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REVIEW

Role of prefrontal cortex in the extinction of drug memories

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Abstract

It has been recognized that drug addiction engages aberrant process of learning and memory, and substantial studies have focused on developing effective treatment to erase the enduring drug memories to reduce the propensity to relapse. Extinction, a behavioral intervention exposing the individuals to the drug-associated cues repeatedly, can weaken the craving and relapse induced by drug-associated cues, but its clinic efficacy is limited. A clear understanding of the neuronal circuitry and molecular mechanism underlying extinction of drug memory will facilitate the successful use of extinction therapy in clinic. As a key component of mesolimbic system, medial prefrontal cortex (mPFC) has received particular attention largely in that PFC stands at the core of neural circuits for memory extinction and manipulating mPFC influences extinction of drug memories and subsequent relapse. Here, we review the recent advances in both animal models of drug abuse and human addicted patients toward the understanding of the mechanistic link between mPFC and drug memory, with particular emphasis on how mPFC contributes to the extinction of drug memory at levels ranging from neuronal architecture, synaptic plasticity to molecular signaling and epigenetic regulation, and discuss the clinic relevance of manipulating the extinction process of drug memory to prevent craving and relapse through enhancing mPFC function.

Keywords Drug memory · Prefrontal cortex · Extinction · Relapse

Introduction

Addiction is a chronic relapsing disorder, and drug-associated cues are crucial contributors to the enduring craving, compulsive drug-taking behaviors and relapse (Baler and Volkow 2006; Everitt and Robbins 2005). Finding effective treatment to prevent the propensity to craving and relapse elicited by drug-associated cues is one of the major goals of addiction research. It has been acknowledged that once entering the brain, the addictive drugs trigger a distorted process of learning and memory during which drug-associated cues (i.e. drugs, drug paraphernalia, environmental context, and et al.) serve as conditioned stimulus (CSs) while drug-associated effects (rewarding or aversive) serve as unconditioned stimulus (UCSs) (Hyman 2005; Milton and Everitt 2012a). Exposure to CSs leads to two processes, reconsolidation and extinction, and both processes reorganize and update the consolidated traces of drug memories (Rich et al. 2016; Taylor et al. 2009). Targeting the mechanisms of reconsolidation and extinction of drug memories is a promising strategy for prevention of drug craving and relapse (Milton and Everitt 2012b; Taylor et al. 2009; Torregrossa and Taylor 2013). Based on the theories of drug memory extinction, cue-exposure has been advocated as a treatment for addiction (Heather and Bradley 1990; Torregrossa and Taylor 2013), but clinically, the efficacy of cue-exposure therapy (CET) is limited. The predominant view is that extinction does not erase the original CS-UCS association. Instead, extinction forms a new association between CS and no UCS, and this new association inhibits the original one (Bouton 2004; Torregrossa and Taylor 2013; Xue et al. 2012). A better understanding of the

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mechanism underlying extinction of drug memory will facilitate the successful use of CET in practice. In this review, we attempt to unveil the mechanistic link between medial prefrontal cortex (mPFC) and the extinction of drug memories, since mPFC holds a central role in the regulation of both cue-induced drug-seeking and response inhibition. There have been a number of excellent reviews regarding the role of mPFC regulating drug-seeking and relapse (George and Koob 2010; Goldstein and Volkow 2011; Gourley and Taylor 2016; Kalivas 2008; Lasseter et al. 2010; Milton and Everitt 2012a; Moorman et al. 2015; Peters et al. 2009; Schoenbaum et al. 2016; Van den Oever et al. 2010). We here focus on recent research progresses on the circuitry and molecular mechanisms responsible for mPFC engagement in extinction of drug memories. We also summarize the studies on mPFC dysfunction in addicted patients and discuss its clinic relevance with deficit of memory extinction. Lastly, we review the manipulations of memory extinction to in an attempt to erase drug memory and prevent drug craving and relapse through enhancing the mPFC function. Before these, we make a brief summary on the anatomy of mPFC and animal model of extinction memory.

mPFC and its role in extinction of drug memory

mPFC anatomy

A great number of literatures have reviewed the definition, anatomy, and function of mPFC (Heidbreder and Groenewegen 2003; Ongur and Price 2000; Ridderinkhof et al. 2004; Uylings et al. 2003), we only make a brief summary on the anatomy of mPFC. Since Broadmann performed the first topographical study of prefrontal cortex (PFC) across species from rodents to primates, continuous effort has been made to understand this brain region in terms of its definition, boundary, subdivision and function. In humans, the PFC is located in the anterior portion of the frontal lobe, and cytoarchitectonically defined as Broadmann area 8 to 14 and Braodamann area 44 to 47 (Ongur et al. 2003). From the functional perspective, the PFC in human are divided into dorsolateral, dorsomedial, ventromedial, and orbital prefrontal subregions. Based on the anatomical and functional criteria, the rodent PFC includes a medial region, the mPFC, and a lateral region, the orbitofrontal cortex (OFC). The mPFC can be further divided into four subregions including anterior cingulate cortex (ACC), precentral cortex (PrC), prelimbic (PL), infralimbic (IL) (Conde et al. 1995; Moorman et al. 2015; Ongur and Price 2000). Evolutionarily, there are considerable homologies in PFC across species. The IL subregion of mPFC in rodent is homologous to the primate orbitomedial cortex, and the PL subregion in rodent to the primate lateral/dorsolateral cortex in function (Vertes 2006). In the studies we discuss here, the dorsal mPFC is frequently referred to PL and ACC, while ventral mPFC (vmPFC) to IL.

