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Role of Prefrontal Cortex Dopamine and Noradrenaline Circuitry in Addiction

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1. Introduction

Understanding the mechanisms of drug dependence has been the goal of a large number of neuroscientists, pharmacologists and clinicians who carried out research with the hope of individuating and proposing an efficacious therapy for this disorder (Sofuoglu, 2010; Kalivas and Volkow, 2011). Unfortunately, although huge efforts, drug dependence is still a relevant health, social and economical problem (Popova et al., 2012; Hiscock et al., 2011; Shorter and Kosten, 2011). Treatments for drug abuse are for the most part ineffective because the molecular and cellular mechanisms through which drugs of abuse alter neuronal circuitry are still unexplained and above all, because drugs of abuse determine a global alteration of cerebral functions that govern behaviour through decision formation, making therefore unfocused the identification of a pharmacological target (Volkow et al., 2011; Schultz 2011). One of the first strategies pursued in drug dependence therapy was directed to removal of pleasure associated with drug taking, but the compliance with the treatment has been always limited, although it could improve when it was supported by psychology based motivational therapy as in alcohol dependence (Krampe and Ehrenreich, 2010; Simkin and Grenoble, 2010). On the other hand it is not infrequent that heavy smokers or heavy drinkers stop suddenly dependence just because their will overcome year-long habits. Decision making is a process based on the interaction between prefrontal cortex (PFC) and subcortical regions involved in reward and motivation, therefore it is likely that failure in self-regulatory behavior, that is common in addicted subjects, could be dependent upon the alteration of interactions between the prefrontal cortex and subcortical regions (Heatherton and Wagner, 2011). In this chapter we will review the role of PFC in addiction with particular attention to dopamine and norepinephrine transmission.

2. Brief overview on the prefrontal cortex

The PFC has a prominent role in governing behavior. This function is achieved through a complex interaction of many different areas within the PFC which cooperate with subcortical areas integrating cognitive and executive functions to produce the "optimal choice". The result of this interaction can be also a deleterious one, as observed in drug

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addicted subjects. This interaction has been elegantly discussed by Kennerley and Walton (2011) by comparing the functional correspondence between neurophysiological and neuropsychological studies to help define the roles of different PFC areas in supporting optimal decision making. The following brief overview on PFC is not intended to be exhaustive, as far as regards discussion of cognitive and executive functions of sub areas of PFC, but it will address specific features of PFC areas in which catecholamine transmission plays relevant role in drug addiction.

Dopamine transmission in PFC is directly involved in cognitive processes (Seamans and Yang, 2004), in the regulation of emotions (Sullivan, 2004), in working memory (Khan and Muly 2011), as well as in executive functions such as motor planning, inhibitory response control and sustained attention (Fibiger and Phillips, 1988; Granon et al., 2000; Robbins, 2002). The association of PFC functions with impulse control is supported by the evidence that damage to the ventromedial PFC causes persistent motivational impulsivity associated with affective instability, reduced capability for decision making, poor executive planning and general apathy towards social life (Damasio et al., 1994). In general damage of PFC function in humans can therefore affect one or more of the above functions producing personal and social difficulties as observed in disorders such as Alzheimer's disease (Melrose et al., 2011), schizophrenia (Arnsten, 2011), and Parkinson's disease (Luft and Schwarz, 2009). Loss of PFC function can be also generated by traumas (Bechara and Van Der Linden, 2005), or can result from drug addiction (Koob and Volkow, 2010; Van den Oever et al., 2010). Moreover, PFC functional or anatomical abnormalities are frequently found in individuals with drug abuse disorders (Liu et al., 1998a and 1998b; Franklin et al., 2002) and at the same time PFC is thought to have an important role in the onset and in the progression of psychiatric disorders associated with poor decision making such as schizophrenia (Arnsten, 2004), attention deficit/hyperactivity disorder (ADHD) (Sullivan and Brake, 2003) and depression (Davidson et al., 2002). Also, clinical studies report that when traumatic brain injury damages the PFC it often facilitate the emergence of drug use disorders (Ommaya et al., 1996, Delmonico et al., 1998).

The knowledge on PFC functions in mammals has been accumulated through research on different species but anatomy differences between primates and rodents is object of discussion when comparing experimental evidence on PFC function. In particular the dorsolateral PFC of mammals is thought to be involved in working memory, in attention processes, in reasoning-based decision making and in the timing of behavioural organization (Curtis and Lee, 2010; Arnsten, 2011). The prominent role of PFC catecholamine transmission in motivation is also supported by its anatomical and functional connection with other important areas of the brain, such as the nucleus accumbens (NAcc) (Di Chiara et al., 2011), and the ventral tegmental area (Omelchenko and Sesack, 2007) (Fig. 1). Chambers et al. (2003) provided an interesting definition for the role of the PFC: - It plays a determining role in the representation, execution and inhibition of motivational drives by influencing patterns of neural ensemble firing in the NAcc and poor PFC function could increase the probability of performing inappropriate motivated drives viewed clinically as impulsive. This view may acquire increasing relevance by integrating it in a scenario in which neural transmission in the NAcc is considered a common molecular pathway for addiction (Nestler, 2005; Di Chiara et al., 2004). Furthermore, one of the primary outputs of the accumbens is the gabaergic innervation (Fig. 2) directed to the ventral pallidum that in turn innervate the mediodorsal thalamic nucleus by GABA neurons. Mediodorsal thalamus

in turn sends and excitatory output to the prelimbic and infralimbic PFC (O'Donnel et al., 1997). The PFC in primates receives the projection from the medio-dorsal nucleus of the thalamus that innervates the dorsolateral, medial and orbital cortices (Vertes, 2006) but in general, the thalamic innervation of PFC is a part of a loop which includes cortical thalamic glutamatergic excitatory projection that has a role in working memory (Watanabe and Funahashi, 2012) and is involved in the reward circuit (Haber and Knutoson, 2010).

Recent reviews suggest that the medial PFC in rat is functionally equivalent to the medial PFC of primates (Brown and Bowman 2002; Wilson et al. 2010). It has also been suggested that the rat PFC is not differentiated and therefore can subserve cognitive function localized in the dorsolateral PFC of primates as discussed elegantly by Brown and Bowman, (2002). These authors recognised that behavioural deficits following PFC damage in rats could reflect impaired behavioural flexibility similar to that reported in primates (De Bruin et al., 1994; Joel et al., 2005) and although the ability of shifting attention from one complex stimulus to another can be characterized by different abstraction level among different species, mammals could share executive processing mechanisms [selective attention, working memory, updating (manipulating the contents of working memory)] and rerouting attention (Shimamura, 2000; Brown and Bowman 2002). Due to the complexity of reciprocal neurotransmitter relationship in PFC, this chapter will mainly consider the role of dopamine and norepinephine in the PFC and their relationship with the effects of drugs of abuse and therapy of addiction. This choice is based on the important role of dopaminergic transmission in the effects of drugs of abuse and on the modulation of cognitive control (van Schouwenburg et al., 2010).

3. Dopamine in the prefrontal cortex: innervation, receptors and functions

The PFC receives multiple ascending innervations (Fig. 1 and Fig. 2). Whereas Acetylcholine (Ach) and serotonin (5-HT), contact widely all the subregions of PFC, dopamine innervations are more localized (e.g., prelimbic and infralimbic cortex) although they have a discrete grade of overlapping with norepinephrine innervation (Del Campo et al., 2011). The PFC is reciprocally connected with the VTA by dopaminergic afferents and glutamatergic efferents. Dopaminergic innervation of the PFC is predominantly provided by VTA dopamine cells sublocated in the parabrachialis pigmentosus nucleus which projects to cortical deep layers that contain the highest density of dopamine D1 and D2 receptors (Oades and Halliday, 1987). The main target of these innervations are the dendritic spines of pyramidal cells that project to GABA neurons of the NAcc which in turn complete a circuit by projecting back to VTA cells (Omelchenko and Sesack, 2007). A small population of PFC neurons that project to the VTA form synaptic contact with dopamine neurons that project onto the PFC, and a second population synapse onto GABA neurons that project to the nucleus accumbens, however no synaptic contact was found between PFC neurons and dopamine neurons that project to the NAcc (Carr and Sesack, 2000b). Lastly, to emphasize the complexity of the circuits in which the PFC is involved, it is important to underline that the majority of PFC terminals within the VTA area appear to target dopamine and GABA neurons that project onto target sites different from PFC and NAcc (Carr and Sesack, 2000a). Among them, some innervate ventral pallidum (Papp et al., 2012) and others, such as the putative gabaergic cells of the rostral linear nucleus that innervate the mediodorsal thalamic nucleus may have relevance in reward mechanism (Del Fava et al., 2007). Efferent

projections from VTA to hippocampus influence spatial working memory performance (Martig and Mizumori, 2011). Dopamine innervation of PFC is functionally inhibitory either by direct action on pyramidal cells or via GABA interneurons (Grobin, and Deutch, 1998) reducing glutamatergic excitatory output to NAcc and VTA. Therefore, an increase in dopamine stimulation of PFC conversely attenuates dopamine activity in striatal and limbic terminal regions (Karreman and Moghaddam, 1996) and attenuates the motor stimulatory effects of systemically administered stimulants such as amphetamine and cocaine (Karler et al., 1998).

