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Review

Progress in understanding mood disorders: optogenetic dissection of neural circuits

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Major depression is characterized by a cluster of symptoms that includes hopelessness, low mood, feelings of worthlessness and inability to experience pleasure. The lifetime prevalence of major depression approaches 20%, yet current treatments are often inadequate both because of associated side effects and because they are ineffective for many people. In basic research, animal models are often used to study depression. Typically, experimental animals are exposed to acute or chronic stress to generate a variety of depression-like symptoms. Despite its clinical importance, very little is known about the cellular and neural circuits that mediate these symptoms. Recent advances in circuit-targeted approaches have provided new opportunities to study the neuropathology of mood disorders such as depression and anxiety. We review recent progress and highlight some studies that have begun tracing a functional neuronal circuit diagram that may prove essential in establishing novel treatment strategies in mood disorders. First, we shed light on the complexity of mesocorticolimbic dopamine (DA) responses to stress by discussing two recent studies reporting that optogenetic activation of midbrain DA neurons can induce or reverse depression-related behaviors. Second, we describe the role of the lateral habenula circuitry in the pathophysiology of depression. Finally, we discuss how the prefrontal cortex controls limbic and neuromodulatory circuits in mood disorders.

Keywords: Animal models, behavior, depression, dopamine, mesolimbic, mood disorders, neural circuits, optogenetics, prefrontal cortex, psychiatry

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The dissection of specific neural circuits involved in mood disorders has been a challenging pursuit given the complexity and diversity of symptoms as well as the heterogeneity of the brain regions and neural circuits that are dysregulated. The birth of a new field of systems neuroscience, enabled by the creation of optogenetic techniques as well as major advances in molecular genetics that allowed for cell-type specific targeting and viral engineering, have reinvigorated dissection of neural circuits (Nieh *et al*. 2012; Osakada *et al*. 2011; Tye & Deisseroth 2012). Optogenetic methods allow the temporally-precise manipulation of specific neurons (Boyden *et al*. 2005) and projections (Lammel *et al*. 2012; Tye *et al*. 2011) using genetically encodable light-sensitive proteins (Deisseroth 2011). As the field of optogenetics has begun to mature beyond infancy, the past year represents a major first step in the renewed advancement in our understanding of specific neural circuits governing reward, aversion, motivation, stress, affect, depression and pathological behavioral states relevant to mood disorders experienced by humans. Recent advances in circuit-targeted approaches have provided new opportunities to study the neuropathology of mood disorders (Tye & Deisseroth 2012) such as anxiety (Kim *et al*. 2013a; Tye *et al*. 2011) and depression (Chaudhury *et al*. 2013; Covington *et al*. 2010; Tye *et al*. 2013; Warden *et al*. 2012). Here, we focus on several recent breakthrough studies that have investigated neural circuits strongly associated with mood disorders and, in particular, major depressive disorders. These neural circuits include upstream and downstream targets of the ventral tegmental area (VTA) dopamine (DA) system, the lateral habenula (LHb) and the prefrontal cortex (PFC).

The role of VTA DA neurons in mood disorders

VTA DA neurons projecting to nucleus accumbens (NAc), comprising the mesolimbic DA system, and the medial prefrontal cortex (mPFC), comprising the mesoprefrontal (mesocortical) DA system, have been associated with many behaviors related to motivation, reinforcement and reward-related learning (Bjorklund & Dunnett 2007; Fields *et al*. 2007; Ikemoto 2007; Salamone & Correa 2012; Schultz 2007; Wise 2004). Dopamine's major role for reward-related

processes has been intensively studied using single unit recordings in primates during a classical conditioning task (Schultz 1997, 2007). According to the reward prediction error hypothesis, VTA DA neurons encode the discrepancy between reward and its prediction. Unpredicted (unconditioned) rewards elicit phasic activation (positive prediction error), fully predicted (conditioned) rewards induce no response, and the omission of predicted rewards elicits a depression of VTA DA neuronal activity (Schultz 1997, 2007). The reward prediction error hypothesis was confirmed in humans using fMRI (D'Ardenne *et al*. 2008) and in rodents using optogenetic single-cell identification of VTA DA neurons (Cohen *et al*. 2012). In addition, direct optogenetic stimulation of VTA DA neurons not only induces behavioral conditioning in freely behaving mice but also is sufficient to support optical self-stimulation, showing unequivocally that activation of VTA DA neurons has positive reinforcing properties (Kim *et al*. 2013b; Tsai *et al*. 2009; Witten *et al*. 2011; but see: Adamantidis *et al*. 2011). However, an increasing number of studies also report that some DA neurons respond to non-rewarding/aversive stimuli (Brischoux *et al*. 2009; Lammel *et al*. 2011; Mantz *et al*. 1989; Matsumoto & Hikosaka 2009a). There is strong evidence that the VTA is comprised of anatomically and functionally distinct DA subsystems (Brischoux *et al*. 2009; Bromberg-Martin *et al*. 2010; Ford *et al*. 2006; Ikemoto 2007; Lammel *et al*. 2013; Roeper 2013).

The reduced ability to experience rewarding feelings and pleasure (anhedonia) as well as a loss of motivation are hallmarks of depression in humans (Beck & Alford 2009; Berton *et al*. 2012). Therefore, it is not surprising that growing evidence suggests that dysregulation in the brain's reward system and specifically the mesolimbic DA system may be involved in mediating depression-related behaviors (Berton *et al*. 2012; Nestler & Carlezon 2006). Yet, the precise mechanisms mediating these changes have been a long-standing mystery. The NAc, in addition to the LHb (Sartorius *et al*. 2010) and prefrontal cortical areas (Mayberg *et al*. 2005), has been shown to be an effective target for deep brain stimulation (DBS) in treatment-resistant patients (Bewernick *et al*. 2010; Malone *et al*. 2009). Indeed, the NAc is a major site for the integration of numerous glutamatergic inputs originating from throughout the corticolimbic system (Britt *et al*. 2012; O'Donnell & Grace 1995; Voorn *et al*. 2004), where these streams of information interact with robust dopaminergic innervation (Bjorklund & Dunnett 2007; Ikemoto & Wise 2004; Schultz 2007; Stuber *et al*. 2011).