The PL and IL are the two most studied mPFC subregions for memory extinction. There is no clear anatomical boundary between the two subregions. Thus, although the PL and IL function differently, they are not poles apart. The projections from PL and IL to the thalamus (for example, the mediodorsal, intermediodorsal, reuniens, and paraventricular nucleus) and the cortex (for example, the medial orbital cortex and insular cortex) are overall similar (Vertes 2004). However, for some other targets such as nucleus accumbens (NAc), amygdala, and brainstem, the projections from these two brain regions differ drastically. While the PL projects to the core and shell of NAc, the IL projects to the shell only. The PL projects to the central and the basolateral nucleus, while the IL to the central, medial, basomedial, and cortical regions of amygdala (Gabbott et al. 2005; McDonald et al. 1996). The PL projects to the median raphe and dorsal nuclei, and the IL to the solitary and parabrachial nuclei of the brainstem (Gabbott et al. 2005; McDonald et al. 1996; Moorman et al. 2015; Vertes 2004).

Extinction of drug memories and the animal models

A great number of literatures have excellently reviewed the animal model of drug craving and relapse (Marchant et al. 2013; Nic Dhonnchadha and Kantak 2011; O'Brien and Gardner 2005; Sanchis-Segura and Spanagel 2006; Shaham et al. 2003; Vanderschuren and Ahmed 2013; Venniro et al. 2016); we would like to give a very brief introduction description of the two most used rodent models for studying the extinction of drug memories. The first one is the self-administration model (Bossert et al. 2013; Crombag et al. 2008; Epstein et al. 2006; Shaham et al. 2003). In this model, animals are firstly trained to acquire the association between an action (usually a nose-poke, a lever-press or a chain-pull) and infusion of drug (typically intravenous), a process called conditioning. During conditioning, a cue (or cues) is presented in conjunction with each drug delivery. The cue can be classified as a discrete cue and a discriminative cue (Burattini et al. 2007; Ciccocioppo et al. 2003; Perry et al. 2014). Drug dosing is response-dependent, which mimics human drug addiction. Animals' motivation for drug is measured by their responses. Then animals go through extinction training in which the same action no longer brings about drug supply, and the self-administration behavior extinguishes gradually. In other cases, animals do not go through extinction training, but are simply enforced to abstain from drug, which is known as withdrawal (Augur et al. 2016; Lu et al. 2004; Tran-Nguyen 1998). Lastly, during the reinstatement test of drug seeking, animals are presented with the same drug-related cues used at the conditioning stage after a passage of time (spontaneous recovery), changed context (renewal) or drug itself (priming), which may trigger the reoccurrence of drug seeking (Luo et al. 2015; Torregrossa et al.

2013; Torregrossa et al. 2010; Xue et al. 2012). The second is the conditioned place preference (CPP)/conditioned place aversion (CPA) model. In the procedure, the event that induces significant motivation (US), typically the drug delivery in CPP, or the drug withdrawal in CPA, is repeatedly presented in a certain environment (CS), and the neutral stimuli (vehicle) are given in a second or third environment. An animal's preference or aversion for drug is measured by its preference for the specific environment paired with the delivery of drug or drug withdrawal. The procedure of CPP/CPA extinction training was similar to the establishment of CPP/CPA, with the exception that the drugs were replaced by saline. During the relapse test of CPP/CPA, animals are exposed to the CPP/CPA context after a passage of time (spontaneous recovery) or drug itself (priming), which may trigger the re-emergence of CPP/CPA (Cunningham et al. 2006; Moorman et al. 2015; Tzschentke 1998). Similar to extinction memory of fear, extinction responding of drug self-administration or CPP is susceptible to reinstatement, and spontaneous recovery (Xue et al. 2012). The ineffectiveness of CET in clinic may be due to the acute exposure to the addictive drug itself (Jaffe et al. 1989; Venniro et al. 2016), the passage of time (Di Ciano and Everitt 2002; Shaham et al. 1997), changes of environmental context (Bouton and King 1983; Hamlin et al. 2008; Khoo et al. 2017; Marchant et al. 2015). Because CET is conducted in a clinical setting, addicted patients may confront the three factors in the real life. Thus, enhancing the extinction of drug memories may prevent relapse under the above circumstances. For the two kinds of animal models, manipulations can be made before, during or after the extinction training to explore whether the manipulations inhibit or facilitate the extinction training (Chen et al. 2016; Gass and Olive 2009; LaLumiere et al. 2010; Wang et al. 2012) and subsequently, influence the priming-induced reinstatement (Malvaez et al. 2010; Reichel et al. 2011; Xue et al. 2012), renewal (Luo et al. 2015; Torregrossa et al. 2013; Torregrossa et al. 2010) or spontaneous recovery (Degoulet et al. 2016; Malvaez et al. 2013; Peters et al. 2008b; Xue et al. 2014) of drug-seeking behaviors.

Roles of different mPFC subregions in drug extinction memories

Pharmacological inactivation of PL causes deficit in pressing for drug during the relapse test, indicating a promoting influence of PL in drug relapse after extinction. The promoting effect of PL in drug relapse was quite similar to its well-established facilitating role in the expression of conditioned fear after extinction. On the other hand, pharmacological inactivation of IL following extinction training augments the drug-seeking behavior, and, activation of this subdivision reduces the relapse, suggesting an active role of IL in limiting drug relapse after extinction (Peters et al. 2008a). In a recent study using cocaine self-administration, it was observed that IL neurons activation via viral-mediated gene transfer of designer receptors (DREADDs) decreased relapse of cocaine seeking triggered by drug-related cues, but only under the condition that previous extinction training was conducted. The findings further support that IL is critical for cocaine memory extinction (Augur et al. 2016).

