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Prefrontal Cortex and Drug Abuse Vulnerability: Translation to Prevention and Treatment Interventions

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Abstract

Vulnerability to drug abuse is related to both reward seeking and impulsivity, two constructs thought to have a biological basis in the prefrontal cortex (PFC). This review addresses similarities and differences in neuroanatomy, neurochemistry and behavior associated with PFC function in rodents and primates. Emphasis is placed on monoamine and amino acid neurotransmitter systems located in anatomically distinct subregions: medial prefrontal cortex (mPFC); lateral prefrontal cortex (lPFC); anterior cingulate cortex (ACC); and orbitofrontal cortex (OFC). While there are complex interconnections and overlapping functions among these regions, each is thought to be involved in various functions related to health-related risk behaviors and drug abuse vulnerability. Among the various functions implicated, evidence suggests that mPFC is involved in reward processing, attention and drug reinstatement; lPFC is involved in decision-making, behavioral inhibition and attentional gating; ACC is involved in attention, emotional processing and self-monitoring; and OFC is involved in behavioral inhibition, signaling of expected outcomes and reward/punishment sensitivity. Individual differences factors (e.g., age and sex) influence functioning of these regions, which, in turn, impacts drug abuse vulnerability. Implications for the development of drug abuse prevention and treatment strategies aimed at engaging PFC inhibitory processes that may reduce risk-related behaviors are discussed, including the design of effective public service announcements, cognitive exercises, physical activity, direct current stimulation, feedback control training and pharmacotherapies. A major challenge in drug abuse prevention and treatment rests with improving intervention strategies aimed at strengthening PFC inhibitory systems among at-risk individuals.

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1. Introduction

Drug abuse vulnerability is related to the personality trait of “sensation seeking," as defined by the need for novel experiences and a willingness to take risks for these experiences (Zuckerman, 1979). Using Cloninger’s Novelty Seeking Scale or Zuckerman's Sensation Seeking Scale, high sensation seekers consistently use and abuse drugs more often than low sensation seekers assessed across various populations (Andrucci et al., 1989; Ball, 2004; Crawford et al., 2003; Donohew et al., 1991; Kosten et al., 1994; Wills et al., 1994; Wills et al., 1998; Zuckerman, 1994). In controlled laboratory studies, high sensation seekers are more sensitive than low sensation seekers to the rewarding effects of abused drugs (Fillmore et al., 2009; Kelly et al., 2006; Stoops et al., 2007). The association between sensation seeking and drug use has led investigators to develop more effective anti-drug prevention messages that specifically target high sensation seekers (Donohew et al., 1998; Palmgreen et al., 2001). To the extent that sensation seeking is biologically-based, a comprehensive understanding of the neural mechanisms underlying this trait may enhance the design and implementation of targeted interventions.

Sensation seeking does not represent a single construct, but instead represents at least two component constructs that can be designated as *reward seeking* and *inhibitory control*, each contributing to drug abuse vulnerability (Baler and Volkow, 2006; Bechara, 2005; Dawe and Loxton, 2004; de Wit and Richards, 2004; Fillmore, 2003; Jentsch and Taylor, 1999). Reward seeking reflects positive incentive motivation and action readiness, whereas inhibitory control refers to the general tendency to show response constraint and sensitivity to punishment. These constructs are similar to “extraversion” and “constraint” defined by Depue and Collins (1999), and both may underlie or contribute to impulsivity.

Similar to sensation seeking, impulsivity is a multi-faceted construct. Two aspects of impulsivity – *impulsive choice* (choice of a small, immediate reinforcer over a large, delayed reinforcer) and *impulsive action* (inability to stop a prepotent behavior) predominate the drug abuse literature (Winstanley et al., 2010), and will be the focus of our discussion of impulsivity. Impulsive choice may arise because of reward seeking (i.e., the subject chooses the less advantageous small-immediate reinforcer due to action readiness or an enhanced sensitivity to immediate reinforcement), or because of a lack of inhibitory control (i.e., the subject chooses a small-immediate reinforcer because they are not able to inhibit the desire for the immediate reinforcer). Similarly, impulsive action may arise from reward seeking (i.e., the action readiness or enhanced sensitivity of a subject propels them into action, even when such action may be disadvantageous) or lack of inhibitory control (i.e., subject cannot inhibit prepotent responses). Because both impulsive choice and impulsive action have operational measures that allow for between-species translation and have been studied frequently with respect to drug abuse, these constructs provide insight into the relationship between sensation seeking and drug abuse, as well as the associated neural systems.

Reward seeking and inhibitory control are each subserved by a distinct neural system. With reward seeking, ascending mesocorticolimbic dopamine (DA) projections emanating from midbrain ventral tegmental area (VTA) to nucleus accumbens and prefrontal cortex (PFC) represent an important component of the neural circuitry (Bardo et al., 1996; Berridge and Robinson, 1998; Kelley and Berridge, 2002; Wise, 1998), and this reward circuitry is most

dominant during the high-risk adolescent period (Galvan et al., 2006). With inhibitory control, various PFC subregions have been implicated, including medial prefrontal cortex (mPFC), lateral prefrontal cortex (lPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). Since the biological connection between these traits and drug abuse vulnerability cannot be assessed fully in human subjects, this area of investigation has benefited from controlled experiments using laboratory animal models.

The main purpose of this article is to review key findings about the involvement of PFC subregions in drug abuse vulnerability based on research from rodents and humans. While various cortical and subcortical regions are involved in drug abuse vulnerability, PFC is an important nexus where reward seeking and inhibitory control processes are integrated (Kalivas and Volkow, 2005). Although several excellent basic science reviews in rodents and humans have been published previously (de Wit and Richards, 2004; Jentsch and Taylor, 1999; Kalivas et al., 2006), these reviews have not emphasized potential applications for drug abuse prevention and treatment. To the extent that the neural substrates of inhibitory control are understood, it may be possible to tailor interventions that engage inhibitory control processes among individuals who are at highest risk.

2. Prefrontal (PFC) areas across species

A comprehensive review of PFC neuroanatomy and function is beyond the scope of the current review. However, there are anatomically-specific PFC subregions implicated in various cognitive processes related to risky behaviors. Although a variety of nomenclatures and subdivisions of PFC structures have been described, the current review uses the general definitions described for both rodents and primates by Price (2007). Price (2007) differentiates between two major PFC networks: the medial and orbital networks. The medial network is viewed primarily as having visceromotor outputs, in large part to nucleus accumbens shell. In contrast, the orbital network is viewed primarily as sensory in nature, receiving input from sensory cortices and sending output to striatum and associated nucleus accumbens core.

The extent to which region-specific neurobehavioral processes are similar across species is controversial, primarily because PFC shows species-specific variation in size relative to other cortical areas (encephalization), anatomical cytoarchitecture, neurochemistry and connectivity (Ongur and Price, 2000; Preuss, 1995). Rather than emphasizing cross-species differences, this review instead will use a common nomenclature where possible to allow for generalizing behavioral results across rodents and primates. The nomenclature and corresponding anatomical features are illustrated in Figures 1 and 2 for rat and human PFC.

2.1. Rodent PFC anatomy

Rodent PFC receives projections from basal ganglia, substantia nigra, VTA, amygdala, lateral hypothalamus, hippocampus, and other cortical areas (Dalley et al., 2004; Groenewegen et al., 1997). These projections are largely reciprocal – PFC projects to substantia nigra, ventral tegmental area (VTA), amygdala, lateral hypothalamus, and hippocampus, as well as lateral septum, mesencephalon, and autonomic regions of the brainstem (Dalley et al., 2004; Groenewegen et al., 1997). Because rodent cortex is exclusively agranular (compared to primate cortex that is made up of agranular, granular, and dysgranular regions; Barbas and Pandya, 1989; Carmichael and Price, 1994), equivalent areas are based on interconnections between specific areas within PFC, as well as between PFC and other brain regions (Price, 2007; Rose and Woolsey, 1948). Based on these interconnections, PFC can be divided into medial and orbital networks as described previously.

Rat mPFC often refers to various structures located along the medial wall of PFC (Dalley et al., 2004; Price, 2007). The precentral cortex (PrC) and ACC together are often referred to as dorsal mPFC, whereas the prelimbic (PrL), infralimbic (IL), medial orbital (MO), and ventral orbital (VO) cortices together are referred to as ventral mPFC. Two additional structures are located more laterally – dorsal agranular insular (AID) and dorsolateral orbital (DLO) cortex. The inclusion of lateral structures in mPFC may seem surprising (in fact, the AID is sometimes included in OFC; Schoenbaum et al., 2006), but there appear to be extensive interconnections between AID and PrL/IL areas, which also have strong connections to other areas on the medial wall (Conde et al., 1995; Vertes, 2004). For the purpose of this review, we will demarcate mPFC (PrL + IL) and ACC as separate PFC regions because, as discussed later, discrete lesions have dissociated the function of these two regions.

mPFC is connected to other brain regions that have been implicated in drug abuse. For example, both PrL and IL project to amygdala, although IL projects to medial, basomedial, cortical and central nuclei and PrL projects mainly to the basolateral nucleus of amygdala (Vertes, 2004; 2006). PrL also sends projections to VTA and medial parts of dorsal striatum, including nucleus accumbens (Vertes, 2004; 2006). mPFC sends projections to hypothalamus and periaqueductal grey (Floyd et al., 2000; 2001; Price, 2007), as well as to ACC and OFC, allowing for communication between different PFC regions (Vertes, 2006). ACC and mPFC also receive dense projections from hippocampus (Swanson, 1981; Tierney et al., 2004; Vertes, 2006). Together, both mPFC and ACC receive substantial input from amygdala and other limbic areas (Price, 2007).