Depression is often described as a stress-related disorder because repeated stress or severely stressful experiences can lead to some of the core symptoms of depression, such as anhedonia, loss of motivation and abnormalities in food intake (Kessler 1997; Willner *et al*. 2012). Therefore, it is not surprising that exposure to stressful events is commonly used to generate animal models of depression. There are three well-established animal models of depression: (1) learned helplessness, which is induced through uncontrollable and unpredictable severe aversive events for one or several days (e.g. foot shock) (Henn & Vollmayr 2005; Li *et al*. 2011), (2) chronic mild stress, which is induced by exposing animals to a series of mild and unpredictable stressors for 8–12 weeks (e.g. wet bedding, cage tilt, disruptive lights/sounds) (Venzala *et al*. 2012a; Willner 2005) and (3) social defeat stress, which is induced by introducing a male experimental mouse ('intruder') into the home cage of a larger, retired breeder male mouse (e.g. CD1 mouse; 'resident') for several minutes during which the experimental mouse is attacked and defeated by the resident mouse. After the physical interaction the experimental mouse usually is exposed to a period of sensory stress during which a perforated plexiglass wall is placed in the middle of the resident mouse's home cage, and the resident and intruder mouse are physically separated but kept in close proximity. The procedure is repeated for several days (usually up to 10 days) (Krishnan *et al*. 2007; Venzala *et al*. 2012b). On the basis of the behavioral changes elicited by the social defeat stress paradigm two phenotypes can be distinguished (Berton *et al*. 2006; Krishnan *et al*. 2007). Susceptible mice show both depression- and anxiety-like symptoms, whereas resilient mice show equivalent signs of anxiety (as measured by the elevated plus maze, open field and dark–light paradigms) but not of depression (social avoidance, anhedonia and metabolic syndrome) (Krishnan *et al*. 2007). Importantly, repeated treatment with antidepressants, but not benzodiazepines, reverses the susceptibility phenotype (specifically social avoidance and anhedonia), making this model relevant to human depression (Berton *et al*. 2006).

Several studies have begun to unravel the role of VTA DA neurons projecting to NAc (i.e. mesolimbic DA system) in depression and the onset of a depression-like phenotype in animal models (Berton *et al*. 2006; Krishnan *et al*. 2007; Willner *et al*. 2005). A recent pair of studies using optogenetic approaches to dissect dopaminergic circuits in the context of depression-related behaviors serves to highlight the complexity of the effects of stress on the dopaminergic system (Chaudhury *et al*. 2013; Tye *et al*. 2013). Both, Chaudhury *et al*. and Tye *et al*. found that VTA DA neurons and their projections to the NAc are critically involved in mediating depression-related symptoms. Specifically, by expressing Channelrhodopsin-2 in midbrain DA neurons of Tyrosine Hydroxylase::Cre mice and stimulating these cells *in vivo* using blue laser light they were able to control depression-related behaviors on the timescale of seconds to minutes. However, Chaudhury *et al*. showed that phasic, but not tonic, light stimulation of VTA DA cells during a social defeat stress paradigm induced persistent depression-like symptoms in mice (susceptible phenotype, i.e. increased social avoidance in the social interaction test and anhedonia in the sucrose preference test) (Chaudhury *et al*. 2013). In contrast, Tye *et al*. observed that phasic stimulation of VTA DA neurons in mice that have been exposed to chronic mild stress for 8–12 weeks elicited an acute antidepressant effect as measured by reversed reductions in motivation on the tail suspension test and hedonia in the sucrose preference test (Tye *et al*. 2013). While it is certainly challenging to give an explanation for the opposing results, it is particularly important to discuss some of the differences between these studies that are critical for interpreting each study's results.

Network effects due to different animal models of depression

In the Chaudhury study, the authors used a repeated social defeat stress paradigm, whereas Tye and colleagues exposed the animals to unpredictable chronic mild stressors twice daily for 8–12 weeks. It has been discussed that social defeat stress induces a variety of altered behaviors and in addition to symptoms of depression (anhedonia and social avoidance), it also elicits core symptoms observed in general anxiety and posttraumatic stress disorders (Venzala *et al*. 2012b). In contrast, chronic mild stress predominantly induces anhedonia (Venzala *et al*. 2012a). It is possible that different brain regions contribute to distinct depression symptoms and because many of the affective circuits are interconnected it could be that optogenetic manipulation of only one brain region (VTA) produces different behavioral responses.

Divergent effects of acute and chronic stress on VTA DA neurons

Strong acute stressors can increase VTA DA neuron firing (Valenti *et al*. 2011), but chronic stressors or incubation periods can reduce VTA DA neuron firing rates (Moore *et al*. 2001; Valenti *et al*. 2012). Furthermore, restraint stress has been reported to have variable effects on putative DA neuron firing and signaling (Anstrom & Woodward 2005; Chang & Grace 2013). Interestingly, a recent study provided the first demonstration of a remarkable phenomenon that severe exposure to an acute stressor, a 2-day forced cold water swim, could cause a 'switch' in the effects of intra-cranial administration of a stress hormone, corticosterone releasing factor (CRF) from rewarding to aversive, and a marked change in the effect of CRF on DA release in the NAc (Lemos *et al*. 2012). This acute stress-induced neuroadaptation lasted at least 90 days following the forced swim, which supports the notion that acute presentations of severe stress can lead to changes in DA function and emotional/motivational valence processing. Thus, different durations and types of stress can have opposing effects on VTA DA neuron firing which may induce distinct behavioral responses. Importantly, the type and intensity of the stressor as well as the time period during which the mouse is exposed to the stressor differ between the two studies (Chaudhury *et al*. 2013; Tye *et al*. 2013). As described initially, during the chronic mild stress paradigm the mouse is exposed to unpredictable, mild stressors presented over several months, i.e. which would span the majority of the mouse's life. In contrast, the social defeat paradigm mainly involves severe social defeat stress for up to 10 days. Nevertheless, certain features of the susceptible phenotype, including social avoidance, metabolic syndrome and increased firing of VTA DA neurons as well as increased BDNF (Brain-derived-neurotrophic factor) signaling in the NAc, are long-lasting and persist for more than a month (Cao *et al*. 2010; Krishnan *et al*. 2007; Razzoli *et al*. 2011).

