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Review

Extinction circuits for fear and addiction overlap in prefrontal cortex

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Extinction is a form of inhibitory learning that suppresses a previously conditioned response. Both fear and drug seeking are conditioned responses that can lead to maladaptive behavior when expressed inappropriately, manifesting as anxiety disorders and addiction, respectively. Recent evidence indicates that the medial prefrontal cortex (mPFC) is critical for the extinction of both fear and drug-seeking behaviors. Moreover, a dorsal-ventral distinction is apparent within the mPFC, such that the prelimbic (PL-mPFC) cortex drives the expression of fear and drug seeking, whereas the infralimbic (IL-mPFC) cortex suppresses these behaviors after extinction. For conditioned fear, the dorsal-ventral dichotomy is accomplished via divergent projections to different subregions of the amygdala, whereas for drug seeking, it is accomplished via divergent projections to the subregions of the nucleus accumbens. Given that the mPFC represents a common node in the extinction circuit for these behaviors, treatments that target this region may help alleviate symptoms of both anxiety and addictive disorders by enhancing extinction memory.

Emotional memories, both in the aversive and appetitive domains, are important for guiding behavior. Regulating the expression of these memories is critical for mental health. Extinction of classical conditioning is one form of emotion regulation that is easily modeled in animals. In the aversive domain, a conditioned stimulus (CS) is typically paired with a shock, while in the appetitive domain, a CS is paired with the availability of food or drug reward. Repeated presentation of the CS in the absence of the reinforcer leads to extinction of conditioned fear or drug-seeking behaviors. In recent years, there have been great advances in our understanding of the neural circuitry responsible for this form of inhibitory learning (for reviews, see Cammarota et al. 2005; Maren 2005; Myers and Davis 2007; Quirk and Mueller 2008). The prefrontal cortex has been strongly implicated in fear expression (Powell et al. 2001; Vidal-Gonzalez et al. 2006; Corcoran and Quirk 2007) and fear extinction (Herry and Garcia 2002; Milad and Quirk 2002; Gonzalez-Lima and Bruchey 2004; Hugues et al. 2004; Burgos-Robles et al. 2007; Hikind and Maroun 2008; Lin et al. 2008; Mueller et al. 2008; Sotres-Bayon et al. 2008), and more recently, in expression of drug seeking after extinction (Peters et al. 2008a,b). These findings are consistent with a well-documented role of the prefrontal cortex in executive function and emotional regulation (Miller 2000; Fuster 2002; Quirk and Beer 2006; Sotres-Bayon et al. 2006).

In this review, we propose that the medial prefrontal cortex (mPFC) regulates the expression of both fear and drug memories after extinction, through divergent projections to the amygdala and nucleus accumbens, respectively. Extinction failure in the aversive domain can lead to anxiety disorders (Delgado et al. 2006; Milad et al. 2006), while extinction failure in the appetitive domain can lead to relapse in addicted subjects (Kalivas et al. 2005; Garavan and Hester 2007). A common neural circuit for extinction of fear and drug memories would suggest shared mechanisms and treatment strategies across both domains.

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Prefrontal control of extinction of conditioned fear

The earliest evidence that the prefrontal cortex might be a critical locus for the extinction of conditioned fear was the observation that prefrontal lesions led to a selective deficit in extinction (Morgan et al. 1993; Sotres-Bayon et al. 2006). Specifically, the ventral subdivision of rodent medial prefrontal cortex, termed infralimbic cortex (IL-mPFC), was responsible for this effect (Morgan and LeDoux 1995; Fig. 1). Since then, accumulating evidence has suggested that plasticity in IL-mPFC is important for extinction memory. Protein synthesis inhibitors (Santini et al. 2004), MAPK inhibitors (Hugues et al. 2004), NMDA receptor blockers (Burgos-Robles et al. 2007; Sotres-Bayon et al. 2008) or pharmacological inactivators (Sierra-Mercado et al. 2006) injected locally into IL-mPFC disrupt the ability to subsequently recall extinction. These data support the long-held notion that extinction learning creates an inhibitory memory trace distinct from that created by conditioning (Konorski 1967; Rescorla 2004).

Activity in IL-mPFC is a key mediator of the inhibitory memory underlying extinction. Single-unit recordings reveal that CS responsiveness in IL-mPFC neurons develops only after extinction learning has occurred, and correlates with the degree of extinction recall (Milad and Quirk 2002). Plasticity within the IL-mPFC has also been demonstrated to promote the maintenance of extinction memory, resulting in the suppression of conditioned fear (Herry and Garcia 2002). Finally, agents that enhance metabolic activity in IL-mPFC (Gonzalez-Lima and Bruchey 2004) and direct electrical stimulation of IL-mPFC (Milad et al. 2004; Vidal-Gonzalez et al. 2006; Fig. 2B), both promote extinction expression. Collectively, these data suggest that IL-mPFC mediates fear inhibition.