Rat OFC is comprised of ventral lateral orbital (VLO), lateral orbital (LO), and ventral agranular insular (AIV) cortices (Price, 2007). In contrast to mPFC, these areas send few projections to hypothalamus or periaqueductal grey (Price, 2007). VLO and LO project to central parts of caudate-putamen and to the lateral part of nucleus accumbens shell (Schilman et al., 2008). There are reciprocal connections between basolateral amygdala and areas within OFC (Kita and Kitai, 1990; Krettek and Price, 1977). These regions also receive afferents from medial temporal lobe, ventral pallidum, and VTA (Groenewegen, 1988; Krettek and Price, 1977; Ray and Price, 1992). Rat OFC is part of the olfactory system, and also receives input from other sensory modalities (Price, 1985; Price, 2007).

2.2. Human PFC anatomy

In humans, there have been various demarcations for different functional networks in PFC. The current review relies primarily on the nomenclature outlined by Ridderinkhof et al. (2004b), which divides PFC into three main cytoarchitecturally distinct divisions, namely medial, lateral and orbital. Within the medial region, we will further demarcate mPFC and ACC, as these regions likely represent similar structures in the rat and are relevant for drug abuse behaviors. One caveat to this nomenclature is that human lPFC, consisting of dorsolateral and ventrolateral subregions, does not generalize directly to rat based on connectivity (Price, 2007). In fact, it has been suggested that lPFC may be unique to human and nonhuman primates (Brown and Bowman, 2002), and thus we used the term for humans, but not for rats (cf. Figures 1 and 2).

The connections involving human mPFC, lPFC, ACC and OFC are numerous. Although ACC is often considered part of the limbic system, its close anatomical and functional connections with mPFC and other PFC regions makes it a transitory region between cortical and limbic systems. Historically, cingulate gyrus (including both anterior and posterior extents) has been considered the main interface between cortical regions and subcortical structures like hippocampus, parahippocampal cortex, hypothalamus, and thalamus (Papez, 1958). Indeed, cingulate gyrus communicates with these structures, but also has connections

with amygdala and brainstem. Importantly, cingulate gyrus is a target region for DA projections originating in midbrain VTA as part of the mesocorticolimbic DA pathway, which is strongly implicated in reward seeking. Primate ACC is a large area that extends posterior to about midway along the cingulate gyrus. While classification of this region is controversial, primate mPFC and ACC cuts across various Brodmann areas that have been termed the rostral cingulate zone (RCZ; (Ridderinkhof et al., 2004b). RCZ includes portions of both Brodmann areas 24 and 32, areas that correspond roughly to ACC and mPFC respectively in rat.

Human lPFC is an extensive region often demarcated into several subregions, each of which is thought to play a role in inhibitory control. Ridderinkhof et al. (2004b) have demarcated three main lPFC subregions: (1) dorsolateral region, which includes Brodmann areas 8, 9 and 46; (2) ventrolateral region, which includes Brodmann areas 44 and 45; and (3) inferior frontal junction, which consists of posterior sulcus located between the medial and inferior frontal gyri, just anterior to Brodmann area 6. These subregions, especially the dorsolateral region, have reciprocal connections to OFC. Although there are no direct connections to primary motor cortex, lPFC is heavily interconnected with premotor areas, which in turn project to motor cortex and spinal cord, thus making it well situated to control a range of behaviors.

Human OFC receives inputs from numerous cortical and subcortical areas and is highly interconnected with other PFC regions. In both macaque and human brain, Brodmann area 47/12 has similar cytoarchitecturally distinct regions within OFC (Petrides and Pandya, 1999; Wallis, 2007). Functional subdivisions within OFC can be demarcated according to the sensory modality providing input to that region. In addition to receiving information from visual, somatosensory, olfactory and gustatory modalities, OFC also receives visceral information. Similar to ACC, there are reciprocal connections with hippocampus and amygdala. OFC also receives projections from midbrain nuclei associated with different neurotransmitter systems, such as VTA, lateral tegmental area and locus coeruleus.

3. PFC involvement in drug abuse

As mentioned above, both medial and orbital PFC networks are implicated in drug abuse vulnerability. Each of these networks mediates reward-related behaviors in a different way, but they appear to do so in both rodents and primates (see Table 1). For example, mPFC monitors task contingencies. That is, when a particular response no longer yields reinforcement, mPFC activation appears to be associated with altering behavior and orienting towards a new response in order to obtain reinforcement. In contrast, OFC activation is associated with reward value and is important for reversal learning and inhibitory control. However, direct comparison of rodent and primate literature is difficult because the tasks used are often species-specific. A challenge for future research will be develop more tasks that translate readily across rodents and primates (e.g., no/no-go), and to continue to identify between-species similarities in PFC structures.

3.1. Medial prefrontal cortex (mPFC)

In rats, mPFC activation is associated with “supervisory” functions such as attention to stimulus features and task contingencies, attentional set-shifting, and behavioral flexibility (Dalley et al., 2004). For example, lesions to this area impair performance when task contingencies change such that a previously-reinforced response is no longer reinforced, and a new response is reinforced instead. mPFC is also necessary for learning tasks with increased cognitive demands, such as those involving complex discriminations and working memory (Frysztak and Neafsey, 1991; 1994; Runyan and Dash, 2004), and it plays a role in

extinction (Lebron et al., 2004; Morgan and LeDoux, 1995; Morgan et al., 1993; Quirk et al., 2000), most likely through interactions with hippocampus (Maren and Quirk, 2004).

PrL and IL subregions within mPFC appear to play distinct roles in learning and impulsive action. IL may influence habitual responding by inhibiting goal-directed actions, while PrL may maintain representations of goals and the relationship between actions and goals (Balleine and Dickinson, 1998; Coutureau and Killcross, 2003; Killcross and Coutureau, 2003). Results from lesioning studies have also implicated PrL and IL in performance on 5-choice serial reaction time task (5CSRT), which measures impulsive action, attention, and compulsivity (Carli et al., 1983); the 5CSRT task is based on the continuous performance test of sustained and divided attention used in clinical settings (Beck et al., 1956). IL damage results in impulsive action (i.e., increased premature responses), whereas PrL damage results in compulsive (i.e., perseverative) responding (Chudasama and Muir, 2001; Chudasama et al., 2003a). PrL may also play a role in active inhibition of habitual responses, suggesting a mutually inhibitory role for PrL and IL, and this active inhibition of habits may allow for more planful cognitive decision-making processes to guide behavior (Jentsch and Taylor, 1999). As would be expected, widespread damage to both IL and PrL results in a loss of goal-directed responding, as well as perseverative habitual responding (Ragozzino et al., 1999).

A number of studies indicate that mPFC function is involved in drug abuse behaviors related to impulsivity. Impulsive choice has been associated with both serotonin release and DA receptor tone in mPFC (Winstanley et al., 2006b). Further, mPFC lesions increase impulsive choice on the delay discounting task (Weissenborn et al., 1997). Individual differences in impulsive action on the 5CSRT task also predict faster rates of self-administration acquisition using cocaine (Dalley et al., 2007; Perry et al., 2005; Perry et al., 2008) or nicotine (Diergaarde et al., 2008), perhaps reflecting altered mPFC function. Together, these results implicate an involvement of mPFC in drug self-administration and in both types of impulsivity.

The involvement of mPFC in drug relapse has been evaluated using the reinstatement model (see Shaham et al., 2003). Similar to results cited previously, there is a differential involvement of IL and PrL subregions within mPFC. Specifically, while inactivation of PrL decreases cocaine- (Capriles et al., 2003), cue- (McLaughlin and See, 2003), context- (Fuchs et al., 2005) and stress- (Capriles et al., 2003) induced reinstatement of cocaine-seeking, inactivation of IL has no effect (Capriles et al., 2003; McFarland et al., 2004; McLaughlin and See, 2003). However, IL inactivation enhances spontaneous recovery of cocaine seeking (Peters et al., 2008), suggesting that while PrL circuitry excites drug-seeking in the presence of reinstating cues, IL circuitry has an inhibitory influence on spontaneous recovery of drug-seeking (Kalivas et al., 2006).

It is difficult to ascertain what preclinical information described above translates directly to human mPFC function. Neuroimaging results support the idea that human mPFC is involved in evaluation of decision-making processes in conflict situations (Kerns et al., 2004; Ridderinkhof et al., 2004a; Ridderinkhof et al., 2004b). As anatomically demarcated previously, activation of primate RCZ is associated with sensitivity to reward contingencies (Ito et al., 2003) and is modulated by DA (Holroyd and Coles, 2002). Anatomical studies in non-human primates and humans indicate subregions in RCZ (mPFC and ACC) have extensive reciprocal interconnections (Bates and Goldman-Rakic, 1993; Koski and Paus, 2000), which may link short-term memory to goal-directed action (Ridderinkhof et al., 2004b). mPFC neurons encode past reward-bearing choices (Paulus et al., 2002), thus providing an update of present reinforcement contingencies. As a unit, RCZ activation is associated with conflicts, identification of errors in choice tasks, and directing attention by

recruiting PFC, including OFC, to execute cognitive control (Ridderinkhof et al., 2004a). Based on this information, one would anticipate that a dysfunction in mPFC, or RCZ more broadly, would impair monitoring of changes in reinforcement contingencies and thus, would impair decision-making aimed at maximizing positive outcomes. In the case of drug use, this could be expressed as a relative insensitivity to judging the value of drug and non-drug alternative reinforcers in a choice situation.

Some evidence indicates that drug abuse in humans is associated with functional alterations in mPFC, which may play a role in the deficits in executive cognitive functioning and gambling decisions typical among at-risk individuals (Fishbein et al., 2007). Acute cocaine administration increases activity in various PFC regions (Breiter et al., 1997) and stimulant abusers show a general loss of gray matter across these various PFC regions (Matochik et al., 2003). With reference to mPFC specifically, abstinent cocaine abusers tested in the Iowa gambling task display less activity in left mPFC, as well as right lPFC, compared to controls (Bolla et al., 2003), which may relate to the deficits in decision-making and response inhibition observed among individuals with substance use disorders (Monterosso et al., 2005; Paulus et al., 2003). This effect is not specific to mPFC, as individuals with a cocaine abuse history also display decreased activity in left ACC and right lPFC while performing a Stroop test (Bolla et al., 2004a). However, since these results in humans are correlational, they need to be supplemented by experiments in which discrete PFC regions are manipulated in laboratory animals under controlled conditions.

