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Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression

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Abstract

The dopamine (DA) system is unique among the brain's modulatory systems in that it has discrete projections to specific brain regions involved in motor behaviour, cognition and emotion. DA neurons exhibit several activity patterns — including tonic and phasic firing — that are determined by a combination of endogenous pacemaker conductances and regulation by multiple afferent systems. Emerging evidence suggests that disruptions within these regulatory systems may underlie the pathophysiology of several psychiatric disorders including schizophrenia and depression.

Graphical Abstract

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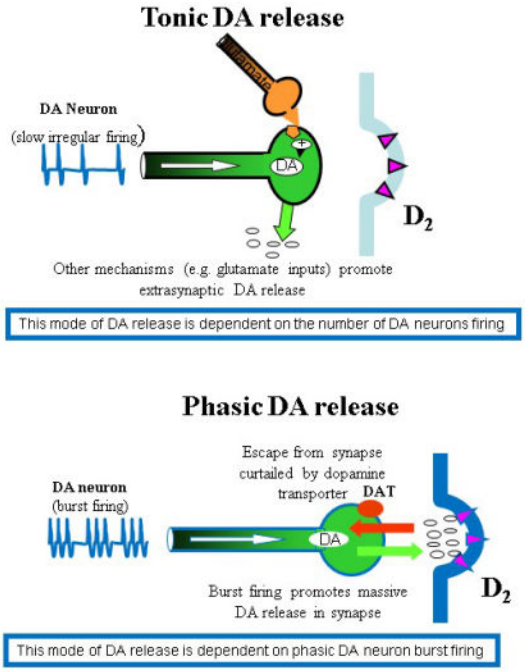


The brain's monoamine (dopamine, serotonin and norepinephrine) systems play major roles in normal behavior and pathology within these circuits is proposed to underlie a number of neurological and psychiatric conditions. The DA system has been implicated in many different aspects of brain function, including locomotion, affect and cognition. The DA system is the last monoamine system to be laid down in the brain during ontogeny[1] which suggests that it may have an important stabilizing and integrative influence on brain circuits, and that its disruption may destabilize a number of these circuits in functionally significant ways.

Norepinephrine and serotonin neurons have extensively branching collaterals that innervate multiple brain regions and therefore can coordinate responses (such as the fight or flight response, or approach or avoidance behaviours) across the multiple brain regions that participate in these behaviours. By contrast, separate populations of dopamine neurons project to specific brain regions [2, 3] and are therefore capable of regulating activity states and modulating information flow discretely in disparate circuits with unique functions. DA neurons also receive distinct sets of afferent input from multiple regions that can drive these unique functions.

In this article, I will discuss the many facets of dopamine neuron regulation, including the unique roles played by the distinct afferent systems that control DA neuron activity patterns. I will also consider how dysfunction in these regulatory mechanisms may negatively impact the DA system in schizophrenia and depression.

Dopamine system properties

Projections

DA neurons, which are mainly situated within the midbrain, can be subdivided with respect to their location, projection sites, and behavioural function. In the rat, the medial portion of the midbrain DA neuron system is the ventral tegmental area (VTA). Neurons in the medial part of the VTA project to the reward-related nucleus accumbens and ventral striatum[4]. At the border between the lateral VTA and the substantia nigra (SN) are DA neurons that project to the associative striatum. Finally, DA neurons in the lateral SN project primarily to the motor-related (dorsolateral) and habit formation-related (dorsomedial) striatum, respectively[5, 6]. Primates do not have a large VTA; instead, DA neurons projecting to the limbic and cortical or associative striatum are located in the SN together with the motor-related neurons; the dorsal tier of the SN is comprised of limbic- and associative- projecting neurons, and the ventral SN tier is comprised of more motor-related neurons[7, 8].

Regulation of dopamine neuron activity

DA neurons in the midbrain show several unique activity states that have implications for the function of the DA system. DA neurons exhibit a pacemaker conductance, which is a spontaneous, slow depolarizing membrane current that maintains their basal activity state[9]; therefore, *in vitro* (when the neurons are removed from afferent control), the neurons fire in a highly regular slow pacemaker pattern [10]. *In vivo*, local circuit and afferent GABAergic inputs[11–14] change the pacemaker firing pattern into a slow-irregular firing pattern[14, 15]. In addition, powerful GABAergic inputs from the ventral pallidum are capable of hyperpolarizing DA midbrain neurons below threshold for firing; indeed, although midbrain DA neurons receive a rich plethora of inputs that impact their firing rate[3, 16–20] the ventral pallidum in particular was found to potently control the proportion of DA neurons that are firing spontaneously[21]

In a normal anesthetized or unanesthetized rat, approximately half of the neurons in the VTA and/or SN are not firing[15, 22, 23] due to VP inhibition[21, 24] (Fig. 1a). In humans, the population activity (that is, the number of spontaneously-firing neurons) of DA neurons is likely reflected by striatal fluorodopa uptake[25] as measured by positron emission tomography (PET) imaging; since fluorodopa is taken up into active terminals, a higher number of active DA neurons should correspond to more active terminals and hence a greater fluorodopa uptake. Tonic (spontaneous) discharge is important in determining the functional output of DA neurons because it sets the level of responsivity of the system to more rapid phasic stimuli[26]. Indeed, it has been proposed that the proportion of DA neurons that are active in the VTA sets the baseline tone of responsivity of the DA system[27].

