The brain reward circuitry in mood disorders

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Abstract | Mood disorders are common and debilitating conditions characterized in part by profound deficits in reward-related behavioural domains. A recent literature has identified important structural and functional alterations within the brain's reward circuitry — particularly in the ventral tegmental area–nucleus accumbens pathway — that are associated with symptoms such as anhedonia and aberrant reward-associated perception and memory. This Review synthesizes recent data from human and rodent studies from which emerges a circuit-level framework for understanding reward deficits in depression. We also discuss some of the molecular and cellular underpinnings of this framework, ranging from adaptations in glutamatergic synapses and neurotrophic factors to transcriptional and epigenetic mechanisms.

Reward

A positive emotional stimulus. In psychological terms, a reward is reinforcing — it promotes repeated responding to obtain the same stimulus.

Anhedonia

Loss of the ability to experience pleasure from normally rewarding stimuli, such as food, sex and social interactions.

Ventral tegmental area

(VTA). A ventral midbrain site containing dopaminergic neurons that are an essential component of the brain's reward circuitry.

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Depressive disorders affect ~20% of people in the United States within their lifetime¹, and roughly one-half of patients do not fully respond to available treatments². The behavioural symptoms of depression are extensive, covering emotional, motivational, cognitive and physiological domains. Large subsets of patients with these disorders exhibit deficits in several aspects of reward, as defined by responses to positive emotional stimuli such as food, sex and social interaction. Prominent among these reward deficits is anhedonia. Depression is highly comorbid with anxiety, and it has been estimated that over 20% of individuals with a mood or anxiety disorder also fulfil criteria for drug addiction and, conversely, that 30-40% of individuals suffering from addictive disorders have a comorbid mood or anxiety disorder³. These considerations suggest a large degree of overlap among the brain regions affected in depression and those affected in drug addiction.

Indeed, increasing evidence in humans and animals suggests that mood disorders and drug addiction are associated with major disruptions within the brain's reward circuitry⁴, which normally serves to guide our attention towards and consumption of natural rewards and ensure our survival. We begin this Review by providing a brief overview of reward circuits in the brain and then summarize findings from studies in humans, which suggest that structural and functional changes in this reward circuitry are associated with reward-related behavioural impairments in mood disorders. We then focus on the more extensive rodent and non-human primate literature to formulate a circuit-level understanding of reward deficits in these disorders, highlighting the molecular and neurophysiological mechanisms that drive these circuit abnormalities. We end by discussing future directions for research, particularly the opportunities for the development of novel therapeutics that target these reward-based deficits.

The brain's reward circuitry

The best characterized reward circuit in the brain comprises dopaminergic neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc), which is part of the ventral striatum. The principal neurons of the NAc are GABAergic medium spiny neurons (MSNs). This VTA-NAc circuit is crucial for the recognition of rewards in the environment and for initiating their consumption⁵, but these regions respond to aversive stimuli as well (see below for further discussion). VTA dopaminergic neurons also innervate several regions of the prefrontal cortex (PFC), central amygdala, basolateral amygdala (BLA) and hippocampus, as well as other areas (FIG. 1). All of these so-called 'brain reward regions' are inter-connected in complex ways: for example, the NAc receives dense glutamatergic innervation from the PFC, amygdala and hippocampus; and the PFC, amygdala and hippocampus form reciprocal glutamatergic connections with one another. The functional output of each of these regions is modulated by several types of GABAergic interneurons and, in the NAc, by cholinergic interneurons as well. Moreover, each of these regions receives serotonergic inputs from midbrain raphe nuclei and noradrenergic



Nucleus accumbens

(NAc). A portion of the ventral striatum, this forebrain nucleus has a crucial role in coordinating responses to rewarding and aversive stimuli.

Medium spiny neurons

(MSNs). Principal GABAergic projection neurons of the NAc and dorsal striatum, comprising > 95% of neurons in these regions.

Optogenetics

A series of recently developed tools that make use of light-activated proteins. Most frequently, light-sensitive ion channels and pumps are used to control the firing rate of neurons, but increasingly other types of proteins are placed under similar light control.

Channelrhodopsin 2

(ChR2). Member of a family of retinylidene proteins (rhodopsins), which are light-gated ion channels that can be expressed in neurons to allow for optogenetic control of electrical excitability with exquisite temporal specificity.

Intracranial self-stimulation

A behavioural paradigm in which animals work (for example, roll a cylinder with their paws) to stimulate a targeted brain region with electrical current. The current at which animals first self-stimulate, termed the brain stimulation reward threshold, is used as a measure of an animal's affective state, with higher thresholds reflecting diminished reward and anhedonia.

D1-type MSNs

(D1-type medium spiny neurons). One of two major subtypes of GABAergic projection neurons located in the nucleus accumbens and dorsal striatum, which are defined by their predominant expression of D1 dopamine receptors. D1-type neurons largely coincide with those of the direct projection pathway. Figure 1 | **VTA–NAc reward circuit.** A simplified schematic of the major dopaminergic, glutamatergic and GABAergic connections to and from the ventral tegmental area (VTA) and nucleus accumbens (NAc) in the rodent brain. The primary reward circuit includes dopaminergic projections from the VTA to the NAc, which release dopamine in response to reward-related stimuli (and in some cases, aversion-related stimuli). There are also GABAergic projections from the NAc to the VTA; projections through the direct pathway (mediated by D1-type medium spiny neurons (MSNs)) directly innervate the VTA; whereas projections through the indirect pathway (mediated by D2-type MSNs) innervate the VTA via intervening GABAergic neurons in the ventral pallidum (not shown). The NAc also contains numerous types of interneurons (FIG. 2). The NAc receives dense innervation from glutamatergic monosynaptic circuits from the medial prefrontal cortex (mPFC), hippocampus (Hipp) and amygdala (Amy), as well as other regions. The VTA receives such inputs from the lateral dorsal tegmentum (LDTg), lateral habenula (LHb) and lateral hypothalamus (LH), as well as both GABAergic and glutamatergic connections from the extended amygdala (not shown). These various glutamatergic inputs control aspects of reward-related perception and memory. The dashed lines indicate internal inhibitory projections. The glutamatergic circuit from the LH to the VTA is also mediated by orexin (not shown). Greater details of these monosynaptic circuits for NAc and VTA are shown in FIG. 2. RTMg, rostromedial tegmentum.

inputs from the pontine locus coeruleus, and several are innervated by hypothalamic peptide systems. Last, there is evidence that VTA 'dopamine' neurons also release glutamate or GABA, which may contribute to their functional effects^{6,7}.

There is now a large literature, stretching from rodents to monkeys to humans, concerning the role this highly complex and inter-connected circuitry has in discerning and reacting to rewarding and aversive stimuli in the environment and in influencing future responses based on past experience. We refer the reader to several recent reviews for a more detailed discussion^{5,8-13}. Historically, brain reward regions have been assigned specific behavioural functions: the VTA-NAc as a 'rheostat' of reward, the amygdala as crucial for forming associative fear- and reward-related memories, the hippocampus as mediating declarative memory, and various regions of the PFC as subserving distinct aspects of working memory and executive control. In reality, these regions have far broader functions in regulating emotional and cognitive behaviour. Indeed, the complexity of the reciprocal connections and local monosynaptic circuits within the larger reward circuitry has made parsing individual pathways and functions a major methodological challenge. The ways in which this circuitry contributes to depression remain even more uncertain.

One view is that the reduced responses to rewarding experiences and exaggerated responses to aversive ones that characterize depression might — together with the associated maladaptive cognitive style — reflect abnormalities in the perception and interpretation of reward valence, in the motivation for rewards and in subsequent decision-making^{5,8–13}.

