OPINION

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

Anthony A. Grace

Abstract | The dopamine 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. Dopamine 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 in these regulatory systems may underlie the pathophysiology of several psychiatric disorders, including schizophrenia and depression.

The brain's monoamine (dopamine, serotonin and noradrenaline) systems have major roles in normal behaviour, and pathology in these circuits is proposed to underlie a number of neurological and psychiatric conditions. The dopamine system has been implicated in many different aspects of brain function, including locomotion, affect and cognition. The dopamine 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 several of these circuits in functionally significant ways.

Noradrenaline and serotonin neurons have extensively branching collaterals that innervate multiple brain regions and can therefore 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. Dopamine neurons also receive distinct sets of afferent input from multiple regions that can drive these unique functions.

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

Dopamine system properties

Projections. Dopamine neurons, which are mainly situated in the midbrain, can be subdivided with respect to their location, projection sites and behavioural function. In the rat, the medial portion of the midbrain dopamine 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 are dopamine neurons that project to the associative striatum. Finally, dopamine neurons in the lateral substantia nigra project primarily to the motor-related (dorsolateral) and habit-formation-related (dorsomedial) striatum[5,6]. Primates do not have a large VTA; instead, dopamine neurons projecting to the limbic and cortical or associative striatum are located in the substantia nigra together with the motor-related neurons; the dorsal tier of the substantia nigra is composed of limbic- and associative-projecting neurons, and the ventral substantia nigra tier is composed of more motor-related neurons[7,8].

Regulation of dopamine neuron activity. Dopamine neurons in the midbrain show several unique activity states that have implications for the function of the dopamine system. Dopamine 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 dopamine midbrain neurons below the threshold for firing; indeed, although midbrain dopamine neurons receive numerous inputs that affect their firing rate[3,16–20], the ventral pallidum in particular was found to potently control the proportion of dopamine neurons that are firing spontaneously[21].

In a normal anaesthetized or un-anaesthetized rat, approximately half of the neurons in the VTA and/or substantia nigra do not fire[15,22,23] owing to ventral-pallidum inhibition[21,24] (FIG. 1a). In humans, the population activity of dopamine neurons is likely to be reflected by striatal uptake of the radiotracer fluorodopa[25], as measured by positron-emission tomography imaging; because fluorodopa is taken up into active terminals, a greater number of active dopamine neurons should correspond to a higher number of active terminals and hence greater fluorodopa uptake. Tonic (spontaneous) discharge is important in determining the functional output of dopamine neurons because it sets the level of responsivity of the system to rapid phasic stimuli[26]. Indeed, it has been proposed that the proportion of dopamine neurons that are active in the VTA sets the baseline tone of responsivity of the dopamine system[27].

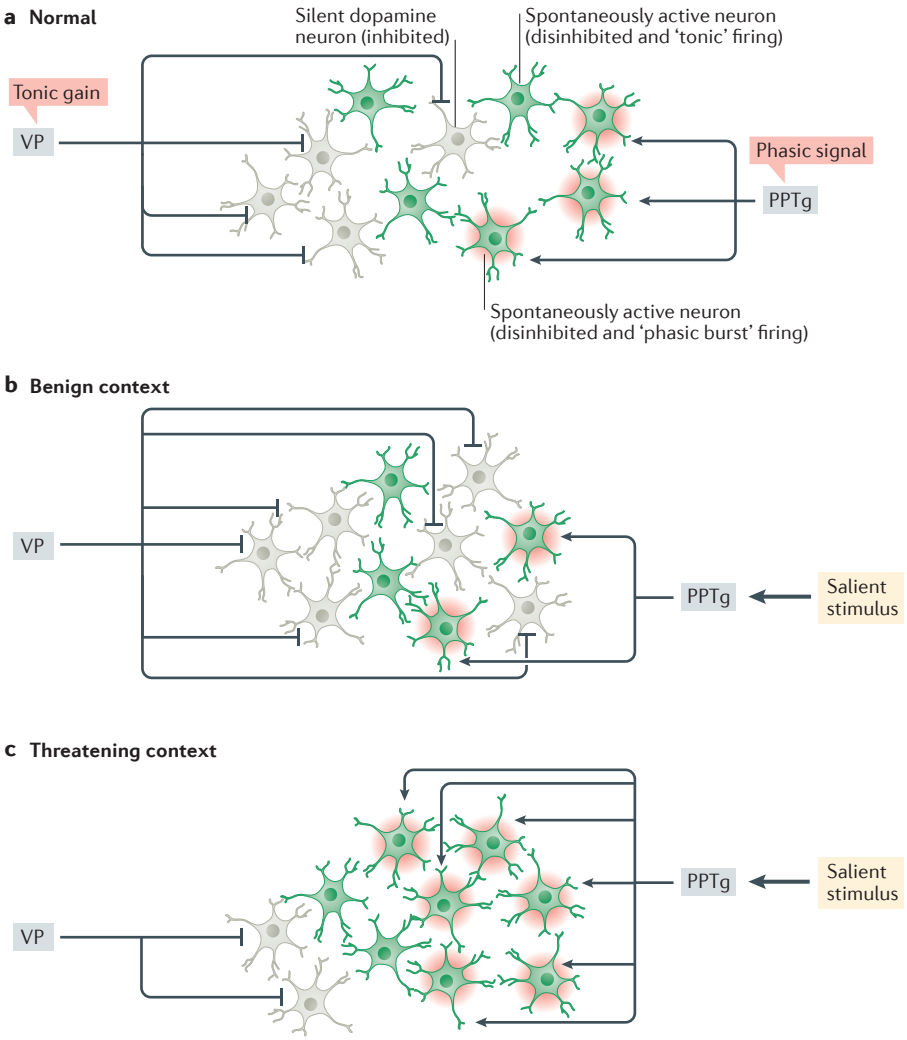


Figure 1 | **Tonic and phasic dopamine neuron regulation. a** | The ventral pallidum (VP) provides a powerful GABAergic inhibitory input to ventral tegmental area dopamine neurons, holding subsets of dopamine neurons in a hyperpolarized, non-firing (silent) state. Input from the pedunculopontine tegmentum (PPTg) acts on glutamatergic NMDA receptors on dopamine neurons to generate phasic bursts of firing; these constitute the behaviourally salient rapid dopamine 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 dopamine 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 dopamine 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. **c** | 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 dopamine neurons to be active, increasing vigilance of 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. Adapted from a figure provided courtesy of P. Belujon, Université de Poitiers, France.

When exposed to behaviourally salient stimuli, such as a potential threat or a reward-related event, VTA dopamine 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 inter-spike interval (3–10 action potentials with a 40–80 ms inter-spike interval), followed by prolonged post-burst inhibition[29]. Burst firing of dopamine neurons in the VTA is potently driven by glutamate from the pedunculopontine tegmentum (PPTg)[21,26] acting on NMDA receptors[30]. Only dopamine neurons that are already firing (in which the Mg^{2+} 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, behaviourally salient phasic response of the dopamine system to stimuli; however, the amplitude of the response depends on the tonic activity of the dopamine system (which represents the gain)[32] (BOX 1).

