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Emerging role for nucleus accumbens medium spiny neuron subtypes in depression

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Abstract

The ventral striatum (nucleus accumbens- NAc) and its role in mood, reward, and motivation has been the focus of significant research. Despite this interest, very little work has addressed cell-type specific distinctions in medium spiny neurons (MSNs), the main projection neurons in the NAc and dorsal striatum, and their function in relation to stress and depression. Previous work demonstrates opposing roles for Dopamine 1 receptor (D1) and dopamine 2 receptor (D2) MSN subtypes, in depression-like outcomes to stress, particularly in regards to repeated neuronal stimulation and excitatory transmission. Yet the mechanisms of action are still unknown. We discuss potential mechanisms by which MSN subtype function promotes dichotomous behavioral outcomes due to differences in cellular plasticity, subcellular signaling pathways, and genetic expression. This review aims to address our current understanding about the role of nucleus accumbens MSN subtypes in stress-related depression behavior and speculates on how currently understood mechanisms contribute to factors which control activity of MSNs.

Keywords

Deep brain stimulation; excitatory synaptic transmission; medium spiny neuron; social defeat; stress; striatum

Introduction

Each year depression affects a significant portion of the world's population and, according to the World Health Organization, it is the leading cause of disability worldwide. Studies examining antidepressant efficacy reveal 30% of depressed patients fail to respond to common antidepressant treatment (1), suggesting a need for new targeted therapies. Treatments with enhanced spatial specificity such as deep brain stimulation (DBS) or transcranial magnetic stimulation (TMS), aimed to restore region-specific hypoactivity,

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show great promise in alleviating treatment-resistant depression in even the most severe cases (2–10). Therefore, targeted therapy to affect activity of these regions may be effective in treating depression.

While acute stress can be adaptive, chronic stress can be biologically damaging, making it a leading factor in the development of depression (11). The overwhelming majority of depression models utilize repeated stress to produce depression-like symptomology in rodent and primate models. Stress promotes central and peripheral adaptations in body systems via the hypothalamic-pituitary-adrenal (HPA) axis, which feeds back on the brain through corticosteroid release (12). Significant focus has been placed on excitatory forebrain structures (see ref (13)) including the hippocampus, amygdala, and prefrontal cortex, among other regions which mediate emotional memory and anxiety. Following repeated stress, these regions display dramatic deficits in local and efferent excitatory signaling to integration regions such as the nucleus accumbens (NAc) (11). NAc integration of this excitatory input triggers emotionally motivated behaviors through corticostriatal thalamic loops within the basal ganglia, eventually driving the dorsolateral striatum to facilitate action-related behaviors (14, 15). These local and global NAc circuit interactions mediate motivated and emotional behavior making it an attractive target for therapeutics. However, the causes of depression in relation to the NAc are muddled due to the diversity of connections and cell-types.

There is a growing understanding that morphologically similar, but transcriptionally distinct neuronal subtypes display differing patterns of information processing and integration. Despite this complication, expression dissimilarity provides an exceptional opportunity to differentially target cell types using drug ligands for unique receptors and other molecular targets or expression constructs in both animals and humans. The NAc is composed of a vast array of transcriptionally distinct neuronal subtypes, where medium spiny neurons (MSNs) make up the majority (>95%) of the cells (16). These neurons are defined by their transcriptional profiles, including dopamine receptor 1 (D1) vs. dopamine receptor 2 (D2) expression, substance P and enkephalin, and other enriched genes (16–18). NAc D1-MSN and D2-MSNs are also distinguished by their projections to target regions: D1-MSNs target the ventral tegmental area (VTA) and ventral pallidum (VP), while D2-MSNs specifically target the VP (FIGURE 1) (19–21). Input and output from the NAc follows a dorsolateral to ventromedial topology (15). NAc core and dorsolateral regions of the NAc project mainly to the dorsolateral VP and substantia nigra (SN) while NAc medial shell projects mainly to the ventromedial VP and VTA (20).

Molecular expression, synaptic plasticity, and structural plasticity changes in NAc MSNs are implicated in depression symptomology (22, 23). Despite a wide array of research displaying differential and often opposing roles of D1- and D2-MSNs in motivation and reinforcement (24–31), very little research has been devoted to understanding how these MSN subtypes are regulated following stress (TABLE 1). Herein, we will review current literature discussing molecular and cellular investigation of these MSN subtypes to understand and treat depression-like symptoms following behavioral stress. We will particularly focus on how these changes or treatments may influence excitatory plasticity at subtype specific synapses and potentially alter activity of these neurons in order to promote

depression symptomology. Furthermore, we will discuss how brain stimulation may interact with excitatory and modulatory circuits to influence this behavior. Finally, we will touch on how modulatory factors and underlying molecular expression patterns may govern these cell-type specific changes and provide an array of possible drug targets to alleviate depression.