Heterogeneity of the VTA

As highlighted in several studies mentioned above, the VTA is a heterogeneous brain region, and even within mesolimbic DA neurons (i.e. DA neurons projecting to NAc lateral shell vs. NAc medial shell and NAc core) there are marked functional differences (Ikemoto 2007; Lammel *et al*. 2008, 2011). Thus, an important question is whether a specific subpopulation of VTA DA neurons contributes to the stress-induced behavioral changes. Both the mesoprefrontal and mesolimbic DA projection have been shown to be affected by stress and the existence of opposite imbalances between mesoprefrontal and mesolimbic DA responding to stress has been the topic of many research studies over the last decades (e.g. Anstrom *et al*. 2009; Berton *et al*. 2006; Butts *et al*. 2011; Di Chiara *et al*. 1999; Imperato *et al*. 1993; Niwa *et al*. 2013; Tidey & Miczek 1996; Wilkinson *et al*. 1998). Importantly, Chaudhury *et al*. found projection-specific differences in promoting stress susceptibility. Optical stimulation of the mesolimbic, but not the mesoprefrontal DA projection induced susceptibility to social defeat (Chaudhury *et al*. 2013). Initially, this finding appears surprising because it is well known that stress increases DA release in the PFC (e.g. Abercrombie *et al*. 1989; Jackson & Moghaddam 2004; Kaneyuki *et al*. 1991; Morrow *et al*. 2000; Thierry *et al*. 1976). However, as discussed above, acute and chronic stress can differentially affect the firing rate of VTA DA neurons and therefore DA release in the respective target areas. This might not only be the case for mesolimbic DA neurons but also for mesoprefrontal DA neurons. Indeed, it has been suggested that the mesoprefrontal DA system is preferentially activated in response to acute stress and attenuated by repeated restraint stress (Jackson & Moghaddam 2004; Tanaka *et al*. 2012). Future studies will have to further analyze how stress influences different DA subpopulations over differing timescales.

Activation of downstream targets

The critical substrate driving behavior could be occurring in downstream targets based on functional DA signaling, thus postsynaptic receptor downregulation (Klimke *et al*. 1999a; Larisch *et al*. 1997) or binding to the DA transporter (Laasonen-Balk *et al*. 1999; Meyer *et al*. 2001) could be playing a role not captured by VTA neuron firing. Indeed, a reduced sensitivity in central DA receptors has been found in patients diagnosed with major depression relative to control subjects (Schmidt *et al*. 2001). Changes in binding or function of DA D2 receptors has also been linked to treatment responsiveness in humans (Klimke *et al*. 1999b), and chronic mild stress treatments that produced anhedonic behaviors also showed a decrease in D2-receptor binding in the limbic forebrain, which is reversed by treatment with an antidepressant (Papp *et al*. 1994).

Experimental considerations

Finally, we would like to highlight a few experimental challenges in the context of stress-mediated depression models that should be considered when comparing seemingly inconsistent or surprising results.

First, the housing conditions of the experimental animals. Importantly, in the Chaudhury *et al*. 2013 study the test mice were single-housed, while in the Tye *et al*. 2013 study they were group-housed (Chaudhury *et al*. 2013; Tye *et al*.

2013). It has been reported that stress promoted parallel activation of mesoprefrontal and mesolimbic DA neurons in group-housed mice. However, individually housed mice exhibited increased mesoprefrontal and reduced mesolimbic DA responses to stress (Cabib *et al*. 2002). The two distinct housing conditions induced opposite behavioral responses in the forced-swim test (FST; Cabib *et al*. 2002). Fone and Porkess found that post-weaning social isolation is associated with hyperfunction of the mesolimbic and hypofunction of the mesoprefrontal DA system (Fone & Porkess 2008). Social isolation also induced both anxiety- and anhedonia-like symptoms as well as reduced cAMP response element-binding protein (CREB) activity in the NAc (Wallace *et al*. 2009).

Second, the time and duration of the light stimulation. One difference regarding the sucrose preference test (the only common assay used between these two studies) was that Chaudhury and colleagues activated or inhibited VTA DA neurons during a manipulation distinct from and prior to the sucrose preference measurement period, while Tye and colleagues activated or inhibited VTA DA neurons during an epoch within the sucrose preference measurement period. Furthermore, the sucrose preference test was quantified over a 12-h period in terms of total volume consumed in the study from Chaudhury and colleagues, while the sucrose preference test was quantified over a 30-min period in terms of total licks in the study from Tye and colleagues.

Third, it is also noteworthy that Chaudhury and colleagues identified the critical contribution of NAc-projecting VTA neurons using a projection-specific targeting strategy that may also have included non-dopaminergic neurons, whereas Tye and colleagues identified the critical contribution of NAc-projecting VTA DA neurons using a pharmacological blockade of DA receptors in the NAc while optogenetically activating VTA DA neurons projecting to multiple downstream targets. A significant number of cells in the VTA are GABAergic and glutamatergic (Nair-Roberts *et al*. 2008). They not only make local connections, but also project to several forebrain regions (Fields *et al*. 2007). Although the number of non-dopaminergic projections neurons in the posterior VTA (Bregma: −3.5 mm; mouse brain) is relatively low (Lammel *et al*. 2011), the proportion seems to be much higher in more anterior regions (Bregma: −3.0 mm) (Lammel *et al*. 2008). Thus, dependent on the location of the optical fiber and light scattering inside the tissue there will be more or fewer non-dopaminergic neurons activated. Future work will need to investigate the role of non-dopaminergic projection neurons in stress-mediated depression models.

From the treatment of depression in humans, it is clear that there is no single one-size-fits-all therapeutic intervention that is effective in all patients diagnosed with clinical depression, as a diverse array of interventions ranging from antidepressant drugs to electroconvulsive therapy or DBS are used, yet some patients remain resistant to all available treatments. This is strong evidence that many different neuropathologies could lead to what we describe as major depressive disorder in human patients. Taken together, we speculate that the differences across these recent studies may depend on several critical parameters including: time course or phase of depression induction, stressor type or severity, heterogeneity within the VTA or that multiple distinct etiologies can result in similar behaviors or symptoms in depression (Fig. 1).

Although this section's focus is the VTA DA system, it is important to mention that additional mechanisms in the NAc may also be involved in mediating stress-elicited symptoms of depression. Work by Lim and colleagues showed that stress-elicited anhedonia requires neuropeptide-triggered, cell-type-specific synaptic adaptation in the NAc (Lim *et al*. 2012). Specifically, repeated restraint stress in mice decreased the strength of excitatory synapses on D1 DA receptor-expressing NAc medium spiny neurons due to activation of the melanocortin (MC) 4 receptor. By blocking the MC4 receptor-mediated synaptic changes *in vivo* the stress-elicited increases in behavioral measurements of anhedonia could be prevented. However, other depression-related symptoms, for example those that induce changes in the forced-swim and tail-suspension tests, were not influenced by inhibiting MC4 receptors indicating that different brain regions, such as the LHb or dorsal raphe nucleus (DRN) may mediate other core symptoms of stress-elicited depression (Lim *et al*. 2012). Abnormalities in cocaine dependent behaviors have been shown in mice with altered levels of MC4 receptors and infusion of a MC peptide antagonist into the NAc blocked the reinforcing, incentive motivational and locomotor sensitizing effects of cocaine (Hsu *et al*. 2005). Thus, the MC4 receptor could be a promising target in the treatment of drug addiction as well as depression (Chaki & Okubo 2007; Hsu *et al*. 2005; Lim *et al*. 2012). Melanocortin 4 receptors are also expressed in the VTA (Kishi *et al*. 2003). Interestingly, injection of a MC3/MC4 agonist into the VTA robustly suppressed feeding for up to 24 h while injection of a MC3/MC4 antagonist increased food intake (Roseberry 2013). It will be interesting to study if chronic stress induces synaptic adaptations through activation of MC receptors in mesolimbic DA neurons similar to those observed in the NAc and how exactly MCs are able to influence feeding through their interaction with the VTA.