3.2. Lateral prefrontal cortex (lPFC)

As indicated previously, rodent PFC does not have a region similar to primate lPFC. In humans, however, damage to this region leads to the so-called “lateral syndrome” (Fuster, 2008). A hallmark feature of the lateral syndrome is disordered attention. Since the lPFC is a relatively large area, including Brodmann areas 8, 9, 10 and 46, the specific characteristics of the attentional deficits depend on the subareas most affected. Some lateral syndrome patients show deficits in selective attention, which is attention focused on a particular item or experience, whereas other patients show deficits in exclusionary attention, which is the inability to suppress unwanted items that interfere with attentional processing. In both cases, the attentional deficits are often overshadowed by aphasia, dysfunction in working memory and general apathy that may be profoundly debilitating.

Studies conducted with normal human subjects also point to a role of lPFC activity in behavioral inhibition and attention. Shackman et al. (2009) examined dorsal lPFC activity using high-resolution electroencephalography among individuals high or low on the Behavioral Inhibition System (BIS) self-report scale. Individuals high on BIS had greater activity in right lPFC. Right lPFC activation also is associated with response inhibition in a stop-signal task (Aron and Poldrack, 2006) and reduced emotional experience during appraisal of aversive images (Wager et al., 2008). Evidence from non-human primates implicate a dorsal-ventral dissociation within lPFC, with ventral lPFC being more directly involved than dorsal lPFC in attentional control (Kennerley and Wallis, 2009).

There is strong evidence that lPFC is involved in drug abuse behaviors. Similar to medications such as amphetamine and methylphenidate that are used to treat attention deficit hyperactivity disorder (ADHD), acute cocaine increases performance on tasks that require inhibitory control (Garavan et al., 2008). In contrast, however, chronic cocaine abuse impairs inhibitory control (Fillmore and Rush, 2002), which may explain the escalating pattern of use that typifies addiction. The loss of inhibitory control following chronic use is accompanied by reduced activity in lPFC, as well as in ACC, during performance on a Stroop test (Bolla et al., 2004a). Similar results are obtained with abstinent heavy marijuana

users (Bolla et al., 2005; Eldreth et al., 2004), indicating drug-induced lPFC impairment is not restricted to a single pharmacological class.

lPFC activation is also implicated in cue-induced craving following a period of drug abstinence. Among individuals with a cocaine abuse history, exposure to drug paraphernalia increases glucose utilization and brain activity in lPFC (Bonson et al., 2002; Grant et al., 1996). However, cue-elicited brain activation is not limited to lPFC, but rather involves extensive activation in ACC, OFC and associated limbic structures. Similar findings are obtained following presentation of cigarette-related stimuli to tobacco smokers (Brody et al., 2007; Yalachkov et al., 2009).

3.3. Anterior cingulate cortex (ACC)

ACC is involved in attentional selectivity and discrimination learning. In rats, lesions of this area impair acquisition of a task involving sequencing different responses (Delatour and Gisquet-Verrier, 2001) and attentional selectivity (Dalley et al., 2004). ACC may also be involved in impulsive action, as premature responding on the 5CSRT task is increased after lesioning this area (Muir et al., 1996; but see Dalley et al., 2004); however, the premature responding also may reflect impaired timing (Chudasama et al., 2003a; Passetti et al., 2002). While ACC lesions do not alter impulsive choice (Cardinal et al., 2001) or compulsivity defined by continued responding despite negative consequences (Joel et al., 2005b), they increase preference for small, low-effort rewards over larger, high-effort rewards (Walton et al., 2002; 2003). The precise involvement of ACC in impulsive action and impulsive choice warrants future study, as these are related to drug abuse.

A key neural substrate underlying reinstatement of drug-seeking behavior involves glutamatergic input to nucleus accumbens core from dorsal mPFC, including ACC (Kalivas and Volkow, 2005; McFarland et al., 2004). ACC inactivation decreases cue-induced reinstatement (McLaughlin and See, 2003), but not context-induced reinstatement (Fuchs et al., 2005), suggesting that this region processes discrete and diffuse drug-associated stimuli differently. In addition, ACC activity is increased when rats are presented with cues associated previously with cocaine self-administration (Thomas et al., 2003). While inactivation of both ACC and PrL has no effect on spontaneous recovery of cocaine-seeking (Peters et al., 2008), stress- and cocaine-induced reinstatement is decreased (McFarland et al., 2004; McFarland and Kalivas, 2001), thus implicating these regions in drug relapse.

ACC also plays a crucial role in fast adaptations of behavior based on immediate reward values. In monkeys, ACC pre-reward activity is correlated with reward value and ACC neuronal activity is observed prior to the monkey’s discovery of the rewarding stimulus value (Amiez et al., 2006). Amiez et al. (2006) also showed that ACC inactivation impaired the ability to choose stimuli associated with optimal reward value. Consistent with the idea that ACC plays a role in reward value assessment, discrete cocaine-associated cues elicit sustained neuronal firing in ACC (Baeg et al., 2009). These results indicate that ACC guides behavior by encoding general task values and received rewards.

ACC and lPFC are proposed to subserve two distinct inhibitory control systems in humans (Garavan et al., 2002). The first system is thought to be important for fast urgent inhibitions, involving primarily ACC. This ACC-driven system is especially important for emotional self-regulation (Posner et al., 2007). In contrast, the second system is thought to be important for slower deliberate inhibitory processes, involving primarily lPFC. Such a distinction may have important implications for the inhibitory control of risk-related behaviors. In the case of drug abuse, exposure to proximal drug stimuli, such as being handed a tobacco cigarette, requires a rapid decision that may involve ACC. In contrast, a more deliberate decision, such as whether to attend a party where drugs will be available,

may involve lPFC. Thus, depending on the temporal proximity of the risky event, different PFC areas may be engaged when choosing or refusing drugs.

Alterations in ACC function have been associated with drug abuse. In non-abusing subjects, methamphetamine increases activity in ACC and OFC (Vollm et al., 2004), suggesting that both decision making and action are affected. In a study by Fishbein et al. (2005), abstinent drug abusers and healthy controls were monitored for brain activity during a risky decision-making task. Drug abusers displayed greater risky choices despite the penalties enforced. The greater risks assumed by the drug abusers was associated with a failure to activate ACC compared to controls. Thus, the deficit in ACC function among drug abusers may play a role in the escalation of intake that occurs during the addiction cycle, despite increasing punishment.

3.4. Orbitofrontal cortex (OFC)

OFC neurons fire in anticipation of expected reward, and activity of these neurons reflects the value of the expected outcome when assessed across different species (Murray et al., 2007; Schoenbaum et al., 2006). With training, these neurons become active during presentation of cues that predict their preferred outcomes. Therefore, OFC plays a role in evoking original learning and integrating it with the new value of an outcome to guide responding (Murray et al., 2007). Consistent with this, OFC lesions impair reversal learning (Chudasama and Robbins, 2003b; Dalley et al., 2004; Murray et al., 2007; Schoenbaum et al., 2003) and prevent integration of information about the consequences of responding for a reward with the subjective value of that rewarding outcome (Schoenbaum et al., 1999; Winstanley, 2007). Furthermore, OFC lesions increase both impulsive action and compulsive responding (Joel et al., 2005a; Joel et al., 2005b; Winstanley, 2007), and the ability to inhibit responding is thought to be mediated by connections between OFC and dorsomedial striatum (Eagle and Robbins, 2003; Eagle et al., 2007).

In human drug abusers, impulsive behavior is proposed to result from drug-induced OFC hyperactivity and this hyperactivity results in a compensatory inhibitory process to normalize OFC activity (Winstanley, 2007). If drug use ceases, drug-induced OFC hyperactivity is no longer present and the compensatory inhibitory process acts to suppress normal OFC activity. Consistent with this idea, Winstanley et al. (2009) showed that cocaine self-administration in rats initially increased impulsive action on the 5CSRT, but that tolerance developed with repeated self-administration. Upon withdrawal, rats again displayed increased impulsive action that was associated with an overexpression of the transcription factor ΔFosB in OFC, thus implicating changes in gene expression in this PFC region.

Accumulating evidence indicates that OFC is involved in drug abuse vulnerability (Schoenbaum and Shaham, 2008). OFC is activated by presentation of stimuli associated previously with self-administered cocaine in rats, nonhuman primates, and humans (Thomas et al., 2003; Thomas and Everitt, 2001). Interestingly, OFC lesions have no effect on acquisition of cocaine self-administration using a simple continuous reinforcement schedule in rats (Hutcheson and Everitt, 2003). However, under a second-order schedule of reinforcement in which completion of a minor chain requirement leads to presentation of a conditioned stimulus, OFC lesions impair acquisition (Hutcheson and Everitt, 2003). Inactivation of lateral OFC also attenuates context-induced reinstatement of cocaine seeking (Lasseter et al., 2009). Thus, the OFC appears to be required for drug-seeking in a task that depends on the conditioned reinforcing properties of cocaine-associated cues (Everitt et al., 2007).

