Chapter 6

The Hippocampus as a Neural Link between Negative Affect and Vulnerability for Psychostimulant Relapse

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Abstract

Psychostimulant dependence (including cocaine, amphetamine, and methamphetamine) is a chronic relapsing disorder with significant personal, health, and financial burdens. Attempts at abstinence produce a severe and protracted withdrawal syndrome characterized by stress hypersensitivity that can facilitate drug craving, anxiety, and dysphoria. These negative withdrawal symptoms can induce relapse, maintaining the addiction cycle. The hippocampus mediates cognitive, emotional, and endocrine responses to stressors. The ventral hippocampus is in a pivotal position to regulate the mesoaccumbal dopamine reward system, and interacts with serotonergic and glucocorticoid systems that mediate anxiety and stress responsiveness. Psychostimulant actions on the hippocampus induce long-term changes to these systems and impact the process of adult neurogenesis in the hippocampus, which may facilitate drug dependence by altering drug-cue learning and emotional regulation. Multiple studies indicate that psychostimulant-induced hippocampal neuroadaptations heighten hippocampal-mesoaccumbal activity to amplify drug- and drug-cue responses while persistent dysregulation of hippocampal emotional systems potentiate negative affect. Understanding how psychostimulants modulate the hippocampus to alter hippocampal-mesoaccumbal activity—and how hippocampal neurogenesis influences drug-related memories and reward—is important for identifying novel treatment strategies that can ameliorate negative affect and relapse vulnerability in psychostimulant addiction.

Keywords: psychostimulant, hippocampus, stress, withdrawal, serotonin, corticosterone, neurogenesis

1. Introduction

1.1. The problem of stimulant abuse

Abuse of psychostimulants such as cocaine and amphetamines affects millions of people worldwide, as psychostimulants are the second most widely abused class of illicit drug globally behind marijuana [1–5]. In general, drug addiction and subsequent relapse vulnerability are thought to occur through counter-adaptive neurochemical changes within brain circuits that normally conserve an emotional homeostasis [6–8]. Dysregulation of the homeostatic system—through genetics, environment (stress), history of drug taking, or current emotive states—produces susceptibility to become dependent and to relapse during long-term abstinence [9, 10]. Psychostimulants produce a severe and protracted withdrawal syndrome which includes symptoms of stress hypersensitivity, intense drug craving, anxiety, and dysphoria [11–16]. These symptoms are reproduced in animal models [17–21], and can induce craving and relapse in humans [13, 22, 23], thus maintaining the addiction cycle [24–27]. The underlying mechanisms that enable stress-sensitive and dysphoric states in withdrawal to induce relapse are thought to involve alterations to the mesolimbic dopamine reward system and anti-reward/stress systems [9, 26, 28] that include the hippocampus [28–30]. Currently, no medications have proven effective for treating psychostimulant withdrawal [13, 16, 31]. Thus, understanding the neurobiology underlying the aversive states during psychostimulant withdrawal is an essential component of relapse prevention [32].

1.2. The hippocampus, stress and addiction

The hippocampus, a brain region associated with spatial learning and memory, has been established as a critical region for reward- and stress-associated responses and drug-seeking behaviors [30, 33–37]. Exposure to conditioned contextual cues and aversive or stressful stimuli are powerful triggers of drug cravings [38–41] and are associated with activation of limbic brain regions, including the hippocampus, in both human and rodent models [42–46]. Dorsal and ventral subdivisions of the rodent hippocampus have been proposed based on anatomical connectivity and behavioral output [47–51]. The rodent dorsal hippocampus, analogous to the human posterior hippocampus, receives *exteroceptive* information from the entorhinal cortex and has a major role in rapid spatial learning (**Figure 1**) [52]. The ventral hippocampus, analogous to the human anterior hippocampus, receives *interoceptive* information through reciprocal connections to limbic regions that modulate motivational and affective states; the other limbic brain regions involved include the nucleus accumbens, amygdala, medial prefrontal cortex, and hypothalamus (**Figure 1**) [50–54]. Notably, both regions of the hippocampus are involved in memory formation [55]; dorsal neurons form contextual representations of specific single events while ventral neurons form representations of multiple events (related by a distinct context) over time [56].

The subiculum, the major output structure of the hippocampus, provides projections to the nucleus accumbens, which also receives input from ventral tegmental area (VTA) dopamine terminals [34, 57–59]. The nucleus accumbens integrates affective and motivational information

