion (0.5mg/kg, i.v.) significantly reduced depressive symptoms in MDD patients within 3 days compared with those that received saline placebo (Berman et al., 2000). A subsequent trial demonstrated that a single low-dose ketamine infusion (0.5mg/kg, i.v.) produced rapid and robust antidepressant effects in treatment-resistant MDD patients, with onset of effects occurring within 2 hours and lasting up to 1 week in a subset of patients (Zarate et al., 2006). Ketamine's fast-acting effects are ideal for providing relief for MDD patients at risk for suicide, as ketamine infusions quickly decrease suicidal ideation in MDD patients within 24 hours (DiazGranados et al., 2010; Price et al., 2009). Moreover, repeated injections have been shown to induce sustained antidepressant effects with mild side effects in treatment-resistant MDD patients (aan het Rot et al., 2010; Murrough et al., 2013b; Phillips et al., 2019; Zheng et al., 2019).

The rapid and robust antidepressant-like effects of ketamine have been replicated in preclinical studies using rodent models relevant to depression, which have enabled researchers to unravel ketamine's mechanisms of action (Browne and Lucki, 2013; Scheuing et al., 2015). In a pivotal study, researchers demonstrated that low dose ketamine injection [10mg/kg, intraperitoneal (i.p.)] rapidly and transiently activates the mammalian target of rapamycin (mTOR) signaling pathway, leading to increased synaptic signaling proteins (e.g. PSD-95, GluR1, and synapsin) and increased number and function of new spine synapses in the medial prefrontal cortex (mPFC) of male rats (Li et al., 2010). Moreover, blockade of mTOR signaling completely prevented ketamine-induced synaptogenesis and behavioral responses in animal models and assays of depressive-like behavior [e.g. forced swim test

(FST), learned helplessness (LH)], indicating that the antidepressant effects on synapses and behavior require mTOR signaling (Li et al., 2010). These findings suggested that the effects of ketamine were opposite to the synaptic deficits resulting from stress exposure and could contribute to the antidepressant actions of ketamine. Indeed, a later study found that rats exposed to 21 days of chronic unpredictable stress exhibited anhedonia (i.e. reduced sucrose preference) and increased anxiety-like behavior (i.e. latency to feed) in the novelty suppressed feeding test, which was associated with decreased expression of synaptic proteins (e.g. PSD-95, GluR1, and synapsin) and reduced spine number within the mPFC; all of which were reversed by ketamine treatment in an mTOR-dependent manner (Li et al., 2011). Furthermore, a causal role for spine formation within the mPFC has recently been demonstrated for the sustained, but not acute, antidepressant effects of ketamine following chronic stress (Moda-Sava et al., 2019). Using two-photon imaging, researchers demonstrated that acute ketamine treatment (10mg/kg, i.p.) reversed branch-specific elimination of dendritic spines via restoration of lost spines in the PFC in stressed animals.

Besides mTOR activation and sustained mPFC spine formation, another mechanism for ketamine's antidepressant effects involves the production and release of brain derived neurotrophic factor (BDNF), which is essential for neuron development, survival and synaptic plasticity, and has been implicated in depression and antidepressant action (Autry and Monteggia, 2012; Duman and Monteggia, 2006). Specifically, ketamine-mediated NMDA receptor blockade deactivates eukaryotic elongation factor 2 (eEF2) kinase (also known as CaMKIII), resulting in reduced eEF2 phosphorylation, de-suppression of translation of BDNF and enhanced BDNF expression within the hippocampus (Autry et al., 2011; Monteggia et al., 2013). Importantly, increased BDNF production and release is required for ketamine's antidepressant action, as demonstrated by the lack of antidepressant-like response to ketamine in BDNF knockout mice (Autry et al., 2011). Additionally, a subsequent study has proposed that ketamine can also increase BDNF signaling via post-synaptic AMPA receptor stimulation, resulting in cell depolarization and activation of L-type voltage-dependent calcium channels, thereby allowing for calcium influx and resultant activity-dependent exocytosis of BDNF (Lepack et al., 2014).

Another mechanism involves a protein called glycogen synthase kinase-3 (GSK3), a master switch serine-threonine kinase implicated in MDD (Beurel et al., 2015; Li and Jope, 2010), the inhibition of which is necessary for ketamine's therapeutic effects (Beurel et al., 2011). Administration of low dose ketamine (10mg/kg; i.p.) quickly inhibits GSK3 within the hippocampus and PFC of mice, and inhibition of GSK3 was shown to be necessary for the rapid antidepressant-like effect of ketamine in mice following learned helplessness (Beurel et al., 2011). Mice expressing constitutively active GSK3, meaning GSK3 knock-in mice in which GSK3 could not be inhibited, were resistant to the antidepressant like effect of ketamine. Furthermore, administering an acute high dose of a GSK3 inhibitor (i.e. lithium) produced antidepressant effects comparable to ketamine (Beurel et al., 2011). These data demonstrated that the rapid antidepressant effect of ketamine in helpless rats requires inhibition of GSK3 and can be mimicked by lithium administration.

In sum, the cellular mechanisms underlying the rapid antidepressant-like effects of ketamine administration include: i) activation of mTOR in the mPFC ii) increased BDNF production

and release, iii) inhibition of GSK3, among others (Hare et al., 2017; Scheuing et al., 2015). However, systems-level mechanisms appear more complex. Over the past 5 years, the antidepressant effects of ketamine have been linked to adaptations within the brain's reward system (i.e. mesolimbic DA system) in humans, non-human primates and rodents, and these dopaminergic effects are thought to contribute to its antidepressant effects (Kokkinou et al., 2018). Indeed, acute ketamine administration leads to DA release in the brain and increases DA levels in the striatum, nucleus accumbens and the prefrontal cortex and produces approximately 62–180% increases in DA neuron activity in chronically stressed rodents (Kokkinou et al., 2018). Thus, in this review we focus on stress and ketamine effects on the mesolimbic DA system, particularly the ventral tegmental area (VTA), in animal models of depression-related symptomatology.

Dopamine deficits in in depression: Evidence from clinical and preclinical studies

Humans.

Deficits in reward and motivation are common symptoms present in several psychiatric disorders, including depression (Admon and Pizzagalli, 2015; Der-Avakian et al., 2016; Lambert et al., 2018). Anhedonia, diminished pleasure and/or decreased reactivity to normally rewarding (i.e. pleasurable) stimuli, is one of the core symptoms in depression (Klein, 1974; Lewinsohn and Graf, 1973; Treadway and Zald, 2011). Importantly, anhedonia encompasses deficits in other complex reward and motivational processes and may include impairments in anticipatory pleasure, reward valuation, reward learning, as well as motivation and effort expenditure (i.e. willingness to work for rewards) (Der-Avakian et al., 2016; Treadway et al., 2012; Treadway and Zald, 2011). In humans, depression has been associated with abnormally reduced positive affect, reward processing, approach behavior and effort-based motivation (Admon and Pizzagalli, 2015; Pizzagalli et al., 2008; Treadway et al., 2012). For example, in the effort expenditure for rewards task (EEfRT), which involves offering subjects a series of trials where they may choose to expend more or less effort (e.g. number of button presses) for the opportunity to win varying amounts of monetary rewards, MDD patients were less willing to expend effort for rewards than controls (i.e. reduced effort expenditure), and were also less able to effectively use information about magnitude and probability of reward to guide their choice behavior (i.e. impaired reward-based decision-making) (Yang et al., 2014).

Although anhedonia is comprised of distinct processes involving different neural circuits, most involve dysfunction within the brain's reward system (Berridge and Kringelbach, 2015; Der-Avakian and Markou, 2012). Indeed, altered reward function is theorized to underlie the loss of pleasure and amotivational syndrome experienced by many MDD patients (Alloy et al., 2016; Martin-Soelch, 2009), and human functional imaging and postmortem tissue studies have identified abnormalities in several brain regions, including nuclei within the brain's reward pathway (Drevets, 2001; Manji et al., 2001; Price and Drevets, 2012; Whitton et al., 2015), which have been recapitulated in rodents (Belujon and Grace, 2017; Fox and Lobo, 2019; Russo and Nestler, 2013). Thus, both anhedonia and depression are linked to dysfunctions in the brain's reward system and, in particular, the mesolimbic DA system

(Belujon and Grace, 2017; Der-Avakian and Markou, 2012; Heshmati and Russo, 2015; Kapur and Mann, 1992; Naranjo et al., 2001; Yadid and Friedman, 2008). Initial data supporting a role for central DA dysfunction in depression came from studies of DA turnover, in which it was observed that MDD patients have decreased cerebrospinal fluid levels of homovanillic acid (HVA)- the primary metabolite of DA- thereby suggesting lowered basal dopaminergic tone in depression (Berger et al., 1980; Lambert et al., 2000; Willner, 1983). Moreover, in depressed patients with anhedonia, PET imaging studies have shown significantly lower DA transporter (DAT) binding compared with healthy subjects, suggesting a downregulation secondary to lower DA concentrations (Meyer et al., 2001; Sarchiapone et al., 2006). Additionally, pharmacological interventions that block or deplete DA can induce or deepen depressive symptoms in currently depressed or remitted individuals (Hasler et al., 2008; Ruhe et al., 2007) and drugs that enhance signaling can have antidepressant effects in depressed patients (Argyropoulos and Nutt, 2013; Treadway and Zald, 2011), further implicating DA dysfunction in MDD. Furthermore, functional neuroimaging studies have documented reduced ventral striatal activation in MDD patients to reward anticipation cues (Forbes et al., 2009; Smoski et al., 2009), reward receipt (McCabe et al., 2009; Pizzagalli et al., 2009), and reward prediction errors (i.e., the difference between experienced versus predicted rewards) (Kumar et al., 2008; Steele et al., 2007; Uhl et al., 2015). Taken together, these data indicate blunted reward-related signaling in MDD patients. Given that reward-related DA signaling is necessary for the attribution of incentive salience to motivational stimuli (Berridge and Robinson, 1998), downregulation of the reward system is thought to drive decreased motivation and goal-related cognitions, increased withdrawal, as well as emotions such as sadness or anhedonia (Alloy et al., 2016; Argyropoulos and Nutt, 2013), which is consistent with disruption of motivation to seek out pleasurable experiences described in MDD patients (Sherdell et al., 2012). This is significant because anhedonia is thought to contribute to the persistence of treatment-resistant depression, since the presence of anhedonic symptoms (i.e. blunted reward learning) is generally a predictor of poor antidepressant treatment response (Spijker et al., 2001; Vrieze et al., 2013), but is also a particularly difficult symptom to treat, as many first line pharmacotherapies (e.g. SSRIs) do not adequately address motivational and reward processing deficits in depression (Treadway and Zald, 2011). In fact, a study conducted in adults with remitted MDD found that they exhibited blunted reward responsiveness, indexed by an inability to modulate behavior as a function of reinforcement history compared with controls, suggesting that alterations of reward function may persist after remission and represent a trait-related abnormality in MDD (Pechtel et al., 2013).

Rodents.