Recent evidence indicates that the more dorsally located prelimbic prefrontal cortex (PL-mPFC) increases fear expression (Fig. 1). Whereas IL-mPFC neurons increase activity to the CS when fear is low, PL-mPFC neurons increase firing during early extinction, when fear is high (Baeg et al. 2001; Gilmartin and McEchron 2005; Laviolette et al. 2005; Burgos-Robles et al. 2009). Furthermore, the time course of CS-evoked conditioned responses in PL-mPFC neurons is highly correlated with the time course of

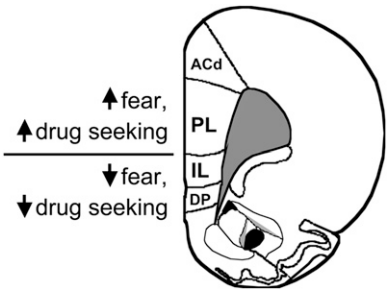

Figure 1. Dorsal versus ventral regions of rodent medial prefrontal cortex differentially control fear and drug seeking. The four major subdivisions of rodent medial prefrontal cortex are depicted along the Paxinos and Watson anatomical boundaries (3.0 mm anterior to bregma) (Paxinos and Watson 2005). Activity in the prelimbic (PL) region promotes the expression of conditioned fear and cocaine-seeking behavior. Dorsal to PL is the dorsal anterior cingulate cortex (ACd), which may also promote fear and drug seeking. The infralimbic (IL) cortex, which lies ventral to PL, promotes the extinction of conditioned fear and cocaine-seeking behavior. The ventral-most dorsopeduncular cortex (DP) may resemble IL in the ability to inhibit fear and drug seeking. Hence, dorsal regions of medial prefrontal cortex increase fear and drug seeking (arrows *up*), while ventral regions exert the opposite effect on behavior, decreasing both fear and drug seeking (arrows *down*).

conditioned freezing (Burgos-Robles et al. 2009). Microstimulation of PL-mPFC increases conditioned fear (Vidal-Gonzalez et al. 2006; Fig. 2A), and pharmacological inactivation of PL-mPFC reduces conditioned fear (Blum et al. 2006; Corcoran and Quirk 2007). Stimulation of more dorsal regions, such as dorsal anterior cingulate cortex (ACd-mPFC), produced no discernible effects on fear (Vidal-Gonzalez et al. 2006); however, a recent study found that ACd-mPFC inactivation was capable of reducing fear expression, and ACd-mPFC neurons are activated by fear stimuli (Bissiere et al. 2008). This suggests that ACd-mPFC may resemble PL-mPFC as a fear-activating site. Thus, there is a functional dorsal-ventral divide within the mPFC which can be conceptualized as an "on–off" switch regulating fear expression (Fig. 1).

Prefrontal outputs that modulate fear expression

Distinct subdivisions of mPFC could differentially regulate fear expression through divergent targets within the amygdala. The projections from mPFC to the amygdala are glutamatergic, excitatory projections (Brinley-Reed et al. 1995). The PL-mPFC region projects primarily to the basal amygdala (BA) (Vertes 2004; Gabbott et al. 2005), which is critical for the expression of conditioned fear (Anglada-Figueroa and Quirk 2005; Herry et al. 2008). The main sites of fear memory storage in the amygdala are the lateral amygdala (LA) (Quirk et al. 1995; Repa et al. 2001), as well as the central nucleus (CE) of the amygdala (Wilensky et al. 2006; Zimmerman et al. 2007). Because there is no direct projection from LA to CE output neurons, the LA is thought to drive fear by an intermediate local projection to the BA, which in turn excites the CE (Blair et al. 2001). PL-mPFC thus excites the CE, in the same manner as the LA, by a relay synapse in the BA (Likhtik et al. 2005). Thus, the net result of increased activity in PL-mPFC is an increased output from CE (Fig. 3), which generates fear via projections to the hypothalamus and brainstem (Hopkins and Holstege 1978; LeDoux et al. 1988).

The IL-mPFC also sends an excitatory projection to the amygdala, but preferentially targets areas containing GABAergic neurons in the lateral subdivision of central nucleus and in the intercalated cell masses (ITCs), which are positioned between the basolateral amygdala complex (BLA) and the CE (McDonald et al. 1996; Berretta et al. 2005; Fig. 3). These ITCs may be a site of plasticity for extinction memory, as they show NMDA receptor-dependent plasticity (Royer and Pare 2002). Activity in IL-mPFC may then promote extinction by engaging ITC-mediated feed-forward inhibition of the CE.