Though a large number of studies suggest the IL/PL dichotomy in drug extinction/drug seeking, increasing researches report inconsistent results and raises controversies over the IL/PL dichotomy (Gourley and Taylor 2016). It is not surprising, as the mPFC is not a single structure but a massive complexity. A mouse study found that optogenetic activation of IL pyramidal cell promoted the extinction of remote memory rather than recent memory of cocaine, whereas inactivation of the same region blocked extinction learning of recent memory rather than remote memory (Van den Oever et al. 2013), suggesting that the IL's role in the extinction of conditioned cocaine memory is dual and time-dependent. Another study employed discriminative-stimulus-based self-administration task to measure cocaine-seeking behavior and found that pharmacological inhibition of IL and PL induced greater lever pressing during the CS presentation (Gutman et al. 2017). Clearly, these results are inconsistent with the classic PL/IL dichotomy and indicate that both IL and PL are involved with the inhibitory control of cocaine seeking.

In contrast with the classic view that IL facilitates cocaine memory extinction, the IL, however, may drive heroine seeking. For example, selective pharmacogenetic inactivation of IL neurons enhanced heroine memory extinction (Bossert et al. 2011), as did administration of CB1 antagonist (Alvarez-Jaimes et al. 2008) and GABA receptor agonists (Alvarez-Jaimes et al. 2008; Rogers et al. 2008) in IL. Likewise, for alcohol addiction, the results are inconsistent for the role of IL in extinction. Inactivation with baclofen/muscimol in IL had no impact on the extinction of alcohol memory, but delayed the first response on test in extinction context (Willcocks and McNally 2013). Besides, inactivating IL with GABA receptor agonist resulted in decreased cue-induced reinstatement of extinguished memory of methamphetamine (Rocha and Kalivas 2010). Thus, it appears that the roles of the IL in extinction of drug memory are not consistent among different studies, which may be attributable to different types of drugs and training protocols.

Mechanisms underlying the role of PFC in the extinction of drug memory

Circuit mechanisms

PFC-NAc circuit

Recent studies have begun to examine the PFC-based circuit mechanisms that mediate extinction of drug-seeking behavior.

The mPFC-NAc pathway may play an important role in regulating extinction and reinstatement of drug seeking after extinction (Bossert et al. 2013; Li et al. 2015; McFarland et al. 2003). The NAc core subregion receives inputs primarily from the PL, whereas the NAc shell subregion receives input primarily from the IL (Krettek and Price 1977; Sesack et al. 1989). A great number of literatures suggests that projections of PrL-NAc core and IL-NAc shell may play different roles in extinction of drug memories (Chen et al. 2016; Kalivas and O'Brien 2008; Peters et al. 2008a). The glutamatergic projections in mPFC-NAc core are mainly involved in regulating drug-seeking responses (Kalivas 2009; Kalivas and McFarland 2003), and pharmacological or optogenetic inhibition of the projection diminishes cue- or drug-induced reinstatement of drug-seeking behavior and the potentiation of transient synaptic potentiation in medium spiny neurons (MSNs) (LaLumiere and Kalivas 2008; Shen et al. 2014; Stefanik et al. 2016). The glutamatergic projections from mPFC (mainly IL) to the NAc shell are primarily engaged in suppressing conditioned drug seeking after extinction learning (Chen et al. 2016; Peters et al. 2009). Blocking this pathway results in resumption of cocaine seeking (Peters et al. 2008a). Pharmacological inactivation of the NAc shell increases cocaine seeking under extinction conditions (Fuchs et al. 2008; Peters et al. 2008a). Furthermore, by using a retro-DREADD approach to confine the expression Gq-DREADD to mPFC neurons that project to the medial NAc shell, it was found that these neurons are responsible for decreasing cue-induced reinstatement of cocaine seeking. Additionally, the effects of mPFC activation on cue-induced reinstatement depend on prior extinction training of self-administration, suggesting that the glutamatergic input from IL-mPFC to the NAc shell may be responsible for extinction learning (Augur et al. 2016). Moreover, extinction training during withdrawal increases the expression of the GluR1 and GluR2/3 subunits of the AMPAR in NAc shell but not core (Sutton et al. 2003). The increased GluR1 expression in NAc shell is positively associated with the degree of extinction achieved during training and negatively associated with cue-induced relapse (Sutton et al. 2003). These findings suggest that mPFC-NAc shell circuit is required for mediating extinction behavior through both presynaptic and postsynaptic mechanisms.

PFC-VTA circuit

Apart from the NAc, the mPFC also sends dense afferents to ventral tegmental area (VTA). The dopaminergic neurons in VTA can be readily activated by primary rewards (abused drugs) and reward-predicting stimuli (Wise 2009). In animals trained to self-administer cocaine, cocaine-predictive cues trigger glutamate release and dopaminergic activation in VTA (You et al. 2007). Recently, Degoulet et al. 2016 found that isradipine, a general LTCC antagonist, blocked the induction of NMDAR LTP and promoted the reversal of previously induced LTP in the VTA. Furthermore, intra-VTA injection of a CaV1.3 subtype-selective LTCC antagonist before extinction training abolished previously acquired cocaine and alcohol CPP on subsequent days, and the effect lasted at least 2 weeks (Degoulet et al. 2016). TA receives numerous glutamatergic inputs from both the PrL and IL of mPFC (Heidbreder and Groenewegen 2003), and electrical stimulation of these inputs increases glutamate release in the VTA (Rossetti et al. 1998), which may in turn trigger dopamine release. Behaviorally, the glutamatergic transmission from mPFC to VTA plays a pivotal role in reinstatement of drug-seeking behavior after extinction training (Wise 2009). However, whether these specific afferents from PrL and IL to VTA regulate extinction of drug-seeking behavior is not yet known.

PFC-MDH circuit

Medial dorsal hypothalamus (MDH) is another downstream target of mPFC that receives extensive projections from the IL of mPFC (Heidbreder and Groenewegen 2003; Thompson and Swanson 1998). In recent years, the MDH has been shown to be associated with the termination of motivated behaviors and, therefore, is recognized as a logical candidate for regulation of extinction learning. Double labeling of retrograde tracer cholera toxin B subunit (CTb) and Fos revealed recruitment of MDH projecting PFC neurons during extinction expression (Marchant et al. 2010). Infusion of the inhibitory neuropeptides known as cocaine- and amphetamine-regulated transcript (CART) into the MDH prevented extinction expression (Marchant et al. 2010), indicating that mPFC-MDH circuit is also involved in extinction expression.