When exposed to behaviourally salient stimuli, such as a potential threat or a reward-related event, VTA DA neurons transition to a phasic burst firing pattern[12, 28]. Burst firing is defined by a rapid series of action potentials occurring with a short interspike interval (3–10 action potentials with 40–80 msec interspike interval) followed by a prolonged post-burst inhibition[29]. Burst firing of DA neurons in the VTA is potently driven by glutamate from the pedunculopontine nucleus (PPTg)[21, 26] acting on NMDA receptors[30] Only DA neurons that

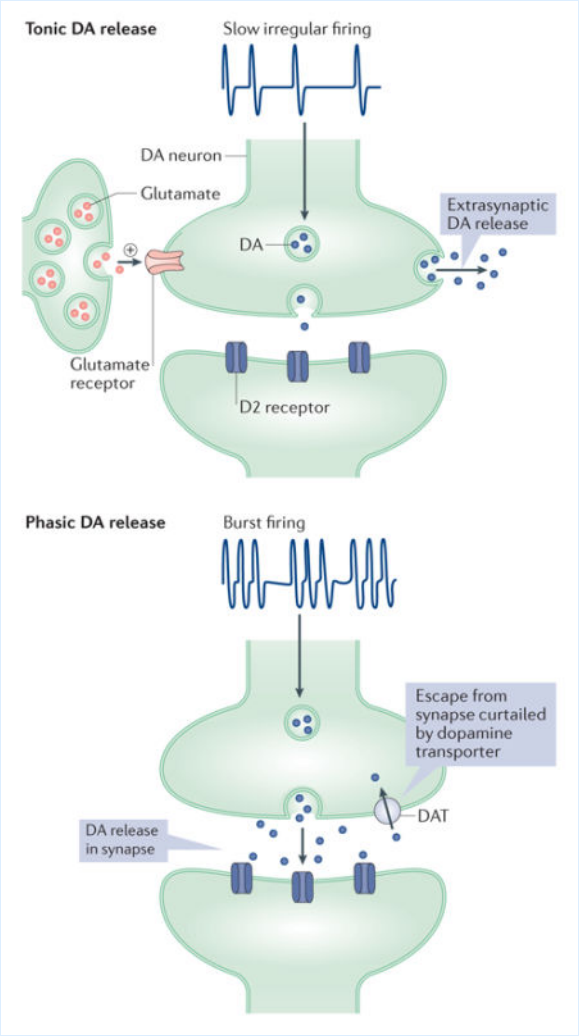
are already firing (in which the Mg2+ block is removed from the NMDA channel[31]) are capable of switching to a burst firing pattern by phasic stimuli (Fig 1a). As such, burst firing is the rapid, behaviorally salient phasic response of the DA system to stimuli; however, the amplitude of the response depends on the tonic activity of the dopamine system (which represents the gain)[32]. (See Box 1).

BOX1

Tonic and phasic dopamine neuron firing and dopamine release

The terms tonic and phasic with respect to the dopamine (DA) system have been used to convey different meanings in different contexts. The terms tonic and phasic were first used to describe extracellular versus synaptic DA release[115] and aimed to account for discrepancies between findings obtained using dialysis and electrophysiology or voltammetry. Since then, the definitions have been modified to include the DA neuron activity states that correspond to these neurochemical findings, with tonic DA neuron population activity related to tonic extrasynaptic DA levels and burst firing to the rapid high-amplitude intrasynaptic phasic release (see the figure) [21, 116, 117]. In general, these parameters appear to correlate, with tonic DA population activity corresponding to microdialysis measures of steady-state extracellular DA and fluorodopa uptake, and phasic burst firing correlating with fast transients recorded using voltammetry and the high-amplitude intrasynaptic DA that leads to raclopride displacement in positron emission tomography (since D2 receptors are concentrated within the synaptic cleft).

When tonic DA neuron firing increases (that is, when more neurons are firing), the amplitude of the phasic response should also increase, since more DA neurons are available to be driven to burst fire. However, although tonic DA would typically correlate with the phasic response amplitude, this may not always be the case – for example, if tonic DA increases independently of population activity (perhaps via presynaptic DA release or diminished reuptake) the consequence will be increased DA terminal autoreceptor-mediated inhibition of phasic DA release[115]. In this case, increased tonic extracellular DA could attenuate the phasic burst firing-driven transient release[21]. Indeed, this has been proposed to be the mechanism by which low doses of oral psychostimulants are an effective treatment for attention-deficit hyperactivity disorder[118].



