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The molecular and cellular mechanisms of depression: a focus on reward circuitry

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Abstract

Depression is a complex disorder that takes an enormous toll on individual health. As affected individuals display a wide variation in their clinical symptoms, the precise neural mechanisms underlying the development of depression remain elusive. Although it is impossible to phenocopy every symptom of human depression in rodents, the preclinical field has had great success in modeling some of the core affective and neurovegetative depressive symptoms, including social withdrawal, anhedonia, and weight loss. Adaptations in select cell populations may underlie these individual depressive symptoms and new tools have expanded our ability to monitor and manipulate specific cell types. This review outlines some of the most recent preclinical discoveries on the molecular and neurophysiological mechanisms in reward circuitry that underlie the expression of behavioral constructs relevant to depressive symptoms.

Introduction

Millions of individuals suffer from depressive disorders worldwide and up to 40% of patients do not adequately respond to antidepressant medications [1]. Major depressive disorder (MDD) is a symptomatically heterogeneous disease, spanning cognitive, emotional, motivational, and physiological domains. Identifying the exact etiology of MDD is challenging, as MDD patients present with a constellation of symptoms that are not likely explained by a single unifying mechanism. However, human functional imaging and postmortem tissue studies have identified abnormalities in several brain regions [2–6] including nuclei within the brain's reward pathway. Altered reward circuit function is theorized to underlie the loss of pleasure and amotivational syndrome experienced by most MDD patients, and many studies have strived to uncover the precise circuit, cellular, and molecular adaptations responsible for this anhedonia.

Preclinical rodent models for studying depression have been useful for identifying the cell-type-specific mechanisms that are otherwise inaccessible in human studies. Although rats and mice do not likely experience the complex cognitive aspects of clinical depression,

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rodents, similar to humans, want to work for rewards such as food, sex, and social interaction. When either species show diminished interest in these rewards, it is termed "anhedonia" and is modeled several ways preclinically. The most common models generate anhedonia with chronic stress or by using animals selectively bred for this behavior [7]. Chronically stressed rodents have reduced reward preference, as measured by a loss of preference for sucrose solutions and time spent interacting with a novel con-specific. Stressed animals also tend to spend less time struggling against inescapable stressors such as forced swimming or tail suspension. The stress-induced behavioral phenotypes are reversed by chronic, but not acute antidepressant treatment, and are thus posited to have both face and predictive validity [8]. However, it is of paramount importance to consider a range of behavioral tests when assessing depression-like behavior in rodents. Compounds that produce acute behavioral effects in a forced-swim or tail-suspension test (i.e., increase struggling time) may not translate to meaningful therapeutics when administered chronically and the meaning of "time spent struggling" has been recently called into question [9]. For the sake of brevity, we will briefly describe the common depression models mentioned in this review and refer the reader to [7, 8] for more in-depth coverage.

Chronic unpredictable stress

One of the more widely used depression models employs a battery of chronic, mild physical stressors, termed chronic mild, variable, or unpredictable stress (herein abbreviated CUS). In this paradigm, rodents are exposed to a series of stressors such as cage tilting and disrupted lights for 8–12 weeks [10], after which animals show reduced sucrose preference. Both male and female rodents can be used in CUS paradigms and the stress results in other "depression-like behaviors," such as increased immobility in the forced-swim test. The pattern of stressors can vary between laboratories and many groups study only animals that lose sucrose preference after stress.

Learned helplessness

In "learned helplessness," rodents are first exposed to a series of unescapable foot shocks. Animals are then given an option to escape the shock: those that fail to escape display "learned helplessness [11]," which attempts to mimic the sense of powerlessness felt by some MDD patients. Although this model also generates a cohort of "resilient" animals (those that escape the shock), it often relies solely on "escape failures" to measure depression-like behavior.

Social defeat stress

In addition to physical stressors, the preclinical field has moved toward psychosocial stressors, as the stressful experiences that precipitate MDD likely represent a combination thereof. The most widely used and standardized psychosocial stressor is chronic social defeat stress (CSDS). CSDS subjects mice to once-daily bouts of agonistic social confrontation with a resident aggressor and continuous sensory interaction with the resident for 10 days [12]. Approximately 70% of mice that undergo CSDS are termed "stress-susceptible," displaying a robust depression-like phenotype marked by reduced social interaction, increased anhedonia, and significant body-weight changes [13]. The remaining ~30% of mice retain preference for social interaction and are termed "stress-resilient."

Historically, CSDS has been restricted to adult male mice, but recent procedural modifications allow for inclusion of female subjects [14–16] and adolescents [17]. Each model for depression affords unique advantages and disadvantages, and we refer the reader to in-depth discussion in Czéh et al. [7].

It is impossible to cover what spans at least six decades of work on the neural underpinnings of depression. Due to the great successes of measuring reward-related behavior in preclinical models, this review will focus on how two key components of reward circuitry, the ventral tegmental area (VTA) and nucleus accumbens (NAc), undergo adaptations in models for studying depression. First, we will describe recent discoveries on how cellular and molecular adaptations in the VTA drive anhedonia. Second, we will cover similar adaptations in the NAc with a focus on the contributions of different neuron subtypes. Third, we will highlight an emerging role for inflammatory and non-neuronal cells within the reward circuit in mediating behavioral constructs relevant to depression.

Ventral tegmental area

Arguably one of the most important nodes in motivation and reward circuitry is the VTA. Reward learning and connectivity between the VTA and striatum is impaired in MDD patients [18, 19]. However, this does not likely represent a weakening of solely reward-related signals. Although dopaminergic neurons in the VTA fire in response to unpredicted reward and in anticipation of impending reward [20], they also respond to aversive events [21, 22], contrary to the old idea that the VTA signals exclusively “positive” events. It is also worth mentioning the VTA contains not only dopaminergic neurons, but GABAergic and glutamatergic neurons. Finally, MDD symptoms often manifest bidirectionally between patients (e.g., increased or decreased appetite), adding additional complexity to the interpretation of altered VTA activity.

To dissect how the VTA is associated with depression symptoms, the preclinical field has invested a great deal of effort characterizing molecular and physiological changes that occur in VTA neurons from animals exhibiting depression-like behaviors. Then, to link these changes to the behavior, researchers have manipulated the cellular and molecular activity to reverse or recapitulate anhedonia. In some instances, decreased VTA activity is enough to elicit anhedonia, whereas in others, increased VTA activity is required. It is becoming increasingly evident that where the VTA dopamine neurons project is as important as the directionality of their activity. Below, we summarize the most recent studies and propose some remaining questions.

Stress-mediated increases in dopamine neuron activity—Chronic physical or psychosocial stressors increase VTA dopamine neuron activity to elicit depression-like behavior. Following CSDS, stress-susceptible animals have increased VTA dopamine neuron firing [13, 23–29] that persists for several weeks after stress termination [28]. Elevated firing appears to drive the susceptible phenotype, as optogenetic stimulation of VTA dopamine neurons recapitulates stress susceptibility in previously resilient animals [23, 24, 30]. However, increased VTA activity drives susceptibility through specific projection targets (Fig. 1, top): inhibiting VTA dopamine neurons that project to the NAc induces resilience

but inhibiting VTA dopamine projections to medial prefrontal cortex (mPFC) promotes CSDS susceptibility [23]. Chronic restraint stress also increases VTA firing [31] and burst firing is increased in vivo during an encounter with an aggressive rat [32]. Dendritic spine density, a proxy for excitatory synapse density and activity, is also increased in the VTA of CSDS-susceptible mice [33]. These lasting increases in VTA dopamine neuron firing after chronic stress appear to drive the susceptible phenotype, but little is known regarding physiological adaptations to VTA non-dopaminergic neurons. Elucidating the cellular and molecular adaptations that promote increased VTA neuronal activity will be important for identifying druggable targets for treating depression symptoms.