Stress-Induced Alterations in NAc MSN Subtype Excitatory Transmission

Stress-induced dysfunction in forebrain excitatory transmission has led to the development of the excitatory synaptic transmission hypothesis of depression (22, 32, 33). Conventional antidepressant therapeutics including selective serotonin reuptake inhibitors (SSRIs) or non-typical therapeutics, including ketamine and brain stimulation, may alleviate depression symptoms by acting on excitatory brain systems (33). It is well known that excitatory synaptic transmission is impaired in many frontal limbic brain regions including the prefrontal cortex and hippocampus following stress (22). Stress can lead to functional decreases in activity across these regions through structural dendritic spine and arbor atrophy, as well as disruption in synaptic plasticity and intrinsic cellular mechanisms (22). These excitatory deficits extend to NAc in human depressed patients, where reduced activity and overall volume is observed in imaging studies (34). Further, a recent study demonstrated stress-induced volume reduction is observed in the NAc of mice (35).

Electrophysiological studies of NAc excitatory transmission following stress reveal stress-model dependent and subregion specific outcomes. Lim et al. found excitatory synaptic transmission following repeated restraint stress promoted long-term depression in D1-MSNs, but not D2-MSNs of the NAc core, suggesting a D1-MSN specific change in excitatory transmission mediates anhedonic outcomes (36). Mice that have been subjected to chronic social defeat stress (CSDS) display a similar outcome in D1-MSNs. CSDS is a well validated stress model which results in mice displaying susceptibility (i.e., depression-like behavior) or resilience (normal behavior) (37, 38). Susceptible mice display an increased number of stubby spines NAc MSNs, which correlates with an increased frequency of miniature excitatory post synaptic currents (mEPSCs) (39). However, it is unknown which specific MSN subtype, if either alone expresses this change. Cell-type specific analysis of NAc shell thin and mushroom spines display enhanced synaptic strength of D1-MSN mushroom spines from resilient animals and reduced strength of D2-MSN mushroom spines (40). While the results suggest resilient mice display opposing adaptive mechanisms at single MSN subtypes, more holistic studies are needed to analyze cell-type specific synaptic changes as they are related to morphological changes and cellular output.

We recently found D1-MSNs display reduced mEPSC frequency and D2-MSNs display enhanced frequency of mEPSCs in CSDS susceptible mice (41). To better understand how changes in mEPSC frequency were related to susceptibility outcomes, we used previously collected data from Francis et al. (41) and conducted correlational analyses between excitatory transmission on MSN subtypes and social interaction times, the primary CSDS behavioral metric. We found D2-MSN mEPSC frequency negatively and strongly correlates with interaction time, while no correlation is observed in D1-MSNs (FIGURE 2A). This data suggests that D2-MSNs, not D1-MSNs, may convey the change in frequency of

mEPSCs observed in non-cell type specific MSN recordings (39). Further, increased frequency may enhance baseline activity of D2-MSNs in susceptible mice, while D1-MSN excitatory activity is dampened. A positive correlation is observed between interaction time and intrinsic excitability of D1-MSNs, while D2-MSNs display no change in intrinsic properties (FIGURE 2B), linking D1-MSN intrinsic excitability to susceptibility. Additionally, a strong negative correlation was observed between interaction behavior and D1-MSN, but not D2-MSN action potential firing (FIGURE 2C). Given the enhancement in excitability and despite the reduced frequency of input in susceptible mice, perhaps during a salient, NAc stimulating event, D1-MSNs may display enhanced firing in a state-dependent fashion via an increase the probability of D1-MSN firing. More research, particularly cell-type specific *in vivo* analysis of neuronal activity, is necessary to determine how these intrinsic and synaptic properties interact during specific behavioral events to mediate depressive-like outcomes.