Recent technological advances in mouse genetics, virus-mediated gene transfer and optogenetics have made it possible to determine the roles of specific neuronal cell types in reward-related behaviour to a degree that was not possible in earlier investigations. In an initial study, Deisseroth and colleagues¹⁴ used a light-activated cation channel, channelrhodopsin 2 (ChR2), to show that stimulation of VTA dopaminergic neurons was sufficient to drive intracranial self-stimulation in rats. Optogenetic stimulation of these neurons also promoted a conditioned place preference, confirming their role in inducing reward, whereas stimulation of GABAergic interneurons in the VTA disrupted reward and promoted conditioned place aversion¹⁵⁻¹⁷. In the NAc, optogenetic stimulation of D1-type MSNs enhanced cocaine-induced place conditioning and locomotor activation, whereas stimulation of D2-type MSNs had the opposite effect¹⁸. Furthermore, optogenetic stimulation of D1-type neurons in the dorsal striatum induced a persistent increase in operant



Figure 2 | Local microcircuitry of the NAc and VTA. a | A close-up view detailing the presynaptic inputs onto D1- and D2-type GABAergic medium spiny neurons (MSNs) and onto several types of interneurons within the nucleus accumbens (NAc). These interneurons include GABAergic interneurons that express calretinin (CALB2), parvalbumin (PV), somatostatin (SOM) or calbindin (CALB1; not shown) and large cholinergic interneurons that express choline acetyltransferase (ChAT). Glutamatergic neurons from the medial prefrontal cortex (mPFC), hippocampus and basolateral amygdala (BLA) release glutamate onto spine synapses to provide excitatory signals to GABAergic MSN projection neurons. These excitatory inputs also synapse directly onto the GABAergic and cholinergic interneurons that modulate MSNs (not shown). D1- and D2-type MSNs also receive signals from dopamine (DA) through shaft or spine neck synapses. The figure does not depict possible differences in glutamatergic innervation of D1-type versus D2-type MSNs, which are only now beginning to be explored. **b** | A close-up view detailing the presynaptic inputs onto ventral tegmental area (VTA) DA neurons and local GABAergic interneurons in the VTA. Glutamatergic neurons from the mPFC and lateral dorsal tegmentum (LDTg) synapse directly onto VTA DA neurons, whereas the extended amygdala sends both glutamatergic and GABAergic projections. By contrast, glutamatergic neurons from the lateral habenula (LHb) synapse directly onto inhibitory GABAergic neurons in the rostromedial tegmentum (RMTg) or VTA proper, which then inhibit DA neurons and promote aversion. DA neurons receive direct excitatory inputs from peptidergic (for example, orexinergic) or glutamatergic neurons in the lateral hypothalamus, which increase DA release and promote reward. Although GABAergic projections from the NAc to the VTA are shown as direct, in fact, roughly half of these projections are indirect, occurring via GABAergic neurons in ventral pallidum (not shown). Moreover, although GABAergic projections from the NAc to the VTA are shown innervating VTA DA neurons, these projections also innervate VTA GABA neurons (not shown).

lever pressing, whereas stimulation of D2-type neurons induced a transient decrease¹⁹. This and related studies support the view that the dorsal striatum is also a crucial site for integrating behavioural responses to both positive reinforcement and punishment²⁰.

A recent study demonstrated the potent ability of optogenetically activated cholinergic interneurons in the NAc to promote the rewarding effects of cocaine²¹, even though these interneurons comprise <1% of all neurons in this region. Perhaps surprisingly, inhibition of the cholinergic interneurons by a small and previously unappreciated GABAergic projection from the VTA enhanced stimulus-outcome learning²². Further work is needed to clarify these findings, but they are interesting in light of pharmacological studies in rodents and monkeys showing that cholinergic agonists are rewarding through their actions within the VTA-NAc circuit^{8,23}. Circuit-specific tools are also being used to study the influence of distinct glutamatergic projections to the NAc (FIG. 2a) on complex behaviour²⁴⁻²⁷. As just one example, optogenetic activation of NAc glutamatergic terminals that derive from the BLA and PFC was reinforcing, although the firing frequency necessary to support reinforcement was different between the two regions^{24,27}.

Recent evidence also points to a role for lateral habenula (LHb) and rostromedial tegmental nucleus (RMTg) neurons in mediating aversion. Specifically, a subset of GABAergic neurons in the RMTg²⁸ — those that project to VTA dopaminergic neurons - receive excitatory projections from LHb neurons that specifically respond to aversive stimuli²⁸ (FIG. 2b). Optogenetic stimulation of LHb glutamatergic terminals in the RMTg inhibited firing of VTA dopaminergic neurons, inducing a greater degree of behavioural avoidance in response to an unpredictable footshock28. VTA dopaminergic neurons themselves are far more heterogeneous than was previously believed: distinct subsets of VTA dopaminergic neurons respond differently to rewarding versus aversive stimuli^{29,30}, and there are topographical (anterior versus posterior) differences in the influence of VTA dopaminergic and GABAergic neurons in regulating reward^{31,32}.

Together, these studies illustrate how genetic, viral vector and optogenetic tools are leading to the formulation of fundamentally new hypotheses regarding reward circuitry function. Such work highlights the cell- and circuit-specificity of neural pathways and neurotransmitter systems that control the VTA and NAc. It is clear that many regions that are not classically defined as 'reward structures' feed onto this circuitry and contribute to the processing of both positive and negative emotional information to guide complex behaviour. With this in mind, we can begin to formulate a detailed circuit-level understanding of reward-related deficits in mood disorders.

Brain imaging studies in humans

The brain imaging literature with regard to depression is extensive and has been reviewed elsewhere in greater detail³³. Here, we highlight only those major

findings that inform our understanding of reward mechanisms in depression. In general, volumetric structural and metabolic activity changes have been identified throughout the reward system in mood disorders. The results are complicated, and often, for each positive finding, opposite or null findings appear in the literature, emphasizing that results should be interpreted with caution. Such variable findings are not surprising, given the considerable heterogeneity among patients with depression. For example, many of the studies that identify volume reductions in reward regions based on grey matter loss are biased towards older individuals, and it is possible that grey matter loss accompanies depression symptoms mainly in these populations but may not be a general biomarker of depression. Keeping this in mind, we review structural and functional changes reported in brain regions that make direct monosynaptic connections with the VTA-NAc circuit. Findings from post-mortem human brains that inform the imaging studies are discussed as well (TABLE 1).

Nucleus accumbens. Numerous studies have shown no change in NAc volume in major depression^{34,35}, although several studies of mainly elderly patients reported a loss of NAc volume^{36,37}. Activity of the NAc (and the ventral striatum as a whole) is consistently reduced in major depression^{38,39}. This is thought to reflect a loss of reward function that drives symptoms such as anhedonia; however, the interpretation of these data is complicated. First, it is estimated that >98% of neurons in the NAc are GABAergic, such that a decrease in blood-oxygenlevel-dependent (BOLD) activity or cerebral blood flow might reflect a decrease in the inhibitory output of this region. Second, the effect of an increase or decrease in the GABAergic output of the NAc on reward behaviour is complex, with opposite effects observed for D1-type versus D2-type MSNs in mice, as stated above¹⁸. These imaging studies of the NAc from patients with mood disorders need to be complemented with neuropathological examination of post-mortem brain tissue (TABLE 1). Recent evidence suggests that genes that promote synaptic remodelling are regulated in the NAc of depressed subjects40, although detailed neuroanatomical studies of NAc structure are not available.

Basolateral amygdala. Although several studies identified volume loss in BLA grey matter in patients with mood disorders upon post-mortem examination^{41,42}, many showed no change^{34,43,44}. There is greater consensus regarding functional changes. Most functional MRI (fMRI) studies have shown the BLA to be hyperactive in a range of mood disorders, both at baseline^{38,45,46} and in response to stimuli such as sad faces or negative words47,48, possibly reflecting the increased negative emotional and cognitive state often seen in these conditions. It remains unclear whether this signal reflects increased activity of glutamatergic projection neurons, GABAergic interneurons, glial cells or other cells, but rodent studies have shown that chronic stress may induce depressionor anxiety-like behavioural responses by increasing the excitatory tone on glutamatergic neurons49.

Prefrontal cortex. Studies of the PFC have largely concentrated on the orbitofrontal cortex (OFC) and medial PFC (mPFC), including the anterior cingulate cortex. Patients with major depression have a smaller cortical volume — including reduced white matter volume — in the OFC and mPFC⁵⁰⁻⁵³. In the ventrolateral and dorsomedial PFC, depressed subjects show smaller BOLD signal changes measured by fMRI during a reversal-learning task54, although it should be noted that Brodmann area 25 (also known as the subgenual anterior cingulate cortex) shows increased activity in depression⁵⁵. The changes in size and activity of the PFC are thought to result, in part, from the loss of glial cells or the neuronal atrophy that is evident in post-mortem tissue^{56,57}. These findings support the hypothesis that mood disorders are characterized in part by a loss of excitatory cortical control over subcortical reward-related structures such as the NAc and amygdala, leading to aberrant processing of rewarding and aversive events. A crucial question, however, as with the amygdala, is what cellular element in the OFC and mPFC is responsible for the reduced cortical activity seen in fMRI studies. Interestingly, a recent study in depressed humans indicates dramatic reductions in excitatory synapses in the mPFC, supporting the hypothesis that a decreased BOLD signal reflects a loss of excitatory tone in this region⁵⁸. Further studies are needed to understand the functional consequences of the reported loss of glial cell density^{56,57}. One possibility is

D2-type MSNs

(D2-type medium spiny neurons). One of two major subtypes of GABAergic projection neurons located in the nucleus accumbens and dorsal striatum, which are defined by their predominant expression of D2 dopamine receptors. D2 type-neurons largely coincide with those of the indirect projection pathway.

