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Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications

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Abstract

The loss of control over drug intake that occurs in addiction was initially believed to result from disruption of subcortical reward circuits. However, imaging studies in addictive behaviours have identified a key involvement of the prefrontal cortex (PFC) both through its regulation of limbic reward regions and its involvement in higher-order executive function (for example, self-control, salience attribution and awareness). This Review focuses on functional neuroimaging studies conducted in the past decade that have expanded our understanding of the involvement of the PFC in drug addiction. Disruption of the PFC in addiction underlies not only compulsive drug taking but also accounts for the disadvantageous behaviours that are associated with addiction and the erosion of free will.

Drug addiction encompasses a relapsing cycle of intoxication, bingeing, withdrawal and craving that results in excessive drug use despite adverse consequences (FIG. 1). Drugs that are abused by humans increase dopamine in the reward circuit and this is believed to underlie their rewarding effects. Therefore, most clinical studies in addiction have focused on the midbrain dopamine areas (the ventral tegmental area and substantia nigra) and the basal ganglia structures to which they project (the ventral striatum, where the nucleus accumbens is located, and the dorsal striatum), which are known to be involved in reward, conditioning and habit formation[1–3]. However, preclinical and clinical studies have more recently brought to light and started to clarify the role of the prefrontal cortex (PFC) in addiction[4]. A number of processes are ascribed to the PFC that are fundamental for healthy neuropsychological function — encompassing emotion, cognition and behaviour — and that help to explain why PFC disruption in addiction could negatively affect a wide range of behaviours (TABLE 1).

On the basis of imaging findings and emerging preclinical studies[5,6], we proposed 10 years ago that disrupted function of the PFC leads to a syndrome of impaired response inhibition and salience attribution (iRISA) in addiction (FIG. 1) — a syndrome that is characterized by

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SUPPLEMENTARY INFORMATION See online article: S1 (table) | S2 (table) | S3 (table) | S4 (table) |S5 (table) | S6 (table) | S7 (table) | S8 (figure)

attributing excessive salience to the drug and drug-related cues, decreased sensitivity to non-drug reinforcers and decreased ability to inhibit maladaptive or disadvantageous behaviours[7]. As a result of these core deficits, drug seeking and taking become a main motivational drive, occurring at the expense of other activities[8] and culminating in extreme behaviours in order to obtain drugs[9].

Here we review imaging studies into the role of the PFC in addiction from the past decade, integrating them into the iRISA model with the aim to gain a greater understanding of the dysfunction of the PFC in addiction. Specifically, this is the first systematic evaluation of the role of distinct regions within the functionally heterogeneous PFC in the neuropsychological mechanisms that putatively underlie the relapsing cycle of addiction. We review positron emission tomography (PET) and functional MRI (fMRI) studies focusing on regions of the PFC that have been implicated in addiction. These include the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (see TABLE 1 for Brodmann areas; see Supplementary information S1 (table) for Brodmann areas that are not discussed in the main text). We consider the results of these studies (FIG. 2) in the context of the role that the PFC plays in iRISA: first, in the response to direct effects of the drug and drug-related cues; second, in the response to non-drug rewards, such as money; third, in higher-order executive function, including inhibitory control; and fourth, in awareness of the illness. We present a simple model that helps to guide our hypotheses regarding the role of the various PFC subregions in the endophenotype of drug addiction (FIG. 3), as described in more detail below. For preclinical studies on the PFC in addiction or in-depth accounts into the executive function of the PFC we refer the reader to other reviews[10,11].

In evaluating this Review, readers need to embrace a myriad of results, which can prove quite confusing as definite conclusions are not always provided. This is particularly true for the localization of functions: for example, are the dorsal ACC and DLPFC involved in the craving response or in control over craving, or in both? Determining which PFC subregion mediates which function can be very difficult, presumably owing to the neuroanatomical and cognitive flexibility of these functions — that is, participants can use multiple strategies when performing neuropsychological tasks, and prefrontal systems seem to have a greater level of functional flexibility than more primary sensorimotor systems. Another decade of research may prove invaluable in our understanding of the PFC's role in drug addiction. Integrating results from preclinical lesion and pharmacological studies, considering other cortical and subcortical structures in addiction — the PFC is densely interconnected with other brain regions (see BOX 1 for a discussion of early studies examining these networks in the context of addiction) — and using computational modelling may help further in ascribing probable psychological functions to select PFC regions and in enhancing our understanding of their involvement in drug addiction. Our Review is a step in this direction.

Direct effects of drug exposure

Here, we review studies that assessed the effects of stimulant and non-stimulant drugs on PFC activity (Supplementary information S2 (table)). Our model predicts drug-induced enhancements of activity in PFC areas that are involved in drug-related processes — including emotional responses, automatic behaviours and higher-order executive involvement (for example, medial OFC (mOFC) and ventromedial PFC in craving, OFC in drug expectation, ACC in attention bias and DLPFC in forming drug-related working memories). It also predicts drug-induced decreases in non-drug related activity in these same PFC regions, most notably during craving and bingeing in drug-addicted individuals, discussed below (FIG. 3). Consistent with the former prediction, intravenous cocaine administration to overnight-abstinent cocaine-addicted individuals increased self-reports of

high and craving, and mainly increased fMRI blood oxygen level-dependent (BOLD) responses in various PFC subregions[12,13]. Interestingly, activity in the left lateral OFC, frontopolar cortex and ACC was modulated by drug expectation (that is, activity was greater after expected versus unexpected intravenous delivery of cocaine), whereas subcortical regions responded mainly to the pharmacological effects of cocaine (that is, there was no modulation by expectation); the specific direction of the effect differed by region of interest (ROI)[13]. In an ^{18}Fluorodyoxyglucose PET (PET FDG) study, administration of the stimulant drug methylphenidate (MPH) to active cocaine users increased whole-brain glucose metabolism[14]. Here, the left lateral OFC showed greater metabolism in response to unexpected than to expected MPH; the opposite pattern to that of the BOLD effect in the above study[13] possibly reflects the different temporal sensitivity of the imaging modalities (see below).

Stimulant drugs also increase PFC activity in laboratory animals. For example, regional cerebral blood flow (rCBF) in drug-naive rhesus monkeys increased in DLPFC after non-contingent administration and in ACC during a simple fixed-rate self-administration of cocaine[15,16]. A PET FDG study in the same animal model showed that cocaine self-administration increased metabolism in OFC and ACC to a greater extent when access to cocaine was extended than when access was limited[17] (note that extended access, but not limited or short access, is associated with transition from moderate to excessive drug intake, as occurs in addiction[18]). Similarly, intracerebroventricular administration of cocaine in rats induced a large fMRI response in selected brain regions, including PFC[19].

Taken together, the main effect of cocaine (and other stimulants such as MPH) on the PFC is to increase PFC activity, as measured by glucose metabolism, CBF or BOLD (although in a recent study, cocaine reduced PFC cerebral blood volume in macaque monkeys[20]). As the length of access to the drug and drug expectation modulate PFC activity, increases in activity that occur during drug administration may be indicative of the neuroplastic adaptations that ensue in the transition from first or occasional use to regular use, such that drug-related neuropsychological processes, including drug-related anticipation (and other conditioned responses), suppress or eclipse non-drug related processes, such as anticipation of — or the motivation to — pursue non-drug related goals (FIG. 3).

In cigarette smokers, rCBF was reduced in the left dorsal ACC (dACC) and this correlated with a decrease in craving after smoking the first cigarette of the day[21]. Similar correlations were reported between rCBF in OFC and craving after acute injections of heroin in people who are heroin-dependent[22]. The disparity between the effects of cocaine (and other stimulants) and other types of drugs on PFC activity may reflect differences in the direct pharmacological effects of the drugs on the PFC and other brain regions (cannabinoid, mu opioid and nicotine receptors, which are targets for marijuana, heroin and nicotine, respectively, have a distinct regional brain distribution) or on non-CNS targets (cocaine and methamphetamine have peripheral sympathomimetic effects that are distinct from the peripheral effects of marijuana or alcohol), or it may reflect variability in methodological factors (for example, whether studies analysed absolute or relative (or normalized) values)[23]. It may also be related to drug-induced craving effects: with drugs like cocaine, craving in addicted individuals increases 10–15 minutes after smoking, whereas the studies discussed above reported decreases in craving immediately after nicotine or heroin administration. Viewed in this light, and consistent with our model, the collective results suggest that when drug intake decreases craving, this is associated with decreases in drug-related PFC activity, and vice versa. Concomitantly with these drug-related decreases, we would expect non-drug related PFC activity to increase, as indeed is the case (see below).

Disparities between results in this section, and throughout this Review, could also be attributed to differences between the various imaging modalities — an issue that should be recognized early on in this Review. For example, PET FDG measures glucose metabolic activity averaged over 30 min, whereas fMRI BOLD and PET CBF reflect faster changes in activation patterns. These modalities also differ in their baseline measures: it is not possible to establish an absolute baseline with BOLD fMRI, whereas it is possible with PET and arterial spin labelling MRI. Another common difference between studies is the baseline state of an individual, for example, the duration of abstinence could impact measures of craving and withdrawal.

Responses to drug-related cues

At the core of drug addiction are the conditioned responses to stimuli associated with the drug that develop in habitual users — such as objects that are used to administer the drugs, people who procure the drug or emotional states that in the past were either relieved or triggered by the use of the drug — that then drive the desire for drug taking and that are important contributors to relapse. Imaging studies have evaluated these conditioned responses by exposing addicted people to drug-related cues, for example, by showing them drug-related pictures. Here, we first review studies that compared the PFC response to cue exposure in addicted individuals and controls (Supplementary information S3 (table)), and then we discuss studies that explored the effect of abstinence, expectation and cognitive interventions on the PFC responses to drug-related cues (Supplementary information S4 (table)). We predict that in addicted individuals, PFC responses to drug-related cues mimic the responses to the drug itself, owing to conditioning, and that intervention causes a reduction of the drug-cue conditioned responses in the PFC.