Clinical case studies and controlled laboratory studies in humans also support a critical role of OFC in risk-related behavior. Humans suffering from OFC damage are often characterized as pathologically impulsive (Kringelbach and Rolls, 2004; Lishman, 1998; Torregrossa et al., 2008). Among the various tasks that have been assessed following OFC damage, impairments in reversal learning are observed consistently in both human and nonhuman primates (Hornak et al., 2004; Izquierdo et al., 2004; Meunier et al., 1997). A role for OFC in reversal learning is supported further by imaging studies in normal human subjects (Cools et al., 2002; Hampton et al., 2006). In addition to its involvement in reversal learning, OFC plays a role in guiding behavior based on the value of an expected outcome (Murray et al., 2007; Schoenbaum and Roesch, 2005; Torregrossa et al., 2008). Neuronal activity in monkey OFC represents not only the value of expected reward (Roesch and Olson, 2004; Tremblay and Schultz, 2000), but also adapts to reflect the importance of different types of reward information in different contexts and time periods (Simmons and Richmond, 2008). Since many gambling tasks involve expectations about the value of an outcome, it is not surprising that OFC-damaged humans make risky gambling decisions (Bechara, 2005).

OFC dysfunction also is implicated in humans with substance use disorders. Individuals with cocaine abuse history show decreased gray matter in OFC (Franklin et al., 2002), suggesting reduced synaptic connectivity. In support of its role in inhibitory control, monkeys exposed to cocaine display a deficit in reversal learning and other cognitive deficits indicative of OFC dysfunction (Jentsch et al., 2002; Olausson et al., 2007). These results suggest that OFC dysfunction in individuals with a substance use disorder is, at least in part, a consequence of drug exposure, rather than an antecedent condition that precedes drug exposure.

A general view has emerged that OFC dysfunction promotes risky behavior because OFC plays a primary role in decision-making, especially decisions that involve adaptation of behavior due to punishing stimuli (Ridderinkhof et al., 2004b; Wrase et al., 2007). Within OFC, the medial portion is proposed to be more sensitive to rewarding stimuli, whereas the lateral portion is more sensitive to punishing stimuli (Kringelbach and Rolls, 2004). For example, Liu et al. (2007) found that human subjects performing a monetary decision-making task showed medial OFC activation to reward outcomes and lateral OFC activation to loss outcomes. However, not all findings fit the medial-lateral distinction of OFC function put forth by Kringelbach and Rolls (2004). In an fMRI study by Alia-Klein et al. (2007), subjects were exposed to the words “Yes” or “No” in a vocally emphatic manner. Rather than observing a medial-lateral distinction in OFC activity, “Yes” evoked a positive signal in right lateral OFC, while “No” evoked a negative signal in right lateral OFC. These latter results suggest that verbally presented rewarding and punishing stimuli are processed differently from nonverbal stimuli. Because “Yes” and “No” are words that have important meaning for either encouraging or prohibiting various behaviors, it will be important to determine if such valenced words are processed differently among individuals who are low or high for drug abuse risk. For example, at-risk individuals who lack strong parental bonding and tend to be noncompliant to authority may be less receptive to externally applied constraints (“no” command) than low-risk individuals who are more responsive to these constraints.

4. Neurochemistry of PFC

Drugs of abuse alter a variety of neurotransmitter systems, including DA, serotonin (5-HT), norepinephrine (NE), glutamate and γ-aminobutyric acid (GABA) systems. Much of our knowledge regarding the neurochemistry of PFC, including the localization and function of these neurotransmitters and the associated receptors and transporters, has been garnered

using animal models because neurochemical mechanisms underlying drug abuse vulnerability cannot be assessed easily using human subjects. In this section, we highlight some key findings about neurotransmitter function within specific PFC regions as they relate to impulsivity.

4.1 Dopamine (DA)

Clinical literature shows that nonspecific DA agonists such as amphetamine or methylphenidate are highly effective in decreasing impulsivity among individuals with ADHD, likely due weakened prefrontal catecholamine function (Arnsten, 2009). However, controlled laboratory studies in humans and rats indicate that DA agonists can either decrease or increase impulsive choice, depending on various factors such as the dose used, baseline level of impulsive choice behavior, and methodological details of the task used (i.e., whether the delay is signaled or unsignaled, type of reinforcer offered), thus making it difficult to generalize across laboratories (Perry and Carroll, 2008). In one study, amphetamine decreased impulsive choice in rats, an effect that was attenuated by the D2 receptor antagonist flupenthixol (Winstanley et al., 2003a). Similarly, increasing extracellular DA concentrations via the DA uptake inhibitor GBR 12909 decreases impulsive choice (van Gaalen et al., 2006). However, administration of selective D1 or D2 DA antagonists has yielded variable results, suggesting that the therapeutic effect of agonist medications involves stimulation of more than one DA receptor subtype.

Dopamine staining is present in most areas of rodent PFC, except for the most lateral portions of OFC (Van De Werd et al., 2010). Regarding the role of DA in PFC subregions in impulsive choice, results indicate that both ACC and OFC are involved, particularly when less effort is required to obtain the small reinforcer than the larger reinforcer. In ACC, blockade of D1 DA receptors, but not D2 DA receptors, enhances preference for a low-cost/low-reward response (Schweimer and Hauber, 2006). Similarly, systemic administration of the D_1/D_2 antagonist flupenthixol increases impulsive choice for a low-cost/low-reward response (Floresco et al., 2008). In OFC, DA utilization is increased during performance on a delay discounting task (Winstanley et al., 2006b); however, inactivation of DA receptors in OFC has yielded mixed results (Winstanley et al., 2007; Winstanley et al., 2004; Zeeb et al., 2010), depending on baseline levels of impulsive behavior and whether cues are used to signal the delay to the larger reward. Nonetheless, the bulk of results suggest that impulsive choice that is both effort- and delay-based is associated with reduced DA activity in ACC and OFC.

The role of specific PFC DA systems in impulsive action remains to be elucidated. Similar to its effects on impulsive choice, systemic administration of nonspecific DA agonists yields inconsistent results on impulsive action (Pattij and Vanderschuren, 2008; Perry and Carroll, 2008). In humans, psychostimulants tend to decrease impulsive action, an effect that is more dramatic in individuals with high levels of impulsive action. These effects are likely moderated by D1 and D2 DA receptors, as antagonism of either of these subtypes increases impulsive action (Passetti et al., 2003; van Gaalen et al., 2006).

Related to its involvement in impulsivity, PFC DA also plays a role in other cognitive functioning that may be important in drug abuse vulnerability, especially when stress is involved. DA is the most reactive monoamine in response to psychological stress (Goldstein et al., 1996), and high levels of DA activity in mPFC lead to working memory impairment. In rats, stress-induced working memory deficits are correlated with increased DA turnover in mPFC (Murphy et al., 1996). These deficits can be reversed in both rats and monkeys by administering D1 or D4 DA receptor antagonists (Arnsten and Goldman-Rakic, 1998; Murphy et al., 1996; Murphy et al., 1997). Stress responses can be mimicked in the rat via direct infusion of a selective D1 antagonist into mPFC (Zahrt et al., 1997), whereas D4

receptor antagonists block memory deficits induced by a pharmacological stressor (Arnsten et al., 2000). Increased DA function may impair mPFC-associated memory capacity in non-human primates. External factors (i.e., noise) can impair memory capacity in a visual memory task, an effect that is improved by administration of DA receptor antagonists (Arnsten and Goldman-Rakic, 1998). In contrast, decreases in PFC DA turnover induced by chronic amphetamine administration also result in impairments in performance in a spatial delayed response task in nonhuman primates (Castner et al., 2005), indicating cognitive impairment. Combined, these results suggest that perturbing mPFC DA neurotransmission, whether it is an increase or decrease in utilization, results in cognitive impairments. Further, they may have important translational relevance, as cognitive impairments induced by stressful life events may explain, at least in part, the relationship between impulsive behavior and drug abuse in humans (Helen et al., 2010).

4.2 Serotonin (5-HT)

PFC receives 5-HT innervation from medial and dorsal raphe nuclei (Mamounas et al., 1991; Steinbusch, 1981; Wilson and Molliver, 1991a; 1991b). 5-HT raphe neurons synthesize and release 5-HT from growing axonal processes as soon as one day after their appearance in brain (Lambe et al., 2000; Lidov and Molliver, 1982), and the effects of 5-HT within the synapse are terminated by re-uptake of the neurotransmitter into the presynaptic nerve terminals through a high-affinity 5-HT transporter (SERT). After re-uptake, 5-HT is degraded subsequently by monoamine oxidase (MAO).

Both preclinical and clinical evidence points to a role of PFC 5-HT in impulsivity. Among humans with pathological impulsive aggressivity, deficits in 5-HT exist in ACC (Frankle et al., 2005). Rats that display high impulsive action on a go/no-go task also show deficits in 5-HT turnover in mPFC and ACC (Masaki et al., 2006). While these results suggest that PFC 5-HT deficits lead to impulsivity, contradictory evidence exists. For example, 5-HT release in mPFC increases premature responding on the 5CSRT task (Dalley et al., 2002; Puumala and Sirvio, 1998). Moreover, the role of specific 5-HT receptor subtypes are poorly understood and are complicated by the identification of 15 different 5-HT receptor subtypes belonging to one of seven families (5-$HT_{1–7}$; Barnes and Sharp, 1999; Hoyer et al., 2002). The 5-HT_1 (specifically the 5-$HT_{1A/1B/1D}$) and 5HT_2 (5-$HT_{2A/2B/2C}$) receptor families have received the most attention for their ability to alter impulsivity, with somewhat mixed results (Evenden and Ryan, 1999; Pattij and Vanderschuren, 2008).

In general, impulsive choice is increased following administration of 5-HT_{1A} receptor agonists (Evenden and Ryan, 1999; Liu et al., 2004; van den Bergh et al., 2006; Winstanley et al., 2005), an effect blocked by antagonism of 5-HT_{1A} receptors (Winstanley et al., 2003b). When administered alone, however, 5-HT_{1A} receptor antagonists have no effect on impulsive choice, nor do 5-HT_{1B} receptor agonists (van den Bergh et al., 2006). Impulsive choice is decreased, however, following administration of the 5-HT_{2C} antagonist SER082 (Winstanley et al., 2004). Therefore, 5-HT_{1A} and 5-HT_{2C} receptors appear to have opposing roles in impulsive choice.