By regulating the number of dopamine neurons firing, the ventral pallidum regulates the gain of the phasic response. This enables the system to be adjusted on the basis of the needs of the organism: specifically, the context in which the stimuli are presented[27,33] (FIG. 1b,c). The ventral hippocampus subiculum controls this context dependency[33–36]. It has been experimentally demonstrated that activation of the subiculum increases striatal–ventral pallidum GABAergic inhibition, thereby releasing dopamine 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 dopamine neuron population activity, and cause phasic stimuli to induce a strong, burst-firing-driven dopamine release, allowing the organism to rapidly deal with the stimulus (FIG. 1c). By contrast, in a safe environment, the same unexpected noise would not generate a large dopamine response because the input from the subiculum keeps VTA dopamine neurons in a low, tonic firing state (FIG. 1b).

Whereas the hippocampal subiculum seems to upregulate dopamine responsivity (depending on the context), the amygdala decreases tonic dopamine 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 dopamine neurons firing[38] in the medial affect-related regions of the rat VTA. This is proposed to occur through a direct or indirect glutamatergic projection to the ventral pallidum, because blocking glutamate in the ventral pallidum prevents BLA activation-induced attenuation of dopamine neuron firing[38]. Downregulation 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 the tonic activity of dopamine neurons, and this effect depends on an intact hippocampus subiculum[39]. Therefore, the opposing modulatory actions of the hippocampus and the amygdala on the dopamine system are determined by ilPFC activity (FIG. 2).

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

Effects of stress on the dopamine system

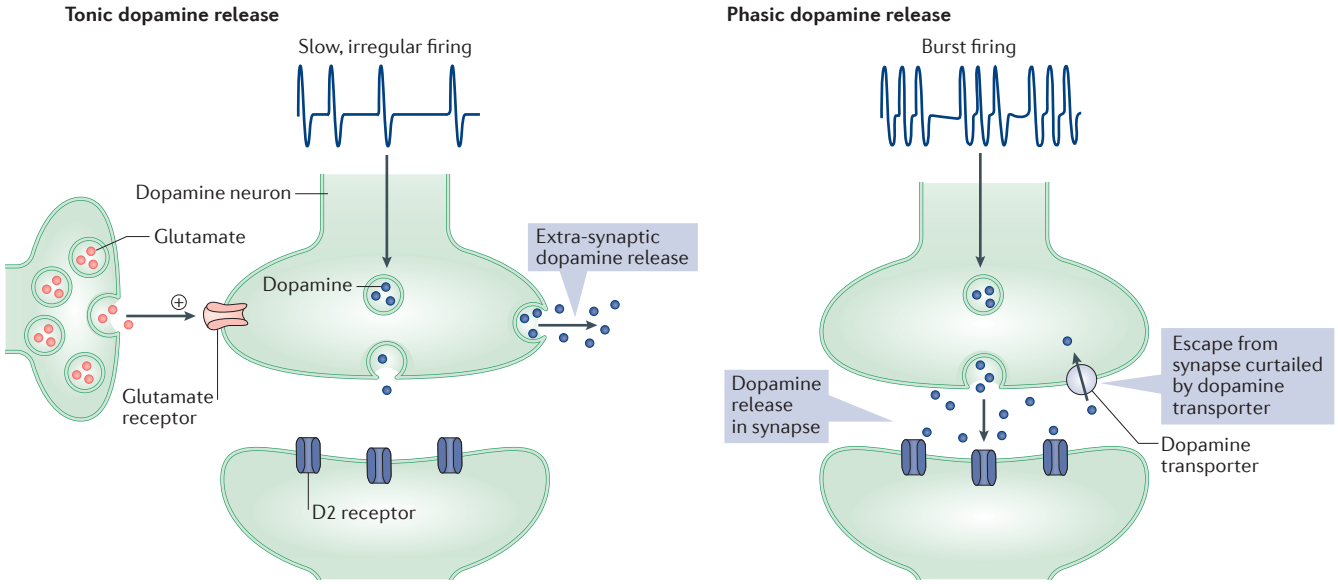
Physiological or emotional stress and the anxiety that it produces enable an organism to avoid dangers and provide motivation to achieve goals. However, excess stress can have deleterious effects, including the emergence of major psychiatric disorders, such as post-traumatic stress disorder (PTSD), depression,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

Prolonged stressors, however, such as repeated footshock[43] or restraint stress[46], increase the population activity of dopamine neurons across the medial–lateral extent of the VTA[43,46] and increase the level of dopamine in the prefrontal cortex (PFC) and nucleus accumbens[47–49]. Because there are more dopamine neurons firing, the behaviourally salient phasic response is augmented; this is observed as an increase in amphetamine-induced locomotion[46]. Both the increase in dopamine neuron activity and amphetamine locomotor response can

Box 1 | **Tonic and phasic dopamine neuron firing and dopamine release**

With respect to the dopamine system, the terms 'tonic' and 'phasic' have been used to convey different meanings in different contexts. They were first used to describe extracellular versus synaptic dopamine release[62] (tonic versus phasic release, respectively) 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 dopamine neuron activity states that correspond to these neurochemical findings, with tonic dopamine neuron population activity being related to tonic, extra-synaptic dopamine levels and burst firing being related to the rapid, high-amplitude, intra-synaptic phasic release (see the figure)[21,117,118]. In general, these parameters seem to be correlated; tonic dopamine neuron population activity corresponds to microdialysis measures of steady-state extracellular dopamine and fluorodopa uptake, and phasic burst firing correlates with fast transients recorded using voltammetry and the high-amplitude intra-synaptic dopamine release that leads to raclopride displacement in positron-emission tomography (as dopamine D2 receptors are concentrated in the synaptic cleft).

When tonic dopamine neuron firing increases (that is, when more neurons are firing), the amplitude of the phasic response should also increase because more dopamine neurons are available to be driven to burst fire. However, although tonic dopamine release would typically correlate with the phasic-response amplitude, this may not always be the case; for example, if tonic dopamine release increases independently of population activity (perhaps through presynaptic dopamine release or diminished reuptake), the consequence will be increased dopamine terminal autoreceptor-mediated inhibition of phasic dopamine release[62]. In this case, increased tonic extracellular dopamine could attenuate the transient release driven by phasic burst firing[21]. Indeed, this has been proposed to be the mechanism by which low doses of oral psychostimulants effectively treat attention-deficit hyperactivity disorder[119].



be normalized by inhibiting the ventral subiculum of the hippocampus. Therefore, with maintained stressors, there is an increase in tonic dopamine population activity, thereby increasing the responsivity of the system to stimuli. Similarly, repeated administration of amphetamine sensitizes the dopamine system through a subiculum-driven increase in tonic dopamine firing[50,51] in a context-dependent manner[52,53]. However, when examined at later time points after stress or amphetamine withdrawal, there is a 50% reduction in tonic dopamine activity[54,55]. This compensatory downregulation after dopamine system activation is referred to as an opponent process[56,57]; that is, when the dopamine system is acutely activated, there is a subsequent, prolonged compensatory decrease in the responsivity of the dopamine system. This subsequent dopamine downregulation is dependent on the BLA[54,55]. Thus, stressors activate the dopamine system acutely by acting on the hippocampus. However, this is followed by a more prolonged, amygdala-driven decrease in the responsiveness of the dopamine system (FIG. 2).