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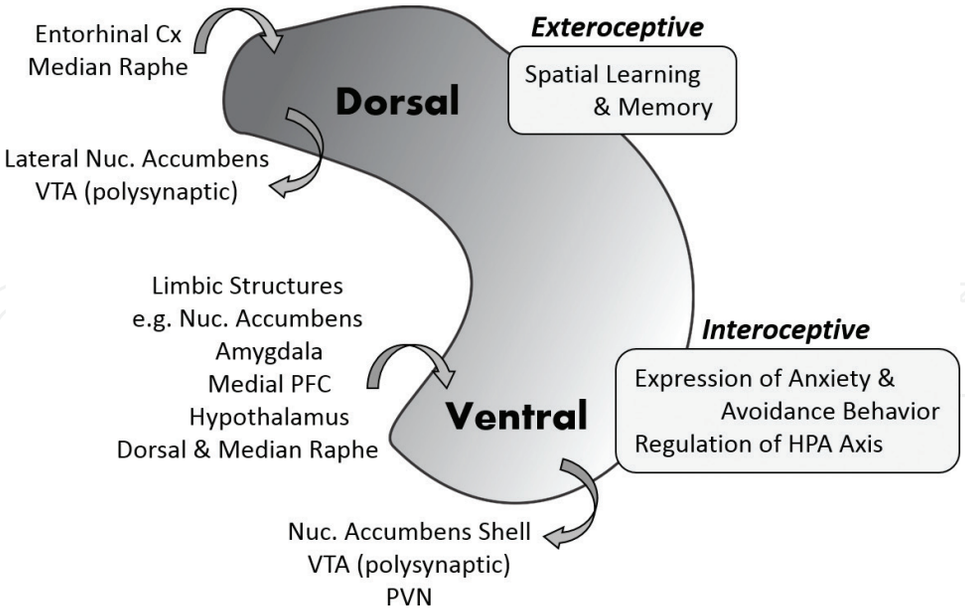

Figure 1. Schematic of afferent/efferent connections and functions of the dorsal and ventral hippocampus related to reward and stress processes. Abbreviations: Cx, cortex; HPA, hypothalamic-pituitary-adrenal; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; VTA, ventral tegmental area.

to produce goal-directed behavioral output [60–62]. Thus, the hippocampus is poised to play an important role in mediating the effects of drugs of abuse (e.g., psychostimulants) through its interactions with the mesoaccumbal dopamine system. Importantly, the dorsal and ventral hippocampus may differentially regulate accumbal activity [60, 63], since the ventral subiculum projects to the medial shell of the nucleus accumbens while the dorsal subiculum projects to the more lateral accumbens and core (**Figure 1**) [51, 54, 64]. The dorsal and ventral hippocampus also influences accumbal activity indirectly, via multi-synaptic projections to the VTA (**Figure 1**) [65–67]. Consequently, glutamatergic output from the hippocampus facilitates dopaminergic activity in the mesolimbic dopamine pathway [34, 57, 68, 69]. In the nucleus accumbens shell, this communication is vital for forming place-reward associations [70–72] and mediating reward salience [63]. Thus, context-related processing within the hippocampus may drive reward-related processes mediated by the nucleus accumbens.

The hippocampus also regulates anxiety and avoidance behaviors. Anxiety is an innate response coordinated to protect an animal from potential harm, which is linked to maximizing chances of reward in approach-avoidance conflict situations. The hippocampus has been proposed to underlie anxiety behaviors by detecting novelty or uncertainty [73, 74] and then increasing attention and behavioral inhibition [75, 76]. However, maladaptive changes to the circuits underlying this response can constrain normal functioning and lead to a disruptive pathological state.

The *ventral* hippocampus in particular plays a predominant role in mediating anxiety/avoidance behaviors. For example, glutamatergic activation of the ventral hippocampus is important for expressing anxiety-like behaviors [77, 78] and lesioning the ventral—but not dorsal—hippocampus reduces innate avoidance behavior in unconditioned anxiety tests, and reduces

conditioned responding to anxiogenic cues [79–84]. Moreover, a recent study in humans found that the anterior (ventral) hippocampus is necessary for passive avoidance behavior [85], and studies in rats and humans have shown that increased activity between the ventral/anterior hippocampus and the medial prefrontal cortex is necessary for expressing anxiety in anxiogenic environments [86–89]. Also, activating basolateral amygdala (BLA) inputs to the ventral hippocampus increases—while inhibition decreases—anxiety-like behaviors [90]. Together, these findings suggest that activation of the ventral hippocampus by glutamatergic input from the BLA and its subsequent communication with regions like the prefrontal cortex is essential for the appropriate expression of anxiety/avoidance behaviors.

Related to its involvement in emotional regulation, the ventral hippocampus also exerts influence on the hypothalamic-pituitary-adrenal (HPA) axis and coordinates stress responses (**Figure 1**) [36, 91, 92]. The HPA axis organizes neuroendocrine responses to physical and psychogenic stressors through release of the glucocorticoid hormone cortisol (humans) or corticosterone (rodents) [92]. The hippocampus is the primary target for glucocorticoids in the brain [93] and the ventral subiculum is thought to be the primary limbic region that utilizes glucocorticoid feedback to inhibit HPA axis activity [91, 94–96]. This feedback inhibition is mediated through corticosteroid activation of corticosterone's mineralocorticoid (MR) and glucocorticoid (GR) receptors that are both cytosolic (genomic) and membrane-bound (non-genomic) [96–99].