Stress-induced alterations in the intrinsic properties of VTA neurons can drive increased VTA activity through changes in neuronal excitability. One modulator of excitability and firing frequency is the hyperpolarization-activated current (I_h), or "pacemaker current," which is conducted through hyperpolarization-activated cyclic nucleotide gated (HCN) channels [34]. The stress-mediated increases in VTA dopamine neuron firing are caused by increased I_h currents [29, 35] (Fig. 1, middle). Increased I_h currents occur specifically in NAc, but not mPFC projecting VTA dopamine neurons [30], aligning with the role of these projections in mediating stress susceptibility [23]. Optogenetic stimulations that promote stress susceptibility also increase dopamine neuron excitability [23]. I_h and intrinsic excitability are upregulated in CSDS-susceptible mice [30], but somewhat paradoxically, I_h is upregulated to a greater extent in resilient mice. Through homeostatic adaptations, resilient mice upregulate K^+ channels to reduce excitability as a consequence of the enhanced I_h [13, 30]. I_h potentiation with repeated lamotrigine increases K^+ currents and decreases neuronal excitability in previously susceptible mice to reverse social and sucrose preference deficits [25]. KCNQ K^+ channels regulate excitability thresholds and counteract membrane depolarizations, and upregulation of this specific inhibitory driving force is thought to underlie altered excitability and resilience. In support of this, KCNQ overexpression or administration of KCNQ-openers rescues depressive behavior [25, 27] by reducing firing of NAc projecting, but not PFC projecting VTA dopamine neurons [25]. KCNQ channel $K_v7.4$ is an attractive target in depression, as this subtype is more selectively expressed in VTA (not substantia nigra) dopamine neurons and $K_v7.4$ currents are reduced in susceptible mice [27]. Sucrose preference deficits, social avoidance, and VTA excitability are reduced by opening $K_v7.4$ channels with fasudil [27], a drug already used in humans [36, 37].

Dopamine neuron excitability is also modulated by receptors expressed on the membrane, as well as intracellular signaling molecules that change receptor expression and trafficking (Fig. 1, middle). For example, norepinephrine released from the locus coeruleus (LC) acts at adrenergic receptors expressed on dopamine neurons to regulate neuronal excitability and CSDS-susceptibility [26]. Repeated activation of VTA projecting LC neurons promotes CSDS-resilience through α_1 and β_3 adrenergic receptors on VTA dopamine neurons [38]. Activation of these receptors balances I_h and K^+ currents to reverse the hyperactivity of NAc projecting VTA neurons [38]. Endo-cannabinoids acting at cannabinoid receptors also alter VTA firing, including cannabinoid receptor CB2. CB2 activation reduces VTA dopamine neuron firing [39] and immobility in forced-swim and tail-suspension tests [40]. Mice over-expressing CB2 have reduced vulnerability to CUS and depression-like behaviors at baseline

[41, 42], whereas CB2 knockout in dopaminergic cells enhances forced-swim and tail-suspension immobility [43]. Acetylcholine through cholinergic receptors further modulates VTA activity, particularly the M5-type muscarinic acetylcholine receptor (mAChR), which enhances tonic excitability of dopamine neurons [44]. Enhanced VTA cholinergic tone increases forced-swim immobility and anhedonia through mAChRs [45], and mAChR or nicotinic acetylcholine receptor (nAChR) antagonism reduces forced-swim immobility [46]. Downstream changes in intracellular signaling cascades can also influence excitability by altering receptor function. For example, chronic stress increases extracellular signal-regulated kinase 2 (ERK2) activity in the VTA and inhibiting VTA ERK2 rescues CSDS-susceptibility and reduces forced-swim and tail-suspension immobility by reducing dopamine neuron excitability [47]. As ERK2 reduces inhibitory currents through $GABA_A$ receptors [48], ERK2 inhibition may suppress dopamine neuron hyperactivity. There are likely additional molecular players that regulate dopamine neuron excitability and compounds targeting these regulators may prove useful therapeutic agents.

Stress-mediated decreases in dopamine neuron activity—As alluded to above ("Stress-mediated increases in dopamine neuron activity"), adaptations to dopaminergic neurons depend on the stressor or depression model. VTA burst firing increases during an agonistic encounter [32] and after repeated social defeat [13], as well as during acute stressors such as restraint or foot-shock [49, 50]. However, chronic mild or chronic cold stress instead reduce VTA population activity [50, 51]. Rats exposed to chronic mild stress have fewer spontaneously active dopamine neurons [52, 53], an effect more pronounced in females [53]. VTA firing is also reduced in mice exposed to CUS and optogenetic stimulation in this context reverses, instead of promotes, stress-induced behavioral deficits [54]. Decreased activity of VTA dopamine neurons may not reflect a weakening of solely reward-related signals, and the time-course and intensity of the stress is likely to generate a different set of molecular and physiological adaptations. It is important to understand the mechanisms underlying opposite physiological changes in models that result in the same behavioral outcome.

Naturally, the mechanisms driving decreased VTA activity after CUS differ from those that cause CSDS-mediated increases in activity. One such mechanism is the L-type voltage gated calcium channel $Ca_v1.3$, which decreases neuronal excitability [55]. Increased VTA $Ca_v1.3$ channel activity enhances anhedonia and social-behavior deficits [56], in agreement with the idea that reduced VTA activity drives specific depressive behaviors [54]. Acetylcholine signaling through β2-nAChRs also modulates VTA activity, whereby β2-nAChR signaling switches dopamine neurons to an excited state [57]. Peroxisome proliferator-activated receptor α (PPARα) signaling increases β2-nAChR phosphorylation, which subsequently decreases VTA dopamine neuron firing [58]. Somewhat paradoxically, long-term activation of PPARα decreases β2-nAChR phosphorylation, increases dopamine neuron bursting, and rescues sucrose self-administration after stress [59]. Apart from excitability, reduced VTA activity can also arise from a loss of excitatory input. Mice that develop anhedonia after systemic lipopolysaccharide have reduced plasma membrane expression of AMPA receptor subunit GluR1 [60], indicative of decreased excitatory input onto dopamine neurons.

Although the bidirectional changes in VTA activity reported in CUS and CSDS studies may reflect methodological differences, it is possible that decreased VTA activity following CUS and increased activity following CSDS reflect subpopulations of dopamine neurons with different projection targets. Those that project to mPFC may have decreased activity, whereas those that project to NAc may have increased activity. Careful dissection of individual cell types is needed to understand this discrepancy and the differing molecular and receptor-level mechanisms changing dopamine neuron activity and excitability.

Classical antidepressant actions on VTA dopamine neuron activity—Similar to stressors, classical antidepressant treatments either increase or decrease VTA dopamine neuron activity. Two weeks of fluoxetine normalizes I_h currents in dopaminergic neurons after CSDS [29], indicating one mechanism of classic antidepressant action may be restoration of baseline dopamine neuron activity. Indeed, both CSDS and CUS-induced firing changes are reversed by I_h current normalization after HCN2 overexpression [30, 61]. Two weeks of escitalopram reduces VTA firing rate and bursting activity [62], whereas other antidepressants or electroconvulsive therapy increase burst firing [63, 64]. However, these disparate findings are difficult to interpret, as both behavioral and serotoninergic effects of anti-depressant citalopram are affected by housing conditions (i.e., group or single housing) [65]. The rats used in ref. [63] were group-housed during treatment, whereas the housing conditions used in ref. [62] are unclear. Perhaps classical antidepressants fail in some individuals because the VTA firing rate is changed incorrectly, i.e., they increase activity when decreased activity would be more therapeutic. Future work could compare how classic and new rapid acting antidepressants alter VTA firing rates in several different stress paradigms or treatment-resistant patients to address this possibility.