Effect of cue exposure on PFC activity

Although there are some exceptions[24–26], fMRI studies report that compared to controls, drug-addicted individuals show enhanced BOLD responses in PFC to drug-related cues relative to control cues (Supplementary information S3 (table)).

These results were reported in the left DLPFC, left medial frontal gyrus and right subcallosal gyrus (Brodmann area 34) in young cigarette smokers[27], and in bilateral DLPFC and ACC in short-term[28] and long-term[29] abstinent alcoholics. Similar increases were reported in studies (including PET FDG studies) of cocaine-addicted individuals watching cocaine-related videos[30] and of heavy smokers watching cigarette-related videos while handling a cigarette[31]. Often, there are no differences between addicted and non-addicted individuals in valence or arousal ratings, or even in autonomic reactions (for example, skin conductance responses) to the drug-related cues[29], which suggests that neuroimaging measures are more sensitive in detecting group differences in conditioned responses to drug-related cues. Importantly, cue-induced PFC responses were correlated with craving[31] and severity of drug use[27], and predicted both subsequent performance on a primed emotion recognition task[32] and drug use 3 months later[29], indicating that these measures have clinical relevance. As no PFC activation was elicited by drug-related masked cues[33] (which activated subcortical regions instead[34]), these effects may only be induced when drug-related cues are consciously perceived, but this needs to be studied further.

An interesting line of studies explores cue-related PFC activation during acute pharmacological drug exposure. In heroin-dependent males receiving heroin injections while viewing drug-related videos, CBF in OFC correlated with the urge to use the drug, and CBF in DLPFC (Brodmann area 9) correlated with happiness[22] (Supplementary information S2 (table)). In this context, it is interesting to note that the mere taste of alcohol (versus litchi juice) can increase BOLD PFC activity in young drinkers, and this response correlates with

alcohol use and craving[35] and is possibly driven by dopamine neurotransmission in the subcortical reward circuit[36]. By contrast, in non-dependent alcohol drinkers or cigarette smokers, cue-related OFC activity was reduced by alcohol or nicotine administration, respectively[37]. This finding resonates with the finding that in non-addicted subjects, intravenous MPH administration decreased metabolism in ventral PFC regions[38] (BOX 2). Future studies could directly compare PFC responses to drug-related cues in non-dependent and dependent individuals and thereby further explore the impact of intoxication on cue-related PFC responses. Modelling of bingeing in drug abusing subjects would be informative for the design of interventions to reduce cue-induced compulsive behaviours.

PFC activation to relevant cues has also been reported in behavioural addictions. For example, young males who played internet games for over 30 hours a week showed BOLD activations in OFC, ACC, medial PFC and DLPFC when viewing pictures of the game, and these activations were correlated with the urge to play[39]. Similarly, compared to control subjects, pathological gamblers watching gambling videos showed increased activation in right DLPFC and inferior frontal gyrus[40], and this activation correlated with the urge to gamble[41]. By contrast, another study in pathological gamblers showed reduced left ventromedial PFC BOLD responses to winning versus losing in a gambling-like task, and the size of the reduction was correlated with the severity of the gambling addiction, as assessed with a gambling questionnaire[42]. The opposite directions of the activity changes (hyperactivations versus hypoactivations as compared to controls) may be driven by the ROI (for example, ventromedial PFC task-related deactivations are often seen and have been attributed to the role of the ‘default brain’ network[43]), differences in craving (craving was reported in REFS 39–41 but not REF. 42), task differences or methodological factors, which are summarized at the end of this section.

Disorders that are characterized by impaired control of food consumption are also associated with abnormal PFC reactivity to cues. This is not unexpected, given that these disorders and addiction involve similar compromises in neuronal circuits[44], including decreased striatal dopamine D2 receptor availability[45]. For example, women with anorexia or bulimia who are passively viewing pictures of foods (versus non-food related pictures) showed increased fMRI BOLD responses in left ventromedial PFC[46]. Compared to patients with bulimia, patients with anorexia showed greater right OFC activation in response to food pictures, possibly implicating this region in overly restrictive self-control; by contrast, left DLPFC activity to these pictures was decreased in patients with bulimia when compared to healthy controls, possibly implicating this region in the loss of control over food intake[46]. In another study, young women with eating disorders, but not control subjects, showed activation of the left ventromedial PFC during the selection of the most negative word from negative body-image related word sets (compared to during the selection of the most neutral word from neutral word sets)[47]. Such differences were not observed for generally negative words, indicating this region’s activation was driven by words that are most strongly related to the actual concerns of this patient group. Taken together with the results in the pathological gamblers described above[42], ventromedial PFC responses may track the emotional relevance of cues of highest concern to the patient population in question (that is, winning or avoiding loss for individuals with pathological gambling, body image for individuals with eating disorders and drug-related cues for drug-addicted individuals) and could serve as a target for tracking therapeutic interventions in addiction, as was recently suggested[48,49].

Effect of abstinence, expectation and cognitive interventions

Here, we propose that cognitive intervention and long-term abstinence attenuate cue-induced responses in the PFC, and that drug-related expectation and shortterm abstinence have the opposite effect. The impact of short-term abstinence on PFC cue-related activity has been most extensively studied in nicotine addiction (Supplementary information S4 (table)). In an

arterial spin labelling MRI study, 12-hour abstinence in smokers increased craving, global CBF and regional CBF in the OFC, and decreased CBF in the right PFC, with CBF changes in all ROIs correlating with craving and withdrawal symptoms[50]. Such enhanced cue reactivity was also reported for longer periods of abstinence — up to 8 days in the DLPFC, ACC and inferior frontal gyrus in female smokers[51] — and also positively correlated with craving[52]. However, some studies report no effect of abstinence on cue-induced PFC activity[53]. This could possibly be attributed to other factors that contribute substantial variability to results, such as the expectation to smoke at the end of the study[54]. Indeed, as discussed above[13], expectation alone may mimic the effects of acute drug intake on PFC activation in addicted individuals. Studies in which all three variables — expectation for drug administration, exposure to drug-related cues and abstinence — are explored for main effects and interaction effects on PFC activity would be useful, particularly if they involve large samples. The temporal dynamics of PFC cue reactivity also remain to be explored in longitudinal studies, tracking the same individual throughout longer-term abstinence periods.

A promising line of research explores behavioural modulation of cue reactivity. For example, a role for the mOFC in the suppression of craving was suggested by findings from a recent PET study in cocaine users. Craving increased after watching a video of cocainerelated cues, and craving levels correlated with glucose metabolism in the medial PFC[55]. Importantly, when participants were instructed — before watching the video — to inhibit craving, metabolism in the right mOFC decreased, and this was associated with activation of the right inferior frontal gyrus (Brodmann area 44), which is a crucial region in inhibitory control. In treatment-seeking cigarette smokers, the instruction to resist craving while viewing smoking-related videos was associated with DLPFC and ACC activation, although unexpectedly, this activation correlated positively with craving[56]. A recent study suggests that the direction of the change in activity and correlation with craving may be modulated by the behavioural strategy that is used to suppress craving. In this elegant study, cigarette smokers were instructed to consider the immediate versus long-term consequences of consuming the stimuli depicted in pictures (cigarette-related versus food-related cues)[57]. Considering the long-term consequences was associated with increased activity in PFC regions associated with cognitive control (DLPFC and inferior frontal gyrus) and with decreased activity in PFC regions associated with craving (mOFC and ACC). In addition, self-reported craving decreased when subjects considered the long-term consequences, and it was negatively correlated with activity in dACC and DLPFC. A mediation analysis showed that the association between increased activity in DLPFC and regulation-related decreases in craving was no longer significant after including decreased activity in ventral striatum in the model. Nevertheless, preclinical studies using ablation or optogenetic tools are necessary to better understand the interaction of the PFC and the ventral striatum in suppressing craving responses. Taken together, results of studies using behavioural approaches to suppress craving provide support to our proposed model (FIG. 3), which distinguishes between PFC regions that facilitate non-drug related cognitive effort and inhibitory control (DLPFC, dACC and inferior frontal gyrus) and those that reflect drug-related emotional concern, craving and compulsive behaviours (mOFC and ventral ACC).

To summarize, exposure to drug-related cues mimics the effects of direct drug administration on PFC activity in drug-addicted individuals, although the impact of duration of abstinence and expectation of drug use (and related processes such as forming of drugrelated memories), and their unique contributions to PFC function, remain to be assessed in large sample sizes. By expanding studies of cue reactivity to include additional neuropsychological functions, and by exploring the direction of correlations between PFC activity and specific end-points (for example, craving), the functional significance of activations of specific PFC regions in addiction will become clearer. A further

recommendation for future studies into cue reactivity is to conduct direct comparisons between sessions (for example, abstinence versus satiety) and task conditions (for example, drug versus neutral cues) and to perform whole-brain correlations with the respective behavioural changes. Future studies could also compare the duration and the pattern of PFC activation following acute drug exposure and following exposure to conditioned cues in the same subjects. Studies in non-addicted individuals could be used to assess the impact of deprivation (for example, of food) and urgent needs (for example, hunger, sexual desire and achievement motivation) on PFC cue reactivity. For example, in young healthy controls, craving of imagined foods — induced by a monotonous diet — was associated with activation in several limbic and paralimbic regions, including ACC (Brodmann area 24)[58].

It is important to note that as we have not reviewed the ventral striatal literature — and therefore direct comparisons cannot be made between PFC and subcortical responses to these stimuli — we cannot infer, however tempting this may be, that PFC activity itself may contribute to the rewarding effects of drugs and drug cues.