Cytosolic MRs (cMRs), with restricted expression (highest in the hippocampus), have 10-fold higher affinity for corticosterone than GRs, and are ~90% occupied under basal conditions [100–103]. They are attributed with regulating HPA inhibition at basal corticosterone levels, and thus determine HPA "set point" [96, 104–108]. cMRs also sustain cellular stability, which maintains stress sensitivity thresholds and preserves limbic network communication [97, 103, 107, 109, 110]. Cytosolic GRs (cGRs) are ubiquitously expressed, with high expression in the hippocampus [95], and regulate delayed feedback inhibition of HPA activity after diurnal corticosterone peaks and acute stress [92, 96, 104, 105]. cGRs are also attributed with normalizing neuronal excitability in response to stress and normalizing network activity, which dampens initial stress responses, and promotes adaptive stress coping [107, 109, 110].

Corticosterone stress responses that occur too quickly to attribute to genomic effects are credited to activation of non-genomic membrane-bound receptors (mMRs/mGRs) in the hippocampus (and other regions). These membrane receptors have ≥10-fold lower affinity for corticosterone than their cytosolic counterparts [97, 103, 108] and thus act as hippocampal "cortico-sensors" [99, 111]. mMRs rapidly and reversibly enhance excitatory glutamatergic transmission in the hippocampus [97, 99, 107]; they contribute to rapid inhibition of HPA activity and activate rapid and reversible behavioral stress responses important for appraisal and coping [99, 110]. mGRs have lower corticosterone affinity than mMRs and augment inhibitory GABAergic interneuronal transmission [112] to suppress excitability; they also promote spinogenesis [97, 113]. Alterations in these receptors' expression, function, and ratios relative to one another—especially within the hippocampus—can diminish stress responsiveness and coping ability, which is associated with multiple disease states, including depression and psychostimulant withdrawal [113, 114].

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Glucocorticoid stress responses in the hippocampus also vary based on hippocampal region (dorsal vs. ventral): acute foot shock rapidly increases corticosterone levels in the dorsal hippocampus, followed by a more delayed elevation in the ventral hippocampus [115]. Also, acute swim stress *decreases* long-term potentiation (LTP) in the *dorsal* hippocampus, but *increases* LTP in the *ventral* hippocampus [116]. This differential response may temporarily suppress the dorsal hippocampus' cognitive cortical communication and facilitate ventral hippocampal transmission of emotional information [117].

1.3. Goals of this review

Overall, the ventral hippocampus is in a pivotal position to play a key role in addictive processes via its role in modulating activity of reward and stress pathways such as the mesoaccumbal dopamine system and HPA axis respectively. This review will provide evidence for psychostimulant-induced changes in the hippocampus leading to negative affect that promotes psychological withdrawal symptoms and maintains the cycle of psychostimulant dependence. Specifically, this review will evaluate and integrate various studies concerning alterations of hippocampal activity and structural plasticity due to chronic drug exposure that contribute to the pathophysiology of drug abuse through maladaptive reward responses and/or the promotion of dysphoric states. In doing so, potential mechanisms underlying psychostimulant withdrawal symptoms and relapse to drug-seeking will be revealed and future directions identified.

2. Psychostimulants and hippocampal-mesoaccumbens circuitry

The mesoaccumbal dopaminergic system (VTA to nucleus accumbens) is involved in reinforcement learning and motivated behavior. Dopamine release in the nucleus accumbens shell is associated with reward salience [63] and drug/reward context conditioning [118], and is enhanced by drug use [42, 118], drug-predictive contexts [118, 119], and during novel environment exploration [120]. In line with its role as a novelty detector, the ventral hippocampus controls the novelty-induced dopamine response in the nucleus accumbens [73]. Novelty-induced activation of the ventral hippocampal-nucleus accumbens pathway is thought to be important for long-term memory formation [121]. In support of this, place-reward associations depend on communication between the ventral hippocampus and the nucleus accumbens shell [68, 69]. Likewise, neuronal activity between the nucleus accumbens, hippocampus, and prefrontal cortex during goal-directed behavior learning is believed to contribute to reward-context memory consolidation and strengthening [122–125]. Finally, co-activation of the anterior (ventral) hippocampus and VTA dopamine neurons is linked to long-term reward-related memory enhancement [126, 127]. Thus, reward enhances memory formation, and this effect is closely linked to reward-context engagement of the hippocampal-mesoaccumbal pathway.

The dopamine system has long been associated with stress/aversion as well as reward-related behaviors [128, 129]. For example, stress increases dopamine levels in the nucleus accumbens shell (but not core) [130]. Preliminary studies in rats suggest that mimicking the hippocampal

glucocorticoid stress response [131–134] by infusing corticosterone into the ventral subiculum stimulates dopamine efflux in the nucleus accumbens shell [29], thus indicating a role for the ventral hippocampus in enabling stress to enhance accumbal dopamine output. Stressors also increase VTA dopamine activity, and this increase is dependent upon ventral hippocampal activity [135]. The ventral hippocampus-VTA dopamine pathway is also potentiated in mice with increased social avoidance after chronic social defeat stress, and is necessary for this behavioral outcome [136]. Thus, it is suggested that the ventral hippocampus uses prior experience to bias the responsive state of accumbal dopamine [135]. In line with this suggestion, mice with increased avoidance behavior following chronic stress also display increased VTA dopamine neuron burst firing [137, 138]. Therefore, a behaviorally salient stimulus (aversive or rewarding) within a given context would heightened activation of the ventral hippocampus-accumbens pathway.