Molecular adaptations in the VTA—Numerous molecular changes accompany the electro-physiological and behavioral changes, including brain-derived neurotrophic factor (BDNF) and signaling molecules downstream of BDNF (Fig. 1, bottom). The appearance of depressive-like behavior following CSDS is mediated in part by increased BDNF signaling in the VTA to NAc circuit, reviewed elsewhere in detail [66]. Optogenetic stimulation of NAc projecting VTA neurons exacerbates susceptibility to social stress in a BDNF-TrkB receptor-dependent manner [24]. However this is circuit specific as BDNF has antidepressant actions in other brain regions that are required for the antidepressant effects of ketamine [67].

Protein kinase B (AKT), downstream of BDNF signaling, is a molecular link between depressive behavior and altered dopamine neuron activity. Decreased AKT is associated with increased VTA dopaminergic neuron excitability and reduced AKT tone leads to reductions in membrane $GABA_A$ receptor expression and GABA release. Activated phospho-AKT is decreased in the VTA of susceptible mice, an effect reversed by fluoxetine and recapitulated by expression of a dominant negative AKT mutant. In rats subject to forced-swim, downregulated AKT in the VTA enhances immobility and decreases sucrose preference [68]. Other downstream kinases, such as Cyclin dependent kinase 5 (Cdk5) also regulate depressive behavior by altering dopamine release. Cdk5 phosphorylates the rate-limiting enzyme for dopamine synthesis, ultimately influencing dopamine release in the

terminal field. VTA Cdk5 knockout decreases sucrose preference and increases immobility in the forced-swim test, an effect reversed by elevating cAMP in dopamine neurons [69].

Psychosocial [13] and unpredictable stress [70, 71] profoundly alter gene expression beyond the BDNF pathway in total VTA tissue (Fig. 1, middle). When differentially expressed genes are classified by Gene Ontology and grouped by gene function, stress alters the expression of genes that regulate actin cytoskeleton, calcium signaling, cholinergic synapses, and dopaminergic synapses. A major goal for the field is to identify the upstream regulators of these transcriptional changes. Recent work has identified the transcription factor *Otx2* as one such upstream regulator responsible for "stress-priming" the VTA [72]. Stress in a late postnatal period primes the VTA to be in a depression-like state by suppressing expression of *Otx2.* Transient VTA *Otx2* overexpression rescues the enhanced CSDS-susceptibility and downregulation of *Otx2*-regulated genes caused by late postnatal stress [72]. Identifying common transcriptional regulators of the genes altered in depression may aid in identifying new therapeutics.

Remaining questions—Together, these recent studies provide insight into how stress exposure alters the physiology of VTA dopamine neurons and provides clues into the underlying molecular mechanisms controlling depressive behavior. However, several questions remain. Namely, are the bidirectional changes in VTA activity after CSDS or CUS a consequence of stress paradigm, such that each stressor causes unique cellular and molecular adaptations? Or can the changes in VTA activity be viewed along a continuum, whereby "too much" or "too little" I_h current disrupts baseline firing? Do the firing changes instead reflect different symptoms—i.e., social withdrawal vs anhedonia? Or do they reflect the activity of separate cell populations within the VTA [73]? Specific VTA afferents regulate reward and aversion [74]. Is there a role for specific inputs onto VTA dopamine neurons in depression? What are the contributions of non-dopaminergic cells in the VTA that receive similar inputs to dopaminergic cells [75]? Finally, what are the molecular mechanisms driving the changes within subpopulations, do they vary within dopaminergic and non-dopaminergic cells, and how can we target them to ameliorate depressive symptoms?

Nucleus accumbens

One of the major projection targets of VTA dopamine neurons is the NAc. The primary projection neurons of the NAc are medium-spiny neurons (MSNs), which are divided into two subtypes based on the expression of dopamine D1 or D2 receptors (D1-MSNs and D2-MSNs, respectively) [76]. There is little anatomical overlap between MSN subtypes or their projection targets [77, 78]. NAc D1-MSNs send projections back to the VTA, as well as the substantia nigra and ventral pallidum (VP), whereas D2-MSNs project exclusively to the VP [77, 78]. Under normal conditions, the actions of D1-and D2-MSNs generate balanced behavioral output [79, 80]. However, biased activity of one subtype over another is hypothesized to lead to depression [81].

NAc function is altered in stressed or anhedonic animals. NAc MSNs undergo structural and physiological changes after chronic stress dependent on MSN subtype. Glutamatergic,

dopaminergic, and peptidergic transmission are also altered by chronic stress in the NAc. Increasing glutamatergic transmission into NAc can either promote or rescue stress-related behaviors dependent on the afferent projection. Similarly, alterations to NAc dopamine release and uptake are contingent on the stress paradigm. An array of transcriptional changes accompanies altered NAc function. These include up-or downregulation of cellular morphology molecules, glucocorticoid and glutamate receptors, and transcription factors. Epigenetic changes are one potential mechanism by which such a vast array of genes exhibit altered expression; however, much of this work has not differentiated between MSN subtype. Given the often oppositional changes in D1-and D2-MSNs, continued effort to identify the physiological and molecular changes in specific subtypes will be key to understanding how the NAc contributes to depression. Below, we summarize the most recent studies and propose some remaining questions.

Bidirectional changes in D1-and D2-MSN activity—Chronic stress alters MSN activity by changing excitatory input and intrinsic excitability. Excitatory input is weakened onto D1-MSNs and strengthened onto D2-MSNs of chronically stressed mice [82, 83] (Fig. 2). Optogenetic D1-MSN stimulation reverses social and sucrose preference deficits, whereas D2-MSN stimulation enhances stress susceptibility [82]. At the level of individual dendritic spines, there is evidence for synaptic strengthening of the larger, mushroom spines on D1-MSNs and weakening of mushroom spines on D2-MSNs in stress-resilient mice [84]. Long-term potentiation correlates with spine enlargement [85], suggesting one mechanism of stress resilience may be a strengthening of glutamatergic input onto D1-MSNs. At baseline, calcium transients in D1-, but not D2-MSN are associated with social interaction [86], consistent with D1-MSN activation being sufficient to drive social behavior [87]. D1-MSN peak calcium transient amplitude is larger in mice that will later become resilient, suggesting increased D1-MSN baseline activity; however, this difference is abolished after the first aggressive encounter [86]. D1-MSN calcium transient frequency is reduced during social interaction in stress-susceptible mice [88]. Thus, reductions in D1-MSN, but not D2-MSN activity, drive social avoidance after CSDS.

Despite reductions in excitatory input, D1-MSNs of susceptible mice have increased excitability [82, 89] and calcium transient amplitudes [88]. Increased D1-MSN excitability may arise as a homeostatic adaptation to the loss of excitatory input through altered structural morphology (see “Structural plasticity” below). One potential mechanism for enhanced D1-MSN excitability is through increased glucocorticoid receptor signaling. Glucocorticoids can enhance excitability [90] and D1-MSN glucocorticoid receptor knockout promotes stress resilience [91]. However, glucocorticoid-mediated plasticity may be NAc subregion-dependent. After cold water forced-swim, synaptic strength is increased in MSNs only from the NAc shell, an effect blocked by pre-administration of a glucocorticoid receptor antagonist [92]. Voltage-gated calcium channels also regulate neuronal excitability. *Cacna1c,* which codes for the voltage-dependent calcium channel-α1C subunit (Cav1.2), is decreased in the NAc of CSDS-susceptible mice. NAc *Cacna1c* knockdown enhances stress susceptibility and increases anhedonia [93], indicating a possible role for calcium channels in depressive behavior. However, it is unclear which MSN subtype undergoes synaptic plasticity in this study. It will be important to characterize the

mechanisms underlying altered synaptic strength in specific cell types due to the bidirectional change in D1-and D2-MSN activity.

