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Brain-derived neurotrophic factor and addiction: Pathological versus therapeutic effects on drug seeking

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Abstract

Many abused drugs lead to changes in endogenous brain-derived neurotrophic factor (BDNF) expression in neural circuits responsible for addictive behaviors. BDNF is a known molecular mediator of memory consolidation processes, evident at both behavioral and neurophysiological levels. Specific neural circuits are responsible for storing and executing drug-procuring motor programs, whereas other neural circuits are responsible for the active suppression of these "seeking" systems. These seeking-circuits are established as associations are formed between drug-associated cues and the conditioned responses they elicit. Such conditioned responses (e.g. drug seeking) can be diminished either through a passive weakening of seeking-circuits or an active suppression of those circuits through extinction. Extinction learning occurs when the association between cues and drug are violated, for example, by cue exposure without the drug present. Cue exposure therapy has been proposed as a therapeutic avenue for the treatment of addictions. Here we explore the role of BDNF in extinction circuits, compared to seeking-circuits that "incubate" over prolonged withdrawal periods. We begin by discussing the role of BDNF in extinction memory for fear and cocaine-seeking behaviors, where extinction circuits overlap in infralimbic prefrontal cortex (PFC). We highlight the ability of estrogen to promote BDNF-like effects in hippocampal–prefrontal circuits and consider the role of sex differences in extinction and incubation of drug-seeking behaviors. Finally, we examine how opiates and alcohol "break the mold" in terms of BDNF function in extinction circuits.

Keywords

Cocaine; Alcohol; Opiates; Brain-derived neurotrophic factor; Extinction memory; Hippocampal–prefrontal systems

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1. Introduction

It has long been recognized that addiction is a disorder of learning and memory (Berke and Hyman, 2000; Di Chiara et al., 1999; Torregrossa et al., 2011; White, 1996). Repetitive drug use strengthens the learned associations between the interoceptive (e.g. rewarding) effects of a drug and various cues that predict drug availability and/or responses that lead to drug reward. The rewarding properties of abused drugs are thought to arise from the release of dopamine in the ventral tegmental area (VTA) projections to the nucleus accumbens, particularly the shell (Roberts et al., 1977; Wise and Bozarth, 1985). Given that dopamine plays an integral role in learning and memory, it can be difficult to distinguish dopamine's effects on the experience of drug reward or the hedonic aspects of drug taking, versus the strengthening of the behavior through reinforcement learning, whereby learned associations between cues and the drug they predict come to drive drug-seeking behavior. Indeed, once a cue becomes predictive of reward, dopamine neurons shift their firing from reward onset to cue onset (Hollerman and Schultz, 1999; Schultz et al., 1997). The incentive sensitization theory of addiction suggests that over time, the incentive salience, or motivational significance, of drug-related cues becomes pathologically amplified (Robinson and Berridge, 1993, 2001). This may account, in part, for the "incubation," or progressive amplification, of drug seeking that has been reported with longer periods of protracted abstinence (Grimm et al., 2001; Tran-Nguyen et al., 1998).

Brain-derived neurotrophic factor (BDNF) has a well-known role not only in neurodevelopment, where it has been shown to support synaptogenesis (Lu and Figurov, 1997; Lu et al., 2009; Shen and Cowan, 2010), but also in memory formation, where it promotes synaptic restructuring (Lu and Figurov, 1997; Lu et al., 2007; Rex et al., 2007; Schjetnan and Escobar, 2010; Yamada et al., 2002). Both of these processes likely contribute to the storage and retrieval of memories, an area of growing interest in the treatment of neuropsychiatric disorders with an etiological basis in learning and memory mechanisms. One of the hallmarks of novel learning is the activation of *N*-methyl-D-aspartate (NMDA) ionotropic glutamate receptors, which promote Hebbian learning by acting as coincidence detectors in the central nervous system (Tsien, 2001). At the cellular level, BDNF appears to support memory, at least in part, by enhancing NMDA receptor currents in neurons via activation of its tyrosine kinase receptor TrkB and subsequent intermediary molecules (e.g. the protein Fyn) (Xu et al., 2006; Yamada and Nabeshima, 2004). BDNF can be presynaptically released from neurons in an activity-dependent manner, and this typically occurs during neuronal bursting (Balkowiec and Katz, 2002), a type of high-frequency activity pattern that has been observed during episodes of memory consolidation (Burgos-Robles et al., 2007; Cooper, 2002). In the postsynaptic neuron, BDNF promotes NMDA receptor-dependent bursting (Levine et al., 1998; Madara and Levine, 2008; Rosas-Vidal et al., 2014) and thus, at a systems level, may work to strengthen neural circuits responsible for memory storage and retrieval.

Memory manipulation tactics are an area of active investigation for the treatment of addiction and other disorders involving a hyper reactivity to cues, including posttraumatic stress disorder (PTSD) (Lee et al., 2006; Milton, 2012; Monfils et al., 2009; Schiller et al., 2012; Spiers and Bendor, 2014). There are two main options for treatment of maladaptive

memories: (1) erasure of the pathological memory, or (2) creation of a new, inhibitory memory that opposes the pathological associations (Kiefer and Dinter, 2011; Merlo et al., 2014; Nic Dhonnchadha and Kantak, 2011). Memory erasure has been achieved through a process termed reconsolidation blockade, which interferes with the "re-storing" of memories once they have been retrieved (Milton and Everitt, 2010; Nader et al., 2000; Schwabe et al., 2014). In contrast, extinction training has been used to suppress pathological responses and is known to involve consolidation of a new inhibitory memory trace (Bouton, 1993; Bouton et al., 2006; Pavlov, 1927). The inhibitory extinction memory is thought to then compete with the original memory trace for control over the expression of conditioned behavior (Quirk et al., 2006). This occurs through the recruitment of inhibitory brain structures that are situated to inhibit expression centers that drive the prepotent conditioned response (Peters et al., 2009; Quirk et al., 2006).

Extinction and incubation have been argued to be opposing mnemonic processes, and BDNF plays a role in both, through its actions in distinct neural circuits. Here we compare BDNF effects on each of these processes, across different classes of abused drugs, focusing primarily on heroin and alcohol (cf. McGinty et al., 2014, for further comparison with cocaine). As estrogen has been shown to produce similar effects to BDNF on learning and memory, we also consider the impact of sex differences on these processes. We begin with a general discussion on the role of BDNF in memory, drawing from a literature on fear learning and memory.