Excitatory synapses

Synapses at which the release of glutamate from presynaptic nerve terminals activates glutamate receptors located on dendritic spines on postsynaptic neurons, which increases the probability of an action potential in that postsynaptic neuron.

Brain region	Human imaging results	Human post-mortem analysis		
Nucleus accumbens	↓ Volume ↓ BOLD signal during reward-related task	↓ Expression of synaptic remodelling gene RAC1		
Ventral tegmental area	NA	NA		
Hippocampus	↓ Volume ↓ BOLD signal during positive word-encoding task	↓ Synapse density ↓ Glial cell density		
Basolateral amygdala	↓ Volume ↑ Resting-state BOLD signal	↓ Grey matter ↓ Glial cell density		
Medial prefrontal cortex	↓ Volume ↓ BOLD signal during reversal-learning task	↓ White matter ↓ Dendritic branching ↓ Glial cell density		

Table 1 | Comparison of brain imaging and post-mortem studies in human depression

BOLD, blood-oxygen-level-dependent; NA, not assessed.

that they contribute to abnormal glutamatergic transmission. It should also be emphasized that monkey studies are particularly important for discerning the influence of distinct PFC regions in mood and motivation, given the relatively rudimentary PFC in rodents.

Hippocampus. Owing to its dense reciprocal connections (direct and indirect) with the VTA and NAc, the hippocampus is thought to strengthen memory encoding based on the valence of a stimulus. It has been suggested that people with mood or anxiety disorders have memory encoding errors that result in exaggerated or misinterpreted experiences of the event⁵⁹. Many studies have found reduced hippocampal volume in depression and other stress-related disorders⁶⁰, although again this seems to be found mostly in studies of middle-aged or elderly subjects. Histological analysis of post-mortem brains from depressed humans suggest that reduced volume is due, in part, to synaptic and glial loss⁶¹.

Studies of hippocampal activity in depression are limited and often conflicting. A recent study showed that depression is associated with a reduced BOLD signal in the right hippocampus during a positive wordencoding task⁶². These findings led the authors to speculate that, in mood and anxiety disorders, the hippocampus does not properly encode rewarding memories and that this may make an individual insensitive to positive information.

Although the literature summarized above has contributed to the formulation of a systems-level understanding of depression, there are still areas of controversy, and major questions remain unaddressed. For example, the VTA and LHb, which are well established as areas that control responses to rewarding and aversive stimuli, are relatively small and have not yet been functionally or structurally characterized in human depression. In general, post-mortem neuroanatomical analyses in support of fMRI data have been limited to the hippocampus and mPFC. Moreover, as we have highlighted, currently available brain imaging methods in humans do not have the resolution to differentiate cell types and cannot distinguish between changes in excitation or inhibition. As discussed below, the ability to genetically target specific cell populations within monosynaptic reward circuits in rodents makes it possible to test the functional relevance of specific cells and circuits in controlling depressionlike behaviour. Such advances may one day enable the development of new imaging methods for diagnostic (biomarker) screens for these syndromes.

Effects of stress in rodent models

Because stress can be a precipitating factor in the onset and severity of depression and anxiety⁶³, investigators have used a wide array of rodent stress models to induce depression- and anxiety-like symptoms and then examined the underlying neural and molecular mechanisms involved. Just as depression and anxiety symptoms co-occur in many patients, all chronic stress models in rodents involve a mixture of abnormalities in both behavioural domains. An overview of stress models is provided in BOX 1. Here, we focus on the structural and functional plasticity of the brain's reward circuitry in these models. A brief description of the behavioural symptoms (or 'endophenotypes') most relevant to reward circuit function is also provided in BOX 1.

Structural and functional synaptic plasticity of reward circuits. Most of the literature on stress-induced structural and functional plasticity in rodent stress models has focused on the hippocampus and PFC, with more recent attention given to the NAc and amygdala. A large majority of this work has addressed structural plasticity of dendrites and dendritic spines, and the associated electrophysiological changes at excitatory synapses, within these reward regions (see below). Analysis of stressinduced changes at inhibitory synapses has received far less attention and will be crucial to understand the net functional change within a particular circuit. With this caveat in mind, we describe here the emerging picture of the effects of chronic stress on excitatory synaptic plasticity of the reward circuitry in rodents. Wherever possible, we frame these data in the context of findings from human imaging and post-mortem studies.

Stress-induced structural plasticity of neurons was first identified by McEwen's group in hippocampal pyramidal neurons⁴⁵. They found that exposure to chronic restraint stress causes dendritic atrophy in both CA1 and CA3 regions of the hippocampus⁶⁴. Ultrastructural analysis of glutamatergic synapses in CA1 revealed that the size of the postsynaptic density — an area that contains many glutamate receptors and scaffolding proteins required for signalling - was increased despite atrophy of the neurons' dendrites65. This suggested that the neurons had become less complex but that their remaining synapses were larger and more mature. These findings are consistent with the reduction in hippocampal volume observed in humans with stress-related disorders³³. Moreover, the results suggest that at least part of this reduction can be attributed to plasticity of excitatory neurons.

The PFC also shows a general atrophy of dendrites and loss of spines in response to chronic restraint and unpredictable stress^{64,66,67}. In rodents, atrophy and loss of spines occurs predominantly on pyramidal glutamatergic neurons in both the prelimbic (PL) and infralimbic (IL) regions of the mPFC; however, subpopulations of IL neurons that project to the BLA seem to be resistant to restraint stress-induced changes67. The finding that cortical plasticity is cell- and projection region-specific underscores the complexity of interpreting brain imaging studies of the human PFC. Conversely, a major limitation of rodent studies, as noted above, is the lack of clarity regarding the rodent homologues of the human PFC. For example, the PL and IL together are considered to be homologues of the human subgenual anterior cingulate cortex (Brodmann area 25) - which mediates antidepressant responses in humans upon deep brain stimulation68 — but recent studies suggest that PL and IL cortices subserve different behavioural functions from one another⁶⁹. Nonetheless, data from human imaging and rodent stress studies support the idea that a loss of excitatory tone within the mPFC in stress-related disorders corresponds to decreased BOLD activity during

Dendritic spines

Small protrusions from a dendrite that are typically associated with synaptic input from glutamatergic axon terminals at the spine's head, but which may receive other inputs along their sides or necks.

Postsynaptic density

A specialization on excitatory dendritic spines, originally identified by electron-microscopy, which contains glutamate receptors and many associated scaffolding and trafficking proteins that are crucial for excitatory synaptic transmission.

Glutamate receptors

Receptors for the major excitatory neurotransmitter in the brain, comprised of ionotropic and metabotropic (G protein-coupled) classes. Ionotropic glutamate receptors are named for specific agonists, AMPA,NMDA and kainate.

Deep brain stimulation

A method that involves implantation of an electrode for stimulation of specific brain areas to treat symptoms of neurological and psychiatric diseases. It is used in the treatment of Parkinson's disease, tremor, dystonia, obsessive-compulsive disorder and depression.

Box 1 | Animals models of depression and measures of anhedonia

Models of depression

It is impossible to fully model depression in an animal because, first, depression in humans is not one illness but a highly heterogeneous syndrome; second, key symptoms of human depression (that is, guilt, suicidality and sadness) cannot be assessed (and may not exist) in animals; and third, the biology underlying the many types of human depression remains poorly understood. However, it is clear that exposure to stress increases the risk for depression in humans⁶³, and consequently, most rodent depression models rely on environmental stressors to induce depression-like symptoms that can be studied mechanistically (see below).

One of the best established models is the chronic social defeat stress model, in which experimental mice are subjected repeatedly to physical and non-physical cues from more aggressive mice^{80,91,110,149,150}. Much like humans, not all C57BL/6J mice develop a depression-like syndrome: in approximately two-thirds of mice, chronic social defeat stress induces social avoidance, anhedonia (reduced interest in sucrose, high-fat food and sex), a metabolic syndrome and anxiety-like behaviours, and these mice are therefore termed 'susceptible'. The remaining one-third only exhibit the anxiety-like symptoms after chronic social defeat stress, and these mice are termed 'resilient' (REF. 80). A similar behavioural profile has recently been demonstrated in mice who witness other mice being subjected to social defeat stress¹⁵⁰.