By regulating the number of DA neurons firing, the ventral pallidum regulates the gain of the phasic response. This enables the system to be adjusted based on the needs of the organism; specifically, the context in which the stimuli are presented (Figure 1b,c)[27, 33]. The ventral hippocampus subiculum controls this context dependency[33–36]. It has been experimentally demonstrated that activation of the subiculum increases striatal-VP GABAergic inhibition, thereby releasing DA neurons from inhibition and causing an increase in population activity[21, 26]. Thus, in a highly charged environment in which an organism must be ready to respond to stimuli, such as an animal hunting for food while avoiding predators, an unexpected noise could have important implications for survival (for example, it could signal a threat or a source of food). Such an activating context (the highly charged environment) would increase subicular activity, increase DA neuron population activity, and cause phasic stimuli to induce a strong burst firing-driven DA release, allowing the organism to rapidly deal with the stimulus (Figure 1c). By contrast, in a safe environment, the same unexpected noise would not generate a large DA response since the input from the subiculum keeps VTA DA neurons in a low tonic firing state (Figure 1b).

Whereas the hippocampal subiculum appears to be capable of up-regulating DA responsivity depending on context, the amygdala decreases tonic DA neuron firing. The amygdala is known to be activated in response to stressors[37], and activation of the basolateral amygdala (BLA) potently and selectively decreases the number of DA neurons firing[38] in the medial affect-related regions of the VTA of the rat. This is proposed to occur via a direct or indirect glutamatergic projection to the VP, because blocking glutamate in the VP prevents BLA activation-induced attenuation of DA neuron firing[38]. A down-regulation of the dopamine system in response to constant stressors may function as a protective withdrawal effect in the face of an inhospitable environment.

Activation of the infralimbic prefrontal cortex (ilPFC) can also potently decrease tonic dopamine neuron firing, an effect that depends on an intact amygdala [39]. Inactivation of the ilPFC has the opposite effect; it increases DA neuron tonic activity, and this effect depends on an intact hippocampus subiculum[39]. Therefore, the opposing modulatory actions on the DA system of the hippocampus and the amygdala are determined by ilPFC activity (Fig. 2).

In summary, the behaviorally salient, rapid phasic response of DA neurons is characterized by burst firing, which is driven by the PPTg. However, burst firing can only be driven in DA neurons that are already spontaneously firing. The number of DA neurons firing is modulated in opposite directions by two brain regions – the hippocampus subiculum, which increases DA responsivity depending on context by increasing tonic DA neuron firing, and the BLA, which down-regulates tonic DA firing and decreases responsivity in the emotion/reward-related DA projection system. As outlined below, these systems are central to understanding the role of DA in major psychiatric disorders (Fig. 2).

Effects of stress on the DA system

Physiological or emotional stress and the anxiety that it produces enable an organism to avoid dangers and provide motivation to achieve goals. However, excess stress can have deleterious effects, including the emergence of major psychiatric disorders such as post traumatic stress disorder (PTSD), depression, drug abuse, and schizophrenia[32]. Stressors, however, are not all the same; they can differ in their intensity, time course, or nature. In the laboratory noxious stimuli, such as a brief shock, produce rapid, transient effects on the DA system. The primary response observed is a brief inhibition of DA neuron firing[13, 40–42] most prominently in the affect-related medial VTA and the SN[43]. By contrast the lateral VTA, which is proposed to be involved in salience,[5] responds to stress with a transient increase in excitation[43, 44] that may be driven by the habenula[3, 45]

By contrast, prolonged stressors such as repeated footshock[43] or restraint stress[46] increase DA neuron population activity across the medial-lateral extent of the VTA[43, 46] and DA levels in the prefrontal cortex and nucleus accumbens[47–49]. Because there are more DA neurons firing, the behaviorally salient phasic response is augmented; this is observed as an increase in amphetamine-induced locomotion[46]. Both the increase in DA neuron activity and amphetamine locomotor response can be normalized by inhibiting the ventral subiculum of the hippocampus. Therefore, with maintained stressors, there is an increase in tonic DA population activity, thereby increasing the responsivity of the system to stimuli. Similarly,

repeated amphetamine sensitizes the DA system through a subiculum-driven increase in tonic DA firing[50, 51] in a context-dependent manner[52, 53]. However, when examined at longer time points following stress or amphetamine withdrawal there is a 50% reduction in tonic DA activity. [54, 55] This compensatory down-regulation following DA system activation is referred to as an opponent process[56, 57]; that is, when the DA system is acutely activated, there is a subsequent, prolonged compensatory decrease in the responsivity of the DA system. This subsequent DA down-regulation is dependent on the BLA [54, 55]. Thus, stressors activate the DA system acutely via an action on the hippocampus. However, this is followed by a more prolonged, amygdala-driven decrease in the responsiveness of the DA system (Fig. 2).

The DA system and schizophrenia

There is substantial evidence that the DA system is hyper-responsive in schizophrenia. All antipsychotic drugs in use today block DA D2 receptors at clinically effective doses[58]. Moreover, drugs that drive DA release or increase DA transmission, such as amphetamine and L-DOPA, will exacerbate psychosis in patients with schizophrenia, and can induce schizophrenia-like symptoms in control individuals if given repeatedly or at high doses[59, 60]. Imaging studies show that amphetamine-induced DA release is increased in the associative striatum of patients with schizophrenia versus controls: furthermore, the amplitude of this increase is correlated with worsening of the psychotic symptoms of schizophrenia (hallucinations and delusions)[61]. Nonetheless, there is little evidence for dysfunction within the DA system itself in individuals with schizophrenia[27] and the focus of much research has turned instead to the dysregulation of the DA system by afferent structures.

