

Review

Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction

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It has long been hypothesized that conditioning mechanisms play major roles in addiction. Specifically, the associations between rewarding properties of drugs of abuse and the drug context can contribute to future use and facilitate the transition from initial drug use into drug dependency. On the other hand, the self-medication hypothesis of drug abuse suggests that negative consequences of drug withdrawal result in relapse to drug use as an attempt to alleviate the negative symptoms. In this review, we explored these hypotheses and the involvement of the hippocampus in the development and maintenance of addiction to widely abused drugs such as cocaine, amphetamine, nicotine, alcohol, opiates, and cannabis. Studies suggest that initial exposure to stimulants (i.e., cocaine, nicotine, and amphetamine) and alcohol may enhance hippocampal function and, therefore, the formation of augmented drug-context associations that contribute to the development of addiction. In line with the self-medication hypothesis, withdrawal from stimulants, ethanol, and cannabis results in hippocampus-dependent learning and memory deficits, which suggest that an attempt to alleviate these deficits may contribute to relapse to drug use and maintenance of addiction. Interestingly, opiate withdrawal leads to enhancement of hippocampus-dependent learning and memory. Given that a conditioned aversion to drug context develops during opiate withdrawal, the cognitive enhancement in this case may result in the formation of an augmented association between withdrawal-induced aversion and withdrawal context. Therefore, individuals with opiate addiction may return to opiate use to avoid aversive symptoms triggered by the withdrawal context. Overall, the systematic examination of the role of the hippocampus in drug addiction may help to formulate a better understanding of addiction and underlying neural substrates.

Addiction is a major worldwide health problem that results in maladaptive behavioral changes, some that can last a lifetime. This behavioral plasticity, often times maladaptive, must be associated changes in neural plasticity. In fact, it has been noted multiple times that there is a high degree of overlap between the neurobiology of learning and memory and the neurobiology of addiction (e.g., White 1996; Kelley 2004; Hyman et al. 2006; Volkow et al. 2014; Goodman and Packard 2016). Drugs of abuse are often linked to disrupted learning, but the relationship between drugs of abuse and learning is more complex as drug use and abuse is also associated with the development of strong but maladaptive memories that contribute to drug-seeking behavior and addiction. It is the overarching premise of this review that initial or acute use of drugs can facilitate the development of maladaptive memories between drug effects and environmental stimuli and that these associated memories can exert strong behavioral control and facilitate drug-seeking behavior and relapse. With continued use of drugs, learning deficits emerge along with cognitive inflexibility. These learning deficits and cognitive inflexibility combined with previously formed maladaptive drug-context/drug-cue associations contribute to the maintenance of addiction.

While there are multiple types of learning, this review will focus on hippocampus-mediated learning. The hippocampus is perhaps the iconic brain region associated with learning and

memory. For instance, the work of Scoville and Milner (1957) with patient H.M., whose severe epilepsy was treated with complete resection of the hippocampus and surrounding medial temporal lobe tissue, demonstrated the critical importance of this brain region in the formation of new long-term declarative memories. The patient H.M. could not maintain new declarative memories. This is particularly problematic because declarative memories contribute to self-definition as they encompass memories of events and autobiographical memories. As part of an essential role in declarative memory formation, the hippocampus is especially good at binding information together to form complex representations (Sutherland and Rudy 1989; for review, see Yonelinas 2013) that are necessary for spatial and contextual memory formation (O'Keefe and Dostrovsky 1971; Kim and Fanselow 1992; Kim and Lee 2011; Loureiro et al. 2012). In addition to involvement in long-term declarative memory formation, the hippocampus is also well known as one of the brain regions that demonstrate a high-level synaptic plasticity, often assessed by changes in long-term potentiation (LTP); (Teyler and DiScenna 1987; Lynch et al. 1990). The high degree of plasticity in the hippocampus and the ability of this region to support contextual and declarative memories may facilitate drug-induced changes in hippocampal function that have a profound effect on behavior.

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It is clear that the physiological effects of drugs of abuse can become associated with contextual information, contributing to future drug-seeking behavior (Bardo et al. 1984; Carr et al. 1988; Bienkowski et al. 1996; Le Foll et al. 2006; Tropea et al. 2008; Kutlu et al. 2015a). Because of the critical role of the hippocampus in learning contextual information (Smith and Mizumori 2006), drug-associated changes in hippocampal function may contribute to the development of maladaptive drug-context associations. With continued drug use, adaptations including tolerance occur and these changes could disrupt hippocampal function. Chronic drug use is often associated with cognitive deficits (Ornstein et al. 2000; Robbins et al. 2008; Stavro et al. 2013), and these deficits could contribute to addiction by interfering with acquisition of adaptive behavior that supports the cessation of drug use. Furthermore, withdrawal symptoms for multiple drugs of abuse include cognitive deficits (Solowij 1995; Jacobsen et al. 2005), which could contribute to relapse when individuals attempt to reverse these deficits (Khantzian 1985; Rukstalis et al. 2005; Patterson et al. 2010). It is beyond the scope of this review to discuss all drugs of abuse; therefore, we will focus on cocaine, amphetamine, nicotine, ethanol, opiates, and cannabis, examining for each drug the effects of acute administration, chronic administration, and withdrawal on hippocampus learning and hippocampal synaptic plasticity. In addition, because there is substantial evidence showing that self-administration and yoked-administration of drugs result in the same effects on hippocampal plasticity (Thomas and Everitt 2001; Thomas et al. 2003; Yamaguchi et al. 2004, 2005; Domínguez-Escribà et al. 2006; Noonan et al. 2008), we will review studies using both contingent and noncontingent drug administration together. Evidence from human subject studies along with laboratory animal studies will be reviewed.

Cocaine

The effects of acute administration on hippocampus-dependent learning and memory

Cocaine, a highly addictive psychostimulant derived from the leaf of *Erythroxylon coca*, is often characterized by compulsive use and obsessive drug seeking (Dackis and O'Brien 2001). Cocaine addiction affects roughly 2 million people in the USA, with 1.5 million of them identified as "cocaine users," and every day there are 1700 new users (U.S. Department of Health and Human Services 2011). In addition to cocaine's negative health consequences including cardiovascular, pulmonary, and psychiatric complications (Brody et al. 1990; Haim et al. 1995; Lange and Hillis 2001), cocaine has been reported to be the most commonly used illicit drug among patients seeking emergency care (40.3%; SAMHSA 2011). These figures highlight cocaine addiction as a disease with devastating consequences; thus, understanding the processes underlying the development and maintenance of cocaine addiction is vital.

Despite its negative health consequences, when acutely administered cocaine activates the brain's reward circuitry, producing a euphoric state that serves as a reinforcer for future cocaine use (Volkow et al. 1999). In addition to the pleasurable effects, acute cocaine has also been shown to improve cognition in humans (Garavan et al. 2008) and enhance learning and memory in laboratory rodents (Wood et al. 2007). However, these procognitive effects during initial cocaine exposure may be responsible for the formation of maladaptive drug-context/-cue associations that may facilitate the development of compulsive drug-seeking behavior. In support of this hypothesis, studies have shown that laboratory rodents learn to self-administer cocaine (e.g., Richardson and Roberts 1996; España et al. 2010) and associate a specific context with cocaine reward (e.g., Spyrali et al. 1982; Vidal-Infer

et al. 2012) remarkably quickly. The rewarding effects of cocaine are so powerful that a number of studies have shown that an especially addiction-prone subset of laboratory animals trained to self-administer cocaine prefer cocaine over feeding and mating and compulsively self-administer cocaine at fatal rates (Deneau et al. 1969; Lenoir et al. 2007; Kerstetter et al. 2012; Perry et al. 2013). This suggests that the coupling of cocaine's procognitive effects with overstimulation of the reward system may result in dysregulated behavioral outcomes rather than enhancement of behavioral control.

