Published in final edited form as:

Int J Dev Neurosci. 2011 May ; 29(3): 207–213. doi:10.1016/j.ijdevneu.2010.08.002.

Developmental pathology, dopamine, stress and schizophrenia

Daniel J. Lodge^{1,*} and Anthony A. Grace²

¹Department of Pharmacology & Center for Biomedical Neuroscience, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

²Departments of Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Psychological stress is a contributing factor for a wide variety of neuropsychiatric diseases including substance use disorders, anxiety, depression and schizophrenia. However, it has not been conclusively determined how stress augments the symptoms of these diseases. Here we review evidence that the ventral hippocampus may be a site of convergence whereby a number of seemingly discrete risk factors, including stress, may interact to precipitate psychosis in schizophrenia. Specifically, aberrant hippocampal activity has been demonstrated to underlie both the elevated dopamine neuron activity and associated behavioral hyperactivity to dopamine agonists in a verified animal model of schizophrenia. In addition, stress, psychostimulant drug use, prenatal infection and select genetic polymorphisms all appear to augment ventral hippocampal function that may therefore exaggerate or precipitate psychotic symptoms. Such information is critical for our understanding into the pathology of psychiatric disease with the ultimate aim being the development of more effective therapeutics.

Psychological stress is a contributing factor for a wide variety of neuropsychiatric diseases including substance use disorders, anxiety, depression and schizophrenia (Nuechterlein and Dawson, 1984; Piazza et al., 1991; Piazza and Le Moal, 1996; McEwen, 2000; Corcoran et al., 2003; Millan, 2003; Thompson et al., 2007b). The central response to a psychological stressor has been extensively examined with the vast majority of work focusing on the regulation of the hypothalamo-pituitary-adrenal (HPA) axis (McEwen, 2007; Miller et al., 2007). Thus, upon exposure to a psychological stressor an animal exhibits several physiological and behavioral responses, including an increase in circulating cortisol and sympathetic nervous system activation (McEwen, 2007; Miller et al., 2007). Although the 'stress-response' is an evolutionarily conserved response vital to the survival of a species, the inability to control or escape a stressor can prove to be deleterious. As yet, it has been difficult to pinpoint what aspects of the stress response contribute to disease processes or augmented symptomology; thus, understanding how stress precipitates or exacerbates psychiatric disease is of critical importance. Given the high co-morbidity between stress and neuropsychiatric diseases, it is likely that stressors engage similar neural systems, with one particular region being the hippocampus.

© 2010 ISDN. Published by Elsevier Ltd. All rights reserved

*Correspondence should be addressed to Dr. Daniel Lodge, Department of Pharmacology & Center for Biomedical Neuroscience, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. LodgeD@uthscsa.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Stress and the hippocampus

The hippocampus is a temporal lobe structure that has a unique role in the integration of declarative and spatial memory processes (Squire and Zola-Morgan, 1991; Squire, 1992). The hippocampus is a heterogeneous structure that, in the rat, is segregated into dorsal and ventral subregions representing functionally distinct structures (Fanselow and Dong, 2010). Thus, the dorsal hippocampus, analogous to the posterior hippocampus in primates, is thought to subserve the more cognitive functions of the hippocampus whereas the ventral regions (anterior in primates) are thought to reflect more limbic portions of the hippocampus (Fanselow and Dong, 2010). Indeed, the ventral hippocampus is thought to be the principle hippocampal area associated with the negative regulation of HPA function in response to psychological stressors (Herman et al., 1992; Herman et al., 1995; Herman and Mueller, 2006). In addition, the ventral hippocampus is not only associated with the stress response, but can also regulate emotion and affect and thus represents a potential site of convergence by which stress could augment symptoms associated with neuropsychiatric diseases. Indeed, alterations in ventral hippocampal structure and function are routinely associated with psychological disorders including schizophrenia (Nelson et al., 1998; Harrison, 1999; Shenton et al., 2001; Heckers and Konradi, 2002; Heckers, 2004).

As mentioned above, the ventral hippocampus (analogous to the anterior hippocampus in primates) is a principle component of the stress response. Indeed, activation of the hippocampus decreases glucocorticoid secretion in both rat and human (Rubin et al., 1966; Dunn and Orr, 1984). Similarly, lesion and ablation studies demonstrate that decreased hippocampal function increases corticosterone and/or ACTH release (Fendler et al., 1961; Knigge, 1961; Knigge and Hays, 1963; Sapolsky et al., 1984). Interestingly, it appears that hippocampal regulation of the HPA axis appears to be stressor-specific. Thus, the hippocampus appears to be engaged during psychological stressors such as restraint (Herman et al., 1995; Valenti and Grace, 2008; Greetfeld et al., 2009; O'Mahony et al., 2010), fear-conditioning (Phillips and LeDoux, 1992; Maren and Quirk, 2004; Lodge et al., 2009) or novelty (Knight, 1996; Lisman and Grace, 2005). Furthermore, neurons of the vHipp are activated by footshock as well as by locus coeruleus afferents (Lipski and Grace, 2009). In contrast, more physiological stressors such as ether inhalation or hypoxia do not appear to be affected by hippocampal manipulations (Mueller et al., 2004; Jankord and Herman, 2008). Interestingly, it is these psychological stressors that are known to augment symptoms of neuropsychiatric diseases such as schizophrenia (Nuechterlein and Dawson, 1984; Corcoran et al., 2003; Thompson et al., 2007a; Thompson et al., 2007b).

A role for the hippocampus in schizophrenia has long been suggested based on anatomical studies in patients (Nelson et al., 1998; Harrison, 1999; Shenton et al., 2001; Heckers and Konradi, 2002; Heckers, 2004). Thus, one of the more robust postmortem findings is a decreased hippocampal volume in human schizophrenia patients (Nelson et al., 1998; Harrison, 1999; Shenton et al., 2001; Heckers and Konradi, 2002; Heckers, 2004); however how aberrant hippocampal transmission contributes to the positive symptoms of the disease is not immediately apparent. We have recently demonstrated that the hippocampus plays a critical role in the regulation of dopamine neuron activity states and, moreover, may be a principal cause for the aberrant dysregulation of the dopamine system in diseases such as schizophrenia and psychostimulant abuse (Lodge and Grace, 2007, 2008).