The dopamine system and schizophrenia

There is substantial evidence that the dopamine system is hyper-responsive in schizophrenia. All antipsychotic drugs in use today block dopamine D2 receptors at clinically effective doses[58]. Moreover, drugs that drive dopamine release or increase dopamine transmission, such as amphetamine and 3,4-dihydroxyphenylalanine (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 dopamine 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 dopamine system itself in individuals with schizophrenia[27,62], and the focus of much research has turned instead to the dysregulation of the dopamine system by afferent structures.

Hippocampal hyperactivity. Substantial evidence implicates the hippocampus in schizophrenia. Post-mortem studies show that the hippocampus is smaller in people with schizophrenia[63]. Moreover, imaging studies show that the anterior hippocampus (which is functionally equivalent to the ventral hippocampus in rodents)[27,64] is hyperactive in individuals with schizophrenia[65–67], and that this hyperactivity correlates with the presence of psychosis[68]. The hyperactivity correlates with a substantial decrease in the numbers of inhibitory parvalbumin-expressing GABAergic interneurons in the hippocampus. Parvalbumin-expressing interneurons are necessary for the generation of gamma rhythms, which are also disrupted in schizophrenia[69,70]. Finally, increased glutamate function in the hippocampus correlates with increased fluorodopa uptake in dopamine terminals in the striatum in individuals with schizophrenia[71]. Together, these data suggest that, in schizophrenia, a hippocampal overdrive leads to increased tonic dopamine neuron firing and a hyper-responsive dopamine 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 that are consistent with schizophrenia, including shrinking of the homologous limbic cortices, resulting in increased cell density, deficits in pre-pulse inhibition of the startle response, behavioural hyper-responsivity to amphetamine and phencyclidine, deficits in set shifting and reversal learning, deficits in latent inhibition, and certain alterations in mRNA levels[72–74]. These rats also exhibit deficits in numbers of parvalbumin interneurons and evoked gamma rhythmicity[75,76]. 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 number of parvalbumin neurons in the ventral hippocampus (as assessed by loss of neurons expressing both parvalbumin and constitutively expressed substance P receptors[77]). Moreover, the number of spontaneously firing dopamine neurons is more than doubled in the VTA in these animals, which is consistent with activation of the ventral hippocampus[76]. The increase in the number of dopamine neurons exhibiting tonic firing is also consistent with the increase in fluorodopa uptake in the striatum[78], which corresponds to an increase in the number of dopamine 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 dopamine system that underlies the positive symptoms of schizophrenia. Thus, if the dopamine system is hyper-responsive, it would cause all stimuli, independent of their importance, to generate a maximal dopamine signal, making it difficult for the individual to segregate relevant stimuli from irrelevant stimuli, and causing them to assign too

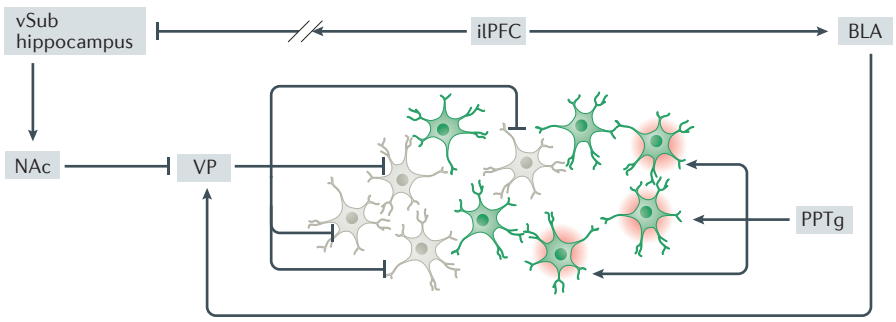


Figure 2 | **Infralimbic prefrontal cortex-mediated modulation of dopamine neuron activity.** The infralimbic prefrontal cortex (ilPFC) provides bidirectional control over ventral tegmental area (VTA) dopamine neuron tonic population activity. Under normal circumstances, the ventral subiculum (vSub) of the hippocampus activates the nucleus accumbens (NAc) to inhibit the ventral pallidum (VP), driving VTA dopamine neuron tonic population activity and increasing the response to afferent drive. Activation of the ilPFC leads to an indirect inhibition of the hippocampus vSub and simultaneously activates the basolateral amygdala (BLA), which in turn activates the VP to decrease dopamine neuron tonic population activity. By contrast, inhibition of the ilPFC removes tonic inhibition of the vSub, which would increase the drive to the NAc and result in inhibition of the VP, thereby driving up tonic dopamine neuron population activity. Therefore, ilPFC activation decreases the response of the dopamine system to phasic events through activation of the BLA, whereas inhibition of the ilPFC increases dopamine system responsivity through disinhibition of the vSub. The double diagonal line indicates that the pathway between two areas is indirect. Adapted from a figure provided courtesy of P. Belujon, Université de Poitiers, France.

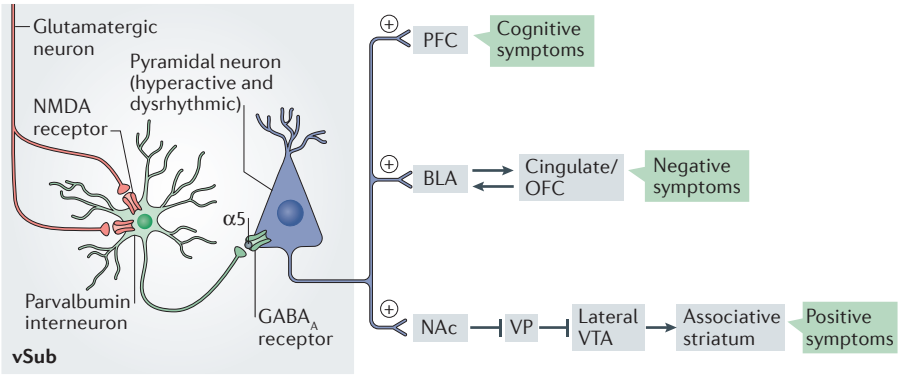


Figure 3 | **Ventral-subiculum dysfunction and schizophrenia symptomatology.** Parvalbumin-labelled GABAergic interneurons in the ventral subiculum (vSub) are driven by glutamate acting on NMDA receptors, and provide a powerful inhibitory input to pyramidal neurons through stimulation of $GABA_A$ receptors containing the α5 subunit. The parvalbumin–pyramidal neuron interaction is necessary to drive gamma rhythmic activity. In the case of schizophrenia, there is a loss of a large number of parvalbumin 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 the responsivity of dopamine neurons, primarily in the lateral ventral tegmental area (VTA), that project to the associative striatum. This is proposed to underlie the dopamine-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 to disrupt multiple interconnected circuits, and could potentially contribute to all three symptom classes of schizophrenia. OFC, orbitofrontal cortex. Adapted from a figure provided courtesy of P. Belujon, Université de Poitiers, France.