Neuronal ensemble mechanisms

Neuronal ensemble is a concept which is proposed by Hebb that learned associations are encoded within specific populations of neurons that were selectively activated by environmental cues. Recently, there has been increasing interest in determining the neuronal ensembles in the mesolimbic system control of drug seeking and relapse (Cruz et al. 2013; George and Hope 2017). Current evidence suggests that different neuronal ensembles in mPFC may be responsible for promotion or inhibition of drug-seeking behavior, respectively. It has been found that a fraction of vmPFC neurons were preferentially activated by the heroin-associated context. Selective pharmacogenetic inactivation of these neurons inhibited context-induced drug relapse (Bossert et al. 2011), suggesting that a subset of neuronal ensembles in vmPFC encode the learned associations between heroin reward and heroin-associated contexts, and promote the cue-induced relapse. However, using animal model of alcohol self-administration, Pfarr et al. reported that activity-dependent ablation of

neuronal ensemble in the IL but not PL induced excessive alcohol seeking (Pfarr et al. 2015). It seems that the targeted neuronal ensemble were specific for the cue-induced response because nonselective inactivation of IL neurons, using pCAG-lacZ rats, only marginally affected the cue-induced reinstatement task. These results indicate that promotional or inhibitory control over drug seeking is exerted by distinct functional ensembles within IL rather than by a general tone of this region. Indeed, two recent studies have demonstrated that Fos-expressing neuronal ensembles mediating reward and extinction memories are intermingled within the vmPFC. In the first study, Warren et al. found that inactivation of the food reward ensembles decreased food seeking, whereas inactivation of the extinction ensembles increased food seeking (Warren et al. 2016). In the second study, Suto et al. found that the same IL area is capable of controlling both promotion and suppression of reward seeking via different neural ensembles, each selectively reactive to associated or non-associated cues, and disruption of IL neurons activated by either cue exclusively altered the behavioral response as well as neural activation uniquely linked to the targeted cue. The neural ensembles in IL mediating the bidirectional control of reward seeking are most likely mutually exclusive rather than overlapping (Suto et al. 2016). These results could explain the inconsistent results about the role of mPFC in drug memory and extinction memory and promote novel strategy for enhancing extinction memory and prevention of drug relapse.

Synaptic mechanisms

Glutamatergic transmission

Glutamate is the primary excitatory neurotransmitter in the brain which acts on the ionotropic glutamate receptors including AMPA receptors (AMPARs), NMDA receptors (NMDARs), kainate receptors and the metabotropic glutamate receptors (mGluRs) (Traynelis et al. 2010). From the behavioral perspective, substantial evidence has existed for the involvement of glutamate system in addiction and extinction of multiple types of abusive drugs. Besides, intra-IL administration of PEPA, a positive allosteric modulator of AMPARs, facilitated extinction of cocaine-seeking (LaLumiere et al. 2010) as well as heroin-seeking behaviors (Chen et al. 2016). For rat model of methamphetamine CPP, transperitoneal administration of ceftriaxone during extinction training, which activates the glutamate transporter (EAAT2), prevents the drug-primed reinstatement with an increase of EAAT2 mRNA expression in mPFC (Abulseoud et al. 2012). However, intracerebroventricular administration of the AMPAR antagonist CNQX augmented the extinction process of rat morphine CPP model, hampered the increased Fos expression and blocked the phosphorylation of cAMP response element-binding protein (CREB) in PFC (Siahposht-Khachaki et al. 2017). The discrepancies of findings between the Siahposht-Khachaki et al and previous studies may be attributable to different types of drugs and routs of administration. The mGluRs are also showed to play roles in drug extinction memories. Infusion of the mGluR1/5 agonist DHPG into the IL of cocaine-experienced rats facilitated extinction of drug seeking (Ben-Shahar et al. 2013). Activation of group I metabotropic glutamate receptor subtype 5 (mGluR5) in IL but not PL facilitates extinction of cue-conditioned alcohol-seeking behavior via potentiation of glutamatergic synaptic plasticity (Gass et al. 2014), suggesting the mGluR5 as a promising drug target for facilitation of extinction learning.

While the importance of the glutamatergic receptors in learning and memory has been long appreciated, recent studies also started to revel how the receptors in mPFC adapt to the extinction of drug memory (Kalivas et al. 2005). Extinction training significantly increases the amplitude of the evoked NMDAR-mediated current in both PL and IL (Fig. 1). In contrast, the AMPAR currents in the PL but not IL are reduced after extinction training (Fig. 1). Not surprisingly, a reduction in the AMPAR/NMDAR current, an indicator of neuronal plasticity, is also found after extinction training in the PL but not IL (Gass et al. 2014). In line with the altered glutamatergic transmission, manipulation of the activity of AMPAR and NMDAR was found to influence the extinction of fear-conditioning as well as drug-seeking behavior (Myers et al. 2011; Peters et al. 2009). Increasing the AMPAR activity in IL via its positive allosteric modulator augments extinction of cocaine seeking (Oliva et al. 2018). Pharmacologically inhibiting NMDAR, particularly those containing the NR2A in IL, facilitates the extinction expression (Hafenbreidel et al. 2017). Few studies investigate how mGluRs in mPFC regulate the extinction of drug memories. A recent study shows that mGlu5R activation significantly reduced calcium activated potassium channel (K_{Ca}) currents in layer V PNs of IL. The mGluR5-dependent facilitation of long-term potentiation can be readily prevented by positive modulation of K_{Ca} channels in IL (Cannady et al. 2017), suggesting that mGluR5-mediated enhancement of extinction of alcohol-seeking behavior and synaptic plasticity in IL involves functional inhibition of K_{Ca} channels.