Alterations in reward and mesolimbic DA system function have been a common finding in animal models for the study of depression (Douma and de Kloet, 2019; Fox and Lobo, 2019; Kaufling, 2019). Most of these models (3 of which will be discussed in the section below) involve some form of chronic stress, since repeated stress is one of the most important factors for precipitating depression in humans (Kendler et al., 1999; Lloyd, 1980). Rodents exposed to chronic stress typically exhibit anhedonia and other behavioral abnormalities relevant to depression, including behavioral despair and/or passive coping behaviors (Scheggi et al., 2018; Slattery and Cryan, 2017). In animals, common measures of

anhedonia include the sucrose consumption and sucrose preference tests (Willner et al., 1987). Briefly, these tests involve measuring the consumption of a palatable sucrose solution during or after exposure to an anhedonia-producing event (i.e. stress) and the preference for a sucrose solution when given a choice between this highly palatable solution and water, respectively. Exposure to various forms of stress decreases sucrose preference in rodents (Katz, 1982; Monleon et al., 1995; Slattery and Cryan, 2017), although the reliability of the sucrose preference test as a measure of anhedonia in animals is subject to controversy (Forbes et al., 1996; Matthews et al., 1995; Weiss, 1997). Nonetheless, decreased consumption or no preference for the sucrose solution over water is thought to reflect anhedonia (Scheggi et al., 2018). Other measures of anhedonia in rodents include elevations in reward thresholds using intracranial self-stimulation (ICSS) and reduced time interacting with a novel conspecific, both of which are thought to reflect hypofunction of mesocorticolimbic reward systems (Carlezon and Chartoff, 2007; Scheggi et al., 2018; Zacharko and Anisman, 1991). Stressed animals also exhibit less time struggling against inescapable stressors such as the FST or tail suspension test (Scheggi et al., 2018; Slattery and Cryan, 2017), which is thought to reflect behavioral despair, and more recently, passive coping (Molendijk and de Kloet, 2019).

In a landmark study, Tye and colleagues revealed a causal role for VTA DA neurons in both the induction of depressive-like symptoms in non-stressed mice and in the alleviation of these symptoms in CMS-exposed mice (Tye et al., 2013). Using optogenetic tools, the authors demonstrated that acute photoinhibition of VTA DA neurons induced a depressive-like state in mice with respect to reduced escape behavior in the tail suspension test and decreased sucrose preference. These depressive-like behaviors were also observed in CMS-exposed mice. Phasic photoactivation of VTA DA neurons in CMS-exposed mice rescued stress-induced behavioral deficits and normalized escape-related behavior and sucrose preference to levels comparable to nonstressed (i.e. control) mice (Tye et al., 2013). Moreover, photoactivation of ChR2-expressing VTA DA neurons increased active escape-related behaviors (i.e. kicks) during the FST in CMS-exposed TH:Cre rats and this behavior was not time-locked to light pulses on the order of seconds, suggesting that it may be modulated by dopaminergic tone rather than driven by individual DA transients. Taken together, these data show bidirectional effects of VTA DA neuron activity on the rapid induction and alleviation of depression-related behaviors in which selective inhibition of VTA DA neurons produces depression-related behavior in measures of both motivation and anhedonia, and acute phasic activation of VTA DA neurons rescues CMS-induced depression-like phenotypes.

Importantly, the effects of stress on the mesolimbic DA system are complex, as different stressors can cause opposite responses from VTA DA neurons depending on pre-exposure, stressor type, timing and severity (Douma and de Kloet, 2019; Fox and Lobo, 2019; Holly and Miczek, 2016; Kaufling, 2019; Valenti et al., 2012). Moreover, the role of DA differs in the induction versus the expression of depression-related behaviors, and the duration of the stressor affects the magnitude and duration of the negative affective state associated with its withdrawal (Grace, 2016; Koob and Le Moal, 2008). For example, acute restraint stress potently activates the DA system (i.e. increases VTA DA neuron population activity) as measured by *in vivo* extracellular recordings conducted shortly after stress exposure (Valenti

et al., 2011). In contrast, 24-hours after restraint stress there is a shift in the opposite direction (i.e. a reduction in DA neuron population activity), as measured using the same *in vivo* technique (Chang and Grace, 2013). Thus, acute activation of the DA system by stress induced VTA DA neuron activation is followed by an attenuation VTA DA neuron activity, as measured by reduced numbers of active DA cells per track. Specifically, our group has also shown that if the stressor is presented over a longer period of time (e.g. chronic cold stress, 4-week CMS paradigm), the consequent depressive-like state and VTA DA neuron attenuation is also maintained for an extended period (i.e. up to 1-week) after removal of the stressor (Chang and Grace, 2014; Moore et al., 2001; Moreines et al., 2017; Rincon-Cortes and Grace, 2017; Valenti et al., 2012). Thus, we propose that the initial increase in DA observed during and immediately after stress drives downstream plasticity, ultimately resulting in depressive-like states (Grace, 2016). This framework is consistent with findings from other studies in rodent models of chronic stress showing that: i) increasing DA neuron activity during a subthreshold chronic social defeat stress (CSDS) paradigm was necessary for the induction of the depressive-like phenotype that followed (Chaudhury et al., 2013), ii) phasic activation of VTA DA neurons drove recovery from the depressive-like phenotype resulting from CMS exposure (Tye et al., 2013), and iii) activation of DA neurons long after CSDS exposure has antidepressant effects (Friedman et al., 2014), suggesting that VTA hypoactivity may be present in this model as well. Consistent with these data, a study assessing c-Fos expression of VTA DA neurons and DA turnover in the mPFC of wild-type mice showed activation of the mesocortical DA pathway in response to social defeat, and attenuation within this pathway following repeated social defeat in wild-type mice (Tanaka et al., 2012). Within the context of these findings, we propose that the initial stress-induced activation of VTA DA neurons leads to the compensatory long-duration downregulation of DA neuron population activity after stressor withdrawal, which is supported by *in vivo* electrophysiological findings from our lab showing DA hypofunction in two different animal models relevant to depression (Belujon and Grace, 2014; Chang and Grace, 2014). Finally, we would like to acknowledge that several studies have reported an increase in VTA DA neuron firing rates in CSDS-exposed mice, which lasts up to 2 weeks in susceptible mice and appear to be specific to CSDS exposure (Cao et al., 2010; Krishnan et al., 2007). However, we will not be focusing on this literature because the primary measure of VTA DA neuron activity (i.e. population activity) used by our group in CMS and LH rats has never been assessed in mice exposed to CSDS and the effects of ketamine on VTA DA neuron activity following CSDS have not been examined.

Effects of ketamine on depression-related behavior and mesolimbic DA activity in animal models of repeated/chronic stress

Animal models of psychiatric disorders are procedures applied to laboratory animals which produce behavioral changes that are thought to be homologous to aspects of psychiatric disorders and can therefore be used as experimental tools to further the understanding of human psychopathology (Willner, 2015). Ideally, an animal model will have construct, face and predictive validity. This means that an animal model should: a) recreate some process, environmental risk factor or agent that causes disease in humans, which replicates neural and behavioral features of the illness (i.e. construct validity); b) recapitulate important

anatomical, biochemical or behavioral features of a human disease (i.e. face validity); and c) respond to treatment in a way that predicts the effects of those treatments in humans (i.e. predictive or pharmacological validity) (Nestler and Hyman, 2010; Willner, 2015). For example, since stress exposure is a risk factor for depression in humans (Kendler et al., 1999; Lloyd, 1980), rodent models of repeated or chronic stress exposure are commonly used to produce behavioral and physiological abnormalities in rodents, including cellular, molecular and morphological changes within stress-sensitive brain regions that resemble those observed in clinical depression (Hare et al., 2017; Slattery and Cryan, 2017). Importantly, many of these stress-associated neurobehavioral changes can be rescued via treatment with traditional antidepressants, but also with fast-acting antidepressants such as ketamine. Below, we discuss stress-induced alterations in depression-related phenotypes with a focus on anhedonia and behavioral despair, which reflect alterations in positive and negative affect, respectively, in rodent models of repeated and/or chronic stress as well as their modulation by ketamine administration.

Chronic Mild Stress (CMS).

CMS is one of the most widely employed animal models used to study stress-induced neurobehavioral adaptations relevant to depression and consists of exposing rodents to a series of mild, repeated and unpredictable stressors (e.g. isolation, water and food deprivation, cage and light cycle disturbances, etc.) over a prolonged period of time (4–6 weeks) (Hill et al., 2012; Willner, 2017). This procedure has been shown to induce anhedonia, or a decreased response to various types of rewards in rodents, suggesting alterations in DA function (Scheggi et al., 2018; Willner et al., 1992). For example, mice and rats exposed to CMS exhibit reduced sucrose consumption and preference, attenuation of conditioned place preference, decreased sexual activity, and increased thresholds for ICSS in the VTA (D'Aquila et al., 1994; Gronli et al., 2005; Li et al., 2011; Monleon et al., 1995; Moreau et al., 1992; Papp et al., 1991; Tye et al., 2013; Willner et al., 1987). CMS also induces depression-related phenotypes (i.e. increased immobility, reduced latency to immobility) in rodent measures of behavioral despair, such as the FST and the TST (Chang and Grace, 2014; Moreines et al., 2017; Rincon-Cortes and Grace, 2017; Tye et al., 2013). Thus, CMS precipitates an anhedonic-like state associated with decreased reward responsiveness and increased behavioral despair, which may also be interpreted as passive coping. Importantly, in vivo electrophysiological studies conducted in CMS-exposed rats have consistently reported a decrease in VTA DA neuron activity that coexists with anhedonic and depressive-like states (Chang and Grace, 2014; Moreines et al., 2017; Rincon-Cortes and Grace, 2017) and is driven by increased activity within the basolateral amygdala (BLA)-ventral pallidal (VP) pathway (Chang and Grace, 2014). Moreover, this attenuation is restricted to the medial VTA DA neurons which project preferentially to the reward-related ventromedial striatum (Moreines et al., 2017). The dopamine deficit observed in CMS-exposed rats appears to be largely conserved in mice: CMS-exposed mice exhibit a decrease in the proportion of active DA neurons, but also in firing rate (Liu et al., 2018; Tye et al., 2013; Zhong et al., 2018).

Acute ketamine (10–15mg/kg; i.p.) treatment reverses the CMS-induced decreases in sucrose consumption in mice and rats (Garcia et al., 2009; Li et al., 2011). Moreover,

systemic ketamine administration (10mg/kg) also reverses depressive-like behavior following CMS, as CMS rats of both sexes treated with ketamine exhibited reduced FST immobility and increased latencies to immobility (Rincon-Cortes and Grace, 2017). Ketamine also restored VTA population activity in CMS animals: CMS rats treated with ketamine exhibited greater numbers of active VTA DA cells compared with vehicle-treated CMS rats (Rincon-Cortes and Grace, 2017). Furthermore, the effects of ketamine on VTA population activity persisted between 2–7 days post-injection, indicating that ketamine induces a sustained increase in VTA population activity in male and female rats following CMS. Collectively, these data suggest that ketamine effects on CMS-induced depression-related phenotypes (i.e. anhedonia, despair) are likely mediated via long-lasting actions on the DA system.

Learned Helplessness (LH).