2. BDNF and extinction memory

Extinction memory has particular therapeutic potential as it can be used to bring conditioned behaviors under cognitive and emotional control (Kantak and Nic Dhonnchadha, 2011; Kaplan et al., 2010). Extinction training is analogous to cue exposure therapy, where drug-related cues are presented in the absence of the outcome they predict (e.g. in the absence of the abused drug) (Davis et al., 2006; Myers and Carlezon, 2012). Over time, the conditioned responses triggered by the cues are diminished, or extinguished, through this new learning that the cues are now meaningless. The inhibitory learning that occurs during cue exposure therapy can be enhanced by pretreatment with the NMDA receptor co-agonist, D-cycloserine (Myers and Carlezon, 2012), and analogous effects have been observed in animal models of PTSD and drug addiction that incorporate an extinction learning phase (Kelamangalath et al., 2009; Ledgerwood et al., 2005; Thanos et al., 2011; Torregrossa et al., 2010). We know from these animal models that extinction of both fear and cocaine seeking rely on the prefrontal cortex (PFC), specifically the ventromedial portion (e.g. rodent infralimbic PFC) (Peters et al., 2008, 2009; Quirk and Mueller, 2007).

For conditioned fear behavior, BDNF produces therapeutic reductions in cue-induced fear, particularly BDNF in the hippocampal–infralimbic pathway (Peters et al., 2010; Rosas-Vidal et al., 2014). Exogenous BDNF applied to either brain site reduces fear in a manner that is reminiscent of extinction-induced reductions in fear (Figs. 1 and 2A). The importance of the hippocampal to infralimbic projection is underscored by the observation that BDNF applied directly to hippocampus can reduce fear in an infralimbic BDNF-dependent fashion (Peters et al., 2010). Furthermore, exogenous application of hippocampal BDNF promotes

neuronal bursting in infralimbic neurons, a known correlate of fear extinction memory consolidation (Rosas-Vidal et al., 2014). Long-term potentiation (LTP) also develops in the hippocampal-prefrontal pathway after extinction learning occurs (Farinelli et al., 2006), and disrupting this potentiation disrupts fear extinction memory retrieval (Farinelli et al., 2006; Inoue et al., 2013; Judo et al., 2010). Given that BDNF promotes LTP in cortical neurons (Abidin et al., 2007; Cabezas and Buno, 2010; Lu et al., 2010, 2007; Messaoudi et al., 2002), it may simulate fear extinction memory by emulating this neurophysiological plasticity.

3. The estrogen–BDNF connection

Estrogen effects on neuronal plasticity and cognition are similar to those of BDNF (Aguirre and Baudry, 2009; Luine and Frankfurt, 2013; Sato et al., 2007; Scharfman and Maclusky, 2005; Sherwin, 2002, 2005; Smith and McMahon, 2006). The most abundant estrogen in the brain, 17β-estradiol, exerts its effects through receptors (ERα and ERβ) on both the cell membrane and the nucleus (Levin, 2002). The gene for BDNF has an estrogen response element, which may mediate the ability of estradiol to increase BDNF protein levels in the PFC and hippocampus (Harte-Hargrove et al., 2013; Liu et al., 2001; but see Murphy et al., 1998), although a transsynaptic mechanism has also been suggested (Blurton-Jones et al., 2003). Estradiol-induced increases in BDNF levels are seen in ovariectomized rats (Scharfman et al., 2007) and in freely cycling rats at the start of proestrus and into estrus, when estradiol levels are high (Harte-Hargrove et al., 2013; Scharfman et al., 2003). These observed increases in hippocampal-prefrontal BDNF may account for estradiol's ability to enhance both spatial (hippocampal) and non-spatial (prefrontal) memories (Luine and Frankfurt, 2013).

Importantly, estradiol has also been shown to enhance fear extinction memory in female rats when administered during memory consolidation, and this effect can be emulated using an ERβ, but not an ERα receptor agonist (Chang et al., 2009; Galvin and Ninan, 2014; Zeidan et al., 2011). In female humans, fear extinction memory recall is better when extinction is conducted during high-estradiol states (Milad et al., 2009, 2010). In both female rats and humans, these effects are associated with enhanced activation and synaptic plasticity in ventromedial PFC (Galvin and Ninan, 2014; Zeidan et al., 2011), as well as downstream activation of NMDA receptors in this region (Galvin and Ninan, 2014). These studies are consistent with observations that low estrogen is associated with extinction failure in females with PTSD (Glover et al., 2012). Following trauma, women are more prone than men to develop anxiety disorders, including PTSD, and low estrogen, including the blockade of estrogen effects by birth control (Graham and Milad, 2012), may in part explain this vulnerability (Lebron-Milad et al., 2012). Even in male rats, estradiol synthesis is required for successful fear extinction formation (Graham and Milad, 2014), suggesting that these effects of estrogen are relevant to both sexes. Though it remains to be shown whether the extinction-enhancing effects of estradiol are BDNF-dependent, they are congruent with the ability of estradiol to increase BDNF in hippocampal-prefrontal circuits where it promotes extinction.

4. BDNF and cocaine seeking

The PFC is an integral part of the extinction circuit for both fear and cocaine memories, but is BDNF and/or TrkB signaling a common mechanism for extinction? A recent study suggests this may be the case; Otis et al. (2014) observed an extinction-enhancing effect of infralimbic-applied exogenous BDNF on cocaine conditioned place preference (CPP) memory (Fig. 2B). However, this BDNF effect only emerged *after* extinction training, whereas infralimbic BDNF is capable of inducing fear extinction independent of training (Otis et al., 2014; Peters et al., 2010). In both cases, NMDA receptor activation is a requisite downstream target of BDNF (Otis et al., 2014; Peters et al., 2010). Furthermore, BDNF may be a downstream mechanism by which AMPAkines facilitate extinction of cocaine seeking (Jourdi et al., 2009; LaLumiere et al., 2010). Whether or not the hippocampus is the source of infralimbic BDNF for cocaine extinction remains an open question. One study revealed increased hippocampal BDNF levels associated with the ability of environmental enrichment to reduce cocaine seeking after abstinence (Thiel et al., 2011). Notably, however, this effect did not preclude the incubation of cocaine seeking.