Consistent with this model of amygdala control of fear expression, recent evidence indicates that extinction may involve a combination of enhanced excitatory drive to ITCs and diminished excitatory output from LA. Specifically, Jüngling et al. (2008) found evidence supporting a presynaptic enhancement of glutamatergic transmission onto ITCs during extinction of conditioned fear. Involvement of ITCs in expression of extinction memory was

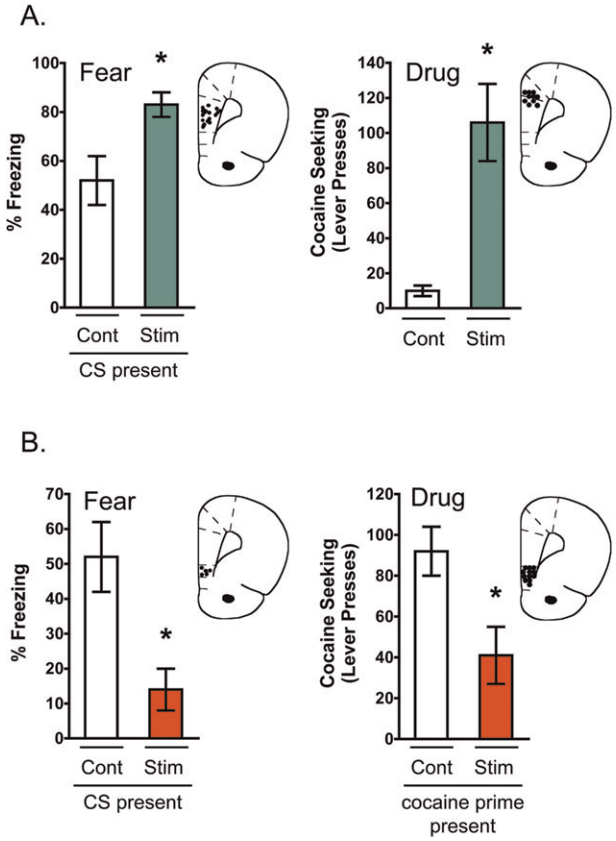

Figure 2. Enhancing activity in prelimbic cortex increases fear and drug seeking, while enhancing activity in infralimbic cortex has the opposite effects. (*A*) Electrical microstimulation (stim) of prelimbic (PL) cortex enhances conditioned fear relative to unstimulated controls (cont). Values on the *y*-axis represent percent freezing to the shock-paired tone CS. Microstimulation was conducted on the first extinction session (Vidal-Gonzalez et al. 2006). For drug seeking, PL was activated by local infusion of dopamine (30 nmol/side) before an extinction session, after extensive extinction training. Baseline extinction responding on the session prior to the PL test is shown as a control (cont). Values on the *y*-axis represent presses on the previously cocaine-paired lever (McFarland and Kalivas 2001). (*B*) Electrical microstimulation (stim) of infralimbic (IL) cortex reduces conditioned fear relative to unstimulated controls (cont). Data collected from the same study (Vidal-Gonzalez et al. 2006) on PL stimulation shown in *A*. For drug seeking, IL was activated by local infusion of AMPA (0.1 nmol/side) before a cocaine-primed (10 mg/kg, i.p.) reinstatement test, after extensive extinction training. Reinstatement of pressing on the previously cocaine-paired lever is used as a measure of cocaine seeking (*y*-axis). Reinstatement values for animals microinfused with vehicle prior to the relapse test are shown as controls (cont) (Peters et al. 2008a). Representative placements of the microstimulating electrode or infusion needle-tips in PL (*A*) and IL (*B*) are shown for both fear and drug-seeking experiments to the *right* of each graph. (*) $P < 0.05$ compared with respective control condition.

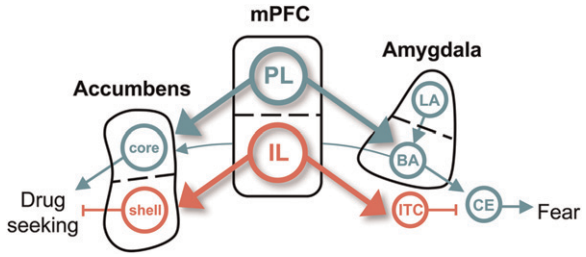

Figure 3. Circuit diagram depicting prefrontal regulation of conditioned fear and cocaine-seeking behaviors. The dorsal and ventral subdivisions of medial prefrontal cortex (PFC) are shown at the *center*, with their respective outputs to the amygdala controlling fear shown at *right*, and those to the nucleus accumbens controlling cocaine seeking shown at *left*. The prelimbic (PL) cortex projects to the basal (BA) nucleus of the amygdala, which excites the central (CE) nucleus of the amygdala, thereby promoting the expression of conditioned fear. The BA also receives excitatory input from lateral (LA) amygdala, which also drives the expression of conditioned fear. The infralimbic (IL) cortex, in contrast, excites a class of GABAergic inhibitory neurons known as the intercalated (ITC) cell masses. These neurons inhibit the CE, thereby inhibiting conditioned fear and promoting extinction. By comparison, PL and IL control cocaine seeking via their differential projections to the core and shell subdivisions of the nucleus accumbens. The PL projects to the core, which promotes the expression of cocaine-seeking behavior. For cue-induced cocaine seeking, this may involve an intermediate projection through the BA to access the core (thin green line). The IL projects to the shell, which promotes the expression of extinction. It remains to be determined how output from these two divisions of the accumbens differentially affects cocaine-seeking behavior (see text for details). Green depicts pathways that activate fear and cocaine seeking. Red depicts pathways that inhibit fear and cocaine seeking.