Hippocampal hyperactivity

Substantial evidence implicates the hippocampus in schizophrenia. Postmortem studies show that the hippocampus is smaller in patients with schizophrenia[62]. Moreover, imaging studies show that the anterior hippocampus (which is functionally equivalent to the ventral hippocampus in rodents[27, 63]) is hyperactive in individuals with schizophrenia[64–66], and that this hyperactivity correlates with the presence of psychosis[67]. The hyperactivity correlates with a substantial decrease in the numbers of inhibitory parvalbumin-expressing GABAergic interneurons in the hippocampus of individuals with schizophrenia. Parvalbumin-expressing interneurons are necessary for the generation of gamma rhythms, which are also disrupted in schizophrenia[68, 69]. Finally, increased glutamate function in the hippocampus correlates with increased fluorodopa uptake in DA terminals in the striatum in patients with schizophrenia[70]. Together, these data suggest that, in patients with schizophrenia, a hippocampal overdrive leads to increased tonic DA neuron firing and a hyper-responsive DA state.

This model is strongly supported by studies in animal models of schizophrenia. Administration of the mitotoxin methyl azoxymethanol acetate (MAM) to a pregnant rat at gestational day 17 results in features in the offspring consistent with schizophrenia, including shrinking of homologous limbic cortices with increased cell packing density, deficits in prepulse inhibition of startle, behavioral hyper-responsivity to amphetamine and

PCP, deficits in set shifting and reversal learning, deficits in latent inhibition, and alterations in mRNA levels consistent with that observed in humans with schizophrenia [71–73]. These rats also exhibit deficits in numbers of parvalbumin interneurons and evoked gamma rhythmicity[74, 75]. Interestingly, before puberty there is a reduction in parvalbumin content in the hippocampus without loss of neurons, whereas in the adult there is a decrease in the numbers of parvalbumin neurons in the ventral hippocampus (as assessed by loss of neurons expressing both parvalbumin and constitutively expressed substance P receptors [76]). Moreover, the number of spontaneously firing DA neurons is more than doubled in the VTA in these animals, which is consistent with activation of the ventral hippocampus [75]. The increase in the number of DA neurons exhibiting tonic firing is also consistent with the increase in fluorodopa uptake in the striatum[77] corresponding to an increase in the number of DA neurons firing (Fig. 3).

Taken together, these data suggest a model in which a loss of parvalbumin interneurons in the limbic hippocampus leads to a hyper-responsive DA system that underlies the positive symptoms of schizophrenia. Thus, if the DA system is hyper-responsive, it would cause all stimuli independent of their importance to generate a maximal DA signal, making it difficult for the patient to segregate relevant from irrelevant stimuli, and to assign too much importance (salience) to stimuli that would otherwise be ignored; a condition referred to as aberrant salience of psychosis. Moreover, given the extensive projections of the ventral hippocampus to the prefrontal cortex, the amygdala, and other regions involved in cognition and emotion[78–81] it is likely to also play a role in the negative and cognitive deficits in schizophrenia. Therefore, if the hippocampus is hyperactive and dysrhythmic, it could lead to deficits across symptom domains (Fig. 3).

Stress and hippocampal pathology

What causes hippocampal parvalbumin interneurons to become damaged in schizophrenia? Stress is known to exacerbate psychosis in schizophrenia patients, and can lead to relapse in individuals in remission. Moreover, stress activates the hippocampus[46, 78]. Stress is also a risk factor for schizophrenia; several studies that have examined children at genetic risk for schizophrenia have shown that those who show abnormally heightened responses to stressors tended to develop schizophrenia later in life[82]. Numerous studies have shown that maintained stressors can lead to dendritic shrinkage and neuronal loss in the hippocampus[83]. In particular, stress leads to a loss of parvalbumin interneurons[84]. Stress also activates the amygdala[37, 85, 86], a region that has glutamatergic projections to the hippocampus subiculum and other hippocampal regions. Interestingly, potent activation of the amygdala by picrotoxin injection causes a loss of parvalbumin interneurons in the hippocampus of rats[87]. MAM rats exhibit increased responsivity to stressors during adolescence[88]. Therefore, stress-induced hyperactivity in the amygdala during adolescence could lead to the loss of parvalbumin interneurons in the hippocampus.