There are several brain regions within the mesolimbic circuit that are directly affected by cocaine, including reward-related regions such as the nucleus accumbens and ventral tegmental area as well as regions that control cognition such as the prefrontal cortex and hippocampus (Bardo 1998; Thomas et al. 2008). Among these regions, the hippocampus may be a critical site for both the rewarding effects of acute cocaine (Kuhar et al. 1991; Koob et al. 1994; Everitt et al. 1999; Dackis and O'Brien 2001; Anderson and Pierce 2005) as well as formation and maintenance of cocaine-context associations (Grant et al. 1996; Childress et al. 1999; Kilts et al. 2001; Wexler et al. 2001) due to its involvement in both reward and learning and memory (Aggleton et al. 1986; Burgess et al. 2002; Daumas et al. 2005; for review, see Tulving and Markowitsch 1997). For example, permanent lesions of the dorsal, but not ventral hippocampus, as well as temporary inactivation of the dorsal hippocampus by local muscimol infusions impaired cocaine conditioned place preference (CPP; Meyers et al. 2003, 2006). Similarly, studies suggest that the dorsal hippocampus controls context-induced reinstatement (Fuchs et al. 2005, 2007; Xie et al. 2010; Wells et al. 2011). In contrast to the dorsal hippocampus, the ventral hippocampus has been shown to mediate cue-induced and cocaine-primed reinstatement of cocaine self-administration (Rogers and See 2007; Ramirez et al. 2009). Moreover, Vorel et al. (2001) showed that theta burst stimulation in the ventral hippocampus resulted in relapse of extinguished cocaine self-administration. It is also possible that dorsal and ventral hippocampus may differentially contribute to the stress-induced relapse to cocaine seeking as studies have shown that stress affects synaptic plasticity in these regions in opposite ways. That is, while stress diminished synaptic plasticity in the dorsal hippocampus, ventral hippocampal synaptic plasticity was enhanced by stress (Maggio and Segal 2007, 2009; Segal et al. 2010). Therefore, ventral hippocampus may assume a greater role in reinstatement of cocaine-seeking behavior during a period of high stress such as cocaine withdrawal. But this hypothesis has not been directly examined.

These studies establish the hippocampus as the focal region for the formation and maintenance of long-term memories that support cocaine-context and cocaine-cue associations. In support of the hippocampus as the primary target of cocaine in modulating drug-related memories, acute cocaine has also been shown to alter hippocampal LTP, a form of synaptic plasticity that may underlie learning and memory (Bliss and Collingridge 1993). However, the effects of cocaine on LTP are mixed (see Table 1 for a summary of results). For example, Smith et al. (1993) found that acute cocaine (30–60 μM) blocked induction of LTP in the CA1 region of the hippocampus without affecting NMDA receptors or already established LTP. In contrast, Stramiello and Wagner (2010) found that enhanced dopaminergic signaling associated with acute cocaine application (6 μM) increased hippocampal LTP in the CA1 subregion. Nevertheless, these contradicting results may be explained by the fact that different drug concentrations were used by these studies: 30–60 μM by Smith et al. (1993) and 6 μM by Stramiello and Wagner (2010). In support of the differential effects of low and high doses of cocaine on LTP, Thompson et al. (2005) showed that while lower cocaine

Table 1. Effects of cocaine on hippocampal LTP

Study	Cocaine admin	Dose	Pathway	Effect
Smith et al. (1993)	Acute cocaine (in vitro)	30–60 μ M	Schaffer collaterals (CA1)	Decreased LTP
Stramiello and Wagner (2010)	Acute cocaine (in vitro)	6 μ M	Schaffer collaterals (CA1)	Enhanced LTP
Thompson et al. (2005)	Acute cocaine (in vitro)	5–30 μ M	Schaffer collaterals (CA1)	Enhanced LTP with lower doses Decreased LTP with a higher dose
Thompson et al. (2002)	Chronic cocaine (in vitro)	15 mg/kg/ d \times 5 d	Schaffer collaterals (CA1)	Enhanced LTP
Thompson et al. (2004)	Chronic cocaine SA	0.5 mg/kg FR1 \times 15 d	Schaffer collaterals (CA1)	Enhanced LTP with short-term withdrawal Decreased LTP with long-term withdrawal
Guan et al. (2009)	Chronic cocaine i.p. injections	20 mg/ kg \times 14 d	Schaffer collaterals (CA1)	Enhanced LTP with short-term withdrawal

(SA) self-administration; (i.p.) intraperitoneal.

concentrations (5–10 μ M) enhanced hippocampal LTP, inhibition of LTP was observed with a higher concentration of cocaine (30 μ M). Also in line with these results, Wood et al. (2007) found that an acute moderate dose of cocaine disrupted contextual and cued fear conditioning, whereas a low dose of acute cocaine enhanced both types of learning. Given that, in the absence of tolerance to cocaine, it is likely that most first-time cocaine users initially administer lower doses of cocaine, and therefore, they are subject to both rewarding and procognitive effects, which may underlie enhanced hippocampal plasticity that leads to maladaptive drug-associated memories.

In addition to acute cocaine-induced enhancement of hippocampal LTP, there is also evidence showing that acute cocaine positively modulates the activation of the proteins within the cell signaling cascades that support long-term memory formation. For example, phosphorylation of extracellular signal-regulated kinases -1 and -2 (ERK1/2), a protein required for both hippocampus-dependent learning and hippocampal LTP (Gooney et al. 2002), was elevated in the dorsal hippocampus following cocaine CPP (Tropea et al. 2008). Similarly, phosphorylation of hippocampal cAMP-response element binding protein (CREB), a transcription factor that plays a major role in synaptic plasticity and long-term memory formation (Abel and Lattal 2001; Trifilieff et al. 2006), was increased following cocaine CPP (Tropea et al. 2008). In addition to ERK1/2 and CREB, cAMP-dependent protein kinase (PKA) seems to be required for the formation and maintenance of cocaine-context memories. For example, Cervo et al. (1997) showed that post-training intracerebroventricular injections of a PKA inhibitor disrupted the consolidation of cocaine CPP. These results suggest that within a limited dose range, acute cocaine augments hippocampal plasticity and activity of cell signaling cascades that support hippocampal LTP, which may enhance the formation of the maladaptive drug-context memories. It is possible that augmented hippocampal function may result in drug-context-triggered cravings and drug seeking as initial cocaine use turns into cocaine addiction with chronic cocaine abuse.

Effects of chronic cocaine and cocaine withdrawal on hippocampal function

In contrast to acute cocaine's procognitive effects, chronic cocaine users have been repeatedly shown to exhibit a variety of neuropsychological deficits ranging from disrupted executive function, visuoperception, and psychomotor function (Bolla

et al. 1999) to impairments of verbal memory and attention (Mittenberg and Motta 1993). These deficits were positively correlated with the severity of cocaine addiction (Ardila et al. 1991; for review, see Robbins et al. 2008). Accordingly, chronic cocaine administration also leads to impaired spatial learning in rodents that were exposed to cocaine during adulthood (Mendez et al. 2008) or adolescence (Santucci et al. 2004; Santucci 2008). Chronic cocaine-induced learning deficits also seem to be long-lasting as studies suggest that the impairing effects of chronic cocaine exposure persist during cocaine withdrawal (Kelley et al. 2005) as long as 3 mo (Mendez et al. 2008). These studies suggest that chronic cocaine exposure may result in a diminished ability to learn new associations. This effect of chronic

cocaine use may be particularly problematic because inability to change established drug-context associations or to learn new associations that may counteract the maladaptive ones may facilitate the maintenance of cocaine addiction. For example, exposure therapy for addiction focuses on reversing learned drug-context and drug-cue associations to reduce context or cue-triggered craving, drug seeking, and drug relapse (Rosenthal and Kutlu 2014). Reduced ability to make new associations during chronic cocaine use or cocaine withdrawal may disrupt cognitive flexibility and increase the likelihood of relapse.

Importantly, reduced hippocampal function during chronic cocaine use and cocaine withdrawal may be responsible for the decreased ability to form adaptive associations to counteract context-drug memories as studies found that hippocampal function was altered with chronic administration of cocaine (London et al. 1990; Beveridge et al. 2006; Gu et al. 2010). For example, cocaine administration produced increased BOLD signal in the hippocampus of cocaine-dependent human subjects compared with saline administration (Breiter et al. 1997), while the strength of connectivity between the hippocampus and dorsomedial prefrontal cortex was decreased in chronic cocaine users (Gu et al. 2010). Also, chronic cocaine self-administration resulted in reduced glucose metabolism in the hippocampus in humans and nonhuman primates (London et al. 1990; Beveridge et al. 2006). These results suggest a central role for changes in the hippocampus in cocaine-induced cognitive deficits.

However, in contrast to reduced hippocampus-dependent learning during chronic cocaine and withdrawal, there is also evidence showing that chronic in vivo cocaine administration resulted in enhanced LTP (Thompson et al. 2002). Thompson et al. (2004) found that prior chronic cocaine self-administration resulted in enhanced hippocampal LTP in the CA1 subregion following 3 d of withdrawal but not following 30 d of withdrawal. In line with these results, other studies found enhanced LTP 3 d after chronic cocaine administration (Guan et al. 2009). Interestingly, Thompson et al. (2004) also found decreased hippocampal LTP 100 d after chronic cocaine self-administration, which suggests that chronic cocaine may have different short-term and long-term effects on hippocampal plasticity. In line with the results of Thompson et al. (2004) showing enhanced LTP during short-term withdrawal, Valzachi et al. (2013) found that chronic cocaine administration resulted in increased phosphorylated CREB levels in the hippocampus following 12 d of withdrawal. Therefore, there is a potential discrepancy between behavioral studies showing disrupted hippocampal learning and memory (Melnick et al.