One theory of addiction postulates that an increase in the incentive salience of drug-associated cues increases relapse vulnerability (Robinson and Berridge, 2008). Sign trackers, animals that track a reward-predictive cue instead of the reward itself, are thought to be more addiction prone compared to their goal-tracking counterparts that track the reward location. Sign trackers have reduced levels of prefrontal BDNF, are more prone to the incubation of cue-elicited fear, and exhibit increased cue-induced reinstatement of cocaine seeking after extinction (Morrow et al., 2014; Saunders and Robinson, 2010; Yager and Robinson, 2012). This suggests a protective role of prefrontal BDNF in reducing the salience of conditioned cues and their propensity to trigger relapse. In light of recent evidence that suggests goal-trackers may be more prone to relapse triggered by contextual cues (Saunders et al., 2014), the types of cues that trigger relapse could be a critically important factor when considering addiction therapeutics that increase prefrontal BDNF.

Prefrontal-applied BDNF has been shown to reduce cocaine seeking, at least in part, by normalizing accumbens glutamate homeostasis (Berglind et al., 2007, 2009). Interestingly, however, this effect is attributed to BDNF actions in prelimbic, not infralimbic, PFC. These dorsal and ventral subregions of medial PFC are known for their opposing influences on behavior, and this dichotomy of function is preserved for both fear and cocaine-seeking behaviors (Peters et al., 2009). The timing of the prelimbic BDNF infusion (immediately after the last cocaine self-administration session) may be of crucial importance for these observed effects on cocaine seeking, and cocaine may need to be “on board” at the time of treatment (Berglind et al., 2009; McGinty et al., 2009). Such a profile suggests that prelimbic BDNF may disrupt reconsolidation of the cocaine memory and consequent action control (Gourley et al., 2012), which is conceptually quite different from the extinction-enhancing effects of infralimbic BDNF (Milton, 2012; Torregrossa and Taylor, 2012). From a treatment perspective, however, both of these mechanisms are viable therapeutic pursuits.

The incubation of cocaine seeking that occurs after prolonged withdrawal has been linked to mesolimbic BDNF (Graham et al., 2007; Grimm et al., 2003; Li et al., 2013; Lu et al.,2004a,

2004b). Local infusion of BDNF into the VTA immediately after the last cocaine self-administration session produces a persistent *increase* in cocaine seeking (Lu et al., 2004a), opposite the *decreases* reported for PFC BDNF discussed above (Berglind et al., 2007, 2009; McGinty et al., 2009; Otis et al., 2014). Similarly, BDNF in the nucleus accumbens appears to promote cocaine seeking and delay extinction, whereas accumbens BDNF knockdown reduces cocaine seeking (Bahi et al., 2008; Graham et al., 2007). These effects may be primarily localized to the nucleus accumbens shell, as BDNF in the accumbens core has been shown to both reduce cocaine seeking (Li et al., 2013) and enhance cocaine cue-mediated behaviors (Horger et al., 1999). Thus, in contrast with the therapeutic effects of BDNF in the PFC, the effects of BDNF in the VTA-accumbens pathway tend to enhance cocaine seeking. This underscores the importance of neural circuitry considerations when considering BDNF-based addiction therapies.

5. BDNF and opiate seeking

The neurobiological and anatomical substrates of opiate seeking appear to be distinct from those identified for cocaine seeking (see Badiani et al., 2011 for review). For example, in contrast to cocaine seeking, heroin seeking appears to incubate independently of accumbens BDNF (Theberge et al., 2012). The role of BDNF in the VTA-accumbens pathway is an area of growing interest and dispute for opiate reward and memory. A recent study from Koo and colleagues (2012) indicates that VTA BDNF opposes the rewarding effects of morphine by reducing activity in presumed accumbens-projecting dopamine neurons (Koo et al., 2012). However, these data stand in stark opposition with earlier work from Vargas-Perez et al. (2009), who found that VTA BDNF neither opposes nor facilitates morphine reward, but rather switches the mechanism for opiate reward from a dopamine-independent to a dopamine-dependent one. This occurs through BDNF's reversal of GABA currents in VTA neurons from inhibitory to excitatory, and this effect is thought to underlie the negative aversive state associated with opiate withdrawal (Vargas-Perez et al., 2014).

The reasons for these discrepancies are unclear, but they point to a need for further investigation of the role of BDNF within the VTA-accumbens pathway. Koo et al. (2014) have also observed a negative relationship between accumbens BDNF and morphine CPP memory, but in a cell-type specific manner. That is, selective ablation of the TrkB BDNF receptor on dopamine D1 receptor-containing medium spiny neurons resulted in reduced GABA-A receptor currents in these neurons, ultimately promoting morphine reward (Koo et al., 2014). Given that morphine exposure led to a similar cell-type specific downregulation of TrkB in D1-neurons, the authors hypothesized that this neuroadaptation contributes to morphine addiction. Notably, however, direct infusion of BDNF into the accumbens did not alter morphine CPP (Koo et al., 2012). Thus, while the precise role of BDNF in the mesoaccumbens system must still be resolved, it is clear that it differs from that reported for cocaine.

Similarly, data are lacking regarding the functional impact of cortical BDNF on opiate memories. However, some evidence supports a potential link between cortical BDNF and the inhibition of opiate behaviors. For example, suppression of the receptor for activated C kinase 1 (RACK1) using a short hairpin strategy blocks morphine CPP memory formation,

while simultaneously increasing BDNF transcription in PFC and hippocampus (Wan et al., 2011). However, it is difficult to directly relate fluctuations in mRNA to functional alterations in BDNF protein, as these measures often do not always correlate (see Table 1). Memantine, a drug with mixed pharmacology, including antagonism of NMDA receptors, also attenuates morphine reward-memory in a CPP paradigm and prevents morphine-induced reductions in BDNF protein within the PFC and nucleus accumbens (Chen et al., 2011). While these studies suggest an association between reduced morphine reward and increased prefrontal (and hippocampal or accumbal) BDNF, another study implicates prefrontal BDNF in extinction of morphine conditioned place *aversion* (Wang et al., 2012). Extinction of this aversive memory was also dependent on NMDA receptor and activation of an ERK-CREB pathway, consistent with mechanisms of extinction for fear and cocaine. This raises the intriguing possibility that the aversive and rewarding components of opiate memories may have distinct neural mechanisms of extinction.