much importance (salience) to stimuli that would otherwise be ignored — a condition referred to as aberrant salience of psychosis[79]. Moreover, given the extensive projections of the ventral hippocampus to the PFC, the amygdala and other regions that are involved in cognition and emotion[80–83], the hippocampus is likely to also play a part 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 people with schizophrenia, and can lead to relapse in individuals in remission. Moreover, stress activates the hippocampus[46,80]. Stress is also a risk factor; 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[84]. Numerous studies have shown that prolonged stressors can lead to dendritic shrinkage and neuronal loss in the hippocampus[85]. In particular, stress leads to a loss of parvalbumin interneurons[86]. Stress also activates the amygdala[37,87,88], 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[89]. Rats that have been exposed to MAM exhibit increased responsivity to stressors during adolescence[90]. Therefore, stress-induced hyperactivity in the amygdala during adolescence could lead to the loss of parvalbumin interneurons in the hippocampus.

The medial PFC potently regulates the response of the amygdala to stress[91,92], and this region is thought to have a role in the aetiology of schizophrenia[69,93]. Therefore, extreme stress, or a failure of the PFC to mitigate the impact of stress, could lead to loss of parvalbumin interneurons in the hippocampus in late adolescence or early adulthood. This in turn would lead to hippocampal hyperactivity and dopamine system overdrive, along with the disruption of other hippocampal targets that control affect and cognition[74,94]. If this were indeed the case, one would predict that decreasing the number or intensity of 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 the levels observed in controls[95]. When tested as adults, the MAM-exposed rats treated with diazepam no longer showed hyperactivity of dopamine 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 crucial interval during puberty, the stress-induced damage to the hippocampus seems to be averted, preventing the emergence of psychosis-like behaviour in the adult[95]. Such findings could be readily translated to humans. Thus, in individuals who have a family history of schizophrenia and who 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 thought to mitigate the effects of stress, such as in the *barrios* surrounding São Paulo, Brazil, there is a significantly lower incidence of schizophrenia[96], whereas in individuals who move to environments where there are high levels of social stress, there is a substantial increase in the incidence of schizophrenia[97].

These data therefore suggest that increased stress responsivity, particularly at crucial developmental stages, could lead to the emergence of psychosis in adults. It is also likely that MAM treatment does not cause schizophrenia but instead causes the animal to have increased responses to stress, which leads to the emergence of psychosis[64]. 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 that have been 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[98], as stress seems to be a common underlying risk factor for both conditions (see below), albeit at different developmental periods.