Deep Brain Stimulation and the Balancing Act of NAc MSN Subtype Neuronal Stimulation in Depression Behavior

Researchers utilize brain stimulation techniques such as TMS and DBS to target hypoactive brain regions in depressed patients (2, 42, 43). High frequency DBS of the NAc, among other regions, shows great promise in alleviating treatment-resistant depression, though its mechanism is still unclear (5, 8, 10). Electrical DBS targets cells without regard to subtype specificity and may stimulate afferents within these regions, such as mPFC or vHipp inputs. Diffuse, or non-specific stimulation makes it particularly difficult to uncover neuronal mechanisms promoting antidepressant outcomes.

First, it is still unclear how synaptic plasticity, at specific excitatory synapses, mediates stress-induced behavioral outcomes. These studies provide the initial means to dissect brain changes caused by DBS. Despite common cellular and physiological changes in excitatory NAc-projecting brain regions, studies examining specific excitatory inputs to the NAc produce varying behavioral outcomes, suggesting contrasting synaptic plasticity at these synapses. For instance, burst-like 100Hz stimulation of the PFC is promotes antidepressive outcomes in mice (44, 45) and “high frequency” 20Hz TMS stimulation of the PFC in humans is antidepressant (46). This stimulation in mice is specific to mPFC-NAc, but not mPFC-amygdala input (45). In comparison, increasing activity of mPFC-NAc inputs via 4Hz optogenetic stimulation promotes resilience to CSDS (47). Still it is unclear which MSN subtype this activity affects or how these inputs interact with other synaptic inputs.

Next, stimulation of different inputs drives opposite behaviors. In contrast to PFC-NAc afferents, enhancing hippocampal and thalamic input to the NAc promotes depressive-like outcomes. Increased synaptic strength is observed on intralaminar thalamic NAc inputs and driving the thalamic inputs promotes susceptibility to CSDS (48). Enhancing activity of ventral hippocampal (vHipp) inputs illustrate similar outcomes (47). In contrast, 1Hz-mediated long-term depression of vHipp inputs to the NAc in CSDS mice restores normal social interaction (47). Interestingly, vHipp-NAc projections are weighted differently in a sub-region specific manner, where larger vHipp excitatory currents in the NAc shell are

observed (49). Additionally, these synapses display larger NMDA currents which may enhance the probability of plasticity as NMDA receptors drive spike-timing dependent calcium-dependent potentiation on MSN subtypes (50). Interestingly, a variety of NMDA receptor antagonists, including ketamine, have displayed efficacy in treating treatment-resistant depression (51), perhaps by disrupting plasticity in depression-related regions including the vHipp (33). Antidepressant effects of NMDAR antagonism may partially be expressed in the NAc by targeting excitatory input to distinct NAc circuits. For instance, knockout of NR1 from Adenosine-2a expressing cells, D2-MSNs in the NAc, but not D1-MSNs, reduces immobility in the forced swim test (52). Taken together, resilience-promoting vHipp-NAc LTD may preferentially target excitatory activity on NAc shell D2-MSNs. This manipulation may balance transmission between MSN subtypes or weight input to D1-MSNs, thereby restoring normal behavior.

Our recent results indicate specific NAc pathway stimulation may best account for the effects of NAc-specific DBS antidepressant outcomes. We based our stimulation study on the idea that excitatory transmission was oppositely changed in NAc MSN subtypes and predicted stimulation of D1-MSNs would promote antidepressant outcomes and stimulation of D2-MSNs would promote depression symptoms. Using optogenetics, NAc neurons were specifically targeted for stimulation (41). Like DBS, repeated high frequency stimulation of all NAc neurons alleviated depression-like outcomes to CSDS. It is likely D1-MSNs mediate this effect as cell-type specific stimulation of D1-MSNs mimicked non-specific NAc neuronal stimulation (41). Furthermore, repeated, but not acute stimulation is necessary for this behavioral effect. It is unclear if direct elevation of D1-MSN activity during stimulation mediates this effect. Several mechanisms could exist to govern these changes. The most favored mechanism is one of homeostatic plasticity. Perhaps it is not stimulation of D1-MSNs, but a dampening of intrinsic excitability that negates the ill-effects of stress. Intrinsic properties driving cell firing is complicated and governed by a variety of complex and interacting mechanisms including alterations in potassium channel function and homeostatic excitatory balance (53). For instance, repeated VTA optogenetic stimulation is sufficient to dampen phasic firing of VTA neurons through alterations in Ih potassium conductance (54), promoting resilience in CSDS mice, and providing a potential parallel in mechanism. Alternatively, optogenetic stimulation allows for dendritic, somatic, and axonal firing at high rates (55). In particular, axonal stimulation may drive higher fidelity firing rates by resisting amplitude dampening observed in the soma of cells (56). Therefore, stimulation may be promoting plasticity in downstream regions such as the VP or VTA. Another possibility is that collateral inhibitory firing between D1-MSNs and D2-MSNs may serve to balance D1-MSN and D2-MSN output (57, 58). D2-MSN stimulation promotes depressive-like outcomes (41), suggesting an imbalance in firing of MSN subtypes could mediate these symptoms. D2-MSN collaterals connect more strongly to D1-MSN than D1-MSNs to D2-MSN (57). Therefore, depressive-like behavior induced by repeated D2-MSN stimulation may rebalance activity towards D2-MSNs. Consequently, repeated stimulation of these subtypes may act through different but overlapping mechanisms in which a homeostatic mechanism is favored in antidepressant D1-MSN stimulation and an imbalanced excitatory signaling mechanism favors depressant D2-MSN stimulation. Likewise, repeated inhibition may facilitate homeostatic process to enhance intrinsic excitability, as we were able to shift