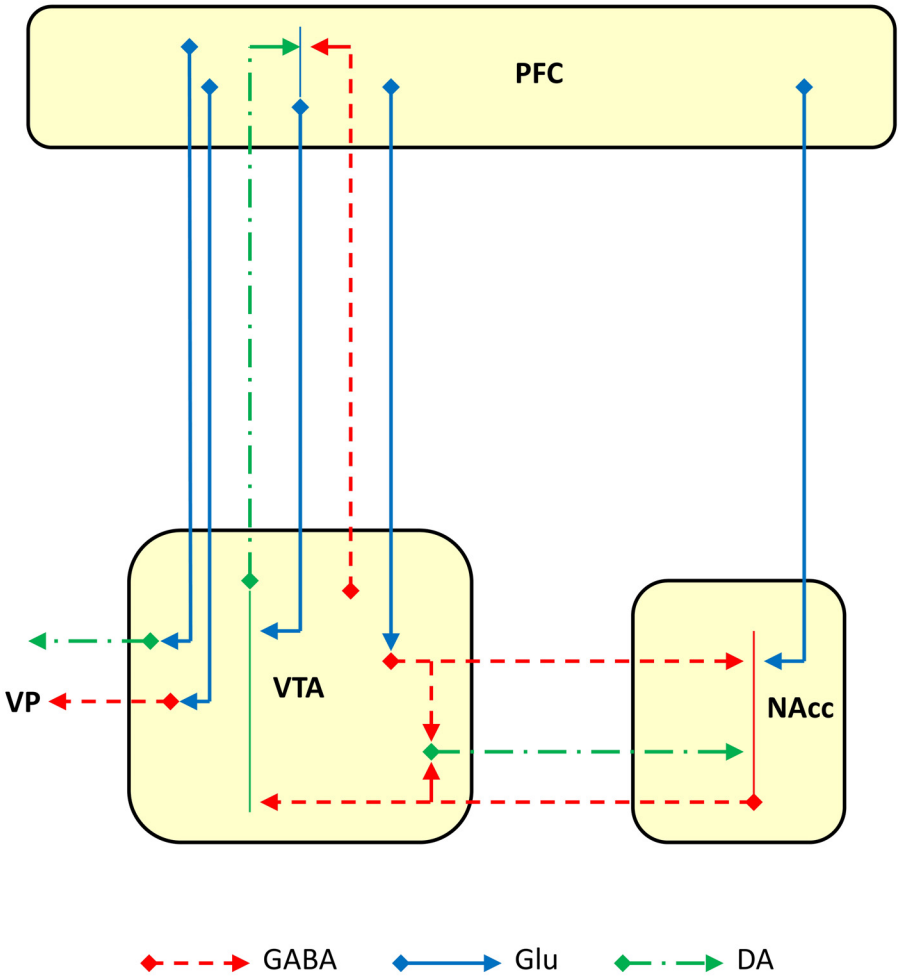

Fig. 1. Schematic representation of few major sites of interaction between prefrontal cortex (PFC) glutamate neurons, ventral tegmental area (VTA) dopamine and GABA neurons, and nucleus accumbens (NAcc) GABA neurons. Dendrites are occasionally represented for drawing clarity.

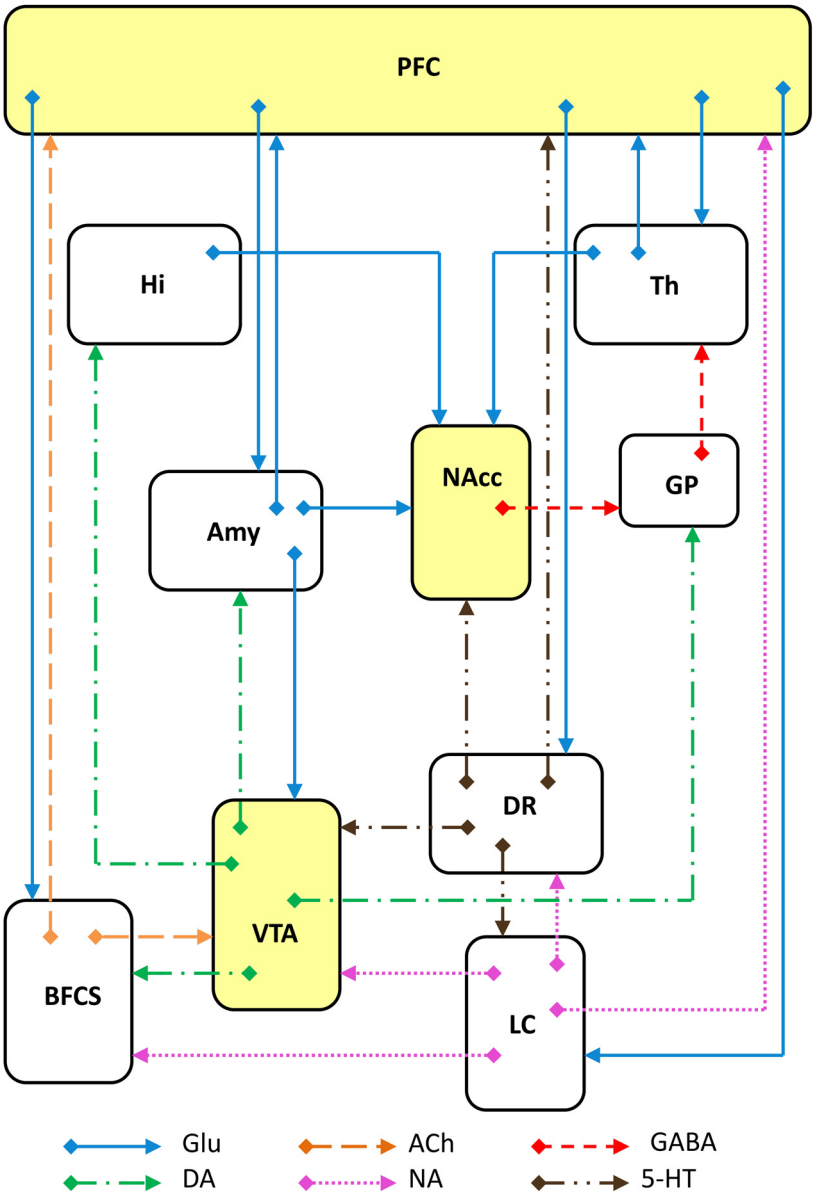

Fig. 2. Schematic representation of several major sites of interaction between prefrontal cortex (PFC) and thalamus (Th), hippocampus (Hi), amygdala (Amy), ventral tegmental area (VTA), dorsal raphe (DR), basal forebrain cholinergic system (BFCS), locus coeruleus (LC) globus pallidus (GP). Glutamate (Glu), Dopamine (DA), GABA, Acetylcholine (Ach), Norepinephrine (NA), and Serotonin (5-HT) neurons and axons are represented. The detailed connection represented in Fig. 1 have been omitted for drawing clarity.

Dopamine is a model of slow synaptic transmission; therefore it does not mediate fast synaptic transmission but instead modulates the response of other systems. The majority of D1 and D2 type receptors in the medial PFC appear to be located on pyramidal cells with the density of D2, apparently considerably lower than that of D1 (see the review by Tzschentke, 2001). Although both receptors are also present in GABAergic interneurons, the D4 subtype in particular (Ariano et al., 1997; Defagot et al., 1997a and 1997b) appears to be located on GABAergic interneurons rather than on pyramidal cells (Mrzljak et al., 1996). It is interesting to note that in the same postsynaptic pyramidal cell of the mPFC, dopaminergic terminals are localized in close opposition to each other with glutamatergic terminal originating in both the mediodorsal thalamus and the controlateral medial PFC. The former is not affected by VTA activation which instead inhibits the excitation of pyramidal cells generated by the input from recurrent collaterals of efferent glutamatergic output (Tzschentke, 2001). By acting on D1 receptors and through cAMP for the activation of cAMP sensitive protein kinase, dopamine determines an increase in the phosphorylation of DARP-32 and an inhibition of phosphatase 1 modulating mechanisms that involve ion channel and transcription factors (Greengard, 2001). D1 receptor optimal stimulation is essential to working memory process (Williams and Goldman-Rakic, 1995) and therefore either an increase or a decrease of the transmission leads to an inverted U response (Desimone, 1995). The involvement of dopamine activity through D1 receptor in cognitive function has a strong impact in schizophrenia research because of the importance of cognitive impairment in this disorder (Barch and Ceaser, 2012).