2001; Santucci et al. 2004; Mendez et al. 2008; Santucci et al. 2008) and electrophysiology studies showing enhanced LTP with chronic cocaine administration (Thompson et al. 2002, 2004; Guan et al. 2009). These contradicting results might have arisen because of the fact that behavioral studies cited in this review tested their subjects in long-term withdrawal between 5 wk and 4 mo. Importantly, Thompson et al. (2004) and Guan et al. (2009) showed that chronic cocaine administration enhanced LTP in short-term withdrawal (3 d), whereas disrupted LTP following long-term withdrawal (100 d). In support of this hypothesis, Del Olmo et al. (2007) found that chronic cocaine self-administration enhanced spatial learning 3 h following the last cocaine infusion. Thus, the dose of cocaine and the length of time from the last drug administration seem to be major determinants of cocaine's effects on hippocampal learning and memory and may explain some of the cognitive deficits exhibited by cocaine users. It is also important to note that increased LTP does not necessarily mean increased learning (Saucier and Cain 1995).

Overall, the studies cited clearly show that initially cocaine enhances hippocampus-dependent learning and memory resulting in strong cocaine-context associations, which may lead to drug-seeking behavior and chronic cocaine abuse. In turn, chronic cocaine exposure alters hippocampus function and results in hippocampal cognitive deficits during withdrawal, which may contribute to impaired cognitive flexibility and inability to reverse cocaine-context associations, contributing to relapse.

Amphetamine

The effects of acute amphetamine on hippocampus-dependent learning and memory

Racemic α -methylphenethylamine (amphetamine, also known as speed) was first discovered by Barger and Dale in 1910 and later synthesized and marketed under the brand name Benzedrine to treat a variety of conditions such as narcolepsy, depression, Parkinson's disease, and pulmonary dysfunction (Heal et al. 2013). However, the euphoric effects of amphetamine were quickly discovered and subsequently amphetamine has been abused for its rewarding properties such as sensations of pleasure, self-confidence, energy, and alertness (CDC 2007). Owing to these effects, millions of Benzedrine tablets, under the name of "Energy tablets," were given to the members of the American and British military (Bett 1946) as well as Japanese soldiers during World War II, and the release of the amphetamine stockpiles after the war resulted in an amphetamine-dependency epidemic in Japan (Masaki 1956). In the USA, early studies that provided a platform for the prescription of amphetamine to reverse combat fatigue largely ignored its addictive properties (Guttman and Sargent 1937; Tidy 1938; Bett 1946), which resulted in a widespread prescription of amphetamine-based medications and eventually amphetamine addiction peaked in mid-2000s (CDC 2007). Today amphetamine dependence is a widespread problem (CDC 2007). According to Substance Abuse and Mental Health Services Administration (SAMHSA 2005), 1.4 million Americans had used methamphetamine, an N-methylated derivative of amphetamine, in the last year. Moreover, the rate of amphetamine or methamphetamine abuse-related hospitalization more than tripled between the years 1993 and 2003 (SAMHSA 2006a). Importantly, despite its initial pleasurable effects, amphetamine has serious negative health consequences with prolonged abuse. These effects include physical symptoms such as decayed teeth, weight loss, skin lesions, stroke, and heart attack as well as mental symptoms such as paranoia, hallucinations, anxiety, irritability, social isolation, aggressiveness, and violence (CDC 2007).

Shortly after its initial release as a prescription drug in 1935, procognitive effects of amphetamine (e.g., improved intelligence, concentration, and intellectual performance) were reported in humans (Guttman and Sargent 1937; Tidy 1938). These initial studies were later confirmed by studies showing enhanced memory consolidation (Soetens et al. 1993), memory recall (Zeeuw and Soetens 2007), attention and psychomotor performance (Johnson et al. 2000; Silber et al. 2006), information processing (Halliday et al. 1994), logical reasoning (Johnson et al. 2000), and working memory (Mattay et al. 2000) by amphetamine and its derivatives such as dextroamphetamine in humans. Because of its attention-improving properties amphetamine was used to treat ADHD but then this treatment was replaced by drugs with fewer psychoactive side effects (Wilens et al. 2008). Animal studies also showed that, similar to other stimulants, acute amphetamine and methamphetamine enhanced hippocampus-dependent learning and memory in the T-maze (Ito and Canselier 2010), Morris water maze (Packard and McGaugh 1994; Brown et al. 2000; Cao et al. 2013), radial arm-maze (Strupp et al. 1991), and avoidance conditioning (Doty and Doty 1966). However, these procognitive effects were dose-dependent as higher doses of acute amphetamine resulted in deficits in hippocampus-dependent learning and memory (Blokland et al. 1998). Studies also showed that amphetamine and methamphetamine produced significant CPP (Carr et al. 1988; Bardo et al. 1999; Parker et al. 2004; Thorn et al. 2012; Han et al. 2014) and self-administration (Lyness et al. 1979; Piazza et al. 1989, 1990, 1991; Krasnova et al. 2010; McClung et al. 2010), which suggests that the rewarding effects of amphetamine and methamphetamine facilitated the formation of drug-context associations. In line with acute amphetamine's enhancing effects on hippocampus-dependent learning and memory, hippocampal LTP was also increased by acute amphetamine (Delanoy et al. 1983; Gold et al. 1984; Morimoto et al. 1987) and methamphetamine administration (Heysieattalab et al. 2016). Moreover, evidence suggests that acute methamphetamine-induced enhancement of hippocampus-dependent learning as well as amphetamine CPP are dependent on the upregulation of ERK1/-2 and CREB in the hippocampus (Gerdjikov et al. 2004; Cao et al. 2013). Therefore, it is possible that enhanced hippocampus-dependent learning and memory by acute amphetamine administration may drive the formation of drug/reward-context associations by enhancing hippocampal plasticity. This hypothesis is supported by the results showing that acute injections of amphetamine enhanced morphine CPP (Blais and Janak 2006) and conditioned approach to sucrose (Blais and Janak 2007). Together with studies showing that acute amphetamine produced procognitive effects as well as enhanced hippocampal plasticity, these results show that development of amphetamine-dependence may be influenced by augmentation of drug-context associations.

Effects of chronic amphetamine use on hippocampal function

In spite of its acute procognitive effects, chronic use of amphetamine and methamphetamine has devastating effects on cognition, including impaired memory, attention, cognitive flexibility, cognitive inhibition, and decision making (Ornstein et al. 2000; Simon et al. 2000, 2001; Salo et al. 2002; for review, see Nordahl et al. 2003). These cognitive deficits persist during amphetamine and methamphetamine withdrawal (Kalechstein et al. 2002; Newton et al. 2004; Johanson et al. 2006). Similar to results from human studies, animal studies also indicate cognitive deficits in hippocampus-dependent spatial learning tasks such as the spatial object recognition, T-maze and Morris water maze during amphetamine (Mandillo et al. 2003) and methamphetamine

(Simões et al. 2007; North et al. 2013; Reichel et al. 2014) withdrawal. In addition, there is evidence showing that deficits in the hippocampus-dependent learning and memory paralleled reductions in hippocampal LTP induced by methamphetamine withdrawal (Swant et al. 2010; North et al. 2013). These results indicate that amphetamine withdrawal disrupts cognition, including hippocampus-dependent learning and memory and associated hippocampal plasticity. These cognitive problems may underlie relapse to amphetamine use as amphetamine administration may be seen as a way to self-medicate these deficits.

Overall, similar to other stimulants, when administered acutely amphetamine has procognitive effects including enhanced hippocampus-dependent learning and memory. Acute amphetamine's procognitive properties may result in augmentation of drug-context associations and contribute to the development of amphetamine addiction. In contrast, withdrawal of amphetamine following chronic use results in deficits in hippocampus-dependent learning and memory. In addition to the failure to reverse already established drug-context associations, relapse to amphetamine use may be motivated by attempts to self-medicate for withdrawal-induced cognitive deficits.