Changes to glutamatergic function in NAc—The NAc receives glutamatergic inputs from several afferents and stress alters excitatory transmission arising from the thalamus, mPFC, and hippocampus (Fig. 2, top) [94–96]. Increased glutamatergic transmission from intralaminar thalamus to NAc synapses promotes CSDS-susceptibility, whereas blocking transmission at these synapses blocks social avoidance [95]. NAc glutamate transporter Vglut2 is increased in female mice after subchronic variable stress [94], similar to CSDS-susceptible male mice [95]. Vglut2 is expressed predominately by the thalamus and brainstem neurons [97], lending further support to enhanced thalamo-accumbal transmission in stress susceptibility. Conversely, glutamate release at mPFC to NAc synapses is decreased in CSDS-susceptible mice and stimulation of inputs from mPFC or amygdala promotes CSDS-resilience [96]. Some evidence suggests ventral hippocampus (vHip) to NAc synapses are strengthened in CSDS-susceptible mice [96]. Stimulation of vHip to NAc synapses is pro-depressive in an acute forced-swim stress but does not impair social behavior in the absence of stress [96]. In contrast, vHip to NAc synapses are weakened following chronic multimodal stress; however, this appears to occur selectively onto D1-MSNs [98]. NAc afferents may differentially target D1-or D2-MSNs [99], begging the question if the changes to glutamatergic inputs are MSN subtype specific.

Glutamate signals through a variety of postsynaptic receptors including ionotropic AMPA and NMDA receptors. Increased NAc AMPA receptor function (increased GluR1:GluR2 ratio) is associated with CSDS-susceptibility [100]. Arc protein regulates AMPA receptor trafficking and promotes endocytosis [101]. Social defeat upregulates NAc Arc protein in rats who exhibit proactive (“fighting back”) coping behavior [102]. It is tempting to speculate that decreased AMPA receptor function, via Arc upregulation, contributes to the more resilient behavioral outcome in proactive-coping rats. Interestingly, mice expressing a G2019S mutation in leucine-rich repeat kinase 2 (LRRK2) are unusually resilient to CSDS and fail to accumulate inward rectifying AMPA currents typical of susceptibility. NAc glutamatergic synapses in LRRK2 mutant mice lack functional inwardly rectifying calcium-permeable AMPARs [103]. Blocking NAc calcium-permeable AMPARs reverses social-behavior deficits [56]. Together, these studies reveal an important role for specific AMPARs in mediating CSDS-susceptibility.

Glutamate signaling through NMDA receptors is key for depressive behavior in D2-MSNs. Anhedonia in chronic pain models is associated with prolonged NMDA receptor signaling in D2-MSNs due to an increase in the proportion of GluN2B containing NMDA receptors [104]. In agreement, rendering NMDA receptors non-functional in D2-MSNs by GluN1 knockout results in a depression-resistant phenotype, marked by prolonged latency to immobility in forced-swim and tail suspension [105]. Further, the antidepressant effects of fluoxetine require downregulation of the NMDA receptor signaling partner CaMKII [106, 107]. As excitatory input is enhanced onto D2-MSNs, it is probably enhanced calcium influx through calcium-permeable AMPA and NMDA receptors on D2-MSNs that drive CSDS-susceptibility.

Dopaminergic function—The NAc receives dense dopaminergic input from the VTA, and for an excellent review on how stress impacts extra-cellular dopamine, we refer the reader to ref. [108]. Acutely, NAc dopamine receptor blockade is pro-depressive during tail suspension [54] and global dopamine receptor antagonism reduces sucrose preference [109]. However, dopamine receptor antagonism during CSDS does not block susceptibility [24]. At both expression and protein level, NAc dopamine receptors and dopamine transporter (DAT) are upregulated in stressed rats (Fig. 1, bottom) and increased D2-family receptor expression is linked to decreased sucrose preference [70]. Work from the Jones lab also supports a role for altered DAT in stress. Rats reared in social isolation have increased NAc dopamine release and faster uptake compared with those reared in group housing but reduced basal dopamine levels [110]. In slice preparations, evoked NAc dopamine release and uptake rates are also increased in socially defeated rats [111]. This contrasts with unaltered dopamine release in socially defeated mice [24]. It is still unclear how altered (or unaltered) NAc dopamine release drives social avoidance and other depression-like behaviors due to the dearth of real-time dopamine measurements in behaving animals.

Neuropeptides—Neuropeptides exhibit diverse, often long-lasting effects on gene expression and excitability. Stress promotes the release of neuropeptide dynorphin and activation of endogenous opioid signaling [112]. Dynorphin mRNA is increased in the NAc shell of CSDS-susceptible mice [113] and expression of structurally similar nociceptin/orphanin FQ is increased in both shell and core of socially defeated rats [114]. NAc dynorphin concentration is decreased in rats reared in social isolation, but this is thought to be a consequence of increased release, as κ-opioid receptors are functionally hyperactive [115]. Although dynorphin is associated with stress susceptibility, enkephalin is associated with stress resiliency [116]. NAc enkephalin mRNA is downregulated following chronic restraint [117] but upregulated in rats resilient to the stress [118]. These small opioid peptides signal through inhibitory G-protein-coupled receptors that modulate MSN excitability. Chronic restraint increases NAc melanocortin receptor MC4R expression and MC4R knockdown prevents stress-induced weight loss and decreased sucrose preference [83]. The ligand for MC4R, α-melanocyte-stimulating hormone, exerts its prodepressive effects through D1-MSNs by altering excitability and increasing calcium-permeable AMPA receptors [119]. Neuropeptides can influence several targets due to volume transmission, but how they influence MSN-subtype excitability seems to be key for their role in depression-like behaviors.

Gene expression—There are several genes implicated in response to stress and depressive behavior (Fig. 2, middle). For example, transcription factor CREB is stimulated in the NAc following stress and its activation drives anhedonia (recently reviewed in ref. [120]). ΔFosB, a truncated isoform of FosB, is induced by stress or antidepressant exposure and is associated with resilience (recently reviewed in refs. [120, 121]), particularly in D1-MSNs [100, 122]. Recent work suggests the protective effect of voluntary wheel running on stress-induced depression is through a CREB-dependent induction of ΔFosB [123] and *Fosb* targeted histone acetylation drives resilience in D1-MSNs, but susceptibility in D2-MSNs [124].

Depressive behavior is mediated in part by increased NAc BDNF signaling (reviewed in ref. [66]). FosB and CREB can regulate BDNF expression, and BDNF upregulation induced by synaptic activity depends on Wnt secretion [125]. Wnt leads to activation of the kinase disheveled (DVL). Activated DVL inhibits glycogen synthase kinase-3β (GSK3β) and regulates several downstream targets including β-catenin (β-cat). DVL is downregulated in the NAc of postmortem MDD patients and GSK3β inhibition promotes CSDS-resilience [126]. β-Cat signaling is down-regulated specifically in D2-MSNs of susceptible mice and excising β-cat from the NAc increases stress susceptibly [127]. β-Cat regulates *Dicer1,* a microRNA regulator that, in turn, modulates other known pro-susceptibility genes such as *Arc* and *Npas4* [127].