The medial prefrontal cortex (PFC) potently regulates the response of the amygdala to stress[89, 90] and this region is thought to play a role in the etiology of schizophrenia[68, 91]. Therefore, either extreme stress, or a failure of the PFC to mitigate the impact of stress, could lead in late adolescence or early adulthood parvalbumin interneuron loss in the

hippocampus. This in turn would lead to hippocampal hyperactivity and DA system overdrive, along with disruption of other hippocampal targets controlling affect and cognition[73, 92]. If this were indeed the case, one would predict that decreasing stressors early in life could prevent the transition to psychosis in early adulthood. This hypothesis was tested by giving MAM-exposed rats the anti-anxiety agent diazepam peripubertally for 10 days (postnatal day 31–40) at a dose that was sufficient to restore anxiety levels and stress responses to levels observed in controls[93]. When tested as adults, the MAM rats treated with diazepam no longer showed hyperactivity of DA neuron firing, did not exhibit increased locomotor responses to amphetamine, and did not show heightened anxiety levels or amygdala hyperactivity. Therefore, by controlling stress during a critical interval around puberty, the stress-induced damage to the hippocampus seems to be averted, preventing the emergence of psychosis-like behavior in the adult[93]. Such findings could be readily translated into the human population. Thus, in individuals that have a family history of schizophrenia and that also show abnormally heightened responses to stressors, mitigating the effects of stress through psychosocial intervention could be effective. Indeed, in societies in which close family ties are believed to mitigate the effects of stress, such as in the barrios surrounding Sao Paulo, Brazil, there is a significantly lower incidence of schizophrenia[94]; whereas in those that move to environments where there are high levels of social stress, there is a substantial increase in the incidence of schizophrenia[95].

These data therefore suggest that increased stress responsivity, particularly at critical developmental stages, could lead to the emergence of psychosis in adults. It is also likely that MAM treatment doesn't cause schizophrenia, but instead causes the animal to have increased responses to stress, which leads to the emergence of psychosis[63]. This could have important implications for genetic studies that have examined the correlations of particular genetic mutations with schizophrenia: that is, it is likely that the genes found to correlate with schizophrenia may also not cause schizophrenia, but instead lead to a condition of hyper-responsivity to stress, which in turn can lead to hippocampal damage and schizophrenia. This could also account for the genetic correlation between schizophrenia and depression[96], since both conditions appear to have stress as a common underlying risk factor (see below), albeit at different developmental periods of exposure.

The DA system and depression

Emerging data has also linked DA system dysfunction to the pathophysiology of depression. Serotonin has traditionally been the transmitter linked with depression, based on pharmacological studies of antidepressant drugs that target the serotonin system, or depletion of serotonin in the CNS[97]. However, many of the symptoms seen in depression — such as anhedonia and amotivation — have been more consistently associated with dysfunctions in the DA system[45, 98–100]. Studies have identified hyperactivity in prefrontal cortical area 25 as a correlate of depression[101]. Indeed, any treatment that is effective in treating depression reversed hyperactivity in this region[101]. Furthermore, the amydala was found to be hyper-responsive to emotionally charged stimuli in depression, primarily to those stimuli that have a negative affective component[102, 103].

Animal models of depression are based on the presentation of stressors, particularly those that are uncontrollable or unpredictable[38]. The duration of the stressor impacts the magnitude and duration of the negative affective state associated with its withdrawal[56, 57]. Thus, acute activation of the DA system by amphetamine or stress-induced DA neuron activation is followed by a depression of DA neuron firing[54, 55]. However, if the stressor is presented over a much longer period of time, the consequent depressive-like state is also maintained for an extended period following withdrawal. Rats exposed to chronic cold or unpredictable chronic mild stressors (UCMS), for example, have been shown to exhibit extended decreases (by approximately 50%) in VTA DA neuron population activity [38, 43]; moreover, the decrease in activity was primarily in the medial VTA, which preferentially projects to the reward-related ventromedial accumbens[5, 6]. This was associated with an increase in immobility in the forced swim test, which models behavioral despair in depression. DA neuron firing could be restored to baseline by inactivating either the ilPFC or the BLA, which is consistent with the idea that hyperactivity in these pathways leads to a down-modulation of DA neuron activity. Therefore, it is possible that the diminished DA neuron activity observed in the UCMS model of depression is driven by hyperactivity in the ilPFC, leading to amygdala overdrive and, via the VP, a decrease in the number of DA neurons firing primarily in the medial, reward-related VTA (Fig. 4a).

I propose that it is the stress-induced activation of VTA DA neurons initially that leads to the compensatory, long-duration down-regulation of DA neuron population activity upon stressor withdrawal. Indeed, studies[104] showed that activation of the DA system during the induction phase will increase the susceptibility of rats to social defeat-induced depression in a manner that is dependent on the ventral hippocampus[105], which is consistent with this model. Moreover, the correlation of decreased VTA DA neuron activity with immobility in the forced swim test is also consistent with studies showing that, following UCMS[106] or social defeat [107], activation of DA neuron firing can reverse the despair state. Therefore, the initial stress-induced activation of DA neuron tonic population activity driven by the hippocampus–ventral striatal–VP circuit engenders a compensatory, long-duration down-regulation of the VTA via increased activity in the ilPFC–amygdala–VP circuit. Once the stressor is withdrawn, the down-regulation of the VTA is maintained, leading to anhedonia and depression. However, one group found that social defeat-induced depression was associated with DA neuron bursting when tested *in vitro* [108], although population activity was not assessed. Given that phasic activation of DA neurons alleviates depression *in vivo*[107] and that the *in vitro* preparation removes ventral pallidal inhibition, it is not clear whether the activation observed reflects a distinct pathophysiology or a rebound from tonic inhibition present in the intact system.