The role of the LHb and its projections in mood disorders

It has been suggested that the LHb is a key structure in the pathophysiology of mood disorders and in particular in major depressive disorders (Berton *et al*. 2012; Hikosaka *et al*. 2008). An increase in LHb activity is observed in humans with depression as well as in animal models of depression, such as learned helplessness (Shumake & Gonzalez-Lima 2003). Rats that have been bred based on their susceptibility to develop learned helplessness show treatment resistance to antidepressive drugs and to electroconvulsive treatment (Sartorius *et al*. 2007). In these animals, stereotactic pharmacological inhibition of the LHb exerts an antidepressive effect (Winter *et al*. 2011). It has been suggested that inhibition of the LHb using DBS is a potential novel treatment for therapy resistant depression (Sartorius *et al*. 2010).

Recently, the LHb has been implicated in the generation of aversion and in the encoding of negative affective

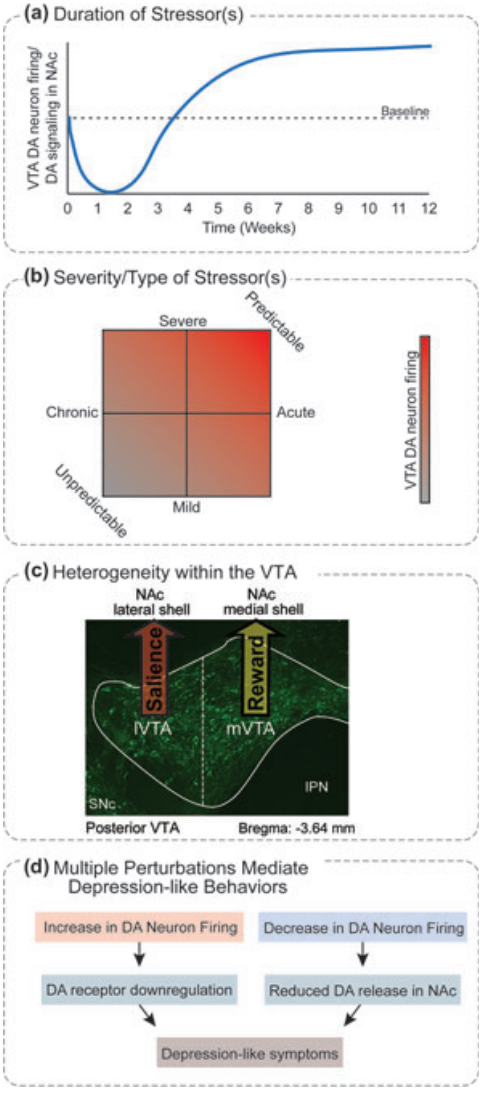

Figure 1: Speculative variables contributing to the divergent results of DA neuron manipulation in depression-related behaviors. Several parameters emerge as carrying potentially critical roles in modulating mood disorders. (a) A critical difference between two recent studies (Tye *et al.* 2013; Chaudhury *et al.* 2013) showing opposing effects of stress on depression-related behaviors could be due to the different duration of the stressors. (b) Severity type, predictability and duration are all factors that could potentially have unique effects on DA neuron firing, and this panel schematizes one possible way in which this may occur. (c) Functional heterogeneity within the VTA could lead to dramatic differences of inhibition or activation of DA neurons, across just a few hundred microns. DA neurons in the lateral VTA (lVTA) projecting to NAc lateral shell may respond to salient stimuli while DA neurons in the medial VTA (mVTA) projecting to NAc medial shell only respond to primary rewards (SNc – substantia nigra pars compacta, IPN – interpeduncular nucleus). (d) Depression may be an umbrella term encapsulating a broad range of neural perturbations, a single example of which is shown here. Multiple etiologies may underlie somewhat similar phenotypes.

states (Bromberg-Martin & Hikosaka 2011; Matsumoto & Hikosaka 2007, 2009b). Furthermore, excitatory synapses onto LHb neurons projecting to the VTA are potentiated in a learned helplessness model of depression, and reducing synaptic transmission onto LHb neurons via DBS leads to the acute reversal of learned helplessness (Li *et al*. 2011). Manipulations of LHb or brain structures linked to the LHb could affect depressive-like behaviors and may provide novel targets for the development of new antidepressant treatments. In this chapter, we focus on recent studies that have started to provide new insights into the role of the LHb in descending control of the midbrain DA system.

Research by Hikosaka and colleagues has established the role of the LHb as a major source of negative reinforcement signals to DA midbrain neurons. Specifically, the LHb is activated by aversive stimuli and reward omission and inhibited by reward-predictive cues or unexpected rewards (Bromberg-Martin & Hikosaka 2011; Matsumoto & Hikosaka 2007, 2009b). The LHb receives input from brain areas such as lateral hypothalamus, lateral preoptic area and entopeduncular nucleus (EP) (Herkenham & Nauta 1977) and it was reported that activation of glutamatergic presynaptic inputs from the EP to the LHb alone produces aversion (Shabel *et al*. 2012). This excitatory projection from the EP to the LHb is also suppressed by serotonin, which is an important finding, because it has been known that the LHb reciprocally projects to serotonin neurons in the dorsal raphe and median raphe nucleus and dysfunctions of this mechanism may also be involved in mood disorders (Bernard & Veh 2012; Hikosaka *et al*. 2008; Shabel *et al*. 2012; Shumake & Gonzalez-Lima 2003). The outputs of the LHb are glutamatergic and target the ventral midbrain (Brinschwitz *et al*. 2010; Geisler *et al*. 2007) (Fig. 2). Electrical stimulation of the LHb suppresses the activity of DA neurons in the VTA (Christoph *et al*. 1986; Ji & Shepard 2007). It has been suggested that this inhibition is achieved through GABAergic neurons in the rostromedial tegmental nucleus (RMTg) (Jhou *et al*. 2009a; Kaufling *et al*. 2009).