The ventral hippocampal-nucleus accumbens pathway also influences psychostimulant responses. Rats with greater dopaminergic responses to novelty will self-administer psychostimulants more readily [139, 140] and rats with repeated cocaine exposure display enhanced accumbal dopamine responses to glutamatergic stimulation of the ventral hippocampus [141]. This is likely reflective of the finding that repeated cocaine exposure and withdrawal selectively potentiates ventral hippocampal input to the nucleus accumbens shell [142, 143]. Furthermore, rats that exhibit behavioral sensitization to amphetamine display enhanced VTA neuronal firing and accumbal dopamine output, and these behavioral and neurophysiological effects are dependent on ventral hippocampal input [144, 145]. Hippocampal activity is also associated with psychostimulant-induced conditioned place preference (CPP) acquisition and expression [146, 147]. For example, lesions or inactivation of the hippocampus inhibit CPP acquisition and context-induced drug-seeking behavior [148–152]. Specifically, interactions between ventral hippocampal glutamatergic projections to neurons expressing postsynaptic D1 dopamine receptors in the nucleus accumbens shell contribute to drug-context memory formation and subsequent drug-seeking reinstatement [37, 153, 154]. Thus, ventral hippocampal facilitation of accumbal dopamine may generate drug-seeking behavior. Further, ventral hippocampal inhibition reduces cocaine- cue- or context-induced reinstatement of drug-seeking behavior [37, 148, 149, 155, 156] and its activity primes context-dependent relapse to drug-seeking for cocaine or d-amphetamine [37, 154, 157]. Overall, it appears that ventral hippocampal enhancement of accumbal dopamine activity likely promotes storage and retrieval of drug-reward information that underlies drug-seeking behaviors (**Figure 2**).

The mechanisms by which psychostimulants enhance ventral-hippocampal-regulated dopamine activity are not fully understood. Stress and repeated cocaine exposure independently increase LTP in the ventral hippocampus [116, 158]. Interestingly, acute *stress-induced* hippocampal plasticity is mediated by MRs and GRs in the ventral hippocampus; whereas *cocaine-induced* hippocampal plasticity seems to instead involve D2 dopamine receptors [116, 158, 159]. Related, repeated cocaine increases trafficking of glutamate receptors toward the membrane in the rat hippocampus [160], suggesting that psychostimulant-induced changes in hippocampal glutamate receptor availability contribute to increased hippocampal excitability and enhanced elevation of accumbal dopamine [141]. Repeated amphetamine exposure

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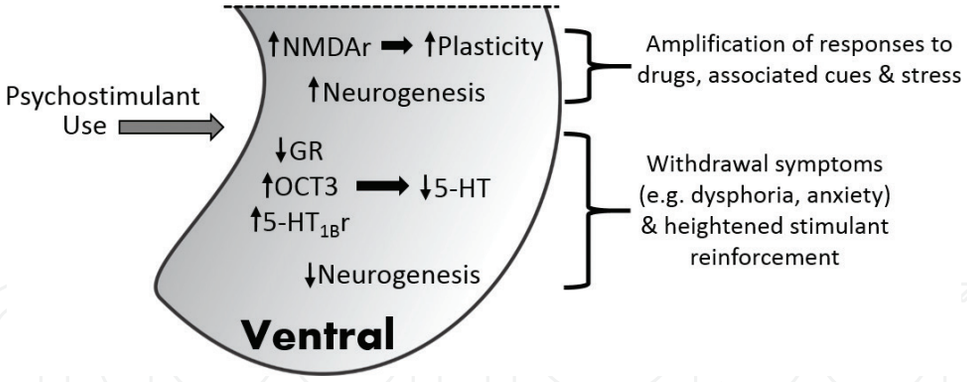

Figure 2. Overview of the effects of psychostimulant use on the ventral hippocampus that lead to increased sensitivity to psychostimulants, cues, stress and withdrawal symptoms**.** As discussed in the text, repeated psychostimulant exposure may either increase or decrease neurogenesis in the hippocampus under differing conditions, with either outcome contributing to the symptoms of dependence. Abbreviations: 5-HT, serotonin; GR, glucocorticoid receptor; OCT3, organic cation transporter 3.

also results in a reduced GR to MR ratio in the ventral hippocampus [114], which could further alter hippocampal excitability [97, 108] and hippocampal-accumbens activity. Further, repeated psychostimulant exposure alters neurotransmitter and endogenous neuropeptide levels in the hippocampus. For example, intrahippocampal oxytocin is decreased following chronic cocaine, whereas exogenous administration inhibits psychostimulant-induced behaviors [161]. Oxytocin alters hippocampal excitability by increasing the firing rate of inhibitory interneurons, likely influencing hippocampal terminal regions including the mesoaccumbal dopaminergic system [162]. Together, these findings suggest that psychostimulants can alter synaptic plasticity in the ventral hippocampus, facilitating hippocampal-accumbal pathways to amplify responses to drug reward- or stressor-associated cues (**Figure 2**).