Responses to non-drug rewards

We propose that in individuals with drug addiction, PFC activity in response to non-drug related rewards is opposite to PFC activity changes that characterize drug-related processing (FIG. 3). Specifically, in addicted individuals who are in a state of craving, intoxication, withdrawal or early abstinence, sensitivity of the PFC to non-drug related rewards will be markedly attenuated compared with that in healthy non-addicted subjects. Indeed, decreased sensitivity to non-drug related rewards is a challenge in the therapeutic rehabilitation of patients with substance use disorders. Therefore, it is important to study how drug-addicted individuals respond to non-drug related reinforcers.

Such decreased sensitivity to non-drug related reward has been explained as an allostatic adaptation[59]. In this interpretation, frequent and high-dose drug use leads to compensatory brain changes that limit appetitive hedonic and motivational processes (‘reward’), instead strengthening aversive (opponent or ‘anti-reward’) systems[60]. This process is similar to tolerance, in which sensitivity to reward is decreased. It is also captured by the opponent-process hypothesis set forth by Slomon and Corbit[61,62], which describes the temporal dynamics of opposing emotional responses; here, negative reinforcement (for example, withdrawal) prevails over positive reinforcement (for example, drug-induced high) in the transition from occasional drug use to addiction. This process is relevant to emotional reactivity and emotion regulation, which, insofar as emotions are defined as ‘states elicited by reinforcers’[63], are bound to be impaired in drug addiction, especially during drug-biased processing such as craving and bingeing.

Anhedonia is a defining characteristic of drug dependence[64], and criteria for major depressive disorder — which includes anhedonia as a core symptom — are met by many drug-addicted individuals (for example, 50% of cocaine-addicted individuals[65]). The strong association between mood and substance use disorders is not limited to depression[66]; for example, emotional distress is a risk factor for drug relapse[67]. However, research on how altered emotion processing is implicated in substance use disorders is in its infancy[68,69], as discussed below (Supplementary information S5 (table)).

Money is an effective abstract, secondary and generalizable reinforcer that acquires its value by social interaction, and it is used in emotional learning in everyday human experience; compromised processing of this reward may therefore point to a socially disadvantageous emotional learning mechanism in addiction. Such a deficit, all the more distinct given the strong motivational and arousal value that is normally associated with this reward, would

corroborate the idea that in addiction, brain reward circuits are 'hijacked' by drugs, although the possibility for a pre-existing deficit in reward processing also cannot be ruled out.

One fMRI study investigated how cocaine-addicted individuals and controls responded to receiving monetary reward for correct performance on a sustained attention and forced-choice task[70]. In controls, sustained monetary reward (gain that did not vary within task blocks and that was fully predictable) was associated with a trend for the left lateral OFC to respond in a graded fashion (activity monotonically increased with amount: high gain > low gain > no gain), whereas the DLPFC and rostral ACC responded equally to any monetary amount (high or low gain > no gain). This pattern is consistent with the OFC's role in processing relative reward, as documented in non-human[71] and human subjects[72–76], and with the DLPFC's role in attention[77]. Cocaine-addicted subjects showed reduced fMRI signals in left OFC for high gain compared to controls and were less sensitive to differences between monetary rewards in left OFC and in DLPFC. Remarkably, more than half of the cocaine-addicted subjects rated the value of all monetary amounts equally (that is, US$10 = US$1000)[78]. Eighty-five percent of the variance in these ratings could be attributed to the lateral OFC and medial frontal gyrus (and amygdala) responses to monetary reward in the addicted subjects. Although these findings need to be replicated in a larger sample size and with more sensitive tasks, they nonetheless suggest that some cocaine-addicted individuals may have reduced sensitivity to relative differences in the value of rewards. Such 'flattening' of the perceived reinforcer gradient may underlie over-valuation or bias towards immediate rewards (such as an available drug)[79] and the discounting of greater but delayed rewards[80,81], therefore reducing sustained motivational drive. These results may be therapeutically relevant as monetary reinforcement in well-supervised environments has been shown to enhance drug abstinence[82], and may also be relevant in predicting clinical outcomes. In line with this idea, in a similar population of subjects, the degree of dACC hypoactivation in a task in which correct performance was monetarily remunerated correlated with frequency of cocaine use, whereas degree of rostroventral ACC (extending to mOFC) hypoactivation correlated with task-induced craving suppression[83]. There was an inverse association of these PFC ROIs with cue reactivity in the midbrain in cocaine-addicted subjects but not in control subjects, which implicates these ACC subdivisions in the regulation of automatic drug responses[84].

It should be noted that in the studies described above, subjects were not asked to choose between monetary rewards. We predict that choice would similarly follow a linear function (choice of higher over lower reward) in healthy controls more so than in addicted individuals, who we expect to show less flexibility in choice (choosing drug over other reinforcers), particularly during craving and bingeing. Studies that allow subjects to choose between reinforcers have mostly been conducted in laboratory animals. These studies have shown that, when given the choice, previously drug-exposed animals choose the drug over novelty[85], adequate maternal behaviour[86] and even food[87–89], indicating that drug exposure can decrease the perceived value of natural rewards, even those that are needed for survival. In a recent human neuroimaging study in which subjects could win cigarettes or money, occasional smokers were more motivated to obtain money than cigarettes, whereas dependent smokers made similar efforts to win money or cigarettes[90]. A similar group by reward interaction was observed in the right OFC, bilateral DLPFC and left ACC, such that in the occasional smokers these regions showed higher activity to stimuli predicting an increasing monetary reward than to stimuli predicting a cigarette reward, whereas the dependent smokers showed no significant differences in such anticipatory brain activity. These regions also showed higher activation to money in the occasional than in dependent smokers[90].

These results, together with behavioural results on neuropsychological tests in cocaine-addicted individuals[91,92] (see also BOX 2), contribute to our understanding of how relative reward preferences may change in addiction such that preference for the drug competes with (and sometimes exceeds) preference for other reinforcers, with a concomitant decrease in the ability to assign relative values to non drug-related rewards.

Emotional reactivity

Several studies that are reviewed above compared PFC responses to non-concern-specific yet emotionally arousing stimuli with responses to concern-related (for example, drug-related) cues[25,26,28,46,47] (Supplementary information S3 (table)). The PFC was hyperactive in response to images from all emotional categories in alcohol-addicted subjects[28], the anterior PFC was hypoactive in response to pleasant pictures in heroin-addicted individuals[26], and in patients with eating disorders PFC responses to aversive pictures were normal[46,47]. Thus, in contrast to our model's predictions (FIG. 3), there were no differences in the PFC response between drug-related and affective yet non-drug related cues in any of these studies. This result, and the variability in the pattern of results, could be attributed to — among other factors — the small number of studies, differences between studies (such as sample sizes, the primary drug of abuse and duration of abstinence) and sensitivity of the measures used. Future studies would benefit from using event-related potential recordings or electroencephalography, which have much higher temporal resolution than fMRI or PET.

A clearer picture emerges when studies incorporate emotional processing into cognitive–behavioural tasks (Supplementary information S5 (table)). For example, when required to empathize with a protagonist in a series of cartoons, each depicting a short story, methamphetamine-addicted individuals provided fewer correct answers than controls to the question "what will make the main character feel better?"[93]. Compared to control subjects, the addicted individuals also showed hypoactivation in OFC (and hyperactivation in DLPFC) when answering this question. With the exception of one study in abstinent heroin-addicted individuals[94], other similar studies also reported differences between addicted and control groups in PFC responses to tasks requiring processing of emotional stimuli such as faces, words or complex scenes. For example, when men with alcohol addiction judged the intensity of five facial expressions, negative expressions were associated with lower activations in the left ACC but higher activations in the left DLPFC and right dACC compared to controls[95]. In addition, compared to healthy controls, cocaine users showed ACC and dorsomedial PFC hypoactivations while performing a letter discrimination task during the presentation of a set of pleasant (versus neutral) pictures and hyperactivations in the bilateral DLPFC during the presentation of unpleasant (versus pleasant) pictures[96]. Similarly, compared to healthy controls, marijuana smokers showed left ACC hypoactivations, and right DLPFC and inferior frontal gyrus hyperactivations in response to presentation of masked angry faces (versus neutral faces); right ACC responses positively correlated with frequency of drug use and bilateral ACC responses correlated with urinary cannabinoid levels and alcohol use[97]. By contrast, the left dACC was hyperactive in methamphetamine-dependent subjects compared to controls when judging emotional expression on faces in an affect matching task (versus judging the shape of abstract figures) and this was associated with more self-reported hostility and interpersonal sensitivity in the addicted subjects[98].

Taken together, these studies indicate that the DLPFC is mostly hyperactive during emotion processing in addicted individuals compared to control subjects, especially for negative emotions. The ACC shows mixed results, although with more studies showing hypoactivity than hyperactivity. It is possible that the DLPFC hyperactivity may be compensating for the ACC hypoactivity, which would explain the lack of difference in task performance between drug abusers and healthy controls in most of these studies. Disadvantageous and/ or

impulsive behaviours may be observed during greater emotional arousal challenges such as stress, craving or more difficult tasks. Clearly, the roles of these regions in relation to the proposed model (FIG. 3) need to be better understood. It is possible that, by prematurely recruiting higher-order PFC executive function (mediated by the DLPFC), negative emotional arousal enhances risk for drug use in addicted individuals, particularly in situations that place additional strain on the limited cognitive control resources. This interpretation is consistent with the competition between drug and non drug-related processes and between 'cold' and 'hot' processes in the model (FIG. 3c).