Although the result of dopamine interaction on pyramidal cells is complex and is influenced by a number of factors (e.g. dopamine concentration, receptor interaction, direct or indirect effect, depolarization status of the cells), dopamine generally, as also described in the previous paragraph, inhibits the activity of pyramidal cells in the medial PFC (see Tzschentke, 2001 for a review). The direct dopamine action on pyramidal cells (Geijo-Barrietos and Pastore, 1995; Gulledge and Jaffe, 1998) or the indirect action by a stimulation of the GABA interneurons may in turn inhibit pyramidal cells (Mercuri et al., 1985; Penit-Soria et al., 1987; Pirot et al., 1992). This latter action appears to be mediated through D2 receptors (Retaux et al., 1991; Grobin and Deutch, 1998). On the other hand, pyramidal cells respond more to NMDA stimulation through D1 receptors in the presence of a low concentration of dopamine, whereas a high concentration would instead reduce this response (Zheng et al., 1999) by acting through D2 receptors. The role of D1/5 receptor is also crucial in suppressing the sustained neuronal firing that takes place during working memory activity (Vijayraghavan et al., 2007). This property is displayed by D1/5 dopamine receptor agonists, which have been found to cause a decrease in extracellular glutamate in PFC in vivo (Abekawa et al. 2000; Harte and O'Connor 2004). Interestingly D1/5 dopamine receptor agonists are also effective in normalizing aberrant network activity induced by both hallucinogens and minimal GABAA antagonism, although clinical efficacy remains to be determined (Aghajanan, 2009). The close relationship between dopamine and glutamate is functionally expressed at NAcc level where medial PFC efferents terminate in close opposition to dopamine terminals originating in the VTA, often in the same spine of GABAergic accumbal cells (Bouyer et al, 1984; Sesack and Pickel, 1992). It is interesting to note that only about 30-40 % of the VTA projection to PFC is dopaminergic, while the rest is likely to be an inhibitory GABAergic innervation (Carr and Sesack 2000a). Of further relevance is that PFC glutamate innervations of the NAcc is part of the motivational circuit

completed by accumbal GABA neurons projecting onto the ventral globus pallidus, by pallidal GABA neurons that project to the thalamus and lastly by thalamic glutamate neurons that project back to the PFC (see Chambers et al., 2003, for a review). Hence, PFC and NAcc work together to produce a behavioral output resulting from brain activity that processes input information concerning the internal status of the individual and the external environment (Dorman and Gaudiano, 1998). Considering that firing patterns in both the NAcc and PFC are influenced by glutamatergic input from the hippocampus and amygdala (Aggleton, 2011; Miller et al., 2010), it may be suggested that abnormalities in these distal structures may produce both psychiatric disorders as well as higher vulnerability to drug addiction (Chambers et al., 2001). As far as regards dopamine transmission in the PFC it is necessary to remind that dopamine could be captured by norepinephrine reuptake system (Carboni et al., 1990; Carboni et al., 2006)

4. Noradrenaline in the prefrontal cortex: Innervation, receptors and interactions

The long established observation that catecholamine depletion in PFC can be considered as destructive as tissue ablation (Brozoski et al., 1979) confirms the prominent role of catecholamine innervation in the PFC. The noradrenergic system that originates in the locus coeruleus and in other small nuclei in the medulla and the pons has the peculiar feature of projecting onto the entire neuraxis, although it originates in a relatively small group of cells. This extensive, irradiating anatomical arrangement allows the noradrenergic system to potentially influence all brain activity. In particular, noradrenaline innervations of PFC depend on neurons located in the locus coeruleus (Foote et al., 1983; Bjorklund and Lindvall, 1986) that project to dendrites of both pyramidal cells and interneurons. An interesting feature of locus coeruleus noradrenergic innervation of the cerebral cortex is that individual locus coeruleus neurons simultaneously innervate functionally and cyto-architectonically distinct cortical regions. In fact, locus coeruleus neurons arborize more extensively in the anterior-to-posterior axis of the cortex and exhibit relatively minimal medial-to-lateral collateralization (Swanson, 1976; Aoki et al., 1998). Individual locus coeruleus cells were also shown to innervate both superficial and deep layers of a cortical region (Loughlin et al., 1982). Furthermore, the PFC projects back to the locus coeruleus thereby completing a circuitry which plays a role in relevant brain activity, i.e. maintaining vigilance (reviewed by Aston Jones, 1985) or modulating the behavioural response to stress (Morilak et. al., 2005). Functionally, the noradrenergic system can be viewed as a modulatory system because it can increase the "signal to noise ratio" of responses evoked by other neurotransmitters that excite or inhibit target cells (Woodward et al., 1991). Modulatory actions of this type can be mediated through either α or β noradrenergic receptors (Waterhouse et al., 1991; Woodward et al., 1991). This modulatory type action is also supported by the fact that in the monkey PFC noradrenaline produces its effects predominantly through α2A adrenoceptors that occur in spines, localized discretely over postsynaptic membranes that are most likely PFC pyramidal cells (Aoki et al., 1998). Yet α2A receptors are most prevalent along axons, and are found also in dendritic shafts and astrocytic processes that lack evident synaptic junction. This suggests that these receptors are activated by volume transmission (Aoki et al., 1998). In particular, axonal α2A adrenoceptors have a pre-terminal location; by closing voltage dependent Ca^{++} channels, they are probably able to reduce neurotransmitter release such as serotonin as well as noradrenaline release (Frankhuyzen and Mulder, 1980; Maura et al., 1982).

Moreover, it appears that noradrenaline receptors with different affinities may mediate responses triggered by different extracellular concentrations of this transmitter. As reviewed by Arnsten (2007), moderate levels of noradrenaline released during waking act on high affinity α2A adrenoceptors coupled with Gi proteins to inhibit cAMP signalling, whereas higher levels released during stress not only activate lower affinity β1 coupled to phosphatidyl inositol signalling but also low affinity β1 adrenoceptors coupled to Gs, to increase cAMP signalling (Arnsten, 2000). In general, the role of noradrenaline in the PFC can be seen as being an inhibitory action with a long onset and protracted effect, and can be defined as being neuromodulatory. By inhibiting ongoing background discharge, noradrenaline produces an increase in the signal–to-noise ratio that helps to filter irrelevant stimuli while enhancing behaviorally significant stimuli (Bjorklund and Lindvall, 1986). According to this view NA is crucial for many PFC functions mediated by α2A post synaptic adrenoceptors, such as working memory, attention regulation, planning and behavioural inhibition as suggested by experimental research on various mammals (Arnsten, 2006 and 2009).

Catecholamine transmission in PFC is also dependent on the location of receptors in the dendritic tree of pyramidal cells and may occur through both α2A adrenoceptors increasing delay-related firing for the preferred spatial direction or through D1 receptor decreasing delay-related firing for the nonpreferred direction (Vijayraghavan et al., 2007). Catecholamine transmission is thus essential for reducing the effect of distracting stimulus, or "noise" (Miller et al., 1996) and inhibiting inappropriate behaviours (Funahashi et al., 1993 Arnsten, 2007). More recent data have indicated that both D1 and α2A adrenoceptors can either stimulate or reduce cAMP production respectively, i.e. may increase or reduce the probability of hyperpolarization-activated cyclic nucleotide gated cation channels opening (HCN) (Arnsten, 2007). Moreover, dopamine and NA can inhibit GABA interneurons in the PFC via D4 receptors for which noradrenaline has a high affinity (Wang et al., 2002).

5. Addiction and prefrontal cortex function: Similarities and differences between humans and other mammals

Addiction is the result of numerous factors and the PFC circuitry contributes to the expression of several behaviours that are associated with addiction (Goldstein and Volkow, 2011; Heatherton and Wagner, 2011, George and Koob, 2010). A large majority of addicted subjects do not seek treatment, likely because they do not even recognize their condition as a disease that requires a therapeutic intervention (Goldstein et al. 2009). This condition is probably generated by viewing the abused substance as an essential ingredient of their life, regardless of the consequences of its use. The knowledge of mPFC role in drug dependence can be improved comparing the results of studies performed in animals with those performed in humans although the complexity of addiction behaviour suggests attention in comparing directly specific components of drug dependence (i.e. chronic drug exposure, drug abstinence, drug seeking, cue or drug induced relapse and stress induced relapse). Indeed, if drug addiction in humans can be considered a disorder of self-control because the reinforcing properties of drugs of abuse prevail on the conscious awareness of the negative consequences of addiction behaviour (Heatherton and Wagner, 2011), in animals drug self-administration is supported mostly by the direct rewarding property of the drug (see O'Connor et al. 2011 for a critical evaluation). Therefore, if a man is conscious of the risk

associated with drug taking either as far as regards legal or health or social consequences, the same cannot apply to monkeys or rats.

A second important difference among humans and animals deals with the beginning of drug taking. In man it is often the consequence of a complex psychological motivation in which expectations is a strong component (Berridge et al., 2009) while it is often a passive outcome in animals. Moreover, the consequences of drug taking may vary substantially depending on the age of the first experience. In fact drug taking can be started in adolescence, or at adult age and the consequences can be very different because the incomplete brain maturation at adolescence age can offer a fertile ground to the strong reinforcing properties of drugs of abuse (Casey and Jones, 2010). On the other hand, at adult age drug taking can be started to react to a stressful situation and although it may have multiple origin, it may offer again a common fertile ground because the altered status of brain circuitry. Now, if drug taking produces relevant changes in the mPFC of humans and animals, those changes are produced upon a rather different brain circuitry status and therefore the intrinsic rewarding effects in humans can be basically different from those produced in other mammals. When a drug of abuse is administered to animals, the effects observed are those produced on a brain circuitry ensemble that is in a balanced basal condition (unless specific treatments have been applied previously), therefore a great caution should be taken comparing those results to men.

6. Drugs of abuse: Acute effects on prefrontal cortex dopamine and noradrenaline transmission

Substantial evidence confirms the direct involvement of mPFC in addiction. Firing of mPFC neurons is strictly related to i.v. injections of cocaine and heroin (Chang et al., 1998), whereas 6-OH dopamine lesions of mPFC enhance cocaine self-administration (Schenk et al., 1991) and excitotoxic lesions of mPFC determine facilitation of cocaine self-administration (Weissenborn et al., 1997). In particular mPFC has a critical role in drug seeking, craving and relapse either triggered by drugs or by stress or cues associated with drug taking either in humans or in animals (Kalivas et al, 2005; Kalivas and Volkow, 2005). Moreover image studies allowed to observe a reduction in blood flow and cellular metabolism in dorsal PFC of individuals who abused psychostimulants and opioids (Daglish et al., 2001; Bolla et al., 2003; Adinoff et al., 2012). On the contrary an increase has been observed when addicts are exposed to drug-associated cues (Goldstein and Volkow, 2002; Langleben et al., 2008). Nevertheless a reduction in blood flow and cellular metabolism in ventral PFC has been observed in cocaine abusers upon exposition to cocaine related cues (Bonson et al., 2002). Taken together these data support the view that drug addiction increases the motivational value of drug-associated cues while, most likely, negatively affects the function of mPFC in reducing the value of natural reinforcers (see Van den Oever et al., 2010).