In humans, the Val66Met polymorphism in the BDNF gene has been linked to incidence and age of onset of heroin abuse (Cheng et al., 2005; Hou et al., 2010), as well as willingness to invest more time and money in obtaining heroin (Greenwald et al., 2012). Given that this polymorphism has been associated with deficits in hippocampal release of BDNF and impaired extinction (Soliman et al., 2010; Yu et al., 2009), one might expect heroin use to be perpetuated by such extinction deficits, provided hippocampal BDNF is a shared mechanism for extinction memory between fear and opiates. Opiate exposure disrupts hippocampal long-term potentiation (LTP) (Salmanzadeh et al., 2003), a proposed neurophysiological correlate of memory, and re-exposure to opiates during withdrawal can restore this hippocampal LTP (Pu et al., 2002), but notably, extinction does not (Portugal et al., 2014). At least one study has suggested the hippocampus is involved in extinction of morphine CPP (Billa et al., 2008), but while molecular changes in hippocampus were observed after extinction, no functional manipulation of hippocampus was performed to test its role in extinction behavior.

We performed an experiment to test the ability of exogenous, hippocampal-applied BDNF to alter heroin extinction and reinstatement in a self-administration model of relapse. BDNF (0.75 μg/side) was infused into hippocampus the day after the last heroin self-administration session. Extinction training commenced the day after this infusion. This design is analogous to the study by Peters et al. (2010), where hippocampal infusions of BDNF the day after fear conditioning reduced fear on the first extinction session the next day. Interestingly, there were no significant effects of hippocampal-applied BDNF on extinction or reinstatement of heroin seeking (Fig. 1B). BDNF can induce LTP when applied exogenously to the hippocampus of naïve animals (Messaoudi et al., 2002), and this may account for its therapeutic, extinction-like effects on fear, particularly given that synaptic potentiation in hippocampus has been associated with extinction memory (Saito et al., 2012). These negative findings in the heroin model suggest that BDNF may not induce LTP in the opiate-exposed hippocampus, that hippocampal LTP may not mediate extinction of heroin seeking, or that conditions are not optimal to detect an effect in our model.

Although hippocampal-applied BDNF did not alter extinction or reinstatement of heroin seeking in our hands, it is notable that animals extinguished their heroin-seeking behavior

rapidly, over just five 1-hour sessions. Thus, they do not appear to be extinction-impaired per se. As recently reviewed by Peters et al. (2013), the infralimbic PFC may play a fundamentally different role in cocaine- versus heroin-seeking behavior. Whereas the infralimbic PFC promotes *extinction* of cocaine seeking (LaLumiere et al., 2010; Peters et al., 2008), it appears to promote *relapse* for heroin (Bossert et al., 2011, 2012). While this may be due to the existence of separate neural ensembles for extinction and relapse within the structure that complicate interpretations of whole-structure manipulations, the lack of involvement of infra-limbic PFC in extinction of heroin seeking, coupled with the lack of hippocampal BDNF involvement, supports the notion that extinction of heroin seeking may rely on fundamentally different neural mechanisms than those for fear and cocaine.

6. BDNF and alcohol seeking

A growing, though mixed, literature has implicated alterations in BDNF in risk for both the development of alcohol use disorders and in propensity to relapse. Serum BDNF levels appear to be decreased in alcohol dependent individuals (Zanardini et al., 2011), but these serum levels may rebound during abstinence (Huang et al., 2010), reaching levels that are in some cases higher than those of control populations (D'Sa et al., 2012). It is unclear, however, how these peripheral findings relate to changes within the central nervous system in humans. In addition to changes in peripheral BDNF levels, considerable evidence points toward a relationship between genetic differences in the BDNF system and alcohol use disorders. Though findings are inconsistent (Nedic et al., 2012), data suggest that the Val66Met BDNF polymorphism may predict the development of alcohol use disorders. Beyond general alterations in BDNF signaling in the alcoholic population, the Val66Met polymorphism has been specifically associated with increased propensity to relapse after shorter abstinent periods (Wojnar et al., 2009). Interestingly, the BDNF Val66Met polymorphism has also been associated with executive function in individuals at risk for alcohol use disorders. In non-alcoholic adults with alcoholic parents, the polymorphism was predictive of cognitive performance on a number of measures (Benzerouk et al., 2013) suggesting that differences in BDNF signaling may promote alcohol use disorders, and potentially relapse, through a more general effect on executive function.

Animal models have added substantially to this literature, with a number of studies showing that alcohol exposure differentially impacts BDNF expression in limbic corticostriatal circuits that mediate reward-seeking and -taking behaviors (Jeanblanc et al., 2009, 2012; Logrip et al., 2009). While some animal models suggest correlations between serum levels and brain BDNF levels (Klein et al., 2010), changes in BDNF after alcohol exposure do not appear to be uniform across the brain, suggesting difficulty in relating peripheral changes to changes within specific brain regions. In particular, chronic ethanol exposure increases BDNF mRNA in the striatum in a RACK1-dependent manner (Leggio et al., 2014; McGough et al., 2004). In contrast, decreases in BDNF mRNA in the hippocampus, hypothalamus and cortex have been reported (Logrip et al., 2009; MacLennan et al., 1995; Tapia-Arancibia et al., 2001). Subchronic ethanol exposure increases TrkB mRNA expression in the basal forebrain and cortex (Miki et al., 2013), and increases in BDNF mRNA have been observed in the hippocampus and hypothalamus after acute withdrawal (Tapia-Arancibia et al., 2001). Thus, the precise timing and extent of ethanol exposure is

likely to be critical in interpreting ethanol effects on BDNF expression. These changes in mRNA expression are likely downstream to ethanol-induced changes in chromatin remodeling, suggesting epigenetic regulation of BDNF expression as a result of ethanol exposure (Stragier et al., 2014).