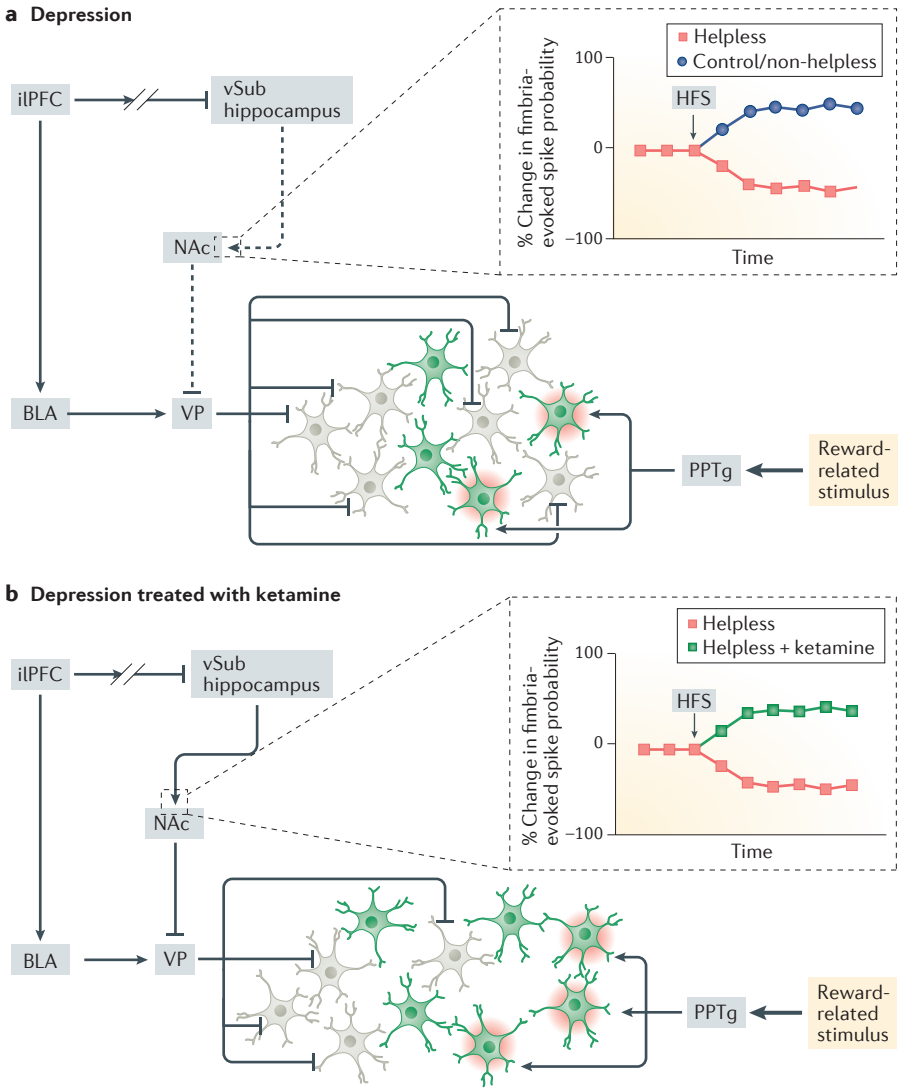


Figure 4 | **Depression circuitry and ketamine actions. a** | In depression in humans, there is reported hyperactivity in subgenual cingulate area 25, which is functionally analogous to the rodent infralimbic prefrontal cortex (ilPFC)[120,121]. In animal models of depression, hyperactivity in the ilPFC drives the basolateral amygdala (BLA). BLA activity, through the ventral pallidum (VP), attenuates reward-related dopamine neuron activity in the medial ventral tegmental area (VTA)[38,39,108]. As a result, reward-related stimuli that normally activate the pedunculopontine tegmentum (PPTg) should produce a significantly smaller dopamine neuron phasic response, leading to a failure to establish a link between stimulus and reward. In the learned helplessness depression model, control rats and non-helpless rats both show fimbria high-frequency stimulation (HFS)-induced long-term potentiation in the ventral subiculum (vSub)–nucleus accumbens (NAc) pathway (see inset), which can offset the BLA–VP-mediated inhibition of the VTA. However, in helpless animals, stimulation instead produces long-term depression, thereby removing this counterbalancing influence. **b** | Ketamine, a fast-acting antidepressant drug, normalizes dopamine neuron firing and re-establishes stimulus-induced long-term potentiation in the vSub–NAc pathway (see inset), thus re-establishing the balance between the dopamine facilitatory and attenuating circuits. The double diagonal line indicates that the pathway between the two areas is indirect. Adapted from a figure provided courtesy of P. Belujon, Université de Poitiers, France.

The dopamine system and depression

Emerging data have also linked dopamine 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[99]. However, many of the symptoms seen in depression — such as anhedonia and amotivation — have been more consistently associated with dysfunctions in the dopamine system[45,100–102]. Studies have identified hyperactivity in PFC area 25 as a correlate of depression[103]. Indeed, any treatment that is effective in treating depression reversed hyperactivity in this region[103]. Furthermore, the amygdala was found to be hyper-responsive to emotionally charged stimuli in depression, primarily to those stimuli that have a negative affective component[104,105].

Animal models of depression are based on the presentation of stressors, particularly those that are uncontrollable or unpredictable[38]. The duration of the stressor affects the magnitude and duration of the negative affective state associated with its withdrawal[56,57]. Thus, acute activation of the dopamine system by amphetamine- or stress-induced dopamine neuron activation is followed by a depression of dopamine 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 after withdrawal. Rats exposed to chronic cold or unpredictable chronic mild stressors (UCMSs), for example, have been shown to exhibit extended decreases (by approximately 50%) in VTA dopamine 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 behavioural despair in depression. Dopamine 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 downmodulation of dopamine neuron activity. Therefore, it is possible that the diminished dopamine neuron activity observed in the UCMS model of depression is driven by hyperactivity in the ilPFC, leading to amygdala overdrive and, through the ventral pallidum, a decrease in the number of dopamine neurons firing primarily in the medial, reward-related VTA (FIG. 4a).

I propose that it is the initial stress-induced activation of VTA dopamine neurons that leads to the compensatory, long-duration downregulation of dopamine neuron population activity on stressor withdrawal. Indeed, studies[106] have shown that activation of the dopamine system during the induction phase increases the susceptibility of rats to social-defeat-induced depression in a manner that is dependent on the ventral hippocampus[107], which is consistent with this model. Moreover, the correlation of decreased

VTA dopamine neuron activity with immobility in the forced swim test is consistent with studies showing that, following UCMS[108] or social defeat[109], activation of dopamine neuron firing can reverse the despair state. Therefore, the initial stress-induced activation of dopamine neuron tonic population activity driven by the hippocampus–ventral striatum–ventral pallidum circuit engenders a compensatory, long-duration downregulation of the VTA through increased activity in the ilPFC–amygdala–ventral pallidum circuit. After the stressor is withdrawn, the downregulation of the VTA is maintained, leading to anhedonia and depression. However, one group found that social-defeat-induced depression was associated with dopamine neuron bursting when tested *in vitro*[110], although population activity was not assessed. Given that phasic activation of dopamine neurons alleviates depression *in vivo*[109] 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 the tonic inhibition present in the intact system.

What causes the downregulation 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 fast-acting antidepressant ketamine[111]. 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 dopamine neuron population activity, whereas the dopamine system in non-helpless rats was unaffected[112]. Furthermore, in control rats and non-helpless rats, tetanic stimulation of the hippocampus–accumbens pathway leads to the induction of long-term potentiation. However, in helpless rats, stimulation resulted instead in long-term depression — that is, the excitatory hippocampal part of the amygdala–hippocampal balance was selectively attenuated in the helpless rats (FIG. 4a).

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

Synthesis

The dopamine system has been implicated in a number of neuropsychiatric disease states. However, evidence indicates that it is not a dysfunction in the dopamine system itself that drives these disorders; instead, the pathophysiology is related to disruptions in the systems that provide afferent control of the dopamine system. Thus, in schizophrenia there are deficits in the hippocampus and PFC that drive dysfunction within the dopamine system. By contrast, in depression the deficits seem to arise in medial frontal cortical regions and involve the amygdala. It is not surprising that dysfunctions in these cortical regions lie at the base of these disorders. I propose that interneuron dysfunction, which is known to have 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 into the developing brain and that interneurons migrate to their final positions to stabilize the excitatory networks that have been laid down[113]. Therefore, it is not surprising that this late-developing system, which is so essential for system-wide stability, is also the most vulnerable to developmental insults. Interneurons are also crucial for the generation of rhythmic activity in brain circuits[114], which is proposed to underlie information transfer and system coherence in the normal functioning brain. It is therefore not surprising that rhythmic activity and coherence across brain regions are found to be disrupted in pathological conditions. And finally, the findings that interneurons are highly susceptible to damage from oxidative stress[115] or glutamatergic drive, particularly early in postnatal development before the protective perineuronal nets are formed[116], suggest that these crucial components of neuronal circuitry show enhanced vulnerability 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, this 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 by targeting specific GABAergic systems in excitatory–inhibitory networks.

Anthony A. Grace is at the Departments of Neuroscience, Psychiatry and Psychology, Department of Neuroscience, A210 Langley Hall, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA.
graceaa@pitt.edu