Nicotine

Effects of acute, chronic, and withdrawal from chronic nicotine on hippocampus-dependent learning and memory

Prolonged exposure to tobacco products, particularly cigarette smoking, continues to be the leading cause of preventable premature death claiming more than 400,000 people's lives in the USA each year (20% of all deaths; Benowitz 2010; U.S. Department of Health and Human Services 2014). Accordingly, active and passive tobacco use has been causally linked to deaths from cancer, cardiovascular disease, and pulmonary disease (Sandler et al. 1985; Carbone 1992; McBride 1992; Sherman 1992). Although nicotine, the main psychoactive component in tobacco, may play less of a role in the development of these conditions compared with other toxins in the tobacco extract, it is the main component leading to addiction. Therefore, by causing repeated use and prolonged exposure to toxins, nicotine should be considered as the indirect cause of the smoking-related diseases and deaths (Benowitz 2010).

An estimated 15%–19% of the U.S. population has been reported to use nicotine products habitually (CDC 2012). Nicotine's rewarding effects seem to play a major role in the development of nicotine dependence (Watkins et al. 2000). In humans, nicotine results in euphoria, increased energy and arousal, and suppressed anxiety (Pomerleau and Pomerleau 1985, 1992; Stolerman and Jarvis 1995; Benowitz 1996). Accordingly, in animals, acute injections of nicotine leads to CPP (Fudala et al. 1985; Risinger and Oakes 1995; Vastola et al. 2002; Grabus et al. 2006; Brielmaier et al. 2008; Kutlu et al. 2015a). Similarly, there is also evidence showing that smokers learn to associate nicotine's effects with specific contexts and cues (Dols et al. 2000, 2002; Thewissen et al. 2005), suggesting humans and animals learn to associate nicotine's rewarding effects with specific contextual cues. In addition to its rewarding effects, acute nicotine has cognitive enhancing properties in humans. Specifically, acute nicotine administration enhances attention (Parrott and Craig 1992; Bates et al. 1995; Hahn et al. 2007; Hong et al. 2011), learning and memory (Mangan and Golding 1983; Peeke and Peeke 1984; Warburton et al. 1986; Colrain et al. 1992), and information processing (Wesnes and Warburton 1983; Provost and Woodward 1991; for review, see Sherwood 1993). In agreement with human studies, there is a great body of evidence suggesting that acute nicotine augments hippocampus-dependent contextual and spatial learning and

memory while not affecting hippocampus-independent subtypes of learning (e.g., cued learning) in rodents. For example, numerous studies from both our group and other laboratories showed that acute nicotine enhanced hippocampus-dependent contextual and trace fear conditioning, but not cued fear conditioning (Gould and Wehner 1999; Gould and Higgins 2003; Gould 2003a; Gould and Lommock 2003; Gould et al. 2004; Wehner et al. 2004; Davis et al. 2006, 2007; Davis and Gould 2006, 2007; Raybuck and Gould 2007; Gulick and Gould 2008; Kenney and Gould 2008; Tian et al. 2011; Portugal et al. 2012a, b), as well as spatial object recognition (Kenney et al. 2011), spatial learning and memory in Morris water maze (Abdulla et al. 1996; Sharifzadeh et al. 2005), and spatial working memory in radial arm maze tasks (Levin and Torry 1996; Levin et al. 1997, 1998). It is possible that the formation of nicotine-context associations may benefit from these procognitive effects of acute nicotine. That is, through promoting hippocampal plasticity, acute nicotine may enhance formation of drug-context associations and promote future nicotine use evoked by contextual and environmental cues. In support of this hypothesis, there is evidence showing that contextual cues associated with nicotine reward reinstate extinguished nicotine self-administration in rats (Diergaarde et al. 2008; Wing and Shoaib 2008). Therefore, these studies support the possibility that acute nicotine-induced enhancement of hippocampus-dependent learning and memory may contribute to development of nicotine-dependence.

Once nicotine dependence is established, it is especially difficult to reverse habitual use of nicotine. There is evidence showing that even though 80% of smokers express willingness to quit (CDC 2002) and 40% of them attempt to quit (CDC 2005), only 3% of them successfully quit (Hughes et al. 2004). One of the main contributors to this low rate of successful quitting is the negative symptoms experienced during nicotine withdrawal. Negative symptoms include irritability and restlessness, anxiety, social problems, increased food consumption, constipation, and craving for nicotine (Benowitz 2008). In addition to these general symptoms, cognitive deficits such as difficulty concentrating (Pomerleau et al. 2000), disrupted working memory (Jacobsen et al. 2005; Mendrek et al. 2006), verbal memory problems (Jacobsen et al. 2005), increased response time (Snyder et al. 1989; Bell et al. 1999), and problems in paired-associate learning (Kleinman et al. 1973) were observed during nicotine withdrawal. In line with these reports, animal studies also showed that while chronic nicotine did not have any effect on hippocampus-dependent contextual and trace fear conditioning, nicotine withdrawal impaired hippocampal learning and memory (Davis et al. 2005; Davis and Gould 2009; Raybuck and Gould 2009; Gould et al. 2012, 2014a; Portugal et al. 2012a, b; Wilkinson and Gould 2013). Overall, human and animal studies demonstrate hippocampus-dependent learning and memory enhancement during initial nicotine exposure and cognitive deficits during nicotine withdrawal. These results may suggest that initial nicotine exposure results in strong nicotine-context associations that support drug-seeking behavior, which may facilitate the transition into chronic nicotine use. Chronic use leads to neuronal adaptations that produce tolerance to the enhancing effects of nicotine and withdrawal deficits in hippocampus learning (Wilkinson et al. 2013; Gould et al. 2014a). Importantly, the nicotine withdrawal deficits in learning may increase the chance of relapse to avoid these negative symptoms. In line with this interpretation is the self-medication hypothesis of addiction, which states that one of the major contributors to addiction is the drive to reduce the negative symptoms that arise during drug withdrawal (Khantzian 1985). In support, nicotine has been shown to alleviate cognitive deficits in various mental disorders such as schizophrenia (Adler et al. 1993; for review, see Parikh et al. 2016) and attention deficit/

hyperactivity disorder (ADHD, Potter and Newhouse 2008; Evans and Drobos 2009; for review, see Kutlu et al. 2015b), two populations that show higher rates of smoking (38%–42% of ADHD population, Pomerleau et al. 1995; 80%–90% in schizophrenia, George and Krystal 2000; de Leon and Diaz 2005). Also in support of the self-medication hypothesis, there is evidence showing that cognitive deficits during nicotine withdrawal predict future relapse to nicotine use (Rukstalis et al. 2005; Patterson et al. 2010). Thus, increased relapse to nicotine use during withdrawal may be a mechanism to self-medicate for withdrawal-induced cognitive deficits akin to what occurs with the cognitive impairments seen in mental disorders.

Modulation of hippocampal plasticity by nicotine

As the previous section explained, while acute nicotine enhances hippocampus-dependent learning and memory, these processes are disrupted during nicotine withdrawal. Evidence from electrophysiology studies support these conclusions and suggest that altered hippocampal plasticity by acute nicotine and withdrawal from chronic nicotine is largely responsible for these effects. For example, Alkondon et al. (2003) found that nicotinic acetylcholine receptor (nAChR) agonists lead to AMPA and NMDA receptor-mediated excitatory postsynaptic currents (EPSCs) in CA1 subregion of the hippocampus. Moreover, several studies showed that hippocampal nAChR activation by nicotine and other nAChR agonists resulted in enhanced hippocampal LTP (Fujii and Sumikawa 2000; Welsby et al. 2006, 2007; Jia et al. 2010); that is, strengthening of weak stimulation-induced short-term LTP (Fujii et al. 1999; Matsuyama et al. 2000; Matsuyama and Matsumoto 2003) as well as direct induction of LTP (He et al. 2000; Matsuyama et al. 2000; Matsuyama and Matsumoto 2003). Moreover, antagonism of nAChRs blocked learning-induced CA1 LTP (Mitsushima et al. 2012). In addition to the effects of acute administration of nicotine and other direct nAChR agonists, hippocampal plasticity has been shown to be altered during nicotine withdrawal. For example, Yamazaki et al. (2006) found that the lowered threshold for hippocampal LTP induction during nicotine administration was reversed during withdrawal. Therefore, the alterations of hippocampal LTP are in parallel with behavioral effects of acute nicotine and nicotine withdrawal on hippocampus-dependent learning. Thus, altered LTP may underlie the development of nicotine addiction through formation of drug-context associations during early use and the development of cognitive deficits during chronic use and withdrawal.