Although several of the above studies used negatively valenced stimuli, a lingering question is whether altered sensitivity to non-drug reinforcers in addicted individuals also applies to negative reinforcers such as money loss. Studies in animals show that 'addicted' subjects manifest persistent drug seeking even if the drug is associated with receiving an electric shock[99]. In humans, hypoactivation in the right ventrolateral PFC in smokers during monetary loss, and in gamblers during monetary gain, have been reported[100] (Supplementary information S5 (table)). Although more studies are clearly needed, the implication of reduced sensitivity to negative reinforcers in addiction has practical implications as, in addition to positive reinforcers (such as vouchers and privileges), negative reinforcers (such as incarceration) are increasingly being used in the management of drug abusers. Interventions could be optimized by selecting the most effective type and dose of reinforcer. Future studies could also help to ascertain whether addicted individuals may resort to taking drugs because they are easily bored, frustrated, angry or fearful, perhaps as a result of altered PFC functioning. Low threshold for experiencing any of these emotions, or the inability to sustain goal-directed behaviour (for example, completing a boring task) when experiencing these emotions, may be associated with impaired inhibitory control (that is, enhanced impulsivity) as reviewed below. In cocaine-addicted individuals, PFC activity habituates prematurely to repeated presentation of an incentive sustained attention task[101], which could be a measure of compromised sustainability of effort and result in inadequate engagement in treatment activities.

Inhibitory control in addiction

Drug addiction is marked by mild, yet pervasive, cognitive disruptions[102] that may accelerate its course, threaten sustained abstinence[103] or increase attrition from treatment[104,105]. The PFC is essential for many of these cognitive processes, including attention, working memory, decision making and delay discounting (TABLE 1), all of which are compromised in addicted individuals, as reviewed elsewhere[106]. Another important cognitive function of the PFC is self-control, and here we focus on the role of the PFC in this process in addiction (Supplementary information S6 (table)). Self control refers, among other operationalizations, to a person's ability to guide or stop a behaviour, particularly when the behaviour may not be optimal or advantageous, or is perceived as the incorrect thing to do. This is pertinent to addiction as, despite some awareness of the devastating consequences of drugs (see also the section below on disease awareness in addiction), individuals who are addicted to drugs show an impaired ability to inhibit excessive drug taking. Impaired inhibitory control, which is a key operation in self-control, is also likely to contribute to engagement in criminal activities in order to procure the drug, and to underlie the impaired regulation of negative emotions, as suggested above. These impairments could also predispose individuals to addiction. Consistent with previous reports[107], children's self-control during their first decade of life predicts substance dependence in their third decade of life[108].

Go/no-go and stop signal reaction time tasks

Tasks that are often used to measure inhibitory control are the go/no-go task and the stop signal reaction time task (SSRT). In the go/no-go task, cocaine-addicted individuals showed more errors of omission and commission than controls and this has been attributed to hypoactivation in dACC during stop trials[109]. In another study, this inhibitory behavioural deficit in cocaine users was exacerbated by a higher working-memory load; again, dACC hypoactivation was associated with deficient task performance[110]. Similarly, heroin-addicted men showed slower reaction times in the go/no-go task, along with hypoactivation in ACC and medial PFC[111]. Results from the SSRT are more difficult to interpret. For example, the ACC was hypoactive during successful response inhibitions compared to failed response inhibitions in cocaine-addicted men, and their behavioural performance was similar to that of controls[112]. The ACC was also hypoactive during both careful behavioural adjustment and risk taking on this task in abstinent alcoholics, particularly in subjects with higher alcohol urge at the time of the fMRI scan[113]. By contrast, the ACC was hyperactive during inhibition errors[113], possibly because the abstinent alcoholics exercised a greater attention in monitoring for the stop signal than controls — a function that is associated with the ACC. Increased activity in other regions of the PFC was also reported in cigarette smokers after a 24-hour abstinence, but (in contrast to expectation for an increased regional activation) accuracy was reduced[114] (Supplementary information S4 (table)).

The large variability in results from these studies is possibly caused by differences in the analyses, the type of comparison and by performance differences between the groups, in addition to other variables. Nevertheless, a pattern emerges in which the dACC is hypoactive during these inhibitory control tasks, and this hypoactivity is mostly associated with impaired performance, particularly with shorter abstinence durations. Targeted cognitive–behavioural interventions may alleviate this dysfunction. For example, informative cueing (such as providing a warning of an impending no-go trial) enhanced inhibitory control in a go/no-go task, and this was correlated with enhanced ACC activation in methamphetamine-addicted individuals[115]. Such cognitive–behavioural interventions could be used as neural rehabilitation exercises and combined with the simultaneous administration of drugs, as discussed below.

Stroop tasks

Inhibitory control can also be assessed using the colour–word Stroop task[116]. Slower performance and more errors during incongruent trials on this task are a hallmark of PFC dysfunction. Neuroimaging research has shown that the dACC and DLPFC are involved in this task[117–119], with distinct roles for these regions in conflict detection (dACC) and resolution (DLPFC)[120].

Studies using the colour–word Stroop task in addicted individuals report results that mostly echo those reported above. For example, cocaine abusers had lower CBF in the left dACC and right DLPFC during incongruent trials compared to congruent trials, whereas the right ACC showed the opposite pattern; moreover, right ACC activation was negatively correlated with cocaine use[121] (Supplementary information S6 (table)). In marijuana-using men, lower CBF during this task was reported in several PFC regions, including perigenual ACC, ventromedial PFC and DLPFC[122]. Methamphetamine-dependent subjects also showed hypoactivations in the inhibitory control network, including dACC and DLPFC while performing this task[123]. Consistent with the impact of abstinence on the go/no-go task reported above[114], cigarette smokers who were tested after a 12-hour abstinence had slowed reaction times, and enhanced dACC and reduced right DLPFC responses to the incongruent trials on the colour–word Stroop task[124] (Supplementary information S4(table)). Importantly, an fMRI study showed that activation of the ventromedial PFC (Brodmann

areas 10 and 32) during a colour–word Stroop task performed 8 weeks before treatment onset predicted treatment outcome in cocaine-addicted individuals[125].

In the emotional variant of this task, colour words are substituted for emotional words or pictures that are related to a particular individual's area of concern, such as alcohol-related words for alcohol-addicted individuals. Although both the classic and the emotional Stroop tests involve the need to suppress responses to distracting stimulus information while selectively maintaining attention on the stimulus property that is needed to complete the task, only the emotional Stroop task uses emotional relevance as a distractor. Such emotional Stroop designs can potentially further demarcate the altered PFC activity in addiction: is it generalizable to any type of conflict or does it occur specifically during conflicts in a drug-related context?

An fMRI study in stimulant users showed attention bias to drug-related words: addicted individuals, but not controls, showed more attention bias to drug-related words (measured as the median response latency of correctly identified colours of drug-related words minus the median response latency of correctly identified colours of matched neutral words), which was correlated with enhanced left ventral PFC responses. Such responses were not observed for the colour–word Stroop task[126]. Similarly, drug-related pictures amplified dACC responses to task-relevant information in cigarette smokers[127]. These findings suggest that in addiction, more top-down resources are needed to focus on cognitive tasks when drug-related cues are present as distractors (thus biasing attention) during the task. Conflicting with these and other results[128] are studies in current cocaine users, in which drug-related words were not associated with slower performance or more errors[83,129]. This disparity could be related to task design or the treatment-seeking status of the study participants; we predict that enhanced conflict between drug-related words and neutral words characterizes those individuals who are trying to abstain from drugs. Evidence for such an effect in cigarette smokers was recently published[130].

Effects of drug administration during inhibitory control tasks

Deficits in emotion regulation and inhibitory control in addicted individuals and enhancement of PFC activity by direct drug administration (see above and Supplementary information S2 (table)) together could support the self-medication hypothesis[131,132]. According to this hypothesis, drug self-administration — and the associated increases in PFC activity — ameliorate the emotional and cognitive deficits that are present in drug-addicted individuals. Such a self-medication effect has previously been recognized by the treatment community, as evidenced by using methadone (a synthetic opioid) as a standard agonist substitution therapy for heroin dependence. In an fMRI study, watching heroin-related cues was associated with less craving during a post-dose than during a pre-dose methadone session in heroin-addicted individuals, with concomitant decreases in cuerelated responses in the bilateral OFC[133] (Supplementary information S4 (table)). Empirical support is starting to accumulate for a similar effect in cocaine-addicted individuals. For example, intravenous cocaine (which increases extracellular dopamine levels) in cocaine users improved inhibitory control in a go/no-go task, and this was associated with normalization of ACC activity and enhanced right DLPFC activation during the task[134]. Intravenous MPH (which also increases extracellular dopamine levels) similarly improved performance on the SSRT in cocaine abusers, and this was positively correlated with inhibition-related activation of the left middle frontal cortex and negatively correlated with activity in the ventromedial PFC; after MPH, activity in both regions showed a trend for normalization[135]. A PET study showed that oral MPH attenuated the reduced metabolism in limbic brain regions — including lateral OFC and DLPFC — that followed exposure to cocaine-related cues in cocaine-addicted individuals[136]. It also decreased errors of commission, a common measure of impulsivity, during a drug-relevant emotional Stroop task, both in cocaine-

addicted individuals and controls, and in the addicted individuals this decrease was associated with normalization of activation in the rostroventral ACC (extending to the mOFC) and dACC; dACC task-related activation before MPH administration was correlated with shorter lifetime alcohol use[137] (FIG. 4). Although it remains to be studied whether or how the noradrenergic effects of MPH contribute to its 'normalizing' effects in cocaine users, taken together these results suggest that the dopamine-enhancing effects of MPH could be used to facilitate changes in behaviour in addicted individuals (for example, improve self-control), particularly if MPH treatment is combined with specific cognitive interventions.

It should be noted that the effect of dopamine agonists on normalizing brain–behaviour responses to emotional or cognitive-control challenges may depend on patterns of compulsive drug use[126] or other individual differences, such as baseline self-control and lifetime drug use, but these possibilities remain to be studied in larger sample sizes. Also, non-dopaminergic probes (for example, cholinergic or AMPA receptor agonists) may offer additional pharmacological targets for cocaine addiction treatment[138].