What causes the down-regulation of the excitatory loop, such that the amygdala-driven inhibition of activity in the VTA predominates? This question has been examined using stress-sensitive Wistar-Kyoto rats in the learned helplessness model of depression. This model allows an acute induction of the anhedonic state, and rapid reversal of this condition by the novel, fast-acting antidepressant ketamine[109]. The rats are exposed for one day to a chamber in which a signal predicts the occurrence of an inescapable footshock. The following day, the rats are given an escape route to avoid the shock. In this study, half of the rats readily escaped the footshock, whereas half remained immobile and received the

footshock. Rats that fail to escape “learned” that they were helpless to avoid the shock, which may model feelings of helplessness and hopelessness experienced by patients with major depression. Only the helpless rats showed a 50% reduction in DA neuron population activity, whereas the DA system in the nonhelpless rats was unaffected[110]. Furthermore, in control rats and in non-helpless rats, tetanic stimulation of the hippocampal-accumbens pathway leads to the induction of long-term potentiation (LTP). However, in the helpless rats, stimulation resulted instead in long-term-depression (LTD) – that is, the excitatory hippocampal part of the amygdala-hippocampal balance was selectively attenuated in the helpless rats (Fig. 4a).

Ketamine selectively restored DA neuron population activity in helpless rats, and this was accompanied by normalized escape behavior and restoration of stimulus-induced LTP in the hippocampal-accumbens pathway (Fig. 4b. Indeed, ketamine was also found to restore DA neuron firing in rats 24 hours after amphetamine withdrawal[55]. Therefore, although acute stressors tend to activate the dopamine system via the hippocampus-accumbens circuit, with prolonged stress and withdrawal there is a compensatory and long-term decrease in VTA DA neuron firing driven by an ilPFC-amygdala pathway.

Synthesis

The DA system has been implicated in a number of neuropsychiatric disease states. However, evidence indicates that it is not a dysfunction in the DA system itself that drives these disorders, but instead that pathophysiology is related to disruptions within the systems that provide afferent control of the DA system. Thus, in schizophrenia there are deficits in the hippocampus and prefrontal cortex that drive dysfunction within the DA system. By contrast, in depression the deficits appear to arise within medial frontal cortical regions and involve the amygdala. It is not surprising that dysfunctions within these cortical regions lie at the base of these disorders. I propose that interneuron dysfunction, which is known to play a prominent role in schizophrenia, will be shown to occur in other disease states as well. Developmental studies have shown that interneurons are the last component to be incorporated in the developing brain, and that interneurons migrate into their final positions to stabilize the excitatory networks that have been laid down[111]. Therefore, it is not surprising that dysregulation of this late-developing system that is so essential for system-wide stability is also the most vulnerable to developmental insults. Interneurons are also critical for generation of rhythmic activity within brain circuits[112], which is proposed to underlie information transfer and system coherence in the normal functioning brain. It is therefore also not surprising that rhythmic activity and coherence across brain regions are also found to be disrupted in pathological conditions. And finally, the findings that interneurons are highly susceptible to damage from oxidative stress[113] or glutamatergic drive, particularly early in postnatal development before the protective perineuronal nets are formed [114], suggest a rationale for the enhanced vulnerability of this critical component of neuronal circuitry to environmentally-induced disruption. Indeed, this could lead to an intriguing explanation for known genetic links between schizophrenia and affective disorders. If these disorders share a common stress sensitivity predisposition, then enhanced stress responsivity and exposure during adolescence leading to parvalbumin neuron loss could predispose to schizophrenia; however if the person is protected peripubertally during

the parvalbumin susceptibility period but experiences enhanced stress responses later in life, it could lead to depression. Therefore, future investigations into the treatment of major psychiatric conditions, particularly those with a developmental or delayed-onset component, may be better addressed via targeting specific GABAergic systems within excitatory-inhibitory networks.

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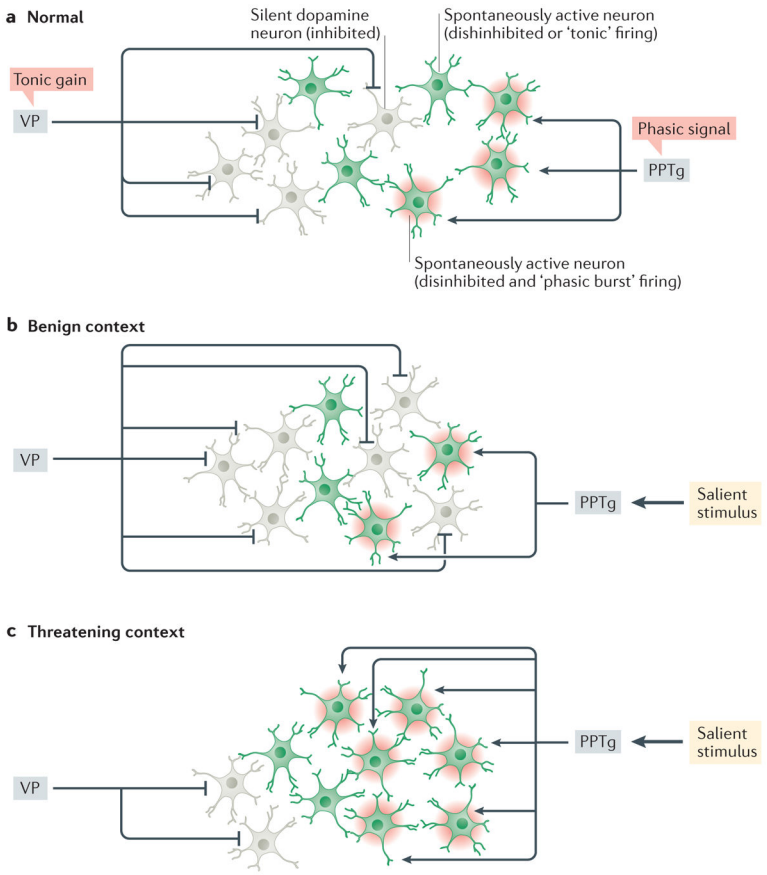