Nevertheless, although the dorsal mPFC is critically involved in reinstatement of drug seeking behaviour after abstinence (Berglind et al., 2007) pharmacological inactivation of the dorsal mPFC had no effect on cocaine seeking induced by cocaine cues (Koya et al., 2009). Psychostimulants and other drugs that block dopamine or noradrenaline carrier increase directly extracellular concentration of these catecholamine in all brain areas innervated by dopamine and noradrenaline neurons (Carboni et al., 1989; Tanda et al., 1997; Carboni et al.,

1990; Carboni et al., 2006) including the PFC. The increase in dopamine extracellular concentration can determine the inhibition of the firing of dopamine neurons through an action on D2 auto-receptors and in turn increase K^+ conductance at cell body level (Mercuri et al., 1992). The simultaneous reduction of firing and increase of transmitter extracellular concentration at terminal level produced by psychostimulants and cocaine on catecholamine transmission in the mPFC cortex and other brain areas determines a complex effect on cognition, attention and learning circuitry. Indeed either an increase or a decrease in dopamine transmission in the mPFC may lead to dysfunctions in the ability to inhibit inappropriate actions or thoughts (Arnsten and Li, 2005).

Investigations on the effects of non-psychostimulants substances of abuse on dopamine and norepinephrine transmission in the rat PFC have produced disaccording results. Devoto et al., (2002) have found that acute morphine reduced extracellular norepinephrine, and failed to modify extracellular dopamine level in the mPFC whereas the administration of naloxone, in morphine dependent rats, precipitated a typical abstinence syndrome associated with a concomitant dramatic increase of extracellular dopamine and noreadrenaline (by about 200 and 100%, respectively) in the PFC. The direct role of norepinephrine transmission in the effects of morphine was demonstrated by the alpha(2)-adrenoceptor agonist clonidine that suppressed naloxone-precipitated abstinence symptoms and brought both noradrenaline and dopamine output in PFC to less than 50 % of basal levels (Devoto et al., 2002). In contrast it has been reported that morphine enhances norepinephrine and dopamine release in the mPFC and that norepinephrine transmission is necessary for morphine rewarding effects, reinstatement and mesoaccumbens dopamine release (Ventura et al., 2005). More recently it was found that the released levels of dopamine and its major metabolites in the anterior cingulate cortex were increased by either the electrical stimulation of VTA neurons or by microinjection of a selective μ-opioid receptor agonist, (D-Ala^2,N-MePhe^4,Gly^5-ol) enkephalin (DAMGO), into the VTA (Narita et al., 2010).

The ability of nicotine to stimulate dopamine and norepinephrine release in the mPFC has been also investigated to assess the involvement of PFC circuitry in the addiction mechanism of nicotine and to explore the potential of modulation of this transmission for cognition enhancement. At this regard Livingstone et al., (2010) reported that a selective alpha7 nicotinic acetylcholine receptors (nAChRs) agonist evoked dopamine overflow in the prefrontal cortex in vivo, and this effect was potentiated by PNU-120596, an allosteric modulator of alpha7 nACh receptor. Moreover, antagonists of NMDA and AMPA receptors blocked [^{3}H]dopamine release from tissue prisms in vitro. On these bases the authors proposed that alpha7 nAChRs were present on glutamate terminals and could increase glutamate release that in turn coordinately could enhances dopamine release from neighboring buttons.

The effect of other drugs of abuse such ethanol and cannabinoids on dopamine and noradrenaline transmission in the PFC received less attention although the effects of these drugs on cognition and mental health are well known. It has been found that posterior VTA dopamine neurons projecting to the ventral pallidum and mPFC are stimulated by local administration of ethanol and that these stimulating effects are mediated, at least in part, by 5-HT(3)receptors (Ding et al., 2011). The presence of cannabinoid receptors in the PFC has been shown by neuroanatomical data suggesting that cortical norepinephrine release may

be modulated, in part, by CB1 receptors that are presynaptically distributed on noradrenergic axon terminals (Oropeza et al., 2006). Moreover, repeated treatment with delta-9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, or WIN 55,212-2 (WIN), a synthetic cannabinoid receptor agonist caused a persistent and selective reduction in mPFC dopamine turnover (Verrico et al., 2003). Thereby these evidences suggest that dopamine and norepinephrine transmission in the PFC are involved in the effects of many drugs of abuse, although their precise role is far to be clarified.

7. Abstinence, dopamine and noradrenaline transmission in the PFC

Although the intrinsic meaning of abstinence, as far as regards drug addiction, is referred to a drug free condition, the status of PFC during abstinence may vary depending on the time interval elapsed from the interruption of drug use. Abrupt drug removal can produce a rather similar abstinence syndrome as both men and rats will experience a neuro-physiological adaptation to drug absence. This effect cannot be trivial considering the strong impact of drug effects on brain. Nevertheless once the acute abstinence has been overtaken, strong differences may be found between men and other mammals, in particular when abstinence is generated by a gradual quitting process in humans or extinction process in animals as in self-administration experiments. For instance, in these experiments, upon removal of the reinforcing drug, rats will soon experience the absence of drug effect. This condition will initially generate an enhanced activity at the operant administration mechanism (e.g. lever pressing, nose poke etc.) that will be followed by a reduction because operant activity becomes emptied of pleasurable consequences. This condition will activate a parsimonious process that drives rat behaviour to ignore the ineffective lever pressing with a come back to the routine cage activity. Thus, drug disappearance can be view as an uncontrollable variable and it is likely that rats will not go through the experience of choosing whether or not going back to the drug. Therefore, although it is hard to appraise in rats the role of memories associated with drug administration, we can suggest that medial PFC circuitry will respond to drug removal through adapting progressive changes, thus generating the relative abstinence condition.

On the other hand in man, abstinence is a multiple component condition in which the lack drug effects is strictly associated with an internal struggle between the desire of the reward associated with drug taking and the evaluation of the consequences of that behaviour in terms of money, social life and health involvement (e.g. smoking, cocaine use). It is therefore likely that mPFC circuitry response to abstinence in man will be unique, although it is obviously dependent on the abused drug and on plenty of other environmental factors such as recreational habits, family or economic problems or other stress related conditions. Therefore, craving for drugs is characterized in animals by an initial stereotyped search for drug, that ends relatively quickly with the reaching of a relatively stable brain circuitry equilibrium. Instead in man, mPFC brain circuitry reaches only a pseudo-equilibrium to which contribute the lack of drug effects and its desire (in common with animals), together with of the effort of self-controlling environmental stimuli that often were those that generated drug addiction. In this scenario the result of the exposition to cues associated with drug taking can trigger relapse either in animals or humans, but again involvement of mPFC circuitry can be completely different. The role of PFC in extinction has been recently investigated in humans and animals though the circuitry involved is poorly understood (See the recent review by Millan et al., 2011).

Here we will briefly discuss mPFC changes related to immediate abstinence generated from drug withdrawal. For instance interruption of nicotine exposure in humans, determines a rather fast appearance of withdrawal syndrome that is characterized by depressed mood, irritability, mild cognitive deficits accompanied by other peripheral physiological symptoms (Shiffman et al., 2004). We observed that either mecamylamine or naloxone determine the precipitation of an abstinence syndrome in rats carrying an osmotic minipump that continuously delivers nicotine (Carboni et al., 2000). This syndrome was characterized by physical abstinence signs appearing to be dissociated from dopamine extracellular concentration. Mecamylamine decreased dopamine in the NAcc while increasing it the mPFC whereas naloxone did not (Carboni et al., 2000). Interestingly withdrawal from a schedule of increasing doses of morphine or the administration of naloxone determined an increase in the extracellular concentration of dopamine mPFC (Bassareo et al., 1995). Preclinical research in animal models have also shown that early nicotine withdrawal is characterized by decreased function of presynaptic inhibitory metabotropic glutamate 2/3 receptors (Markou, 2008). At the same time it has been observed an increased expression of postsynaptic glutamate receptor subunits in limbic and frontal brain sites. This increase may explain why a protracted abstinence may be associated with increased glutamate response to stimuli associated with nicotine administration (as reviewed by Markou, 2008).

As far as regards cocaine addiction it has been reported (Kalivas et al., 2005) that enhanced D1 activity would lead to an increased inhibitory state of the PFC during withdrawal, so that only particularly strong stimuli, such as those associated with drug consumption, would be able to activate and guide behaviour. Moreover repeated cocaine administration change functional properties of the D1 receptors in the PFC through an enhancement of the activity of the G protein signalling 3 (AGS3), coupled to D1 receptors, whereas the G protein activity coupled to D2 was reduced following cocaine withdrawal (Bowers et al., 2004). These alterations in the mPFC may determine alteration of prefrontal glutamatergic innervation of the accumbens promoting the compulsive character of drug seeking in addicts by decreasing the value of natural rewards, diminishing cognitive control (choice), and enhancing glutamatergic drive in response to drug-associated stimuli.