In summary, results of studies into inhibitory control in drug addiction suggest that there is dACC hypoactivity and deficient inhibitory control in drug-addicted individuals. Enhanced PFC activity has been reported after short-term abstinence, upon exposure to drug-related cues and to the drug itself (or similar pharmacological agents). However, although drug exposure is also associated with better performance in these cognitive tasks, short-term abstinence and exposure to drug-related cues have the opposite result on task performance. Viewed in the context of the proposed model (FIG. 3), although drugs of abuse offer temporary relief, chronic self-medication with these drugs has long-term consequences — reduced inhibitory control mechanisms and associated emotional disruptions — that may not be alleviated with short-term abstinence, and that are prone to be rekindled upon exposure to drug-related cues. Normalizing these functions, using empirically based and targeted pharmacological and cognitive–behavioural interventions — in combination with the relevant reinforcers — should become a goal in the treatment of addiction.

Disease awareness in addiction

The capacity for insight into our internal world (encompassing interoception but extending to higher-order emotional, motivational and cognitive self-awareness) is partly dependent on the PFC. Given the impairments in PFC function in people with addiction reviewed above, it is possible that a restricted awareness of the extent of the behavioural impairment or of the need for treatment may underlie what has traditionally been ascribed to 'denial' in drug addiction — that is, the assumption that the addicted patient is able to fully grasp his or her deficits but chooses to ignore them may be erroneous. Indeed, studies have recently suggested that addicted individuals are not fully aware of the severity of their illness (that is, their drug seeking and taking behaviour and its consequences) and this may be associated with deficits in the control network[139].

Several studies have provided evidence for a dissociation between self-perception and actual behaviour in addiction. For example, in healthy controls the speed and accuracy of responses for a high monetary condition compared to a neutral cue in a monetarily remunerated forced-choice sustained attention task was correlated with self-reported engagement in the task; by contrast, cocaine subjects' reports of task engagement were disconnected from their actual task performance, indicating discordance between self-reported motivation and goal-driven behaviour[70]. Using a recently developed task in which participants selected their preferred pictures from four types of pictures and then reported what they thought was their most selected picture type[91], the discordance between self-report and actual choice —

indicating impaired insight into one's own choice behaviour — was most severe in current cocaine users, although it was also discernible in abstinent users, in whom it was correlated with frequency of recent cocaine use[92].

An underlying mechanism of this dissociation may be an uncoupling of behavioural and autonomic responses during reversal learning, such as has been shown to occur after OFC lesioning in monkeys[140]. There is some evidence for similar neural–behavioural dissociations also in humans. In an event-related potential study using the task reported above[70], control subjects showed altered electrocortical responses and reaction times in the high-money condition compared to the neutral cue condition, and these two measures of motivated attention were intercorrelated. This pattern was not observed in the cocaine-addicted group, in which the ability to respond accurately to money (that is, the more the behavioural flexibility to this reinforcer), negatively correlated with the frequency of recent cocaine use[141]. Another study showed that, in a gambling task, control subjects' choices were guided by both actual and fictive errors, whereas cigarette smokers were only guided by the actual errors that they had made, even though the fictive errors induced robust neural responses[142], again pointing to neural–behavioural dissociations in addiction. In the proposed model (FIG. 3), this mechanism is represented by a decreased input from higher-order cognitive control regions to regions that are associated with emotional processing and conditioned responses.

Importantly, in humans this neural–behavioural dissociation can be validated by comparing patients' self-reports with those of informants[137] such as family members or treatment providers, or with objective measures of performance on neuropsychological tests[143]. It is important to remember that self-report measures provide an important glimpse into such dissociations, but given the limitations of self-reports, the development of more objective measures of insight and awareness is crucial for both research and clinical purposes. Two promising measures are error awareness and affect matching. Error awareness in a go/no-go task was found to be reduced in young marijuana abusers and this was associated with reductions in bilateral DLPFC and right ACC, and with greater current drug use[144]. In metham-phetamine-dependent subjects, the bilateral ventrolateral PFC was hypoactive during affect matching and this was associated with more self-reported alexithymia[145]. As better awareness of the severity of drug use predicted actual abstinence for up to 1 year after treatment in alcoholics[146], this budding line of research could greatly enhance our understanding of relapse in drug addiction, potentially improving currently available intervention approaches, for example, by targeting addicted individuals who have reduced self awareness for tailored interventions.

Study limitations and future directions

The main limitation of this Review is our selective focus on the PFC at the expense of excluding all other cortical brain regions and subcortical structures. The architecture supporting higher-order executive function and top-down control is complex and is thought to involve several functional networks that include, in addition to the PFC, other regions such as the superior parietal cortex, insula, thalamus and cerebellum[147]. Consequently, and also given the inherent limitations of cross-sectional human neuroimaging studies, attribution of causality should be avoided — that is, the PFC may not directly drive the deficits described in this review. Future meta-analyses in which the disruption of these functional networks in addiction is explored should be imbued with results from mechanistic studies in laboratory animals.

A notable issue with many of the reviewed studies pertains to their use of functional ROI analyses that sometimes lack the more stringent statistical corrections of whole-brain

analyses. For example, to overcome issues of low power, reported results are sometimes restricted to post-hoc analyses in regions that showed significant results across all subjects to all task conditions; wholebrain analyses of the main (for example, group or type of stimulus) or interaction effects, or of correlations with task performance or clinical end-points, are not consistently performed. Therefore, such ROI results could represent a Type I error but they could also miss the key neural substrates that are involved in the phenomenon under investigation, for example, craving or control of craving. A way to circumvent the limitations of post-hoc analyses is to perform both whole-brain analyses and use *a priori* defined anatomical ROIs[148,149], which could also help to standardize the nomenclature of ROIs across studies. Other common issues pertain to incomplete presentation of the actual data (such as not providing both mean and variance, or not providing scatterplots when reporting correlations), which can obscure the direction of an effect (activation versus deactivation), potentially adding to the variability in published results (for example, a hyperactivation could refer to higher activations or lower deactivations from baseline). In summary, this field would benefit from standardization — of procedures related to imaging, tasks, analyses and subject characterization — that would facilitate the inter-pretability of the findings. Standardization is also crucial for allowing integration of data sets from various laboratories — such data pooling will be particularly important for genetic studies that are aimed at understanding the interplay between genes, brain development, brain function and the effects of drugs on these processes. For example, the creation of large imaging data sets are going to be important in understanding how genes that are associated with vulnerability for addiction affect the human brain both after acute and repeated drug exposures. Moreover, the ability to integrate large imaging data sets — as has recently been done for MRI images of resting functional connectivity[150] — will allow a better understanding of the neurobiology of addiction that in the future may serve as biomarker to guide treatment.

Although there are a few exceptions (implicating the right PFC, particularly the ACC and DLPFC, in compensatory inhibitory processes) the data reviewed here show no clear pattern indicating lateralization of brain changes in addicted individuals. However, lateralization was not the focus of investigation in any of the reviewed studies. Given that there is evidence for disrupted laterality during finger-tapping in cocaine abusers[151], studies that specifically investigate PFC lateralization in iRISA in addiction are needed. Furthermore, there are clear gender differences in responses to drugs and in the transition to addiction, and imaging studies are increasing our understanding of the sexually dimorphic features of the human brain. However, so far, few wellcontrolled studies have focused on sex differences in the role of the PFC in addiction; instead, many studies use either female or male subjects (mostly males). Studies are also needed to explore the potentially modulating effects of other individual characteristics; of particular interest are the impact of co-morbid disorders (for example, depression may exacerbate deficits in addicted individuals[152]) and of the recency of drug use and duration of abstinence (for example, cocaine may reduce or mask underlying cognitive[153] or emotional[154] impairments in cocaine-addicted individuals). Longitudinal studies would enable examination of these issues, which are of particular importance to those who abstain from drugs in the hope that PFC functioning will recover. Furthermore, comparison between different types of abused substances would allow differentiation between factors that are specific to certain drugs from factors that could be common across addiction populations. Instead of treating the heterogeneity of neural and behavioural changes in addiction as noise, studies could explore it with the goal of answering key questions: is PFC dysfunction in iRISA more prominent in certain addicted individuals than in others? Does self-medication drive drug taking more in some individuals than in others? How does co-morbid drug use, which is more the rule than the exception (for example, most alcoholics are nicotine-addicted), affect the neurobiology in addiction? What is the implication of this variability to treatment outcome and recovery? Most importantly,

how can we use these laboratory results on the PFC functioning in addiction to inform the design of effective treatment interventions?