Many studies have focused on signaling pathways downstream of BDNF signaling. Indeed, phospho-extracellular signaling regulated kinase is increased in the NAc shell of D1-MSNs in susceptible mice [24]. Transcription factors downstream of BDNF, such as transforming growth factor β-inducible early gene-1 [102], and Early Growth Response 3 (*Egr3*) [88] are also upregulated after social defeat (Fig. 2, middle). *Egr3* is upregulated specifically in D1-MSNs of susceptible mice and its knockdown can prevent altered synaptic activity and stress susceptibility [88]. Genes that are under the control of these upregulated transcription factors also exhibit increased expression. For example, the mitochondrial biogenesis regulator PPAR-γ coactivator 1-α (*PGC1α*) is regulated by both CREB [128] and *Egr3* [129]. Social defeat increases NAc PGC1α and its downstream myokine FNDC5, and FNDC5 is upregulated more in resilient mice [130]. FNDC5 induces thermogenesis and elevates mitochondrial gene expression [131], and resilient mice have increased NAc metabolism [132]. These mitochondrial and metabolic changes may allow for increased expression of other resilience-associated genes by providing more ATP and are worth further investigation.

Beyond CREB and *Egr3*, other transcription factors regulate gene expression to contribute to stress-related behaviors. Estrogen receptor-α (ERα), a ligand-gated transcription factor, upregulates the expression of genes associated with nervous system development and downregulates genes associated with immune system processes. In female mice subject to chronic variable stress, NAc ERα is decreased in the nuclear fraction of both D1-and D2-MSNs. In both male and female mice, NAc ERα overexpression increases sucrose preference and promotes CSDS-resilience in males [133]. NAc ERα overexpression in male mice also induces a transcriptional profile similar to that of resilient mice [133]. Ligand-activated transcription factors may be useful targets for pharmacotherapy, as expression of resilience-related genes could be turned off and on.

Modern genetic approaches allow for transcriptional profiling of select cell types [134] and this approach has afforded new insights into genes changed exclusively in D1-or D2-MSNs (Fig. 2, bottom). For example, the MDD risk gene *SLC6A15* [135] is decreased in postmortem MDD NAc. In mice susceptible to CSDS, *Slc6a15* is decreased selectively in D2-MSNs and stress susceptibility is recapitulated by decreasing *Slc6a15* specifically in D2-MSNs [136]. Similar to opposing electrophysiological changes in D1-and D2-MSNs, genes important for synapse maintenance and dendritic architecture are differentially expressed between the cell types. Synaptic cell-adhesion molecule Neurologin 2 (*Nlgn2*) is decreased specifically in D1-MSNs of susceptible mice. D1-MSN *Nlgn2* knockdown leads to

susceptibility, whereas *Nlgn2* knockdown in D2-MSNs confers resilience [137]. The GTPase RhoA, which negatively regulates dendritic complexity, is increased specifically in D1-MSNs of susceptible mice [138]. *RhoA* is transcriptionally regulated by *Egr3* [88] and in stress-naive mice, increased RhoA in D1-MSNs decreases sucrose preference in males, grooming behavior in females, and forced-swim immobility. Upregulation of RhoA in D1-MSNs either by *Egr3* overexpression or *RhoA* over-expression promotes stress susceptibility [88, 138]. After CSDS, inhibiting downstream effector Rho-kinase reverses social withdrawal and forced-swim immobility [138]. These cell-type-specific changes in gene expression are candidate mechanisms for bidirectional changes in activity (discussed above in "Bidirectional changes in D1-and D2-MSN activity") and structure (discussed below in "Structural plasticity"). Future work using this approach is likely to uncover additional candidate mechanisms within the cell types.

Epigenetic mechanisms—Epigenetic modifications are a candidate mechanism for how stress alters gene expression to convey the risk for depression. DNA methyltransferases (DNMTs), histone methyltransferases, and histone deacetylases (HDAC) alter the structure and function of chromatin to regulate gene expression [139]. Repressive histone modifications are both up-and downregulated after social defeat stress, and these changes are linked to genes with known roles in CSDS-susceptibility. The repressive histone lysine methyl-transferase G9a decreases TrkB-CREB signaling and G9a expression is decreased in the NAc of CSDS-susceptible mice [140]. G9a overexpression promotes resilience, thought to occur by normalization of TrkB-CREB signaling [140]. Permissive acetylation on the *Rac1* promotor, a GTPase downregulated by CSDS, is significantly reduced in susceptible mice, and susceptible mice have enhanced methylation directly upstream of the promotor [141]. Similarly, there is increased repressive trimethylation along the promoter region of *Rac1* after social isolation stress [142]. Intra-NAc HDAC inhibition reverses social avoidance induced by CSDS, likely caused by increased *Rac1* expression [141]. CSDS upregulates transcriptional repressor *Dnmt3a* in the NAc and chronic intra-NAc DNMT inhibition restores social interaction [143]. Subchronic stress also upregulates NAc *Dnmt3a*, but to a greater extent in stressed females. *Dnmt3a*overexpression makes both sexes susceptible to 3 days of subchronic variable stress [144], indicating transcriptional repression is a shared mechanism of stress susceptibility between the sexes.

Apart from DNMTs, epigenetic modifications such as hydroxymethylation can also repress gene expression. The hydroxymethylase 10–11 translocation methylcytosine dioxygenase 1 (Tet1) catalyzes the conversion of 5-methycytosine to 5-hydroxymethlcytosine. *Tet1* is decreased in the NAc of susceptible mice. Paradoxically, NAc *Tet1* knockout increases sucrose preference and social interaction in stressed mice. However, *Tet1* overexpression induces a resilience-like NAc gene expression profile [145]. The replacement of canonical histones with histone variants ("histone turnover") can also alter DNA binding and subsequent gene expression. Expression of activity-dependent histone variant H3.3 (*H3f3b*) is increased in the NAc in postmortem MDD tissue, after early life stress, and in CSDS-susceptible mice, an effect prevented in mice by environmental enrichment [146]. Stalling histone turnover with viral knockdown of H3.3 produces resilience after CSDS partly due to normalization of transcriptional dysregulation of genes associated with morphology and

plasticity [146]. Although stressors clearly regulate gene expression through epigenetic mechanisms, we have little insight into how they function in cell subtypes. Indeed, the deacetylase SIRT1 promotes CSDS-susceptibility through D1-MSNs [147]. Histone acetylation on the *Fosb* promotor drives resilience in D1-MSNs, but susceptibility in D2-MSNs [124]. Thus, manipulating the epigenetic mechanisms in specific MSN subtypes might allow for more precise control over gene expression and novel therapeutics.

Structural plasticity—Morphological changes are a consequence of altered gene expression and excitatory input after CSDS. Indeed, social avoidance correlates with reductions in volume of the cingulate cortex, NAc, thalamus, raphe, and bed nucleus of the stria terminalis, suggesting the neurons in these regions may undergo structural atrophy [148]. In the NAc, dendritic complexity of D1-, but not D2-MSNs, is reduced in CSDS-susceptible mice. Reduced D1-MSN complexity is sufficient to drive CSDS-susceptibility [88, 138]. NAc MSN spine density, dendritic length, and branch points are decreased after stress hormone corticosterone [149] or gestational stress [150]. Reduced dendritic complexity largely agrees with changes in other brain regions [151, 152] and is associated with reduced excitatory input but increased intrinsic excitability [88, 89], which may reflect homeostatic self-tuning [153]. The mechanism underlying structural plasticity of MSNs in CSDS is altered expression and activity of Rho GTPases [88, 89, 138, 141].

In contrast, CUS increases dendritic length of NAc core MSNs, which is reversed by imipramine or fluoxetine treatment [154]. MSN spine density is also increased in rats susceptible to learned helplessness [155]. However, many of these studies did not examine dendritic complexity or spine density in specific MSN subtypes. Spine density is unchanged in D1-MSNs [88, 89], yet there is evidence MSNs from susceptible mice have more stubby spines [156]. Pro-susceptibility *Dnmt3a* overexpression [143] or constitutively active IκB kinase (IKK) [156, 157] both increase MSN spine density. Thus, we believe the stress-related changes to spine density occur on D2-MSNs, as D2-MSNs do not undergo dendritic atrophy but have enhanced excitatory input [82]. Future work should confirm increased NAc spine density occurs specifically on D2-MSNs and identify the mechanisms causing increased dendritic length after CUS.

