Developmental pathology, dopamine, stress and schizophrenia

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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.

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1. 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 principal hippocampal area associated with the negative regulation of HPA function in response to psychological stressors (Herman et al., 1992, 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; Greeffeld 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; Lism 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 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 physiological 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, 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).

2. 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, 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 prominent structures being the hippocampus (Nordahl et al., 1996; Heckers et al., 1998; Nelson et al., 1998; Harrison, 1999; Medoff et al., 2001; Meyer-Lindenb erg 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 2 ms 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 4.5 Hz (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, neurones 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; Mercure 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 pedunculopontine 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, 2006a,b).

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, 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, 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, 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, 2003). Indeed, intra-acumbens kynurinic 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, 2009).

3. 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 neurological 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 regulation 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 schizophrenic patients, we examined the locomotor-enhancing effects of amphetamine. The administration of low doses of amphetamine (0.5 mg/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 (Fig. 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.

4. 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 min. 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 immuno-histochemistry, 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 hyperresponsivity 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 dopaminergic innervation that acts, in part, to regulate long-term plasticity (Frey et al., 1990, 1991; Mathies et al., 1997; Granado et al., 2008). Thus, it is likely that the repeated administration of amphetamine, followed by a period of withdrawal, induces a significant increase in both single-spike and burst firing of vlipp pyramidal neurons (Lodge and Grace, 2008). This increase in vlipp 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 vlipp inactivation (Lodge and Grace, 2008).

5. 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 arbor, 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; Schmidt et al., 2005; Cho et al., 2006; Basar-Eroğlu 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 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 patient. 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, 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).

6. 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 (Fig. 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 five 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 block-ade has been of limited efficacy in the treatment of schizophrenia, since it is treating the dysregulated dopamine system five 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