directly tested by Pare and coworkers, who showed that selective lesions of ITCs caused extinguished fear to return (Likhtik et al. 2008). In addition to potentiation of inhibition, recent evidence suggests that extinction involves depotentiation of excitiatory pathways (Kim et al. 2007). These authors found that extinction reversed the conditioning-induced increases in AMPA receptor surface expression in the LA, and blocking AMPA receptor endocytosis within the LA impaired extinction. Collectively, these data suggest that extinction results from a combination of enhanced drive to amygdala regions that inhibit fear expression (ITCs) and diminished output from regions that drive fear expression (LA), an idea supported by recent computational modeling (Li et al. 2009).

Prefrontal control of extinction of conditioned drug seeking

For drug-seeking behavior, we focus on a cocaine self-administration model of relapse. In this model, rats learn to press a lever for intravenous cocaine delivery in a cocaine-specific context over several days until responding is stable. When cocaine is replaced with saline, extinction of responding on the cocaine-paired lever occurs over a period of 1–2 wk. Following extinction, cocaine seeking can be reinstated by presenting a discrete cue that was paired with cocaine delivery, low doses of cocaine itself, or stress (De Wit and Stewart 1981; Shaham et al. 2003; Epstein et al. 2006). This reinstatement of drug seeking following extinction is thought to model clinical relapse. Relapse-inducing stimuli can activate cocaine seeking via dopaminergic mechanisms within the PL-mPFC (Ciccocioppo et al. 2001; McFarland and Kalivas 2001; McFarland et al. 2004; Fig. 2A). Both D1 and D2 dopamine receptors have been implicated in the ability of prefrontal dopamine to trigger relapse, though the evidence is somewhat stronger for D1 receptors (Ciccocioppo et al. 2001; Capriles et al. 2003; Sanchez et al. 2003; Sun and Rebec 2005). Indeed, administering cocaine directly into the PL-mPFC triggers cocaine relapse (Park et al. 2002), presumably due to local inhibition of the dopamine transporter (Komiskey et al. 1977).

The neural circuits mediating relapse to cocaine seeking have been recently mapped by pharmacologically inactivating discrete brain regions prior to the reinstatement test (McFarland and Kalivas 2001; McFarland et al. 2004; See 2005). The PL-mPFC was found to be critical for cocaine relapse, triggered by multiple forms of relapse-inducing stimuli, including cocaine-paired cues, cocaine itself, and stress (McFarland and Kalivas 2001; Capriles et al. 2003; McLaughlin and See 2003; McFarland et al. 2004; Di Pietro et al. 2006; but see Di Ciano et al. 2007). Thus, infusion of pharmacological inactivators or dopamine antagonists into PL-mPFC leads to decreased pressing for cocaine during relapse testing. More recently, inactivation of PL-mPFC was also found to reduce relapse for heroin induced by both heroin-paired cues and heroin itself (LaLumiere and Kalivas 2008; Rogers et al. 2008; but see Schmidt et al. 2005). The majority of these studies suggest that the PL-mPFC represents a final common node in the relapse circuit for both cocaine and heroin. Hence, similar to PL-mPFC's role in fear expression, PL-mPFC also supports theexpression of conditioned drug-seeking behavior (Fig. 1).

Given its proposed inhibitory role, inactivation of IL-mPFC should result in increased pressing for cocaine after extinction. This, however, has not been observed in previous studies (McFarland and Kalivas 2001; Capriles et al. 2003; Fuchs et al. 2005; McLaughlin and Floresco 2007; Koya et al. 2008). Two factors can account for this. The first is that IL-mPFC was typically inactivated prior to administering some relapse-inducing stimulus, which results in high levels of cocaine seeking, against which further increases in cocaine seeking would be difficult to detect (i.e., a ceiling effect). The second is that discrete cues paired with cocaine delivery were never extinguished prior to the IL-mPFC test; thus, Pavlovian extinction was incomplete (Capriles et al. 2003; Koya et al. 2008). If IL-mPFC is inactivated following extinction of cocaine or heroin seeking, there is a robust return of drug seeking, consistent with an inhibitory role for this structure (Ovari and Leri 2008; Peters et al. 2008a,b). Furthermore, pharmacologically stimulating IL-mPFC prior to a relapse test reduces the degree of observed relapse (Peters et al. 2008a; Fig. 2B), further implicating the IL-mPFC in suppression of drug seeking. Collectively, the available evidence suggests that PL-IL supply an on–off switch for expression of conditioned drug-seeking behavior, as they do for expression of conditioned fear, especially after extinction (Figs. 1, 2).