Figure 1. Tonic and phasic dopamine neuron regulation

a| The ventral pallidum (VP) provides a powerful GABAergic inhibitory input to ventral tegmental area (VTA) dopamine (DA) neurons, holding subsets of DA neurons in a hyperpolarized, nonfiring (silent) state. Pedunculopontine tegmentum (PPTg) input acts on glutamatergic NMDA receptors on DA neurons to generate phasic bursts of firing: these constitute the behaviorally salient rapid DA response. However, only neurons that are firing spontaneously can burst fire; hyperpolarized neurons exhibit a magnesium block of the NMDA channel and therefore will not be driven to burst fire. Thus input from the PPTg provides the phasic signal, whereas the VP, by controlling the number of DA neurons firing, determines the tonic gain, or the level of amplification, of the phasic signal. b| If an organism is in a safe, benign context, the number of DA neurons firing is kept low and the PPTg will only activate phasic bursting in a small population of neurons. As a result, a salient stimulus will trigger a calm orienting response. By contrast, in a threatening or opportunistic environment, such as that present when an animal is out hunting, the VP allows a large population of DA neurons to be active, increasing vigilance to the environment. Now the same salient stimulus will cause a much larger phasic response, enabling the organism to rapidly orient to the stimulus to prepare an appropriate response.

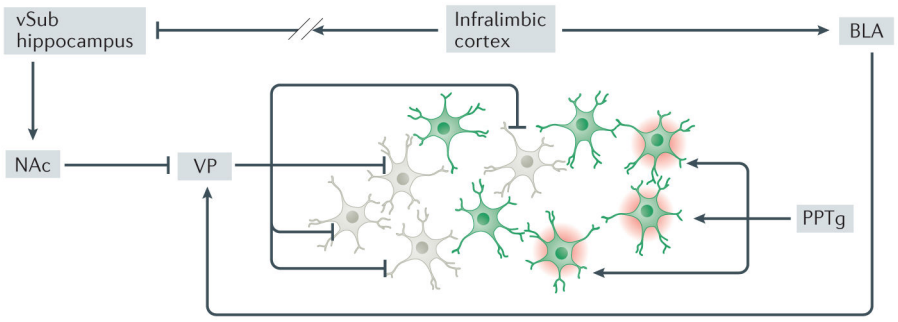

Figure 2. ilPFC Modulation of DA Neuron Activity

The infralimbic prefrontal cortex (ilPFC) provides bidirectional control over VTA DA neuron tonic population activity. Under normal circumstances, the ventral subiculum (vSub) of the hippocampus activates the nucleus accumbens (NAc) to inhibit the VP, driving VTA DA neuron tonic population activity and increasing the response to afferent drive. Activation of the ilPFC provides an indirect inhibition of the hippocampus vSub and simultaneously activates the BLA, which in turn activates the VP to decrease DA neuron tonic population activity. By contrast, inhibition of the ilPFC removes a tonic inhibition of the vSub, which would increase the drive to the NAc and result in inhibition of the VP, thereby driving up tonic DA neuron population activity. Therefore, ilPFC activation decreases the response of the DA system to phasic events via activation of the BLA, whereas inhibition of the ilPFC increases DA system responsivity via disinhibition of the vSub.