In this paradigm, rats are exposed to an inescapable stressor (i.e. shock) on day 1 in one chamber of a two-chamber shuttle box with the escape route blocked, and tested for active avoidance (i.e. escaping the shock by crossing to the other chamber) on the next consecutive days with the escape route open (Seligman and Beagley, 1975; Wagner et al., 1977). Failures to escape and the latency to escape are used to discriminate between nonhelpless and helpless rats: helpless rats typically exhibit a deficit in escape behavior, as indexed by increased number of failures to escape and longer latencies to escape compared with nonhelpless rats (Koike et al., 2011). Helpless rats also exhibit hyposensitivity to rewarding events, such as a reduced preference for sucrose (Sanchis-Segura et al., 2005), suggesting alterations in DA system function. Indeed, DA activity is different in helpless versus nonhelpless rats. A recent electrophysiological study conducted in Wistar-Kyoto rats found that rats exposed to the learned helplessness paradigm fell into two groups despite identical treatment: those showing helpless behavior and those showing normal escape. The nonhelpless rats had numbers of spontaneously active DA neurons (i.e. population activity) that were comparable to no-shock controls (Belujon and Grace, 2014). However, rats that exhibited helpless behavior showed a significant reduction in the number of active DA neurons within the VTA (Belujon and Grace, 2014). Thus, in helpless animals, a decrease in the number of spontaneously active DA neurons in learned helplessness is consistent with a decrease in VTA activity driving stress-induced depressive-like behavior following CMS exposure (Grace, 2016; Tye et al., 2013).

Injection (5–10mg/kg) of repeated or acute ketamine restored escape behavior in helpless rats, in that the rats had fewer escape failures and exhibited faster latencies to escape compared with vehicle-treated helpless rats (Belujon and Grace, 2014; Koike et al., 2011). This is in accordance with a prior study conducted in mice, which found that a single injection of ketamine (2.5mg/kg, i.p.) significantly reduced both the number of escape failures and the latency to escape in mice that had developed helplessness (Maeng et al., 2008). Furthermore, both repeated and acute ketamine treatment reversed the decrease in VTA population activity observed in helpless rats, and this effect was found to be mediated by restored plasticity (i.e. long-term potentiation) within the hippocampus-accumbens pathway (Belujon and Grace, 2014).

Chronic Social Defeat Stress (CSDS).

This paradigm focuses on social stressors and is based on resident-intruder paradigms in rodents, in which an adult animal (i.e. the intruder) is introduced into the home cage of a more aggressive dominant male of the same species (i.e. the resident), which leads to an antagonistic encounter involving fights and hostile interactions that results in the intruder adopting a submissive posture (Bartolomucci, 2009; Berton et al., 2006; Miczek, 1979). This physically stressful interaction is brief and generally followed by physical separation of two animals by a transparent plastic plate pierced with holes that is placed in the middle of the resident cage. This allows adding an emotional or psychogenic stress to the brief physical stress since the intruder will be able to see and smell the resident. In case of chronic models, the intruder is subjected to assault of a new resident every day or intermittently according to the protocol. Notably, this model results in the creation of two types of subjects: susceptible vs resilient: 40–50% of mice subjected to this paradigm will not develop depressive-like states (Krishnan et al., 2007). Thus, this model recapitulates the resilience phenomenon also observed in humans. CSDS profoundly alters the motivation for social interactions (Berton et al., 2006; Toth and Neumann, 2013) and brain reward function (Der-Avakian et al., 2014) in rodents. In contrast to undefeated (i.e. control) or resilient mice, mice susceptible to CSDS exhibit social avoidance and spend less time in close proximity to the unfamiliar, novel mouse (Bagot et al., 2017; Berton et al., 2006; Browne et al., 2018; Krishnan et al., 2007). This effect (i.e. social avoidance) lasts up to 4 weeks after the last defeat in susceptible mice (Berton et al., 2006; Krishnan et al., 2007) and is accompanied by alterations in the firing rates of VTA DA neurons, as measured using *ex vivo* and *in vivo* preparations, that are negatively correlated with social avoidance behavior (Cao et al., 2010; Krishnan et al., 2007). Specifically, mice exposed to CSDS exhibit a significant increase in VTA DA neuron firing rates the day after the last defeat, and this increase in firing rate persists up to 2 weeks in susceptible mice (Krishnan et al., 2007). In addition, rats and mice exposed to CSDS show other depression-related phenotypes including anhedonia, as indexed by reduced sucrose preference (Donahue et al., 2014; Dong et al., 2017; Krishnan et al., 2007) and elevated ICSS thresholds (Der-Avakian et al., 2014; Donahue et al., 2014), as well as negative affect, as indexed increased FST and TST immobility (Der-Avakian et al., 2014; Dong et al., 2017; Rygula et al., 2005).

Acute ketamine treatment reverses the socially-avoidant phenotype in CSDS mice and increases time spent in social interaction, but this effect has typically been observed at higher doses ranging from 10mg/kg to 20mg/kg i.p. in both male and female mice (Bagot et al., 2017; Donahue et al., 2014; Newman et al., 2019) and a recent study using 10mg/kg i.p. found no effect of ketamine on social avoidance in male mice (Browne et al., 2018). Despite its effect on social avoidance, acute ketamine treatment (20mg/kg, i.p.) failed to block the anhedonic effects of CSDS on ICSS (Donahue et al., 2014). However, a lower dose of ketamine (10mg/kg, i.p.) was sufficient to reverse anhedonia in the sucrose preference test, as susceptible CSDS mice treated with ketamine exhibited increases in sucrose preference (Dong et al., 2017; Wang et al., 2019). Moreover, this dose of ketamine also reversed behavioral despair in susceptible CSDS mice, as ketamine-treated susceptible mice exhibited reduced immobility in both the FST and the TST compared to vehicle-treated mice (Dong et al., 2017; Wang et al., 2019). The effects of ketamine administration on CSDS-induced

electrophysiological alterations within VTA DA neurons remain to be determined. However, preclinical studies using molecular and genetic tools have revealed a vast array of changes in multiple regions within the mesolimbic DA system that are interconnected with the VTA, such as the PFC, the amygdala, and the nucleus accumbens (Bagot et al., 2017).

Circuitry Underlying Ketamine Actions on VTA Population Activity in the LH and CMS Rodent Models

As reviewed above, downregulation of the DA system has been described in the LH and CMS models, and this downregulation is reversed by ketamine (Belujon and Grace, 2014; Rincon-Cortes and Grace, 2017). Furthermore, a mechanism underlying ketamine's antidepressant effects following learned helplessness has been identified (Belujon and Grace, 2014). In helpless rats, there is alteration of synaptic plasticity within the hippocampal-accumbens circuit responsible for activation of DA neuron population activity: the ventral subiculum (vSub)- NAc pathway. Briefly, activation of the vSub induces an increase in the number of spontaneously active DA neurons (i.e. population activity) without impacting average firing rate or bursting activity (Lodge and Grace, 2006), and this occurs via a polysynaptic pathway through the NAc and ventral pallidum (VP)(Floresco et al., 2001) (see Fig. 1 for overview of afferent regulation of VTA population activity).

Tetanic stimulation of the vSub-NAc pathway induced the expected long-term potentiation (LTP) in control and non-helpless rats; however, in the helpless rats the same stimulation induced long-term depression (LTD) (Belujon and Grace, 2014). This finding has been replicated using chronic multimodal stress in mice, in which stressed mice exhibit anhedonia and impaired LTP induction at hippocampal-NAc synapses (LeGates et al., 2018). Collectively, these data suggest that altered excitability (i.e. downregulation) within the vSub-NAc-VP (i.e. activating) pathway in helpless rats contributes to the decrease in VTA DA neuron population activity and anhedonia. This is consistent with Koob's opponent process model (Koob and Le Moal, 2008), in which we posit initial stress activates the vSub-NAc-VP-VTA pathway to activate the DA system, but this causes a delayed but prolonged compensatory activation of the BLA-VP-VTA inhibitory circuit, which attenuates DA neuron population activity in the VTA. Thus, once the vSub-NAc pathway is taken offline by the chronic stress, the BLA-VP inhibitory pathway predominates and drives VTA DA neuron attenuation (Fig. 2). Importantly, ketamine administration restored stimulus-induced LTP (i.e. excitatory drive) in the vSub-NAc-VP pathway, which was accompanied by normalized escape behavior and restored DA neuron population activity in helpless rats (Belujon and Grace, 2014).

One question that remains is whether the site of action of ketamine is in the PFC or the hippocampus. In normal (i.e. naïve) rats, antidepressant-like effects of ketamine have been demonstrated in the FST and this effect is dependent on the infralimbic PFC (Fuchikami et al., 2015) and a ventral-hippocampal-mPFC pathway (Carreno et al., 2016). However, this was not tested in animal models for depression, in which our data show primary effects in the vSubaccumbens pathway in helpless rats. One potential explanation is that the impact in the vSub-NAc-VP pathway can only be observed when the rats are in a pathological-like

state (i.e. chronic stress) in which the vSub-NAc-VP pathway has been down-regulated (Belujon and Grace, 2014). On the other hand, our group has previously showed that the mPFC is required for the vSub to exert maximal excitatory drive on the NAc and plays an essential facilitatory role in regulating vSub-NAc-VP information flow (Belujon and Grace, 2008). These data suggest that interference with the mPFC could disrupt the vSub-NAc-VP circuit in normal animals; however, in the depressive-like state, normalization of the vSub-NAc downregulation can account for the impact of ketamine.

Sex differences in the rapid and sustained antidepressant-like effects of ketamine

Women are diagnosed with depression at twice the rates of men (Kessler, 2003; Kornstein et al., 2000), and this has been partially attributed to pronounced sex differences in both the anatomy and function of the brain (Altemus et al., 2014; Grigoriadis and Robinson, 2007). As discussed above, stress exposure is a critical risk factor for mood disorders that are more prevalent in females (i.e. anxiety, depression), and sex differences in behavioral and physiological responses to stress are thought to contribute to this enhanced vulnerability (Bangasser and Valentino, 2014; Goel and Bale, 2009; Hodes and Epperson, 2019; Rincon-Cortes et al., 2019). Moreover, there are important sex differences in the pharmacokinetics and pharmacodynamics of antidepressants as well as in antidepressant treatment response (Damoiseaux et al., 2014; Keers and Aitchison, 2010; Sramek et al., 2016), and this extends to rodent models of depression and antidepressant action (Dalla et al., 2010; Williams and Trainor, 2018). However, until recently, most preclinical studies examining the neurobiological mechanisms of mood disorders and antidepressants have focused only on males (Beery and Zucker, 2011; Karp and Reavey, 2018). Growing awareness of sex differences in neurobiology and behavior, along with recent research policies at the National Institutes of Health (NIH) (Clayton and Collins, 2014; Zakiniaez et al., 2016), have increased focus on implementing sex as a biological variable and assessing how it can modulate behavioral responses to pharmaceuticals with antidepressant properties. This shift could ultimately contribute to better treatment for mood disorders. Clinical evidence supports the notion that responsiveness to traditional antidepressant drugs (e.g. SSRIs, tricyclic antidepressants) is sex-dependent and modulated by ovarian hormones (Damoiseaux et al., 2014; Keers and Aitchison, 2010; Sloan and Kornstein, 2003), and here we review preclinical evidence that these sex differences extend to ketamine's antidepressant actions.