Cholinergic interneurons—Approximately 95% of NAc neurons are MSNs; however, the remaining cells, namely interneurons, also contribute to depression-like behaviors. Silencing NAc cholinergic interneurons (ChIs) results in anhedonia and increases immobility in the forced-swim and tail-suspension tests [158]. Decreased ChI activity may modulate local MSN activity to cause depressive behaviors, as optogenetic inhibition of ChI enhances MSN spiking [159]. The role of ChIs is also interesting to consider in the context of NAc dopamine. The dopamine release thought to be important for driving anti-depressive behavior [54] may arise from synchronized NAc ChI activity and be independent of altered VTA activity [160, 161], although this remains untested. One molecular mechanism that contributes to NAc ChI involvement in anhedonia is the calcium binding protein p11. Mice lacking p11 [162], p11 reductions in NAc [163], or p11 knockout in NAc ChIs [158] is sufficient to reduce sucrose preference and increase forced-swim immobility (Fig. 2, top). In the PFC, reduced p11 is associated with increased repressive methylation on the p11

promotor [164], but it is unclear if this also occurs in NAc ChIs. Continued effort to identify the molecular and physiological changes to all cell types in the NAc will be critical for understanding how the NAc encodes depressive behaviors.

Remaining questions—Together, these studies provide insight into how stress exposure alters NAc MSN physiology to elicit depressive behavior. We now have many clues as to the underlying mechanisms, but several questions remain. Why do many divergent transcriptional alterations in the NAc result in the same behavioral outcome and are they a cause or a consequence of anhedonia? How do cellular and molecular changes in NAc projection neurons lead to stress adaptations in target regions including the VTA and VP, the latter which displays distinct circuit alterations after stress [165]? Although hypothesized, is the BDNF critical for CSDS-induced depression actually released from dopaminergic terminals in the NAc? TrkB, but not dopamine receptor antagonism blocks the induction of social avoidance. However, BDNF may be modulating local dopamine release [166, 167] to drive other aspects of anhedonia. Do BDNF and dopamine act on specific MSN subtypes to drive depression? What are the upstream mechanisms governing MSN-subtype-specific atrophy after stress? Both BDNF [168] and dopamine [169] mediate dendritic growth. Dopamine denervation drives atrophy of striatal MSNs, but to a greater extent in D1-MSNs [170], suggesting there may yet be a dopaminergic component to CSDS-susceptibility. Further work is needed to determine the precise mechanisms by which these signaling molecules cause transcriptional changes to alter the morphology and physiology of the two MSN subtypes.

Non-neuronal cell types in reward circuitry

At least 40% of cells in the rodent [171] and human [172] brain are non-neuronal, but how non-neuronal cells interact with reward circuitry in MDD is unknown. There is particular interest in how inflammatory cell types in the brain cause depressive symptoms, as anti-inflammatory treatments reduce depressive symptoms in humans [173] and chronic stress enhances inflammation in animal models [174]. In the periphery, chronically stressed mice upregulate the pro-inflammatory cytokine interleukin 6 (IL-6) [175–177]. IL-6 drives production of inflammatory T-helper 17 (Th17) cells, which promote learned helplessness and social avoidance, and mice unable to produce Th17 are resilient to learned helplessness [178]. CSDS-susceptible mice upregulate cytokines IL-1β and CXCL1, and have more circulating leukocytes [175]. Further, prolonged restraint stress decreases anti-inflammatory IL-4 and IL-10 [176]. In the brain, cytokines such as interferon-α promote depressive behaviors [179] and serotonin reuptake inhibitors have anti-inflammatory properties [180]. CSDS promotes recruitment of circulating monocytes and macrophages into the brain perivascular space via complement 3 receptor and CX3C chemokine receptor 1 signaling [181–183]. Chronic stress also increases the leakiness of the blood-brain barrier to permit infiltration of peripheral immune cells and cytokines such as IL-6 [184].

Microglia—As microglia are the resident immune cells of the central nervous system (CNS) and microglial transcripts are upregulated after stress [185], they are an attractive linker between inflammation and depression in the brain. Microglia can be neuroprotective or neurotoxic dependent on the release of pro-inflammatory or anti-inflammatory factors.

Their dichotomous function is typically described by the M1/M2 paradigm (reviewed in ref. [186]). M1 microglia respond to injury or infection by releasing pro-inflammatory cytokines such as IL-1β. M2 microglia dampen pro-inflammatory immune responses with anti-inflammatory cytokines and can enhance neurotrophic factors. Microglia play a key role in altering synaptic landscape and for an excellent review we refer the reader to ref. [187].

Chronic stress alters microglia density, morphology, and function dependent on stress duration and brain region [188]. Anhedonia caused by high-fat diet or restraint stress is associated with increased ionized calcium-binding adaptor molecule 1-positive microglia in several brain regions including the NAc [189, 190]. Microglia from socially defeated mice have an increased inflammatory profile and produce more IL-6 after lipopolysaccharide (LPS) stimulation [191], similar to enhanced IL-6 release from the peripheral leukocytes of stressed mice [175]. Microglia in CUS mice have enhanced colony stimulating factor 1 receptor expression and enhanced phagocytotic activity, paralleled by *CSF1* elevations in postmortem MDD tissue [185]. Viral knockdown of neuronal *Csf1* attenuates dendritic spine pruning on mPFC neurons and prevents stress-induced anhedonia and forced-swim immobility [185]. As phagocytotic microglia contribute to dendritic remodeling in the mPFC, it is tempting to speculate microglia may also contribute to dendritic spine changes on NAc MSNs.

Microglia release pro-inflammatory cytokines such as tumor necrosis factor-α and IL-1β, which go on to activate other signaling molecules such as IKK and downstream transcription factor nuclear factor (NF)-κB. CSDS increases IKK and NF-κB, along with the number of immature dendritic spines in the NAc of susceptible mice [156, 157]. In the absence of stress, constitutively active IKK increases thin spine density, increases forced-swim immobility, and decreases sucrose preference after acute stress [156, 157]. Viral inhibition of IKK and NF-κB in NAc also prevents neuroinflammation and forced-swim immobility caused by high-fat diet [190]. It remains to be determined which specific cytokines are released by microglia in the NAc to activate IKK and drive changes to dendritic spines and behavior. Cytokines can also be released by neurons and in a spinal nerve ligation model of anhedonia, cytokine CCL2 is upregulated in both NAc D1-and D2-MSNs. *Ccl2* reduction with short hairpin RNA restores sucrose preference and increases swimming in the forced-swim test [192]. As CCL2 recruits monocytes to the site of inflammation, this molecule may serve as another link between inflammation and dendritic remodeling. Further work is needed to identify the precise cytokines that contribute to maladaptive neuroinflammation in stress and depression.