Together, the clinical and preclinical data implicate innate and alcohol-induced alterations in BDNF in alcohol use disorders. A number of studies have shown that manipulating BDNF or its signaling partners can alter ethanol consumption. For example, BDNF heterozygotes exhibit reduced ethanol consumption (McGough et al., 2004), similar to that observed with TrkB antagonism, which also opposes ethanol-induced changes in the dopamine system (Leggio et al., 2014). Interestingly, BDNF infusions directly into the VTA do not alter expression of ethanol CPP, but do convert the underlying mechanism for this CPP from a dopamine-dependent to a dopamine-independent one (Ting-A-Kee et al., 2013). As with opiates, this simulates the endogenous switch that occurs during withdrawal, despite the fact these dopamine contingencies are opposite for ethanol and opiates (Ting-A-Kee et al., 2013; Vargas-Perez et al., 2009, 2014; but see Koo et al., 2012). By contrast, loss of BDNF in the dorsolateral striatum impairs both ethanol CPP memory and free consumption (Bahi and Dreyer, 2013), as well as intake in a self-administration model (Jeanblanc et al., 2009). The mechanism by which BDNF signaling reduces ethanol consumption, preference and self-administration is unclear. Consistent with other drugs of abuse, uncontrolled drug seeking characterizes alcohol use disorders. Chronic ethanol exposure has been shown to result in impairments in behavioral flexibility (Kroener et al., 2012; Trantham-Davidson et al., 2014), and at least adolescent ethanol exposure impairs extinction learning (Gass et al., 2014). Notably, chronic ethanol exposure can also impair extinction of fear, suggesting that ethanol exposure itself can produce changes in extinction neural circuits (Holmes et al., 2012), though a role for ethanol-induced changes in BDNF has not to our knowledge been implicated in these effects.

Like other reinforcers, extinction of ethanol seeking appears to involve the infralimbic PFC. Ethanol extinction can be facilitated by modulation of mGluR5 signaling that is infralimbic-dependent (Gass et al., 2014). In addition, individual differences in resistance to ethanol extinction are associated with innate differences in the expression of PSA-NCAM, a proplasticity molecule, in the infralimbic PFC (Barker et al., 2012). Loss of PSA-NCAM selectively within the infra-limbic, but not prelimbic PFC results in the inability to extinguish ethanol seeking. Given this role for infralimbic PFC in the extinction of ethanol seeking, we investigated whether infralimbic BDNF infusions would facilitate extinction. Surprisingly, we saw no facilitation of extinction learning (Fig. 2C) after infusion of BDNF (0.4 μg/μl, 0.2 μl/side) into the infralimbic PFC. Importantly, while animals in this study self-administered ethanol, these animals were not ethanol dependent. Because ethanol dependence itself alters extinction learning (Gass et al., 2014; Holmes et al., 2012), it remains possible that BDNF administration within the infralimbic PFC may rescue dependence-induced impairments in extinction learning.

These data suggest that BDNF administration within the infralimbic PFC is not sufficient to mimic extinction memory, in contrast with fear extinction (Peters et al., 2010). Interestingly, the role of infralimbic PFC in ethanol extinction is less clearly established relative to

cocaine. Inactivation of the infralimbic PFC does not prevent expression of extinction of ethanol seeking as it does for cocaine and fear (Peters et al., 2009; Willcocks and McNally, 2013). Though infralimbic PFC plasticity appears to be involved in ethanol extinction (Barker et al., 2012; Gass et al., 2014) and extinction of fear in ethanol-dependent animals (Holmes et al., 2012), inactivation after the acquisition of extinction does not impact subsequent expression of that extinction. This may in part be because ethanol engages different subcortical structures than cocaine that may mediate extinction despite the loss of infralimbic activity. Because alcohol is a caloric reinforcer – as opposed to other drugs of abuse – it is important to consider that there may be a greater involvement of satiety circuitry. As with cocaine, inactivation of the nucleus accumbens shell has been shown to reinstate extinguished ethanol seeking (Millan et al., 2010; Peters et al., 2008). How interactions between the shell and infralimbic PFC are involved in the extinction of ethanol seeking is as yet unknown. Interestingly, these authors expanded upon this finding by demonstrating that nucleus accumbens shell mediates ethanol extinction by inhibiting hypothalamic neurons that are largely involved in signaling satiety. Indeed, the context-induced reinstatement of ethanol seeking is associated with activation of the nucleus accumbens shell to lateral hypothalamus pathway, and inactivation of the lateral hypothalamus prevent reinstatement (Marchant et al., 2009). Together with findings implicating infralimbic projections to the dorsomedial hypothalamus in the expression of ethanol extinction (Marchant et al., 2010), these data suggest a larger network through which infralimbic PFC may interact with hypothalamic targets to drive the extinction and reinstatement of ethanol seeking. This interaction suggests that the profile of ethanol extinction may share overlapping features with food or other caloric reinforcers, rather than other drugs of abuse, due to the engagement of hypothalamic satiety circuits.

7. Sex differences, BDNF, and drug seeking

Importantly, the data described above were collected primarily in male animals. Notable sex differences exist in a number of components of addictive behavior, in both animal models and in human populations (Becker and Hu, 2008; Carroll and Anker, 2010; Lynch et al., 2002; Yu et al., 2007). Female rats tend to show greater resistance to cocaine extinction (Fuchs et al., 2005; Hilderbrand and Lasek, 2013; Kippin et al., 2005; Kosten and Zhang, 2008), as well as heightened reinstatement, cue reactivity (Bobzean et al., 2010; Feltenstein et al., 2011; Lynch and Carroll, 2000), and incubation of cocaine seeking (Kerstetter et al., 2008). In female rats, 17β-estradiol is required for extinction of cocaine CPP, and chronic treatment with 17β-estradiol can facilitate extinction (Larson and Carroll, 2007). It is possible that these effects are mediated through estrogen interactions with BDNF signaling, as with fear (Lebron-Milad and Milad, 2012; Milad et al., 2009, 2010), though direct evidence for this is lacking with regards to cocaine.

There are significant sex differences in ethanol seeking behaviors that appear to be both sex chromosome and gonadal hormone related. Female mice have been shown repeatedly to self-administer higher volumes of ethanol than male animals (Barker et al., 2010), though chromosomal male mice developed ethanol-seeking habits more rapidly. While to our knowledge, sex differences in extinction of ethanol seeking have not been reported, as described above, sex drives differential roles for BDNF in learning and memory.

Importantly, sex also appears to mediate the expression of hippocampal BDNF during acute alcohol withdrawal, with females showing extensive increases in BDNF, and males showing a more restricted increase (Alele and Devaud, 2013). Interestingly, these changes were independent of current gonadal status. Since early withdrawal is a known stressor, it is difficult to determine whether these effects were due to ethanol withdrawal, stress, or a combination thereof.