The chronic 'mild' stress paradigm, sometimes referred to as chronic variable stress (CVS) or chronic unpredictable stress (CUS), is another established depression model¹⁵¹. The stressors involved are typically physical in nature — they can include restraint, tail suspension, disruption of the light–dark cycle, cage tilt, food or water restriction, changing of cagemates, temperature reductions, exposure to soiled or wet bedding and footshocks — and are given in an unpredictable order. Animals exposed to these regimens generally develop anhedonia-like symptoms, deficits in grooming and compromised immune function¹⁵¹.

Unlike chronic social defeat stress in C57BL/6J mice, which works in male mice only, CUS can be used to study stress responses in females, a critical under-studied area of basic depression research and a high priority for future work¹¹⁵. Importantly, a recent report demonstrated effects of social defeat stress in females of a different rodent species¹⁵².

Learned helplessness is another commonly used measure of depression in rodents. In this task, an animal is exposed to an inescapable stress, commonly a footshock¹⁵³. When subsequently presented with an active avoidance task, in which an operant response is now required to terminate the stress, some previously stressed animals fail to learn the active avoidance test compared with controls. Still another paradigm is prolonged social isolation during adulthood, which also results in a mixture of anhedonia- and anxiety-like symptoms¹²⁴.

Measuring anhedonia

Appetitive tasks are generally used to measure anhedonia, a core symptom of depression (for a review, see REF. 154), in laboratory animals. Initial first-pass screens for anhedonia often involve sucrose preference tests, in which a rodent can choose between a sucrose solution and water. Many variations of the procedure are employed, but in a commonly used version of this test, rats or mice are given access to a bottle of 1% sucrose and a bottle of water for 1–2 hours¹⁵⁵ or overnight⁸⁰. The percent sucrose intake is used as a measure of natural reward. An animal's degree of social interaction may also be related to anhedonia, as rodents are social animals and find these interactions highly rewarding. Various chronic stress models (for example, chronic social defeat stress, prolonged social isolation and CUS; see above) and several genetic manipulations cause decreased sucrose preference and social avoidance^{91,115,124}, whereas chronic treatment with standard antidepressants can reverse these deficits.

Sexual activity has also been used to assess anhedonia-like behaviour — it is considered a measure of natural reward¹⁵⁶. This measure also has face validity, given that many depressed humans exhibit sexual dysfunction or lack of interest. Another measure of reward function is intracranial self-stimulation^{154,157}. In this model, animals volitionally work (for example, by rolling a cylinder with their paws) to stimulate an electrode that is implanted directly into one of several brain areas, most often the medial forebrain bundle, which contains dense dopaminergic fibres emanating from the VTA. The minimum current that is necessary to support an operant response is termed the brain stimulation reward threshold. Chronic stress increases reward thresholds, which is thought to reflect a reward deficit (that is, anhedonia), whereas antidepressant treatments and drugs of abuse have the opposite effect^{154,158}.

cortex-driven reward tasks. This scheme is also consistent with the idea that depression involves a reduction in top-down cortical control over subcortical limbic structures⁷⁰. However, this idea is rather simplistic and contrary to the increased activity of subgenual anterior cingulate cortex seen in many depressed patients⁶⁸.

Several recent animal studies have investigated whether chronic stress alters excitatory synaptic plasticity in the amygdala⁷¹. Most studies suggest that stress causes cell type- and amygdala nucleus-specific increases in spine formation and dendritic hypertrophy. For example, chronic restraint stress increases dendritic arborization and spine density selectively in BLA spiny glutamatergic neurons^{49,72}. Interestingly, unlike in the hippocampus, these changes are enduring and correlate with sustained anxiety-like behaviour. This could explain why syndromes such as post-traumatic stress disorder persist even after the precipitating threat has long receded. These structural findings are also in line with functional imaging studies in humans, which suggest that the amygdala is hyperactive in depression and anxiety³³.

With regard to the NAc, chronic social defeat stress in mice (BOX 1) has been shown to increase spine density on MSNs^{73,74}. Accordingly, stress increases the frequency of AMPA-mediated mini-excitatory postsynaptic currents (mEPSCs), indicating a greater number of functional glutamatergic synapses^{73,75}. It is difficult to interpret these rodent data within the context of human studies. Patients with depression generally show decreased BOLD fMRI responses in the NAc, and deep brain stimulation of this

Epigenetic

A mechanism of a stable change in gene expression that does not involve changes in DNA sequence. A small subset of epigenetic changes can be transmitted to subsequent generations.

Resilience

The ability to maintain normal physiological and behavioural function in the face of severe stress.

Susceptibility

The vulnerability to succumb to the deleterious effects of stress.

and nearby regions has antidepressant effects⁷⁶. These contrasting findings may reflect the fact that, as noted earlier, the NAc consists mainly (>98%) of GABAergic neurons or the possibility that deep brain stimulation stimulates fibres of passages that synapse outside the NAc. Moreover, although stress increases excitatory tone in the NAc, it seems to induce an even larger decrease in inhibitory tone, which is driven by a stress-induced loss of inhibitory synapses⁷⁷. This supports the hypothesis that decreased NAc BOLD responses in patients with depression could actually reflect a decrease in inhibition that may be normalized by deep brain stimulation.

Future studies are needed to clarify these findings and to identify the specific monosynaptic pathways that are influenced by these changes in excitatory and inhibitory synapses. For example, is the increased excitatory tone on NAc MSNs associated with chronic stress73,75,78 related to PFC, amygdala or hippocampal inputs, and how does stress influence the integration of these excitatory inputs in the NAc⁷⁹? Furthermore, the two main subtypes of GABAergic output neurons from the NAc (that is, D1-type and D2-type MSNs) have opposite effects on reward behaviour¹, emphasizing the need for further delineation of cell type-specific effects of stress. Far more must also be learned about the strength of innervating presynaptic nerve terminals, the functional state of the new dendritic spines and the underlying molecular mechanisms involved in stress-induced structural plasticity. Our work has identified a subset of transcriptional and epigenetic targets induced by chronic social defeat stress that selectively increase immature (for example, stubby) spines on NAc MSNs, however, it is not yet clear whether this reflects plasticity of D1-type versus D2-type MSNs73.

Functional studies of monosynaptic reward circuits. Recent work has started to investigate the role of discrete monosynaptic connections within the brain's reward circuitry in depression- and anxiety-like behaviour in rodents. Although a definitive circuit perspective of mood and anxiety cannot yet be obtained from

Box 2 | The VTA-NAc reward circuit in pain and analgesia

There is growing evidence in humans and rodents that reward circuits are important in pain responses. Imaging studies in humans have shown that greater functional connectivity between the nucleus accumbens (NAc) and the prefrontal cortex predicts pain persistence in patients with chronic back pain¹⁵⁹. Interestingly, the degree of dopamine release in the NAc is associated with the anticipated and subjectively perceived effectiveness of a placebo and reductions in continuous pain ratings¹⁶⁰. These studies raise the possibility that opiate pain medications might promote pain relief partly by changing the perception of analgesia through augmentation of dopamine-and opioid-dependent signalling in the ventral tegmental area (VTA)–NAc circuit.

In mice, chronic neuropathic pain models, in which the sciatic nerve is ligated, inhibit dopamine signalling in the VTA and dopamine release in the NAc through a μ -opioid receptor-dependent mechanism¹⁶¹. In addition, a still smaller number of recent studies have identified signalling cascades in the NAc that regulate opiate-mediated analgesia as well as analgesic tolerance to repeated opiate administration. For example, regulator of G protein signalling 4 (RGS4) promotes analgesia, whereas Δ FOSB reduces sensitivity to analgesia and promotes a greater degree of tolerance^{162–164}. These studies highlight the delicate balance between pleasure and pain systems and may explain the high comorbidity of mood disorders and chronic pain syndromes.

these studies, it is clear that specific glutamatergic and dopaminergic systems exert distinct and, in some cases opposite, functional effects.

Chronic social defeat stress increases phasic firing of VTA dopaminergic neurons in susceptible mice only^{80,81}, and this effect is specific to dopamine neurons that innervate the NAc82. Indeed, dopamine neurons that innervate the mPFC show reduced firing after chronic stress⁸². Silencing all VTA neurons (regardless of projection region or cell type) by locally overexpressing a K+ channel subunit prevents social defeat stress-induced social avoidance and anhedonia (that is, it renders animals resilient), whereas exciting all VTA neurons by overexpressing a dominant negative mutant K⁺ channel has the opposite effect⁸⁰. Although these early studies suggested the involvement of hyperexcitable VTA dopamine neurons in stress-induced behavioural pathology, greater cell, circuit and temporal specificity of the manipulations was needed to confirm this idea. Recent experiments involving the expression of ChR2 or halorhodopsin (NpHR) in VTA dopamine neurons projecting to the NAc versus the mPFC showed that increased phasic (burst) firing of dopamine neurons projecting to the NAc, but not those projecting to the mPFC, mediates the increased social avoidance and anhedonia that characterizes susceptible mice82. Preventing this firing rate increase optogenetically increased resilience to subsequent stress and also produced antidepressant-like responses in previously stressed animals. By contrast, optogenetic suppression of VTA neurons projecting to the mPFC, which mimics the effect of stress⁸², promoted susceptibility. These findings are interesting in light of further evidence that VTA-to-PFC neurons control behavioural responses to pain-related information²⁹. BOX 2 details increasing evidence that the VTA and its targets in the reward circuitry have a crucial role in the perception of pain as well as in opiate-induced analgesia.