Prefrontal outputs that modulate drug seeking

Just as distinct prefrontal–amygdala connections support an on–off switch for conditioned fear, the anatomy of prefrontal–accumbens connections support an on–off switch for cocaine seeking. The nucleus accumbens core (core) receives input primarily from the PL-mPFC, whereas the nucleus accumbens shell (shell) receives input primarily from the IL-mPFC (Sesack et al. 1989; Brog et al. 1993; Voorn et al. 2004). Glutamate released from PL-mPFC within the core triggers relapse for both cocaine and heroin (McFarland et al. 2003, 2004; LaLumiere and Kalivas 2008; Fig. 3) via AMPA-mediated transmission (Cornish and Kalivas 2000; Park et al. 2002; LaLumiere and Kalivas 2008). The IL-mPFC projection to the shell, in contrast, promotes extinction of cocaine seeking, as disconnection of this pathway after extinction results in a return of conditioned cocaine seeking reminiscent of that seen with IL-mPFC inactivation (Peters et al. 2008a). Furthermore, as extinction proceeds, shell expression of the GluR1 subunit of the AMPA receptor increases, but core expression does not (Sutton et al. 2003). Shell expression of GluR1 correlates positively with the

degree of behavioral extinction and negatively with cue-induced relapse (Sutton et al. 2003). Thus, the IL-mPFC is a candidate glutamatergic input to the shell that may be responsible for signaling extinction (Fig. 3).

Both the core and the shell send GABAergic projections to the ventral pallidum, which controls motor output necessary for drug seeking (Walaas and Fonnum 1979; Zahm and Heimer 1990; Heimer et al. 1991; Kalivas et al. 1999). GABA agonists injected into the ventral pallidum reduce cocaine seeking (McFarland and Kalivas 2001), and in some cases locomotion (Mogenson and Nielsen 1983; Hooks and Kalivas 1995). Hence, the GABAergic projection from the accumbens to the pallidum would be expected to suppress drug seeking. This is consistent with IL-mPFC-mediated inhibition of drug seeking after extinction, but is not consistent with PL-mPFC-mediated activation of drug seeking. Activation of drug seeking via the core may involve the neuropeptide enkephalin. Medium spiny neurons projecting from the core to the pallidum express enkephalin (Zahm et al. 1985), which, when released during high frequency firing, could stimulate pallidal μ opiod receptors (Waldhoer et al. 2004) causing a reduction in local GABA levels and reduced inhibition within the pallidum (Kalivas et al. 2001; Schroeder and Schneider 2002). Indeed, a μ opiod-dependent decrease in pallidal GABA is necessary for cocaine relapse (Tang et al. 2005), an effect likely mediated through co-release of enkephalin in the accumbens core–pallidal pathway (Torregrossa et al. 2008). Thus, PL-mPFC projections through core to the pallidum could conceivably activate drug seeking.

Caveats to the model

Though our model proposes an overlap in the extinction circuits for fear and addiction within the prefrontal cortex and a divergence in the subsequent downstream effectors responsible for the expression of each of these behaviors, this divergence may not be as distinct as we propose. In addition to the expression of conditioned fear, the amygdala may also play a role in the expression of conditioned drug seeking. Activity in the BA is a necessary component of the circuitry underlying cue-induced drug seeking (Kantak et al. 2002; McLaughlin and See 2003). This is presumably mediated in part by reciprocal connections between the PL-mPFC and BA, as well as projections from the BA directly to the core (Di Ciano and Everitt 2004; Fuchs et al. 2007). Thus, at least for cue-induced drug seeking, there appears to be an overlap in the role of the projection from PL-mPFC to BA in initiating both fear and drug seeking (Fig. 3). Importantly, the CE of the amygdala is also capable of initiating drug seeking, particularly for stress-induced reinstatement (Erb et al. 2001; Leri et al. 2002; McFarland et al. 2004). Hence, enhanced CE output may be a common mechanism underlying the initiation of both fear and drug-seeking behavior.

In addition to its role in the expression of drug-seeking behavior, the nucleus accumbens may also be involved in the expression of fear. For instance, pharmacological inactivation of the shell is sufficient to elicit place avoidance as well as defensive fear behaviors in rats (Reynolds and Berridge 2001, 2002). While this suggests that activity in the shell may tonically inhibit fear expression, there is also some evidence to the contrary, where shell lesions have reduced fear expression (Jongen-Relo et al. 2003). However, the literature is mixed, perhaps partially owing to the general disregard for core vs. shell distinctions (Haralambous and Westbrook 1999; Schwienbacher et al. 2004; for review, see Levita et al. 2002). Future studies are necessary to determine the extent to which the amygdala and accumbens are exclusively dedicated to the expression of fear and drug seeking, respectively.