In further support of nicotine modulating synaptic plasticity, nicotine can alter key cell signaling kinases and transcription factors known to modulate hippocampal learning and plasticity such as PKA, ERK1/2, and CREB (for review, see Kutlu and Gould 2016). For example, Gould et al. (2014b) showed that infusions of a subthreshold dose of the PKA inhibitor PKI 14–22 amide into the dorsal hippocampus reversed enhancement of contextual fear conditioning by acute nicotine. Similarly, the same study also showed a temporal shift in learning-related dorsal hippocampal PKA peak activation as a result of systemic acute nicotine administration. There is also evidence showing that acute nicotine administration increased ERK1/2 phosphorylation (Nakayama et al. 2001) and this effect was reversed by PKA inhibitors (Dajas-Bailador et al. 2002), suggesting that acute nicotine-induced alterations of PKA translates into changes in downstream MAPK signaling. Finally, nicotine also modulates the activation of the transcription factor CREB in the hippocampus. For example, acute nicotine enhanced CREB activation (Nakayama et al. 2001; Hu et al. 2002). CREB activity was also enhanced during nicotine CPP (Pascual et al. 2009) and acute nicotine-induced enhancement of contextual fear conditioning (Kenney et al. 2012),

suggesting that CREB may be critical for the formation of drug-context memories. Overall, the above-mentioned studies provide strong evidence indicating that nicotine's control over hippocampal cell signaling cascades and consequently hippocampal plasticity may be an underlying factor for enhancement of drug-context memories by acute nicotine and cognitive deficits observed during nicotine withdrawal.

In summary, the results of the cited studies suggest that initially nicotine enhances drug-context associations, which leads to the development of sustained nicotine use and consequently nicotine dependence. While chronic nicotine does not seem to alter hippocampus-dependent learning and memory, these processes are impaired during nicotine withdrawal. This effect also seems to contribute to maintenance of nicotine dependence as smokers may self-medicate for withdrawal-induced cognitive deficits by returning to nicotine use.

Alcohol

The effects of acute ethanol on hippocampus-dependent learning and memory

Alcoholism is a complex behavioral and physiological phenomenon in which the abuser progressively loses control over alcohol consumption despite its negative health consequences (Koob et al. 1998). Indeed, severe health problems have been associated with alcohol overconsumption, including medical conditions ranging from cardiovascular and psychiatric diseases to certain cancers (e.g., mouth, liver, and esophageal cancers), and liver cirrhosis (Rehm et al. 2003). In its 2014 “Global status report on alcohol and health” the World Health Organization (WHO) stated that alcohol abuse is linked to more than 200 health problems and responsible for ~3.3 million deaths world-wide every year (5.9% of all deaths), which establishes alcohol as one of the most harmful drugs of abuse to human health.

In addition to the overall health problems caused by alcohol abuse, alcoholism is also known to cause cognitive impairments (Ryan and Butters 1983; see Stavro et al. 2013 for a meta-analysis) with over 50% of alcoholics reporting memory and cognition problems (Vetreno et al. 2011). The results from laboratory animal studies also demonstrate alcohol's impairing effects on cognition. Specifically, acute ethanol administration impaired hippocampus-dependent learning and memory in the Morris Water Maze (Markwiese et al. 1998; Shimizu et al. 1998; Matthews et al. 2002; Berry and Matthews 2004), the radial arm maze (Matthews et al. 1995, 1999; Vandergriff et al. 1995; White et al. 1997, 1998), the sandbox maze (Rajendran and Spear 2004), and contextual fear conditioning (see Table 2 for the summary of acute ethanol's effects on hippocampus-dependent learning and memory) (Melia et al. 1996; Gould 2003b; Gould and Lommock 2003; Wehner et al. 2004; Gulick and Gould 2007, 2008).

In contrast, there is evidence showing that light to moderate alcohol intake (1–2 drinks per day) may decrease the risk of cardiovascular mortality, coronary heart disease, and stroke in humans (Fagrell et al. 1999; O'Keefe et al. 2014), which suggests that lower doses of ethanol may have some beneficial effects on human health. In addition, there is evidence showing that unlike higher doses of ethanol, lower doses are required for ethanol-induced dopaminergic reward signaling (Gessa et al. 1985), successful ethanol self-administration (Sinden and Le Magnen 1982) and ethanol CPP (Bienkowski et al. 1996; Cunningham and Henderson 2000). In fact, higher doses resulted in decreased ethanol self-administration and conditioned place aversion (CPA; Cunningham and Henderson 2000). Furthermore, Sinden and Le Magnen (1982) showed that low-dose ethanol self-administration linearly increased during 5 d of training whereas

Table 2. Effects of acute alcohol on hippocampus-dependent and hippocampus-independent learning

Study	Subjects	Alcohol Admin	Dose	Task	Effect
Shimizu et al. (1998)	Adult Wistar rats	Acute (oral) 20 min before training	2.0 g/kg	MWM	Impaired HDM
Matthews et al. (2002)	Adult Sprague-Dawley rats	Acute (i.p.) 30 min before testing	1.0–2.0 g/kg	MWM	Impaired HDM
Berry and Matthews (2004)	Adult C57BL/6j mice	Acute (i.p.) 30 min before testing	1.25–2.25 g/kg	MWM	Impaired HDM
Markwiese et al. (1998)	Adult and Adolescent Sprague-Dawley rats	Acute (i.p.) 30 min before training	1.0–2.0 g/kg	MWM	Impaired HDM in adolescents No effect on HIM
Rajendran and Spear (2004)	Adult and Adolescent Sprague-Dawley rats	Acute (i.p.) 30 min before training	0.5–1.5 g/kg	Sandbox maze	Impaired HDM in adults No effect on HIM
Matthews et al. (1995)	Adult Long-Evans rats	Acute (i.p.) 30 min before training	0.75–2.5 g/kg	Radial-arm maze	Impaired HDM
White et al. (1997)	Adult Long-Evans rats	Acute (i.p.) 30 min before testing	0.75–2.0 g/kg	Radial-arm maze	Impaired HDM
White et al. (1998)	Adult Long-Evans rats	Acute (i.p.) 20 min before training	0.7–2.1 g/kg	Radial-arm maze	Impaired HDM
Matthews et al. (1999)	Adult Long-Evans rats	Acute (i.p.) 30 min before testing	1.0–2.0 g/kg	Radial-arm maze	Impaired HDM Enhanced HIM with higher dose
Melia et al. (1996)	Adult Sprague-Dawley rats	Acute (i.p.) 10 min before training	0.5–1.5 g/kg	Contextual and Cued FC	Impaired HDM No effect on HIM
Gould and Lommock (2003)	Adult C57BL/6j mice	Acute (i.p.) 15 min or immediately before training	1.0 g/kg	Contextual and Cued FC	Impaired HDM No effect on HIM
Gould (2003b)	Adult C57BL/6j mice	Acute (i.p.) 15 min before training and/or testing	0.5–1.5 g/kg	Contextual and Cued FC	Impaired HDM Impaired HIM with higher doses
Wehner et al. 2004	Adult C57BL/6j mice ^a	Acute (i.p.) 15 min before training	1.0–2.0 g/kg	Contextual and Cued FC	Impaired HDM
Gullick and Gould (2007)	Adult C57BL/6j mice	Acute (i.p.) 15 min before training	0.25–1.0 g/kg	Contextual and Cued FC	Impaired HIM with the highest dose Impaired HDM and HIM with higher doses
Gullick and Gould (2008)	Adult C57BL/6j mice	Acute (i.p.) 15 min before training	0.25–1.5 g/kg	Contextual and Cued FC	Enhanced HDM and HIM with lower doses Impaired HDM and HIM with higher doses Enhanced HDM and HIM with lower doses

(MWM) Morris water maze; (i.p.) intraperitoneal; (HDM) hippocampus-dependent memory; (HIM) hippocampus-independent memory.

^aWild-type to nAChR knock-out strains.

self-administration of a high-dose ethanol decreased significantly below saline levels. In line with these observations, Gulick and Gould (2007) found that while higher doses of acute ethanol resulted in deficits in both hippocampus-dependent contextual and hippocampus-independent cued fear conditioning, lower doses of ethanol enhanced both types of learning. This report is critical in terms of understanding how alcohol-context and alcohol-cue associations are formed following initial alcohol consumption. That is, Gulick and Gould's (2007) results suggest that lower doses of ethanol may enhance the formation of ethanol-context/cue associations initially, which may facilitate future ethanol intake. The data showing sustained self-administration and CPP with lower doses and decreased self-administration and CPA with higher doses of ethanol are also in support of this hypothesis. Therefore, these results suggest that a lower dose of ethanol facilitates maladaptive ethanol-context associations by enhancing reward processes and contextual and cued learning necessary for these maladaptive associations to occur.