3. Psychostimulants and hippocampal affect regulation: spotlight on serotonin and glucocorticoids

A critical modulator of hippocampal activity is serotonin (5-HT). The serotonergic median raphe nucleus innervates the entire dorsal-ventral axis of the hippocampus while the ventral hippocampus receives additional projections from the dorsal raphe nucleus (**Figure 1**) [161, 162]. Thus, the ventral hippocampus receives a higher density of serotoninergic innervations than the dorsal hippocampus [163]. The expression of 5-HT receptors is also differentiated along the dorsal-ventral axis of the hippocampus [164], which supports distinct 5-HT contributions to regionally distinct hippocampal functions.

Various stressors increase extracellular 5-HT levels in the hippocampus [165–172], and this is thought to be mediated by GR activation [114, 172, 173]. In rats, total brain 5-HT depletion increases stress sensitivity and abolishes stress adaptation [174], while specific 5-HT depletion in the ventral hippocampus increases anxiety-like behavior [175]. This supports the role of the ventral hippocampus as regulating anxiety behavior, and comports findings that suggest 5-HT acts as an inhibitory modulator in the hippocampus by activating inhibitory

5-HT_{1A} receptors [176–182]. For example, 5-HT_{1A} receptor activation in the hippocampal dentate gyrus inhibits LTP and impairs fear-related memory acquisition and consolidation [183–185]. Also, post-stress injection of a selective 5-HT reuptake inhibitor or activation of 5-HT_{1A} receptors in the hippocampus prevents stress-induced behavioral deficits [186–188]. Overall, increased 5-HT in the hippocampus seems to be important for repeated stress habituation, while reduced ventral hippocampal 5-HT heightens anxiety [172, 175, 189, 190].

A reciprocal and regulatory interaction exists between the serotonergic and glucocorticoid systems [191–193]. Systemic corticosterone enhances—and blocking corticosterone synthesis or GRs reduces—hippocampal 5-HT turnover and release [114, 194, 195]. These and other findings suggest that hippocampal GR activation in response to stress enhances hippocampal 5-HT transmission [114, 174], which may hold implications for behavioral and emotive stress responses such as anxiety [172, 175]. For example, many antidepressants that decrease anxiety states increase GR expression and 5-HT transmission [196]. In relation to psychostimulant use, chronic amphetamine pretreatment reduces GR protein expression in the ventral hippocampus and abolishes the 5-HT response to physiologically relevant hippocampal corticosterone levels after 24 hours of withdrawal [114], when heightened anxiety states emerge [197]. Overall, blunted stress-induced 5-HT signaling in the ventral hippocampus may contribute to negative affect during psychostimulant withdrawal.

Interestingly, rats with high anxiety behavior and diminished stress-induced 5-HT release also have increased levels of 5-HT transporter (SERT) in the raphe and hippocampus, suggesting enhanced 5-HT clearance from the synaptic cleft also contributes to a reduced serotonergic stress response [189]. Acute amphetamine administration can increase SERT activity at the membrane [198]; however, repeated administration of amphetamine or its derivatives consistently fails to alter SERT expression or function in the hippocampus [199–204]. Therefore, while psychostimulants interact acutely with SERT, chronic psychostimulant exposure does not appear to alter SERT expression or function in the hippocampus to alter 5-HT activity during withdrawal.

The organic cation transporter 3 (OCT3) is a low affinity, high capacity transporter that contributes to 5-HT clearance, and a high density of OCT3 is present in the hippocampus [205–210]. OCT3 is directly linked to anxiety behavior, as OCT3 knockout mice display an anxiolytic phenotype [211] and OCT3 inhibition has antidepressant-like effects in rats [210]. Similarly, *SERT* knockout mice consistently display heightened OCT3 activity in the hippocampus [212, 213] and increased anxiety-like behavior [214, 215], as well as increased OCT3 mRNA in the hippocampus (but not other brain regions) [213]. This suggests that OCT3 may have a region-specific role for 5-HT reuptake in the hippocampus [209, 211, 213, 216]. Accordingly, amphetamine inhibits OCT3 monoamines transport [208, 217] (although see [218]) and withdrawal from methamphetamine is associated with decreased OCT3 mRNA in *whole brain* homogenates [212]. However, OCT3 expression and function are *increased* in the ventral hippocampus of rats at 24 hours of withdrawal from chronic amphetamine, resulting in increased 5-HT clearance in this region [203, 204]. Thus, psychostimulant exposure may enhance OCT3-mediated serotonin uptake in the hippocampus to produce the heighten anxiety states observed in these animals.