A common prefrontal pathology for PTSD and addiction?

There is increasing evidence supporting the notion that post-traumatic stress disorder (PTSD) is associated with extinction failure. In human imaging studies, both thickness (Milad et al. 2005) and activity (Phelps et al. 2004; Kalisch et al. 2006; Milad et al. 2007b) of ventral mPFC (vmPFC) correlate positively with extinction recall. PTSD patients exhibit decreased activity within vmPFC when exposed to traumatic reminders (Bremner et al. 1999; Shin et al. 2004; Phan et al. 2006), suggesting that the vmPFC in humans is analogous to IL-mPFC in the rodent. In fact, it has recently been shown that PTSD patients are deficient in extinction recall (Milad et al. 2008). Failure to activate these regions supports the hypothesis that PTSD results from extinction failure due to an inability to activate the vmPFC-off switch for fear (Fig. 4). It is also possible that PTSD occurs from an overactive on switch, as the thickness and activity of dorsal anterior cingulate (dACC) cortex, a functional homolog of rat PL-mPFC, correlates with fear expression (Milad et al. 2007a; Fig. 4).

In an analogous manner, drug addicts appear to suffer from an overactive on switch for drug seeking. Cocaine-related cues activate dACC in addicts (Grant et al. 1996; Childress et al. 1999; Garavan et al. 2000), and this activation correlates positively with subjective ratings of cocaine craving (Childress et al. 1999; Fig. 4). Hence, these "drug on" regions may be analogous to PL-mPFC in rodent studies of cocaine relapse. Indeed, these regions are anatomically homologous with rodent PL-mPFC (Ongür and Price 2000; Stefanacci and Amaral 2002). The possibility that these "drug on" regions overlap with "fear on" regions is suggested by

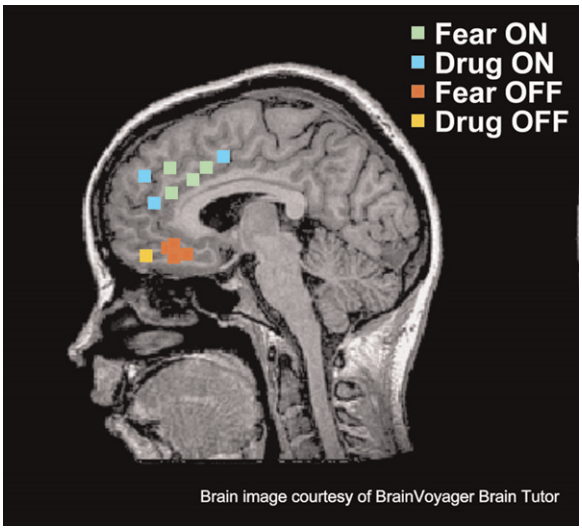

Figure 4. Human homologs of rodent prefrontal areas that modulate fear and addiction. Green dots represent regions of human dACC correlated with fear expression, as assessed by fMRI (Phelps et al. 2004; Milad et al. 2007a). Blue dots represent regions in human addicts correlated with cocaine craving after exposure to cocaine-related cues, as assessed by fMRI (Garavan et al. 2000) or PET mapping of cerebral blood flow using ^{15}O-labeled water (Childress et al. 1999). Red dots depict approximate regions of vmPFC that are correlated with fear extinction recall, as assessed by fMRI (Phelps et al. 2004; Kalisch et al. 2006; Milad et al. 2007b). Yellow dot represents the vmPFC equivalent in addicted subjects. This region is deactivated, as assessed by PET metabolic mapping with 2-deoxyglucose, during states of cocaine craving, suggesting a failure to engage extinction (Bonson et al. 2002). Collectively, these studies suggest that this vmPFC is homologous to rodent IL, whereas the dorsal regions of dACC are homologous to rodent PL. (MRI brain image duplicated with permission from BrainVoyager Brain Tutor software, by Brain Innovation BV, Maastricht, Netherlands.)

the observation that exposure to trauma-related cues in PTSD patients with comorbid substance dependency triggers cocaine craving (Coffey et al. 2002).

In addition to this cocaine-induced activation of dACC, addicts exhibit widespread decreases in prefrontal metabolism during resting states (Goldstein and Volkow 2002). Studies in monkeys indicate that the ventral-most regions of the prefrontal cortex are the first to show deficits in metabolism after chronic cocaine exposure (Porrino and Lyons 2000; Porrino et al. 2007). Hence, the prefrontal off switch for cocaine seeking may become compromised by cocaine use. Future studies are necessary, however, to determine whether human addicts exhibit deficient prefrontal metabolism even prior to cocaine use, which may render them vulnerable to drug abuse.