Effects of prolonged alcohol exposure on hippocampal function

As described earlier, both rewarding and procognitive effects of initial alcohol exposure may predict increased rates of subsequent alcohol intake through enhanced drug-context learning. In addition to possible enhancement of hippocampus-dependent learning and memory with low doses of ethanol, studies also showed that prolonged ethanol consumption uniformly resulted in hippocampus-dependent spatial learning deficits (Bond and Di Giusto 1976; Beatty et al. 1984; Ehrlich and Humpel 2012), which were shown to be irreversible in some cases (Cippitelli et al. 2010). Binge ethanol exposure also results in necrotic cell death and neurodegeneration in the hippocampus (Obernier et al. 2002; Hamelink et al. 2005). Moreover, evidence from studies examining the effects of ethanol on hippocampal plasticity suggests that chronic ethanol inhibits hippocampal LTP (Durand and Carlen 1984; Tremwel and Hunter 1994; Roberto et al. 2002, 2003), which may underlie chronic ethanol-induced deficits in hippocampus-dependent learning and memory. Ethanol inhibition of LTP may result from decreased excitability of hippocampal neurons due to blockage of NMDA receptors, specifically NR1/NR2A or NR1/NR2B subtypes (Hoffman et al. 1989; Lovinger et al. 1989; Schummers and Browning 2001; Izumi et al. 2005; for review, see Allgaier 2002) as well as activation of inhibitory GABA_A receptors (Allan and Harris 1986; Aguayo 1990; Reynolds et al. 1992; Schummers and Browning 2001). In addition to alterations of NMDA and GABA receptor function in the hippocampus, ethanol-induced suppression of hippocampal LTP has been associated with the inhibition of MAPK signaling (Sanna et al. 2002; Roberto et al. 2003; Chandler and Sutton 2005; Wang et al. 2012). Roberto et al. (2003) showed that following chronic intermittent ethanol treatment, both LTP and ERK1/2 activation were reduced in the hippocampus. Similarly, multiple studies found that ERK1/-2 phosphorylation was reduced in the hippocampus after chronic ethanol administration, whereas this effect was reversed during ethanol withdrawal and occurred again during ethanol reexposure (Sanna et al. 2002; Chandler and Sutton 2005; Wang et al. 2012). Moreover, CREB phosphorylation in the hippocampus was also inhibited following chronic ethanol exposure while ethanol withdrawal enhanced hippocampal CREB (Bison and Crews 2003). The ethanol-induced changes in MAPK-CREB pathway are crucial to understanding the molecular mechanisms underlying the hippocampal deficits during chronic ethanol exposure because numerous studies have shown that activation of this cell signaling pathway is necessary for long-term

memory formation (e.g., Atkins et al. 1998; Vianna et al. 2000) and LTP (e.g., Winder et al. 1999; Kelleher et al. 2004; for review, see Kutlu and Gould 2016). Overall, these studies show that chronic ethanol can inhibit cell signaling cascades involved in learning through activation of GABAergic receptors and blockage of NMDA receptors in the hippocampus.

Evidence from human studies seems to be in agreement with animal studies showing chronic ethanol-induced cognitive impairments and disrupted hippocampal function. For example, impairments in learning and memory (Ryan and Butters 1983; Vetreno et al. 2011), attention and executive function (Loeber et al. 2009), and abstraction (Klisz and Parsons 1977; for review, see Bates et al. 2002) were reported after chronic alcohol use. These cognitive deficits also persisted during abstinence (Fein et al. 1990; Stavro et al. 2013). These learning and memory problems may contribute to relapse to alcohol use and maintenance of alcohol addiction as individuals with withdrawal-induced cognitive deficits attempt to self-medicate.

In line with chronic ethanol's impairing effects on cognition is a condition known as Wernicke-Korsakoff syndrome (WKS), which results from a prolonged alcohol exposure-induced thiamine deficiency. WKS is characterized by gradual impairments in memory function that spread into other cognitive domains as chronic alcohol use is maintained (Ryan et al. 1980; Cermak et al. 1988; for review, see Isenberg-Grzeda et al. 2012). Thus, WKS is associated with myriad of cognitive deficits such as impairment in verbal processing (Cermak et al. 1973, 1974; Oscar-Berman et al. 2004), discrimination learning (Jones et al. 1975), decision making (Brand et al. 2005), and spatial working memory (Joyce and Robbins 1991). WKS patients exhibited extensive damage to the hippocampus that was linked to the memory deficits (Sullivan and Marsh 2003; Caulo et al. 2005; Sullivan and Pfefferbaum 2009). Specifically, hippocampal volume in WKS patients was greatly reduced to a level comparable to patients with Alzheimer's disease (Sullivan and Marsh 2003). Moreover, an fMRI study showed that the hippocampal activity detected in controls during memory encoding and recognition was absent in the patients with WKS (Caulo et al. 2005). Results from WKS patients clearly indicate that prolonged alcohol exposure has deleterious effects on hippocampus function and morphology, which may be the source of hippocampus-dependent learning and memory deficits. Therefore, ethanol-induced neural damage and hippocampus-dependent learning deficits may contribute to the negative symptoms of alcoholism.

In conclusion, lower doses of acute ethanol enhance both hippocampus-dependent contextual and hippocampus-independent cued learning while higher doses of ethanol disrupt both types of learning. Nevertheless, hippocampus-dependent learning may be especially sensitive to the effects of acute ethanol because numerous studies suggest that acute ethanol alters hippocampal function. In contrast, chronic ethanol's detrimental effects on hippocampus-dependent learning and hippocampal function are relatively ubiquitous and one-sided. That is, chronic ethanol exposure alters hippocampal anatomy, disrupts hippocampal plasticity, and changes hippocampal cell signaling leading to impairments in hippocampus-dependent learning. These effects may contribute to the cognitive deficits that characterize ethanol-related syndromes such as WKS. Overall, given that acute ethanol enhances and chronic ethanol disrupts hippocampus-dependent learning, it is possible that initially learned drug-context memories are enhanced by acute ethanol and remain relatively unaltered during chronic ethanol use due to an inability to reverse established ethanol-context memories. This hindered ability to update drug-context association with new information may contribute to the persistence of and relapse to ethanol addiction.

Opiates

The effects of acute and chronic opiate exposure on hippocampus-dependent learning and memory

Opiates are a class of psychoactive compounds naturally derived from the opium poppy or synthetically produced that include morphine, diacetylmorphine (diamorphine or heroin), codeine, oxycodone, and methadone. Opiates such as oxycodone are legally prescribed to patients for pain management. Importantly, legally prescribed opiates lose their analgesic effects as tolerance develops, which, in some cases, results in drug dependence as patients try to achieve analgesic potency or avoid withdrawal symptoms. Consequently, although the prevalence of opiate addiction in the U.S. population is ~8% (SAMHSA 2006b), opiate prescription use in chronic pain patients can be as high as 90% (Chabal et al. 1997; Manchikanti et al. 2004) and up to 16% of these patients have been documented to abuse prescribed opiates (Manchikanti et al. 2006). This suggests that opiate addiction is a potential risk to widespread segments of the population.

In addition to its analgesic effects, opiate-induced euphoria is the leading cause for opiate-seeking in nontherapeutic addicts but not in therapeutic addicts who abuse opiates for its analgesic potency (McAuliffe et al. 1985). However, as Koob et al. (1989) hypothesized, opiates' positive effects are counterbalanced by severe negative consequences of opiate withdrawal such as aches and pain, agitation, anxiety, muscle cramps, nausea, and sleep disturbances (Alexander and Hadaway 1982; Jaffe 1990; West and Gossop 1994). Accordingly, while laboratory rodents learn CPP for morphine (Bardo et al. 1984, 1995; Tzschentke and Schmidt 1995; Milekic et al. 2006), heroin (Bozarth 1987; Bardo et al. 1995), methadone (Steinpreis et al. 1996), and oxycodone (Niikura et al. 2013), they also show CPA to the contexts associated with spontaneous withdrawal (Myers and Carlezon 2010) and precipitated withdrawal induced by opiate receptor antagonists such as naloxone (Jin et al. 2005; Stinus et al. 2005; Li et al. 2007; Manwell et al. 2009). It is important to note that development of CPA to withdrawal symptoms is in line with the fact that opiate withdrawal symptoms are usually considered more severe than symptoms associated with stimulant withdrawal (e.g., amphetamine and cocaine). Thus, it is possible that avoidance of withdrawal plays an especially important role in opiate dependence.