The finding that VTA–NAc dopamine neuron firing is increased in susceptible mice seems to be at odds with the general notion that such activation is associated with reward and with preliminary findings from deep brain stimulation in humans showing that stimulation of the VTA (or the medial forebrain bundle) has anti-depressant effects (T. Schlaepfer, personal communication). However, we know that distinct subpopulations of VTA dopamine neurons, with at least partly distinct inputs and outputs, respond differently to rewarding and aversive stimuli^{28,29,83}.

Additional studies have highlighted the complexity of VTA dopamine neurons and their possible bidirectional role in stress. For example, chronic restraint stress and social defeat stress both increase VTA dopamine neuron firing, whereas chronic cold stress decreases the neurons' activity⁸⁴. Cold stress is a mild stressor compared to restraint or social defeat, suggesting that the intensity of stress exposure influences the animal's physiological responses to the stressor. Indeed, a recent study showed that optogenetic activation of VTA dopamine neurons that project to the NAc has antidepressant effects in several behavioural domains in mice exposed to chronic unpredictable stress⁸⁵, which contrasts with

line: resp show

Brain-derived neurotrophic factor

(BDNF). The major neurotrophin (nerve growth factor) expressed in the brain.

TRKB

A tyrosine kinase receptor, located at the plasma membrane, which mediates the actions of brain-derived neurotrophic factor.

Cyclic AMP-responsive element-binding protein

(CREB). A transcription factor that can be activated by cyclic AMP, Ca²⁺ and brain-derived neurotrophic factor– TRKB-induced signalling cascades. the finding that VTA–NAc dopamine neuron firing is increased in mice that are susceptible to chronic social defeat stress⁸². The discrepant findings from these various studies underscore the need for further research, particularly to better relate different rodent models to human disorders.

As noted above, it has been proposed that motivational disorders, such as addiction and depression, are associated with reduced glutamatergic (PFC) transmission in the NAc^{5,86}. An initial study⁸⁷ showed that optogenetic activation of the mPFC (PL and IL) in mice had antidepressant-like effects in the social defeat paradigm. However, in this study, ChR2 was expressed in both glutamate- and GABA-containing cells in the PL and IL regions, and in the glutamate cells that project to the amygdala, VTA and other regions in addition to the NAc. When ChR2 was expressed specifically in PFC glutamatergic pyramidal neurons, stimulation of the terminals of these neurons in the NAc exerted antidepressant-like actions, whereas stimulation of thalamic terminals in the NAc produced the opposite effects⁸⁸. Interestingly, the NAc is a major projection region of the subgenual anterior cingulate cortex, the PFC area that is targeted in deep brain stimulation studies in humans⁶⁸. Although these findings suggest that stimulation of the mPFC-NAc monosynaptic circuit is antidepressant, it remains unclear whether this is due to a pro-reward response. For example, rodents will not self-stimulate projections from the mPFC to the NAc, and optogenetic stimulation of PFC glutamatergic terminals in the NAc does not promote greater sucrose intake27,88. Together, these studies in rodents and humans highlight the importance of defining the precise glutamatergic inputs to the NAc that control emotional behaviour.

There is also evidence that cholinergic interneurons in the NAc control stress-related behaviours. A recent study showed that toxin-mediated silencing of NAc cholinergic neurons promotes depression-like behavioural responses⁸⁹. The anticholinergic drug scopolamine has shown promise for its rapid antidepressant properties in humans90, and most tricyclic antidepressants have anticholinergic activity, although it is unclear whether this is related to any important therapeutic effects. Although these clinical data suggest that anticholinergic agents administered systemically may act as antidepressants, it is not known which brain loci mediate their effects. The rewarding action of cholinergic agonists administered directly into the NAc^{8,23} and the conflicting influence of cholinergic interneurons on reward-related measures cited earlier²² emphasize the need for further research to define the contribution of cholinergic mechanisms acting in distinct brain reward circuits to depression-like behaviour and antidepressant responses.

In summary, newly developed experimental approaches are allowing basic scientists to begin to formulate a circuit-level understanding of depression-like behaviour with far greater precision than was previously possible. To eventually translate the sometimes conflicting observations to human conditions, it will be important to apply these methods to non-human primates and more ethologically valid depression models.

Molecular mechanisms in the VTA-NAc circuit

It is generally thought that experience-dependent plasticity within these many discrete monosynaptic reward circuits shapes the ways in which an individual adapts (or maladapts) to changes in the environment. It is possible that the molecular mechanisms underlying this plasticity become 'overwhelmed' in response to severe stress in a subset of individuals and consequently promote pathological behaviours. Although the field is still in its early stages, substantial progress has been made in understanding how molecular changes within specific cell types of brain reward regions control adaptive and maladaptive plasticity - mediating resilience and susceptibility (as defined in BOX 1), respectively — in response to chronic stress (FIGS 3,4). In the subsequent sections, we discuss some of the best-established molecular mechanisms within the VTA-NAc circuit and their relevance to depression-like behaviour. Importantly, an increasing number of these mechanisms have been validated in post-mortem human brain tissue. A major goal of current research is to understand how these diverse molecular mechanisms underlie the synapseand circuit-level changes seen in animal models and depressed humans.

BDNF-TRKB. Chronic social defeat stress increases brain-derived neurotrophic factor (BDNF) signalling from the VTA to the NAc, where increased activation of the receptor tyrosine kinase TRKB (also known as NTRK2) promotes greater susceptibility to the deleterious effects of stress^{80,91}. This induction of BDNF signalling is mediated by the stress-induced increase in burst firing of VTA dopamine neurons discussed above^{80,81}. Conversely, blockade of BDNF-TRKB signalling, or of downstream effectors such as extracellular signal-regulated kinase (ERK; also known as MAPK), promotes resilience; that is, it makes animals less susceptible to stress. BDNF-TRKB-ERK signalling exerts a similar pro-depression-like effect in the VTA itself⁹²⁻⁹⁴, where another downstream target of BDNF-TRKB, the serine/threonine kinase AKT, is also pro-depressant⁹⁵. Several of these stress-induced changes in the BDNF pathway have been documented in the VTA and NAc of depressed humans^{80,95}. A key aim now is to identify the targets downstream of the BDNF-TRKB-ERK and BDNF-TRKB-AKT signalling cascades that mediate these pathological responses. One target is the transcription factor cyclic AMP-responsive element-binding protein (CREB), which is discussed in greater detail below (FIG. 4).

The fact that stress-induced activation of the BDNF signalling pathway in the VTA–NAc reward circuit promotes susceptibility is in direct contrast to stress-induced suppression of this pathway in the hippocampus and PFC — in these areas, activation of this pathway has antidepressant-like actions⁹⁶. However, it is not unreasonable to assume that a particular protein can have different effects on behaviour depending on the neuronal cell type and larger neural circuits involved. Nevertheless, the discovery of BDNF signalling as a pro-depressant mechanism in the VTA–NAc circuit is interesting with respect to the discussion of dopamine



Figure 3 | Molecular mechanisms controlling depression-related circuit plasticity. Examples of maladaptive molecular processes that confer susceptibility to chronic social defeat stress are shown. In the medial prefrontal cortex (mPFC), including infralimbic and paralimbic regions, susceptible animals display molecular evidence of decreased neural activity, which can be targeted through optogenetic stimulation with channelrhodopsin 2 (ChR2) to promote resilience. Stimulation of ChR2 in glutamatergic terminals in the nucleus accumbens (NAc) reverses stress-induced social avoidance behaviour. Ventral tegmental area (VTA) dopamine neurons of susceptible animals show a stress-induced increase in firing rate that drives maladaptive responses to social defeat stress. The result is greater release of brain-derived neurotrophic factor (BDNF) and dopamine from VTA terminals in the NAc to promote depression-like behaviour. The increased excitability of VTA dopamine neurons of susceptible animals results from an increased cationic current, which is completely compensated for in resilient animals via induction of K⁺ channels, driving neuronal firing back to normal levels. In the NAc, susceptibility is associated with increased glutamatergic responses by medium spiny neurons. The presynaptic input responsible for the increased glutamate tone is not known. Susceptible mice exhibit reduced Rac1 gene transcription in the NAc, which is associated with reduced histone pan-acetylation (indicated by A) and increased lysine 27 methylation (indicated by M) and leads to reorganization of the actin cytoskeleton and increased excitatory synapse numbers and function. In addition, there appear to be Δ FOSB-mediated transcriptional events (not shown) that control the types of glutamate receptors functioning at these synapses among many other changes. Susceptible animals have lower levels of GluA2 (which is encoded by Gria2), a Ca²⁺-impermeable AMPA glutamate receptor subunit, which in resilient mice limits overactive glutamate tone in the NAc. HAT, histone actyltransferase; HDAC, histone deactylase; HMT, histone methyltransferase; P, phosphorylation; TF, transcription factor.