The function of microglia in stress and depression is not limited to neurotoxic signaling but may also involve a degree of neuroprotection. When lymphocytes from socially defeated mice are transplanted into *Rag2*$^{-/-}$ lymphopoenic mice, recipient mice exhibit more social interaction and less tail-suspension immobility [193]. The “stress programmed” lymphocytes alter the microglia in *Rag2*$^{-/-}$ mice, causing them to skew toward a more neuroprotective, M2-like profile [193]. Similarly, intraperitoneal injection of Gram-negative bacterial endotoxin LPS typically elicits a rapid inflammatory response, globally activates microglia, and produces depressive behavior. However, in mice previously exposed to CUS, LPS decreases forced-swim immobility [188]. Does microglial activation instead help prune

the immature dendritic spines generated by stress in NAc or other brain regions [156, 157]? Support for this idea comes from mice with autophagy-deficient microglia. Mice that lack microglial autophagy-related protein 7 exhibit impaired social interaction and increased immature synapses [194]. Further, severe combined immunodeficiency mice have impaired social preference [195]. Thus, although M1 microglia and infiltrating macrophages may contribute to depressive behavior via increased inflammatory signaling, there may be a neuroprotective role of M2 microglia or beneficial synaptic pruning by M1. Microglia found in healthy reward circuitry are incredibly diverse [196] and more work is needed to profile their function in pathologic states. Further, how microglia either respond or contribute to the altered neurochemical environment referenced above remains unknown.

Non-inflammatory cell types—Bacteria in the gastrointestinal tract directly influence neural activity through sensory neurons, or by modulating the function of the hypothalamic–pituitary–adrenal axis (reviewed in ref. [197]). Recent work indicates gut microbiota can also influence neural metabolism [198]. The gut microbiome controls gut permeability and inflammation, and may thus participate in the neuroimmune mechanisms of depression [197]. More work is needed to determine the precise mechanisms by which microbiota interact with both neuronal and non-neuronal cell types in reward circuitry or other brain regions to produce depressive behavior.

It is important to note other non-inflammatory glial cells may contribute to depression. Indeed, CUS can downregulate myelin and oligodendrocyte-specific transcripts in the NAc [199]. Mice with reduced glutamate transporter GLT-1 expression in habenular astrocytes are more stress-susceptible and exhibit increased tail-suspension immobility at baseline [200], in agreement with reduced glutamate transporter expression in learned helpless rats [201]. As glutamate clearance modulates neuronal excitability [200] and glutamatergic synapse strength contributes to depression [202], how astrocytic glutamate clearance contributes to excitatory synapse strength and subsequent depressive behavior is also worth further investigation in the reward circuit.

Remaining questions—Together, these studies provide compelling evidence for reward circuit non-neuronal and neuroimmune mechanisms of depression. It will be important to profile how interactions between glial cells, macrophages, and neurons shift from a normal to pathologic state and how this leads to anhedonia. How do microglia remodel synapses in depression? Do they prune specific spines on specific cell types, or participate in the formation of new spines [203]? What causes the blood–brain barrier to degrade in some brain regions but not others [184, 204]? Are these changes a consequence of physical stressors or would they also extend to emotional stressors [205]? How does the gut microbiome influence anhedonia and how is this altered by changes in food intake during depressive episodes? Neuroscientists must not discount the contribution of the periphery to the changes in CNS function that drive MDD.

Concluding remarks

Dysregulation of the brain’s reward circuitry is heavily implicated in the symptomology of depression and the use of genetic and viral tools has enabled us to define the precise cell

types that contribute to anhedonia. These studies have revealed important adaptations in both dopaminergic and glutamatergic function within the VTA and NAc, and notably these adaptations can differ in directionality based on cell type or stress paradigm. However, much remains to be investigated, especially with respect to the contribution of non-neuronal and inflammatory cell types in depressive behavior. Further, we must define the precise molecular mechanisms that explain the discrepancies involving the contribution of dopamine release and changes to burst firing and excitability of VTA neurons. It is difficult to understand how different stress paradigms yield similar behavioral outcomes but divergent cellular adaptations. Although frustrating for preclinical scientists, the unique adaptations after differing stressors is perhaps unsurprising and may afford an opportunity to address the heterogeneity of MDD in humans.

Although rapid tests such as forced swim and sucrose preference have been important for screening new antidepressant compounds due to their high-throughput nature, these tests should be combined with more complex assessments of motivated behavior and assessed across stress paradigms. It will be important to include behaviors that separate rodents based on response to classical antidepressants [206]. The “treatment-resistant” population may undergo adaptations yet undiscovered and might be more helpful in identifying compounds for treatment-resistant depression. Similarly, although we know changes to NAc D1-and D2-MSN function are bidirectional, most of this work was done solely in male rodents. Moving forward, we must determine the contribution of specific cell types in anhedonic females and the extent to which circulating gonadal hormones, among other unidentified sex differences, alter the development of depression. This is especially important to consider in the context of post-partum depression, which is both uniquely female and inadequately addressed in preclinical models.

Finally, despite significant progress made in elucidating the cellular and molecular mechanisms driving anhedonia and depressive behavior in rodents, new antidepressant treatments have not been approved for use in humans. Much of the validation of the molecular changes found in rodents relies on tissue collected from postmortem MDD brains. It is possible we are ruling out valid molecular targets by predominately measuring changes in gene expression from MDD patients who have completed suicide. This subset of patients certainly does not represent the entirety of individuals suffering from MDD and we must try to identify biomarkers that are more readily accessible in living humans with MDD. By improving our understanding of the specific cellular and molecular mechanisms of depression, we have the potential to uncover new treatments that may ameliorate symptoms in otherwise antidepressant resistant populations.

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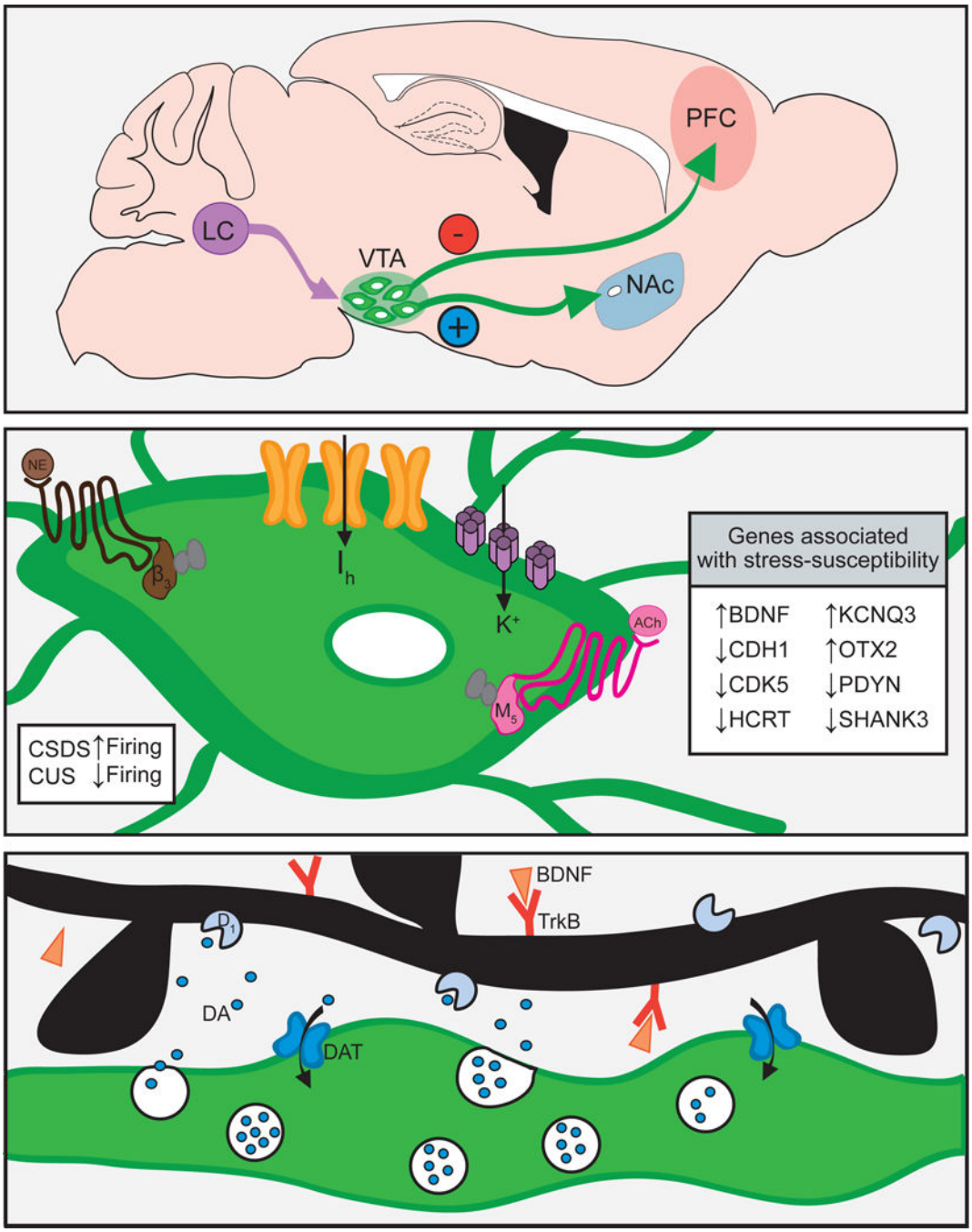