resilient mice to a depressed state with repeated D1-MSN chemogenetic inhibition, where inhibition of D2-MSNs had no effect (41). This bidirectional manipulation of behavior promotes the idea that D1-MSNs may provide a reversible switch for depression-like behavior, while aberrant D2-MSN activity may be involved in the transition to or expression of a depression state. Brain stimulation or DBS itself may also act as a neuromodulator for excitatory activity, facilitating or inhibiting neuronal transmission directly or by release of modulatory neurotransmitters and peptides.

Stress Induced Modulatory Transmission in the NAc

Modulatory factors contribute to neuronal function and aid in amplifying or dampening neuronal excitatory transmission and eventually cellular output. The NAc and its targets are littered with potential modulatory drug targets including peptides, growth factors, and other neuromodulatory factors that modify cell firing properties and synaptic transmission (59). The balance of this chemical cocktail may produce drastic stress-dependent behavioral alterations. Pharmacological and optogenetic studies have attempted to tease out the roles of these substances and enlighten our understanding of cell-type specific control of stress-related behaviors.

Dopamine (DA), a potent neuromodulator in the NAc, is important for the expression of depression-related symptoms (e.g., reward, hedonia, and motivation) (60). The NAc receives dense innervation from the VTA, which supplies the region with dopamine (DA), GABA, and brain derived-neurotrophic factor (BDNF). MSN enrichment with either D1 or D2 receptors, and the opposing nature of DA receptor signaling cascades suggests DA may act to oppositely regulate subtype-specific MSN output following stress. Chronic mild stress promotes altered NAc dopamine D2 receptor sensitivity (61) and restraint stress studies have revealed NAc D1-like receptor density increases (62). Further, cAMP/PKA signaling, activated by dopamine receptor signaling, plays a role in stress. NAc D1-MSN specific knockout of Cdk5 reduces cAMP levels, increases PKA activity, and promotes antidepressant outcomes (63). Enhanced DA release is observed following a single social defeat stress episode (64), suggesting acute high-intensity stressors promote DA release. These results further suggest enhancing D1 receptor signaling on D1-MSNs promotes stress-induced susceptibility and high dopamine tone may act as a catalyst for excitatory plasticity in the NAc. The effect of chronic stress on VTA DA neuron firing is lasting (37, 65, 66), is driven by activity of intrinsic potassium channels (54), and phasic but not tonic optogenetic stimulation of VTA-NAc projecting neurons promotes susceptibility to CSDS (54, 66–68). Thus, it would seem appropriate to conclude DA tone is enhanced following chronic stress and lower affinity D1 receptors would be activated by phasic DA release, thereby preferentially enhancing activity of D1-MSNs. However, this effect is not as straightforward as it seems. It may appear DA, potentially through D1-MSNs, provides temporary and acute relief from depression symptomology, while other factors drive the long-lasting depressive state. First, phasic firing changes in VTA DA neurons are inconsistent across stress models (66, 69). Furthermore, a recent paper using DA voltammetry in the NAc discovered VTA dopamine release was unaltered following CSDS and blockade of dopamine receptors had no effect on depression-like outcomes (67). Rather, BDNF was responsible for stress

susceptibility and antagonism of the BDNF receptor TrkB, prevented susceptibility (37, 38, 54, 65, 67, 68).