Figure 4 | Enhanced vulnerability to stress via priming of BDNF signalling in the NAc. Increased vulnerability to the depression-like effects of chronic social defeat stress occurs in part via priming of brain-derived neurotrophic factor (BDNF) signalling in the nucleus accumbens (NAc). Under control conditions (part a), BDNF activation of receptor tyrosine kinase TRKB signalling is limited. However, after some prior stimulus that increases susceptibility (for example, repeated stress or chronic cocaine exposure) (part b), BDNF-TRKB signalling is increased in the NAc, causing enhanced phosphorylation (indicated by P) and activity of several downstream signalling mediators, including cyclic AMP-responsive element-binding protein (CREB). This maladaptive response occurs not only through increased BDNF release into the NAc from the ventral tegmental area (VTA) but also through epigenetic modifications that further prime BDNF signalling cascades. For example, chronic stress increases Ras expression in the NAc of susceptible animals by decreasing G9a binding at the H-Ras1 gene promoter, causing reduced levels of repressive H3K9me2 (dimethyl-Lys9-histone H3, a major form of repressive histone methylation (indicated by M)). Ras also appears to be a target for CREB, creating a pathological feedforward loop that promotes CREB activation and Ras expression as well as depression-like behaviour (not shown). The figure also shows the induction of another pathway downstream of BDNF, including nuclear factor-κB (NF-κB) and inhibitor of NF-κB kinase (IKK) — possibly downstream of the neurotrophin receptor p75^{NTR} (also known as NGFR) — in the NAc after chronic social defeat stress in susceptible animals. A, acetylation; DAR, dopamine receptor; ERK, extracellular signal-regulated kinase; ΙκΒα, inhibitor of NF-κB-α: MEK. ERK/MAPK kinase.

systems and depression-like behaviour outlined in previous sections. Thus, in most brain regions, including the VTA⁹⁷, BDNF is thought to act in part by promoting plasticity at glutamatergic synapses. Assuming this is also the case in the NAc, we speculate that under conditions of severe stress, the VTA-NAc reward circuit undergoes a strong and inflexible form of learning that is mediated by abnormal glutamatergic plasticity, which under less severe conditions may be adaptive. The advanced molecular and optogenetic tools reviewed earlier make it possible to directly test this hypothesis. The opposing behavioural effects of BDNF-TRKB pathway activation in the VTA-NAc versus cortical regions suggests that this pathway may not be a suitable target for novel antidepressant treatments, unless it were possible to target this pathway selectively in a particular brain area or circuit.

Cytokines and nuclear factor-*kB*. Increasing attention has focused on the role of pro-inflammatory cytokines in depression98. For example, there is an increased prevalence of mood and anxiety disorders in patients suffering from illnesses with strong immune and inflammatory features, such as multiple sclerosis and lupus erythematosus⁹⁸. Conversely, patients with depression are at increased risk for inflammation-related conditions, such as cardiovascular disease and stroke99. Moreover, administration of the pro-inflammatory cytokine interferon-a (IFNa) induces depression symptoms in humans with hepatitis C100 and in normal rodents101. Analysis of peripheral inflammation markers consistently identifies increases in interleukins interleukin-6 and interleukin-1ß and tumour necrosis factor- α (TNF α) in patients with mood disorders¹⁰². Altered central levels of these factors have been identified as well. Rodent studies have largely

Interleukins

A group of cytokines that were first known for their role in immune and inflammatory responses but more recently have been found to regulate neural function.

Nuclear factor-κB

(NF-xB). A transcription factor first characterized for its regulation of immune and inflammatory responses but more recently has been implicated in controlling neural function.

RAC1

A small G protein (GTPase) that, in the nervous system, plays a critical part in regulating dendritic spine outgrowth.

Melanocortin

First characterized for its regulation of melanocytes, melanocortin is also a peptide neurotransmitter secreted by hypothalamic neurons, where it exerts potent anorexogenic effects. In addition, it is implicated in the regulation of mood via actions on the brain's reward circuitry.

Orexin

Also known as hypocretin, this peptide neurotransmitter is secreted by neurons in the lateral hypothalamus to promote wakefulness and attention. It also promotes reward by direct projections to ventral tegmental area dopamine neurons.

Leptin

A peptide hormone secreted by adipocytes. One of the major anorexigenic peptides known, leptin suppresses feeding behaviour through actions on hypothalamus. It has also been implicated in regulation of mood.

Ghrelin

An orexigenic peptide hormone secreted by the stomach epithelium after periods of fasting, which acts in hypothalamus and perhaps other brain regions to stimulate appetite. It has been implicated in mood regulation as well.

RNA-seq

A high-throughput method to sequence whole-genome cDNA in order to obtain quantitative measures of all expressed RNAs in a tissue.

Chromatin

The mixture of DNA and proteins that comprise the cell nucleus.

confirmed that interleukin-6 and interleukin-1 β , acting in the hippocampus or the NAc, increase depression-like behavioural responses to chronic stress^{103,104}. A central question in the field is whether cytokines derived from the periphery versus those locally synthesized in the brain (by neurons or glia) are primarily responsible for the pro-susceptibility effects of these molecules.

The signalling cascades downstream of cytokines that mediate these effects are beginning to be delineated. Nuclear factor-kB (NF-kB) is a transcription factor best known for its role in peripheral immune and inflammatory responses, but it is also a well-established downstream target of interleukin-6, interleukin-1 β and TNFa, in both the brain and peripheral tissues. Recent evidence suggests that the NF-KB signalling pathway regulates the reward circuitry in depression and addiction models73,105-107. For example, in the hippocampus, NF-KB activation is required for the stress-induced impairment of neurogenesis and induction of anhedonia (for example, decreased sucrose preference)105. In the NAc, chronic social defeat stress increases levels of inhibitor of NF-KB kinase (IKK), which then increases downstream NF-KB signalling by phosphorylating inhibitor of NF-kB (IkB) and triggering its dissociation from NF-κB⁷³ (FIG. 4). NF-κB activation mediates the formation of new immature excitatory spine structures on NAc dendrites73. Such induction of NF-KB and new spines occurs in susceptible animals but is not seen in resilient individuals73. Interestingly, similar molecular and structural changes are induced in the NAc by chronic cocaine administration¹⁰⁷. Direct inhibition of IKK in the NAc prunes these new synapses and reverses the associated depression- and addiction-like phenotypes73,107. Current studies focus on the intracellular signalling pathways through which cytokines regulate NF-KB activity in the context of stress- and addiction-related pathology, and also aim to identify the transcriptional targets of NF-κB that mediate these effects. One target may be RAC1, a small G protein that has recently been implicated in stress- and cocaine-triggered induction of immature spines in this brain region (see below)^{40,108}. These studies illustrate how inflammatory signalling pathways influence glutamatergic neurotransmission in NAc circuits to influence depression-like behaviour.

Metabolic mechanisms. The past decade has revealed that the VTA-NAc reward circuit is strongly influenced by several peptides that are known for their role in controlling food intake and peripheral metabolism and that are produced in the periphery or in the hypothalamus. This is not surprising, because these factors, which presumably reflect physiological measures of hunger or satiety, interface with brain systems that control motivational drive and reward. Thus, hypothalamic neurons expressing peptides such as melanocortin, melanin-concentrating hormone or orexin (also known as hypocretin) send dense projections to the NAc or VTA⁴. Likewise, peripheral peptides, such as leptin (derived from fat) or ghrelin (derived from stomach epithelium), control the activity of the VTA-NAc circuit most likely indirectly, through their effects in the hypothalamus, although direct effects have also been implicated¹⁰⁹. High levels of comorbidity between depression and obesity support an interplay between feeding systems and the brain's reward circuitry.