Hippocampus and Dopamine System Regulation

Aberrant dopamine system function has been demonstrated to play a significant role in the expression of a number of neuropsychiatric diseases including drug abuse and schizophrenia (Koob and Le Moal, 1997; Berridge and Robinson, 1998; Laruelle and Abi-Dargham, 1999;

Carlsson et al., 2000; Abi-Dargham, 2004). Thus, schizophrenia patients display a significantly enhanced response to dopamine agonists, such as amphetamine (Snyder, 1976) and human imaging data has demonstrated increases in mesolimbic dopamine transmission in patients that is directly correlated with the positive symptoms of the disease (Laruelle and Abi-Dargham, 1999; Abi-Dargham, 2004). It should be noted that while the dopamine-dependent symptoms generally relate to the psychotic symptoms of schizophrenia, recent studies have suggested that an increase in dopamine transmission may also play a role in cognitive disruption (Kellendonk et al., 2006). Despite this, a considerable amount of research into the pathophysiology of schizophrenia has failed to demonstrate a primary pathology within the dopamine cell body region leading to the suggestion that the pathology may actually be upstream of the dopamine system resulting in a dysregulation of dopamine system function.

Extensive post-mortem investigations, combined with functional and structural imaging data, have demonstrated reliable pathological changes that are limited to a number of brain regions, with a prominent structures being the hippocampus (Nordahl et al., 1996; Heckers et al., 1998; Nelson et al., 1998; Harrison, 1999; Medoff et al., 2001; Meyer-Lindenberg et al., 2001; Shenton et al., 2001; Heckers and Konradi, 2002; Heckers, 2004; Lahti et al., 2006; Weiss et al., 2006). Understanding how these structures regulate dopamine system function is critical for our understanding into the potential dysregulation of the dopamine system in schizophrenia.

An early preclinical study demonstrated that vHipp activation induces increases in dopamine efflux in forebrain targets, such as the nucleus accumbens, suggesting that the vHipp can augment dopamine neuron activity (Legault and Wise, 1999). However, given that the vHipp does not directly innervate the dopamine neurons of the midbrain, the mechanisms underlying this effect were not immediately apparent. The use of in vivo electrophysiology to examine the afferent regulation of dopamine system function has provided significant information linking alterations in neurotransmitter levels with distinct dopamine neuron activity states in the ventral mesencephalon. It was demonstrated over 25 years ago that VTA dopamine neurons can be identified based solely on their electrophysiological waveform and firing rate/pattern when recorded extracellularly in chloral hydrate anesthetized, adult rats (Grace and Bunney, 1983; Grace et al., 2007). Specifically, dopamine neurons display a biphasic, long-duration action potential greater than 2msec in duration, mirroring that observed by differentiation of the intracellular waveform (Grace and Bunney, 1983). Being able to reliably distinguish dopamine neurons in vivo led to the discovery that dopamine neurons demonstrate three distinct, independently regulated, patterns of activity. The first is a tonic, single-spike firing mode. Thus, the biophysical properties of dopamine neurons limit the range of activity and, as such, dopamine neurons in vivo typically fire between 1 and 10 Hz with an average firing rate around 4.5Hz (Grace and Bunney, 1984b). This spontaneous activity is observed in vitro and has been demonstrated to be intrinsically generated by pacemaker conductances that can be further modified by afferent inputs (Grace and Bunney, 1984b). The second activity state of the dopamine neuron is known as burst firing and is considered to be the functionally relevant signal conveyed to post-synaptic targets to indicate reward or to encode an error prediction signal (Schultz, 1998). Dopamine neuron bursts are largely independent of baseline firing rates and are described as transient periods of high frequency activity, requiring glutamatergic and other afferent input (Grace and Bunney, 1984a). Thus, neurons recorded in vitro do not display spontaneous burst firing, nor can they be made to burst by the bath application of glutamate alone (Grace and Onn, 1989; Seutin et al., 1990; Mercuri et al., 1992; Wang and French, 1993). We have reported that dopamine neurons require a tonic input from the laterodorsal tegmental nucleus in order for glutamate to induce burst firing in dopamine neurons (Lodge and Grace, 2006b). In addition to a permissive input, glutamatergic inputs,

such as those arising from the pedunculo pontine tegmental area, can regulate the amount of burst firing emitted by dopamine neurons. Thus, iontophoretically applied glutamate or activation of glutamatergic afferents will increase dopamine neuron burst firing in vivo (Grace and Bunney, 1984a; Floresco et al., 2003; Lodge and Grace, 2006b, a).

The third activity state of the dopamine neuron relates to the state of spontaneous activity, in that dopamine neurons can either be in a spontaneously firing state or an inactive or hyperpolarized state. When recorded intracellularly in vivo, approximately 50% of the VTA dopamine neurons do not display spontaneous activity; rather these neurons appear to be bombarded by GABAergic inhibitory post-synaptic potentials (IPSPs) (Grace and Bunney, 1985). These IPSPs likely arise from GABAergic neurons located in the ventral pallidum (Floresco et al., 2001; Floresco et al., 2003); neurons that are known to fire spontaneously at high rates (Johnson and Napier, 1997). Although perhaps not immediately apparent, this spontaneous activity state is of critical importance with respect to dopamine system function. Thus, changes in afferent activity can result in increases or decreases in the number of spontaneously active dopamine neurons (Lodge and Grace, 2006a). Moreover, given that burst firing is an NMDA-dependent process, burst firing only occurs in dopamine neurons that are spontaneously active, due to magnesium blockade of the NMDA receptor at hyperpolarized membrane potentials (Mayer et al., 1984). Thus, whereas burst firing is the behaviorally relevant signal, the number of cells that are active at a given time sets the gain of the system, or the number of dopamine neurons that can be made to burst fire. The region that has been demonstrated to selectively regulate dopamine neuron population activity is the hippocampus (Floresco et al., 2001; Floresco et al., 2003; Lodge and Grace, 2006a).