Human addicts resemble patients with vmPFC lesions on certain measures of cognitive inhibitory control (Bechara 2005). Both groups are characterized by a type of behavioral impulsivity resulting from an inability to experience negative arousal states normally associated with risky decision making (Bechara et al. 1996; Bechara and Damasio 2002). Interestingly, deactivation of vmPFC has been observed in addicts exposed to cocaine-related cues using positron emission tomography (PET) for glucose metabolism (Bonson et al. 2002). These data suggest that addicts suffer from a deficient off switch in vmPFC, rendering them more susceptible to relapse in the presence of cocaine-related cues. Thus, we suggest that addiction, like anxiety disorders, may result in part from extinction failure.

Comorbidity of anxiety and addiction

An interaction between circuits for fear and addiction is consistent with behavioral findings. Lifetime cocaine use has been associated with increased feelings of anxiety, a three- to fourfold increase in occurrence of panic attacks, and comorbidity with PTSD (Cox et al. 1990; Wasserman et al. 1997; O'Brien et al. 2005). If subjects are first screened for the presence of an anxiety disorder, the incidence of cocaine use is increased, even after adjusting for sociodemographic traits and other psychotic disorders (Goodwin et al. 2002; Sareen et al. 2006).

A fundamental pathology in prefrontal cortex could conceivably predispose an individual to both anxiety disorders and addiction. Given that vmPFC lesions result in behavioral impulsivity in both humans and rodents (Bechara et al. 1994; Davidson et al. 2000; Best et al. 2002; Chudasama et al. 2003), decreased vmPFC function may result in a high-risk phenotype. In support of this, it has been shown that PTSD patients (Chemtob et al. 1994; Aidman and Kollaras-Mitsinikos 2006; Dileo et al. 2008) and drug addicts (Bechara and Vander 2005; Verdejo-Garcia et al. 2007) are characterized by an impulsive phenotype. However, longitudinal studies with behavioral screening prior to trauma exposure are necessary to determine whether this impulsive phenotype is evident prior to the development of PTSD.

Abnormalities in prefrontal function could arise from stressful life experiences, including trauma, thereby predisposing individuals to develop PTSD and addiction (Anderson et al. 2000; Weber and Reynolds 2004; Hyman et al. 2007). There is epidemiological evidence suggesting a greater incidence of early childhood trauma in PTSD patients (Caffo and Belaise 2003). In rodents, both early life stress and adulthood stress can lead to deficits in fear extinction (Garcia et al. 2008; Matsumoto et al. 2008), possibly due to dendritic retraction in IL-mPFC (Izquierdo et al. 2006). Similarly, stress precipitates relapse in animal models of drug abuse and in humans (Shaham et al. 2000; Sinha et al. 2006).

The effects of stress exposure on prefrontal function could interact with genetic factors to produce a susceptible phenotype. For example, the presence of the dopamine D2 receptor A1 allele has been associated with increased susceptibility to PTSD (Comings et al. 1996) as well as cocaine abuse (Noble et al. 1993; Comings et al. 1994). The presence of this allele results in reduced brain levels of D2 receptors (Noble 2000), which is reminiscent of the deficiencies in striatal dopamine D2 receptor binding observed in human addicts (Volkow et al. 2002). Greater reductions in striatal D2 receptors have furthermore been correlated with greater deficits in resting prefrontal metabolism in addicts (Volkow et al. 1993). Though it must be determined whether these D2 deficits are the cause or the result of addiction, the findings are consistent with a possible genetic determinant for the development of addiction (Noble et al. 1997).

Treating addicts like trauma victims

Agents that enhance extinction signaling in vmPFC may be effective treatments for disorders that arise from extinction failure. To date, the greatest clinical success has been achieved with D-cycloserine (DCS), a partial agonist of the NMDA receptor, administered in conjunction with exposure therapy for the treatment of anxiety disorders. DCS has been shown to facilitate extinction of acrophobia (Ressler et al. 2004; Davis et al. 2006), social anxiety disorder (Hofmann et al. 2006), and obsessive compulsive disorder (Kushner et al. 2007; Wilhelm et al. 2008). Only recently is DCS being investigated as a possible treatment for addiction (Brady et al. 2008), but studies in rodents support its ability to facilitate extinction of cocaine seeking in a conditioned place preference model of drug reward (Botreau et al. 2006; Paolone et al. 2008). While DCS is thought to act in the amygdala (Ledgerwood et al. 2003), it may also act in the vmPFC, where NMDA-dependent consolidation of extinction takes place (Burgos-Robles et al. 2007; Sotres-Bayon et al. 2008).