In addition, chronic cocaine administration increases $5HT_{1B}$ autoreceptors [219], which regulate serotonin release and anxiety-like behavior in the ventral hippocampus [220, 221]. Thus, psychostimulant-induced increases of $5HT_{1B}$- and OCT3 expression in the ventral hippocampus may reduce ventral hippocampal 5-HT levels and enhance anxiety/avoidance behavior during withdrawal (**Figure 2**) [175, 197, 222–225]. Furthermore, reductions in evoked 5-HT release in the ventral hippocampus have been linked to augmented reinforcing properties of cocaine and ecstasy (MDMA) [226, 227]. Overall, psychostimulant exposure can induce multiple detrimental effects on serotonin signaling during withdrawal that can alter hippocampal activity, disrupt hippocampal communication with reward processing regions (nucleus accumbens), and may culminate in maladaptive behaviors (**Figure 2**).

The hippocampal *glucocorticoid stress* system may play a key role in anhedonia and dysphoria that drive relapse during psychostimulant withdrawal. In support of this suggestion, major depressive disorder—with core features of anhedonia and dysphoria—is associated with reduced hippocampal GR to MR ratio (GR/MR) [228] and reduced GR expression and function [229–231]. Knocking out central GR expression (except in the hypothalamus) produces a reliable depression-like phenotype in rodents, which is restored with tricyclic antidepressant treatment [232]. Antidepressants also increase hippocampal GR/MR ratio, expression, and function [233–236], and short-term treatment with the GR antagonist mifepristone improves depressive symptoms in hypercortisolemic patients [237, 238].

Repeated psychostimulant exposure—which produces dysphoric states in withdrawal [13, 16, 239, 240]—also results in reduced GR expression—and a reduced GR/MR ratio—in the ventral hippocampus (in rats) [114]. The reduced GR/MR ratio may result in MRs having a more pronounced effect in the ventral hippocampus [114], which may function to preserve HPA regulation and homeostasis, since MRs are thought to preserve basal HPA tone [103, 104]. In support of this possibility, neither plasma nor hippocampal corticosterone levels are altered under basal conditions after repeated amphetamine exposure [114]. However, reduced GR/MR ratio is associated with depression [228], and may thus contribute to the dysphoric states that cause relapse during psychostimulant withdrawal. Further, the reduced GR/MR ratio may alter hippocampal excitability and result in dysregulated serotonin- and dopamine responses to stress (Section 2 and [114]).

Interestingly, *protracted* amphetamine withdrawal (2 weeks) results in an enhanced corticosterone stress response in the ventral hippocampus, without altering basal hippocampal or plasma corticosterone levels, or *stress-induced* plasma corticosterone levels [134]. This enhanced hippocampal corticosterone stress response—paired with the possible persistence of lower GR/MR ratio in the ventral hippocampus [114]—may affect hippocampal regulation of accumbal dopamine output and drug salience (Section 2 and [29]). For example, preliminary findings suggest that a stress-relevant concentration of corticosterone infused into the ventral hippocampus rapidly enhances accumbal shell dopamine output (Section 2 and [29]), which may enable stress to enhance reward value [63] and promote goal-oriented behavior [60]. In amphetamine withdrawal, infusing corticosterone into the ventral hippocampus may *reduce* accumbal dopamine output [29]. Thus, corticosterone in the ventral hippocampus may enable stress to *reduce* reward value during psychostimulant withdrawal, thereby contributing

to anhedonia and dysphoria that can prompt relapse [13, 16]. Overall, these recent findings support a role for hippocampal corticosterone in mediating reward responses to stress, and suggest that dysregulated corticosterone signaling in the ventral hippocampus may contribute to stress-induced relapse during psychostimulant withdrawal.

Acute stress exposure has also been found to produce an immediate 3-fold increase of free corticosterone levels in the dorsal hippocampus [241]. GR/MR ratio is also altered in the dorsal hippocampus during psychostimulant withdrawal [114, 241]. In Ref. [241] an *increase* in GR/MR mRNA ratio was observed in the dorsal dentate and CA1 in response to withdrawal from extended access to daily cocaine self-administration, accompanied by increased GR mRNA in the dentate and CA3, and increased MR mRNA in the dentate. In contrast, others have shown that repeated amphetamine administration selectively *down*-regulates GR mRNA in the dorsal hippocampus (when sampled as a whole) [242–245]. Furthermore, in Ref. [114] a *reduction* in dorsal hippocampal GR/MR protein ratio was observed in response to repeated amphetamine exposure during acute (24 h) withdrawal, even though neither GR nor MR protein expression were significantly reduced [114]. The lack of change in GR protein expression was also observed after cocaine self-administration [246]. These differences suggest a possible dissociation between mRNA and protein expression, and may also suggest that psychostimulant exposure has differential effects on GR/MR regulation, dependent upon the exposure model, duration of drug abstinence, and hippocampal sub-region assessed.