Initially, the RMTg was named 'tail of the VTA' (tVTA) because it rostrally extends beyond the defined borders of the posterior VTA (Kaufling *et al*. 2009). Thus, defining the boundaries of the RMTg is challenging (Bourdy & Barrot 2012) given the murky differentiation between RMTg GABAergic neurons and the classically described VTA GABAergic neurons (VTA interneurons). Here, we will simply refer to the RMTg and include classical VTA GABAergic neurons because, similar to RMTg neurons, these cells make inhibitory synaptic connections on VTA DA neurons and direct optogenetic stimulation of VTA GABAergic neurons has been reported to promote aversive behaviors and disrupt reward consumption (Tan *et al*. 2012; van Zessen *et al*. 2012). However, there seem to be functionally different inhibitory microcircuits in the ventral midbrain because substantia nigra (SN) GABAergic neurons also provide robust inhibition to DA neurons (Pan *et al*. 2012). Moreover, it has also been reported that VTA GABAergic neurons project to the mPFC and NAc (Brown *et al*. 2012; Carr & Sesack 2000a) and these subpopulations may be functionally different from the classical VTA GABAergic neurons. For example, work from Luscher and colleagues indicate that mesolimbic GABAergic

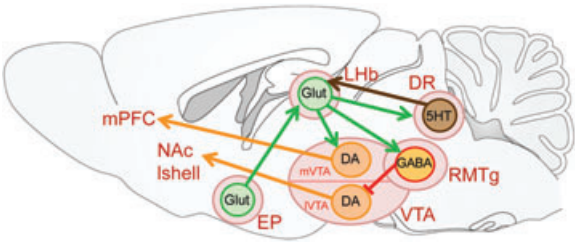

Figure 2: Neuronal circuits that are linked to the LHb and may underlie susceptibility to mood disorders. Schematic drawing showing that the LHb receives glutamatergic (Glut, green) input from the EP and controls release of serotonin (5HT, brown) in the dorsal raphe (DR) as well as possibly DA (orange) release in the medial prefrontal cortex (mPFC) and lateral shell of the NAc (lshell), i.e. activation of the LHb directly excites DA neurons in the medial ventral tegmental area (mVTA) projecting to mPFC and inhibits DA neurons in the lateral VTA (lVTA) projecting to NAc lshell. GABAergic (red) neurons in the RMTg serve as a relay structure in the LHb mediated inhibition of DA neurons projecting to NAc lshell. The colour version of this figure may be found online at the publisher's website.

neurons enhance stimulus-outcome learning by inhibiting NAc cholinergic interneurons (Brown *et al*. 2012).

The RMTg receives strong input from the LHb and sends dense projections to the VTA where they make inhibitory synapses on DA neurons (Balcita-Pedicino *et al*. 2011; Goncalves *et al*. 2012; Jhou *et al*. 2009b; Kaufling *et al*. 2009; Matsui & Williams 2011). The RMTg, like the LHb, is activated in response to aversive stimuli and reward omission, but inhibited by appetitive conditioned or unconditioned stimuli (Hong *et al*. 2011; Jhou *et al*. 2009b). Importantly, the firing patterns of LHb and RMTg neurons encoding negative reinforcement are opposite to the high-frequency burst firing of putative DA neurons, which occurs following rewards or reward-predictive cues and are strongly inhibited by reward omission or aversive stimuli (Matsumoto & Hikosaka 2007). Thus, the RMTg is an inhibitory relay brain structure in a di-synaptic pathway that connects the LHb to DA neurons (Hong *et al*. 2011).

The upstream structure that drives the activity of RMTg GABAergic neurons, has also been identified by optogentic manipulation in mice (Lammel *et al*. 2012; Stamatakis & Stuber 2012). These studies show that between 70 and 100% of RMTg GABAergic neurons receive direct excitatory inputs from the LHb (Lammel *et al*. 2012; Stamatakis & Stuber 2012). Meanwhile, only 50% of VTA GABAergic neurons receive synaptic input from the LHb (Stamatakis & Stuber 2012) which is consistent with reports describing functional heterogeneity within the GABAergic cell population in the ventral midbrain (Brown *et al*. 2012; Carr & Sesack 2000a; Margolis *et al*. 2012; Pan *et al*. 2012). Interestingly, light stimulation of LHb terminals in the VTA induces IPSCs in DA neurons projecting to NAc lateral shell but not in DA neurons projecting to NAc medial shell (Lammel *et al*. 2012). Thus, RMTg neurons may be an important inhibitory relay structure to fine-tune the bursting activity specifically in DA neurons projecting to NAc lateral shell.

The LHb also makes direct excitatory synaptic connections onto a small population of VTA DA neurons which project to the mPFC (Lammel *et al*. 2012). This is consistent with ultrastructural studies showing a comparatively modest number of LHb excitatory synapses onto VTA DA neurons (Brinschwitz *et al*. 2010; Omelchenko *et al*. 2009) and that electrical stimulation of the LHb activates the mesoprefrontal DA pathway (Lecourtier *et al*. 2008). Attentional disturbances have been reported following bilateral lesions of the LHb in rats (Lecourtier & Kelly 2005) and cognitive symptoms such as attention deficits and cognitive-affective bias are common in depressed patients (Berton *et al*. 2012; Disner *et al*. 2011; Lecourtier & Kelly 2007). As discussed in chapter 2, the balance between mesoprefrontal and mesolimbic DA response to stress represents a major diathesis in depression. Chronic stress and social isolation are associated with a hypofunctional mesoprefrontal DA system which induces impairment of spatial working memory (Fone & Porkess 2008; Mizoguchi *et al*. 2000, 2008). The observation that the LHb may be involved in the regulation of both cortical and subcortical DA is important because it suggests that certain behavioral changes observed in depression and other neuropsychiatric disorders could be caused by pathological alterations in the LHb.

Prefrontal control of limbic and neuromodulatory circuits in mood disorders

Decades of evidence implicate the frontal cortex as a primary locus of dysfunction in affective disorders. Initial clues suggesting its critical role came from observations of behavioral changes in human patients with frontal ablations (Damasio *et al*. 1990; Drevets 1999; George *et al*. 1994). These studies defined three broad frontal regions that are currently thought to be responsible for mediating different aspects of behavior (Cummings 1995; Duffy & Campbell 1994; Mega & Cummings 1994): medial prefrontal damage typically led to apathy and reduced motivation (Barris & Schuman 1953; Fesenmeier *et al*. 1990); orbitofrontal damage produced disinhibition and impaired both empathy and social interaction (Zamboni *et al*. 2008); and lateral prefrontal damage resulted in deficits in executive function and planning (Benton 1968; Manes *et al*. 2002). Although definitive conclusions about precise roles of frontal regions can be difficult to reach given the variable nature and extent of spontaneously occurring lesions, these cases provided a framework for the study of frontal function and motivated subsequent imaging and interventional studies.