NMDA activation of the vHipp produces a 2-fold increase in the number of spontaneously active dopamine neurons observed per electrode track, a standard measure of the activity of the population of dopamine neurons in the VTA (Floresco et al., 2001; Floresco et al., 2003; Lodge and Grace, 2006a). This involves a polysynaptic pathway starting with a glutamate-mediated increase in accumbens output which in turn inhibits ventral pallidal activity, resulting in a disinhibition of dopamine neuron activity (Floresco et al., 2001; Floresco et al., 2003). Indeed, intra-accumbens kynurenic acid can prevent the vHipp mediated increase in dopamine neuron population activity, whereas intra-VP bicuculline will promote a similar increase in activity (Floresco et al., 2001; Floresco et al., 2003). Thus, the vHipp appears to be critical for the assigning of gain to the dopamine signal (Lodge and Grace, 2006a). More specifically, during periods of low stimulation, the number of spontaneously active dopamine neurons will be relatively low and any phasic signal will likely have little consequence. In contrast, during extremely salient conditions augmented hippocampal activity will increase the number of active dopamine neurons that will drastically enhance the phasic signal and promote attention to the stimulus. Thus, normal hippocampal function is essential for ascribing salience to an environmental signal based on context (Lisman and Grace, 2005). Furthermore, a pathological alteration in hippocampal activity is likely to result in a dysregulation of dopamine system function. Indeed, a routine observation in post-mortem studies as well as those from human imaging studies is that the hippocampus is a site of pathology in schizophrenia patients (Nordahl et al., 1996; Heckers et al., 1998; Nelson et al., 1998; Harrison, 1999; Medoff et al., 2001; Meyer-Lindenberg et al., 2001; Shenton et al., 2001; Heckers and Konradi, 2002; Heckers, 2004; Lahti et al., 2006; Weiss et al., 2006). On the other hand, recent studies have focused on how alterations in the hippocampus may first occur early in development to lead to this alteration in regulation in the adult. To examine the relationship between hippocampal dysfunction and dopamine activity as a consequence of developmental alteration we utilized an animal model of schizophrenia, the MAM E17 treated rat (Lodge and Grace, 2007; Lodge and Grace, 2009).

Developmental Disruption as a Model of Schizophrenia

There are a number of diverse animal models of schizophrenia, based on genetic, pharmacological or neurodevelopmental models. One model which was demonstrated by us and verified by others, involves injecting pregnant female rats with a mitotoxin, methylazoxymethanol acetate (MAM), specifically on gestational day 17 (Grace and Moore, 1998; Moore et al., 2006). This treatment has no observable effects on the dam; however her adult offspring display a variety of histological, behavioral and neurophysiological abnormalities consistent with deficits observed in human patients (for review see: (Lodge and Grace, 2009)). Using this model, we have recently investigated the regulation of dopamine system function in an attempt to provide a possible correlation between the dopamine-dependent psychosis and hippocampal pathology observed in patients. Interestingly, when examining baseline dopamine neuron population activity, the only observable difference between MAM and saline treated rats was the number of neurons spontaneously active per electrode track (Lodge and Grace, 2007). Specifically, MAM-treated rats displayed a ~2-fold increase in the number of spontaneously active dopamine neurons with no significant differences in average firing rate or burst firing of active cells (Lodge and Grace, 2007). To determine whether the regulation of dopamine system responsivity was preserved in the MAM-treated rats, we examined the effect of NMDA activation of two afferent regions known to differentially regulate burst firing and population activity, namely the PPTg and vHipp, respectively (Lodge and Grace, 2006a). Whereas the ability of PPTg afferents to induce burst firing remained intact in the MAM model, vHipp activation was not able to significantly increase dopamine neuron population activity, likely attributable to a ceiling effect (Lodge and Grace, 2007). Given evidence for pathology within the hippocampus, we investigated whether the aberrant increase in dopamine population activity in MAM rats was attributable to an increase in vHipp activity. Indeed, MAM-treated rats display a 3-fold increase in spontaneous vHipp activity when compared to control rats (Lodge and Grace, 2007). Furthermore, this augmented vHipp activity appeared to be the cause of the aberrant dopamine system function, since inactivation of the vHipp with the sodium channel blocker TTX was able to reverse the increased dopamine neuron population activity (Lodge and Grace, 2007). These data suggest that the aberrant dopamine system function observed in MAM-treated rats can be directly attributable to an augmented vHipp activity. To determine whether this increase in dopamine neuron population activity was responsible for the behavioral hyper-responsivity to psychomotor stimulants, a constant observation in both animal models of schizophrenia as well as in schizophrenia patients, we examined the locomotor-enhancing effects of amphetamine. The administration of low doses of amphetamine (0.5mg/kg i.p.) produced a significantly greater locomotor response in MAM-treated rats and this was completely normalized by vHipp inactivation (Lodge and Grace, 2007). Importantly, TTX inactivation of the vHipp produced no significant effects on amphetamine-induced locomotion in control animals. These data parallel that observed in our electrophysiological studies, leading us to posit that the aberrant increase in dopamine system function and associated behaviors can be directly attributed to an augmented vHipp activity (Figure 1). Interestingly, recent imaging studies from a number of distinct labs have demonstrated an increase in regional cerebral blood volume/flow in anterior hippocampal regions of human schizophrenia patients (Nordahl et al., 1996; Heckers et al., 1998; Lahti et al., 2006). Moreover, this increased activity can be directly correlated with clinical measures of positive symptoms of the disease.