Similar to cocaine and ethanol, opiate abuse also correlates with long-lasting cognitive deficits in humans (Rogers et al. 1999; Darke et al. 2000; Ornstein et al. 2000; Curran et al. 2001; Davis et al. 2002). Abusers of morphine, heroin, and methadone show impairments in episodic memory (Curran et al. 2001), visual memory, verbal memory, information processing, problem solving (Darke et al. 2000), word fluency and attention (Davis et al. 2002), and spatial tactile and verbal memory (Hill and Mikhael 1979; Ornstein et al. 2000). In addition to the effects of chronic abuse of opiates, Curran et al. (2001) showed that a single dose of methadone resulted in impaired episodic memory in a population tolerant to opiates. Although several studies have suggested that opiate abuse-related cognitive decline may be linked to compromised frontal lobe function (Robinson and Kolb 1999; Ornstein et al. 2000), studies examining the effects of opiate exposure on hippocampus morphology and hippocampus-dependent learning and memory suggested that some of the cognitive deficits observed in opiate abusers may be related to altered hippocampal function. For example, opiates have been shown to inhibit adult neurogenesis in the hippocampus (Eisch et al. 2000) and alter proteins associated with hippocampal synaptic density such as clathrin (Morón et al. 2007). Moreover, acute morphine has also been shown to disrupt spatial memory retention in

Morris water maze (Farahmandfar et al. 2010) and Y-maze (Ma et al. 2007), another hippocampus-dependent task (Retailleau et al. 2013). There is also evidence showing that chronic heroin and morphine impair hippocampus-dependent spatial learning in Morris water maze (Means et al. 1996; Tramullas et al. 2008), radial arm maze and Y-maze (Spain and Newsom 1991). Moreover, the impairing effects of chronic administration of opiates on spatial memory have been linked to an increase in proteins associated with apoptosis such as Fas, FasL, and Bad in the cortex and hippocampus (Tramullas et al. 2008), which suggests that chronic opiates may interfere with hippocampus-dependent learning through increased hippocampal neurotoxicity and cell-death. Finally, in addition to their effects on hippocampus-dependent learning and hippocampal function, both acute (Ito et al. 2001) and chronic opiate exposure (Ito et al. 2001; Salmanzadeh et al. 2003) have been shown to disrupt hippocampal plasticity in the form of decreased hippocampal LTP. These results show that both acute and chronic opiate administration result in deficits in hippocampus-dependent learning and memory and, therefore, it is difficult to explain sustained opiate use by enhanced drug-context memories in this case as there is no evidence suggesting that acute administration of opiates may enhance hippocampus-dependent learning and memory. Nevertheless, studies showing that laboratory rodents successfully learn CPP to opiates suggest that normal drug-context learning occurs through the reinforcing effects of the opiates.

Opiate withdrawal-induced enhancement of drug-context associations

Opiates may be different from the other drugs of abuse reviewed here as low doses of opiates do not enhance memory; instead, opiate withdrawal may alter hippocampal function contributing to formation of memories linking the aversive effects of withdrawal and withdrawal context. As mentioned, opiate withdrawal is often more severe than stimulant withdrawal (Alexander and Hadaway 1982; Jaffe 1990; West and Gossop 1994). Earlier models of opiate addiction, such as Wikler's (1948), proposed that avoidance of withdrawal symptoms is a major motivator for continued drug use. Also, latter models followed Wikler's hypothesis by describing opiate addiction as a balance between positive (reward) and negative (withdrawal) reinforcers (Koob et al. 1989). In line with these models, rodents learn to avoid contexts paired with spontaneous (Myers and Carlezon 2010) or opioid antagonist precipitated opiate withdrawal (Jin et al. 2005; Stinus et al. 2005; Li et al. 2007; Manwell et al. 2009). Human studies also report conditioned withdrawal symptoms to specific contexts (O'Brien et al. 1977; Childress et al. 1986; McLellan et al. 1986). For example, O'Brien et al. (1977) precipitated unconditioned withdrawal symptoms such as tearing, yawning, decreased skin temperature, increased heart rate, and rhinorrhea by using naloxone injections in a methadone-dependent group. These withdrawal symptoms occurred in a sound-attenuated room in the presence of a specific background music and odor. Conditioned withdrawal symptoms were tested following saline injections. The results of this study showed that participants exhibited strong conditioned withdrawal symptoms to the withdrawal context in the absence of naloxone. Moreover, there is qualitative evidence suggesting that contexts associated with withdrawal increased drug craving in opiate addicts (Wikler 1973). These results suggest that human opiate addicts also learn conditioned place aversion to the withdrawal context, which may contribute to future use of opiates in attempts to self-medicate to reduce negative symptoms associated with a withdrawal context.

Interestingly, opiate withdrawal is linked to normalization and enhancement of hippocampus-dependent learning and

memory. For example, studies showed that while short-term withdrawal disrupted performance in the Y-maze (Ma et al. 2007) and Morris water maze (Dougherty et al. 1996), long-term withdrawal and naloxone-precipitated withdrawal reversed chronic opiate-induced impairments in these tasks (Dougherty et al. 1996; Li et al. 2001; Ma et al. 2007). Furthermore, there are data showing that spontaneous withdrawal from chronic morphine enhanced the acquisition of cocaine-self administration (He and Grasing 2004), suggesting that drug-context learning may be enhanced during opiate withdrawal. More direct evidence for enhancement of future drug seeking as a result of associations between withdrawal symptoms and withdrawal context came from Kenny et al. (2006) who showed that associations between contextual cues and naloxone-induced precipitated withdrawal symptoms enhanced heroin self-administration in heroin-dependent rats. These studies indicate that hippocampus-dependent drug withdrawal-context associations may reinforce future drug use to avoid negative withdrawal symptoms.

Studies examining hippocampal plasticity are in agreement with the view of enhanced opiate withdrawal-related memories. For example, Mansouri et al. (1997) found that hippocampal LTP was increased during withdrawal following 20 d of chronic morphine treatment via drinking water. Similarly, Ito et al. (2001) showed that hippocampal LTP was attenuated following acute (1 h) intracerebroventricular morphine administration via osmotic minipumps whereas it was enhanced when tested in withdrawal following 72 h of chronic morphine administration via the same route. This effect was reversed when the slices were treated with morphine, suggesting reexposure to morphine following withdrawal reversed the withdrawal-induced enhancement of hippocampal plasticity. Similarly, Salmazadeh et al. (2003) showed that while LTP was reduced in hippocampal slices treated with morphine following chronic morphine administration via drinking water, treatment with artificial cerebrospinal fluid (ACSF, spontaneous withdrawal) or naloxone (precipitated withdrawal) reversed the chronic morphine-induced impairments in hippocampal LTP. There was also another study showing that morphine withdrawal following repeated injections of morphine reduced hippocampal LTP (Pu et al. 2002). However, discrepancies between chronic morphine administration regimens (continuous vs. intermittent) employed by these studies make it difficult to compare results. Still, it is possible that continuous administration of opiates via osmotic mini-pumps or drinking water may mimic prolonged opiate abuse better than short-term intermittent injections. Finally, there is evidence showing that hippocampal ERK1/-2 phosphorylation is enhanced during heroin withdrawal (Edwards et al. 2009), which indicates upregulated MAPK signaling may underlie opiate-induced enhancement of hippocampal plasticity. In summary, in contrast to acute and chronic opiate administration, converging evidence from multiple studies suggests that hippocampal plasticity may be enhanced during opiate withdrawal.

Overall, the studies reviewed here suggest a potential contributing factor for sustained opiate abuse. That is, strong memories are formed about the rewarding effects of opiates, as reflected by strong CPP, whereas the association between aversive withdrawal symptoms and the context is augmented by enhanced hippocampus-dependent learning and plasticity during withdrawal from chronic opiate administration. Thus, the withdrawal-associated context may produce a strong drive for self-medication in an attempt to ameliorate severe context-evoked withdrawal symptoms, which could result in relapse to opiate use and continued addiction. This effect may be dependent on the enhancement of hippocampal LTP and phosphorylation of cell signaling kinases critical for hippocampal plasticity such as MAPKs.