Consistent with these findings, BDNF is observed to be increased in the NAc of human depressed patients (37). Stress-induced BDNF release primarily occurs between the VTA-NAc circuit and VTA-specific knockout of BDNF promotes resilience to CSDS (38). Increased BDNF and TrkB receptor activation are observed in NAc tissue from susceptible mice (37). These results provide strong evidence for the role of VTA supplied, NAc BDNF in depression. TrkB is enriched in D2-MSNs and BDNF signaling through TrkB has different roles in NAc MSN subtypes in psychostimulant and opiate motivation (26, 70), but depression-related BDNF signaling in MSN subtypes is unclear. BDNF is highly involved in structural remodeling and plasticity. Perhaps the structural plasticity observed increases in NAc stubby spine growth (48) can be explained by a persistent release of BDNF and ongoing remodeling of synapses, in a D2-MSN specific manner.

BDNF interacts with a variety of other signaling pathways to promote these depression-like effects, including factors involved in glucocorticoid signaling. The HPA-axis acts to release corticosterone in mice, which can feedback on neurons within the brain (12). Glucocorticoid receptor knockout specifically in NAc D1-MSNs, but not VTA-DA neurons, promotes resilience to CSDS (64) and heightened DA release is blunted following an acute social defeat stress episode, suggesting glucocorticoid signaling plays a dynamic role in affecting VTA signaling in the NAc. Further, another molecule involved in stress signaling, corticotropin releasing factor (CRF), enhances release of BDNF in the NAc and promotes susceptibility to stress caused by the paired induction of phasic firing and social stress (68). These results may suggest BDNF and glucocorticoids coordinate molecular programming on distinct MSN subtypes to affect overarching stress-related behavior.

Among the many neuropeptides found within the NAc, cell subtype enriched peptides such as dynorphin and enkephalin play a role in depression (71, 72). Dynorphin is enriched in D1-MSNs of the striatum. Restraint stress, the forced swim test, and inescapable shock increases NAc dynorphin (73) and NAc specific infusion of kappa opioid receptor (i.e., the primary target of dynorphin) antagonists has antidepressant effects (74). Further, inhibition of dynorphin in the NAc produces antidepressant effects (75). Activation of kappa opioid receptors promotes aversion, potentially through regulation of dopamine terminals in the NAc (76). Yet, it is not simply an enhancement of dynorphin which promotes depression. Rather, activation of dynorphin cells can produce either aversive or reinforcing outcomes in a region specific manner (77), suggesting heterogeneous populations of striatal MSNs may drive depression symptomology differentially as well. In contrast, enkephalin, which is highly enriched in striatal D2-MSNs (17), is thought to be antidepressant. Chronic mild stress reduces NAc enkephalin (78) and chronic antidepressant treatment increases striatal enkephalin levels (79). Additionally, agonism of the delta-opioid receptor, the primary receptor target of enkephalin, promotes antidepressant outcomes (80), while delta receptor knockout promotes depressive-like behavior (81). These results indicate peptide release from MSN subtypes may actively oppose activity-driving factors on NAc subtypes. That is, dynorphin signaling may oppose and provide balance for D1-MSN firing and enkephalin signaling may oppose enhanced D2-MSN activity. This interpretation would be consistent

with observed excitatory changes on NAc MSN subtypes as well as stimulation-mediated antidepressant outcomes (41).

Molecular Correlates Regulating Stress-Induced Activity of MSN Subtypes

Many of the aforementioned cellular signaling cascades converge on one another or are activated in conjunction or in parallel with other cascades to coordinate molecular expression and cellular output. The need for new molecular targets is growing and despite the emergence of various molecular tools to probe specific cell subtypes, very little research has been conducted examining molecular expression profiles in MSN subtypes following stress. Further, observed molecular expression in one MSN subtype could be occluded by examining total NAc expression. Despite the lack of research, information can be gleaned from analysis of molecular manipulation in all MSNs.