8. Relapse, dopamine and noradrenaline transmission in the prefrontal cortex

The relapse to drug use is a major problem in drug addiction therapy. Essentially, relapse can be categorized in three major types: drug induced relapse, reinstatement of self-administration behaviour upon exposition to drug related cues and stress induced relapse (Stewart, 2003; Crombag et al., 2008; Van den Oever et al., 2010). Drug-induced relapse could be associated with similar processes in humans and animals and will determine the resumption of drug intake behaviour, whereas cue-induced relapse may engage different brain circuitry depending on the involvement of self-control mechanisms. If a rat will just start pressing a lever, a man, who probably went through a strong involving process to achieve drug taking interruption, will go through a complex decision making process (e.g. a man will evaluate the strong effect of the cue and only when self control processes will be defeated will resume drug taking; alternatively he can resume drug taking without craving, or even he can rationally decide to take the drug because he has the conviction to be able to control drug taking). Thus, it is likely that reinstatement in man involves a more complex mPFC circuitry than in other mammals. Nevertheless one of the major determinants of reinstatement to cocaine use among human addicts is acute re-exposure to the drug, which

often precipitates cocaine craving and relapse (Cromabag et al., 2008; Volkow et al., 2010). As far as regards animal studies, it has been reported that the mPFC plays a major role during reinstatement, either because its direct role in cognition or because its connections with subcortical areas (Kalivas et al., 2005; Crombag et al., 2008; Van den Oever et al., 2010). Projections from the mPFC to the NAcc are stratified in a dorso-ventral pattern with the dorsal mPFC projecting predominantly to the NAcc core and the ventral mPFC projecting to the NAcc shell (Heidbreder and Groenewegen, 2003; Voorn et al., 2004). These anatomical features have been used to assume that during reinstatement the increase in extracellular glutamate in the NAcc core is associated with an increased excitatory activity of pyramidal neurons of dorsal mPFC that in turn may drive heroin (LaLumiere and Kalivas, 2008) or cocaine seeking behaviour in rats (Mac Farland et al., 2003).

On the other hand, glutamatergic projections from the ventral mPFC to the NAcc shell have been found to suppress conditioned drug seeking after extinction learning (Peters et al., 2009) whereas interruption of this neuronal link or pharmacological inactivation of the NAcc shell produce resumption of drug craving (Peters et al., 2008; Fuchs et al., 2008). At this regard it has been proposed that the mPFC regulates the expression of both fear and drug memories after extinction, through divergent projections to the amygdala and nucleus accumbens, respectively. Therefore a common neural circuit for extinction of fear and drug memories would suggest shared mechanisms and treatment strategies across both domains (Peters et al., 2009). These experimental evidences support the view of mPFC neurons controlling drug craving whereas its suppression may occur through two separate but balanced pathways by acting directly in the two NAcc sub-regions. This view has been contradicted by numerous studies (for a review see Van den Oever et al., 2010) and therefore it can be suggested that drug dependence in rats cannot be the product of a single neuronal pathway

VTA dopaminergic neurons that innervate the dorsal mPFC have been reported to be involved in the initiation of drug seeking responses (for a review see Crombag et al., 2008 and Van den Over et al., 2010). In particular dopamine administration into the dorsal mPFC has been shown to be sufficient to elicit a reinstatement of self-administration behavior (McFarland and Kalivas, 2001), whereas microinjections of the D1/D2 antagonist fluphenazine into the dorsal PFC but not into the NAcc core or ventral pallidum, prevented cocaine induced reinstatement (McFarland and Kalivas 2001). A role for dopamine transmission in reinstatement is also supported by the findings of Park and coworkers (Park et al., 2002). These authors showed that intra-mPFC administration of the dopamine antagonist flupentixol blocked cocaine reinstatement triggered by systemic cocaine administration in rats that were first trained to self-administer cocaine intravenously and later underwent through extinction by substitution of cocaine (i.v.) with saline (Park et al., 2002). These authors also showed that reinstatement of cocaine seeking behavior could be induced by intra-mPFC cocaine and could be blocked by local administration of the AMPA receptor antagonist CNQX into NAcc shell or the border with the core (Park et al., 2002). Interestingly, it has been recently reported that the infralimbic mPFC, and specifically its glutamatergic and beta-adrenergic systems, regulates the consolidation of extinction of cocaine self-administration. Therefore the transmission at level of infralimbic cortex can be manipulated to influence the retention of extinction (LaLumiere and Kalivas, 2008).

Moreover, a role for dopamine transmission in the mPFC has been also proposed in cue and in stress induced reinstatement of self-administration behavior. In fact intracranial infusion

of the dopamine D1 receptor antagonist, SCH 23390 into the prelimbic cortex potently, and dose dependently, attenuated heroin-seeking in response to either cue presentations or a priming dose of heroin, confirming that dopamine D1 receptors regulate prefrontal cortex pathways necessary for the reinstatement of heroin-seeking in rats (See, 2009). In addition systemic blockade of D1 receptors prevents an increase in Fos expression in the dorsal mPFC (Ciccocioppo et al., 2001) suggesting an increase in dopamine transmission in this area during reinstatement. Moreover the role of the mPFC and in particular the involvement of dopamine transmission in stress induced reinstatement of cocaine seeking have been investigated in rats (Capriles et al., 2003). These authors have shown that inactivation of prelimbic cortex by tetrodotoxin blocked reinstatement of cocaine seeking induced by either foot shock or by cocaine priming, whereas the effects of tetrodotoxin injections in the orbitofrontal cortex (OFC) were mixed. Moreover, Capriles and coworkers found that infusion of the D1 dopamine antagonist SCH23390 into either the prelimbic or into the OFC blocked foot-shock induced reinstatement. These results suggest that the prelimbic and the orbitofrontal cortices form part of the circuitry mediating the effects of foot shock stress in reinstatement of drug seeking and that the prelimbic region may be a common pathway for cue, drug and foot-shock stress-induced reinstatement of drug seeking (Capriles et al., 2003). Nevertheless, the dichotomy in mPFC function, attributing to dorsal mPFC (prelimbic, cingulate subregions) promotion of drug seeking and to ventral mPFC (infralimbic) inhibition of drug seeking in cocaine-experienced rats (Peters et al., 2009), has been challenged by studies on heroin self-administration suggesting that heroin seeking is promoted by a minority of selectively activated ventral mPFC neurons (Bossert et al., 2011). These authors thus suggested that different brain mechanisms mediate heroin and cocaine relapse in the rat model.

9. Genetic variation, catecholamine transmission in the prefrontal cortex and predisposition to addictions

Dopamine neurons projecting to the PFC possess an interesting feature as compared with other systems. In fact they have a higher baseline rate firing and a higher rate of dopamine turnover. This feature renders them very sensitive to alteration in dopamine synthesis and metabolism either underlained by gene variation or induced by drugs of abuse (Bannon et al., 1981; Hallman, 1984; Garris et al., 1993; Garris and Wightman, 1994; Cass and Gerhardt, 1995). Improved performances in cognitive tasks requiring working memory and inhibition have been observed in subjects that carry variations in the catechol-O-methyltransferase (COMT) gene (Dumontheil et al., 2011). COMT degrades the catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine. A functional polymorphism in the COMT gene (val^{158}met) accounts for a four-fold variation in enzyme activity (Heinz and Smolka, 2006). The low activity met^{158} allele causes approximately 75 % reduction in dopamine methylation and increased dopamine function. This has been associated with improved working memory, executive functioning, and attention control, but is also linked to a higher risk of anxiety-related behaviours. The latter, in turn, may be related to an excessive activation of the HPA axis and relative responses due to elevated noradrenaline transmission in the PFC (Heinz and Smolka, 2006). On the other hand, limbic and prefrontal activation elicited by unpleasant stimuli in subjects with more met^{158} alleles might contribute to the observed lower emotional resilience against negative mood states (Smolka, et al., 2005). The increase in dopamine function is particularly relevant in areas such as the prefrontal cortex because it contains significantly less dopamine transporter (Sesack et al.,

1998; Lammel et al., 2008), and because dopamine clearance (approx. 60 %) is carried out by the COMT enzyme, unlike in other dopamine areas such as the striatum where dopamine is cleared promptly by the reuptake system (Karoum et al., 1994).

Furthermore, Adele Diamond (2007) makes an interesting observation on the difference found between males and females. COMT activity in females is in fact roughly 30 % lower, due probably to estrogen activity (Cohn and Axelrod, 1971; Boudikova et al., 1990). This gender variation may render females able to better perform cognitive tasks because of the more elevated dopamine function in the PFC whereas they perform worse under even minor stress. On the other hand there is also substantial evidence that males perform better or no worse if slightly stressed (Shors and Miesegaes, 2002; Shors and Leuner, 2003; Shansky et al., 2004). This observation fits well with the above reported characteristics of the PFC dopamine function being highly sensitive to stress (Thierry et al., 1972; Reinhard et al., 1982; Roth et al., 1988; Deutch and Roth, 1990; Arnsten and Goldman-Rakic 1998; Arnsten, 1999 and 2000). Thus, as reported by Diamond (2007), cognitive functioning in men would benefit from the expression of COMT variation with reduced activity whereas females would instead benefit from the expression of a faster-acting valine version of the COMT enzyme that would moderate excess dopamine functioning in the PFC. Altered activity of COMT, which has a primary role in the degradation of dopamine in the frontal cortex (Karoum et al., 1994), might thus also be involved in the magnification of the reinforcing properties of drugs of abuse. Considering that the increase of extracellular dopamine and norepinephrine in PFC is a peculiar effect of drugs such as amphetamine and cocaine one can wonder if subjects that carry variations in the catechol-O-methyltransferase (COMT) gene are predisposed to psychostimulant addiction. Genetic studies suggest that while occasional use of drugs of abuse is predominantly linked to environmental or familiar factors, over 60 % of the cocaine users inherited their vulnerability to heavy use and dependence (Kendler et al., 2000; Kendler and Prescott, 1998).