Dissociable roles for different frontal regions in the regulation of mood and depressive state are supported by evidence from neuroimaging (Drevets *et al*. 2008; Mayberg *et al*. 1999). These studies have consistently found that patients with a diagnosis of major depressive disorder show decreased metabolic activity in the lateral PFC coupled with hyperactivity in the subgenual cingulate region of the mPFC. On the basis of these results, Mayberg *et al*. targeted the subgenual cingulate for therapeutic DBS. A profound and often immediate antidepressant response was

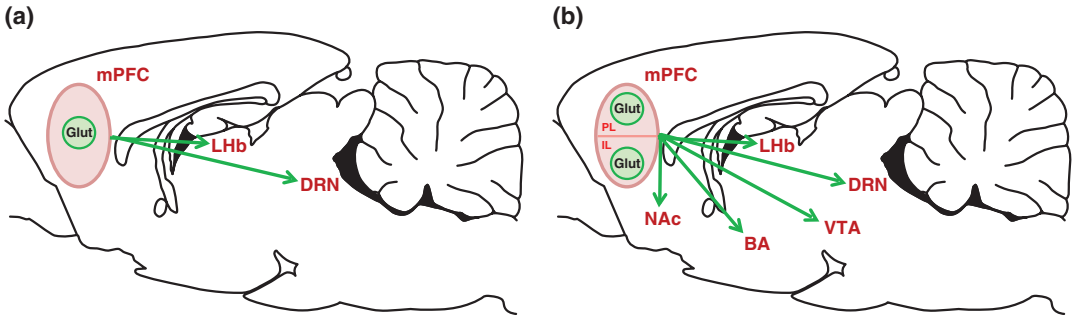

Figure 3: Prefrontal control of limbic and neuromodulatory circuits in affective disorders. (a) Optogenetic control of depression-related behavior. Some studies (Covington *et al*. 2010; Kumar *et al*. 2013 FST) have shown that optogenetic stimulation of medial prefrontal (mPFC) neuronal cell bodies reduces depression-related behavior, while others (Warden et al 2012; Kumar *et al*. 2013 social interaction) have found no effect of stimulation. We hypothesize that these differential effects depend on which specific mPFC circuits (subdivisions, cell types or projections) are activated. Supporting this hypothesis, optogenetic stimulation of specific glutamatergic (Glut, green) mPFC projections to either the DRN or the LHb has been shown to lead to increased or decreased escape-related activity in the FST, respectively (Warden *et al*. 2012). (b) Suggested future targets for optogenetic mPFC analysis. Rodent mPFC can be divided into PL and IL subregions, which may perform different functions in the regulation of affective state (Sierra-Mercado *et al*. 2011; Vidal-Gonzalez *et al*. 2006). Additionally, mPFC sends glutamatergic projections to a variety of limbic regions including DRN, LHb, VTA, NAc, and basal amygdala (BA), which have been implicated in affective disorders (Der-Avakian & Markou 2012). Activation of specific mPFC subregions or projections is likely to have differential effects on depression-related behavior. The colour version of this figure can be found at the publisher's website.

observed in the majority of stimulated patients, particularly compelling evidence given that the subjects of these clinical trials were patients with deep and highly refractory depression. Additionally, post-stimulation fMRI revealed a normalized network activity pattern, with reduced activity in the stimulated subgenual cingulate region and enhanced activity in the lateral PFC (Mayberg *et al*. 2005).

It is of considerable interest to understand how subgenual cingulate stimulation functions to alleviate depressive symptoms, and along these lines reverse translational rodent models have been developed (Covington *et al*. 2010; Hamani *et al*. 2010a,b, 2011; Kumar *et al*. 2013; Warden *et al*. 2012). However, the precise correspondence between human and rodent prefrontal cortical regions is a subject of some debate. While most investigators agree that rodents lack a cortical region homologous to primate dorsolateral PFC, there is a widespread consensus that rodents and primates possess functionally analogous medial and orbital prefrontal cortical areas (Brown & Bowman 2002; Ongür & Price 2000; Preuss 1995; Wallis 2011; Wise 2008). Electrodes in the Mayberg *et al*. clinical trials were located in Brodmann area 25 (BA25) and the ventral portions of BA32 and BA24 of the subgenual mPFC (Hamani *et al*. 2009). Evidence from local cellular microarchitecture and anatomical connectivity points toward homologies of these regions to rodent infralimbic (IL), prelimbic (PL) and cingulate cortex (Cg), respectively (Brown & Bowman 2002; Ongür & Price 2000; Preuss 1995; Wallis 2011; Wise 2008). While results obtained from these homologous cortical areas in rodents must be interpreted with caution, these studies are likely to yield information that will help to clarify the underlying mechanism.

Along these lines, several interesting and provocative, though sometimes apparently conflicting, results have recently been obtained with electrical and optogenetic stimulation of mPFC and its efferents in rodent models (Fig. 3a) (Covington *et al*. 2010; Hamani *et al*. 2010a,b, 2011; Kumar *et al*. 2013; Warden *et al*. 2012). High-frequency electrical stimulation in the ventromedial prefrontal cortex (vmPFC), which encompasses both IL and ventral PL, has been showed to both decrease immobility in the FST and increase sucrose consumption in the sucrose preference test in rats (Hamani *et al*. 2010a,b, 2011), effects which are thought to reflect changes in motivation and hedonia, respectively (Porsolt *et al*. 1977; Willner *et al*. 1987). Stimulation in these experiments mimicked the high-frequency 130 Hz stimulation conventionally used in human DBS, and may have acutely decreased local neuronal activity in vmPFC; this effect would be consistent with the antidepressant-like results found after muscimol inhibition of rodent IL cortex (Slattery *et al*. 2011). However, the net effect of high-frequency DBS has been shown to vary with local neural architecture (Dostrovsky & Lozano 2002; Vitek 2002), and it may function to preferentially activate axons of passage – an alternative explanation for this behavioral effect. Remarkably, animals treated with ibotenic acid in mPFC – a manipulation that is thought to lesion local cell bodies while largely sparing axons (Schwarcz *et al*. 1979) – still showed a reduction in FST immobility after electrical stimulation (Hamani *et al*. 2010a), a result which supports the latter hypothesis. The currently available evidence does not permit final determination of the mechanism of vmPFC DBS at this time, but subsequent projection-specific optogenetic experiments, discussed below, may shed some light on this debate (Warden *et al*. 2012).