Significant research on the immediate early gene FosB has demonstrated its role in resilience to stress. NAc FosB expression is significantly reduced in human depressed patients (82). Additionally, NAc FosB expression is significantly enhanced in mice resilient, but not susceptible to CSDS (82). CSDS mice treated with the common SSRI fluoxetine display enhanced FosB expression and enhanced resilience (82). Further, NAc overexpression of FosB using a bitransgenic mouse line 11A, promotes resilience to CSDS, which is thought to be through enhancement of GluR2 expression (82). Interestingly, the 11A mouse line serendipitously expresses FosB in D1-MSNs, suggesting this resilience effect is primarily due to D1-MSN enrichment of FosB (83) and a facilitation of excitatory activity. Comparatively, FosB expression is enhanced in D1-MSNs of resilient mice and enhanced in D2-MSNs of susceptible mice in both NAc core and shell regions (84). These results further suggest FosB may mediate adaptive resilience through D1-MSNs. Despite enhancements in overall resilience and excitatory transmission following expression of

FosB in all NAc neurons, overexpression in a stress naïve mice decreased excitatory synaptic strength in D1-MSNs via an increased number of silent synapses and stubby spines, while in D2-MSNs, overexpression increased excitatory transmission in the shell and decreased silent synapses (85). These results seem at odds with previously mentioned stress-mediated results revealing the complexity of signaling within the NAc and MSN subtypes and may reflect a stress-driven shift in baseline electrophysiological properties. During a stress state, FosB could facilitate differential plasticity in stressed and non-stressed animals. Rac1 expression, which is significantly decreased in human depressed patients, has been shown to mediate changes in stubby spine formation in mice via an epigenetic mechanism (86). It is possible FosB and signaling pathways involved in regulating Rac1 are coordinated to produce these results. More research is necessary to tease out the cell-type specificity of these results.

FosB has been found to interact with molecules that regulate plasticity. CaMKII, a protein kinase, is sufficient to activate long-term synaptic potentiation (87) and could play a role in storage of aversive memories during stress states. FosB binds to the promoter of CaMKII α and CSDS enhances its binding enrichment on this promoter (88). Chronic treatment with the SSRI fluoxetine reduces binding of FosB to the CaMKII promoter and NAc overexpression of CaMKII blocks the antidepressant efficacy of fluoxetine in stressed mice.

These effects are through an epigenetic mechanism of reducing acetylation and increasing H3meK9 methylation. SSRI treatment results may seem inconsistent with previous literature discussing increased FosB expression in resilient animals. It is possible that FosB differentially affects CamKII α expression in MSN subtypes and mediates this curious effect. In that regard, enhanced binding of FosB to the CaMKII α promoter in D2-MSNs may induce structural plasticity and potentiation in these cells, weighting excitatory signaling in D2-MSNs more heavily. This outcome would be consistent with our results showing enhanced excitatory signaling to D2-MSNs following stress and other results showing overexpression of a constitutively active CaMKII promotes plasticity (89), while developmental inhibition of CaMKII reduces functional numbers of synapses (90).

These changes extend to other parallel, susceptibility-promoting signaling cascades in D2-MSNs. Disheveled (DVL1) activity inhibition in the WNT-DVL- β -catenin signaling cascade promotes susceptibility to CSDS and DVL1 is found to be significantly downregulated in the NAc of human depressed patients. Comparatively, pharmacological and dominant negative activity inhibition of the downstream inhibition target of DVL1, GSK3 β , promotes resilience to CSDS (91). β -catenin is activated by the non-phosphorylated form of GSK3 β . In fact, β -catenin expression in NAc D2-MSNs, but not D1-MSNs promotes resilience to CSDS (92). This effect was specific to expression of a microRNA synthesis related protein Dicer1 downstream of β -catenin signaling, suggesting post-transcriptional regulation of a wide variety of mRNAs by β -catenin in D2-MSNs in part mediate outcomes to social stress.

Conclusions and Future Directions

There is emerging evidence for functional changes in MSN subtypes to differentially and in some cases oppositely mediate outcomes to stress. While both subtypes appear to be involved in and control stress-mediated depression symptomology, the degree to which each subtype is involved. The majority of these studies were conducted in male rodents despite the higher female incidence of depression (93). Currently, only a handful of studies addressed how stress differentially affects the NAc of female animals (52, 94–97) and only one provides a MSN subtype specific examination. It is necessary to determine if sex-specific alterations in these cells account for larger incidence of depression in females. Overall, the development of a cohesive model of stress-induced changes in NAc MSN subtypes will require a multitude of factors and analyses. These factors along with differences in circuit function, cell signaling, and molecular genetic expression in these cell types will better provide a clearer picture of NAc subtype function in depression.