While female rats have been shown to acquire heroin self-administration more rapidly than males (Lynch and Carroll, 1999) and appear to be more motivated to seek heroin (Carroll et al., 2002), to our knowledge no data exist showing sex differences in the extinction of heroin seeking. Given that craving for opioids is significantly higher in women (Back et al., 2011), and susceptibility to cue-induced craving and relapse may be greater in women than men with comorbid cocaine and heroin addiction (Kennedy et al., 2013), it will be important to consider sex differences in the ability to extinguish conditioned responses to drug-associated cues.

8. Conclusions

The available literature implicates a cyclical interaction between BDNF and drug seeking behavior for all drugs of abuse. Indeed, chronic drug exposure appears to impact BDNF levels in both human and rodents (see Table 1), and innate differences in BDNF have been associated with the development of addiction for multiple substances of abuse, including cocaine, heroin and ethanol. BDNF signaling appears to be involved in multiple facets of addiction, including reward and motivation, but critically its expression and function is known to mediate many of the learning and memory processes that are dysregulated in addiction. The loss of the ability to acquire and express extinction may be involved in the initial development of addiction as well as the chronic relapse that defines the disorder.

The particular brain sites and neural pathways where BDNF is expressed and released are critically important for determining whether BDNF actions will be pro-relapse or pro-extinction (Fig. 3). The incubation effect, wherein relapse is amplified after longer periods of abstinence, involves the VTA-accumbens pathway (Bahi et al., 2008; Graham et al., 2007; Grimm et al., 2003; Li et al., 2013; Lu et al., 2004a), at least for cocaine and perhaps also opiates, though there are conflicting reports (Koo et al., 2012; Vargas-Perez et al., 2009, 2014). Some evidence supports the importance of accumbens subregions in BDNF's effects, with the shell being pro-relapse, but the core being capable of both pro-relapse and pro-extinction functions (Horger et al., 1999; Li et al., 2013). Perhaps this relates to differential sources of BDNF input to the accumbens core. It is possible that accumbal-BDNF derived from the PFC produces therapeutic reductions in drug seeking (McGinty et al., 2009), whereas accumbal-BDNF derived from the VTA may promote drug seeking. The hippocampal-prefrontal pathway, by contrast, promotes fear extinction (Peters et al., 2010; Rosas-Vidal et al., 2014), but data is notably lacking from drug addiction models. At present, negative data suggest that infralimbic PFC may not be required for the extinction of alcohol and heroin seeking (Peters et al., 2013; Willcocks and McNally, 2013; Fig. 2C), and that hippocampal BDNF does not enhance extinction of heroin seeking (Fig. 1B).

The reason for this apparent incongruence between extinction neural circuits across different drug classes requires further investigation. One of the hallmarks of addiction is decreased behavioral flexibility and tendency to perseverate in drug-seeking behavior, and the hippocampal-prefrontal BDNF projection is critical for flexible behavior, including extinction (Sakata et al., 2013). In particular, CA1 neurons project to infralimbic PFC (Hoover and Vertes, 2007), and these are the putative cells that supply BDNF to infralimbic neurons, thus enhancing bursting and inducing extinction memory (Peters et al., 2010; Rosas-Vidal et al., 2014). Sakata et al. (2013) recently demonstrated that BDNF-dependent LTP in CA1 neurons is critical for flexible behaviors including fear extinction. These data suggest that BDNF-LTP in the CA1 projection neurons may be a critical substrate for behavioral flexibility, raising the intriguing possibility that exogenous-applied BDNF in this pathway may be capable of inducing LTP (Messaoudi et al., 2002) and reducing drug seeking, at least for drugs that require the hippocampal–prefrontal projection for extinction.

Importantly, while there are notable sex differences in drug seeking and taking, sex differences in the relationship between BDNF signaling and drug seeking are only beginning to be understood. Data indicate that estrogens interact with BDNF to impact the learning and memory processes that are thought to go awry in addictive behavior, suggesting a likely mechanism by which BDNF would differentially impact drug-seeking behavior in males and females, and perhaps across estrus cycle. Low estrogen leads to a loss of hippocampal LTP (Kramar et al., 2009) and cognitive deficits (Sherwin, 2005), both of which can be ameliorated by replacing estrogen (Kramar et al., 2009; Sherwin, 2002; Smith and McMahon, 2006). Hence, the therapeutic potential of BDNF to enhance the extinction of drug seeking requires a careful consideration of sex differences, and especially the role of BDNF-estrogen interactions.

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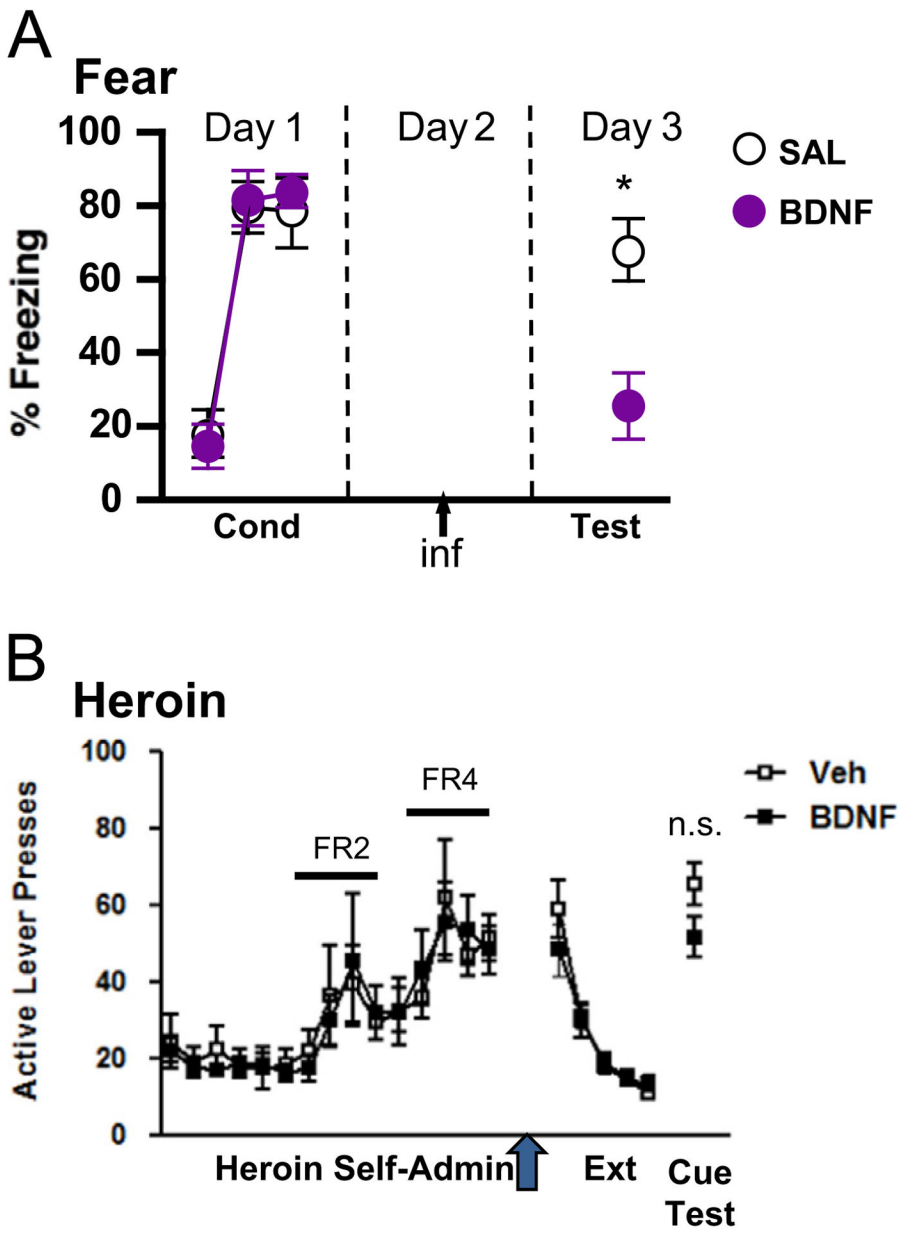