Prefrontal control of the DRN, previously shown to be important for the protective effect of behavioral control on learned helplessness (Amat *et al*. 2005; Baratta *et al*. 2009),

appears to be at least partially responsible for mediating the behavioral effect of vmPFC DBS. An intact serotonergic system was required in these experiments, as serotonin (5-HT) depletion in the DRN with 5,7-DHT prevented the stimulation-induced decrease in FST immobility, while norepinephrine depletion had no effect (Hamani *et al*. 2010a). Serotonin microdialysis in the hippocampus during and immediately following stimulation showed elevated levels of 5-HT, further implicating this pathway (Hamani *et al*. 2010a). Interestingly, in these experiments stimulation was delivered for a period of several hours before the onset of behavioral testing, not during testing itself, suggesting that the resulting behavioral effect may be due to a relatively long-lasting plastic change in vmPFC circuitry. The time course of this effect corresponds well to the persistent effect of human subgenual DBS, and investigation of the resultant alterations in neural connectivity and neurophysiology would be of particular interest.

Subsequently, a series of optogenetic studies has investigated the role of different classes of mPFC neurons on depression-related behavior. Covington *et al*. published the first optogenetic study of the mPFC in a mouse model of depression (Covington *et al*. 2010), in which neurons in mPFC (encompassing both IL and PL) were optogenetically activated with Channelrhodopsin-2 (ChR2) (Boyden *et al*. 2005). Stimulation in these experiments drove an antidepressant-like behavioral effect that was detected in both social interaction and sucrose preference tests following chronic social defeat. The viral vector used in these experiments, herpes simplex virus (HSV) with ChR2 under the control of the ubiquitous IE4/5 promoter, is capable of infecting excitatory and inhibitory neurons and glial cells within the mPFC as well as afferents to these areas from other brain regions (Neve *et al*. 2005), which include limbic and brainstem neuromodulatory regions (Hoover & Vertes 2007). It remains to be determined whether the antidepressant-like behavioral effects were driven by enhanced excitatory or inhibitory transmission within the mPFC; elevated c-Fos was detected in both neural populations. Changes in glial activity, either driven by direct optogenetic activation (Sasaki *et al*. 2012) or by astrocyte toxicity resulting from HSV expression (Itoyama *et al*. 1991), may additionally have affected network activity and subsequent light-driven changes in affective state.

A recent paper by Warden *et al*. (2012) investigated the role of different mPFC efferents in depression-related behavior, and showed that the net effect of mPFC stimulation was highly dependent on which specific mPFC circuits were activated. In these experiments, ChR2 was expressed in both the IL and PL regions of the mPFC under the control of the CaMKIIα promoter, which restricted ChR2 expression to excitatory neurons (Anikeeva *et al*. 2012; Lee *et al*. 2010; Yizhar *et al*. 2011). The mPFC was transduced via an AAV5 viral vector, which infected only local cell bodies. When excitatory mPFC neurons were directly activated, by stimulation through a fiber optic placed above the mPFC, no effect on depression-related behavior in either the FST or the open field was noted, differing from the Covington *et al*. experiments. However, stimulation of specific efferents from the mPFC to different subcortical regions – accomplished by illuminating ChR2-expressing mPFC axons – had different and very specific behavioral effects. When the projection from the mPFC to the DRN, the major source of serotonin to the forebrain, was stimulated, immobility in the FST decreased without affecting locomotor activity in the open field. Conversely, stimulation of the projection from the mPFC to the LHb, an area known to exhibit elevated firing in response to the omission of reward (Matsumoto & Hikosaka 2007, 2009b), increased immobility. These two results in combination suggest that the effect of mPFC stimulation on behavior may be highly dependent on which specific mPFC circuits are affected.

Although the mPFC projection to the VTA has not yet been optogenetically interrogated in animal models of mood disorders, anatomical evidence suggests a role for this circuit in modulating affective state. The mPFC projection to the VTA is arranged with a precise topology that is determined by downstream VTA efferent wiring patterns. Medial prefrontal cortex neurons synapse onto both DA and GABA VTA neurons, but mPFC afferents only contact a select subset of these neurons (Carr & Sesack 2000b). VTA DA neurons that receive direct synaptic connections from the mPFC are those that reciprocally project back to the mPFC but do not project to the NAc. Conversely, the VTA GABA neurons that receive direct projections from the mPFC are those that project directly to the NAc. Future studies will need to investigate the functional role of mPFC input to the VTA. Given that aversive stimuli increase the synaptic strength of excitatory synapses on mesoprefrontal DA neurons (Lammel *et al*. 2011) a role for this circuit in modulating affective state could be possible. However, any effect of stimulation of the mPFC-VTA circuit would likely depend on stimulation parameters; interestingly, electrical stimulation of the mPFC at high frequencies (60 Hz) has been shown to increase DA release in the NAc, while low frequency stimulation (10 Hz) does the opposite (Jackson *et al*. 2001).

Warden *et al*. neurophysiological recordings from the mPFC during the FST revealed neuronal classes with distinct firing patterns which appeared to be dependent on behavioral state (Warden *et al*. 2012). Interestingly, some mPFC neurons were selectively inhibited during immobility in the FST, while other neurons were selectively activated. If immobility in the FST does corresponds to a subjective state of hopelessness or behavioral despair, as has been suggested (Porsolt *et al*. 1977), these neuronal responses may reflect changes in affective or motivational state. Complicating this interpretation of FST immobility are the differential effects of antidepressant compounds such as fluoxetine on affective state in human patients and rodent models. Although weeks of administration are required for mood changes in depressed patients, some rodent studies have showed an acute (Cryan *et al*. 2002a) or subchronic effect (Dulawa *et al*. 2004) of high doses of fluoxetine on FST immobility. However, it has been shown that low doses ineffective at driving an acute reduction of FST immobility can be effective when used chronically, which corresponds well to human behavior following pharmacological intervention (Cryan *et al*. 2002b). Intriguingly, human subgenual DBS often induces an immediate antidepressant effect occurring with the onset of stimulation, indicating that acute changes in

affective state are indeed possible with some forms of circuit manipulation (Mayberg *et al*. 2005). These fast changes in neural activity between mobile and immobile behavioral states reported in Warden *et al*. may reflect this kind of acute change, although this interpretation does rely on an imperfect correspondence between low mood in humans and immobile FST states. It is unknown if these recorded mPFC neurons correspond to the neuronal populations activated in the optogenetic projection experiments described above, but these optogenetic and neurophysiological results together clearly imply that the mPFC should be approached as a collection of microcircuits that differ in their anatomical connectivity and encoding of behavioral state, and likely have different functions in the regulation of affective behavior.