The first preclinical study to consider sex differences in the antidepressant effects of ketamine was conducted in stress naïve rats and demonstrated that female rats are much more sensitive to ketamine compared to male rats. Specifically, a low dose (2.5 mg/kg, i.p.) of ketamine was sufficient to reduce FST immobility and latency to feed in a novel environment in female Sprague-Dawley rats, but not in males (Carrier and Kabbaj, 2013). The researchers also found that the antidepressant-like response induced by ketamine was abolished in ovariectomized (OVX) female rats, but effective in OVX female rats that received replacements of both estrogen and progesterone mimicking the 4-day estrous cycle in intact rats, suggesting that the gonadal hormones estrogen and progesterone mediate the

high sensitivity to low dose ketamine in female rats (Carrier and Kabbaj, 2013). A subsequent study conducted in rats exposed to CMS highlighted sex differences in stress-induced alterations on behavior and DA system function, although male and female rats exhibited comparable sensitivity to the rapid and sustained antidepressant effects of a higher dose (10mg/kg, i.p.) of ketamine on FST immobility and DA activity, respectively. Acute ketamine administered 30-minutes prior to the FST effectively reduced immobility in stressed animals and increased VTA DA neuron activity for up to 1 week in both sexes compared with vehicle-treated animals (Rincon-Cortes and Grace, 2017).

The greater sensitivity of female rodents to low dose ketamine was confirmed in later studies conducted in stress-naïve C57BL/J male and female mice (Dossat et al., 2018; Franceschelli et al., 2015; Zanos et al., 2016). Pre-treatment with a low dose (3mg/kg, i.p.) of ketamine 30-minutes prior to the FST reduced immobility in female mice but not in male mice (Franceschelli et al., 2015), and this sensitivity was enhanced in proestrus (i.e. high estrogen) females, which exhibited an antidepressant-like response in the FST to even lower doses (1.5 mg/kg, i.p.) of ketamine (Dossat et al., 2018). Sex differences in FST performance were also observed 24-hours post injection: females receiving 5mg/kg or 10mg/kg of ketamine exhibited reduced FST immobility, whereas only males receiving 10mg/kg (i.e. the highest dose) exhibited reduced FST immobility (Franceschelli et al., 2015). Thus, stress-naïve female mice are more sensitive to both the rapid and the sustained antidepressant-like effects elicited by ketamine, and these effects were demonstrated to be due to a different pharmacokinetic profile of ketamine metabolites in male versus female mice (Zanos et al., 2016). When given the same dose of ketamine, levels of (2S,6S;2R,6R)-HNK, the metabolite proposed to underlie the antidepressant actions of ketamine, were approximately three-fold higher in the brains of female mice compared to males (Zanos et al., 2016). Importantly, the study led by Franceschelli also compared antidepressant actions of ketamine in CMS-exposed male and female mice and found no effect of ketamine on CMS-induced decreases in sucrose consumption and a sex-dependent effect in FST immobility, in which a 10mg/kg dose reduced FST immobility at days 1 and 7 in males, but only at day 1 in females (Franceschelli et al., 2015). Taken together, these data suggest that stress-naïve female mice are more sensitive to the rapid and sustained antidepressant effects of ketamine in the FST and that CMS-exposed females are more reactive to the earlier antidepressant effects of ketamine (i.e. at 30-min, 24h), although the antidepressant effects of ketamine on FST performance following CMS are longer lasting in males.

Sex differences have also been reported in the antidepressant effects of ketamine following isolation stress. Chronic social isolation (8–11 weeks) during adulthood alters behavior, spine density, and synaptic molecules in the mPFC in a sex-dependent manner (Sarkar and Kabbaj, 2016). Male rats exposed to social isolation exhibited reduced sucrose preference, greater FST immobility duration, a decline in mPFC spine density, and reduced levels of synaptic proteins (PSD-95, GluR1, synapsin). Similar alterations were observed in socially-isolated female rats, with the exception of reduced sucrose preference (i.e. no effect in females). In male rats, acute administration of ketamine (5mg/kg, i.p.) rescued the isolation-induced reduction in sucrose preference and increase in FST immobility time (Sarkar and Kabbaj, 2016). These effects were dose-dependent, as a 2.5 mg/kg dose of ketamine did not improve behavior in the sucrose preference and FST in males. In females, no effect of

ketamine was found for sucrose preference, and both doses (2.5mg/kg, 5mg/kg) elicited a reduction in FST immobility time. Importantly, sex-dependent ketamine effects on mPFC spine density were observed: ketamine increased the density of thin spines, but not mushroom spines, in isolated male rats but had no effect on spine density in females (Sarkar and Kabbaj, 2016). Consistent with the behavioral and spine density experiments, a single injection of ketamine (5mg/kg) reversed the decline in levels of synapsin 1, PSD-95 and attenuated the decline in GluR1 in isolated male rats. However, in contrast to male rats, ketamine did not elevate the levels of these proteins in isolated female rats, which is consistent with the lack of effect of ketamine on sucrose preference and spine density in female rats (Sarkar and Kabbaj, 2016). Altogether, these data demonstrate sex differences in the effects of chronic isolation stress and ketamine administration on behavior, mPFC spine density and synaptic protein levels, thereby suggesting divergent underlying mechanisms for the efficacy of ketamine in the two sexes.

Ketamine as a prophylactic against stress-induced adaptations relevant to depression

In addition to reversing a wide variety of stress-induced deficits across various models of chronic stress, there has been growing interest in discovering manipulations and treatments that might increase resistance/resilience to the effect of future stressors (Snijders et al., 2018). This has led some groups to investigate whether ketamine can protect against the neurobehavioral impact of future stress exposure. Parise and colleagues were the first to show that repeated ketamine administration (20mg/kg; i.p.; twice a day $\times$ 15-days) resulted in an enduring stress-resistant (i.e. resilient) phenotype that was detectable up to 2 months after the last dose (Parise et al., 2013). The researchers found that rats treated with ketamine during adolescence (postnatal days 35–49) or adulthood (postnatal days 75–89) spent more time in the open arm of the EPM, indicating an anxiolytic effect, and had longer latencies to immobility and reduced immobility duration in the FST compared with age-matched, vehicle-treated controls. Moreover, repeated ketamine administration increased active coping behavior (i.e. swimming) in the FST (Parise et al., 2013). Similar behavioral effects were observed regardless of whether the ketamine was administered in adolescence or adulthood, suggesting that these effects were independent of age at the time of ketamine administration (i.e. no sensitive period for the prophylactic effects of ketamine). Moreover, these prophylactic effects could not be attributed to ketamine-induced changes in basal locomotor activity, because no differences were detected 2 months after drug exposure (Parise et al., 2013). Collectively, these data show that repeated ketamine exposure yields long-lasting (~2 months) resilience against anxiety and depression-like behavioral responses in adolescent and adult rats.

Importantly, the prophylactic effect of ketamine is also observed in mice and rats that have been exposed to chronic stress. In mice, a single injection (30mg/kg; i.p.) of ketamine administered 1-week prior to 2-weeks of CSDS prevented the stress-induced increase in FST immobility, as indexed by reduced immobility levels in defeated mice treated with ketamine compared with vehicle-treated mice that underwent CSDS, as well as social avoidance in defeated mice (Brachman et al., 2015). These effects were specific to depression-related

phenotypes, as ketamine did not protect against CSDS-induced increases in anxiety-like behavior in the EPM. Moreover, a later study found that prophylactic ketamine (30mg/kg; i.p.) effects in defeated mice are mediated by increased expression of Δ FosB, a transcription factor that regulates synaptic plasticity in brain reward regions and mediates resilience to stress (Nestler et al., 1999; Vialou et al., 2010) in the ventral CA3 region of the hippocampus (Mastrodonato et al., 2018). Furthermore, this same dose of ketamine given 1-week before LH training also protected against helpless behavior: mice injected with ketamine exhibited reduced latencies to escape the shock and shorter session lengths compared with saline-treated mice (Brachman et al., 2015). In addition to the CSDS and LH models, ketamine's protective effects were also demonstrated in the chronic CORT model, which consisted of 3-weeks of chronic CORT administration in C57BL/6NTac mice. Chronic CORT treatment increased FST immobility duration and latency to groom in the sucrose splash test. Here, ketamine prevented increases in FST immobility duration and grooming latency, although the effective dose was substantially higher (90mg/kg; i.p.) (Brachman et al., 2015). Taken together, these findings indicate that ketamine can induce persistent stress resilience against depressive-like behaviors in 3 distinct mouse models of chronic stress. In rats, a single dose (10mg/kg; i.p.) of ketamine given 2 hours, 1 week or 2 weeks before inescapable shock protects against the neurochemical (i.e. increased 5-HT release in BLA) and behavioral (i.e. reduced social investigation) changes that typically follow inescapable, uncontrollable tail shocks (Amat et al., 2016). These results support findings (Brachman et al., 2015) using a different species, different stressor paradigm and different behavioral endpoints, suggesting that the finding of prophylactic ketamine effects has generalizability and replicability. Furthermore, these data also indicate that ketamine not only reverses the effect of past stressors but can also buffer against the effects of future stressors.

Given that the antidepressant effects of ketamine are known to be sex-specific, future studies should determine whether the prophylactic effects of ketamine extend to female animals and whether they vary depending on stressor type. Since all studies aimed at exploring the prophylactic effects of ketamine have been conducted in males, this is an important question that remains to be determined. Another future direction involves exploring whether the prophylactic effects of ketamine translate to humans. To date, only one group has explored the effect of prophylactic ketamine administration in humans. Ma and colleagues found that 0.5mg/kg given 10 minutes after child birth reduced the prevalence of postpartum blues and postpartum depression on postpartum depression in Chinese women that had undergone cesarean section (Ma et al., 2019).

It is important to keep in mind that ketamine is a powerful psychotomimetic agent that can produce transient dissociative and psychotic-like effects (especially at high or prolonged doses), and is a drug of abuse, which limits its widespread use in humans (Gerhard and Duman, 2018; Zhu et al., 2016). Since the ultimate goal of drug development efforts is to identify rapid acting agents that reverse and or prevent stress-induced neuronal deficits caused by stress and depression, but with fewer side effects, this has sparked further investigation into the chemical makeup of ketamine in hopes of discovering a more specific and efficacious treatment (Gerhard and Duman, 2018). Notably, ketamine is metabolized into an array of metabolites, and recent evidence suggests that an active metabolite of ketamine (2R,6R)-HNK exerts antidepressant-like effects in mice, but without the side effect

behaviors involving sensory dissociation, ataxia, and abuse liability (Zanos et al., 2016; Zanos et al., 2018), as well as prophylactic efficacy in rodents (Chen et al., 2019). Importantly, HNK metabolites have also been detected in humans following ketamine infusion, with (2R,6R;2S6S)-HNK and (2S,6R;2R,6S)-HNK being the predominant circulating HNKs in plasma (Zanos et al., 2018; Zarate et al., 2012; Zhao et al., 2012). However, clinical trials are required to determine the efficacy and side effect profile of (2R,6R)-HNK as a potential prophylactic agent in humans, as findings in rodent models do not always translate to the clinical setting. Finally, there is also the possibility that new compounds with safer pharmacological profiles will be used as prophylactics, as a recent report suggests prophylactic efficacy of serotonin 4 receptor (5-HT₄R) agonists against stress in mice (Chen et al., 2019).