Fig. 1.

Hippocampal BDNF substitutes for fear extinction, but not extinction of heroin seeking. (A) BDNF was infused into hippocampus on the day between conditioning and test in an auditory conditioned fear paradigm. BDNF reduced fear at test, as though it substituted for extinction training (Republished with permission from Peters et al., 2010). (B) BDNF was infused into hippocampus the day prior to initiating extinction training in a heroin self-administration model. This treatment did not alter extinction learning and memory, nor did it alter cue-induced reinstatement of heroin seeking one week later (see text for additional experimental details).

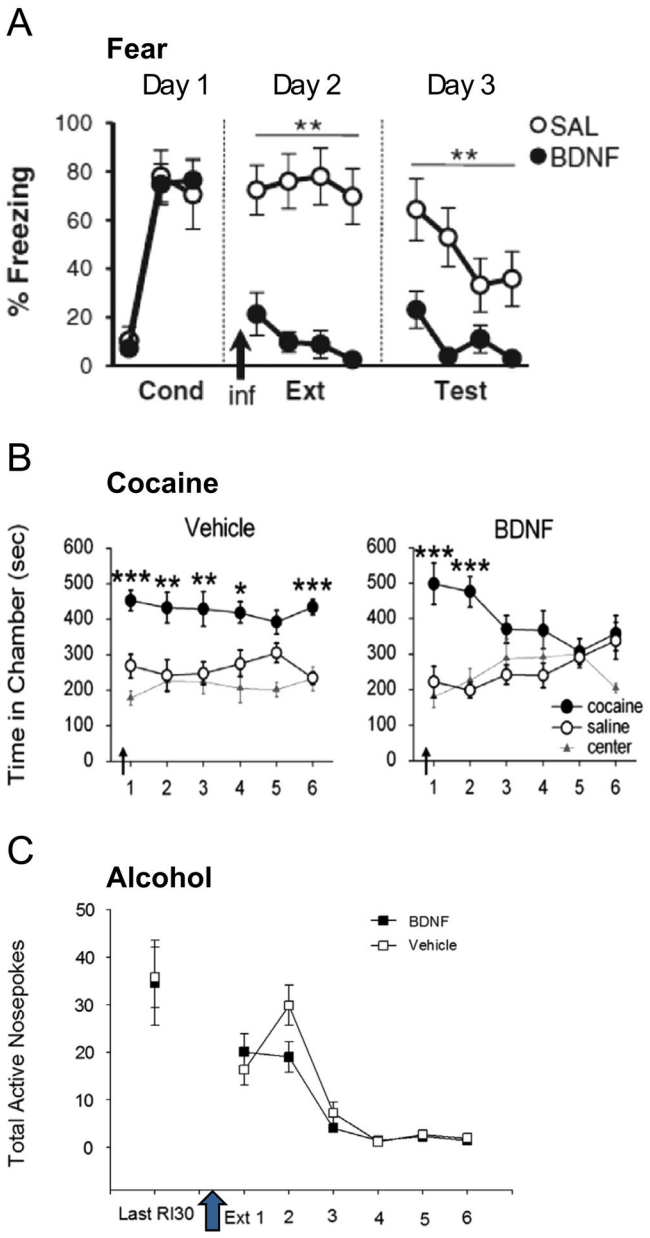

Fig. 2.

BDNF has extinction-like effects on fear and cocaine memories, but not alcohol seeking. (A) BDNF was infused into infralimbic PFC just prior to the initial extinction training session in an auditory conditioned fear paradigm. Immediate reductions in fear were observed that persisted the following day (Republished with permission from Peters et al., 2010). (B) BDNF was infused into infralimbic PFC prior to the first of several repeated extinction trials in a cocaine conditioned place preference model. Though no immediate effects of BDNF were evident, BDNF facilitated extinction learning over trials (Republished with permission of Journal of Neuroscience, from "Infralimbic BDNF/TrkB enhancement of GluN2B currents facilitates extinction of a cocaine-conditioned place preference," Otis et al., 2014; permission conveyed through Copyright Clearance Center, Inc.). (C) Adult male CD1 mice

were trained to self-administer 10% ethanol. Mice were food restricted to approximately 95% of free feeding weights, but had ad libitum access to water throughout training. Testing was performed in the light cycle. Mice were trained to lever press on a fixed ratio schedule, and then were graduated to a random interval 30 s schedule in which each response after a randomly generated interval was reinforced. Reinforcer delivery was paired with presentation of a tone+light compound cue. BDNF was infused into the infralimbic PFC at AP+1.9, ML +/−0.4, DV −2.2 prior to testing in extinction. During test sessions, levers were extended into the chambers, but responses did not produce reinforcer delivery or cue presentation.