A recent paper by Kumar *et al*. (2013) further illustrates the complexity of the effect of prefrontal stimulation on behavior. Thy1-ChR2 mice, which express ChR2 in layer five pyramidal neurons in the mPFC, as well as afferents from other brain regions, were implanted with optical fibers over anterior PL. These circuits were stimulated with a natural spike train at roughly 4 Hz, which produced mixed effects on depression-related behavior. Thy1-ChR2 mice stimulated with this pattern exhibited decreased immobility in the (FST) relative to wild type control mice, but this effect was coupled with increased distance traveled in the open field. Stimulation had no detectable effect on social interaction time following chronic social defeat, also differing from Covington *et al*. Additionally, mPFC stimulation in the Kumar *et al*. study induced a robust anxiolytic effect in the elevated plus maze, while stimulation in the Covington *et al*. study did not.

Kumar *et al*. additionally provide an electrophysiological characterization of the effect of optogenetic prefrontal stimulation on downstream brain areas. Thy1-ChR2 mice were implanted with an optical fiber over PL, as before, and were additionally implanted with microwire arrays over a variety of downstream regions, which included the basal amygdala (BA), the NAc and the VTA. In each of these regions, PL stimulation induced a change in neural activity as detected through local field potential and single unit recordings. Furthermore, when changes in coherence between regions were examined it was found that PL stimulation induced beta band synchrony between pairs of these regions. Intriguingly, when pulse-triggered average LFPs were examined in these downstream regions, the peak of the response occurred earlier for neuromodulatory regions (VTA and DRN), and later for NAc and BA, which suggests a possible direction of information flow in these highly interconnected circuits. It remains to be determined how coherence between brain regions would be affected by changes in depression-related behavioral state; these results would perhaps predict a decrease in beta synchrony between limbic regions. It also remains to be determined if different stimulation regimes affect synchrony differentially.

The contradictory behavioral results obtained in these studies highlight the importance of discerning the contributions of different prefrontal circuits to affective state (Fig. 3b). An impressive body of literature unambiguously assigns separate roles to IL and PL rodent cortex in fear extinction, in which they are thought to mediate opposite effects (Sierra-Mercado *et al*. 2011; Vidal-Gonzalez *et al*. 2006). Likewise, more precise targeting of defined circuits within mPFC is likely to reveal differences in function in tests for depression. Almost all of the above studies utilized stimulation of both IL and PL, with the exception of Kumar *et al*., which targeted anterior PL. Infralimbic and PL may indeed mediate separate and possibly opposite effects on affective state, and differences in behavioral consequences may depend on which structure is preferentially activated upon stimulation. Interestingly, follow up detailed electrical stimulation experiments by Hamani *et al*. showed that mPFC stimulation had a greater effect on behavior when electrodes were located in PL, with non-significant behavioral effects following IL stimulation (Hamani *et al*. 2010b).

Choice of stimulation frequency is also likely to affect which mPFC circuits are recruited. All of the above studies used different stimulation protocols: 130 Hz in the Hamani study, 100 Hz burst in the Covington, 20 Hz in the Warden, and 4 Hz in the Kumar. These frequencies may have distinctive net effects on circuit coupling in addition to different effects on long-term plasticity, which may provide another potential explanation for the observed behavioral differences. Additionally, different circuits within a given mPFC subdivision may mediate differential behavioral effects. The above studies all differ in which cell types were stimulated: Covington *et al*. stimulated both excitatory and inhibitory mPFC neurons as well as mPFC afferents and possibly local glial cells; Warden *et al*. stimulated excitatory mPFC neurons in all layers and specific mPFC projections; and Kumar *et al*. stimulated layer 5 excitatory mPFC neurons and cortical mPFC afferents. These differences in targeted mPFC neuronal populations may partially explain differences in the behavioral consequences of stimulation. Optogenetic activation of two different mPFC efferents (mPFC-DRN and mPFC-LHb) has been shown to have dissociable behavioral effects (Warden *et al*. 2012), which suggests that another possible explanation for the variety of behavioral effects found upon mPFC stimulation may be the unintentional selective activation of different efferent populations thought to be important in regulating affective state (Der-Avakian & Markou 2012). Much work remains to be carried out in the quest to obtain a full characterization of the role of the mPFC in affective disorders, and increased specificity in microcircuit-level analysis would likely enable the reconciliation of the diversity of depression-related behavioral changes following mPFC stimulation.

Conclusion

Here, we have reviewed VTA DA, habenular, and prefrontal neural circuits that are thought to be of fundamental importance in the neural encoding of reward, aversion, and motivation, and whose dysfunction is hypothesized to underlie disorders of mood, affective state and depression. We have focused on a series of recent studies that have examined the functional role of these brain regions and the projections between them, studies that have been facilitated by the recent development and application of genetically-encodable optical tools for the selective activation

or inhibition of specific neural circuits. Specifically, we have reviewed mesocorticolimbic circuits, particularly VTA DA projections to the NAc, which are thought to play particularly important roles governing affective state, reward and motivation; the LHb and its role in descending control of the midbrain DA system; and the mPFC and its control of limbic and neuromodulatory structures including the DRN and the LHb.

Different, and sometimes opposite, results from studies targeting similar neural circuits highlight the need for increased specificity in circuit identification and targeting in future work. For example, both pro-depressant and antidepressant-like behavioral changes have been shown to result from phasic optogenetic activation of VTA DA neurons (Chaudhury *et al*. 2013; Tye *et al*. 2013), one possible explanation of which may be the activation of differently projecting subpopulations of VTA DA neurons (Lammel *et al*. 2012). Likewise, the effect of optogenetic mPFC stimulation in rodent models of depression may depend on which specific mPFC regions are targeted, what types of neurons are affected, and where these neurons ultimately project (Covington *et al*. 2010; Kumar *et al*. 2013; Warden *et al*. 2012).

An increase in the specificity of circuit analysis may also facilitate a more sophisticated understanding of the neural mechanisms underlying mood disorders. For example, although several different manifestations of depressed mood (including changes in pleasure seeking, motivation, energy, sleep patterns, food consumption and cognitive function) may be tested in animal models, it is unknown whether different neural circuit elements mediate these different aspects of depression. Indeed, many of the brain regions and projections discussed in this review have been shown to play a role in more than one aspect of depression-related behavior in rodent models. However, it is possible that different neural substrates underlie at least some of these functions – particularly given the range of subtypes seen in major depressive disorder (e.g. the marked differences between melancholic and atypical depression). Investigating these neural circuits with the greater specificity made possible by the next generation of optical, molecular and observational tools promises to be a productive direction for future research by offering unprecedented insight into the mechanisms underlying mood disorders.

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