Hippocampus and risk factors for schizophrenia

Given the central role of the hippocampus in the regulation of dopamine neuron activity, this region may be a site of convergence by which a number of risk factors can contribute to or

exacerbate the dopamine-dependent symptoms of diseases such as schizophrenia. For example, the vHipp is known to be activated by psychological stressors suggesting that stress may augment dopamine system function; indeed, there is a significant literature demonstrating that psychological stressors, such as footshock or restraint, increase dopamine efflux in the nucleus accumbens (Kalivas and Duffy, 1995; Takahashi et al., 1998; Chrapusta et al., 2003; Young, 2004; Doherty and Gratton, 2007). These data suggest that stress augments dopamine neuron activity; however a significant literature demonstrates that noxious stimuli in the form of acute foot or tail shock stress actually inhibit dopamine neuron activity (Grace and Bunney, 1979; Ungless et al., 2004), although a sub-population of neurons are excited by aversive stimuli (Brischoux et al., 2009; Matsumoto and Hikosaka, 2009). Thus, there appears to be a disconnect between the inhibitory effects of aversive stimuli on dopamine neuron activity and the excitatory effects on dopamine efflux in forebrain targets. One reason for this apparent disparity may be the temporal resolution of the techniques used; i.e. the decrease in dopamine neuron activity, examined by electrophysiology, is time-locked to the stimulus, usually lasting for seconds, whereas changes in dopamine efflux, measured using microdialysis, occur on the order of minutes and can persist for hours following the termination of the stimulus. To more fully understand the relationship between the effects of aversive stimuli on dopamine system function, we have recently investigated the effect of stressors on the population of dopamine neurons located in the VTA. When examined in isolation, acute aversive stimuli inhibit the activity of the majority of dopamine neurons, consistent with a wealth of previously published data. Interestingly, a different effect on dopamine system function was revealed when the population of dopamine neurons were examined as a whole. Specifically, a pronounced increase in the number of spontaneously active dopamine neurons was observed following noxious foot-shock stress (Valenti and Grace, 2008). Moreover, in contrast to the transient, time-locked inhibition of dopamine neuron activity, the increase in dopamine neuron population activity persisted for ~ 90 minutes. Similarly, exposure to a psychological stressor such as restraint stress induced a similar but sustained increase in dopamine neuron population activity, suggesting that psychological stressors can indeed augment dopamine neuron activity and provide a physiological explanation for the stress-induced increase in dopamine efflux consistently observed in rodents. Moreover, this paradigm produced a robust activation of the vHipp, as determined by c-fos immunohistochemistry, suggesting that the increase in dopamine system function may be secondary to vHipp activation (Valenti and Grace, 2008). Indeed this was confirmed in subsequent studies where vHipp inactivation was able to normalize both the stress-induced increase in dopamine neuron population activity as well as the stress-augmented behavioral hyper-responsivity to amphetamine (Valenti and Grace, 2008).

While stress has been consistently demonstrated to augment symptoms of schizophrenia, co-morbid substance use disorders are also a significant confound to treatment and outcome (Dixon, 1999). Thus, schizophrenia patients display higher than normal levels of illicit drug use, with cannabis and cocaine being the most often abused (Dixon, 1999). Psychostimulants have been demonstrated to precipitate psychosis-like symptoms at relatively low doses in schizophrenia patients, whereas the repeated intake of stimulant drugs can produce a psychotic state in the general population (Snyder, 1976). It is widely known that psychomotor stimulants such as cocaine and amphetamine produce their acute effects by inhibiting dopamine transporters (Ritz et al., 1987), resulting in increased dopamine levels throughout the neuraxis; however, the consequence of this enhanced dopamine signaling in regions such as the hippocampus has not been conclusively demonstrated. The hippocampus receives a significant dopamine innervation that acts, in part, to regulate long-term plasticity (Frey et al., 1990; Frey et al., 1991; Matthies et al., 1997; Granado et al., 2008). Thus, it is likely that repeated stimulant administration produces enduring changes in hippocampal information processing. Indeed, the repeated

administration of amphetamine, followed by a period of withdrawal, induces a significant increase in both single-spike and burst firing of vHipp pyramidal neurons (Lodge and Grace, 2008). This increase in vHipp activity is associated with a corresponding increase in VTA dopamine neuron population activity and an enhanced behavioral response to a challenge dose of amphetamine. Moreover, the augmented dopamine system function observed following chronic amphetamine administration essentially mirrors that observed in the MAM-treated rat and is completely normalized by vHipp inactivation (Lodge and Grace, 2008).

Hippocampal hyperactivity and GABAergic dysfunction

Taken together, the vHipp represents a site of convergence whereby stress or substance use can augment neuronal systems that are already pathologically altered in schizophrenia. The reasons underlying this pathological increase in hippocampal activity have not been conclusively demonstrated; however there is increasing evidence that it may be attributable to alterations in GABAergic transmission (Woo et al., 1998; Zhang and Reynolds, 2002; Lewis et al., 2005; Lodge et al., 2009). Thus, a decrease in GABA system function is the most consistent observation in both human and animal models of schizophrenia. Moreover, it appears that the decrease in GABAergic transmission can be attributed to a subset of interneurons, i.e. the perisomatic targeting interneurons that contain the calcium binding protein parvalbumin (Woo et al., 1998; Zhang and Reynolds, 2002; Lewis et al., 2005; Lodge et al., 2009). A decrease in parvalbumin expression is observed throughout the cortex and hippocampus in a wide variety of diverse animal models (Berretta et al., 2004; Penschuck et al., 2006; Abdul-Monim et al., 2007; Harte et al., 2007; Lodge et al., 2009) as well as in post-mortem studies from schizophrenia patients (Woo et al., 1998; Zhang and Reynolds, 2002; Lewis et al., 2005). Similarly, we have reported a decrease in parvalbumin interneuron staining throughout the medial prefrontal cortex and ventral subiculum of the hippocampus in the MAM model (Lodge et al., 2009). Parvalbumin interneurons are fast-spiking and extensively connected with wide dendritic arbors, making them perfectly situated to regulate coordinated neuronal activity. Indeed, fast-spiking interneurons are critical for the coordinated, high-frequency gamma rhythms observed during task performance in EEG studies; rhythmic states that are known to be disrupted in schizophrenia (Gonzalez-Hernandez et al., 2003; Schmiedt et al., 2005; Cho et al., 2006; Basar-Eroglu et al., 2007). To determine whether the decrease in interneuron function observed in the MAM model (~25%) was sufficient to alter information processing, we examined evoked gamma oscillations throughout the vHipp during the latent inhibition behavioral paradigm (Lodge et al., 2009). Interestingly, the behavioral deficits in latent inhibition observed in MAM-treated rats were correlated with an inability to recruit cortical and hippocampal ensembles as determined by a dramatically lower evoked gamma-band activity when compared to saline-treated control rats. Thus, the decrease in parvalbumin interneuron function appears sufficient to drastically alter coordinated neuronal activity. Moreover we posit that such a deficit in interneuron function is likely responsible for the aberrant vHipp activity thought to underlie the dopamine-dependent psychosis in schizophrenia. Furthermore, this GABAergic dysfunction may be attributed, at least in part, to alterations in a number of genes, known to have associations with schizophrenia. Indeed, a significant number of GABA-related genes have been identified in genetic association studies of schizophrenia patients. Such genes include enzymes for GABA synthesis (GAD1 [2q31]), ionotropic GABA_A receptors (GABRA1 [5q34-q35], GABRA6 [5q34]), and metabotropic GABA_B receptors (GABRB2 [5q34]) -- for review see (Cherlyn et al., 2010). In addition, genes for which an association with GABAergic system function may not be as apparent can actually induce similar deficits in interneuron function. For example, it has been recently demonstrated that neuregulin 1 and its receptor ERBB4, significant risk genes for schizophrenia, actually control the developmental connectivity of parvalbumin-containing interneurons throughout the