Several of these feeding peptides have been shown to regulate depression-like behaviour in animal models by influencing the VTA-NAc circuit. In one study, chronic stress-mediated downregulation of pro-opiomelanocortin (POMC) signalling was shown to promote resilience (reduce stress susceptibility), but this was accompanied by obesity and related peripheral metabolic derangements¹¹⁰. Chronic stress induces this downregulation of POMC in the hypothalamic arcuate nucleus via increased sympathetic tone and β3-adrenergic receptor activation and decreased blood leptin levels. POMC downregulation in turn decreased melanocortin signalling to the NAc and other target regions, causing increased feeding and antidepressant-like behavioural effects¹¹⁰. Consistent with this model, a recent study showed that chronic unpredictable stress activated melanocortin 4 receptor signalling in D1-type MSNs of the NAc, which decreased the strength of excitatory synapses on these neurons - an effect that was associated with anhedonia¹¹¹.

In addition, chronic social defeat stress induces peripheral ghrelin secretion, as well as activation of central orexinergic neurons in the lateral hypothalamus of resilient mice only, thus contributing to the absence of depressionlike behaviour^{112,113}. The site of action of these peptides remains unknown but might involve ghrelin-induced activation of orexinergic neurons and subsequent orexininduced activation of several reward-related regions, particularly the VTA. Meanwhile, leptin has been implicated in the regulation of depression-like behaviour at the level of the hippocampus¹¹⁴.

These are examples of just some of the prominent feeding peptides that deserve attention in the field of depression. Of particular note is that perturbation of these feeding mechanisms may produce very different effects in different subtypes of depression. It is conceivable that individuals in whom depression is characterized by reduced activity and weight gain respond differently to such perturbations than individuals who exhibit increased activity, anxiety and weight loss. It is also possible that different perturbations in feeding peptides are associated with (or may underlie) different subtypes of depression.

Transcriptional and epigenetic mechanisms. Genomewide methods have increasingly been used to obtain an unbiased view of molecular changes in the VTA and NAc that relate to susceptibility versus those that relate to resilience or to antidepressant responses in animal models of depression^{80,91,115,116}. Earlier studies focused on gene expression microarrays, whereas more recent studies have used deep sequencing of expressed RNAs (RNAseq), which better captures alternative splice variants as well as non-coding RNAs. There is also growing use of genome-wide chromatin assays, including chromatin immunoprecipitation (ChIP) followed by promoter chips (ChIP-chip), ChIP followed by deep sequencing (ChIPseq) and several methods to study DNA methylation. The rationale for studying epigenetic end points is, first, that they can reveal the precise molecular mechanisms

Chromatin

immunoprecipitation (ChIP). A method that enables the identification of histone modifications or transcriptional regulatory proteins at a given gene promoter. DNA is crosslinked to nearby proteins by light fixation, the material is sheared, then immunoprecipitated with an antibody to a particular protein of interest, and genes in the final immunoprecipitate are quantified by the polymerase chain reaction.

ChIP-chip

(Chromatin immunoprecipitation followed by promoter chips). A method that enables a global analysis of genes associated with a particular histone modification or transcriptional regulatory protein. Immunoprecipitated chromatin is analysed on a microarray gene chip, enriched in promoter regions.

ChIP-seq

(Chromatin immunoprecipitation followed by deep sequencing). A method that allows for global identification of histone modifications or transcriptional regulatory proteins. ChIP is coupled to high-throughput sequencing to obtain analysis across the entire genome, and in this sense differs from ChIP–chip.

ΔFOSB

A FOS family transcription factor that, once induced, is particularly long-lived in the brain owing to its stability.

Serum response factor

(SRF). A transcription factor, which, in conjunction with another factor termed ELK1, binds to serum response elements within certain genes to regulate their expression.

β-catenin

A transcription factor that is activated by the WNT– Frizzled–Dishevelled signalling cascade. It appears to mediate resilience to stress at the level of the nucleus accumbens.

Transcription factors

Proteins that bind to specific DNA sequences (called response elements) within responsive genes and thereby increase or decrease the rate at which those genes are transcribed. by which stress regulates gene expression and, second, that they represent plausible 'molecular scars' at particular genes that stably alter the genes' inducibility in response to subsequent stress. According to the 'molecular scar' hypothesis, stress-induced chromatin modifications across a person's lifetime contribute to an individual's inherent vulnerability or resistance to stressrelated disorders¹¹⁷⁻¹¹⁹. Studies of chromatin regulation in stress models therefore promise to reveal new insight into the neurobiological mechanisms involved. To date, most attention has been given to the NAc because of its large size; it is now important to carry out analogous studies of the VTA and other brain reward regions.

The best characterized transcriptional mechanism controlling depression-like behaviour in the NAc involves CREB (FIG. 4). In contrast to its antidepressantlike effects in the hippocampus, CREB activity in the NAc promotes depression-like behaviour (that is, it increases stress susceptibility) but concomitantly induces anxiolytic-like responses in numerous behavioural assays¹²⁰. This has been demonstrated in studies using viral vectors and inducible bitransgenic mice in which CREB or a dominant negative mutant CREB (mCREB) is targeted to the NAc120, in studies using constitutive CREB knockout mice121 and, more recently, in studies using local knockout of CREB from the NAc122. Gene expression microarray analyses of mouse NAc in which CREB or mCREB were overexpressed and ChIP-chip studies of the NAc of wild-type mice exposed to chronic stress have revealed a host of CREB target genes that are likely to mediate these depressant and anxiolytic effects^{116,123,124}. Some prominent targets that are upregulated by CREB are specific K⁺ channel subunits, glutamate receptor subunits, dynorphin and other neuropeptides. The induction of dynorphin in D1-type NAc MSNs induces depression-like behaviour, and this is mediated by activation of κ -opioid receptors on VTA dopamine neurons^{125,126}. Another target that is upregulated in the VTA by CREB is BDNF and several components of BDNF signalling cascades¹²². As these cascades themselves activate CREB, this could establish a feedforward mechanism that underlies susceptibility to chronic stress. CREB is known to increase the intrinsic excitability of NAc MSNs and to promote glutamatergic plasticity^{127,128}, which could be the basis for working hypotheses to relate CREB's transcriptional effects to circuit-level changes that promote depression. NF-κB is another pro-depression transcription factor in the NAc; it will be important to use genome-wide methods to define its gene targets in stress models as well as to study possible interactions with CREB.

In contrast to CREB and NF- κ B, which control susceptibility, studies have identified Δ FOSB (a FOS family transcription factor), serum response factor (SRF) and β -catenin (which acts downstream of WNT signalling cascades) as mediating resilience. All three factors are preferentially induced by chronic stress in the NAc of resilient mice, where they have been shown to prevent depression-like behaviour¹²⁹⁻¹³¹. Δ FOSB and SRF also induce antidepressant-like responses in previously susceptible animals. Several candidate target genes through

which Δ FOSB promotes resilience have been identified. An example is the GluA2 AMPA glutamate receptor subunit, which is induced by Δ FOSB in the NAc and reduces glutamatergic tone¹³⁰, thereby opposing the enhanced glutamatergic innervation of these neurons that seems to promote susceptibility (see above and FIG. 3). One target of SRF is Δ FOSB itself: stress-induced increases in Δ FOSB in the NAc are mediated by this factor¹²⁹. These data highlight the need for genome-wide ChIP–seq assays to comprehensively define the transcriptional targets of Δ FOSB, SRF and β -catenin that mediate resilience and, in some cases, antidepressant action.

Transcription factors regulate gene expression in concert with complex changes in chromatin structure, which involve post-translational modifications of histones and DNA and the recruitment of hundreds of co-activators or co-repressors to regulated genes¹³². Chronic stress models have been shown to alter the expression levels of several chromatin-modifying enzymes in the NAc, including specific histone deacetylases (HDACs), histone methyltransferases (HMTs) and DNA methyltransferases (DNMTs), and some of these changes are associated with altered global levels of the corresponding modification (for example, total tissue levels of an acetylated or methylated histone) in this brain region^{122,133-135}. Similar types of modifications have been demonstrated for other reward regions, particularly in the hippocampus¹³⁶⁻¹⁴⁰. Moreover, several of the modifications found in animal models have been validated in post-mortem human brains^{122,141}. Importantly, some of these enzymes and modifications, for example, through local intra-NAc inhibition of certain HDACs or DNMTs or activation of certain HMTs^{40,122,133,141}, have been directly associated with antidepressant-like effects in animal models, suggesting potential paths for novel drug discovery efforts.