In contrast to impulsive choice, a role for 5-$HT_{1A/1B}$ receptors has not been found in impulsive action. Instead, impulsive action is increased following systemic and intra-OFC administration of the 5-$HT_{2A/2C}$ receptor agonist (±)-2, 5-dimethoxy-4-iodoamphetamine (DOI; Hadamitzky and Koch, 2009; Koskinen et al., 2000; Koskinen and Sirvio 2001), and decreased following both systemic and intra-mPFC administration of 5-HT_{2A} antagonists (Fletcher et al., 2007; Higgins et al., 2003; Passetti et al., 2003; Robinson et al., 2008a; Ruotsalainen et al., 1997; Winstanley et al., 2003b). Blockade of 5-HT_{2C} receptors also increases impulsive action in the 5CSRT task (Fletcher et al., 2007; Robinson et al., 2008a). The differential roles of 5-$HT_{1A/1B}$ and 5-$HT_{2A/2C}$ subtypes in impulsive choice and

impulsive action, respectively, suggests that selective pharmacotherapies may be useful for treating different facets of impulsive behavior.

4.3 Norepinephrine (NE)

Central NE neurons are localized in brainstem nuclei and project diffusely to almost every part of the brain, including PFC. NE cell bodies in locus coeruleus receive reciprocal innervation from mPFC (Heidbreder and Groenewegen, 2003). NE release into the synapse is deactivated by rapid uptake by the NE transporter (NET) into presynaptic terminals, followed by MAO metabolism (Bonisch and Bruss, 2006; Dostert et al., 1989). Three families of receptors are activated by NE, including α1-, α2-, and β-adrenergic receptors (Bylund et al., 1994). α2 NE receptors have received the most research focus, because ADHD is proposed to involve a deficit in PFC α2 NE activity (Arnsten et al., 2000). α2 NE agonists reduce impulsive choice, impulsive action and inattention in mice (Franowicz et al., 2002), rats (Tanila et al., 1996), monkeys (Arnsten et al., 1988; Rama et al., 1996) and humans (Jakala et al., 1999a; Jakala et al., 1999b).

NE plays a role in both impulsive choice and impulsive action. While impulsive choice is decreased by elevating extracellular NE via NET inhibition (Blondeau and Dellu-Hagedorn, 2007; Robinson et al., 2007), it is increased by direct stimulation of the α2 receptors with clonidine (van Gaalen et al., 2006). These contradictory results likely reflect a preferential activation of presynaptic α2 autoreceptors by clonidine, which may decrease NE release, thus resulting in an increase in impulsivity similar to NET inhibition. In any case, results from these studies suggest that α2 receptors, rather than α1 or β receptors, have a key role in impulsive choice.

Similar to impulsive choice, α2 NE receptors appear to play a role in impulsive action. Saporin-induced lesions of NE afferents to PFC do not alter impulsive action (Milstein et al., 2007). However, NET inhibition decreases impulsive action on 5CSRT and stop-signal tasks (Robinson et al., 2007; van Gaalen et al., 2006). Consistent with these preclinical observations, the NET inhibitor atomoxetine decreases stop-signal reaction time in healthy human volunteers (Chamberlain et al., 2006). Inhibition of NE transport would be expected to increase activation of postsynaptic NE receptors, thus leading to the observed reduction in impulsive action. The reduction in impulsive action likely reflects α2 NE receptor stimulation, as the α2 NE antagonist yohimbine increases premature responding in the 5CSRT task, as well as increasing phosphorylation of cyclic adenosine monophosphate response element binding (CREB) protein in OFC (Sun et al., 2010). Further, impulsive action in the 5CSRT task is increased by α2 NE antagonists, but not by α1 NE antagonists (Koskinen et al., 2003), indicating a selective involvement of α2 receptors. However, the α1 NE antagonist prazosin reduces impulsive action induced by methylphenidate, and the β-adrenoceptor antagonist propranolol eliminates methylphenidate-induced increases in impulsive action (Milstein et al., 2010). Combined, these results suggest that NE α2 receptors, perhaps in OFC, play a primary role in both types of impulsivity under normal conditions, but that α1 and β NE receptors also may contribute in the presence of high extracellular DA levels induced by stimulant drugs.

4.4 Glutamate

Glutamate is a major excitatory neurotransmitter in PFC, including both corticostriatal and corticothalamic efferents (Bromberg et al., 1981; Fonnum et al., 1981a; Fonnum et al., 1981b). Excitatory glutamatergic neurons from PFC control DA release in VTA and nucleus accumbens (Del Arco and Mora, 2008; Krystal et al., 2003). An imbalance in glutamate homeostasis (synaptic and non-synaptic glutamate balance), which impairs communication between PFC and nucleus accumbens, has been linked to impulsive drug seeking behavior

and drug abuse (Hyman et al., 2006; Kalivas, 2009). Recent clinical research also reveals a positive correlation between ACC glutamate levels and self-reported levels of impulsivity measured on the Barrett scale (Hoerst et al., 2010).

Glutamate acts via stimulation of both ionotropic glutamate receptors (iGluRs) and metabotropic receptors (mGluRs). iGluRs, including N-methyl-D-aspartate (NMDA), kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, are ligand-gated nonselective cation channels, which allow K^+, Na^+ and sometimes Ca^{2+} flux in response to glutamate binding to its recognition site on the protein (Tikhonov and Magazanik, 2009). NMDA receptors and the associated specific subunits NR1–3 have been studied in detail, since these are thought to be involved in learning and memory (Dingledine, 1983). mGluRs, which include mGlu1–8 receptors, are a heterogeneous family of G-protein-coupled receptors which function to modulate brain excitability via presynaptic, postsynaptic and glial mechanisms (Conn and Pin, 1997; Schoepp, 2001).

Impulsivity is modulated by NMDA receptors, specifically the NR2B subunit. Impulsive choice is increased after administration of ketamine, an NMDA antagonist (Floresco, 2007). Similarly, impulsive action is increased by NMDA antagonists administered either systemically or into mPFC (Higgins et al., 2003; Mirjana et al., 2004; Murphy et al., 2005; Paine et al., 2007). The selective NR2B NMDA receptor antagonist Ro63–1908 increases impulsive action (Higgins et al., 2003).

mGluRs also have a role in impulsivity, particularly mGluR1 and mGluR5 subtypes. Blockade of mGluR1 receptors in rats improves working memory and reduces impulsive choice (Sukhotina et al., 2008). In contrast, administration of mGluR1 receptor antagonists increases impulsive action (Sukhotina et al., 2008). Antagonism of the mGluR5 receptor has similar effects (i.e., increased impulsive action); however, antagonism of mGluR2/3 receptors has no effect on impulsive action (Semenova and Markou, 2007). Collectively, these findings indicate that inhibition of glutamate neurotransmission increases both impulsive choice and impulsive action, although little is known about the PFC subregions involved beyond mPFC.

4.5 GABA

About one fourth of all PFC neurons utilize GABA, the prime inhibitory synaptic transmitter and most abundant of all neurotransmitters in the CNS. PFC GABA neurons generally do not project directly the reward-relevant nucleus accumbens (Christie et al., 1987); however, subcortical regions can be affected indirectly due to the inhibitory role of GABA in several PFC regions (Brailowsky et al., 1986; Matsumura et al., 1992). There are two types of GABA receptors: $GABA_A$ and $GABA_B$. $GABA_A$ is the postsynaptic receptor and $GABA_B$ has been identified as mainly an autoreceptor involved in the self-regulation of GABA. $GABA_B$ receptors are widely distributed in several brain areas related to drug seeking, where they modulate both excitatory and inhibitory effects pre-and postsynaptic mechanisms (Thompson and Gahwiler, 1992). In PFC, $GABA_B$ receptors are localized on the presynaptic terminals of the glutamatergic nerve endings and/or cell bodies, (Margeta-Mitrovic et al., 1999) and on GABA neurons where they act as autoreceptors (Calver et al., 2002).

Few studies have investigated the role of GABA in impulsivity, although some evidence implicates a role for $GABA_A$ receptors. Local injections of the $GABA_A$ antagonist bicuculline into nonhuman primate PFC increases impulsive action (Sawaguchi et al., 1988). In human subjects, oral administration of benzodiazepines, which allosterically augment $GABA_A$ receptor function and increase extracellular concentrations of GABA in brain, is positively correlated with increased self-reports of impulsivity (Deakin et al., 2004; Lane et

al., 2005). However, controlled laboratory studies evaluating the effects of benzodiazepines on impulsivity are mixed. One report showed that diazepam does not alter impulsive choice or impulsive action (Reynolds et al., 2004), while another found that triazolam increases impulsive action in a stop-signal task (Fillmore et al., 2001). In rats, benzodiazepines are reported to either increase or produce no change in impulsive choice (Cardinal et al., 2001; Charrier and Thiebot, 1996; Evenden and Ryan, 1996). Thus, more research is necessary to elucidate the effects of benzodiazepines on impulsivity.

The $GABA_A$ agonist muscimol decreases lever pressing for preferred food and increases consumption of a less preferred food, a possible measure of impulsive choice (Farrar et al., 2008). In addition, microinjection of muscimol into median raphe increases impulsive action and reinstates alcohol seeking in alcohol-dependent rats (Le et al., 2008), indicating an interaction between GABA and 5-HT systems. Thus, $GABA_A$ antagonists may represent a novel target for intervention of impulsive behaviors involved in reinstatement of drug seeking.