hippocampus (Fazzari et al., 2010). Additionally, prenatal infection, a significant environmental risk factor for schizophrenia (Yolken and Torrey, 1995), also produces alterations in hippocampal structure and function. Specifically, neonatal viral inoculation has been demonstrated to augment hippocampal output and disrupt associated behaviors (Pearce et al., 1996; Pearce et al., 2000). Moreover, this appears to be associated with a decrease in parvalbumin immunoreactivity, further implicating a deficit in intrinsic GABAergic signaling as a contributing factor to aberrant hippocampal activity (Pearce et al., 1996).

Summary and implications

Taken as a whole, the ventral hippocampus represents a site of convergence by which distinct risk factors can regulate limbic system function (Figure 2). Specifically, the central role of the vHipp in the regulation of dopamine neuron population activity provides a foundation by which aberrant GABAergic signaling can induce psychosis. Moreover, the ability of stress or substance abuse to exacerbate or precipitate symptoms is likely attributable to increases in vHipp output that would further augment the already pathologically enhanced vHipp regulation of dopamine system function, resulting in an inability to accurately ascribe gain to salient and non-salient stimuli. Indeed, an abnormality in the attribution of salience has been proposed as a potential underlying factor in the psychotic state (Kapur, 2003).

Therefore, although schizophrenia has been attributed to an aberrant dopamine system for nearly 5 decades, current evidence suggests that the dopamine system is indeed “normal,” but is being dysregulated by areas such as the hippocampus. Given this condition, it should not be surprising that dopamine receptor blockade has been of limited efficacy in the treatment of schizophrenia, since it is treating the dysregulated dopamine system 5 synapses downstream from the proposed site of pathology within the hippocampus. Therefore, a more effective approach to treatment could be to target the site of deficit – e.g., GABAergic regulation of hippocampal activity.

References

- Abdul-Monim Z, Neill JC, Reynolds GP. Sub-chronic psychotomimetic phencyclidine induces deficits in reversal learning and alterations in parvalbumin-immunoreactive expression in the rat. *Journal of Psychopharmacology*. 2007; 21:198–205. [PubMed: 17329300]
- Abi-Dargham A. Do we still believe in the dopamine hypothesis? New data bring new evidence. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2004; 7(Suppl 1):S1–5. [PubMed: 14972078]
- Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C. Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol*. 2007; 64:39–45. [PubMed: 16962192]
- Berretta S, Lange N, Bhattacharyya S, Sebros R, Garces J, Benes FM. Long-term effects of amygdala GABA receptor blockade on specific subpopulations of hippocampal interneurons. *Hippocampus*. 2004; 14:876–894. [PubMed: 15382257]
- Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain research*. 1998; 28:309–369.
- Brischoux F, Chakraborty S, Brierley DI, Ungless MA. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:4894–4899. [PubMed: 19261850]
- Carlsson A, Waters N, Waters S, Carlsson ML. Network interactions in schizophrenia - therapeutic implications. *Brain research*. 2000; 31:342–349.