doi:10.1038/nrn.2016.57
Published online 3 Jun 2016

1. Lauder, J. M. & Bloom, F. E. Ontogeny of monoamine neurons in the locus coeruleus, Raphe nuclei and substantia nigra of the rat. I. Cell differentiation. *J. Comp. Neurol.* **155**, 469–481 (1974).
2. Swanson, L. W. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. *Brain Res. Bull.* **9**, 321–353 (1982).
3. Menegas, W. *et al.* Dopamine neurons projecting to the posterior striatum form an anatomically distinct subclass. *eLife* **4**, e10032 (2015).
4. Sesack, S. R. & Grace, A. A. Cortico–basal ganglia reward network: microcircuitry. *Neuropsychopharmacology* **35**, 27–47 (2010).
5. Ikemoto, S. Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens–olfactory tubercle complex. *Brain Res. Rev.* **56**, 27–78 (2007).
6. Lammel, S. *et al.* Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. *Neuron* **57**, 760–773 (2008).
7. Szabo, J. Organization of the ascending striatal afferents in monkeys. *J. Comp. Neurol.* **189**, 307–321 (1980).
8. Lynd-Balta, E. & Haber, S. N. The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. *Neuroscience* **59**, 625–640 (1994).
9. Grace, A. A. & Bunney, B. S. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons — 1. Identification and characterization. *Neuroscience* **10**, 301–315 (1983).
10. Grace, A. A. & Onn, S. P. Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded *in vitro*. *J. Neurosci.* **9**, 3463–3481 (1989).
11. van Zessen, R., Phillips, J. L., Budygin, E. A. & Stuber, G. D. Activation of VTA GABA neurons disrupts reward consumption. *Neuron* **73**, 1184–1194 (2012).
12. Cohen, J. Y., Haesler, S., Vong, L., Lowell, B. B. & Uchida, N. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* **482**, 85–88 (2012).
13. Grace, A. A. & Bunney, B. S. Paradoxical GABA excitation of nigral dopaminergic cells: indirect mediation through reticulata inhibitory neurons. *Eur. J. Pharmacol.* **59**, 211–218 (1979).