Recent studies have begun to use genome-wide assays to map the genetic loci in the NAc that are influenced by these chromatin marks in chronic stress models. Some of the early implications are interesting: there is substantial overlap between the chromatin changes seen in resilience and those induced by chronic antidepressant treatment in susceptible animals¹¹⁶. This suggests that one mechanism by which antidepressants work is to induce, in vulnerable individuals, some of the same genomic changes in the NAc that occur naturally in inherently more resilient individuals. A corollary of this observation is that the development of new antidepressants could be based not only on approaches aimed at preventing the deleterious effects of stress but also on approaches aimed at inducing resilience. It is expected that, as these genome-wide efforts continue, many novel targets of epigenetic regulation will be identified. One example, alluded to earlier, is the small G protein RAC1, a critical regulator of the actin cytoskeleton, which is reduced in NAc in both depression and addiction models. This suppression of RAC1 is crucial for stress- and cocaine-induced growth of immature dendritic spines on NAc MSNs and for attendant depression- and addiction-like behaviour40,108. Recent work has shown that the gene encoding RAC1 displays stable epigenetic modifications selectively in this brain region, both in rodent stress models and in depressed humans⁴⁰.

It will now be important to define the precise signalling pathway by which reduced RAC1 activity, and presumably many other mediators, control excitatory synapses on NAc MSNs and which specific monosynaptic connections are affected.

Conclusions and future directions

Research over the past decade has shown that the reward circuitry has a role in at least some of the symptoms of mood disorders. Human imaging studies have identified gross abnormalities in reward circuit structure and function related to anhedonia and reward-related perception and memory deficits. Novel genetic, viral and optogenetic tools in rodents are now enabling the field to precisely define the very complex network of cells and synapses within the reward circuitry that control specific symptoms associated with depression. Such work has confirmed an important role for dopaminergic and glutamatergic circuits within the VTA and NAc. However, much remains to be investigated. We need to more precisely define specific cells within these discrete monosynaptic circuits that control a diverse range of reward-related behavioural deficits. We also need to determine the molecular mechanisms within each cell type that control these complex adaptive processes. A recent study142 performed cell-specific molecular profiling using a transgenic mouse expressing a bacterial artificial chromosome-translating ribosomal-associated protein (bacTRAP) specifically within layer 5 pyramidal neurons in regions of the frontal cortex. They found that a cell-specific molecular profile regulated by the

serotonergic co-activator protein p11 (also known as S100A10) in these cells is necessary for antidepressant responses. p11 acting selectively in cholinergic interneurons of the NAc mediates a similar antidepressant-like response⁸⁹. Future studies using bacTRAP and related technology, along with newer methods for cell type-specific genome-wide profiling of epigenetic modifications¹⁴³, in combination with well-established rodent stress models will uncover fundamentally new information about the cell type-specific molecular mechanisms driving reward circuit plasticity in stress susceptibility versus resilience and in antidepressant responses.

Studies to date have demonstrated a perhaps unexpectedly complex relationship between the brain's reward circuitry and mood disorders. One might have assumed that 'more reward' equals 'less depression': for example, that a protein acting in a certain brain structure that increases cocaine's rewarding effects would exert an antidepressant-like effect based on the assumption that the protein also boosts natural reward. To put it another way: one might expect that the influence of a protein in depression models can be predicted from its effects in addiction models and vice versa. However, this is clearly not the case: there is no predictable relationship between the effects of a given protein in the NAc in depression models versus drug addiction models (TABLE 2); this is despite the considerable comorbidity between depression and addiction syndromes stated earlier. One complicating factor is that addiction probably involves adaptations that impair brain reward and others that promote reward-related memories^{5,10,11}.

Table 2 Examples of molecular actions in the NAc in depression versus addiction models				
Protein class	Protein	Effect in depression models	Effect in addiction models	
Transcription factor	CREB	↑ Susceptibility	\downarrow Drug reward	
	NF-ĸB	↑ Susceptibility	↑ Drug reward	
	ΔFOSB	↓ Susceptibility	↑ Drug reward	
	SRF	↓ Susceptibility	No effect	
	β-catenin*	↓ Susceptibility	NA	
Signalling	BDNF-TRKB	↑ Susceptibility	\uparrow Cocaine reward or \downarrow cocaine reward^‡	
			\downarrow Morphine reward	
	GluA2	↓ Susceptibility	↑ Drug reward	
	RGS4	↓ Susceptibility [§]	\downarrow Drug reward	
	RAC1	↓ Susceptibility	\downarrow Drug reward	
	Dynorphin	↑ Susceptibility	\downarrow Drug reward	
Epigenetic	HDAC (class I) inhibition	↓ Susceptibility	↑ Drug reward [∥]	
	HDAC5 ¹	↓ Susceptibility	\downarrow Drug reward	
	G9a inhibition	↑ Susceptibility	↑ Drug reward	
	DNMT inhibition	↓ Susceptibility	↑ Drug reward	

BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP-responsive element-binding protein; DNMT, DNA methyltransferase; HDAC, histone deactylase; NA, not assessed; NF- κ B, nuclear factor- κ B; RGS4, regulator of G protein signalling 4; SRF, serum response factor. *The influence of β -catenin is derived from studies of upstream proteins (for example, Dishevelled and glycogen synthase kinase $3\beta^{131}$. †The influence of BDNF-receptor tyrosine kinase TRKB signalling in the nucleus accumbens on cocaine reward is opposite in D1-type versus D2-type medium spiny neurons, although the net effect is to promote reward¹⁸. §Based on REF. 164. ^{II}Although short-term inhibition drives increased reward, longer-term inhibition does the opposite¹⁶⁵. ^{II}A class II HDAC.

Histone deacetylases

(HDACs). Enzymes that catalyse the deacetylation of histone amino-terminal tails.

Histone methyltransferases (HMTs). Enzymes that catalyse the methylation of histone amino-terminal tails.

DNA methyltransferases

(DNMTs). Enzymes that catalyse the methylation of cytosine nucleotides, in CpG sequences, in DNA.

The heterogeneity of cell types within a given reward structure is another likely explanation for the different effects observed for a protein in stress models versus drug models. For example, in the NAc, TRKB has opposing roles in reward-related behaviours in D1- versus D2-type MSNs18. However, a difference in cell types is not the only explanation. For instance, CREB appears to have very different target genes in the NAc in depression versus addiction models, even within the same cell types^{116,122-124}. This suggests that the stimulus itself (that is, stress or drugs) can engage different intracellular pathways, thereby regulating chromatin structure and gene expression in their own unique ways. Future studies using cell-selective molecular profiling and viral gene transfer approaches can shed light on these complex stimulus-specific effects on reward-related behaviour.

An important caveat regarding the work described in this article is that most of it was done solely in male rodents, despite the fact that, in humans, females are twice as likely to suffer from a mood disorder than are males¹⁴⁴, and rodent models consistently show that females display greater depression-like behaviour after experiencing chronic stress^{115,145}. It has been suggested that organizational differences in the development of reward-related neural circuits might predispose women to depression¹⁴⁶. In addition, the direct actions of circulating gonadal hormones on the reward circuitry might change a female's sensitivity to stress across the oestrous cycle¹⁴⁷. Studies in rodents have indeed shown that ovarian hormones alter brain stimulation reward thresholds (BOX 1), which means that during certain phases of the oestrous cycle, females are more prone to anhedonia¹⁴⁸. This should be an extremely high priority for future studies; we must determine the extent to which the mechanisms discussed above apply to female depression models.

Last, despite the fact that we are experiencing a revolution in the field of basic psychiatric neuroscience, drug development efforts have arguably led to only two mechanistically distinct antidepressant medications (ketamine and scopolamine) over the past half century, and their use for depression has still not been approved by the US Food and Drug Administration (FDA). The difficulty partly comes from the fact that patients are diagnosed and treated on the basis of clusters of behavioural symptoms that are heterogeneous across disorders and are likely to be caused by numerous and divergent biological factors. A clear example of this challenge is the fact that, even within a disorder like depression, two patients can exhibit entirely non-overlapping clusters of symptoms, but their official diagnosis and treatment are identical. Another aspect of this challenge is that the distinction between depression and anxiety is poorly defined, with >50% of patients with one disorder showing symptoms of the other. Psychiatry desperately needs a diagnostic system that is based on the underlying genetic and neurobiological factors that define subtypes of these broad syndromes. An intermediate step would be, if possible, to identify biomarker signatures that accompany specific domains of behavioural abnormalities and predict distinct treatment responses. The identification of new biomarker targets based on bona fide disease mechanisms could vastly improve depression treatment for subsequent generations. For example, identification of sex-specific depression mechanisms might help us to develop specialized gender-based medicine. A greater understanding of the circuits controlling reward-related behaviour might identify new surgical targets for deep brain stimulation as well. Ultimately this information can lead to new treatments with improved efficacy and fewer side effects, as well as providing relief to patients that are resistant to all currently available therapies.

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Competing interests statement

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