- Cherlyn SYT, Woon PS, Liu JJ, Ong WY, Tsai GC, Sim K. Genetic association studies of glutamate, GABA and related genes in schizophrenia and bipolar disorder: A decade of advance. *Neuroscience and Biobehavioral Reviews*. 2010; 34:958–977. [PubMed: 20060416]
- Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103:19878–19883. [PubMed: 17170134]
- Chrapusta SJ, Egan MF, Wyatt RJ, Weinberger DR, Lipska BK. Neonatal ventral hippocampal damage modifies serum corticosterone and dopamine release responses to acute footshock in adult Sprague-Dawley rats. *Synapse*. 2003; 47:270–277. [PubMed: 12539200]
- Corcoran C, Walker E, Huot R, Mittal V, Tessner K, Kestler L, Malaspina D. The Stress Cascade and Schizophrenia: Etiology and Onset. *Schizophrenia Bulletin*. 2003; 29:671–692. [PubMed: 14989406]
- Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophrenia research*. 1999; 35:S93–S100. [PubMed: 10190230]
- Doherty M, Gratton A. Differential involvement of ventral tegmental GABAA and GABAB receptors in the regulation of the nucleus accumbens dopamine response to stress. *Brain research*. 2007; 1150:62–68. [PubMed: 17395162]
- Dunn JD, Orr SE. Differential plasma corticosterone responses to hippocampal stimulation. *Experimental Brain Research*. 1984; 54:1–6.
- Fanselow MS, Dong H-W. Are the Dorsal and Ventral Hippocampus Functionally Distinct Structures? *Neuron*. 2010; 65:7–19. [PubMed: 20152109]
- Fazzari P, Paternain AV, Valiente M, Pla R, Luján R, Lloyd K, Lerma J, Marín O, Rico B. Control of cortical GABA circuitry development by Nrg1 and ErbB4 signalling. *Nature*. 2010; 464:1376–1380. [PubMed: 20393464]
- Fendler K, Karmos G, Telegdy G. The effect of hippocampal lesion on pituitary-adrenal function. *Acta physiologica Academiae Scientiarum Hungaricae*. 1961; 20:293–297. [PubMed: 13892267]
- Floresco SB, Todd CL, Grace AA. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *J Neurosci*. 2001; 21:4915–4922. [PubMed: 11425919]
- Floresco SB, West AR, Ash B, Moore H, Grace AA. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nature neuroscience*. 2003; 6:968–973.
- Frey U, Schroeder H, Matthies H. Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. *Brain research*. 1990; 522:69–75. [PubMed: 1977494]
- Frey U, Matthies H, Reymann KG, Matthies H. The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. *Neuroscience Letters*. 1991; 129:111–114. [PubMed: 1833673]
- Gonzalez-Hernandez JA, Cedeno I, Pita-Alcorta C, Galan L, Aubert E, Figueredo-Rodriguez P. Induced oscillations and the distributed cortical sources during the Wisconsin card sorting test performance in schizophrenic patients: new clues to neural connectivity. *Int J Psychophysiol*. 2003; 48:11–24. [PubMed: 12694897]
- Grace AA, Bunney BS. Paradoxical GABA excitation of nigral dopaminergic cells: indirect mediation through reticulata inhibitory neurons. *European journal of pharmacology*. 1979; 59:211–218. [PubMed: 527646]
- Grace AA, Bunney BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons--I. Identification and characterization. *Neuroscience*. 1983; 10:301–315. [PubMed: 6633863]
- Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: burst firing. *J Neurosci*. 1984a; 4:2877–2890. [PubMed: 6150071]
- Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: single spike firing. *J Neurosci*. 1984b; 4:2866–2876. [PubMed: 6150070]
- Grace AA, Bunney BS. Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. *Brain Res*. 1985; 333:271–284. [PubMed: 2986775]

- Grace AA, Onn SP. Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded in vitro. *J Neurosci*. 1989; 9:3463–3481. [PubMed: 2795134]
- Grace, AA.; Moore, H. Regulation of information flow in the nucleus accumbens: A model for the pathophysiology of schizophrenia. In: Lenzenweger, MF.; Dworkin, RH., editors. *Origins and development of schizophrenia: Advances in experimental psychopathology*. American Psychological Association Press; Washington D.C.: 1998. p. 123-157.
- Grace AA, Floresco SB, Goto Y, Lodge DJ. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends in Neurosciences*. 2007; 30:220–227. [PubMed: 17400299]
- Granado N, Ortiz O, Sua?rez LM, Marti?n ED, Cen?a V, Soli?s JM, Moratalla R. D1 but not D5 dopamine receptors are critical for LTP, spatial learning, and LTP-induced arc and zif268 expression in the hippocampus. *Cerebral Cortex*. 2008; 18:1–12. [PubMed: 17395606]
- Greetfeld M, Schmidt MV, Ganea K, Sterlemann V, Liebl C, M?ller MB. A single episode of restraint stress regulates central corticotrophin-releasing hormone receptor expression and binding in specific areas of the mouse brain. *Journal of Neuroendocrinology*. 2009; 21:473–480.
- Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain*. 1999; 122(Pt 4):593–624. [PubMed: 10219775]
- Harte MK, Powell SB, Swerdlow NR, Geyer MA, Reynolds GP. Deficits in parvalbumin and calbindin immunoreactive cells in the hippocampus of isolation reared rats. *Journal of neural transmission*. 2007; 114:893–898. [PubMed: 17594127]
- Heckers S. The hippocampus in schizophrenia. *American Journal of Psychiatry*. 2004; 161:2138–2139. [PubMed: 15514431]
- Heckers S, Konradi C. Hippocampal neurons in schizophrenia. *Journal of neural transmission*. 2002; 109:891–905. [PubMed: 12111476]
- Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nature neuroscience*. 1998; 1:318–323.
- Herman JP, Mueller NK. Role of the ventral subiculum in stress integration. *Behavioural brain research*. 2006; 174:215–224. [PubMed: 16876265]
- Herman JP, Cullinan WE, Young EA, Akil H, Watson SJ. Selective forebrain fiber tract lesions implicate ventral hippocampal structures in tonic regulation of paraventricular nucleus corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) mRNA expression. *Brain research*. 1992; 592:228–238. [PubMed: 1333341]
- Herman JP, Cullinan WE, Morano MI, Akil H, Watson SJ. Contribution of the ventral subiculum to inhibitory regulation of the hypothalamo-pituitary-adrenocortical axis. *Journal of Neuroendocrinology*. 1995; 7:475–482. [PubMed: 7550295]
- Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Ann N Y Acad Sci*. 2008; 64–73. [PubMed: 19120092]
- Johnson PI, Napier TC. GABA- and glutamate-evoked responses in the rat ventral pallidum are modulated by dopamine. *European Journal of Neuroscience*. 1997; 9:1397–1406. [PubMed: 9240397]
- Kalivas PW, Duffy P. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. *Brain research*. 1995; 675:325–328. [PubMed: 7796146]
- Kapur S. Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry*. 2003; 160:13–23. [PubMed: 12505794]
- Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, Moore H, Kandel ER. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron*. 2006; 49:603–615. [PubMed: 16476668]
- Knigge KM. Adrenocortical response to stress in rats with lesions in hippocampus and amygdala. *Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine*. 1961; 108:18–21. New York, N Y.