Fig. 1.

Stress alters ventral tegmental area dopamine neurons to generate depressive behavior. Top: Simplified schematic of ventral tegmental area (VTA) projections associated with stress susceptibility. Inhibition of the VTA to prefrontal cortex (PFC) projection is pro-depressant. Stimulation of the VTA to nucleus accumbens (NAc) projection is pro-depressant. Noradrenergic neurons from the locus coeruleus (LC) project to the VTA where they modulate excitability and stress-susceptibility. Middle: VTA dopamine neuron firing is increased in mice susceptible to social defeat (CSDS) and decreased after chronic

unpredictable stress (CUS). Excitability of VTA dopamine neurons is modulated by norepinephrine through α_1 and β_3 receptors (brown), acetylcholine through muscarinic receptors (pink), and a balancing of I_h and K^+ currents through HCN (orange) and KCNQ channels (purple). Inset box details genes associated with stress susceptibility in the VTA. Bottom: Dopamine varicosity (green) releasing dopamine in the NAc. Stress is associated with greater phasic dopamine release, upregulation of dopamine transporters (DAT), dopamine receptors, and BDNF-TrkB signaling

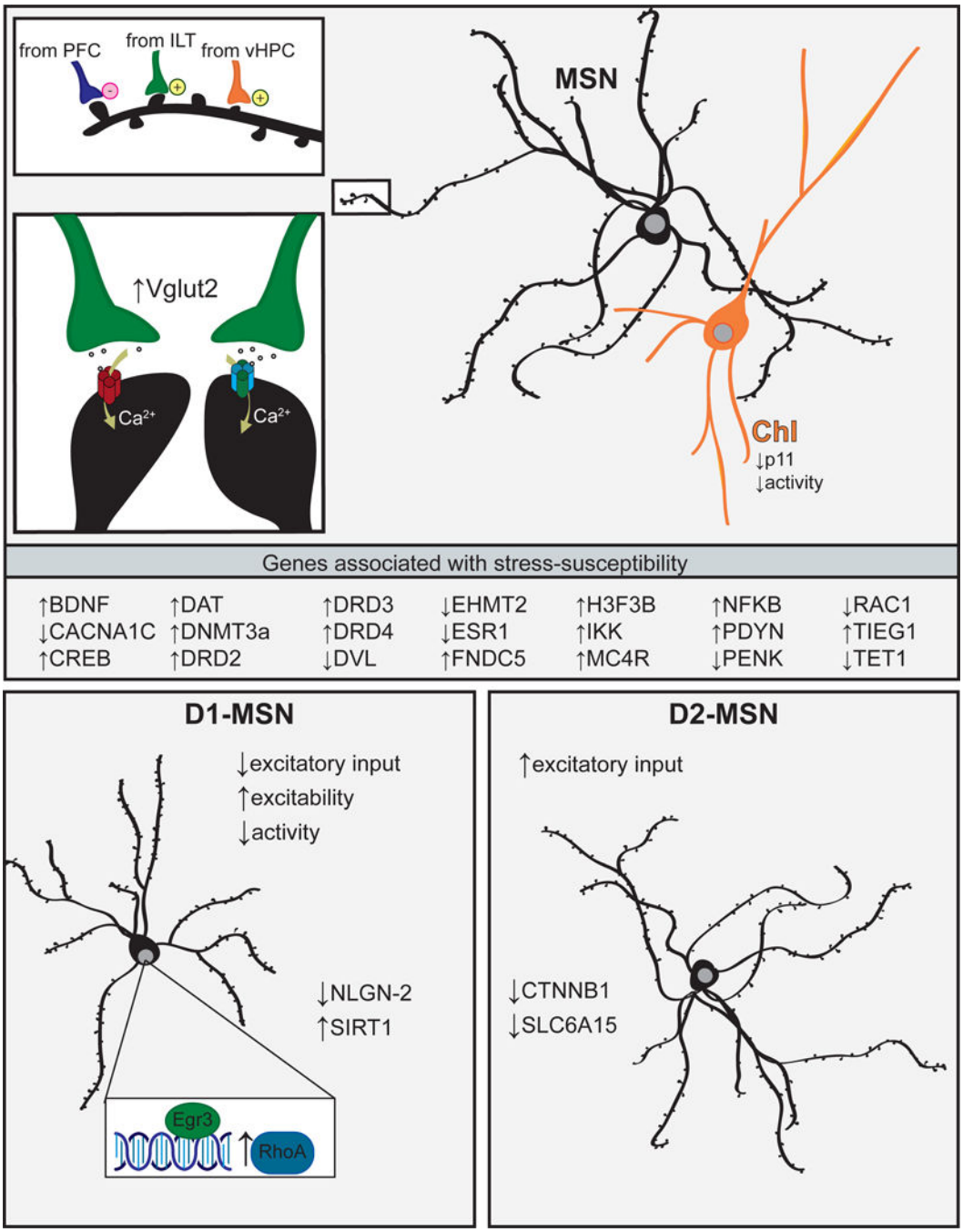

Fig. 2.

Depression is associated with cell-type-specific adaptations to nucleus accumbens medium-spiny neurons. Top, upper left: Susceptibility to social defeat stress is associated with a weakening of gluta-matergic inputs from prefrontal cortex (PFC) and strengthening of inputs from intralaminar thalamus (ILT) and ventral hippocampus (vHPC) to nucleus accumbens medium-spiny neurons (NAc MSNs). Top, lower left: Stress-susceptible mice have increased expression of glutamate transporter Vglut2, increased calcium-permeable AMPA receptors (red), and increased GluN2B containing NMDA receptors (blue). Top, right: Cholinergic

interneurons (ChI) have reduced protein p11 and ChI inhibition induces depressive behavior. Middle: Genes associated with stress susceptibility in the NAc. Bottom, left: In stress-susceptible mice, dopamine D1 receptor expressing MSNs undergo dendritic atrophy. D1-MSNs also have decreased excitatory input, increased intrinsic excitability, and reduced activity in vivo. Neuroligin-2 (NLGN-2) expression is decreased selectively in D1-MSNs. Sirtuin-1 (SIRT1), Early Growth Response 3 (Egr3), and RhoA expression are increased selectively in D1-MSNs. Inset: Egr3 transcriptionally regulates expression of RhoA in stress-susceptible mice. Bottom, right: In stress-susceptible mice, dopamine D2 receptor expressing MSNs do not undergo dendritic atrophy, but may increase spine density. D2-MSNs have increased excitatory input. β-catenin (CTNNB1) and transporter Slc6a15 expression are reduced selectively in D2-MSNs