Summary and conclusions

In general, neuroimaging studies have revealed an emerging pattern of generalized PFC dysfunction in drug-addicted individuals that is associated with more negative outcomes — more drug use, worse PFC-related task performance and greater likelihood of relapse. In drug-addicted individuals, widespread PFC activation upon taking cocaine or other drugs and upon presentation of drug-related cues is replaced by widespread PFC hypoactivity during exposure to higher-order emotional and cognitive challenges and/or during protracted withdrawal when not stimulated. The PFC roles that are most pertinent to addiction include self-control (that is, emotion regulation and inhibitory control) to terminate actions that are not advantageous to the individual, salience attribution and maintenance of motivational arousal that is necessary to engage in goal-driven behaviours, and self-awareness. Although activity among PFC regions is highly integrated and flexible, so that any one region is involved in multiple functions, the dorsal PFC (including the dACC, DLPFC and inferior frontal gyrus) has been predominantly implicated in top-down control and meta-cognitive functions, the ventromedial PFC (including subgenual ACC and mOFC) in emotion regulation (including conditioning and assigning incentive salience to drugs and drug-related cues), and the ventrolateral PFC and lateral OFC in automatic response tendencies and impulsivity (TABLE 1). Dysfunction of these PFC regions may contribute to the development of craving, compulsive use and ‘denial’ of illness and the need for treatment — characteristic symptoms of drug addiction. This PFC dysfunction may in some instances precede drug use and confer vulnerability for developing substance use disorders (BOX 3). Irrespective of the direction of causality, the results of the neuroimaging studies that are reviewed here suggest the possibility that specific biomarkers could be targeted for intervention purposes. For example, perhaps these PFC abnormalities could be used to identify the children and adolescents who would benefit most from intensive drug abuse prevention efforts, and perhaps medications can ameliorate these deficits and help addicted individuals to engage in rehabilitation treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

^{18}Fluorodyoxyglucose PET	(^{18}F-PET). Positron emission tomography (PET) with a radioligand to image regional glucose uptake, a measure of metabolic activity that can also be used to assess global brain function.
Methylphenidate	(MPH). A mild stimulant (approved for treatment of attention deficit hyperactivity disorder) with similar pharmacological effects to cocaine (it blocks the dopamine transporter) but

	with lower abuse potential owing to slower rates of clearance from the synapse.
Non-contingent administration	Administration of a certain drug that is not dependent on the subject's behaviour
Fixed-rate self-administration	Self-administration of a certain drug on a ratio between drug delivery and behaviour that is fixed by an experimenter (for example, after emission of a certain number of responses or after a certain time has elapsed following the previous response).
Arterial spin labelling	(Also known as arterial spin tagging). An MRI technique that is capable of measuring cerebral blood flow *in vivo*. It provides cerebral perfusion maps without requiring the administration of a contrast agent or the use of ionizing radiation, as it uses magnetically labelled endogenous blood water as a freely diffusible tracer.
Masked cue	A cue that is presented below conscious processing level (that is, outside of conscious awareness). This is usually achieved with a very short duration of cue presentation followed by presentation of another cue that is consciously perceived (longer duration).
Ketamine	An NMDA receptor antagonist primarily used for the induction and maintenance of general anaesthesia. In addition, it can induce analgesia, elevated blood pressure and hallucinations, and it has been used as a recreational drug.
[^{11}C]carfentanil	A positron emission tomography (PET) receptor radioligand that competes with endogenous opiates for binding to the mu opiate receptor.
Affect matching	A neuropsychological test in which images of faces are matched based on their emotional facial expressions. This task can be used to assess impairments in emotional (or social) processing.
Go/no-go task	A neuropsychological task that is commonly used to assess inhibitory control. Subjects are required to press a button when one stimulus type appears and withhold a response when another stimulus type appears.
Stop signal reaction time task	(SSRT). A neuropsychological test that measures the ability to stop a response that has already been initiated. It is used clinically as an index of inhibitory control. Slower SSRT is associated with disruption of executive functions.
Errors of omission and commission	Errors on a go/no-go task: a subject had to go but they did not go (omission of a response) or had to withhold a response but pressed a button instead (commission of an unnecessary response). The former is an index of inattentiveness while the latter is an index of impulsive (premature) responding.
Stroop task	A neuropsychological task in which conflict is created between an automatic response (for example, reading) and a

	slower response (for example, colour naming), with both competing for the same processing resources. Impaired performance on Stroop tasks is associated with prefrontal cortex dysfunction.
Alexithymia	A state of deficiency in understanding, processing or describing emotions, including the difficulty in identifying and/ or describing one's own feelings and externally oriented thinking.

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Box 1

Addiction-related changes in PFC connectivity and structure

The prefrontal cortex (PFC) is densely interconnected with other cortical and subcortical brain regions and networks, including the 'default mode network' (DMN) and the 'dorsal attention networks', which are implicated in executive control processes such as attention and inhibition[43,155,156]. Although the question of how these networks — and other interconnected brain regions — impact drug addiction has only recently begun to be explored, resting-state functional connectivity studies have already shown promise in revealing patterns that predict disease severity and treatment outcomes. For example, in cigarette smokers, dorsal anterior cingulate cortex (dACC)–striatal connectivity is inversely correlated with the severity of nicotine addiction; using a nicotine patch significantly enhanced the coherence strength of several ACC connectivity paths, including those to frontal midline structures[157]. In addition, in abstinent smokers, withdrawal symptom improvement after nicotine replacement therapy was associated with an increased inverse correlation between the executive control network and the DMN, with altered functional connectivity within the DMN, and with altered functional connectivity between the executive control network and regions implicated in reward[158]. More recent studies into nicotine addiction adapted an important multi-imaging approach in which connectivity is explored with regard to grey matter integrity and cue reactivity[159,160].

Network-specific functional connectivity strength is also decreased in other addictions. In cocaine-addicted individuals, the rostroventral ACC (part of the DMN) had lower connectivity with the midbrain, where dopamine neurons are located[161], and similar results have been reported in other studies[162]. Reductions in functional connectivity have also been reported in heroin addiction[163], in whom connectivity was modulated by drug-related cues[164] and associated with longer duration of heroin use[165]. Further studies are needed to determine whether resting-state connectivity predicts task performance, and how drugs of abuse or potential medications change these measures — for example, does drug administration increase both resting-brain connectivity and task-induced activations or could an elevated resting or baseline state be associated with reduced task-induced activations? These questions are important because the answers will help to determine individually tailored clinical end-points — for example, medication dose could be tapered based on an individual's own baseline resting-state functional connectivity.

Structural imaging studies have shown reduced PFC grey matter density or thickness across addiction populations (up to 20% loss). For example, grey matter PFC decrements, specifically in the dorsolateral PFC (DLPFC), have been documented in individuals who are addicted to alcohol. These decrements are associated with longer lifetime alcohol use[166,167] and worse executive function[167], and persist from 6–9 months up to 6 years or more of abstinence[168–170]. Despite some conflicting results[171], most studies in individuals who are addicted to cocaine[172–174], methamphetamine[175], heroin[176] (even when on methadone replacement therapy[177,178]) and nicotine[159,160,179,180] report similar PFC grey matter reductions — which are most evident in the DLPFC, ACC and orbitofrontal cortex (OFC) — that are associated with longer duration or increased severity of drug use. The persistence of these structural changes beyond the end of drug use and into long-term abstinence suggests an influence of pre-morbid or stable factors that might predispose individuals to drug use and addiction during development (BOX 3). Nevertheless, such structural abnormalities are not seen in adolescent users of alcohol[181] or marijuana[182], which suggests these PFC decrements could also be a dose-dependent consequence of drug use. Whether it predisposes to addiction or is a consequence of addiction, such lower PFC grey matter volume, particularly in the medial

OFC, is associated with disadvantageous decision making[183] that could lead to the catastrophic consequences in the lives of addicted individuals.

Box 2

The role of dopamine and other neurotransmitters

Dopamine D2 receptors, which are most densely expressed in subcortical regions such as the midbrain and dorsal and ventral striatum, are also distributed throughout the prefrontal cortex (PFC). A series of positron emission tomography (PET) studies reported lower striatal dopamine D2 receptor availability in individuals who are addicted to methamphetamine[184], cocaine[38] or alcohol[185], and in people with morbid obesity[186], and these reductions were associated with decreased baseline metabolic activity in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). This suggests that loss of dopamine signalling through D2 receptors may underlie some of the deficits in prefrontal function that are seen in addiction — an idea that is supported by preliminary data showing that striatal dopamine D2 receptor availability was correlated with medial PFC response to money in cocaine-addicted individuals[187]. Reduced striatal dopamine D2 receptor availability was also reported in male heavy smokers, both after smoking as usual and after 24 hours of abstinence; in the sated condition, the dopamine D2 receptor availability in the bilateral ACC was negatively correlated with the desire to smoke (positive correlations were observed for the striatum and OFC)[188]. Evidence for dopamine depletion in the dorsolateral PFC (DLPFC) was also reported in young chronic ketamine users, and levels of depletion were correlated with higher weekly drug use[189]. Other PET studies reported markedly attenuated striatal dopamine release in response to intravenous administration of a stimulant drug (for example, methylphenidate) in cocaine abusers and alcoholics, with a parallel decrease in self-reported experiences of feeling high[38,185].

Consistent with data from animal studies, these results in addicted individuals point to a blunted striatal dopaminergic function — both at baseline and in response to a direct challenge — that is associated with enhanced craving and severity of use. A blunted striatal dopamine response is predictive of actual choice for cocaine over money in abstinent cocaine-addicted individuals, suggesting that it may predispose subjects to relapse[190]. The results also suggest that, by regulating the magnitude of dopamine increases in the striatum[185], the OFC assumes a crucial role in the modulation of the value of reinforcers; disruption of this regulation may underlie the increased value attributed to a drug reward in addicted subjects. Consistent with this suggestion, metabolism in the medial OFC and ventral ACC in cocaine abusers increased after intravenous stimulant administration, whereas it was reduced in controls; the regional metabolic increases in the abusers were associated with drug craving[38].

Endogenous opioids also mediate the rewarding responses of many drugs of abuse, particularly heroin, alcohol and nicotine. Repeated drug use has been associated with decreased release of endogenous opioids, an effect that may contribute to withdrawal symptoms, including dysphoria. A study using [^{11}C]carfentanil showed that cocaine abusers had higher PFC mu opiate receptor binding potential (indicative of lower endogenous opioid levels) than healthy non-addicted controls, and that this persisted in the anterior frontal cortex and ACC throughout 12 weeks of abstinence[191]. Elevated mu opiate receptor binding in the DLPFC and ACC before treatment was associated with greater cocaine use and shorter duration of abstinence, and was suggested to be a better predictor of treatment outcome than baseline drug and alcohol use[192]. Similar results were reported in abstinent alcoholic men[193], whereas the level of mu (or kappa) opiate receptor binding is reversed by chronic methadone in heroin-addicted individuals[194].