Nevertheless there are no convincing studies that correlate cocaine addiction with variation of genes related to dopaminergic system such as the genes DRD2, COMT, SLC6A3 (coding for the dopamine transporter DAT) and DBH (coding for the dopamine beta hydroxylase). However an interesting hypothesis (Brousse et al., 2010) suggested that individuals carrying genetic variation of the DBH gene, that has particularly been linked with the psychotic effects caused by cocaine, could be predisposed to cocaine-induced psychosis making the development of cocaine addiction less probable. This can also apply to mutations of the Val158Met of the gene COMT, TaqI A of the gene DRD2 and VNTR 9 repeat of the DAT. On the other hand Hosak et al., (2006) found that consumers of methamphetamine carrying the Met allele of the COMT gene Val158Met polymorphism showed higher novelty seeking scores. This polymorphism is associated with low COMT enzyme activity and high endogenous dopamine synaptic levels in the PFC. According to the authors this leads to a decrease in dopaminergic neurotransmission in the NAcc and a need to stimulate it through novelty seeking behaviour or psychostimulant use.

10. Prefrontal cortex dopamine transmission in adolescence and drug addiction

Adolescence (see chapter XX) is a crucial developmental period of life in which physical and psychological remarkable changes occurring after puberty, model the personality to allow

the assumption of adult roles and responsibilities (Dahl, 2004a and 2004b; Steinberg, 2008). In this scenario PFC represents a crucial brain area because its function in expressing a specific behaviour. This may be the outcome of multiple interactions such as those between the hormonal triggered desires, and the representation of increasingly complex and distant social goals. The shaping of this objective in turn will be influenced by the social and family environment. Therefore the maturation of PFC occurring in adolescence may definitively shape the adult personality and at the same time, dysfunctions happening in this process may constitute a milieu necessary and often sufficient for developing psychiatric disorders such as schizophrenia and depression or for predisposing individuals to a high vulnerability to drug addiction (see Davey, et al., 2008).

The PFC has a prominent role in controlling impulsiveness (Fineberg et al., 2010) and in adolescence it is likely that this control is insufficient due to incomplete maturation of cognitive function. Accordingly, working memory, abstract thinking and complex problem solving improve during adolescence to peak at late adolescence (Feinberg, 1983; Woo et al., 1997; Williams et al., 1999). These acquired abilities are supported by distinct developmental changes occurring in the PFC during adolescence and involve changes in densities of dendritic processes and synapses, increased myelination, increased neuronal membrane synthesis and in turn, increase in white matter (Paus et al., 1999; Giedd et al., 1999a, 1999b). Among these changes, synaptic pruning has been considered a way to reduce energy use through a selective reduction of synaptic contacts that are not necessary to sustain a particular ability; in humans PFC synaptic density, after reaching a maximum at the age of 5 years, diminishes by about 35 % by late adolescence (Lewis, 1997). This synapse reduction involves mostly local PFC circuits (Woo et al., 1997) and both excitatory and inhibitory inputs are implicated (Anderson et al., 1995). During the pruning that occurs in adolescence there is a prevalent reduction of the excitatory stimulation that reaches the PFC (Rakic et al., 1994). In particular synapse elimination of presumed glutamatergic inputs occurs in PFC. Binding to NMDA receptors in rat brain peaks at 28 post natal day (PND) whereas a successive reduction leads to a 33 % reduction by the 60 PND (Insel et al., 1990).

On the contrary, dopamine functional activity in the PFC increases in adolescence, peaking to levels much higher than those seen in adulthood (for a review see Lewis et al., 1998). In rats, dopamine innervation is maximum at 35 PND in superficial layers and at 60 PND in deeper layers (Kalsbeek et al., 1988); moreover, the density of DAT, often used as an index of dopamine innervation in the PFC, is about 70 % of adult levels in weaning rats. On the other hand the increase in dopamine fiber density observed in development may be associated to a decline in synthesis and turnover; in fact synthesis peaks at PND 30 and then declines in late adolescence (Andersen, et al., 1997). Adolescence has a peculiar feature from an energetically point of view. In fact cortex energy consumption in humans peaks at 3-4 years and is maintained up to the age of 20, to progressively decline in later life (Chugani et al., 1987). In general synaptic pruning and myelination can be considered parallel processes that apparently have the role of strengthening regularly used innervations rendering them able to fire in a more concerted pattern (Lewis, 1997; Miller, 1996). At the same time infrequently used innervations are eliminated (Rutherford et al., 1998). Furthermore dopamine modulation of fast-spiking interneurons changes dramatically during adolescence (PND 45-50 in rats) with D2 agonists switching from being mildly inhibitory in prepubertal rats to strongly excitatory in young adult rats. In vivo recordings in adult rats reveal that deep-layer pyramidal neurons respond to endogenous DA release with suppression of firing

while interneurons are activated (Tseng and O'Donnell, 2007; Gruber et al., 2010). Thus the increase in dopamine functional activity that peaks in adolescence together with the reduction of excitatory innervation are two delicate processes which reduce the activity of pyramidal cells. Therefore either a deficiency in excitatory reduction or a defective increased inhibitory activity may lead to an excessive pyramidal cell activity that in turn may be reflected by the onset of a psychiatric disorder or drug abuse.

Substantial evidence points to the higher risk of drug exposure in adolescence (Barron et al., 2005; Crews and Hodge, 2007; Schramm-Sapyta et al., 2009). In particular alcohol consumption during adolescence causes diffuse brain alterations and greatly increases the likelihood that an alcohol use disorder will develop later in life (Nixon and McClain, 2010). Diffusion tensor imaging studies have shown that adolescent binge drinking damages white matter tracts throughout the brain, including main hippocampus efferent fibers and those interconnecting the PFC (McQueeny et al., 2009; Jacobus et al., 2009). Adolescents respond to the effects of alcohol distinctly from adults in fact they are less sensitive to negative effects of alcohol, they do no perceive cues that may suggest reduction of intake, but are more sensitive to positive effects such as those related to social interaction, which may serve to reinforce or promote excessive intake (Spear et al., 2005). Adolescence is also critical for cannabis abuse, indeed it is widely reported that cannabis use during adolescence increases the risk of developing psychotic disorders later in life (Bossong and Niesink, 2010, Malone et al, 2010). However, although the neurobiological processes underlying this relationship are unknown, alteration of PFC circuitry is more than likely. Very recently it was found that marijuana users had decreased cortical thickness in right caudal middle frontal, bilateral insula and bilateral superior frontal cortices (Lopez-Larson, 2011). These results suggest that age of regular use may be associated with altered PFC gray matter development in adolescents. According to the authors of this study reduced insular cortical thickness may be used as a biological marker for ascertain increased risk of substance dependence (Lopez-Larson, 2011). An interesting comparison in adolescent alcohol and marijuana users has been proposed by evaluating participants who performed a verbal paired associates encoding task during functional magnetic resonance imaging (fMRI) scanning. The results of this study suggested that adolescent substance users demonstrated altered fMRI response relative to non-using controls, yet binge drinking appeared to be associated with more differences in activation than marijuana use (Schweinsburg et al., 2011). Alcohol and marijuana may have interactive effects that alter these differences, particularly in prefrontal brain regions (Schweinsburg et al., 2011).

As far as regards cocaine effects, rats with adolescent-onset cocaine self-administration experience were more impaired in an OFC-related learning task than rats with adult-onset cocaine self-administration experience (Harvey et al., 2009). Treatment with cocaine during adolescence also caused acute alterations in the expression of genes encoding cell adhesion molecules and transcription factors within the PFC. In particular, a decrease in histone methylation was observed and this effect may indicate a role for chromatin remodelling in gene expression patterns. These findings allowed the authors to suggest that exposure to cocaine during adolescence has extensive molecular and behavioural effects in the rat PFC. These consequences develop over time and endure long after drug administration has ceased (Black et al., 2006). Smoking and nicotine exposure during adolescence is a very relevant heath problem because the higher dependence developed in individuals who start smoking early (see O'Dell, 2009 for review). Early tobacco use is facilitated by the legal

possibility to purchase tobacco in most of the western countries. Besides other health consequences, tobacco smoking and nicotine exposure during adolescence interfere with PFC development and leads to cognitive impairments in later life with enduring attentional disturbances (Cunotte et al., 2009). Among molecular alteration, early nicotine exposure determines reduced mGluR2 protein and function on presynaptic terminals of PFC glutamatergic synapses. Interestingly restoring mGluR2 activity in vivo by local infusion of a group II mGluR agonist in adult rats that received nicotine as adolescents rescued attentional disturbances (Counotte et al., 2011).

Among others, novelty directed behavior is highly expressed in adolescence. It may represent a strong risk for the use of addictive drugs and consequently for the developing of drug dependence. Novelty directed behavior can be observed in periadolescent rats, in fact they show a strong exploratory behavior in a novel open field. Although it is not clear the role of dopamine and norepinephrine transmission in this behavior, periadolescent rats show hypo-responsivity to dopamine agonists and hypersensitivity to antagonist action suggesting that their dopamine transmission is hyperactive as compared with adult rats (Spear and Brake, 1983). Moreover the response of adolescent animals to amphetamine (an indirect dopamine and noradrenaline agonist) supports the peculiarity of catecholamine transmission in adolescence (Mathews and McCormick, 2011). Paradoxically amphetamine reduces novelty preference when adolescent mice are paired with a novel environment while it increases novelty preference when this test is performed in normal adult mice (Adriani et al., 1998). Thus we can hypothesize that typical adolescent behaviors such as novelty seeking, impulsivity and risk taking are the result of a natural drive that emerges in adolescence possibly linked to the need of spreading individuals of a species in a territory. It may be likely that this behaviour could be maintained by an overactive excitatory transmission in the prefrontal cortex and in subcortical areas that are balanced by an increasing active inhibitory catecholamine transmission. On the other hand catecholamine innervations reaching their maximal inhibitory activity at the end of adolescence, may have a role in stabilizing those brain processes that have been developed in adolescence and will be then acquired as behaviour reference in adult life.