In addition to altering the expression and function of glutamatergic receptors in mPFC, extinction of drug memories also causes structural remodeling of glutamatergic synapses in mPFC (Fig. 1). Gass and colleagues demonstrate that extinction training significantly increases the spine density in basal dendrites of layer V PNs in IL as compared with the forced abstinence (Gass et al. 2014). The extinction-associated increase was further potentiated by treatment with mGluR5 positive allosteric modulator which facilitates extinction learning (Gass et al. 2014). The increased spine density in IL following extinction was primarily due to an increase in the number of mature, mushroom spines (Gass et al. 2014) and associated with increased expression of F actin (Toda et al. 2006),

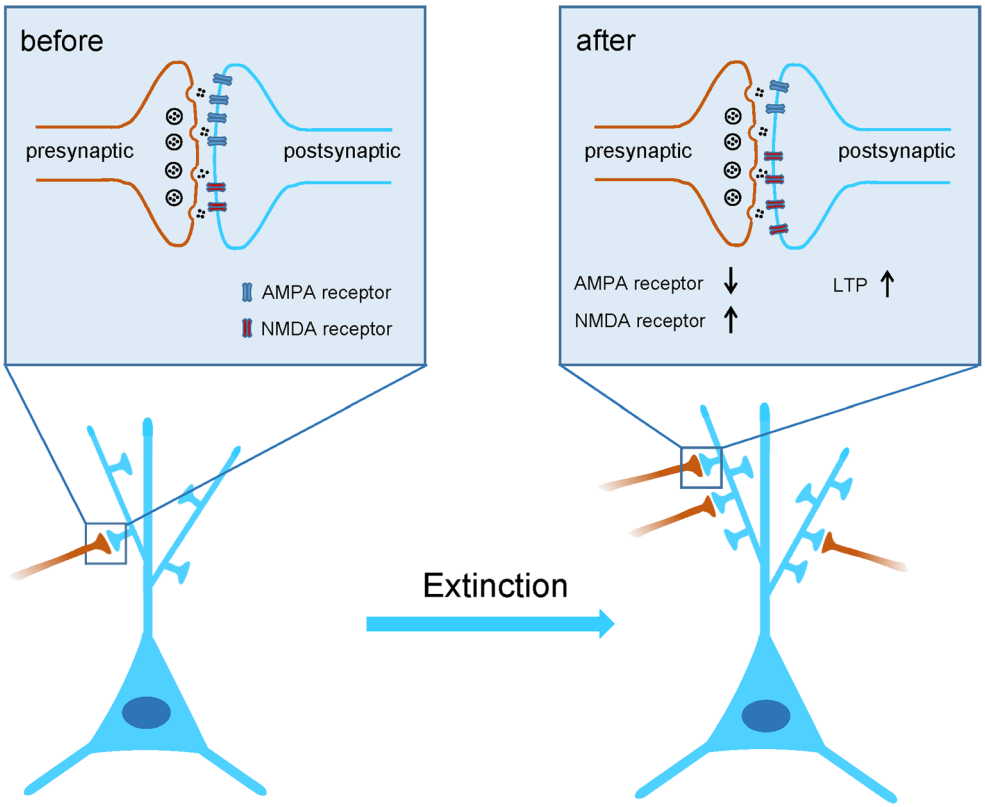

Fig. 1 Schematic showing the synaptic remodeling following extinction of drug memory in the prelimbic subregion (PL) of medial prefrontal cortex. Extinction training causes robust spinogenesis in the projection neurons of PL with redistribution of glutamatergic receptors inside the synapses. It increases the number of AMPA receptors but decrease that of NMDA receptors, accompanied by an enhancement of the long-term potentiation of glutamatergic transmission onto these neurons. Please note that the synaptic remodeling by extinction varies across the mPFC subregions such as the prelimbic and infralimbic regions

suggesting an enhanced glutamatergic transmission. Extinction training activates Rho GTPase Rac1 in the mPFC in a brain-derived neurotrophic factor (BDNF)-dependent manner (Wang et al. 2017), and, both in vivo and vitro studies show that Rac1 plays a crucial role in spine morphogenesis through regulating the size and density of spines in neurons (Luo 2000; Nakayama et al. 2000). Despite this, whether extinction-induced Rac1 activation also contributes to the altered dendritic and spine morphology is not yet known.

The signaling pathways that regulate the glutamatergic receptors trafficking are also suggested to be important for the extinction of drug memories. Neuronal activity-regulated pentraxin (Narp) is an immediate early gene product that is secreted and binds to AMPAR (O'Brien et al. 1999). Although the Narp knockout (KO) mice are intact in instrumental and Pavlovian learning, they are deficient in extinction of morphine CPP (Crombag et al. 2009; Johnson et al. 2007). Blouin et al. suggest that it is the Narp in IL that mediates this phenotype. Viral-mediated expression of a Narp dominant-negative construct in IL of mice blocks extinction of morphine CPP while reintroduction of Narp into IL of KO mice rescues the impaired extinction of morphine CPP (Blouin et al. 2013a). Notably, viral-mediated knockdown of Narp in IL had little effect on the extinction of heroin self-administration, indicating a possibility that Narp differently affects the extinction of memory of different drugs (Blouin et al. 2013b). PKMζ, an autonomously active isozyme of protein kinase C, regulates NSF/GluR2-dependent AMPAR trafficking (Migues et al. 2010; Yao et al. 2008). He et al. showed that inhibiting PKMζ activity in IL but not PL, disrupted the expression of extinction memory of CPP and CPA, indicating that PKMζ in IL is required for the maintenance of extinction memory of morphine reward-related cues and morphine withdrawal-related aversive cues (He et al. 2011).