Decreased PFC binding potential for a serotonin transporter radioligand has been reported in abstinent methamphetamine abusers[195], young recreational MDMA users[196]

and in recovered alcoholics[197]. Reduced serotonin transporter availability may reflect neuroadaptations to increased synaptic serotonin, but it could also reflect damage to serotonergic nerve terminals. Other neurotransmitter systems that regulate the PFC and are involved in the neuroadaptations that occur with repeated drug use in laboratory animals include the glutamate[198] and the cannabinoid[199,200] systems. However, so far there are no published studies with radiotracers to image these systems in human addiction.

See Supplementary information S7 (table) for an overview of studies comparing neurotransmitter systems between addicted individuals and healthy controls.

Box 3

Vulnerability and predisposition to drug use

Studies on how pre-morbid vulnerabilities — such as prenatal exposure to drugs, family history or selected gene polymorphisms and their interactions — impact prefrontal cortex (PFC) function are crucial for the design of future intervention and possibly prevention efforts; these studies highlight the importance of targeting clear biomarkers of vulnerability to drug use and addiction. For example, reduced absolute global cerebral blood flow (CBF) (–10%), and enhanced relative CBF in the dorsolateral PFC (DLPFC) (9%) and anterior cingulate cortex (ACC) (12%) were reported in adolescents with heavy prenatal cocaine exposure[201]. A hyperactive PFC was also reported in young users of MDMA[202], marijuana[203] or alcohol[204] during the go/no-go task, in which they performed normally (Supplementary information S6 (table)). Similarly, compared to control children and children who had alcoholic parents but were resilient, children who had alcoholic parents and were vulnerable to alcohol drinking (classified based on the level of problem drinking over the course of adolescence) had a hyperactive right dorsomedial PFC, while the bilateral orbitofrontal cortex (OFC) was hypoactive, despite a lack of behavioural differences when silently reading emotional words. Across the entire sample, such dorsomedial PFC hyperactivity was associated with more externalizing symptoms and with aggression[205] (Supplementary information S5(table)). Thus, such changes in PFC activity may be compensatory in the short-term (as evidenced by equal task performance), but in the long-term may promote substance abuse and addiction in these individuals, although this remains to be ascertained.

The mechanism that underlies such vulnerability to, or that confers protection against, developing addiction may involve altered dopaminergic neurotransmission. For example, striatal dopamine D2 receptor availability and regional PFC metabolism were higher in young, unaffected members of alcoholic families than in subjects without such family history, which is the opposite to results commonly reported in addicted individuals (BOX 2; see Supplementary information S7 (table))[206]. The individuals with a family history of alcohol abuse reported lower positive emotionality, and this was associated with both lower striatal dopamine D2 receptor availability and lower OFC metabolism. It is therefore possible that the higher dopamine D2 receptor availability and the enhanced metabolic activity in PFC in individuals with a family history of alcohol abuse increased the level of positive emotionality — although this nonetheless remained below the level in healthy controls — to levels that may have protected these individuals against developing addiction. It is also possible that optimal conditions are needed for the maintenance of such protection, and that suboptimal conditions (for example, chronic stress) could expose these same individuals to addiction later in life, but this remains to be determined in longitudinal studies. Other mechanisms, such as brain dysmorphology[207], may also be important in conferring vulnerability to addiction.

Genetic contributions to vulnerability to addiction are also important. For example, regular marijuana users with risk alleles of genes that encode the cannabinoid receptor 1 (CB1) or the fatty acid amino hydrolase 1 (FAAH; the enzyme that metabolizes endogenous cannabinoids) had greater drug-related cue reactivity in limbic PFC areas[208]. Importantly, such gene by environment interactions may be used to predict future disadvantageous behaviour. For example, 1-year increases in body mass of healthy adolescent girls could be predicted by activation of the lateral OFC induced by food-related cues, but only in carriers of the dopaminergic risk alleles dopamine receptor D4 (*DRD4*) 7-repeat allele or the *DRD2 TaqIA A1* allele[209]. Recent studies also suggest that interactions between certain polymorphisms and familial — including prenatal — drug exposure can influence OFC development[210,211]. For example, a recent study showed

that medial OFC (mOFC) grey matter volume was modulated by the monoamine oxydase A genotype, such that the low-activity variant of this gene drove the mOFC grey matter decreases in cocaine-addicted individuals[212], and this was correlated with longer lifetime cocaine use.

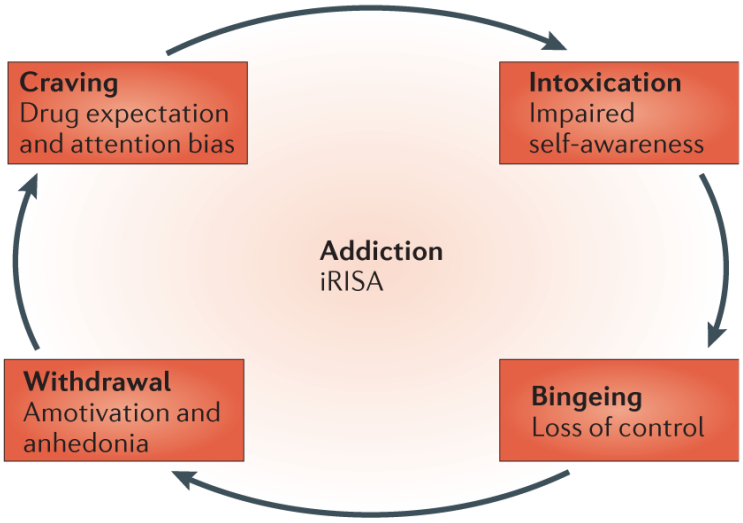

Figure 1. Behavioural manifestations of the iRISA syndrome of drug addiction

This figure shows the core clinical symptoms of drug addiction — intoxication, bingeing, withdrawal and craving — as behavioural manifestations of the impaired response inhibition and salience attribution (iRISA) syndrome. Drug self-administration may lead to intoxication, depending on the drug, amount and rate of use, and individual variables. Bingeing episodes develop with some drugs, such as crack cocaine, and drug use becomes compulsive — much more of the drug is consumed and for longer periods than intended — indicating reduced self-control. Other drugs (for example, nicotine and heroin) are associated with more regimented drug use. After discontinuation of excessive or repeated drug use, withdrawal symptoms develop, including lack of motivation, anhedonia, negative emotion and enhanced stress reactivity. Excessive craving or drug wanting, or other, more automatic processes such as attention bias and conditioned responses, can then pave the way to additional drug use even when the addicted individual is trying to abstain (see TABLE 1 for clinical characteristics of addiction in the context of iRISA and the role of the PFC in addiction). Figure is modified, with permission, from REF. 7 © (2002) American Psychiatric Association.

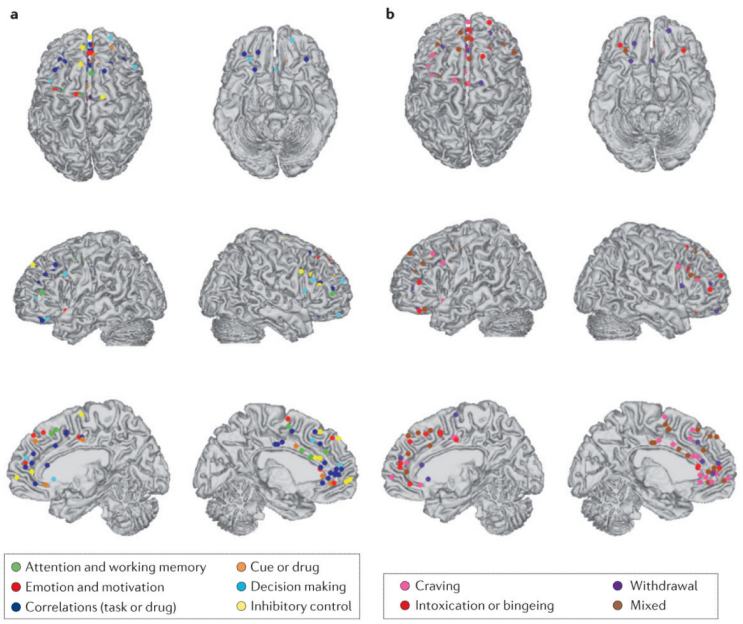

Figure 2. Recent neuroimaging studies of PFC activity in drug-addicted individuals

The areas of activation (measured using MRI, positron emission tomography (PET) or single-photon emission computed tomography (SPECT)) (Supplementary information S1 (table)) are plotted in stereotaxic space, shown rendered on the dorsal and ventral surfaces (top part) and the lateral and medial surfaces (middle part and bottom part, respectively) of the human brain. **a** | Activity changes related to neuropsychological features in addiction. Prefrontal cortex (PFC) areas show differences in activity between individuals with addiction and healthy controls during tasks involving attention and working memory (shown in green), decision making (shown in light blue), inhibitory control (shown in yellow), emotion and motivation (shown in red), and cue reactivity and drug administration (shown in orange). In addition, in some PFC areas activity correlates with task performance or drug use (shown in dark blue). **b** | Activity changes related to clinical features in addiction, including intoxication and bingeing (shown in red; drugs were used within 48 hours of the study), craving (shown in pink; drugs were used 1–2 weeks before the study) and withdrawal (shown in purple; drugs were used more than 3 weeks before the study). Areas that showed activation in studies in which the stage of addiction was not specified or could not be determined are also indicated (shown in brown). These are the same studies as those depicted in **a**. Studies were included only if *x*, *y* and *z* coordinates were provided and if these coordinates were within PFC grey matter; studies in which *x*, *y* and *z* coordinates could not be located or were incorrectly labelled were not included. All *x*, *y* and *z* coordinates were converted to Talairach space (using GingerAle, a Cross-platform Java application for Meta-Analysis) before plotting. The Multi-Level Kernel Density Analysis toolbox[213,214] was used (see the University of Colorado CANLab software Web site; see also Supplementary information S8 (figure)).