As far as nicotine effect in adolescents, we observed that nicotine-stimulated dopamine release was higher in the mPFC of adolescent rats as compared with adults (Carboni et al., 2010). These results suggest that the higher response observed in adolescents might be correlated to their higher sensitivity to the effects of nicotine. This trait might have a contributory role in the strong nicotine addiction that is observed in smokers who start nicotine abuse during adolescence (see the review of O'Dell, 2009). In fact, although nicotine abuse has much in common with other drugs of abuse in that it increases dopamine output in the NAcc shell (Di Chiara, 2000) or in other brain areas (Carboni et al., 2000), its ability to determine a higher increase of dopamine in the PFC of adolescents could potentially be correlated to the alteration of the brain maturation process that occurs in adolescent smokers (Carboni et al., 2010). Consequently this feature may alter the PFC's role in the ability to establish a rational evaluation of smoking even during adult age. We also observed that nicotine increased noradrenaline release in the PFC (Carboni et al., 2010) thus suggesting that this increase may have a role in the nicotine enhancement of cognition (see the review of Poorthuis et al., 2009). Furthermore local infusion of nicotine in the prelimbic mPFC can increase mPFC glutamate extracellular concentration supporting the role of nAChRs in modulating thalamocortical input to the PFC (Gioanni et al., 1999). These findings therefore

suggest that such a mechanism may be relevant to the cognitive effects of nicotine and nicotinic agonists.

11. Role of stress (prenatal, adolescent and adult) on prefrontal cortex function and drug addiction

Acute stress modulates the neuronal activity of brain regions such as mPFC (Hains and Arnsten, 2008), amygdala (Goldstein et al., 1996), hippocampus (Belujon and Grace 2011) , OFC (Capriles et al., 2003), insula, and striatum (Koob, 2009) that are also areas of the brain involved in regulation of appetitive behaviors, such as feeding and drug taking (Marchant et al., 2012). These areas share common a consistent dopaminergic innervation pointing to a role of dopamine in stress-induced reinstatement of drug taking (Erblich et al., 2004; Shaham and Stewart, 1995; Shaham et al., 2003). The preclinical early work of Piazza and collaborators has shown a clear relationship between drugs of abuse, stress and glucocorticoids levels (Piazza et al., 1996), although most of their work was focused on sub-cortical areas. They have indeed shown that drugs of abuse acutely activate the hypothalamic-pituitary-adrenal (HPA) axis and that drug dependence was characterized by a dysregulation of HPA axis (Piazza and Le Moal, 1996). Moreover they showed that stressors facilitate the acquisition of cocaine and amphetamine self-administration (Piazza and Le Moal, 1998). Stress plays and important role in drug addiction either by triggering relapse in abstinent addicts, or by altering PFC function thus predisposing for drug use and abuse (Stewart, 2003; George and Koob, 2010; Van den Oever et al., 2010). Human studies suggested that the incapacity to resist to drug cues, such as the sight of drug, can also be amplified by stress (Swan et al., 1988; Breese et al., 2011; Potenza et al., 2012). Although moderate stress can have a positive value on cognition, strong or repeated stress will either be deleterious for cognitive functions or may be a determining factor in vulnerability to mental illness and drug addiction, likely through an alteration of catecholamine transmission in the PFC (Holmes and Welman 2009, George and Koob, 2010; Goldstein and Volkow, 2011). Indeed, it has recently been reported (Radley et al., 2008) that selectively ablating noradrenergic input into the rat medial PFC attenuates the effects of stress in the paraventricular hypothalamic nucleus, as well as the HPA axis secretory responses, while stress-induced Fos expression in dorsal medial PFC was enhanced and was negatively correlated with stress-induced paraventricular hypothalamic nucleus activation. These observations identify the locus coeruleus as an upstream component of a circuitry providing for dorsal medial PFC modulation of emotional stress-induced HPA activation. Since noradrenergic projection, and its innervations of the prefrontal cortex play an important role in the modulation of working memory and attention, it may be likely that noradrenaline release in the medial PFC could modulate stress response, depending on the evaluation and comparison of environmental stimuli with past experience in mounting adequate behaviourally adaptive responses to emotional stress and environmental challenge in general.

Further, the artificial activation of catecholamine transmission in the PFC, such as that produced by amphetamine administration, similarly to stress, can have beneficial or a deleterious effects on cognition depending on the dose and on basal dopamine and noradrenaline transmission. The ability of stress to alter neuronal function has been investigated in 15 smokers undergoing functional magnetic resonance imaging who were exposed to a psychosocial stressor, followed by smoking drug cues (Dagher et al., 2009). The

results allowed to observe a significant change in neural activity during stress with an increased neural response to drug cues in the medial prefrontal cortex, posterior cingulate cortex, dorsomedial thalamus, medial temporal lobe, caudate nucleus, and primary and association visual areas. A stress-induced limbic deactivation that predicted subsequent neural cue-reactivity was also observed. The authors thus suggested that stress increases the incentive salience of drug cues (Dagher et al., 2009). The role of mPFC in the ability of stress to enhance the reinforcing properties of morphine has been recently investigated (Rozeske et al., 2009). The results obtained show that escapable stress activates the ventral regions of the mPFC while inescapable stress does not. On the other hand inescapable stress potentiates morphine-conditioned place preference while escapable stress does not. Moreover these effects are modulated by intra-mPFCv microinjection of the GABAA agonist muscimol 1 h before stress session (Rozeske et al., 2009).

It was early reported that the adult offspring of stressed pregnant rats exhibited higher locomotor response to novelty and to an injection of amphetamine but also a higher level of amphetamine self-administration, suggesting that prenatal stress (PNS) could determine an individual predisposition to drug self-administration (Deminiére et al., 1992). The effect of PNS was also observed to elevate active lever responding in rats either during extinction or in cocaine-primed reinstatement, but not during self-administration or in conditioned-cued reinstatement, thus suggesting that early environmental factors contribute to an individual's initial responsiveness to cocaine and propensity to relapse to cocaine-seeking (Kipping et al., 2008). We recently investigated in rats the effect of PNS on dopamine and noradrenaline transmission in the mPFC (Carboni et al., 2010) and in the NAcc shell (Silvagni et al., 2008). We observed that PNS did not change dopamine but decreased noradrenaline basal output in the PFC of both adolescents and adult rats (Carboni et al, 2010). Moreover we observed that PNS decreased amphetamine stimulated dopamine output and increased amphetamine-stimulated noradrenaline output. PNS decreased nicotine-stimulated noradrenaline (but not dopamine output) in adults, though not in adolescents (Carboni et al., 2010). These data support a contributing role of PNS in the development of psychiatric disorders and that its effect may augment drug addiction vulnerability.

12. Areas of prefrontal cortex, decision making and drug addiction.

Preclinical and human studies have provided unequivocal evidence that drug addiction involves many subregions of the PFC. Nevertheless the correspondence between these subregions among rodents and primates has been long debated (Brown and Bowman, 2002). Moreover it is claimed that PFC function is more than the sum of the functions of individual PFC sub-regions (Wilson et al., 2010). An exhaustive review of PFC dysfunction in addiction has been recently provided (Goldstein and Volkow, 2011). In this section we will briefly consider some preclinical and human studies on the involvement of the OFC in addiction because this PFC sub region has recently received much attention in drug addiction (Shoenbaum et al., 2006). The orbitofrontal area is interconnected in both rat and primates with mediodorsal talamus, the basolateral amigdala and NAcc, and has been proposed to use associative information handled by this circuitry to guide behaviour on the basis of the expected outcome of a specific action (See the review of Shoenbaum et al., 2006 for specific anatomical location and relationship with other brain areas). In particular this area is activated in humans during anticipation of expected outcomes and therefore can allow

prediction of reward or punishment using this information to guide decisions (Arana et al., 2003). Rats with OFC lesions fail to behave correctly in reinforcing devaluation tasks where they have to make decisions on the basis of outcome expectancies (Gallagher et al., 1999). As far as regards addicted they may suffer of OFC circuitry alteration because, often under the control of drug-associated cues, they are unable to control drug-seeking behaviour despite they are aware of adverse consequences associated with their compulsive and impulsive behaviour and despite a stated desire to stop. The alteration of OFC have been detected by imaging studies of addicts and in particular it has been observed a reduction in OFC activation during acute withdrawal whereas an over-activation of OFC associated with high level of craving has been observed in addicts exposed to drug-related cues (see the review of Dom et al., 2005). Furthermore, in addicts are observed impairments of OFC-dependent behaviours that strongly parallel those that are observed in individuals carrying OFC damage (Grant et al., 2000).