GABAergic transmissions

Relatively little is known about the role of GABAergic transmission in mPFC in the formation and retention of extinction memory. In the rat model of cocaine self-administration, IL inactivation with the transcranial injection of the GABA receptors agonist baclofen and muscimol during late extinction enhanced drug seeking (Peters et al. 2008a). However, in the animal model of alcohol self-administration, reversible inactivation of IL had no effect on the reinstatement or reacquisition of alcoholic beer-seeking and had no effect on extinction expression, while IL inactivation did, however, increase the latencies with which animals responded on test but only when animals were tested in the extinction context (Willcocks and McNally 2013). In the animal model of cocaine addiction, IL inactivation after extinction leads to the re-emergence of conditioned place preference (Ovari and Leri 2008), an effect which relates to the suppression of GABAergic transmission and facilitation of long-term potentiation (LTP) in vmPFC. Moreover, extinction training decreases

the expression of surface $GABA_AR$ β3 subunit through dynamin-dependent $GABA_AR$ endocytosis (Wang et al. 2017), but has little influence on the AMPAR endocytosis. The extinction training induced $GABA_AR$ endocytosis may result from Rac1 activation in the vmPFC via a BDNF-dependent manner (Wang et al. 2017).

Dopaminergic transmission

Despite the extensive dopaminergic innervation of mPFC, the role of dopamine receptor in mPFC subregions in the reinstatement of cocaine seeking is far from being clearly identified. Using rat model of cocaine self-administration, it was found that IL microinfusion of the dopamine receptor 2 (D2)-like agonist quinpirole before extinction attenuated cue-primed relapse in adolescents (Zbukvic et al. 2016). There is evidence that the dysfunction of dopamine signaling may contribute to the deficit in extinction learning and susceptibility to relapse during adolescence. Extinction of drug cue associations was facilitated in adolescents by elevating dopamine and norepinephrine in the PFC with atomoxetine during extinction training. Direct microinjection of the D1 receptor agonist SKF38393 mimicked this effect and facilitated extinction in adolescent subjects (Brenhouse et al. 2010). Furthermore, infusion of quinpirole into IL prior to extinction significantly reduced cue-induced reinstatement in adolescents. This effect was replicated by acute systemic treatment with the atypical antipsychotic aripiprazole (Abilify), a partial D2R-like agonist (Zbukvic et al. 2016).

Adrenergic transmission

Using animal model of self-administration, LaLumiere et al. found that injection of clenbuterol, a β_2-adrenergic receptor (AR) agonist, in IL after extinction training facilitates the retention of extinction. Local administration of β_2-AR antagonist ICI in IL before extinction training inhibited extinction retention (LaLumiere et al. 2010). Consistent with this, Huang et al. found that β-arrestin-based β-adrenergic signaling in IL regulated extinction learning of cocaine-associated memories using animal model of CPP (Huang et al. 2018). Within 10 min after extinction, the administration of the nonbiased β-AR antagonist propranolol, but not the G protein-biased β-AR antagonist carvedilol, blocked extinction learning of cocaine-conditioned place preference and the associated extracellular signal-regulated kinase (ERK) activation in IL. Genetic deletion of β-arrestin2 in IL, specifically in excitatory neurons, impaired extinction learning of cocaine-conditioned place preference, which was not rescued by carvedilol (Huang et al. 2018). The adrenergic system may also strengthen the extinction memory through increasing the excitability of IL neurons in a β-AR- and PKA-dependent manner. During extinction, blockade of noradrenergic receptors with propranolol in IL prevented the acquisition of extinction memory, and, interfering with noradrenergic receptors, PKA, transcription, or protein synthesis in IL impairs retention of extinction (Mueller et al. 2008).

Molecular and epigenetic mechanisms

Despite the accumulating literature on the molecular mechanisms underlying extinction of fear memory, little is known on the extinction of drug memory. BDNF is widely known to be critical for synaptic plasticity (Korte et al. 1995; Lohof et al. 1993) and extinction of fear memory (Peters et al. 2010). Otis JM et al. found that IL infusion of BDNF enhanced the extinction of cocaine-CPP, and of ANA-12, an antagonist for BDNF tropomyosin-related kinase B (TrkB) receptor, impaired cocaine-CPP extinction. Consistently, systemic administration of the TrkB receptor agonist facilitated extinction of cocaine-CPP, indicating BDNF signaling as a promising adjunct for extinction therapy (Otis et al. 2014). It is interesting to note that infusion of BDNF in mPFC also suppresses cocaine seeking-induced molecular adaptations within the NAc (Berglind et al. 2007; Berglind et al. 2009; Sun et al. 2014), arguing for a critical role of BDNF in the extinction of drug memory. Previous studies also highlighted BDNF engagement in the extinction of learned fear, such that BDNF infusion into the IL reduced conditioned fear even in the absence of extinction training (Peters et al. 2010). Thus, BDNF appears to act as a co-regulator of the extinction for both drug and fear memory. Other neurotrophic factors, such as basic fibroblast growth factor (bFGF or FGF2) in IL, also showed a role in the formation of extinction memory of addiction. Following cocaine exposure, bFGF is increased in IL, and blocking bFGF in IL-mPFC before extinction training resulted in facilitation of subsequent extinction. However, blocking bFGF alone was not sufficient to facilitate extinction, indicating separate roles of BDNF and bFGF in the extinction of drug memories. In addition, multiple protein kinase signaling pathways, such as cyclin-dependent kinase 5, ERK and Rho GTPase Rac1 are shown to be involved in the extinction of addiction memories (Castino et al. 2018; Wang et al. 2012; Wang et al. 2017). It was found that extinction training of CPA memory led to activation of ERK and CREB in IL and intra-vmPFC infusion of ERK inhibitor U0126 (1,4-diamino-2,3-dicyano-1,4-bis(methylthio)butadiene) before extinction training diminished extinction of CPA behavior and the related epigenetic regulation of BDNF gene transcription (Wang et al. 2012). Extinction of CPA also activates Rho GTPase Rac1 in IL in a BDNF-dependent manner, which affects $GABA_AR$ endocytosis via triggering synaptic translocation of activity-regulated cytoskeleton-associated protein (Arc) through facilitating actin polymerization. Knockdown of Rac1 expression within the vmPFC of rats using Rac1-shRNA suppressed $GABA_AR$ endocytosis and CPA extinction, whereas expression of a constitutively active form of Rac1 accelerated $GABA_AR$ endocytosis and CPA extinction.