4. Age- and sex-related differences in prefrontal cortex

4.1. Developmental differences

Initiation of drug use occurs most often during adolescence and early adulthood (Spear, 2000). One of the most important features that characterizes the transition from childhood to adolescence is a shift away from parental control to social bonding with peers. The move away from a parent-centered life to a peer-centered life is necessary for reproductive fitness and mating. During this developmental period, it is not surprising that risk-related behaviors become more prominent, with hedonic limbic structures being more dominant than inhibitory PFC structures. Although many regions of the brain undergo structural changes during this period, mPFC and superior temporal sulcus sculpt the social brain (Blakemore, 2008). The functional consequence of this anatomical maturation includes changes in face recognition and mental-state attribution (Blakemore, 2008), with each of these processes playing a role in social interaction.

Considerable work with laboratory animals shows that synaptogenesis during development initially yields an excess of potential synaptic connections, but that many nonfunctional connections are pruned during maturation (Cragg, 1974; 1975; Zecevic et al., 1989). In humans, several longitudinal and cross-sectional neuroimaging studies have captured the changes in white and gray matter volumes in various brain regions from childhood to young adulthood (Giedd et al., 1999; Gogtay et al., 2004; Olson et al., 2009; Paus et al., 1999; Sowell et al., 2003). A general conclusion from these studies is that PFC white matter increases linearly across this age period, whereas gray matter decreases. Studies using functional magnetic resonance imaging (fMRI) show that activity in mPFC is highest during the adolescent period, which coincides with synaptic pruning leading to a higher signal-to-noise ratio for PFC networks in the mature brain (Blakemore, 2008). In rat, mPFC also shows a loss of neurons from adolescence to adulthood (Markham et al., 2007), consistent with the idea of streamlining of PFC connectivity across this transitional developmental period.

Although adolescents show superior performance on various inhibitory tasks compared to children (Lamm et al., 2006), evidence indicates that PFC connections are not developed fully until early adulthood (Cunningham et al., 2002; Gogtay et al., 2004). Galvan et al. (2006) examined event-related fMRI activity of OFC and nucleus accumbens in children, adolescents and young adults participating in a task that measured choice of varying reward values. Across these age groups, adult-like patterns of accumbal activity occurred earlier in development than OFC activity. A direct comparison between adolescents and adults

indicated that OFC activity was lower in adolescents than adults at the anticipatory stage of the task. Similarly, other work has shown that adolescents have lower OFC activation than adults at the decision point of a risky economic choice (Eshel et al., 2007). To the extent that the nucleus accumbens mediates reward seeking and OFC mediates behavioral inhibition, these findings provide neural evidence that attraction to rewarding stimuli during adolescence is not counterbalanced by the type of inhibitory control that characterizes most adults.

The reduced PFC activity noted in children and adolescents compared to adults does not generalize across all tasks. For example, in contrast to results obtained with risky choice tasks, children show greater mPFC, lPFC, ACC and OFC activity than adults when instructed to suppress their reactions to emotional stimuli (Levesque et al., 2004). One interpretation of this finding is that emotional self-regulation in children requires the recruitment of more connections within the immature PFC compared to more practiced adults. This interpretation is consistent with work showing that adolescents with conduct disorder recruit relatively more PFC tissue than controls in order to normalize their performance on the Stroop test (Banich et al., 2007). However, an alternative interpretation of the greater PFC activation in children is that this age-related difference may be secondary to differences in amygdala activity, since PFC and amygdala have reciprocal connections (Lewis and Stieben, 2004).

In addition to maturation of emotional self-regulatory processes, PFC development across the periadolescent period is thought to play a vital role in memory processing. Ofen et al. (2007) investigated declarative memory in children and adults in a neuroimaging study. Subjects studied various scenes and were asked to remember the scenes for later view. When subsequently asked whether the scenes were old or new, recognition memory improved with age and this age-related improvement in memory was accompanied by greater activation in various PFC regions. These results suggest that the immature PFC in children hinders the ability to retrieve old information, thus making previously viewed stimuli appear as novel. Interestingly, there is considerable evidence suggesting that individuals who are most responsive to novel stimuli (i.e., high novelty seekers) are also more responsive to drugs of abuse (Bardo et al., 1996). To the extent that an immature PFC enhances the relative novelty of various stimuli that motivate behavior, this may represent an important factor to explain why periadolescents are at increased risk for drug use.

Environmental influences during development may alter the trajectory of PFC connectivity and functionality. Among the most important influences is the amount of social and environmental enrichment experienced during development. Adolescent rats reared in an enriched environment with social cohorts and novel objects show an accelerated cortical maturation compared to isolated rats raised without cohorts or objects (Renner and Rosenzweig, 1987). Enriched rats also show decreased vulnerability to stimulant self-administration (Bardo et al., 2001), which is associated with decreased DA transporter function in mPFC (Zhu et al., 2005). While exposure to novel objects is thought to play a role in the enrichment effects, a strong influence of social factors is also important. In particular, maternal interactions early in life have long-lasting consequences for PFC function during young adulthood (Denenberg, 1964; Meaney et al., 1996). Bock et al. (2008) found that early social experience was especially important in promoting dendritic spine density in ACC.

Environment-dependent neurobehavioral changes also have been observed in non-human primates. Lyons et al. (2002) separated young squirrel monkeys from their mothers on intermittent occasions from 13 to 21 weeks of age. These separations provoked repetitive peep-calls, agitated locomotion and elevated cortisol levels in the offspring, effects

indicative of distress. When evaluated as young adults, separated monkeys had a larger ventromedial PFC, consisting of portions of both mPFC and lPFC, compared to non-separated controls. This cytoarchitectural change was asymmetric, being evident in the right hemisphere only. This asymmetry may be important because negative emotional experiences are thought to be linked to the right hemisphere in humans (Ahern et al., 1994).

Clinical studies in children with ADHD show an altered developmental trajectory in PFC maturation. Anomalous PFC functioning has been observed in children with ADHD compared to controls (Bush et al., 1999; Ernst et al., 2003). An interesting feature of ADHD, however, is that a substantial portion of children with ADHD show a normalization of behavior with age. To determine if there is an anatomical dissociation among ADHD children with positive or negative clinical trajectories, Shaw et al. (2006) conducted a longitudinal study that examined cortical thickness in various PFC regions from approximately 8 to 15 years of age. At the younger age, individuals with ADHD had a thinned mPFC and ACC compared to controls, an effect that persisted across the study. Children with the worst clinical outcomes had thinner left mPFC at baseline compared to children with a better clinical outcome. However, it is not clear to what extent this difference in mPFC thickness reflects an alteration in synaptic density related to attention or impulsivity.

4.2. Sex differences

Notable sex differences exist in brain structure (Luders et al., 2004), basal measures of brain functioning (Andreason et al., 1994; Gur et al., 1995) and functional measures of neural responding (Cahill et al., 2001). Sex differences also exist in cognitive functioning and working memory on tasks that require PFC regions (Overman, 2004). Furthermore, following exposure to stress, there is a sexual dimorphism in performance on behavioral tasks and associated neurochemical changes in PFC (Bowman et al., 2003; Bowman et al., 2009; Lin et al., 2009).

Among the various tasks used to assess sex differences in decision-making and cognitive impulsivity in humans, the Iowa Gambling Task has been studied the most widely. This task requires participants to choose from decks of cards that result in either high reward with infrequent but high sporadic losses (disadvantageous decks) or low reward with more frequent but low sporadic losses (advantageous decks). While control participants learn to choose the advantageous decks, this winning strategy is impaired among patients with PFC damage (Bechara et al., 1994; Bechara et al., 1997; Clark et al., 2008), drug abusers (Grant et al., 2000), violent offenders (Fishbein, 2000), individuals with eating disorders (Liao et al., 2009), and pathological gamblers (Cavedini et al., 2002; Forbush et al., 2008). Interestingly, normal males also choose the advantageous decks more than females (Crone et al., 2005; Garon and Moore, 2004; Kerr and Zelazo, 2004; Overman, 2004; Reavis and Overman, 2001), likely due to a sex difference in the strategy employed (Overman, 2004). While males learn to maximize monetary outcomes in the long run by choosing only advantageous decks, females tend to choose decks that have the lowest probability of resulting in a loss, even if the loss is large (as it is with disadvantageous decks). This suggests that males are more sensitive to long-term monetary gains, while females are more sensitive to immediate loss.

Sex differences in PFC activity during performance on the Iowa Gambling Task accompany the sex differences in performance on this task. In males, brain activation is more lateralized to the right hemisphere, and males show more activation in right lPFC and right lateral OFC than females (Bolla et al., 2004b). While females show activation in both hemispheres, more activation in left lPFC also occurs in females than in males (Bolla et al., 2004b). Previous studies have shown that right PFC damage results in impairment on the Iowa Gambling

Task and decision-making in real life, whereas left PFC damage has no effect (Bechara et al., 2000a; Bechara et al., 2000b; Manes et al., 2002; Tranel et al., 2002). Taken together, these results suggest that increased activity in right lPFC and/or lateral OFC could underlie the propensity of males to select cards from advantageous decks.

Other measures of decision-making and impulsivity have yielded inconsistent sex differences in both performance and brain activation. No reliable sex differences in performance are observed on impulsive action measured by the stop signal reaction time task, even though sex differences in brain activation may occur (Li et al., 2006). In the Stroop task, no reliable sex differences in brain activation are observed (Bolla et al., 2004b). On other measures of risk taking or impulsivity, discrepant reports have shown males to be more impulsive (Kirby and Marakovic, 1996; Rosenblitt et al., 2001; Van Leijenhorst et al., 2008; Whiteside and Lynam, 2003), less impulsive (Reynolds et al., 2006; Wallace, 1979) or equally impulsive (Fillmore and Weafer, 2004; Reynolds et al., 2006; Skinner et al., 2004), compared to females. Experimental conditions seem to play an important role in these mixed results, possibly because males and females use different strategies on the various tasks employed. For example, females discount delayed hypothetical reinforcers at a higher rate than males (i.e., show greater impulsive choice), but when real reinforcers were offered, males discount at a higher rate than females (Heyman and Gibb, 2006). Understanding sex differences in making risky or impulsive decisions may have important implications for maximizing prevention and treatment strategies targeted toward either males or females.