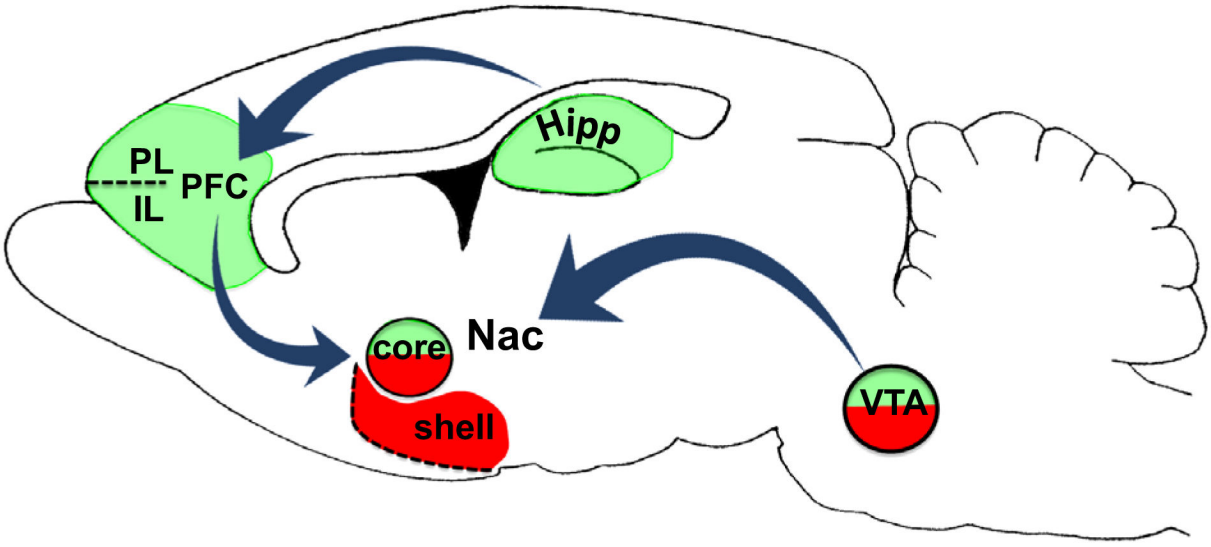

Fig. 3.

BDNF produces therapeutic versus pathological effects on drug and fear conditioned behaviors depending on its locus of action within mesolimbic and corticostriatal circuits. Therapeutic (green) reductions in fear and drug seeking have been linked to elevated BDNF protein in the hippocampus (Peters et al., 2010, fear), prelimbic (PL; Berglind et al., 2007, 2009; McGinty et al., 2009, cocaine) and infralimbic (IL; Otis et al., 2014, cocaine; Peters et al., 2010, Rosas-Vidal et al., 2014, fear) prefrontal cortices, and nucleus accumbens (Nac) core (Li et al., 2013, cocaine), although for the core, a pathological (red) enhancement of drug seeking has also been observed (Horger et al., 1999). Enhancement of drug-seeking behavior has also been associated with elevated BDNF protein in the Nac shell (Graham et al., 2007; Bahi et al., 2008; Li et al., 2013, cocaine) and ventral tegmental area (VTA; Grimm et al., 2003; Lu et al., 2004a, cocaine; Vargas-Perez et al. 2009, 2014, opiates; Ting-A-Kee et al., 2013, alcohol). Conflicting evidence suggests that BDNF in the VTA may be therapeutic for opiate memories (Koo et al., 2012).

Table 1

Effects of ethanol and opiate exposure on BDNF mRNA and protein expression. While BDNF and opiates appear to impact BDNF expression, the direction and magnitude of these effects depends on the duration and method of exposure as well as where changes are measured. A greater understanding of the role of BDNF in opiate and alcohol seeking behavior requires a more thorough analysis of the time course and loci of these effects.

Species	Drug exposure	Measure	Change	Reference
Ethanol				
Human (dependent alcoholics)	Self-administration	Serum BDNF protein	↓in serum	Zanardini et al. (2011)
Human (abstinent alcoholics)	Self-administration	protein	↑in serum =in plasma	D'Sa et al. (2012)
Human (30 day abstinent alcoholics)	Self-administration	protein	↓in plasma	Joe et al. (2007)
Mouse	Acute injection (2 mg/kg) Self-admin, 4 weeks	mRNA	↑in hippocampus and dorsal striatum =in PFC ↑in dorsal striatum =in PFC and hippocampus	McGough et al. (2004)
Mouse	Vapor chamber, 2 weeks	mRNA	↓in PFC =in accumbens and hippocampus	Melendez et al., (2012)
Mouse	Self-admin Acute Chronic, 6 weeks	mRNA	↑in dorsal striatum =in accumbens and cortex =in dorsal striatum and accumbens ↓in ventral PFC, frontal and posterior cortex	Logrip et al. (2009)
Rat	Liquid diet, 28 weeks	mRNA	↓in hippocampus	MacLennan et al. (1995)
Rat	Vapor chamber, 10 days	Protein	↓in hippocampus	Hauser et al. (2011)
Rat	Vapor chamber, 4 weeks 12 hours withdrawal	mRNA	↓in CA1 and dentate gyrus, supraoptic nucleus of hypothalamus ↓in CA1, dentate gyrus at control levels. ↑in CA3 and supraoptic nucleus	Tapia-Arancibia et al. (2001)
Rat	Vapor chamber, 7 weeks	mRNA	↓in medial PFC	Tapocik et al. (2012, 2014)
Opiate				
Rat	Heroin injection, 5 days	Protein	↑in prelimbic PFC ↓in dorsal hippocampus =in ventral hippocampus and nucleus accumbens	Zilkha et al. (2014)
Rat	Self-administration, 1, 11, or 30 days abstinent	mRNA and protein	=in nucleus accumbens and dorsal striatum	Theberge et al. (2012)
Human (dependent)	Self-administration	Protein	↑in serum	Heberlein et al. (2011)

Species	Drug exposure	Measure	Change	Reference
Human (dependent)	Self-administration	Protein	↓in serum	Angelucci et al. (2007)
Human (dependent)	Self-administration In withdrawal	Protein	↓in serum No change	Zhang et al. (2014)