Epigenetics refers to the process of altering gene functions without inducing mutations of DNA. The major types of epigenetic modifications include DNA methylation, chromatin modification, non-coding RNAs, post-translational histone regulations, etc. (Nestler 2014). A great number of studies has demonstrated that the persistence of drug memories and relapse propensity are attributed to drug-induced epigenetic mechanisms regulating long-lasting drug-induced molecular alterations (Anier et al. 2010; Garrison and Potenza 2014; Nestler 2014; Pascual et al. 2012; Robison and Nestler 2011; Tian et al. 2012; Wright et al. 2015). Recently, emerging studies have been trying to reveal the epigenetic mechanisms underlying extinction memory and its inhibition on drug relapse. Sadakierska-Chudy et al. studied the effect of extinction training of cocaine self-administration on a few of genes including those encoding histone-modifying enzymes and histone proteins that control the chromatin state. It was found that at the end of extinction training, most of the analyzed genes in the rats that either actively or passively experienced cocaine administration returned to the control level (Sadakierska-Chudy et al. 2017). However, it is still needed to explore the causal link between the changes of histone-modifying enzymes in extinction of cocaine self-administration memory. Using the animal model of CPA, Wang et al. investigated the role of epigenetic regulation of BDNF gene expression in extinction of morphine-associated withdrawal memory (Wang et al. 2012). The results showed that CPA extinction training induced an increase in acetylation of histone H3 at the promoters of BDNF exon I transcript and increased BDNF mRNA and protein expression in the vmPFC of acute morphine-dependent rats. The epigenetic regulation of BDNF gene transcription could be facilitated by intra-vmPFC infusion of HDAC inhibitor trichostatin A before extinction training. Correspondingly, disruption of the epigenetic regulation of BDNF gene transcription blocked extinction of CPA behavior. Histone modifications are also found to be involved in extinction of drug-seeking in rats. A history of nicotine exposure significantly decreased H3K14 acetylation at the BDNF exon IV promoter, and this effect was abolished with extinction training combined with NaB treatment (Castino et al. 2018). Despite these, it is not yet known about the role of DNA methylation and other types of epigenetic modifications in mPFC in the regulation of formation or expression of extinction of drug memories.

Clinic relevance for the role of mPFC in drug extinction memories

Effects of addictive drugs or drug-related cues on PFC activity

Direct drug exposure alters the activity of PFC across species. Intracerebroventricular injection of cocaine in rats induced a significant increase in fMRI blood oxygen level-dependent (BOLD) signal intensity in PFC (Rothbaum and Davis 2003). Non-contingent cocaine administration in drug-naïve rhesus monkeys resulted in activation of dorsolateral PFC (Beylergil et al. 2017). Intravenous cocaine administration to abstinent cocaine-addicted patients improved BOLD responses in anterior prefrontal cortex (aPFC) and OFC (Wolstenholme et al. 2017). Besides, drug cue exposure has pronounced influence on PFC activation. For human nicotine-addictive individuals, fMRI test revealed that cigarette-related cues activated left dorsolateral prefrontal cortex (DLPFC) (Peters et al. 2008a). Similarly, in human abstinent alcoholics, alcohol-related stimuli elicited activation of bilateral ACC and DLPFC (LaLumiere et al. 2012; Ovari and Leri 2008). In cocaine abusers, cocaine cues induced activation of left lateral OFC activation and right DLPFC, whereas deactivation of left mPFC (Ben-Shahar et al. 2013). A PET study showed that when presented with cocaine-related cues, rhesus monkey trained to self-administrate cocaine displayed robust activation in PFC (Beylergil et al. 2017).

Effects of extinction of drug-related cues on mPFC activity

Until now few studies explored the PFC activity during the extinction of drug-associated cues, although substantial evidence has showed that fear extinction critically depends on the vmPFC (Milad et al. 2005; Milad et al. 2007; Mueller et al. 2014; Phelps et al. 2004). Konova et al. studied neural mechanisms of extinguishing drug and pleasant cue associations in human addiction using fMRI. They found that like fear extinction, non-fear-based extinction relies on the vmPFC. Cocaine users showed vmPFC abnormalities for both CSs, which, in the case of the drug-related images, correlated with craving. The study suggests a global deficit in extinction learning in this group that may hinder extinction-based treatment (Konova et al. 2017). The dysfunction of mPFC may underlie the resistance of drug cue associations to extinction in addiction. On the one hand, PFC dysfunction makes individuals vulnerable to drug use. Bechara (Bechara 2005) argued that like individuals with vmPFC lesions, the addicted individuals' ability of inhibition is impaired, largely due to the relatively weaker function of reflective PFC compared with the impulsive amygdala. A research recruited teenagers with parental history of alcoholism and compared the children who were resilient to alcohol with those vulnerable to alcohol (according to the level of problem drinking). They found that the vulnerable group had greater activation of the dorsomedial PFC in fMRI (Heitzeg et al. 2008).

On the other hand, repeated drug use impairs the PFC function. When compared with rats with short access of cocaine, those with long access performed worse in the sustained attention task, indicating impaired cognitive flexibility. Decrease of D2 receptor mRNA expression and D2 protein levels in the medial prefrontal cortex, and of D2 mRNA in the

orbitofrontal cortex were also observed (Briand et al. 2008). A human PET study showed that during Iowa Gambling Task, cocaine-addicted patients have higher activation of right OFC and lower activation of right DLPFC and left mPFC compared with control group (Bolla et al. 2003). This research suggested functional impairment in prefrontal cortex that participates in decision-making exists in drug abusers. Adults rodents with alcohol exposure during adolescence showed weaker baseline connectivity between PFC-striatum and among PFC subregions, as well as alterations in the expression of genes related with myelin and histone demethylation in PFC (Wolstenholme et al. 2017).