- Knigge KM, Hays M. Evidence of Inhibitive Role of Hippocampus in Neural Regulation of Acth Release. *Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine*. 1963; 114:67–69. New York, N Y.
- Knight RT. Contribution of human hippocampal region to novelty detection. *Nature*. 1996; 383:256–259. [PubMed: 8805701]
- Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. *Science*. 1997; 278:52–58. [PubMed: 9311926]
- Lahti AC, Weiler MA, Holcomb HH, Tamminga CA, Carpenter WT, McMahon R. Correlations between rCBF and symptoms in two independent cohorts of drug-free patients with schizophrenia. *Neuropsychopharmacology*. 2006; 31:221–230. [PubMed: 16123774]
- Laruelle M, Abi-Dargham A. Dopamine as the wind of psychotic fire: new evidence from brain imaging studies. *Journal of Psychopharmacology*. 1999; 13:358–371. [PubMed: 10667612]
- Legault M, Wise RA. Injections of N-methyl-D-aspartate into the ventral hippocampus increase extracellular dopamine in the ventral tegmental area and nucleus accumbens. *Synapse*. 1999; 31:241–249. [PubMed: 10051104]
- Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nature Reviews Neuroscience*. 2005; 6:312–324.
- Lipski, WJ.; Grace, AA. Locus coeruleus stimulation and norepinephrine application produce opposite effects on accumbens-projecting neurons in the ventral subiculum. *Neuroscience Meeting Planner* 815.10; 2009.
- Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*. 2005; 46:703–713. [PubMed: 15924857]
- Lodge DJ, Grace AA. The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology*. 2006a; 31:1356–1361. [PubMed: 16319915]
- Lodge DJ, Grace AA. The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. *Proceedings of the National Academy of Sciences of the United States of America*. 2006b; 103:5167–5172. [PubMed: 16549786]
- Lodge DJ, Grace AA. Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. *J Neurosci*. 2007; 27:11424–11430. [PubMed: 17942737]
- Lodge DJ, Grace AA. Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. *J Neurosci*. 2008; 28:7876–7882. [PubMed: 18667619]
- Lodge DJ, Grace AA. Gestational methylazoxymethanol acetate administration: A developmental disruption model of schizophrenia. *Behav Brain Res*. 2009; 204:306–312. [PubMed: 19716984]
- Lodge DJ, Behrens MM, Grace AA. A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2009; 29:2344–2354. [PubMed: 19244511]
- Maren S, Quirk GJ. Neuronal signalling of fear memory. *Nature Reviews in Neuroscience*. 2004; 5:844–852.
- Matsumoto M, Hikosaka O. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature*. 2009; 459:837–841. [PubMed: 19448610]
- Matthies H, Becker A, Schroeder H, Kraus J, Holt V, Krug M. Dopamine D1-deficient mutant mice do not express the late phase of hippocampal long-term potentiation. *Neuroreport*. 1997; 8:3533–3535. [PubMed: 9427321]
- Mayer ML, Westbrook GL, Buthrie PB. Voltage-dependent block by Mg²⁺ of NMDA responses in spinal cord neurones. *Nature*. 1984; 309:261–263. [PubMed: 6325946]
- McEwen BS. The neurobiology of stress: From serendipity to clinical relevance. *Brain research*. 2000; 886:172–189. [PubMed: 11119695]
- McEwen BS. Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological reviews*. 2007; 87:873–904. [PubMed: 17615391]
- Medoff DR, Holcomb HH, Lahti AC, Tamminga CA. Probing the human hippocampus using rCBF: contrasts in schizophrenia. *Hippocampus*. 2001; 11:543–550. [PubMed: 11732707]

- Mercuri NB, Stratta F, Calabresi P, Bernardi G. A voltage-clamp analysis of NMDA-induced responses on dopaminergic neurons of the rat substantia nigra zona compacta and ventral tegmental area. *Brain Res.* 1992; 593:51–56. [PubMed: 1360865]
- Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, Berman KF. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *The American journal of psychiatry.* 2001; 158:1809–1817. [PubMed: 11691686]
- Millan MJ. The neurobiology and control of anxious states. *Progress in Neurobiology.* 2003; 70:83–244. [PubMed: 12927745]
- Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin.* 2007; 133:25–45. [PubMed: 17201569]
- Moore H, Jentsch JD, Ghajarnia M, Geyer MA, Grace AA. A neurobehavioral systems analysis of adult rats exposed to methylazoxymethanol acetate on E17: implications for the neuropathology of schizophrenia. *Biol Psychiatry.* 2006; 60:253–264. [PubMed: 16581031]
- Mueller NK, Dolgas CM, Herman JP. Stressor-selective role of the ventral subiculum in regulation of neuroendocrine stress responses. *Endocrinology.* 2004; 145:3763–3768. [PubMed: 15142982]
- Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: A meta-analytic study. *Archives of general psychiatry.* 1998; 55:433–440. [PubMed: 9596046]
- Nordahl TE, Kusubov N, Carter C, Salamat S, Cummings AM, O'Shara-Celaya L, Eberling J, Robertson L, Huesman RH, Jagust W, Budinger TF. Temporal lobe metabolic differences in medication-free outpatients with schizophrenia via the PET-600. *Neuropsychopharmacology.* 1996; 15:541–554. [PubMed: 8946428]
- Nuechterlein KH, Dawson ME. A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin.* 1984; 10:300–312. [PubMed: 6729414]
- O'Mahony CM, Sweeney FF, Daly E, Dinan TG, Cryan JF. Restraint stress-induced brain activation patterns in two strains of mice differing in their anxiety behaviour. *Behav Brain Res.* 2010
- Pearce B, Steffensen S, Paoletti A, Henriksen S, Buchmeier M. Persistent dentate granule cell hyperexcitability after neonatal infection with lymphocytic choriomeningitis virus. *J Neurosci.* 1996; 16:220–228. [PubMed: 8613788]
- Pearce BD, Valadi NM, Po CL, Miller AH. Viral infection of developing GABAergic neurons in a model of hippocampal disinhibition. *Neuroreport.* 2000; 11:2433–2438. [PubMed: 10943699]
- Penschuck S, Flagstad P, Didriksen M, Leist M, Michael-Titus AT. Decrease in parvalbumin-expressing neurons in the hippocampus and increased phencyclidine-induced locomotor activity in the rat methylazoxymethanol (MAM) model of schizophrenia. *European Journal of Neuroscience.* 2006; 23:279–284. [PubMed: 16420437]
- Phillips RG, LeDoux JE. Differential Contribution of Amygdala and Hippocampus to Cued and Contextual Fear Conditioning. *Behav Neurosci.* 1992; 106:274–285. [PubMed: 1590953]
- Piazza PV, Le Moal M. Pathophysiological basis of vulnerability to drug abuse: Role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annual Review of Pharmacology and Toxicology.* 1996:359–378.
- Piazza PV, Maccari S, Deminiere JM, Le Moal M, Mormede P, Simon H. Corticosterone levels determine individual vulnerability to amphetamine self-administration. *Proceedings of the National Academy of Sciences of the United States of America.* 1991; 88:2088–2092. [PubMed: 2006148]
- Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science.* 1987; 237:1219–1223. [PubMed: 2820058]
- Rubin RT, Mandell AJ, Crandall PH. Corticosteroid responses to limbic stimulation in man: Localization of stimulus sites. *Science.* 1966; 153:767–768. [PubMed: 5940897]
- Sapolsky RM, Krey LC, McEwen BS. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. *Proceedings of the National Academy of Sciences of the United States of America.* 1984; 81:6174–6177. [PubMed: 6592609]