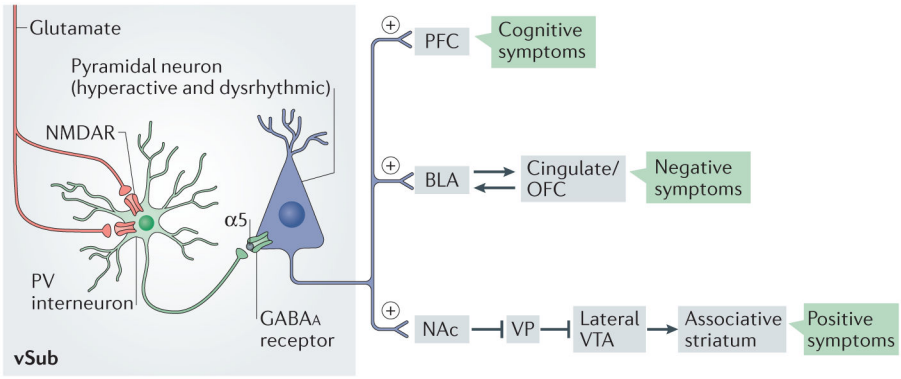

Figure 3. vSub dysfunction and schizophrenia symptomatology

Parvalbumin (PV)-labeled GABAergic interneurons in the ventral subiculum (vSub) are driven by glutamate acting on NMDA receptors, and provide a powerful inhibitory input to pyramidal neurons via stimulation of GABA-A receptors containing the alpha-5 subunit. The PV-pyramidal neuron interaction is necessary to drive gamma rhythmic activity. In the case of schizophrenia, there is a loss of a large number of PV interneurons, causing the pyramidal neurons to be hyperactive and dysrhythmic. This leads to an overdrive of the nucleus accumbens (NAc), which inhibits the ventral pallidum (VP) and increases responsivity of DA neurons primarily in the lateral ventral tegmental area (VTA) that projects to the associative striatum. This is proposed to underlie the DA-dependent positive symptoms of schizophrenia. However, if the vSub is hyperactive and dysrhythmic, it can also interfere with the function of other circuits. Thus, the vSub-prefrontal cortex (PFC) projection would lead to disruption of PFC activity and rhythmicity, leading to cognitive disruption. Moreover, the vSub-basolateral amygdala (BLA) projection would interfere with the BLA-limbic cortical control of emotional responses, possibly leading to negative symptoms. Therefore, a hyperactive, dysrhythmic vSub has the potential of disrupting multiple interconnected circuits, and could potentially contribute to all three symptom classes of schizophrenia. OFC, orbitofrontal cortex.

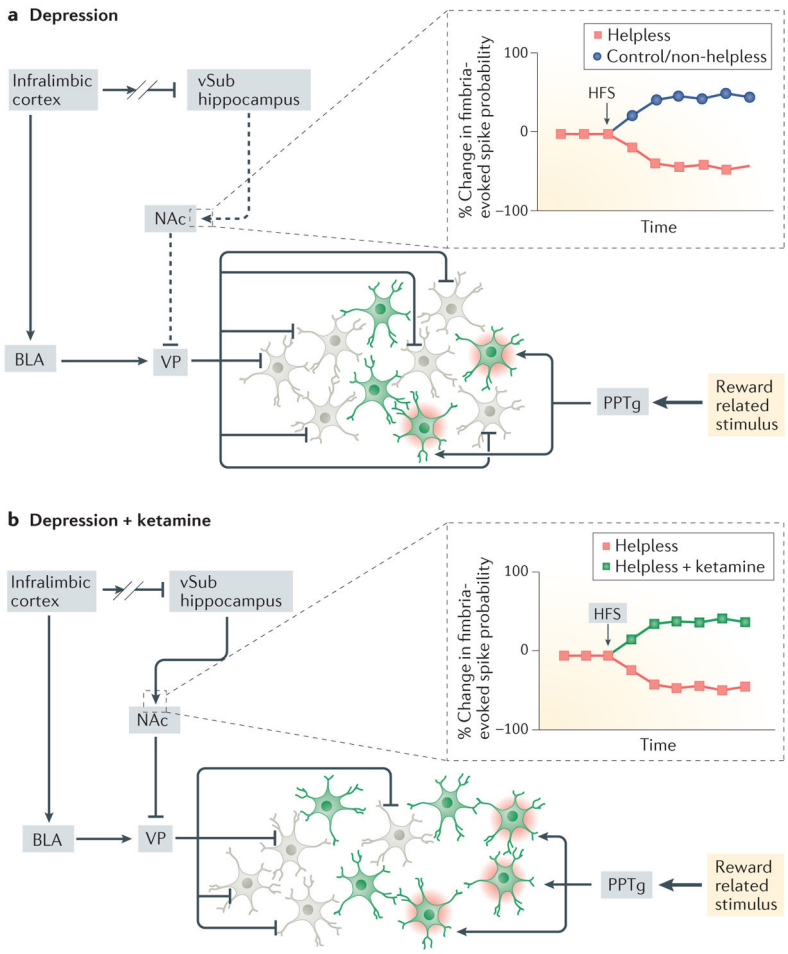

Figure 4. Depression circuitry and ketamine actions

a|. In depression in humans, there is reported hyperactivity in subgenual cingulate Area 25, which is functionally analogous to the rodent ilPFC. In animal models of depression, hyperactivity in the ilPFC drives the BLA. BLA activity, via the VP, attenuates reward-related medial VTA DA neuron activity[38,39,106]. As a result, normally reward-related stimuli that activate the PPTg should produce a significantly smaller DA neuron phasic response, leading to a failure to establish a link between stimulus and reward. In the learned helplessness depression model, control rats and nonhelpless rats both show stimulation-induced LTP in the vSub-NAc pathway (see inset) which can offset the BLA-VP inhibition of the VTA. However, in the helpless animals, stimulation instead produces a LTD, thereby removing this counterbalancing influence b| Ketamine, a fast-acting antidepressant drug, normalizes DA neuron firing and re-establishes stimulus-induced LTP in the vSub-NAc pathway (see inset), thus re-establishing the balance between the DA facilitatory and attenuating circuits.