Overall, the effects of psychostimulant exposure in the dorsal hippocampus seem to alter GR/MR protein ratio as well as GR and MR mRNA levels. The reduced GR/MR ratio in the dorsal hippocampus could reduce corticosterone-induced serotonin activity in that region [195], similar to the reduction observed in the ventral hippocampus [114]. This has not yet been tested; however, if present, reduced corticosterone-induced serotonin activity in the dorsal hippocampus could impair serotonin-mediated processing of stress-related memories [186] and thus disrupt stress adaptation. The resultant reduced stress coping ability could contribute to stress-induced relapse during psychostimulant withdrawal, as has been reported in humans [13]. Furthermore, the dorsal hippocampus sends excitatory projections to the nucleus accumbens core [51], where dopamine release is associated with coordinating motor programs necessary for drug-seeking [63]. However, dorsal hippocampal stimulation reduces extracellular dopamine in the accumbens core [247] where differential dopaminergic responses are observed in response to appetitive stimuli (increased dopamine) and aversive stimuli (decreased dopamine), while the dopaminergic response in the shell is enhanced regardless of stimulus type [248, 249]. Thus, future research should further dissect the differential roles of the dorsal and ventral hippocampus in contributing to psychostimulant abuse and withdrawal pathology through interactions with the mesolimbic dopamine system and stress responsivity.

4. Psychostimulant regulation of hippocampal structural plasticity: drug-context and negative affect

Psychostimulants dramatically alter structural plasticity; inducing long-term changes to dendrite and dendritic spine morphology [250], and potently altering adult neurogenesis, the

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process by which new neurons are generated in adulthood. Adult neurogenesis enables experience to alter neuronal circuitry (structural plasticity) in the hippocampus and other regions [251–254]. Adult neurogenesis in the dentate gyrus sub-region of the hippocampus, an essential region for drug-reward-memory formation [152], plays a role in hippocampal-dependent learning and memory [253, 255, 256], as well as hippocampal regulation of stress responses [257, 258] and anxiety-like behaviors [259].

Learning processes increase long-term survival of new neurons [260, 261] and contextual learning and remembering (novel object recognition) depend upon neuron survival for the ability to rearrange circuits (structural plasticity) [262–265]. Interestingly, removing new neurons after contextual fear- or water maze- training degrades memory [266]; however, increasing neurogenesis after training promotes *forgetting* of hippocampal-dependent recent memory, but not remote- or hippocampus-*independent* memory [267, 268]. Thus, augmented hippocampal neurogenesis can weaken existing memories and facilitate encoding of new experiences, whereas diminished neurogenesis can stabilize existing memories and impede new memory encoding. Similarly, adult neurogenesis promotes cognitive flexibility and inhibitory control, behaviors regulated by the ventral hippocampus, suggesting ventral hippocampal neurogenesis significantly contributes to these behaviors [269–272].

Importantly, dorsal-ventral differences are distinguished in hippocampal neurogenesis processes. Several studies indicate predominant neurogenesis in the *dorsal*- compared to the *ventral*- dentate gyrus [224, 273–277]. However, new neurons mature more slowly in the ventral dentate than in the dorsal, suggesting a prolonged period in which immature neurons could be influenced by activity and incorporated or removed from local circuitry [278, 279]. Therefore, a larger pool of potential new neurons in the *dorsal* dentate gyrus might contribute to rapid spatial memory formation, whereas slower maturation in the *ventral* dentate gyrus may support the regulation of affective states. In support of this notion, an enriched environment preferentially increases neurogenesis in the *dorsal* dentate, whereas antidepressant treatment increases neurogenesis and chronic stress decreases neurogenesis to a greater degree in the *ventral* dentate gyrus [280–284].

The specific role of dentate gyrus neurogenesis in regulating anxiety and negative affect remains unclear [285]. Several studies correlate reduced neurogenesis with increased anxiety-like behaviors [259, 286–288]. For example, antidepressants that reduce anxiety states stimulate neurogenesis in the rodent and human hippocampus [289–292]; however, suppressing neurogenesis alone does not seem to be sufficient to induce anxiety-like behaviors [293–296]. Events that induce negative affect—such as chronic stress—also suppress adult hippocampal neurogenesis [297] and increasing adult neurogenesis reduces anxiety and depression-like behaviors in mice treated chronically with corticosterone [298], supporting a role for neurogenesis in mediating hippocampal responses to stress. Stress-induced suppression of cell proliferation in the hippocampus may occur through GRs, which are expressed on proliferating cells [299]. Further, impaired neurogenesis is associated with weakened HPA axis feedback inhibition and increased glucocorticoid levels after acute stress [257, 258]. This suggests that neurogenesis may maintain hippocampal regulation of HPA activity. Thus, impaired neurogenesis may intensify subsequent glucocorticoid effects on hippocampal function, in part through altered serotonergic neurotransmission (see Section 3). This may induce long-term stress sensitivity and negative affect.