14. Grace, A. A. & Bunney, B. S. Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. *Brain Res.* **333**, 271–284 (1985).
15. Grace, A. A. & Bunney, B. S. The control of firing pattern in nigral dopamine neurons: single spike firing. *J. Neurosci.* **4**, 2866–2876 (1984).
16. Watabe-Uchida, M., Zhu, L., Ogawa, S. K., Vamanrao, A. & Uchida, N. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* **74**, 858–873 (2012).
17. Hjelmstad, G. O., Xia, Y., Margolis, E. B. & Fields, H. L. Opioid modulation of ventral pallidal afferents to ventral tegmental area neurons. *J. Neurosci.* **33**, 6454–6459 (2013).
18. Lecca, S., Melis, M., Luchicchi, A., Muntoni, A. L. & Pistis, M. Inhibitory inputs from rostromedial tegmental neurons regulate spontaneous activity of midbrain dopamine cells and their responses to drugs of abuse. *Neuropsychopharmacology* **37**, 1164–1176 (2016).
19. Balcita-Pedicino, J. J., Omelchenko, N., Bell, R. & Sesack, S. R. The inhibitory influence of the lateral habenula on midbrain dopamine cells: ultrastructural evidence for indirect mediation via the rostromedial mesopontine tegmental nucleus. *J. Comp. Neurol.* **519**, 1143–1164 (2011).
20. Ji, H. & Shepard, P. D. Lateral habenula stimulation inhibits rat midbrain dopamine neurons through a $GABA_A$ receptor-mediated mechanism. *J. Neurosci.* **27**, 6923–6930 (2007).
21. Floresco, S. B., West, A. R., Ash, B., Moore, H. & Grace, A. A. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat. Neurosci.* **6**, 968–973 (2003).
22. Bunney, B. S. & Grace, A. A. Acute and chronic haloperidol treatment: comparison of effects on nigral dopaminergic cell activity. *Life Sci.* **23**, 1715–1727 (1978).
23. Freeman, A. S. & Bunney, B. S. Activity of A9 and A10 dopaminergic neurons in unrestrained rats: further characterization and effects of apomorphine and cholecystokinin. *Brain Res.* **405**, 46–55 (1987).
24. Floresco, S. B., Todd, C. L. & Grace, A. A. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *J. Neurosci.* **21**, 4915–4922 (2001).
25. Modinos, G., Allen, P., Grace, A. A. & McGuire, P. Translating the MAM model of psychosis to humans. *Trends Neurosci.* **38**, 129–138 (2015).
26. Lodge, D. J. & Grace, A. A. The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology* **31**, 1356–1361 (2006).
27. Grace, A. A. Dopamine system dysregulation by the hippocampus: implications for the pathophysiology and treatment of schizophrenia. *Neuropharmacology* **62**, 1342–1348 (2011).
28. Schultz, W. Reward functions of the basal ganglia. *J. Neural Transm. (Vienna)* http://dx.doi.org/10.1007/s00702-016-1510-0 (2016).
29. Grace, A. A. & Bunney, B. S. The control of firing pattern in nigral dopamine neurons: burst firing. *J. Neurosci.* **4**, 2877–2890 (1984).
30. Chergui, K. *et al.* Tonic activation of NMDA receptors causes spontaneous burst discharge of rat midbrain dopamine neurons *in vivo*. *Eur. J. Neurosci.* **5**, 137–144 (1993).
31. Mayer, M. L., Westbrook, G. L. & Guthrie, P. B. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. *Nature* **309**, 261–263 (1984).
32. Belujon, P. & Grace, A. A. Regulation of dopamine system responsivity and its adaptive and pathological response to stress. *Proc. Biol. Sci.* **282**, 20142516 (2015).
33. Grace, A. A. Ventral hippocampus, interneurons and schizophrenia: a new understanding of the pathophysiology of schizophrenia and its implications for treatment and prevention. *Curr. Direct. Psychol. Sci.* **19**, 232–237 (2010).
34. Fanselow, M. S. Contextual fear, gestalt memories, and the hippocampus. *Behav. Brain Res.* **110**, 73–81 (2000).
35. Jarrard, L. E. What does the hippocampus really do? *Behav. Brain Res.* **71**, 1–10 (1995).
36. Maren, S. Neurotoxic or electrolytic lesions of the ventral subiculum produce deficits in the acquisition and expression of Pavlovian fear conditioning in rats. *Behav. Neurosci.* **113**, 283–290 (1999).
37. LeDoux, J. E. Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23**, 155–184 (2000).
38. Chang, C. H. & Grace, A. A. Amygdala–ventral pallidum pathway decreases dopamine activity after chronic mild stress in rats. *Biol. Psychiatry* **76**, 223–230 (2014).
39. Patton, M. H., Bizup, B. T. & Grace, A. A. The infralimbic cortex bidirectionally modulates mesolimbic dopamine neuron activity via distinct neural pathways. *J. Neurosci.* **33**, 16865–16873 (2013).
40. Bunney, B. S., Walters, J. R., Roth, R. H. & Aghajanian, G. K. Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. *J. Pharmacol. Exp. Ther.* **185**, 560–571 (1973).
41. Ungless, M. A., Magill, P. J. & Bolam, J. P. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* **303**, 2040–2042 (2004).
42. Lammel, S. *et al.* Input-specific control of reward and aversion in the ventral tegmental area. *Nature* **491**, 212–217 (2012).
43. Valenti, O., Gill, K. M. & Grace, A. A. Different stressors produce excitation or inhibition of mesolimbic dopamine neuron activity: response alteration by stress pre-exposure. *Eur. J. Neurosci.* **35**, 1312–1321 (2012).
44. Brischoux, F., Chakraborty, S., Brierley, D. I. & Ungless, M. A. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc. Natl Acad. Sci. USA* **106**, 4894–4899 (2009).
45. Eshel, N., Tian, J., Bukwich, M. & Uchida, N. Dopamine neurons share common response function for reward prediction error. *Nat. Neurosci.* **19**, 479–486 (2016).
46. Valenti, O., Lodge, D. J. & Grace, A. A. Aversive stimuli alter ventral tegmental area dopamine neuron activity via a common action in the ventral hippocampus. *J. Neurosci.* **31**, 4280–4289 (2011).
47. Abercrombie, E. D., Keefe, K. A., DiFrischia, D. S. & Zigmond, M. J. Differential effect of stress on *in vivo* dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *J. Neurochem.* **52**, 1655–1658 (1989).
48. Kalivas, P. W. & Duffy, P. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. *Brain Res.* **675**, 325–328 (1995).
49. Holly, E. N. & Miczek, K. A. Ventral tegmental area dopamine revisited: effects of acute and repeated stress. *Psychopharmacology (Berl.)* **233**, 163–186 (2016).
50. Segal, D. S. & Mandell, A. J. Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. *Pharmacol. Biochem. Behav.* **2**, 249–255 (1974).
51. Lodge, D. J. & Grace, A. A. Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. *J. Neurosci.* **28**, 7876–7882 (2008).
52. Badiani, A., Browman, K. E. & Robinson, T. E. Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. *Brain Res.* **674**, 291–298 (1995).
53. Antelman, S. M., Eichler, A. J., Black, C. A. & Kocan, D. Interchangeability of stress and amphetamine in sensitization. *Science* **207**, 329–331 (1980).
54. Chang, C.-H. & Grace, A. A. Amygdala β-noradrenergic receptors modulate delayed down-regulation of dopamine activity following restraint. *J. Neurosci.* **33**, 1441–1450 (2012).
55. Belujon, P., Jakobowski, N. L., Dollish, H. K. & Grace, A. A. Withdrawal from acute amphetamine induces an amygdala-driven attenuation of dopamine neuron activity: reversal by ketamine. *Neuropsychopharmacology* **41**, 619–627 (2015).
56. Koob, G. F., Stinus, L., Le Moal, M. & Bloom, F. E. Opponent process theory of motivation: neurobiological evidence from studies of opiate dependence. *Neurosci. Biobehav. Rev.* **13**, 135–140 (1989).
57. Koob, G. F. & Le Moal, M. Review. Neurobiological mechanisms for opponent motivational processes in addiction. *Phil. Trans. R. Soc. B* **363**, 3113–3123 (2008).
58. Kapur, S. & Remington, G. Dopamine D_2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol. Psychiatry* **50**, 873–883 (2001).
59. Janowsky, D. S., El-Yousef, K., Davis, J. M. & Sekerke, H. J. Provocation of schizophrenic symptoms by intravenous administration of methylphenidate. *Arch. Gen. Psychiatry* **28**, 185–191 (1973).
60. Angrist, B., Sathananthan, G., Wilk, S. & Gershon, S. Amphetamine psychosis: behavioral and biochemical aspects. *J. Psychiatr. Res.* **11**, 13–23 (1974).
61. Laruelle, M. & Abi-Dargham, A. Dopamine as the wind of psychotic fire: new evidence from brain imaging studies. *J. Psychopharmacol.* **13**, 358–371 (1999).
62. Grace, A. A. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* **41**, 1–24 (1991).
63. Suddath, R. L., Christison, G. W., Torrey, E. F., Casanova, M. F. & Weinberger, D. R. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N. Engl. J. Med.* **322**, 789–794 (1990).
64. Grace, A. A. Dopamine system dysregulation and the pathophysiology of schizophrenia: insights from the methylazoxymethanol acetate model. *Biol. Psychiatry* http://dx.doi.org/10.1016/j.biopsych.2015.11.007 (2015).
65. Heckers, S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus* **11**, 520–528 (2001).
66. Malaspina, D. *et al.* SPECT study of visual fixation in schizophrenia and comparison subjects. *Biol. Psychiatry* **46**, 89–93 (1999).
67. Medoff, D. R., Holcomb, H. H., Lahti, A. C. & Tamminga, C. A. Probing the human hippocampus using rCBF: contrasts in schizophrenia. *Hippocampus* **11**, 543–550 (2001).
68. Silbersweig, D. A. *et al.* A functional neuroanatomy of hallucinations in schizophrenia. *Nature* **378**, 176–179 (1995).
69. Lewis, D. A., Hashimoto, T. & Volk, D. W. Cortical inhibitory neurons and schizophrenia. *Nat. Rev. Neurosci.* **6**, 312–324 (2005).
70. Benes, F. M. *et al.* Regulation of the GABA cell phenotype in hippocampus of schizophrenics and bipolars. *Proc. Natl Acad. Sci. USA* **104**, 10164–10169 (2007).
71. Stone, J. M. *et al.* Altered relationship between hippocampal glutamate levels and striatal dopamine function in subjects at ultra high risk of psychosis. *Biol. Psychiatry* **68**, 599–602 (2010).
72. Moore, H., Ghajarnia, M., Geyer, M., Jentsch, J. D. & Grace, A. A. Selective disruption of prefrontal and limbic corticostriatal circuits by prenatal exposure to the DNA methylation agent methylazoxymethanol acetate (MAM): anatomical, neurophysiological and behavioral studies. *Schizophr. Res.* **49**, 48 (2001).
73. Hradetzky, E. *et al.* The methylazoxymethanol acetate (MAM-E17) rat model: molecular and functional effects in the hippocampus. *Neuropsychopharmacology* **37**, 364–377 (2012).
74. Grace, A. A. in *Neurodevelopment and Schizophrenia* (eds Keshavan, M. S., Kennedy, J. L. & Murray, R. M.) 273–294 (Cambridge Univ. Press, 2004).
75. Lodge, D. J., Behrens, M. M. & Grace, A. A. A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J. Neurosci.* **29**, 2344–2354 (2009).
76. Lodge, D. J. & Grace, A. A. Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. *J. Neurosci.* **27**, 11424–11430 (2007).
77. Gill, K. M. & Grace, A. A. Corresponding decrease in neuronal markers signals progressive parvalbumin neuron loss in MAM schizophrenia model. *Int. J. Neuropsychopharmacol.* **17**, 1609–1619 (2014).
78. Egerton, A. *et al.* Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol. Psychiatry* **74**, 106–112 (2013).
79. Kapur, S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* **160**, 13e23 (2003).
80. Herman, J. P. & Mueller, N. K. Role of the ventral subiculum in stress integration. *Behav. Brain Res.* **174**, 215–224 (2006).
81. Groenewegen, H. J., Vermeulen-Van der Zee, E., te Kortschot, A. & Witter, M. P. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of *Phaseolus vulgaris* leucoagglutinin. *Neuroscience* **23**, 103–120 (1987).
82. Jay, T. M. & Witter, M. P. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaseolus vulgaris*-leucoagglutinin. *J. Comp. Neurol.* **313**, 574–586 (1991).