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Figure 1. Afferent and efferent connections of the Nucleus Accumbens

Upper left The Prelimbic cortex of the mPFC innervates the NAc Core (NAcC) and the infralimbic region of the mPFC innervates the NAc Shell (NAcS). *Lower left* Thalamic and basolateral amygdala (BLA) inputs do not display preferential innervation for NAc subregions. The dorsal hippocampus (dHipp) preferentially innervates the lateral NAcS. The arcuate nucleus (Arc) of the hypothalamus innervates shell regions of the NAc with melanocortin input. The lateral hypothalamus (LH) is innervated preferentially by D1-MSNs. *Center* NAc MSNs display a dorsolateral to ventromedial innervation and projection topology. NAcC D1-MSNs project to substantia nigra reticulata (SN) and D1-MSNs and D2-MSNs project to dorsolateral regions of the VP. NAcS D1-MSNs project to VTA and both subtypes in the NAcS project to ventromedial VP. *Upper right* Ventral hippocampus (vHipp) projects preferentially to ventromedial NAc and VTA provides diffuse terminals to all of the NAc. *Lower right* Lateral VP regions project to SN and medial VP projections project to VTA.

Figure 2. Electrophysiological properties correlate with stress-induced behavioral changes in MSN subtypes

(A) D2-MSN mEPSC frequency displays a strong negative correlation with time in interaction zone (Pearson $r(12) = -0.750$, $p = 0.003$, $N = 13$) and D1-MSNs show no correlation (Pearson $r(12) = 0.180$, $p = 0.557$, $N = 13$). (B) A moderate positive correlation between D1-MSN rheobase and time in interaction zone was observed (Pearson $r(25) = 0.573$, $p = 0.002$, $N = 26$) and D2-MSNs displayed no correlation (Pearson $r(15) = -0.195$, $p = 0.470$, $N = 16$). (C) In agreement with rheobase measures, correlations between the number of spikes in D1-MSNs (elicited by a 250pA, 500msec square pulse of current) and time in the interaction zone negatively correlated (Pearson $r(10) = -0.668$, $p = 0.025$, $N = 11$), a correlation not observed between D2-MSNs spiking and time in the interaction zone (Pearson $r(10) = -0.049$, $p = 0.879$, $N = 11$). Each point represents the average rheobase, mEPSC frequency, or number of spikes for each individual mouse. All mice in this study were 8–14 week old D1-GFP or D2-GFP male mice on a C57 wild-type background.

Table 1

List of current studies examining D1-MSNs and D2-MSNs in stress related behaviors.

Reference	Genotype	Strain background	Sex	Age	Finding
Barik et al. 2013 (ref 65)	Nr3c1 (loxP/loxP) X D1-Cre	C57BL/6	Male	8–16 weeks	Glucocorticoid receptor knockout in D1-MSNs prevents susceptibility to CSDS
Dias et al., 2014 (ref 93)	D1-Cre, D2-Cre, D1-GFP, D2- GFP	C57BL/6	Male	7–9 weeks	Studied role of β -catenin in promoting resilience to CSDS
Francis et al. 2015 (ref 41)	D1-Cre, D2-Cre	C57BL/6	Male	8–14 weeks	Optogenetic stimulation and chemogenetic inhibition oppositely facilitates depressive-like behavior in MSN subtypes
Francis et al. 2015 (ref 41)	D1-GFP, D2- GFP	C57BL/6	Male	8–14 weeks	Chronic stress oppositely regulates frequency of excitatory transmission, Stress increases intrinsic excitability in D1-MSNs
Joffe et al. 2016 (ref 52)	D1-Cre, A2a-Cre	C57BL/6	Male and Female	6–12 weeks	Characterized behavioral despair in D1-MSN and/or D2- MSN NR1 knockout
Lim et al. 2013 (ref 36)	D1-tdTomato X D2-GFP	C57BL/6	Male	6–8 weeks	Anhedonia associated with D1- MSN reduction in synaptic transmission
Lobo et al., 2013 (ref 85)	D1-GFP, D2- GFP	C57BL/6	Male	8–10 weeks	FosB differentially regulated in D1- MSNs and D2-MSNs following stress
Plattner et al., 2015 (ref 64)	D1-Cre X conditional Cdk5 knockout	C57BL/6	Male	12–14 weeks	Explored the role of D1-MSNs Cdk5 in stress
Vialou et al. 2010 (ref 83)	NSE-tTA X TetOp- FosB (Line 11A, D1-MSN enriched)	C57BL/6	Male	8–11 weeks	Examined role of FosB in mediating resilience to stress