Conclusions

In summary, depression is characterized by alterations in both negative and positive affect (i.e. depressed mood, anhedonia) and is associated with dysfunction of the mesolimbic DA system. These changes are recapitulated in rodent models of repeated or chronic stress, which are widely used to produce depression-related behaviors (i.e. despair, anhedonia) and mesolimbic DA deficits. Traditional antidepressants act via blocking the reuptake of monoamines, particularly serotonin. However, although they block uptake sites immediately and rapidly increase serotonin levels, weeks to months of treatment are required to obtain a therapeutic response. This suggests that it is not the increase in serotonin per se that is the therapeutic effect, but instead reflects a brain adaptation to the increased serotonin. In other words, a change in brain circuit activity or plasticity. In contrast, there are treatments that act faster, such as electroconvulsive therapy (ECT) and ketamine. The precise mechanisms through which these treatments act is a matter of intense research. Indeed, acute ketamine administration is sufficient to improve depressive symptoms in humans and reverse stress-induced changes in behavior and DA function in stressed animals. These antidepressant effects are mediated via actions on afferent circuits that regulate VTA DA neuron activity. Thus, we posit that ketamine and ECT have the same general effect – an alteration of synaptic plasticity, but over a more rapid time course. Therefore, rather than treating a persistent deficit in neurotransmission, these actions most likely alter synaptic strength between brain regions involved in affective regulation. Our work suggests that, at least with respect to the DA system, this involves a delicate balance between pathways that drive the DA system (i.e., the vSub-NAc-VP-VTA pathway) and the pathway that attenuates DA system function (i.e., the BLA-VP-VTA pathway; Fig. 1). Normally these systems would be in balance. However, if a stressor overdrives the hippocampal pathway, it would cause an activation of the DA system. This would be offset by a slower but persistent compensatory down-regulation via the ilPFC-BLA-VP pathway (Grace, 2016). This is consistent with Koob's opponent process model of addiction (Koob and Le Moal, 2001, 2008) – i.e., initial activation of the VTA DA system is followed by a persistent down-regulation of this system and negative affect. Indeed, our studies suggest that high dose amphetamine may produce the same consequence – acute DA activation during the reinforcement phase, followed by an amygdala-driven persistent down-regulation producing negative affect (Belujon et al., 2016; Rincon-Cortes et al., 2018). Moreover, in rodents, both stress and antidepressant effects of

ketamine vary between sexes, with females showing greater stress-induced neurobehavioral deficits while also exhibiting antidepressant-like responses to lower doses of ketamine. Whether there are sex differences with regard to ketamine's clinical efficacy in humans remains to be determined. Finally, novel preclinical evidence suggests that, in addition to antidepressant effects, ketamine also has prophylactic effects and can circumvent the neurobehavioral impact of future stressors. Therefore, ketamine may serve as a type of system stabilizer, in that its impact on normal systems is transient, but can restore and may even prevent abnormal plasticity in cases of persistent stress-induced pathological changes.

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References

- aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ, 2010 Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological psychiatry* 67, 139–145. [PubMed: 19897179]
- Admon R, Pizzagalli DA, 2015 Dysfunctional Reward Processing in Depression. *Curr Opin Psychol* 4, 114–118. [PubMed: 26258159]
- Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, Meaney MJ, Nestler EJ, 2018 Treatment resistant depression: A multi-scale, systems biology approach. *Neuroscience and biobehavioral reviews* 84, 272–288. [PubMed: 28859997]
- Alloy LB, Olino T, Freed RD, Nusslock R, 2016 Role of Reward Sensitivity and Processing in Major Depressive and Bipolar Spectrum Disorders. *Behav Ther* 47, 600–621. [PubMed: 27816074]
- Altemus M, Sarvaiya N, Neill Epperson C, 2014 Sex differences in anxiety and depression clinical perspectives. *Frontiers in neuroendocrinology* 35, 320–330. [PubMed: 24887405]
- Amat J, Dolzani SD, Tilden S, Christianson JP, Kubala KH, Bartholomay K, Sperr K, Ciancio N, Watkins LR, Maier SF, 2016 Previous Ketamine Produces an Enduring Blockade of Neurochemical and Behavioral Effects of Uncontrollable Stress. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 36, 153–161. [PubMed: 26740657]
- Argyropoulos SV, Nutt DJ, 2013 Anhedonia revisited: is there a role for dopamine-targeting drugs for depression? *J Psychopharmacol* 27, 869–877. [PubMed: 23904408]
- Arnsten AF, 2009 Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci* 10, 410–422. [PubMed: 19455173]
- Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM, 2011 NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 475, 91–95. [PubMed: 21677641]
- Autry AE, Monteggia LM, 2012 Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacol Rev* 64, 238–258. [PubMed: 22407616]
- Bagot RC, Cates HM, Purushothaman I, Vialou V, Heller EA, Yieh L, LaBonte B, Pena CJ, Shen L, Wittenberg GM, Nestler EJ, 2017 Ketamine and Imipramine Reverse Transcriptional Signatures of Susceptibility and Induce Resilience-Specific Gene Expression Profiles. *Biological psychiatry* 81, 285–295. [PubMed: 27569543]
- Bangasser DA, Valentino RJ, 2014 Sex differences in stress-related psychiatric disorders: neurobiological perspectives. *Frontiers in neuroendocrinology* 35, 303–319. [PubMed: 24726661]
- Bartolomucci A, Fuchs E, Koolhaas JM, Ohl F, 2009 Acute and Chronic Social Defeat: Stress Protocols and Behavioral Testing, in: Gould T (Ed.), *Mood and Anxiety Related Phenotypes in Mice*. Humana Press, Totowa, NJ, pp. 261–275.

- Beery AK, Zucker I, 2011 Sex bias in neuroscience and biomedical research. *Neuroscience and biobehavioral reviews* 35, 565–572. [PubMed: 20620164]
- Belujon P, Grace AA, 2008 Critical role of the prefrontal cortex in the regulation of hippocampus-accumbens information flow. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 28, 9797–9805. [PubMed: 18815264]
- Belujon P, Grace AA, 2014 Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. *Biological psychiatry* 76, 927–936. [PubMed: 24931705]
- Belujon P, Grace AA, 2015 Regulation of dopamine system responsivity and its adaptive and pathological response to stress. *Proceedings. Biological sciences / The Royal Society* 282.
- Belujon P, Grace AA, 2017 Dopamine System Dysregulation in Major Depressive Disorders. *Int J Neuropsychopharmacol* 20, 1036–1046. [PubMed: 29106542]
- Berger PA, Faull KF, Kilkowski J, Anderson PJ, Kraemer H, Davis KL, Barchas JD, 1980 CSF monoamine metabolites in depression and schizophrenia. *The American journal of psychiatry* 137, 174–180. [PubMed: 7352572]
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH, 2000 Antidepressant effects of ketamine in depressed patients. *Biological psychiatry* 47, 351–354. [PubMed: 10686270]
- Berridge KC, Kringelbach ML, 2015 Pleasure systems in the brain. *Neuron* 86, 646–664. [PubMed: 25950633]
- Berridge KC, Robinson TE, 1998 What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain research. Brain research reviews* 28, 309–369. [PubMed: 9858756]
- Berton O, McClung CA, Dileone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ, 2006 Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311, 864–868. [PubMed: 16469931]
- Beurel E, Grieco SF, Jope RS, 2015 Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacology & therapeutics* 148, 114–131. [PubMed: 25435019]
- Beurel E, Song L, Jope RS, 2011 Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Molecular psychiatry* 16, 1068–1070. [PubMed: 21502951]
- Brachman RA, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C, Gardier AM, Mendez-David I, David DJ, Hen R, Denny CA, 2015 Ketamine as a Prophylactic Against Stress-Induced Depressive-Like Behavior. *Biological psychiatry*.
- Browne CA, Falcon E, Robinson SA, Berton O, Lucki I, 2018 Reversal of Stress-Induced Social Interaction Deficits by Buprenorphine. *Int J Neuropsychopharmacol* 21, 164–174. [PubMed: 29020387]
- Browne CA, Lucki I, 2013 Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. *Frontiers in pharmacology* 4, 161. [PubMed: 24409146]
- Cao JL, Covington HE 3rd, Friedman AK, Wilkinson MB, Walsh JJ, Cooper DC, Nestler EJ, Han MH, 2010 Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 30, 16453–16458. [PubMed: 21147984]
- Carlezon WA Jr., Chartoff EH, 2007 Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. *Nature protocols* 2, 2987–2995. [PubMed: 18007634]
- Carreno FR, Donegan JJ, Boley AM, Shah A, DeGuzman M, Frazer A, Lodge DJ, 2016 Activation of a ventral hippocampus-medial prefrontal cortex pathway is both necessary and sufficient for an antidepressant response to ketamine. *Molecular psychiatry* 21, 1298–1308. [PubMed: 26619811]
- Carrier N, Kabbaj M, 2013 Sex differences in the antidepressant-like effects of ketamine. *Neuropharmacology* 70, 27–34. [PubMed: 23337256]
- Chang CH, Grace AA, 2013 Amygdala beta-noradrenergic receptors modulate delayed downregulation of dopamine activity following restraint. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 33, 1441–1450.