Potential application of extinction combined with mPFC modulation in the treatment of drug abuse

CET includes repeated presentation of drug-related stimuli without reinforcement. The goal of CET is to form new associations between drug cues and the absence of drug, thus inhibiting the expression of drug memory and preventing cue-induced drug seeking. However, the efficacy of CET appears to be limited (Conklin and Tiffany 2002). It is not surprising considering that extinction is a new learning but not an erasure of drug-related memory (Torregrossa and Taylor 2013). Compared with drug-related memory, extinction memory is unstable and vulnerable to forgetting (Myers et al. 2011). During and after CET, drug memory remains intact, and tends to reemerge with the passage of time, or exposure to drug or drug-related cues (Conklin and Tiffany 2002). Given the role of mPFC in the extinction of drug memories in animal models mentioned above, combination of extinction therapy with mPFC modulation may help to reduce craving and relapse in addicted patients.

Mounting evidence suggests that repetitive transcranial magnetic stimulation (rTMS) localized at the DLPFC, which is more superficial than the vmPFC and functionally connected with vmPFC, is effective in treating human with substance addiction (Bellamoli et al. 2014; Jansen et al. 2013; Salling and Martinez 2016). The mechanisms are still unclear, one of the possibilities is the regulation of activity in the brain regions related with addiction behaviors (Gorelick et al. 2014). To our knowledge, no human research has combined TMS with extinction training for the intervention of drug addiction, but in the field of fear memory, a study found that rTMS with imaginal exposure therapy attenuated hyperarousal symptoms, and altered the catecholamine and hormone levels in posttraumatic stress disorder (PTSD) patients (Osuch et al. 2009). Transcranial direct current stimulation (tDCS) has been proved to enhance abstinent rate in crack-cocaine-addicted patients (Batista et al. 2015). Alcohol-dependent patients who underwent bilateral tDCS of the DLPFC had lower subjective craving for alcohol as well as higher startle amplitudes, in comparison with those receiving placebo tDCS. In this study, the startle amplitude is the objective measurement for cue reactivity, and furthermore, the objective measurement for craving level (Wietschorke et al. 2016). Similarly, deep brain stimulation (DBS) has been proved as a future treatment for addiction (Peisker et al. 2018; Salling and Martinez 2016), yet more studies are needed to reveal the underlying mechanisms and how those physical interventions can be co-used with extinction therapy to yield more satisfactory treatment outcomes.

There are some other extinction-based interventions for drug relapse, such as memory retrieval-extinction procedure and combination of extinction training and vagus nerve stimulation (VNS). These interventions are related to the changes of mPFC activities, although mPFC are not directly stimulated. A retrieval-extinction procedure is referred to giving an extinction training after a memory retrieval manipulation. The effects only emerged when the interval between retrieval and extinction training is shorter than the reconsolidation time window. The memory retrieval-extinction procedure has been shown to reduce drug craving and relapse, both in abstinent human individuals addicted with heroin and nicotine, and rat model of cocaine, morphine, heroin, and alcohol relapse (Germeroth et al. 2017; Millan et al. 2013; Sartor and Aston-Jones 2014; Xue et al. 2012). The mechanism underlying memory retrieval-extinction procedure may at least be partially due to the alterations of mPFC activities (Xue et al. 2012). In rats self-administered with cocaine, VNS conducted during extinction attenuated cue-elicited reinstatement, and decreased the expression of the phosphorylated transcription factor CREB (pCREB) in the PFC (Childs et al. 2017), which regulates drug-seeking behaviors (Zhou and Zhu 2006). With the development of transcutaneous VNS in a broader range of neuropsychological disorders (Ben-Menachem et al. 2015; Genheimer et al. 2017; Jin and Kong 2017; Kong et al. 2018; Nichols et al. 2011; Shi et al. 2013), pairing VNS with extinction has begun to show potential for the treatment of drug addiction in clinic.

Conclusive remarks

Aberrant drug memories of the association between the drug-taking behavior and drug-related environmental cues contribute to the high rate of relapse after abstinence. Memory extinction weakens the strength of drug memories and reduces the propensity to relapse. However, since extinction training only causes temporary suppression but not permanent erasure of memories, drug memories are often spontaneously recovered after a long period of abstinence, reinstated by a priming dose of drugs, or renewed after exposure to drug-associated stimulus in a new environment. The ultimate goal of exploring the mechanisms underlying extinction of drug memories is to augment the persistence of memory extinction or prevent the

original drug memories from relapse under the above-mentioned circumstances. Converging evidence from clinical and animal studies have suggested a critical role of mPFC, especially the IL-mPFC, in the extinction of drug memories, and manipulation of neural activity, synaptic plasticity or signaling pathway in IL-mPFC is effective in altering the persistence of extinction memory of drugs. To better understand the role of mPFC in the extinction memory of drugs and enhance the clinic translation for the use of memory extinction therapy, future studies in the following directions are needed. First, the causal relationship between mPFC and extinction memory in drug-addicted patients remains to be identified. Second, clinical and preclinical studies should be developed to ascertain whether manipulating the function of mPFC may be sufficient to reduce the reappearances of drug memories in addicted patients. Lastly, given the sufficiency of memory retrieval-extinction behavioral procedure in reducing the drug-seeking behavior and relapse, it is urgent to understand whether mPFC participates in this process, and if yes, how to enhance the anti-relapse effect of the behavioral procedure in both animal models and addicted patients through manipulating the mPFC function.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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