Psychostimulants directly regulate the process of adult hippocampal neurogenesis. In rats, chronic but not acute cocaine exposure reduces proliferation rates in the dentate gyrus, but does not alter newborn cell survival rates [300–302]. However, in mice, cocaine seems to increase proliferation [303], and its effects on neuron survival appear to depend on existing vulnerability and drug dosage [304, 305]. Amphetamines have less of an impact on proliferation rates (relative to cocaine), but a greater tendency to reduce the long-term survival of newborn cells [224, 306, 307]. However, methamphetamine exposure reduces both proliferation and survival of new neurons [308, 309]. While most research has focused on the negative regulation of neurogenesis by drugs of abuse, multiple positive effects on neurogenesis have also been observed, particularly during withdrawal. These include increased markers of immature neurons during withdrawal [302, 303, 310, 311] and increased survival of hippocampal progenitors [312, 313]. It appears that drug-seeking behaviors persist independent of recovery from initial drug-induced decreases in new neuron proliferation [302]. However, altered hippocampal neurogenesis impacts drug-taking behaviors. When hippocampal neurogenesis is impaired prior to cocaine self-administration training, rats take greater amounts of cocaine and display higher breakpoints (vs controls), suggesting an intensification of drug reward [314]. Natural reward (sucrose administration) is not altered by this process [314], although transgenic mice with impaired neurogenesis exhibit no sucrose preference, which is an indication of anhedonia [258]. Further, impairing neurogenesis prior to cocaine self-administration training does *not* alter relapse to drug-seeking [314], yet impairing neurogenesis *after* self-administration training—or before CPP—increases context-induced drug-seeking behavior and impedes extinction [314, 315]. This suggests that impaired neurogenesis enhances potency of drug-associated environmental cues in a time-dependent fashion, and *enhancing* neurogenesis may promote *forgetting* of recent hippocampal-dependent drug-reward memory [267]. Increased neurogenesis elicited by voluntary wheel-running or environmental enrichment *before* conditioning also delays extinction of cocaine CPP, whereas running that occurs *after* conditioning accelerates cocaine CPP extinction [316, 317] (although see [318]). Together, these studies suggest that hippocampal neurogenesis may play a role in drug-reward-context memory formation and relapse to drug-seeking.

Psychostimulants may alter neurogenesis processes at least partially through their interactions with the hippocampal dopamine system. Dopamine is known to selectively modulate neurogenesis and immature neuron activity [319], and the ventral hippocampus receives a higher density of dopaminergic inputs than the dorsal hippocampus [320], which may contribute to the dorsa-ventral differences observed in hippocampal neurogenesis processes (described above). Interestingly, dopamine receptor activation promotes adult hippocampal neurogenesis [321, 322], but dopamine can also decrease the capacity of young neurons to express LTP by persistently attenuating young neuron inputs [319]. Psychostimulant-induced alterations to hippocampal dopamine output could then selectively modulate the activity of immature neurons and dictate their subsequent integration into hippocampal circuitry. In support of this suggestion, cocaine enhances LTP magnitude selectively in the ventral hippocampus (where dopamine innervation is highest) in a dopamine-receptor-dependent fashion [158]. Likewise, cocaine-induced CPP stimulates context-dependent activation of adult-born neurons to a greater extend in the ventral dentate gyrus [323]. Altogether, these findings suggest that psychostimulants may exert dynamic effects on

hippocampal neurogenesis, promoting functional integration or reducing proliferation or survival, depending upon hippocampal region and age of the newly-generated cells at the time of drug experience (**Figure 2**) [324]. This preferential activation could promote formation and incubation of drug-context associations. Additionally, altered neurogenesis—perhaps through changes in immature neurons—could indirectly influence hippocampal networks involved in mediating anxiety states—including those induced by drug use and withdrawal—depending upon individual susceptibility, experience, and withdrawal state (**Figure 2**). Overall, more studies are necessary to determine the long-term impact of psychostimulants and withdrawal on new neuron integration along the dorsal-ventral extent of the hippocampus. Specifically, it will be important to uncover the subsequent impact of psychostimulant-induced neurogenesis on drug memory reinstatement, and further identify the underlying mechanisms at play, to develop new therapeutic strategies.

5. Conclusions

Together, the literature reviewed indicates that the hippocampus contributes to drug-reward processes, drug-related memory formation, and drug-induced anxiety and dysphoria. Neuroadaptations following repeated drug administration lead to heightened hippocampal-mesoaccumbal activity, thus amplifying responses to psychostimulants and associated cues. At the same time, a persistent dysregulation of the hippocampal component of the brain's emotional system produces a bias toward negative affect-like responses (**Figure 2**). Moreover, long-term alterations of neurogenesis within the hippocampus may contribute to relapse vulnerability through enhanced drug sensitivity, enhanced drug memory, or anxiogenic stimuli. However, further study is necessary to determine how psychostimulants modulate the hippocampus to heighten hippocampal-mesoaccumbal activity, and particularly how hippocampal neurogenesis functions to influence drug-reward and drug-related memories. Future studies should also explore the functional implications of the impact of drugs of abuse and withdrawal on the hippocampus regarding its dorsal-ventral axis. A better understanding of regional differences may help clarify the roles of neurogenesis in changes induced by psychostimulants on different types of hippocampus-dependent behavior. Taking into consideration the activity of these hippocampal systems under drug naïve conditions, chronic psychostimulant-induced alterations to the hippocampus produce ineffective maladaptive behavioral responses to stress and environmental challenges. Restoration of these abnormalities within the hippocampus, either in neuronal activity, neurochemical levels, or neurogenesis could provide an effective therapeutic option to ameliorate negative affect and relapse vulnerability in psychostimulant addiction.

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