- Chang CH, Grace. AA, 2014 Amygdala-ventral pallidum pathway decreases dopamine activity after chronic mild stress in rats. *Biological psychiatry* 76, 223–230. [PubMed: 24209776]
- Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, Koo JW, Ferguson D, Tsai HC, Pomeranz L, Christoffel DJ, Nectow AR, Ekstrand M, Domingos A, Mazei-Robison MS, Mouzon E, Lobo MK, Neve RL, Friedman JM, Russo SJ, Deisseroth K, Nestler EJ, Han MH, 2013 Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 493, 532–536. [PubMed: 23235832]
- Chen BK, Mendez-David I, Luna VM, Faye C, Gardier AM, David DJ, Denny CA, 2019 Prophylactic efficacy of 5-HT4R agonists against stress. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*.
- Clayton JA, Collins FS, 2014 Policy: NIH to balance sex in cell and animal studies. *Nature* 509, 282–283. [PubMed: 24834516]
- Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, Scientific Advisory B, the Executive Committee of the Grand Challenges on Global Mental, H., Anderson W, Dhansay MA, Phillips A, Shurin S, Walport M, Ewart W, Savill SJ, Bordin IA, Costello EJ, Durkin M, Fairburn C, Glass RI, Hall W, Huang Y, Hyman SE, Jamison K, Kaaya S, Kapur S, Kleinman A, Ogunniyi A, Otero-Ojeda A, Poo MM, Ravindranath V, Sahakian BJ, Saxena S, Singer PA, Stein DJ, 2011 Grand challenges in global mental health. *Nature* 475, 27–30. [PubMed: 21734685]
- Conrad CD, 2008 Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. *Rev Neurosci* 19, 395–411. [PubMed: 19317179]
- Covey JR, Crawford AN, Lowe DK, 2012 Intravenous ketamine for treatment-resistant major depressive disorder. *Ann Pharmacother* 46, 117–123. [PubMed: 22190250]
- Coyle CM, Laws KR, 2015 The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Hum Psychopharmacol* 30, 152–163. [PubMed: 25847818]
- D'Aquila PS, Brain P, Willner P, 1994 Effects of chronic mild stress on performance in behavioural tests relevant to anxiety and depression. *Physiology & behavior* 56, 861–867. [PubMed: 7824585]
- Dalla C, Pitychoutis PM, Kokras N, Papadopoulou-Daifoti Z, 2010 Sex differences in animal models of depression and antidepressant response. *Basic & clinical pharmacology & toxicology* 106, 226–233. [PubMed: 20050844]
- Damoiseaux VA, Proost JH, Jiawan VC, Melgert BN, 2014 Sex differences in the pharmacokinetics of antidepressants: influence of female sex hormones and oral contraceptives. *Clin Pharmacokinet* 53, 509–519. [PubMed: 24859034]
- Der-Avakian A, Barnes SA, Markou A, Pizzagalli DA, 2016 Translational Assessment of Reward and Motivational Deficits in Psychiatric Disorders. *Current topics in behavioral neurosciences* 28, 231–262. [PubMed: 26873017]
- Der-Avakian A, Markou A, 2012 The neurobiology of anhedonia and other reward-related deficits. *Trends in neurosciences* 35, 68–77. [PubMed: 22177980]
- Der-Avakian A, Mazei-Robison MS, Kesby JP, Nestler EJ, Markou A, 2014 Enduring deficits in brain reward function after chronic social defeat in rats: susceptibility, resilience, and antidepressant response. *Biological psychiatry* 76, 542–549. [PubMed: 24576687]
- DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV, 2015 The promise of ketamine for treatment-resistant depression: current evidence and future directions. *Annals of the New York Academy of Sciences* 1345, 47–58. [PubMed: 25649308]
- DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, Machado-Vieira R, Zarate CA Jr., 2010 Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 71, 1605–1611. [PubMed: 20673547]
- Donahue RJ, Muschamp JW, Russo SJ, Nestler EJ, Carlezon WA Jr., 2014 Effects of striatal DeltaFosB overexpression and ketamine on social defeat stress-induced anhedonia in mice. *Biological psychiatry* 76, 550–558. [PubMed: 24495460]
- Dong C, Zhang JC, Yao W, Ren Q, Ma M, Yang C, Chaki S, Hashimoto K, 2017 Rapid and Sustained Antidepressant Action of the mGlu2/3 Receptor Antagonist MGS0039 in the Social Defeat Stress Model: Comparison with Ketamine. *Int J Neuropsychopharmacol* 20, 228–236. [PubMed: 27765808]

- Dossat AM, Wright KN, Strong CE, Kabbaj M, 2018 Behavioral and biochemical sensitivity to low doses of ketamine: Influence of estrous cycle in C57BL/6 mice. *Neuropharmacology* 130, 30–41. [PubMed: 29175352]
- Douma EH, de Kloet ER, 2019 Stress-Induced Plasticity and Functioning of Ventral Tegmental Dopamine Neurons. *Neuroscience and biobehavioral reviews*.
- Drevets WC, 2001 Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol* 11, 240–249. [PubMed: 11301246]
- Duman RS, Monteggia LM, 2006 A neurotrophic model for stress-related mood disorders. *Biological psychiatry* 59, 1116–1127. [PubMed: 16631126]
- Fava M, Kendler KS, 2000 Major depressive disorder. *Neuron* 28, 335–341. [PubMed: 11144343]
- Floresco SB, Todd CL, Grace AA, 2001 Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 21, 4915–4922. [PubMed: 11425919]
- Forbes EE, Hariri AR, Martin SL, Silk JS, Moyses DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE, 2009 Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *The American journal of psychiatry* 166, 64–73. [PubMed: 19047324]
- Forbes NF, Stewart CA, Matthews K, Reid IC, 1996 Chronic mild stress and sucrose consumption: validity as a model of depression. *Physiology & behavior* 60, 1481–1484. [PubMed: 8946494]
- Fox ME, Lobo MK, 2019 The molecular and cellular mechanisms of depression: a focus on reward circuitry. *Molecular psychiatry*.
- Franceschelli A, Sens J, Herchick S, Thelen C, Pitychoutis PM, 2015 Sex differences in the rapid and the sustained antidepressant-like effects of ketamine in stress-naïve and “depressed” mice exposed to chronic mild stress. *Neuroscience* 290, 49–60. [PubMed: 25595985]
- Friedman AK, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, Li X, Dietz DM, Pan N, Vialou VF, Neve RL, Yue Z, Han MH, 2014 Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science* 344, 313–319. [PubMed: 24744379]
- Fuchikami M, Thomas A, Liu R, Wohleb ES, Land BB, DiLeone RJ, Aghajanian GK, Duman RS, 2015 Optogenetic stimulation of infralimbic PFC reproduces ketamine’s rapid and sustained antidepressant actions. *Proceedings of the National Academy of Sciences of the United States of America* 112, 8106–8111. [PubMed: 26056286]
- Garcia LS, Comim CM, Valvassori SS, Reus GZ, Stertz L, Kapczinski F, Gavioli EC, Quevedo J, 2009 Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. *Progress in neuro-psychopharmacology & biological psychiatry* 33, 450–455. [PubMed: 19439250]
- Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ, 2009 What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv* 60, 1439–1445. [PubMed: 19880458]
- Gerhard DM, Duman RS, 2018 Rapid-Acting Antidepressants: Mechanistic Insights and Future Directions. *Curr Behav Neurosci Rep* 5, 36–47. [PubMed: 30034992]
- Goel N, Bale TL, 2009 Examining the intersection of sex and stress in modelling neuropsychiatric disorders. *Journal of neuroendocrinology* 21, 415–420. [PubMed: 19187468]
- Grace AA, 2016 Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci*.
- Grace AA, Floresco SB, Goto Y, Lodge DJ, 2007 Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends in neurosciences* 30, 220–227. [PubMed: 17400299]
- Grigoriadis S, Robinson GE, 2007 Gender issues in depression. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists* 19, 247–255. [PubMed: 18058282]
- Gronli J, Murison R, Fiske E, Bjorvatn B, Sorensen E, Portas CM, Ursin R, 2005 Effects of chronic mild stress on sexual behavior, locomotor activity and consumption of sucrose and saccharine solutions. *Physiology & behavior* 84, 571–577. [PubMed: 15811392]
- Gross JJ, Munoz RF, 1995 Emotion Regulation and Mental-Health. *Clin Psychol-Sci Pr* 2, 151–164.

- Hammen C, 2005 Stress and depression. *Annual review of clinical psychology* 1, 293–319.
- Hare BD, Ghosal S, Duman RS, 2017 Rapid Acting Antidepressants in Chronic Stress Models: Molecular and Cellular Mechanisms. *Chronic Stress* (Thousand Oaks) 1.
- Hasler G, Fromm S, Carlson PJ, Luckenbaugh DA, Waldeck T, Geraci M, Roiser JP, Neumeister A, Meyers N, Charney DS, Drevets WC, 2008 Neural response to catecholamine depletion in unmedicated subjects with major depressive disorder in remission and healthy subjects. *Archives of general psychiatry* 65, 521–531. [PubMed: 18458204]
- Henriksson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsä ET, Kuoppasalmi KI, Lonnqvist JK, 1993 Mental disorders and comorbidity in suicide. *The American journal of psychiatry* 150, 935–940. [PubMed: 8494072]
- Heshmati M, Russo SJ, 2015 Anhedonia and the brain reward circuitry in depression. *Curr Behav Neurosci Rep* 2, 146–153. [PubMed: 26525751]
- Hill MN, Hellemans KG, Verma P, Gorzalka BB, Weinberg J, 2012 Neurobiology of chronic mild stress: parallels to major depression. *Neuroscience and biobehavioral reviews* 36, 2085–2117. [PubMed: 22776763]
- Hodes GE, Epperson CN, 2019 Sex Differences in Vulnerability and Resilience to Stress Across the Life Span. *Biological psychiatry*.
- Hofmann SG, Sawyer AT, Fang A, Asnaani A, 2012 Emotion dysregulation model of mood and anxiety disorders. *Depression and anxiety* 29, 409–416. [PubMed: 22430982]
- Holly EN, Miczek KA, 2016 Ventral tegmental area dopamine revisited: effects of acute and repeated stress. *Psychopharmacology* 233, 163–186. [PubMed: 26676983]
- Holsboer F, 2001 Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *Journal of affective disorders* 62, 77–91. [PubMed: 11172875]
- Ikemoto S, 2007 Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain research reviews* 56, 27–78. [PubMed: 17574681]
- Kapur S, Mann JJ, 1992 Role of the dopaminergic system in depression. *Biological psychiatry* 32, 1–17. [PubMed: 1391289]
- Karp NA, Reavey N, 2018 Sex bias in preclinical research and an exploration of how to change the status quo. *Br J Pharmacol*.
- Katz MM, Tekell JL, Bowden CL, Brannan S, Houston JP, Berman N, Frazer A, 2004 Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 29, 566–579. [PubMed: 14627997]
- Katz RJ, 1982 Animal model of depression: pharmacological sensitivity of a hedonic deficit. *Pharmacology, biochemistry, and behavior* 16, 965–968.
- Kaufling J, 2019 Alterations and adaptation of ventral tegmental area dopaminergic neurons in animal models of depression. *Cell Tissue Res*.
- Keers R, Aitchison KJ, 2010 Gender differences in antidepressant drug response. *Int Rev Psychiatry* 22, 485–500. [PubMed: 21047161]
- Kendler KS, Karkowski LM, Prescott CA, 1999 Causal relationship between stressful life events and the onset of major depression. *The American journal of psychiatry* 156, 837–841. [PubMed: 10360120]
- Kessler RC, 2003 Epidemiology of women and depression. *Journal of affective disorders* 74, 5–13. [PubMed: 12646294]
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE, 2005 Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry* 62, 593–602. [PubMed: 15939837]
- Klein DF, 1974 Endogenous depression. A conceptual and terminological revision. *Archives of general psychiatry* 31, 447–454. [PubMed: 4420562]
- Koike H, Iijima M, Chaki S, 2011 Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. *Behavioural brain research* 224, 107–111. [PubMed: 21669235]