Nevertheless in humans it is difficult to state that functional deficits at the level of OFC are due to drug exposure because it could be attributable to pre-existing condition. At this regard Volkow and collaborators proposed an interesting hypothesis (Volkow et al., 2009). They suggested an association between an impairment of the OFC and other PFC areas involved in addiction, and a decrease of striatal dopamine D2 receptors availability. This condition would render subjects more vulnerable to drug addiction (Volkow et al., 2009). Further, a study done in subjects who have a high risk for alcoholism but were not alcoholics showed higher than normal striatal D2 receptor levels and a normal metabolism in OFC, anterior cingulate cortex and dorsolateral PFC (Volkow et al., 2006). On this basis the authors proposed that normal PFC function may have protected these subjects from alcohol abuse. A further recent evolution of this hypothesis suggested that OFC and cingulate function are involved in individual positive emotionality which in turn is a defence against drug of abuse vulnerability (Volkow et al., 2011). Nevertheless these stimulating hypotheses have to be evaluated taking into account that dopoamine D2 availability does not distinguish between an increase in the released dopamine or in a decrease of receptors. On the other hand rats trained to self-administer amphetamine show a long term (one month) reduction of dendritic spine density specifically in the OFC whereas spine density was increased in the medium spiny neurons of the NAcc and in pyramidal neurons of the mPFC (Crombag et al., 2005). Moreover others have reported an increase of dendritic spine density in the medial PFC and in the NAcc after treatment with psychostimulant (Robinson and Kolb, 1999). It has been reported that chronic cocaine use causes long lasting impairment in OFC function as established by studies on reversal learning in animals, thus suggesting that this damage is expressed by the inability of using the value of predicted outcome to guide behavior (Shoenbaum et al., 2004, 2006 and 2009). The results of these experiments allowed Shoenbaum et al. (2006) to claim that "cocaine use can drive to the loss of outcome expectancies making addicts to continue to seek drugs despite the almost inevitable negative consequences of such behaviour concluding that changes in the OFC-dependent signal would by themselves contribute powerfully to a transition from normal goal-directed behaviour to compulsive habitual responding".

Moreover a dysregulation of the ventral, dorsomedial and dorsolateral striatal systems has been hypothesized to play a fundamental role in the transition from voluntary drug use to more habitual and compulsive drug use (Everitt and Robbins, 2005; Belin and Everitt, 2008). These sub cortical areas are strictly connected with PFC regions and in particular the NAcc

shell receives glutamatergic inputs from the ventromedial PFC and insular cortex, the NAcc core receives glutamatergic inputs from the dorsomedial PFC, insular cortex and OFC whereas the dorsomedial and the dorsolateral striatum receive glutamatergic inputs from the OFC, the anterior cingulate cortex and the sensory and motor cortices (Reynolds and Zahm, 2005; Gabbott et al., 2005). Therefore it is objectively possible that the dysfunction in the cortical areas observed after chronic cocaine use (Shoenbaum et al., 2006 and 2009) are a consequence of a complex neural adaptative response that occurs during the transition from voluntary drug use to a more habitual and compulsive drug use. This transition has been hypothesized to be mediated at neural level through a shift from PFC to striatal control over drug seeking and drug taking (Everitt and Robbins, 2005). Nevertheless a recent review of neuroimaging studies have revealed a generalized PFC dysfunction in drug addicted individuals and although the activity of PFC regions is highly integrated and plastic, pre-existing dysfunction of specific PFC regions may confer individual vulnerability to drug addiction (Goldstein and Volkow, 2011).

13. Addiction a disorder of awareness, motivation, or self-control

Addiction may be considered the product of an imbalance between two separate, but interacting, neural systems: an immediate one that generates decision making, based on the impulsivity-related amygdala system for signalling pain or pleasure of immediate prospects and a reflective one, based on PFC circuitry for elaborating the value of signalling pain or pleasure of future prospects (Bechara, 2005). The capacity of controlling behavior is challenged by the ability of cues associated with reinforcing activities (food, sex, drugs of abuse, pleasure) of activating circuitry in which dopamine release in the NAcc has a fundamental value (Schultz, 2010). On the other hand self-control efforts involve increased activity in regions of the PFC regulating emotions and cognition (i.e. dorsolateral and ventrolateral PFC) and a reduced activity in regions associated with reward processing and craving. These brain areas include the ventral striatum, subgenual cingulate, amygdala, ventral tegmental area and OFC as observed in neuroimaging studies in cocaine users (Volkow et al., 2010) or smokers (Kober et al., 2010) when they are required to inhibit craving. In smokers a decrease in craving correlated with a decrease in ventral striatum activity and an increase in dorsolateral prefrontal cortex activity, with ventral striatal activity fully mediating the relationship between lateral prefrontal cortex and reported craving (Kober et al., 2010).

Interestingly, the activation of similar regions was seen in healthy volunteers who were requested to control response to cues associated with monetary rewards (Delgado et al., 2008). Therefore, emotional and cognitive processes that influence decision-making and which may also lead to impulsive behavior or motivational disturbances such as food abuse, drug addiction, excessive spending, risky sexual behavior, may be indicative of an abnormal functioning of PFC or subcortical ventral striatal regions as observed in neuroimaging studies (Breiter et al., 2001). A further feature of PFC role in cognition deals with the overlapping dopamine and ACh innervations in the PFC. It suggests that all the cognitive processes in which are involved these two transmitters may occur involving local mechanisms (Briand et al., 2007). In particular it is of relevance that dopamine agonists increase Ach release and social cognition in rats (Di Cara et al., 2006). Several authors suggested that dopaminergic modulation of PFC cholinergic output is mediated primarily through activation of D1 and D5 type receptors (see Briand et al., 2007 for a review).

Moreover the importance of PFC in expressing self-control is supported by the fact that failure occurs when frontal executive control is compromised such as following alcohol consumption or injury (Crews and Boettinger, 2009) as reported in patients with frontal lobe damage (Sellito et al., 2010) and in subjects who were subjected to transient disruption of functions in the lateral PFC by repetitive transcranial magnetic stimulation in lateral PFC (Figner et al., 2010). The lateral PFC is considered the area which activity allows self-control as proposed by the top-down model although two types of subcortical activities could be distinguished: one related to drug addiction that involves primarily the control of PFC over NAcc and one related to amygdala that controls the emotions. Therefore PFC could be associated with long term outcomes whereas sub-cortical activity is associated with more immediate outcomes. The prevalence of subcortical areas in managing drug taking is gained progressively during drug taking experience. At this regard Belin and Everett (2010) have proposed the incentive habit hypothesis. According to these authors drug seeking habits progressively dominate goal directed drug seeking behavior that in turn ca be highly influenced by Pavlovian incentive mechanisms. This process in humans may crucially affect the transition from drug use to drug abuse, involves a strong emotional component but the outcome of this process likely depends on the individual resilience of neuronal circuit to resist to the neurochemical insult of the drug abused. In fact drug addiction depending on the situation can involve a strong component of emotion (Burke et al., 2008; Heatherton and Wagner, 2011; Artiges et al., 2009). The similarity between the control over drug addiction and over emotion share many commonalities although reactivity to emotion may involve an immediate response while drug addiction control is the result of a complex outcome of brain elaborating activity. According to a simplified point of view addiction is the result of a hypersensitivity of the brain reward systems that escapes the control from PFC regions (Bechara, 2005; Koob et al. 2008). In fact it has been reported that during alcohol intoxication, together with a shift toward right versus left brain metabolic laterality, can be observed a shift in the predominance of activity from cortical to limbic brain regions (Volkow et al., 2008). The widespread nature of these brain changes may contribute to the marked disruption of behaviour, mood, cognition and motor activity induced by alcohol (Volkow et al., 2008) or other drugs of abuse (Goldstein and Volkow, 2011) and can cause degeneration in cortical areas deputed to controlling impulsivity in case of heavy alcohol use (Crews and Bottinger, 2009).

14. Concluding remarks

In summary it has been proposed that according to the theory of top-down control, the PFC and in particular the lateral PFC is responsible for controlling different domains of behavior (Cohen and Lieberman, 2010) regardless their content that may vary depending on the subcortical area involved. It may range from food intake, to drug addiction behaviour up to control of emotions and may explain why the effect of resource depletion are no tied to any one self-regulatory domain, as discussed by Heatherton and Wagner (2010). Among PFC areas many are definitively involved in drug addiction as well as in self-control and decision making. Nevertheless an interesting observation suggested that the PFC is involved in cognitive functions exceeding the sum of specific functions attributed to its subregions (Wilson et al., 2010). Thus if behaviour and decision making are considered as an overall result of PFC activity it is interesting to investigate the reason why self-control fails in drug addicts. Thus it could be hypothesized as mentioned before, that chronic exposure to a drug

of abuse could disrupt the balance between cortical and sub-cortical activities but it is less clear why some people start taking drugs of abuse. Do they miss an unspecified activity in brain (genetic theory) or is the environment (psychological pressure and need to emulate companion behaviour to be accepted in the group), or is the sum of each factor to push to drug use. Fortunately, in the case of prevalence of the second factor drug taking may not necessarily lead to drug abuse. Considering that an optimal therapy for drug addiction is far to be proposed it remains to pursue prevention by involving young subject, and especially those at risk for drug use and abuse with involving activities in order to occupy brain activities in thoughts that are far from drug taking. Nevertheless drug therapy aimed at controlling drug taking impulse could be directed on improving the awareness of the consequences associated with pleasure directed behaviours and the capacity to take decisions directed to break the vicious circle of drug dependence.

Abbreviations

HPA, hypothalamic-pituitary-adrenal; NAcc Nucleus Accumbens; nAChRs, nicotinic acetylcholine receptors; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PND, postnatal day; PNS, prenatal stress; VTA, ventral tegmental area.

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