Cannabis

The effects of cannabis on hippocampus-dependent learning and memory

Cannabis is a flowering plant that has long been used for the production of hemp-based goods (e.g., hemp oil and hemp fiber) and medicinal purposes (Hillig 2005). Some subspecies of cannabis that are selectively bred for a high yield of Δ^9 -tetrahydrocannabinol (THC), the main psychoactive constituent in the cannabis, are used in recreational drugs such as hashish and marijuana. Cannabis use currently receives increasing amount of attention in the USA as both medicinal and recreational marijuana are legalized or decriminalized in more than 20 states. In addition to the discussions on legalization of cannabis products, with 40% of the population having used marijuana at least once in their lifetime and ~23% current users, the prevalence of marijuana use is well-above cocaine, heroin, methamphetamine, inhalant abuse; matching cigarette smoking and alcohol use (SAMHSA 2014). Although usually perceived as a milder form of drug, like other drugs of abuse, short-term and long-term marijuana use has been linked to adverse health effects such as anxiety, psychosis, pulmonary problems as well as cognitive problems with prolonged use (Hall and Degenhardt 2009; Volkow et al. 2014). However, marijuana users also self-report positive effects of cannabis, including relaxation, analgesia, happiness, creativity, social benefits, and improved sleep (Goode 1970; Berke and Hernton 1974; Green et al. 2003). In line with the positive emotional effects of cannabis, THC-induced CPP (Valjent and Maldonado 2000; Braida et al. 2004; Ji et al. 2006; Le Foll et al. 2006) and THC self-administration (Takahashi and Singer 1979; Justinova et al. 2003; Braida et al. 2004) have been shown in laboratory animals. In these regards, cannabis exhibits similar properties with other drugs of abuse, namely rewarding effects with initial use. However, like opiates and unlike ethanol, cocaine, amphetamine, and nicotine, acute administration of THC and cannabidiol have been shown to disrupt hippocampus-dependent spatial learning in the Morris water maze and radial arm maze (Lichtman et al. 1995; Lichtman and Martin 1996; Da Silva and Takahashi 2002; Cha et al. 2007; Niyuhire et al. 2007) as well as contextual fear conditioning (Lemos et al. 2010; Stern et al. 2012). In line with the animal studies, human studies also suggest that acute cannabinoids result in impaired memory (Tinklenberg et al. 1970; Ferraro 1980; for review, see Ranganathan and D'Souza 2006). Therefore, in the case of cannabis, drug-context associations are formed in spite of hippocampal learning difficulties associated with cannabis use.

Cannabis dependence also results in a withdrawal syndrome during abstinence, which is characterized by heightened anxiety, irritability, negative mood, restlessness, shakiness, sleeping difficulty, stomach pain, strange dreams, sweating, and weight loss (Kouri and Pope 2000; Budney et al. 2003; for review, see Budney and Hughes 2006). These symptoms have been shown to be reversed by reexposure to THC (Budney et al. 2007). Comparative studies found that nicotine and cannabis withdrawal syndromes share similar negative symptoms (Vandrey et al. 2005, 2008; Budney et al. 2008). Moreover, as shown by self-report studies, the majority of cannabis users indicated that negative withdrawal symptoms were the major reason for their inability to quit and they attempted to self-medicate these symptoms, which usually resulted in relapse to cannabis use (Budney et al. 1998, 1999; Crowley et al. 1998; Copeland et al. 2001; Coffey et al. 2002; Stephens et al. 2002; Vandrey et al. 2005; Copersino et al. 2006). Also similar to nicotine withdrawal, marijuana users show cognitive deficits during abstinence from cannabis such as impaired mathematical skills, disrupted verbal expression, altered

encoding and retrieval of verbal memories, attentional problems, and executive function deficits (Block and Ghoneim 1993; Solowij 1995; Pope and Yurgelun-Todd 1996). There is evidence showing that rats undergoing THC withdrawal show deficits in hippocampus-dependent spatial learning (Wise et al. 2011). Overall, these studies suggest that both acute administration and abstinence from cannabis result in difficulties in cognition. Therefore, in line with self-medication hypothesis, it is possible that while hippocampus-dependent memory enhancement seen with nicotine is not apparent for cannabis, relapse to cannabis use due to withdrawal-induced cognitive and emotional deficits is a possible contributing factor for the maintenance of cannabis addiction.

Alterations in hippocampal plasticity by cannabinoids

Disruption of hippocampus-dependent learning as a result of acute cannabis use may result from deficits in hippocampal plasticity. For example, acute THC reduced the amplitude of both spontaneous and conditioned stimulus evoked potentials in the hippocampus (Campbell et al. 1986a,b). Moreover, THC eliminated the firing of the neurons in the CA1 subregion of the hippocampus induced by delayed match-to-sample task performance (Heyser et al. 1993). Furthermore, like THC, acute cannabinoid receptor agonists (e.g., WIN-55,212-2 and CP 55,940) also disrupted spatial memory in rats (Lichtman et al. 1995) and reduced hippocampal LTP (Nowicky et al. 1987; Collins et al. 1994, 1995; Terranova et al. 1995; Puighermanal et al. 2009; for review, see Sullivan 2000). For example, Puighermanal et al. (2009) showed that cannabinoid receptor CB1 activation impaired hippocampal LTP and this effect was associated with amnesic effects of acute THC in a hippocampus-dependent context recognition task. Moreover, enhanced hippocampal plasticity has been documented in mice lacking CB1 receptors (Bohme et al. 1999). In line with a modulatory role of CB1 receptors in hippocampal plasticity, CB1 activation has been shown to inhibit glutamatergic synapses in the hippocampus (Takahashi and Castillo 2006), indicating a negative regulation of NMDAR-dependent long-term memory formation by CB1 receptors. Although a majority of studies examining the effects of acute cannabinoids on hippocampal plasticity reported impaired hippocampal LTP, there is also evidence for disruption of LTP during withdrawal following chronic THC administration (Hoffman et al. 2007). Specifically, Hoffman et al. (2007) found that withdrawal following 3 or 7 d of chronic THC administration, but not following 1 d of administration, resulted in decreased hippocampal LTP 24 h after the last injection. Similarly, Fan et al. (2010) showed that following 7 d of repeated administration of THC, hippocampal LTP as well as phosphorylation of hippocampal CREB were attenuated during withdrawal and these effects were reversed by inhibition or deletion of hippocampal CB1 receptors. However, human chronic marijuana smokers have been shown to exhibit downregulated CB1 receptors in a variety of brain regions including the hippocampus (Hirvonen et al. 2012). This result seems to be conflicting with studies showing improved hippocampal plasticity with deletion or inhibition of CB1 receptors. The downregulation does not speak to the functional state of the receptors and thus, it is possible that these receptors may be more responsive to endocannabinoids, which may result in increased efficiency of the endocannabinoid system compared with systems where CB1 receptors are inhibited or completely absent. Thus, these studies suggest that both acute and withdrawal from chronic THC disrupted hippocampal LTP and these effects were associated with CB1 receptor activation. Given the apparent parallels between impairments in hippocampus-dependent learning and memory and disrupted hippocampal LTP, it is likely that disrupted hippocampal plasticity may underlie the hippocampus-

dependent learning and memory deficits observed following acute cannabinoid agonism and withdrawal from chronic cannabinoid administration.

Overall, the studies cited here clearly show that both acute administration of THC and THC withdrawal lead to cognitive deficits and these effects are mediated by CB1 receptor-mediated disruption of hippocampal plasticity. Given that removal of cognitive deficits exhibited by chronic marijuana smokers is one of the major motivators for relapse to smoke marijuana (Budney et al. 1998, 1999; Crowley et al. 1998; Copeland et al. 2001; Coffey et al. 2002; Stephens et al. 2002; Vandrey et al. 2005; Copersino et al. 2006), it is possible that hippocampal cognitive deficits trigger a self-medication response and contributes to maintenance of cannabis addiction.

Conclusion

In summary, the studies reviewed here provide evidence for the involvement of hippocampus-dependent learning and memory as well as hippocampal plasticity in development and maintenance of addiction. Specifically, acute administration of stimulants such as cocaine, nicotine, and amphetamine, as well as alcohol enhances hippocampus-dependent learning and memory. It is possible that this augments drug-context associations and contributes to future drug use. On the other hand, opiates and cannabis seem to disrupt hippocampus-dependent learning and memory following acute administration. Nevertheless, both opiates and cannabis produce strong CPP, suggesting that successful drug-context associations are formed regardless. In addition to the enhancement of drug-context associations during acute administration of these drugs, all drugs of abuse reviewed here except opiates produce strong deficits in hippocampus-dependent learning and memory and attenuated hippocampal plasticity during withdrawal, which may motivate attempts to self-medicate resulting in relapse and maintenance of drug use. In the case of opiates, unlike other drugs of abuse, withdrawal leads to enhanced hippocampus-dependent learning and memory, which may facilitate the development of context-evoked withdrawal symptoms that could facilitate relapse. Overall, human and laboratory animal studies suggest a significant role of drug-induced alterations of hippocampus-dependent learning and memory in development and maintenance of drug addiction.

Competing interest statement

We declare no potential conflict of interest.

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