- Kokkinou M, Ashok AH, Howes OD, 2018 The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. *Molecular psychiatry* 23, 59–69. [PubMed: 28972576]
- Koob GF, Le Moal M, 2008 Review. Neurobiological mechanisms for opponent motivational processes in addiction. *Philos Trans R Soc Lond B Biol Sci* 363, 3113–3123. [PubMed: 18653439]
- Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, Gelenberg AJ, Ryan CE, Hess AL, Harrison W, Davis SM, Keller MB, 2000 Gender differences in chronic major and double depression. *Journal of affective disorders* 60, 1–11. [PubMed: 10940442]
- Kraus C, Rabl U, Vanicek T, Carlberg L, Popovic A, Spies M, Bartova L, Gryglewski G, Papageorgiou K, Lanzenberger R, Willeit M, Winkler D, Rybakowski JK, Kasper S, 2017 Administration of ketamine for unipolar and bipolar depression. *Int J Psychiatry Clin Pract* 21, 2–12. [PubMed: 28097909]
- Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ, 2007 Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 131, 391–404. [PubMed: 17956738]
- Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD, 2008 Abnormal temporal difference reward-learning signals in major depression. *Brain* 131, 2084–2093. [PubMed: 18579575]
- Kurdi MS, Theerth KA, Deva RS, 2014 Ketamine: Current applications in anesthesia, pain, and critical care. *Anesth Essays Res* 8, 283–290. [PubMed: 25886322]
- Lambert C, Da Silva S, Ceniti AK, Rizvi SJ, Foussias G, Kennedy SH, 2018 Anhedonia in depression and schizophrenia: A transdiagnostic challenge. *CNS Neurosci Ther* 24, 615–623. [PubMed: 29687627]
- Lambert G, Johansson M, Agren H, Friberg P, 2000 Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. *Archives of general psychiatry* 57, 787–793. [PubMed: 10920468]
- LeGates TA, Kvarta MD, Tooley JR, Francis TC, Lobo MK, Creed MC, Thompson SM, 2018 Reward behaviour is regulated by the strength of hippocampus-nucleus accumbens synapses. *Nature* 564, 258–262. [PubMed: 30478293]
- Lepack AE, Fuchikami M, Dwyer JM, Banasr M, Duman RS, 2014 BDNF release is required for the behavioral actions of ketamine. *Int J Neuropsychopharmacol* 18.
- Lewinsohn PM, Graf M, 1973 Pleasant activities and depression. *J Consult Clin Psychol* 41, 261–268. [PubMed: 4147832]
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS, 2010 mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329, 959–964. [PubMed: 20724638]
- Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS, 2011 Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biological psychiatry* 69, 754–761. [PubMed: 21292242]
- Li X, Jope RS, 2010 Is glycogen synthase kinase-3 a central modulator in mood regulation? *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 35, 2143–2154. [PubMed: 20668436]
- Liu D, Tang QQ, Yin C, Song Y, Liu Y, Yang JX, Liu H, Zhang YM, Wu SY, Song Y, Juarez B, Ding HL, Han MH, Zhang H, Cao JL, 2018 Brain-derived neurotrophic factor-mediated projection-specific regulation of depressive-like and nociceptive behaviors in the mesolimbic reward circuitry. *Pain* 159, 175. [PubMed: 29076919]
- Lloyd C, 1980 Life events and depressive disorder reviewed. II. Events as precipitating factors. *Archives of general psychiatry* 37, 541–548. [PubMed: 7377910]
- Lodge DJ, Grace AA, 2006 The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 31, 1356–1361. [PubMed: 16319915]

- Ma JH, Wang SY, Yu HY, Li DY, Luo SC, Zheng SS, Wan LF, Duan KM, 2019 Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section(). Psychiatry research.
- Maeng S, Zarate CA Jr., Du J, Schloesser RJ, McCammon J, Chen G, Manji HK, 2008 Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biological psychiatry 63, 349–352. [PubMed: 17643398]
- Manji HK, Drevets WC, Charney DS, 2001 The cellular neurobiology of depression. Nat Med 7, 541–547. [PubMed: 11329053]
- Martin-Soelch C, 2009 Is depression associated with dysfunction of the central reward system? Biochemical Society transactions 37, 313–317. [PubMed: 19143654]
- Mastrodonato A, Martinez R, Pavlova IP, LaGamma CT, Brachman RA, Robison AJ, Denny CA, 2018 Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior. Biological psychiatry 84, 846–856. [PubMed: 29615190]
- Matthews K, Forbes N, Reid IC, 1995 Sucrose consumption as an hedonic measure following chronic unpredictable mild stress. Physiology & behavior 57, 241–248. [PubMed: 7716198]
- McCabe C, Cowen PJ, Harmer CJ, 2009 Neural representation of reward in recovered depressed patients. Psychopharmacology 205, 667–677. [PubMed: 19529923]
- McEwen BS, 2004 Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Annals of the New York Academy of Sciences 1032, 1–7. [PubMed: 15677391]
- McEwen BS, Morrison JH, 2013 The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79, 16–29. [PubMed: 23849196]
- Meyer JH, Kruger S, Wilson AA, Christensen BK, Goulding VS, Schaffer A, Minifie C, Houle S, Hussey D, Kennedy SH, 2001 Lower dopamine transporter binding potential in striatum during depression. Neuroreport 12, 4121–4125. [PubMed: 11742250]
- Miczek KA, 1979 A new test for aggression in rats without aversive stimulation: differential effects of d-amphetamine and cocaine. Psychopharmacology 60, 253–259. [PubMed: 108702]
- Moda-Sava RN, Murdock MH, Parekh PK, Fetcho RN, Huang BS, Huynh TN, Witzum J, Shaver DC, Rosenthal DL, Alway EJ, Lopez K, Meng Y, Nellissen L, Grosenick L, Milner TA, Deisseroth K, Bito H, Kasai H, Liston C, 2019 Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science 364.
- Molendijk ML, de Kloet ER, 2019 Coping with the forced swim stressor: Current state-of-the-art. Behavioural brain research 364, 1–10. [PubMed: 30738104]
- Monleon S, D'Aquila P, Parra A, Simon VM, Brain PF, Willner P, 1995 Attenuation of sucrose consumption in mice by chronic mild stress and its restoration by imipramine. Psychopharmacology 117, 453–457. [PubMed: 7604147]
- Monteggia LM, Gideons E, Kavalali ET, 2013 The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. Biological psychiatry 73, 1199–1203. [PubMed: 23062356]
- Moore H, Rose HJ, Grace AA, 2001 Chronic cold stress reduces the spontaneous activity of ventral tegmental dopamine neurons. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 24, 410–419. [PubMed: 11182536]
- Moreau JL, Jenck F, Martin JR, Mortas P, Haefely WE, 1992 Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 2, 43–49. [PubMed: 1638173]
- Moreines JL, Owrutsky ZL, Grace AA, 2017 Involvement of Infralimbic Prefrontal Cortex but not Lateral Habenula in Dopamine Attenuation After Chronic Mild Stress. Neuropsychopharmacology 42, 904–913. [PubMed: 27813530]
- Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ, 2013a Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. The American journal of psychiatry 170, 1134–1142. [PubMed: 23982301]

- Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV, 2013b Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biological psychiatry* 74, 250–256. [PubMed: 22840761]
- Naranjo CA, Tremblay LK, Busto UE, 2001 The role of the brain reward system in depression. *Progress in neuro-psychopharmacology & biological psychiatry* 25, 781–823. [PubMed: 11383978]
- Nestler EJ, Hyman SE, 2010 Animal models of neuropsychiatric disorders. *Nature neuroscience* 13, 1161–1169. [PubMed: 20877280]
- Nestler EJ, Kelz MB, Chen J, 1999 DeltaFosB: a molecular mediator of long-term neural and behavioral plasticity. *Brain research* 835, 10–17. [PubMed: 10448191]
- Newman EL, Covington HE 3rd, Suh J, Bickaci MB, Ressler KJ, DeBold JF, Miczek KA, 2019 Fighting Females: Neural and Behavioral Consequences of Social Defeat Stress in Female Mice. *Biological psychiatry*.
- Nutt D, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, Carrasco JL, Stahl S, 2007 The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacol* 21, 461–471. [PubMed: 17050654]
- Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, Mohr DC, Schatzberg AF, 2016 Major depressive disorder. *Nat Rev Dis Primers* 2, 16065. [PubMed: 27629598]
- Pani L, Porcella A, Gessa GL, 2000 The role of stress in the pathophysiology of the dopaminergic system. *Molecular psychiatry* 5, 14–21. [PubMed: 10673764]
- Papp M, Willner P, Muscat R, 1991 An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. *Psychopharmacology* 104, 255–259. [PubMed: 1876670]
- Parise EM, Alcantara LF, Warren BL, Wright KN, Hadad R, Sial OK, Kroeck KG, Iniguez SD, Bolanos-Guzman CA, 2013 Repeated ketamine exposure induces an enduring resilient phenotype in adolescent and adult rats. *Biological psychiatry* 74, 750–759. [PubMed: 23790225]
- Pechtel P, Dutra SJ, Goetz EL, Pizzagalli DA, 2013 Blunted reward responsiveness in remitted depression. *J Psychiatr Res* 47, 1864–1869. [PubMed: 24064208]
- Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, Owøye O, Batten LA, Blier P, 2019 Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial. *The American journal of psychiatry* 176, 401–409. [PubMed: 30922101]
- Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M, 2009 Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *The American journal of psychiatry* 166, 702–710. [PubMed: 19411368]
- Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M, 2008 Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res* 43, 76–87. [PubMed: 18433774]
- Price JL, Drevets WC, 2012 Neural circuits underlying the pathophysiology of mood disorders. *Trends Cogn Sci* 16, 61–71. [PubMed: 22197477]
- Price RB, Nock MK, Charney DS, Mathew SJ, 2009 Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biological psychiatry* 66, 522–526. [PubMed: 19545857]
- Rincon-Cortes M, Grace AA, 2017 Sex-Dependent Effects of Stress on Immobility Behavior and VTA Dopamine Neuron Activity: Modulation by Ketamine. *Int J Neuropsychopharmacol* 20, 823–832. [PubMed: 28591782]
- Rincon-Cortes M, Herman JP, Lupien S, Maguire J, Shansky RM, 2019 Stress: Influence of sex, reproductive status and gender. *Neurobiol Stress* 10, 100155. [PubMed: 30949564]
- Ruhe HG, Mason NS, Schene AH, 2007 Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Molecular psychiatry* 12, 331–359. [PubMed: 17389902]