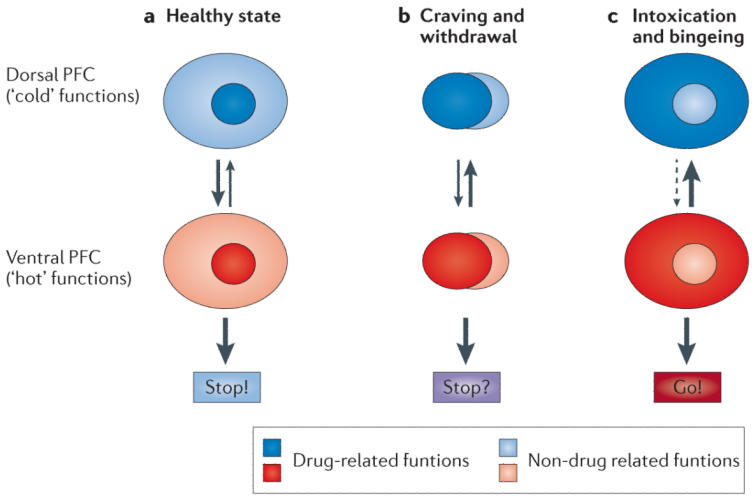

Figure 3. A model of PFC involvement in iRISA in addiction

A model of how interactions between prefrontal cortex (PFC) subregions may regulate cognitive, emotional and behavioural changes in addiction. The model shows how changes in the activity of PFC subregions in addicted individuals relate to core clinical symptoms of addiction — intoxication and bingeing, and withdrawal and craving — compared to PFC activity in healthy, non-addicted individuals or states. The model focuses particularly on inhibitory control and emotion regulation. The blue ovals represent dorsal PFC subregions (including the dorsolateral PFC (DLPFC), the dorsal anterior cingulate cortex (dACC) and the inferior frontal gyrus; see TABLE 1) that are involved in higher-order control ('cold' processes). The red ovals represent ventral PFC subregions (the medial orbitofrontal cortex (mOFC), the ventromedial PFC and rostroventral ACC) that are involved in more automatic, emotion-related processes ('hot' processes). Drug-related neuropsychological functions (for example, incentive salience, drug wanting, attention bias and drug seeking) that are regulated by these subregions are represented by darker shades and non-drug related functions (for example, sustained effort) are represented by lighter shades. **a** | In the healthy state, non-drug related cognitive functions, emotions and behaviours predominate (shown by the large light-coloured ovals) and automatic responses (emotions and action tendencies that could lead to drug taking) are suppressed by input from the dorsal PFC (shown by the thick arrow). Thus, if a person in the healthy state is exposed to drugs, excessive or inappropriate drug-taking behaviour is prevented or stopped ('Stop!'). **b** | During craving and withdrawal, drug-related cognitive functions, emotions and behaviours start to eclipse non-drug related functions, creating a conflict regarding drug taking ('Stop?'). Decreased attention and/or value is assigned to non-drug related stimuli (shown by smaller light-shaded ovals), and this reduction is associated with reduced self-control and with anhedonia, stress reactivity and anxiety. There is also an increase (shown by the larger dark-shaded ovals) in drug-biased cognition and cue-induced craving and drug wanting. **c** | During intoxication and bingeing, higher-order non-drug related cognitive functions (shown by the small light blue oval) are suppressed by increased input (shown by the thick arrow) from the regions that regulate drug-related, 'hot' functions (large dark red oval). That is, there is decreased input from higher-order cognitive control areas (shown by the thin dashed arrow), and the 'hot' regions come to dominate the higher-order cognitive input. Thus, attention narrows to focus on drug-related cues over all other reinforcers, impulsivity increases and basic emotions — such as fear, anger or love — are unleashed, depending on the context and individual predispositions. The result is that automatic, stimulus-driven behaviours, such as compulsive drug consumption, aggression and promiscuity, predominate ('Go!'). This model does not

take into account the challenge of localizing PFC functions or the evidence that some addicted individuals use drugs to ‘self-medicate’ in an attempt to normalize PFC functions (although part **a** could represent an approximation of the normalized PFC functions in these individuals).

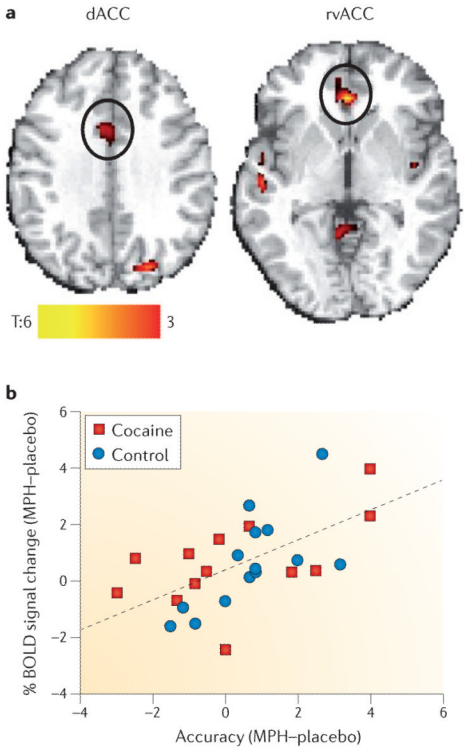

Figure 4. The effect of oral methylphenidate on anterior cingulate cortex activity and function in cocaine addiction

Methylphenidate enhances functional MRI cingulate responses and reduces commission errors on a salient (remunerated cue reactivity) cognitive task in individuals with cocaine addiction. **a** | An axial map of the cortical regions that showed enhanced responses to methylphenidate (MPH) compared to a placebo in cocaine-addicted individuals. These regions are the dorsal anterior cingulate cortex (dACC; Brodmann areas 24 and 32) and the rostroventromedial ACC (rvACC) extending to the medial orbitofrontal cortex (mOFC; Brodmann areas 10 and 32). The significance levels (T scores) of the activations are colour-coded (shown by the colour scale). **b** | Correlation between BOLD signal (presented as % signal change from placebo) in the rvACC extending to the mOFC ($x = –9$, $y = 42$, $z = –6$; Brodmann areas 10 and 32) during processing of drug-related words and accuracy on the fMRI task (both are delta scores: MPH minus placebo). The subjects are 13 individuals with cocaine use disorders and 14 healthy controls. Figure is reproduced, with permission, from REF. 215 © (2011) Macmillan Publishers Ltd. All rights reserved.

Table 1

Processes associated with the prefrontal cortex that are disrupted in addiction

Process	Possible disruption in addiction	Probable PFC region
Self-control and behavioural monitoring: response inhibition, behavioural coordination, conflict and error prediction, detection and resolution	Impulsivity, compulsivity, risk taking and impaired self-monitoring (habitual, automatic, stimulus-driven and inflexible behavioural patterns)	DLPFC, dACC, IFG and vlPFC
Emotion regulation: cognitive and affective suppression of emotion	Enhanced stress reactivity and inability to suppress emotional intensity (for example, anxiety and negative affect)	mOFC, vmPFC and subgenual ACC
Motivation: drive, initiative, persistence and effort towards the pursuit of goals	Enhanced motivation to procure drugs but decreased motivation for other goals, and compromised purposefulness and effort	OFC, ACC, vmPFC and DLPFC
Awareness and interoception: feeling one's own bodily and subjective state, insight	Reduced satiety, 'denial' of illness or need for treatment, and externally oriented thinking	rACC and dACC, mPFC, OFC and vlPFC
Attention and flexibility: set formation and maintenance versus set-shifting, and task switching	Attention bias towards drug-related stimuli and away from other stimuli and reinforcers, and inflexibility in goals to procure the drug	DLPFC, ACC, IFG and vlPFC
Working memory: short-term memory enabling the construction of representations and guidance of action	Formation of memory that is biased towards drug-related stimuli and away from alternatives	DLPFC
Learning and memory: stimulus–response associative learning, reversal learning, extinction, reward devaluation, latent inhibition (suppression of information) and long-term memory	Drug conditioning and disrupted ability to update the reward value of non-drug reinforcers	DLPFC, OFC and ACC
Decision making: valuation (coding reinforcers) versus choice, expected outcome, probability estimation, planning and goal formation	Drug-related anticipation, choice of immediate reward over delayed gratification, discounting of future consequences, and inaccurate predictions or action planning	lOFC, mOFC, vmPFC and DLPFC
Salience attribution: affective value appraisal, incentive salience and subjective utility (alternative outcomes)	Drugs and drug cues have a sensitized value, non-drug reinforcers are devalued and gradients are not perceived, and negative prediction error (actual experience worse than expected)	mOFC and vmPFC

Orbitofrontal cortex (OFC) includes Brodmann area (BA) 10–14 and 47 (REF. 216), and inferior and subgenual regions of anterior cingulate cortex (ACC) (BA 24, 25 and 32) in the ventromedial prefrontal cortex (vmPFC)[217]; ACC includes rostral ACC (rACC) and dorsal ACC (dACC) (BA 24 and 32, respectively), which are included within the medial PFC (mPFC). The mPFC also includes BA 6, 8, 9 and 10 (REF. 218); dorsolateral PFC (DLPFC) includes BA 6, 8, 9 and 46 (REF. 219); and the inferior frontal gyrus (IFG) and ventrolateral PFC (vlPFC) encompass inferior portions of BA 8, 44 and 45 (REF. 220). These various processes and regions participate to a different degree in craving, intoxication, bingeing and withdrawal. lOFC, lateral OFC; mOFC, medial OFC; PFC, prefrontal cortex.