- Schmiedt C, Brand A, Hildebrandt H, Basar-Eroglu C. Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls. *Brain Res Cogn Brain Res*. 2005; 25:936–947. [PubMed: 16289526]
- Schultz W. Predictive reward signal of dopamine neurons. *Journal of neurophysiology*. 1998; 80:1–27. [PubMed: 9658025]
- Seutin V, Verbanck P, Massotte L, Dresse A. Evidence for the presence of N-methyl-D-aspartate receptors in the ventral tegmental area of the rat: an electrophysiological in vitro study. *Brain Res*. 1990; 514:147–150. [PubMed: 1972637]
- Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophrenia research*. 2001; 49:1–52. [PubMed: 11343862]
- Snyder SH. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. *American Journal of Psychiatry*. 1976; 133:197–202. [PubMed: 1251927]
- Squire LR. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*. 1992; 99:195–231. [PubMed: 1594723]
- Squire LR, Zola-Morgan S. The medial temporal lobe memory system. *Science*. 1991; 253:1380–1386. [PubMed: 1896849]
- Takahashi H, Takada Y, Nagai N, Urano T, Takada A. Effects of nicotine and footshock stress on dopamine release in the striatum and nucleus accumbens. *Brain research bulletin*. 1998; 45:157–162. [PubMed: 9443833]
- Thompson KN, Berger G, Phillips LJ, Komesaroff P, Purcell R, McGorry PD. HPA axis functioning associated with transition to psychosis: Combined DEX/CRH test. *Journal of psychiatric research*. 2007a; 41:446–450. [PubMed: 16403528]
- Thompson KN, Phillips LJ, Komesaroff P, Yuen HP, Wood SJ, Pantelis C, Velakoulis D, Yung AR, McGorry PD. Stress and HPA-axis functioning in young people at ultra high risk for psychosis. *Journal of psychiatric research*. 2007b; 41:561–569. [PubMed: 16831447]
- Ungless MA, Magill PJ, Bolam JP. Uniform Inhibition of Dopamine Neurons in the Ventral Tegmental Area by Aversive Stimuli. *Science*. 2004; 303:2040–2042. [PubMed: 15044807]
- Valenti, O.; Grace, AA. Acute and repeated stress induce a pronounced and sustained activation of VTA DA neuron population activity. *Neuroscience Meeting Planner* 479.11; 2008.
- Wang T, French ED. L-glutamate excitation of A10 dopamine neurons is preferentially mediated by activation of NMDA receptors: extra- and intracellular electrophysiological studies in brain slices. *Brain Res*. 1993; 627:299–306. [PubMed: 7905352]
- Weiss AP, Goff D, Schacter DL, Ditman T, Freudenreich O, Henderson D, Heckers S. Fronto-Hippocampal Function During Temporal Context Monitoring in Schizophrenia. *Biol Psychiatry*. 2006
- Woo TU, Whitehead RE, Melchitzky DS, Lewis DA. A subclass of prefrontal gamma-aminobutyric acid axon terminals are selectively altered in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95:5341–5346. [PubMed: 9560277]
- Yolken RH, Torrey EF. Viruses, schizophrenia, and bipolar disorder. *Clinical Microbiology Reviews*. 1995; 8:131–145. [PubMed: 7704891]
- Young AMJ. Increased extracellular dopamine in nucleus accumbens in response to unconditioned and conditioned aversive stimuli: Studies using 1 min microdialysis in rats. *Journal of Neuroscience Methods*. 2004; 138:57–63. [PubMed: 15325112]
- Zhang ZJ, Reynolds GP. A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. *Schizophrenia research*. 2002; 55:1–10. [PubMed: 11955958]

Figure 1.

Ventral hippocampal (vHipp) regulation of dopamine neuron activity in normal and diseased states. (left) In the normal individual, the vHipp regulates the number of spontaneously active dopamine neurons in the VTA via a multisynaptic pathway. Therefore, low levels of activity in the non-stimulated condition lead to low levels of glutamatergic drive (red arrow) of GABAergic neurons in the accumbens (Acb). As a result, there is a low level of inhibition of GABAergic neurons in the ventral pallidum (VP, black arrow). The VP, in turn, produces a potent inhibition of DA neuron firing (black arrow), allowing only a small proportion of VTA dopamine neurons to fire spontaneously. (right) In schizophrenia, aberrant high levels of vHipp activity causes the Acb to potentially inhibit the VP, thereby dramatically increasing the number of spontaneously active dopamine neurons in the VTA

Figure 2.

The ventral hippocampus represents a site of convergence by which distinct risk factors can regulate limbic system function. Thus, hippocampal pathology, driven by genetic and environmental factors, is likely to be exacerbated by stress or substance abuse. This aberrant vHipp activity augments dopamine transmission leading to psychosis.