By the same token, one might consider treating trauma victims like drug addicts. Recent data suggest that *N*-acetylcysteine, an over-the-counter cysteine prodrug, may be effective in treating cocaine dependence (LaRowe et al. 2007). This drug is thought to act by restoring glutamate levels in the accumbens of addicts based on data from rodent studies (Baker et al. 2003). Self-administration of cocaine reduces extracellular glutamate in accumbens by producing an enduring reduction in cystine–glutamate exchange, and *N*-acetylcysteine restores exchanger activity (Baker et al. 2003; Madayag et al. 2007). The restoration of extracellular glutamate by *N*-acetylcysteine inhibits relapse in animal models by stimulating release-regulating group II metabotropic glutamate receptors (mGluR2/3) (Moran et al. 2005). Importantly, mGluR2/3 agonists reduce both anxiety and the reinstatement of drug seeking in rodents (Schoepp et al. 2003; Baptista et al. 2004; Peters and Kalivas 2006), supporting a glutamatergic link between fear and relapse circuitry. Furthermore, *N*-acetylcysteine is capable of reducing cravings elicited by cocaine-related cues in humans (LaRowe et al. 2007), as well as cue-induced activity in cingulate cortex (LaRowe et al. 2005). Such a "glutamate restoration" approach could conceivably ameliorate the loss of glutamate resulting from an underactive IL-mPFC, thereby acting to suppress both anxiety and drug seeking.

Testing the model

Addiction has been recognized as a disorder of learning and memory (Kelley 2004; Hyman 2005). However, few studies have directly compared the neural circuitry controlling an adaptive aversive memory, such as that acquired through Pavlovian fear conditioning, with a maladaptive appetitive memory, such as that acquired in self-administration models of drug abuse. Future studies should be designed to test the validity of the circuitry model we have proposed (Fig. 3) as well as to determine additional

components of the circuit, be they points of convergence or divergence for fear and addiction.

One approach that would be useful is testing both conditioned fear and conditioned drug-seeking behaviors in the same rat. Burke et al. (2006) used a similar approach to evaluate the effects of chronic cocaine exposure on subsequent extinction of conditioned fear and found that cocaine-exposed rats extinguished more slowly than saline controls. The investigators concluded that cocaine-induced neuroadaptations in prefrontal cortex or its efferent targets impaired the prefrontal-based inhibition of behavior. This is an interesting hypothesis that remains to be investigated. For example, cocaine increases expression of activator of G-protein signaling 3 (AGS3) protein in prefrontal cortex, and reversing this cocaine-induced neuroadaptation reduces cocaine seeking in subsequent relapse tests (Bowers et al. 2004). It would be interesting if reversing this cocaine-induced increase in prefrontal AGS3 expression were sufficient to ameliorate the deficits in fear extinction observed in the Burke et al. (2006) study. Such within-subject testing of both fear and drug seeking should be coupled with lesion techniques, c-fos expression studies, and single-unit recordings to further assess the overlap of extinction circuits.

Recently, the cannabinoid system has received attention for its role in fear extinction (Marsicano et al. 2002; Lin et al. 2008). Agonists for the CB1 cannabinoid receptor, when microinfused into prefrontal cortex, facilitate fear extinction, whereas CB1 antagonists applied locally within prefrontal cortex impair fear extinction (Lin et al. 2008). These effects parallel those of systemic administration of CB1 agents on fear extinction (Marsicano et al. 2002; Chhatwal et al. 2005; Pamplona et al. 2006). While the effects of CB1 agents on the extinction of drug seeking have not been explicitly studied, their effects on the reinstatement of drug seeking contradict the aforementioned findings on fear extinction. That is, CB1 agonists administered systemically induce reinstatement of cocaine and heroin seeking, whereas CB1 antagonists block reinstatement of drug seeking (De Vries et al. 2001, 2003). For heroin seeking, these effects have been localized to the core and IL-mPFC (Alvarez-Jaimes et al. 2008). Hence, these effects of CB1 agents on drug seeking are in apparent opposition to their effects on fear extinction. Future studies are necessary to determine the underlying mechanism behind this discrepancy in the model.

Though we have proposed that extinction results, at least in part, from increased activity within the inhibitory circuit, extinction may also occur via decreased activity within the excitatory circuit. There is evidence that GABAergic inhibitory circuits within PL-mPFC are active on the first cocaine extinction session (Miller and Marshall 2004). This deactivation in PL-mPFC may be necessary to allow activation in IL-mPFC to facilitate extinction learning. The PL-mPFC and IL-mPFC of rodents, and the corresponding homologs in monkeys and humans, are anatomically interconnected regions (Ongür and Price 2000; Chiba et al. 2001; Jones et al. 2005). Future studies are necessary to determine whether reciprocal inhibition occurs between the excitatory and inhibitory output stations of mPFC, or whether PL-mPFC and IL-mPFC compete for control of behavior. Pharmacotherapeutics that shift the balance of activity toward activation of the vmPFC combined with deactivation of the dACC would be ideal candidates for the treatment of both anxiety and addiction. Perhaps the two birds of anxiety and addiction can be killed with one prefrontal stone.

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