- Russo SJ, Nestler EJ, 2013 The brain reward circuitry in mood disorders. *Nat Rev Neurosci* 14, 609–625. [PubMed: 23942470]
- Rygula R, Abumaria N, Flugge G, Fuchs E, Ruther E, Havemann-Reinecke U, 2005 Anhedonia and motivational deficits in rats: impact of chronic social stress. *Behavioural brain research* 162, 127–134. [PubMed: 15922073]
- Sanchis-Segura C, Spanagel R, Henn FA, Vollmayr B, 2005 Reduced sensitivity to sucrose in rats bred for helplessness: a study using the matching law. *Behavioural pharmacology* 16, 267–270. [PubMed: 15961967]
- Sapolsky RM, 2000 Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of general psychiatry* 57, 925–935. [PubMed: 11015810]
- Sarchiapone M, Carli V, Camardese G, Cuomo C, Di Guida D, Calcagni ML, Focacci C, De Risio S, 2006 Dopamine transporter binding in depressed patients with anhedonia. *Psychiatry research* 147, 243–248. [PubMed: 16952448]
- Sarkar A, Kabbaj M, 2016 Sex Differences in Effects of Ketamine on Behavior, Spine Density, and Synaptic Proteins in Socially Isolated Rats. *Biological psychiatry* 80, 448–456. [PubMed: 26957131]
- Scheggi S, De Montis MG, Gambarana C, 2018 Making Sense of Rodent Models of Anhedonia. *Int J Neuropsychopharmacol* 21, 1049–1065. [PubMed: 30239762]
- Scheuing L, Chiu CT, Liao HM, Chuang DM, 2015 Antidepressant mechanism of ketamine: perspective from preclinical studies. *Front Neurosci* 9, 249. [PubMed: 26257598]
- Seligman ME, Beagley G, 1975 Learned helplessness in the rat. *J Comp Physiol Psychol* 88, 534–541. [PubMed: 1150935]
- Sherdell L, Waugh CE, Gotlib IH, 2012 Anticipatory pleasure predicts motivation for reward in major depression. *Journal of abnormal psychology* 121, 51–60. [PubMed: 21842963]
- Slattery DA, Cryan JF, 2017 Modelling depression in animals: at the interface of reward and stress pathways. *Psychopharmacology* 234, 1451–1465. [PubMed: 28224183]
- Sloan DM, Kornstein SG, 2003 Gender differences in depression and response to antidepressant treatment. *Psychiatr Clin North Am* 26, 581–594. [PubMed: 14563099]
- Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, Dichter GS, 2009 fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of affective disorders* 118, 69–78. [PubMed: 19261334]
- Snijders C, Pries LK, Sgammeglia N, Al Jowf G, Youssef NA, de Nijs L, Guloksuz S, Rutten BPF, 2018 Resilience Against Traumatic Stress: Current Developments and Future Directions. *Front Psychiatry* 9, 676. [PubMed: 30631285]
- Spijker J, Bijl RV, de Graaf R, Nolen WA, 2001 Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand* 103, 122–130. [PubMed: 11167315]
- Sramek JJ, Murphy MF, Cutler NR, 2016 Sex differences in the psychopharmacological treatment of depression. *Dialogues Clin Neurosci* 18, 447–457. [PubMed: 28179816]
- Steele JD, Kumar P, Ebmeier KP, 2007 Blunted response to feedback information in depressive illness. *Brain* 130, 2367–2374. [PubMed: 17586866]
- Tanaka K, Furuyashiki T, Kitaoka S, Senzai Y, Imoto Y, Segi-Nishida E, Deguchi Y, Breyer RM, Breyer MD, Narumiya S, 2012 Prostaglandin E2-mediated attenuation of mesocortical dopaminergic pathway is critical for susceptibility to repeated social defeat stress in mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32, 4319–4329. [PubMed: 22442093]
- Toth I, Neumann ID, 2013 Animal models of social avoidance and social fear. *Cell Tissue Res* 354, 107–118. [PubMed: 23760888]
- Treadway MT, Bossaller NA, Shelton RC, Zald DH, 2012 Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *Journal of abnormal psychology* 121, 553–558. [PubMed: 22775583]
- Treadway MT, Zald DH, 2011 Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neuroscience and biobehavioral reviews* 35, 537–555. [PubMed: 20603146]

- Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, Finkelstein J, Kim SY, Adhikari A, Thompson KR, Andelman AS, Gunaydin LA, Witten IB, Deisseroth K, 2013 Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature* 493, 537–541. [PubMed: 23235822]
- Uhl B, Kuehner C, Kirsch P, Ruttorf M, Diener C, Flor H, 2015 Altered neural reward and loss processing and prediction error signalling in depression. *Soc Cogn Affect Neurosci* 10, 1102–1112. [PubMed: 25567763]
- Valenti O, Gill KM, Grace AA, 2012 Different stressors produce excitation or inhibition of mesolimbic dopamine neuron activity: response alteration by stress pre-exposure. *The European journal of neuroscience* 35, 1312–1321. [PubMed: 22512259]
- Valenti O, Lodge DJ, Grace AA, 2011 Aversive stimuli alter ventral tegmental area dopamine neuron activity via a common action in the ventral hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 31, 4280–4289. [PubMed: 21411669]
- Vialou V, Robison AJ, Laplant QC, Covington HE 3rd, Dietz DM, Ohnishi YN, Mouzon E, Rush AJ 3rd, Watts EL, Wallace DL, Iniguez SD, Ohnishi YH, Steiner MA, Warren BL, Krishnan V, Bolanos CA, Neve RL, Ghose S, Berton O, Tamminga CA, Nestler EJ, 2010 DeltaFosB in brain reward circuits mediates resilience to stress and antidepressant responses. *Nature neuroscience* 13, 745–752. [PubMed: 20473292]
- Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, Schmidt M, Claes S, 2013 Reduced reward learning predicts outcome in major depressive disorder. *Biological psychiatry* 73, 639–645. [PubMed: 23228328]
- Wagner HR 2nd, Hall TL, Cote IL, 1977 The applicability of inescapable shock as a source of animal depression. *J Gen Psychol* 96, 313–318. [PubMed: 559062]
- Wang W, Liu L, Yang X, Gao H, Tang QK, Yin LY, Yin XY, Hao JR, Geng DQ, Gao C, 2019 Ketamine improved depressive-like behaviors via hippocampal glucocorticoid receptor in chronic stress induced- susceptible mice. *Behavioural brain research* 364, 75–84. [PubMed: 30753876]
- Weiss JM, 1997 Does decreased sucrose intake indicate loss of preference in CMS model? *Psychopharmacology* 134, 368–370; discussion 371–367. [PubMed: 9452179]
- Whitton AE, Treadway MT, Pizzagalli DA, 2015 Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current opinion in psychiatry* 28, 7–12. [PubMed: 25415499]
- WHO, 2017 Depression and Other Common Mental Disorders: Global Health Estimates, Geneva.
- Williams AV, Trainor BC, 2018 The impact of sex as a biological variable in the search for novel antidepressants. *Frontiers in neuroendocrinology* 50, 107–117. [PubMed: 29859882]
- Willner P, 1983 Dopamine and depression: a review of recent evidence. I. Empirical studies. *Brain research* 287, 211–224. [PubMed: 6140979]
- Willner P, 2015 Animal models for psychiatric states, in: Stoleran IP, Price LH (Ed.), *Encyclopedia of Psychopharmacology*. Springer, Berlin, Heidelberg.
- Willner P, 2017 The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiol Stress* 6, 78–93. [PubMed: 28229111]
- Willner P, Muscat R, Papp M, 1992 Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neuroscience and biobehavioral reviews* 16, 525–534. [PubMed: 1480349]
- Willner P, Towell A, Sampson D, Sophokleous S, Muscat R, 1987 Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology* 93, 358–364. [PubMed: 3124165]
- Yadid G, Friedman A, 2008 Dynamics of the dopaminergic system as a key component to the understanding of depression. *Progress in brain research* 172, 265–286. [PubMed: 18772037]
- Yang XH, Huang J, Zhu CY, Wang YF, Cheung EF, Chan RC, Xie GR, 2014 Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. *Psychiatry research* 220, 874–882. [PubMed: 25262638]
- Zacharko RM, Anisman H, 1991 Stressor-induced anhedonia in the mesocorticolimbic system. *Neuroscience and biobehavioral reviews* 15, 391–405. [PubMed: 1956607]
- Zakariaez Y, Cosgrove KP, Potenza MN, Mazure CM, 2016 Balance of the Sexes: Addressing Sex Differences in Preclinical Research. *Yale J Biol Med* 89, 255–259. [PubMed: 27354851]

- Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr., Gould TD, 2016 NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 533, 481–486. [PubMed: 27144355]
- Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, Pereira EFR, Albuquerque EX, Thomas CJ, Zarate CA Jr., Gould TD, 2018 Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev* 70, 621–660. [PubMed: 29945898]
- Zarate CA Jr., Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, Moaddel R, Wainer IW, 2012 Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biological psychiatry* 72, 331–338. [PubMed: 22516044]
- Zarate CA Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK, 2006 A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry* 63, 856–864. [PubMed: 16894061]
- Zhao X, Venkata SL, Moaddel R, Luckenbaugh DA, Brutsche NE, Ibrahim L, Zarate CA Jr., Mager DE, Wainer IW, 2012 Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. *Br J Clin Pharmacol* 74, 304–314. [PubMed: 22295895]
- Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, Chen LJ, Li MD, Ning YP, 2019 Neurocognitive performance and repeated-dose intravenous ketamine in major depressive disorder. *Journal of affective disorders* 246, 241–247. [PubMed: 30590286]
- Zhong P, Vickstrom CR, Liu X, Hu Y, Yu L, Yu HG, Liu QS, 2018 HCN2 channels in the ventral tegmental area regulate behavioral responses to chronic stress. *Elife* 7.
- Zhu W, Ding Z, Zhang Y, Shi J, Hashimoto K, Lu L, 2016 Risks Associated with Misuse of Ketamine as a Rapid-Acting Antidepressant. *Neurosci Bull* 32, 557–564. [PubMed: 27878517]

Figure 1. Afferent regulation of VTA DA neuron activity by two opposing circuits.

The DA system is under regulation by an activating circuit consisting of the ventral subiculum of the hippocampus (vSub)-nucleus accumbens (NAc)-ventral pallidum (VP) as well as an inhibitory circuit consisting of the basolateral amygdala (BLA)-VP pathway. At baseline, about half of all VTA DA neurons are firing spontaneously. The spontaneous tonic firing state is regulated by the vSub through excitatory projections to the NAc, which in turn, inhibit the VP and release silent DA neurons from inhibition resulting in spike activity. Thus, activation of the vSub induces an increase in the number of spontaneously active DA neurons, without affecting burst firing. This is significant since only DA neurons that are firing spontaneously can respond to rapid phasic activation with bursts of action potentials, and this is driven by activation of the pedunculopontine tegmental nucleus (PPTg) glutamatergic afferents acting on NMDA receptors. This activation can be offset by the BLA, which can excite the VP and inhibit VTA DA neuron population activity. Normally these systems are in balance, keeping the DA neurons in an active state but capable of responding rapidly to an activating stimulus but kept in check by the inhibitory circuit.

Figure 2. Circuit mechanisms underlying reduced VTA population activity following chronic or repeated stress.

Regulation of tonic DA activity is under 2 distinct and opposing circuits: an activating circuit (vSub-NAc-VP), which releases DA neurons from VP GABAergic inhibition and one inhibitory circuit (BLA-VP), which increases VP GABAergic inhibition of DA neurons (see Figure 1). In animal models of chronic stress, there is a downregulation in VTA population activity, as indexed by reduced numbers of spontaneously active DA neurons, which limits the amplitude of the phasic DA response that is driven by the PPTg. Activation of the BLA by chronic or repeated stress drives an attenuation in VTA DA neuron population activity via enhanced excitatory drive onto the VP, which increases inhibition of DA neuron firing. Chronic stress also attenuates excitation within the vSub-NAc-VP pathway, which increases the number of DA neurons that are under inhibitory control by the VP. Hence, chronic stress increases drive of the BLA-VP (i.e. inhibiting) circuit while also decreasing excitatory drive within the vSub-NAc-VP (i.e. activating) circuit, both of which converge to inhibit VTA DA neuron firing.