5. Translation to applied interventions

5.1. Prevention

Drug abuse prevention interventions commonly consist of educational, family- or peer-based programs aimed at middle and high school age adolescents (Botvin and Griffin, 2007; Sussman et al., 2004; Velleman et al., 2005). Some interventions, termed universal interventions, are designed for use among all members of a population. Other ‘targeted’ interventions are designed specifically for a subset of individuals characterized by some common endophenotype associated with risk, such as high sensation seekers or adolescents with conduct disorder (Fishbein et al., 2006). With both universalistic and targeted approaches, prevention can result from teaching refusal skills, as well as from reinforcing choices that promote healthier lifestyles. A major hurdle in conducting prevention science relates to the high cost of evaluation studies. As a case in point, the National Youth Anti-Drug Media Campaign sponsored by the U.S. Office of National Drug Control Policy took 5 years to develop and test, at a total cost of $2 billion (Palmgreen et al., 2007). Thus, the use of controlled laboratory-based experiments that establish proof-of-concept results are desirable prior to implementing time-consuming and expensive interventions.

One way to establish proof-of-concept results is to use neuroimaging results to determine if a novel prevention intervention engenders PFC activation patterns associated with self-controlled decisions and desired behavioral outcomes. For example, development of televised public service announcements (PSAs) may benefit from neuroimaging technologies (Ray et al., 2008). Mass media campaigns that target high sensation seekers with high arousal messages reliably decrease risky decision-making involving drug use and unsafe sex (Palmgreen and Donohew, 2003). Recent neuroimaging studies have examined the activation patterns of PFC and related structures following presentation of arousing stimuli. For example, Joseph et al. (2009) examined brain activation patterns during an emotional induction task in high and low sensation seekers. When exposed to emotional images, high sensation seekers displayed a rapid and pronounced activation of insula, a brain region implicated in arousal (Craig, 2005) and drug craving (Naqvi and Bechara, 2008). Insula activation was followed rapidly by ACC activation. In contrast to high sensation

seekers, however, low sensation seekers showed an early response in ACC, but a minimal response in insula, which may explain why they have greater emotional control than high sensation seekers. ACC activation may reflect a compensatory mechanism that inhibits the initial arousal response in insula.

Likewise, high and low sensation seekers show differences in brain anatomy (Martin et al., 2007) and brain function in a novelty detection task (Jiang et al., 2009; Smith et al., 2008). Jiang et al. (2009) measured cortical evoked potentials following exposure to a series of familiar or novel visual stimuli. High sensation seekers had reduced ventral PFC responses to novel stimuli compared to low sensation seekers. These results are consistent with a report by De Pascalis et al. (2009) showing that subjects high on impulsivity measured on the Zuckerman-Kuhlman Personality Questionnaire show delayed event-related neural potentials. These formative results illustrate how neuroimaging techniques may be used to identify pre-existing differences in brain function associated with sensation-seeking status. Moreover, neuroimaging technologies may prove to be useful for screening various intervention stimulus materials prior to the design and implementation of expensive and time-consuming field-based prevention efficacy trials.

Although high message sensation value PSAs may be important for attracting the attention of high sensation seekers, there is some evidence that “deep” processing of message content may be more effective when delivered with low message sensation value. Langleben et al. (2009) examined brain activity and recognition memory in regular tobacco smokers exposed to anti-smoking PSAs. Although it is not clear whether the subjects used in this study were high or low sensation seekers, low sensation value PSAs were recognized more accurately and produced greater PFC activation than high sensation value PSAs. These results suggest that attention-intensive formats may compete with message information for cognitive resources. Thus, when combined with previous results (Palmgreen et al., 2001), it is possible that PSAs that initially attract attention with high arousal stimuli and then transition into a low arousal persuasive message for deep processing may be most effective.

Since at-risk adolescents are thought to be impulsive due to immature PFC function, training exercises that specifically engage PFC areas involved in decision-making may offer a useful prevention intervention strategy. Conrod et al. (2006) implemented a prevention intervention that targeted adolescents high in either sensation seeking or anxiety. The intervention was a multi-dimensional cognitive-behavioral approach that included lessons on the consequences of coping strategies that centered around high-risk personality dimensions such as sensation seeking. Subjects completed activities designed to recognize automatic thoughts and engaged in group exercises based on real-life scenarios. Compared to a non-intervention control group, impulsive binge drinking was reduced by the intervention. It would be interesting to determine if the reduction in binge drinking was associated with increased activity in PFC regions.

Although training exercises designed to engage PFC inhibitory processes may seem like an appealing idea to reduce drug abuse vulnerability, there may be a paradoxical risk to such a strategy. While the ability to exert inhibitory control over thoughts, emotions and actions is a central process of human existence, self-control is a limited resource that can be exhausted under certain situations. This phenomenon has been demonstrated in laboratory experiments in which subjects that are required to exert inhibitory control in one task show a deficit in inhibitory control in a second task that requires the same resource (Baumeister and Heatherton, 1996; Muraven et al., 1998). This finding may have important implications for prevention interventions aimed at enhancing inhibitory control over drug use. Rather than being protective, intervention strategies that drain self-control resources immediately prior to the opportunity to use or refuse drugs may actually exacerbate the problem of drug use.

This “boomerang” effect may be negated by insuring that training exercises in self-control are not implemented shortly before entering a situation where drugs are available.

The depletion of self-control resources that occurs with repeated exertion involves ACC. Inzlicht and Gutshell (2007) monitored electroencephalographic waveforms associated with ACC in subjects that were instructed to suppress their emotions while viewing a movie depicting animals that were suffering. Subjects subsequently performed the Stroop test in which good performance required suppression of the tendency to read a word (red or green) in order to rapidly name the color used to print the word. Subjects instructed to suppress their emotions in the movie performed worse on the Stroop test compared to control subjects. This deficit in performance was associated with a diminution of ACC activity, suggesting a depletion of inhibitory function in this region.

Engaging in physical activity also may be an effective strategy for promoting PFC-mediated inhibitory processes. Using a confirmatory multivariate analysis in adolescents, Wills et al. (2007) found that self-control constructs are related to both dietary intake and physical activity. Individuals who were poor at self-control (i.e., impulsive) were least likely to engage in physical activity, thus raising the risk for drug use. Consistent with this, children showing good aerobic fitness between the ages of 7 and 12 years have better Stroop test performance (Buck et al., 2008), while obese children show less inhibitory control compared to lean counterparts (Nederkoorn et al., 2006).

Preclinical evidence also indicates that physical activity has direct neurobehavioral effects on PFC functioning. Rats given access to a running wheel display an increase in glioneogenesis in mPFC, including greater numbers of both astrocytes and oligodendrocytes that support neuronal activity (Mandyam et al., 2007). Similarly, rats raised during the periadolescent period in an enriched environment that promotes physical activity display a decrease in DA transporter function in mPFC (Zhu et al., 2005), which presumably leads to an increase in extracellular DA available in this region. Physical activity induced by access to a running wheel or exposure to enrichment decreases cocaine and amphetamine self-administration (Bardo et al., 2001; Cosgrove et al., 2002; Smith et al., 2008), as well as decreasing impulsive choice on a delay discounting task (Perry et al., 2008). Thus, physical activity and enriched environments appear to protect against PFC-mediated impulsivity and drug abuse vulnerability, at least in preclinical models.

One of the most salient examples of how an understanding of PFC dysfunction may inform prevention intervention strategies rests with work conducted in maltreated children raised in foster care. Children raised in foster care display a deficit in salivary cortisol levels measured in the early morning and this deficit may be normalized with suitable interventions (Fisher et al., 2000; Fisher et al., 2007; Gunnar and Fisher, 2006). mPFC is an important component of the neurocircuitry that regulates pituitary secretion of adrenocorticotropic hormone via the paraventricular nucleus of the hypothalamus (Gunnar and Fisher, 2006). This raises the possibility that maltreated children have a deficit in mPFC inhibitory processes involved in the hypothalamic-pituitary adrenal axis, as well as in self-control. To the extent that an intervention can normalize the blunted cortisol response, this may serve as a marker for determining the effectiveness of intervention strategies targeting stress-related risky behaviors.

Among the various predisposing psychopathological factors that predict risk for drug abuse, the presence of ADHD is thought to be a significant contributor. Adolescents with ADHD are impulsive in a variety of tasks (Solanto, 2002) and stimulant drugs such as amphetamine and methylphenidate are effective in treating ADHD. While there is some controversy in the field, evidence suggests that non-medicated ADHD children are at increased risk for drug

abuse, and this risk factor may be mitigated by medication (Winstanley et al., 2006a). ADHD is thought to stem, at least in part, from PFC dysfunction (Castellanos and Tannock, 2002), suggesting that stimulant drugs may decrease risk by normalizing inhibitory control in PFC.

5.2. Treatment

A more complete understanding of PFC involvement in behavioral inhibition also may have important implications for drug abuse treatment. Impulsivity confers greater risk for initiation and escalation of drug use among adolescents and is known to accompany substance use disorders. While it is difficult to disentangle whether impulsivity precedes or results from drug use, controlled studies using laboratory animals indicate that drug use can decrease inhibitory control, thus leading to greater impulsive choice and impulsive action. However, in a delay discounting task, impulsive choice is decreased by methamphetamine (Richards et al., 1999) and increased by nicotine (Dallery and Locey, 2005), indicating that general conclusions cannot be made across different stimulant drugs. Nonetheless, repeated administration of amphetamine, methamphetamine or nicotine enhances impulsive choice, even when rats are tested in a drug free state following withdrawal (Dallery and Locey, 2005; Richards et al., 1999). These latter findings indicate that chronic exposure to stimulant drugs produces lasting deficits in inhibitory control.