83. Sirota, A. *et al.* Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. *Neuron* **60**, 683–697 (2008).
84. Owens, D. G., Miller, P., Lawrie, S. M. & Johnstone, E. C. Pathogenesis of schizophrenia: a psychopathological perspective. *Br. J. Psychiatry* **186**, 386–393 (2005).
85. Sapolsky, R. M. Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. *Stress* **1**, 1–19 (1996).
86. Czeh, B. *et al.* Chronic stress decreases the number of parvalbumin-immunoreactive interneurons in the hippocampus: prevention by treatment with a substance P receptor (NK1) antagonist. *Neuropsychopharmacology* **30**, 67–79 (2005).
87. Rosenkranz, J. A. *et al.* Opposing influence of basolateral amygdala and footshock stimulation on neurons of the central amygdala. *Biol. Psychiatry* **59**, 801–811 (2006).
88. Rosenkranz, J. A. & Grace, A. A. Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *J. Neurosci.* **21**, 4090–4103 (2001).
89. Berretta, S. *et al.* Long-term effects of amygdala GABA receptor blockade on specific subpopulations of hippocampal interneurons. *Hippocampus* **14**, 876–894 (2004).
90. Zimmerman, E. C., Bellaire, M., Ewing, S. G. & Grace, A. A. Abnormal stress responsivity in a rodent developmental disruption model of schizophrenia. *Neuropsychopharmacology* **38**, 2131–2139 (2013).
91. Rosenkranz, J. A., Moore, H. & Grace, A. A. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. *J. Neurosci.* **23**, 11054–11064 (2003).
92. Rosenkranz, J. A. & Grace, A. A. Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons *in vivo*. *J. Neurosci.* **22**, 324–337 (2002).
93. Lewis, D. A., Hashimoto, T. & Morris, H. M. Cell and receptor type-specific alterations in markers of GABA neurotransmission in the prefrontal cortex of subjects with schizophrenia. *Neurotox. Res.* **14**, 237–248 (2008).
94. Thompson, J. L., Pogue-Geile, M. F. & Grace, A. A. The interactions among developmental pathology, dopamine, and stress as a model for the age of onset of schizophrenia symptomatology. *Schizophr. Bull.* **30**, 875–900 (2004).
95. Du, Y. & Grace, A. A. Peripubertal diazepam administration prevents the emergence of dopamine system hyperresponsivity in the MAM developmental disruption model of schizophrenia. *Neuropsychopharmacology* **38**, 1881–1888 (2013).
96. Menezes, P. R. *et al.* Incidence of first-contact psychosis in Sao Paulo, Brazil. *Br. J. Psychiatry Suppl.* **51**, s102–s106 (2007).
97. Hickling, F. W. Double jeopardy: psychopathology of black mentally ill returned migrants to Jamaica. *Int. J. Soc. Psychiatry* **37**, 80–89 (1991).
98. Gatt, J. M., Burton, K. L., Williams, L. M. & Schofield, P. R. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. *J. Psychiatr. Res.* **60**, 1–13 (2015).
99. Carlsson, A. The contribution of drug research to investigating the nature of endogenous depression. *Pharmakopsychiatr. Neuropsychopharmakol.* **9**, 2–10 (1976).
100. Wise, R. A. Dopamine, learning and motivation. *Nat. Rev. Neurosci.* **5**, 483–494 (2004).
101. Wise, R. A. Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotox. Res.* **14**, 169–183 (2008).
102. Pandit, R. *et al.* Melanocortin 3 receptor signaling in midbrain dopamine neurons increases the motivation for food reward. *Neuropsychopharmacology* http://dx.doi.org/10.1038/npp.2016.19 (2016).
103. Mayberg, H. S. *et al.* Deep brain stimulation for treatment-resistant depression. *Neuron* **45**, 651–660 (2005).
104. Leppanen, J. M. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr. Opin. Psychiatry* **19**, 34–39 (2006).
105. Kalia, M. Neurobiological basis of depression: an update. *Metabolism* **54**, 24–27 (2005).
106. Chaudhury, D. *et al.* Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* **493**, 532–536 (2013).
107. Bagot, R. C. *et al.* Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nat. Commun.* **6**, 7062 (2015).
108. Tye, K. M. *et al.* Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature* **493**, 537–541 (2013).
109. Friedman, A. K. *et al.* Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science* **344**, 313–319 (2014).
110. Krishnan, V. *et al.* Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* **131**, 391–404 (2007).
111. Berman, R. M. *et al.* Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **47**, 351–354 (2000).
112. Belujon, P. & Grace, A. A. Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. *Biol. Psychiatry* **76**, 927–936 (2014).
113. Sultan, K. T., Brown, K. N. & Shi, S. H. Production and organization of neocortical interneurons. *Front. Cell Neurosci.* **7**, 221 (2013).
114. Buzsaki, G. & Draguhn, A. Neuronal oscillations in cortical networks. *Science* **304**, 1926–1929 (2004).
115. Steullet, P. *et al.* Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology? *Schizophr. Res.* http:dx.doi.org/10.1016/j.schres.2014.06.021 (2014).
116. Cabungcal, J. H. *et al.* Perineuronal nets protect fast-spiking interneurons against oxidative stress. *Proc. Natl Acad. Sci. USA* **110**, 9130–9135 (2013).
117. Moore, H., Todd, C. L. & Grace, A. A. Striatal extracellular dopamine levels in rats with haloperidol-induced depolarization block of substantia nigra dopamine neurons. *J. Neurosci.* **18**, 5068–5077 (1998).
118. Hollerman, J. R., Abercrombie, E. D. & Grace, A. A. Electrophysiological, biochemical, and behavioral studies of acute haloperidol-induced depolarization block of nigral dopamine neurons. *Neuroscience* **47**, 589–601 (1992).
119. Grace, A. A. in *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience* (eds Solanto, M. V., Arnsten, A. F. T. & Castellanos, F. X.) 134–157 (Oxford Univ. Press, 2000).
120. Room, P., Russchen, F. T., Groenewegen, H. J. & Lohman, A. H. Efferent connections of the prelimbic (area 32) and the infralimbic (area 25) cortices: an anterograde tracing study in the cat. *J. Comp. Neurol.* **242**, 40–55 (1985).
121. Reep, R. Relationship between prefrontal and limbic cortex: a comparative anatomical review. *Brain Behav. Evol.* **25**, 5–80 (1984).

Acknowledgements
The author thanks P. Belujon for her help in constructing the figures. This work was supported by US Public Health Service grants MH57440, MH191180 and MH104320.

Competing interests statement
The author declares competing interests: see Web version for details.