Similar to the effects observed with experimenter-administered stimulants, repeated self-administration of stimulants in rats increases impulsive choice in a delay discounting task (Gipson and Bardo, 2009). Rats learning to self-administer cocaine show an initial loss of inhibitory control, although tolerance to this effect is observed across repeated testing (Winstanley, 2007). Upon termination of the cocaine self-administration, a deficit in inhibitory control re-emerges, suggesting a long-term neural adaptation due to the cocaine self-administration regimen. OFC may be altered by cocaine self-administration, as fMRI studies with cocaine-abusing humans tested during a period of abstinence show hypoactivity in this PFC region (Volkow et al., 2004).

Medication is a viable treatment intervention approach (Vocci, 2008). Among the various pharmacotherapeutic options, perhaps the most relevant for altering PFC function are drugs that work selectively on monoamine and amino acid neurotransmission. As described previously, these neurotransmitter systems subserve PFC circuitry and impulsivity (Pattij and Vanderschuren, 2008). Preclinical evidence indicates that impulsive action in the 5CSRT task is decreased by the NE reuptake inhibitor atomoxetine (Robinson et al., 2008b) and increased by the NE autoreceptor agonist clonidine (van Gaalen et al., 2006). In humans, atomoxetine is used to treat ADHD and shows promise for treatment of stimulant abuse (Sofuoglu and Sewell, 2008; Stoops et al., 2008). Buspirone may also be useful, as it a partial agonist at 5-HT autoreceptors and it is currently used to treat anxiety. Consistent with this, repeated administration of buspirone lowers 5-HT levels in mPFC and decreases impulsive choice (Liu et al., 2004). Finally, antagonism of mGluRs may also have utility because recent preclinical evidence indicates that blockade of these receptors decreases impulsive action (Sukhotina et al., 2008).

An alternative neurobehavioral approach to reduce risky behavior involves the application of direct current stimulation to PFC. High-frequency transcortical magnetic stimulation of the skull overlying the right PFC reduces craving for cocaine (Camprodon et al., 2007). While the precise mechanisms and extent of brain subregions affected need to be characterized more fully, the decrease in craving likely relates to enhanced cortical excitability of critical inhibitory areas of right lPFC in proximity to the stimulation site. In contrast to the decrease in drug craving, however, low-frequency transcortical magnetic stimulation of the right

lPFC increases risky behavior in a decision-making task (Knoch et al., 2006), an outcome that would be disadvantageous for promoting abstinence.

Simultaneous application of excitatory anodal current to the right lPFC and inhibitory cathodal current to the left lPFC also has been investigated. Fecteau et al. (2007) examined the effect of this asymmetrical transcortical technique on performance among healthy young adults in a gambling task involving rewards and penalties. Treated subjects showed a significant increase in choosing low-risk options compared to sham-stimulated subjects, as well as compared to subjects who were stimulated with a reverse procedure (i.e., anodal current to left lPFC and cathodal current to right lPFC). These results suggest that excitation of the right PFC and/or inhibition of the left PFC enhances inhibitory control. While this noninvasive and safe treatment is innovative, the treatment is limited primarily to surface brain structures. It would be interesting to determine if selective stimulation of deeper brain regions, such as OFC, would alter risk-taking.

Individuals also can learn to control fMRI activation of selected brain regions using feedback training. Posse et al. (2003) used real-time fMRI feedback in subjects exposed to sad and neutral faces. Subjects given immediate feedback of amygdala activation to reinforce mood induction displayed heightened left-side amygdala activation, which correlated with the intensity of self-rated sadness, indicating that individuals may be able to control discrete limbic brain regions. More recent evidence indicates that PFC regions also may be trained by feedback control. deCharms et al. (2005) used real-time fMRI to train chronic pain patients to alter activity of right ACC, a structure involved in pain perception. Patients trained to control right ACC brain activation reported a reduction in ongoing pain. Perhaps similar technology could be used to train individuals to recruit discrete PFC regions involved in inhibitory control in order to reduce impulsive and unhealthy behaviors.

Finally, craving among drug abusing subjects may be especially sensitive to treatments designed to alter PFC activity. When drug abusing individuals are exposed to cues associated previously with cocaine, such as a crack pipe or syringe, there is an increase in subject-rated and physiological craving. Although many cortical and subcortical brain regions subserve craving, PFC areas play a prominent role (Bonson et al., 2002; Childress et al., 1999; Grant et al., 1996; Wang et al., 1999). For example, Childress et al. (1999) reported that detoxified male cocaine users exposed to cocaine-related videos experienced craving and showed limbic activation, including ACC. Bonson et al. (2002) extended these findings by showing that cue-elicited cocaine craving also involves OFC activation (defined by increased glucose metabolism measured with positron emission tomography) and that this activation is correlated with craving intensity. Cue-elicited craving was also associated with mPFC deactivation, suggesting that craving involves a neural network of co-activation and deactivation of multiple PFC regions. Future research should determine what specific therapeutic approaches are most effective in reducing drug craving mediated by PFC circuits.

6. Final comment

While this review has emphasized the role of PFC in inhibitory control related to drug abuse and other risk-related behaviors, much information about PFC function has been ignored for the sake of clarity. The large human PFC, which accounts for 30% of cortical mass, is inextricably tied to many functions that define the whole human experience, including emotion, attention, reward, rule learning and memory formation. While a long-standing idea is that mPFC and OFC are associated with behavioral inhibition and lPFC is associated with attention and memory (Goldman-Rakic, 1987), this demarcation is more heuristic than precise. Nonetheless, there is a general view that PFC serves as a “top-down” modulator of

underlying neural circuits, rather than being in series with underlying neural circuits (Miller and Cohen, 2001). This view suggests that PFC exerts influence on other brain structures, thus integrating behaviorally relevant information that maximizes an adaptive capacity which prevents an overreliance on fixed action patterns, prepotent thoughts and feelings. Without PFC, compulsive behaviors driven by structures in the brainstem (e.g., VTA) would dominate. In the case of drug abuse vulnerability, these well-established neural pathways would be those that subserve addictive behaviors, such as ascending mesocorticolimbic DA projections. Therefore, strengthening the descending projections from the prefrontal cortex that are responsible for inhibitory control could decrease drug abuse vulnerability or the likelihood of relapse, and may be especially important for at-risk individuals. As mentioned in the previous section, a number of strategies for promoting PFC-mediated inhibitory control are emerging. It would be beneficial for these strategies to be employed in a manner that appeals to or targets vulnerable populations (e.g., high sensation seekers, adolescents). Thus, a major challenge in drug abuse prevention and treatment rests with identifying individuals at-risk due to deficits in PFC function and improving intervention strategies aimed at strengthening PFC inhibitory systems among these individuals.

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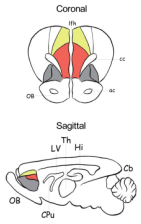

Figure 1.

Illustrations showing medial prefrontal cortex (in red), anterior cingulate cortex (in yellow) and orbitofrontal cortex (in gray) in rat brain viewed in coronal and sagittal planes. Abbreviations: OB, olfactory bulb; Cb, cerebellum; lfh, longitudinal fissure of hemisphere; cc, corpus callosum; ac, anterior commissure; CPu, caudate putamen; LV, lateral ventricle; Th, thalamus; Hi, hippocampus. Figure based on Dalley et al. (2004) and Paxinos and Watson (2005).

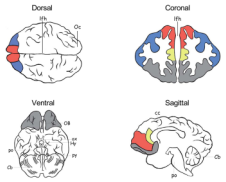

Figure 2.
Illustrations showing medial prefrontal cortex (in red), lateral prefrontal cortex (in blue), anterior cingulate cortex (in yellow) and orbitofrontal cortex (in gray) in human brain viewed in dorsal, ventral, coronal and sagittal planes. Abbreviations: OB, olfactory bulb; Cb, cerebellum; lfh, longitudinal fissure of hemisphere; Oc, occipital cortex; cc, corpus callosum; ox, optic chiasm; Hy, hypothalamus; py, pyramidal tract; po, pons. Figure based on Mai et al. (1997).

Table 1

Summary of some putative functions of mPFC (prelimbic and infralimbic), lPFC, ACC and OFC from rat and human studies.

	Rat		Human	
Brain Region	**Putative Functions**	**Example References**	**Putative Functions**	**Example References**
mPFC	Reward processing Attention Impulsivity Drug reinstatement (prelimbic) Habit learning (infralimbic)	Bardo et al. (1996) Cardinal et al. (2001) Coutureau and Killcross (2003) McLaughlin and See (2003)	Reward processing Attention Conflict decision making	Kerns et al. (2004) Ridderinkhof et al. (2004a)
lPFC	N/A	N/A	Decision making Attentional gating Behavioral inhibition Working memory Emotion regulation	Fuster (2008) Shackman et al. (2009) Wager et al. (2008)
ACC	Attention Discrimination learning Timing of reward Drug reinstatement	Dalley et al. (2004) Dietrich and Allan (1998) McFarland et al. (2004)	Attention Emotional processing Self-Monitoring Processing of social stimuli	Fuster (2008) Kringelbach and Rolls (2004) Posner et al. (2007)
OFC	Behavioral Inhibition Signaling expected outcomes Reversal learning	Chudasama and Robbins (2003b) Winstanley (2007) Schoenbaum and Roesch (2005)	Behavioral Inhibition Reward sensitivity (medial) Punishment sensitivity (lateral) Emotional decision-making Reversal learning	Kringelbach and Rolls (2004) Liu et al. (2007) Cools et al. (2002)

Abbreviations: mPFC, medial prefrontal cortex; lPFC, lateral prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; N/A, not applicable.