Why does moderate exposure to a drug reward make natural rewards increasingly attractive to organisms, whereas prolonged exposure to the same drug reward has the opposite effect? The paradox behind that question remains unsatisfactorily captured by current theories of addiction. The incentive-sensitisation theory is viewed as a promising approach to this paradox, although it provides no mechanism to explain the decrease in interest of natural rewards as time exposure to a drug increases. To attempt to remedy this problem, I describe a model called the anticipatory dynamics model (ADM) that suggests a pivotal role of anticipation and attention in motivational interactions. In addition to relying on strong neuropsychopharmacological data, the ADM provides an original conception of motivational specificity. The ADM is an extension of the incentive-sensitisation theory that hypothesizes how drugs interact with natural rewards. It has not been tested empirically, although a possible experiment to test two predictions in the field of addiction is presented.
It is well established that extended exposure to drugs of abuse leads to the development of compulsive drug-seeking and drug-taking behaviours in humans as well as in animals (e.g. Wolffgramm and Heyne, 1995; Bradberry, 2000; Robinson and Berridge, 2000; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004, 2005). Compulsive behaviours are essentially characterised by their inflexible directedness toward a drug, at the expense of activities previously considered important (e.g. feeding and social relationships) and in spite of negative consequences related to a decline in these activities, as well as by the appearance of physical problems, such as weight loss and gastric ulcers (American Psychiatric Association, 1994). Importantly, according to the DSM-IV of the American Psychiatric Association, compulsion – or addiction – is categorized as an abnormal development of motivation. Although tolerance and physical dependence are two possible criteria among the seven items characterising substance dependence in the DSM-IV, three criteria are necessary to obtain a diagnosis of drug dependence. Thus, the diagnosis of dependence must include one to three items among the five related to abnormal drug motivation (reported by Di Chiara, 2002).

A strong addictive motivation can result from the administration of a high dosage of a drug (e.g. Lenoir and Ahmed, 2007) or from the administration of smaller doses over a prolonged period (e.g. Bradberry, 2000). A combination of both parameters also is encountered in experimental studies. For instance, Heyne and Wolffgramm (1998) allowed rats to consume water or a solution of d-amphetamine (100, 200 or 400 mg/l) during a 47-week period. Indeed, the duration of drug administration is critical to the appearance of uncontrolled drug taking (Deroche-Gamonet et al., 2004). In one study by Wolffgramm and Heyne (1995), rats were given access to ethanol for several weeks. These authors report: ‘After 22 weeks, none of the rats had developed an addiction, after 32 weeks only a few individuals revealed signs of addictive behaviour, whereas after 42 weeks nearly all the rats were alcohol-addicted’. So, provided that the administration period is of sufficient duration, significant neuronal adaptations occur that result in long-lasting modifications of the behaviour of rats in relation to the drug (White and Kalivas, 1998; Robinson and Berridge, 2000).

The almost exclusive interest an individual may develop in a drug reward seems to contradict the evidence that repeated drug administration causes an increased attractiveness of natural rewards. For instance, repeated pre-treatment with morphine or d-amphetamine in rats facilitates the appetitive phase of sexual behaviour towards a partner (Mitchell and Stewart, 1990; Fiorino and Phillips, 1999). Similarly, pre-treatment consisting of amphetamine microinjections in the nucleus accumbens increases the desire for sucrose, even when the rats are tested drug-free (Wyvell and Berridge, 2000, 2001). This phenomenon happens with low or moderate drug use, within the first days of repeated administration. It must be noted that drug-induced attractiveness of natural rewards cannot be explained within the framework of Pavlovian conditioning because this phenomenon occurs when associations are learned before the development of sensitisation (e.g. Wyvell and Berridge, 2001; see also Anagnostaras and Robinson, 1996; Tirelli et al., 2003, 2005). The idea that sensitisation does not result from a conditioning process is supported by evidence that persistent neuroadaptations can be produced in vitro in slices of striatal tissue (Castaneda et al., 1988) as well as in anaesthetised animals (Henry and White, 1991). Several results even indicate that sensitisation boosts associative learning. Repeated exposure to d-amphetamine facilitates the learning of a stimulus that predicts sucrose availability (Harmer and Phillips, 1998, 1999). Cocaine increases water-directed responses of rats in a reinforcement procedure (Taylor and Horger, 1999) and enhances the learning of Pavlovian associations during the appetitive phase of behaviour (Taylor and Jentsch, 2001).

How can drug rewards result in both an increase and then a decrease in the interest of organisms for natural rewards? Although the consequences of drug seeking and drug taking remain unexplained to a large extent (Wellman et al., 2005), it is argued here that the incentive-sensitisation theory proposed by Robinson and Berridge (1993) is a good candidate for yielding a solution to this apparent paradox. In addition to being supported by a considerable number of experimental facts (for reviews, see Berridge and Robinson, 1998; Berridge, 2007), this view explains remarkably well how a drug can stimulate the neural substrate of other categories of rewards. However, it is suggested that the incentive-sensitisation theory is incomplete regarding the purpose of this paper because it lacks a concept of motivational specificity. Thus, the theory does not provide any mechanism to account for the decrease in interest in natural rewards as time exposure to a drug increases. If a drug can stimulate different categories of rewards, why does that stimulation stop after some time?

To attempt to remedy this problem, I present an attentional control model – called the anticipatory dynamics model (ADM) – that encompasses the role of anticipation and attention in motivation. The ADM describes a plausible neuropsychopharmacological mechanism for motivational specificity, which implies that an individual’s motivational interactions are constrained by the individual’s attentional resources and that anticipation determines how these resources are shared (Anselme, 2007). The model currently remains hypothetical, but a proposed experiment is briefly described to test the ADM in the field of drug addiction. Before proceeding to this model, the reward processes are examined next because they are the ‘cornerstone’ of all theories of addiction.

2. Neuropsychopharmacology of reward

A reward is an incentive stimulus that positively reinforces behaviour, that is, it increases the probability of the behaviour’s occurrence due to its pleasure-related effects. Natural rewards mainly include food, water, sex, novelty, play, and social relationships; whereas the most common drug rewards are cocaine, amphetamine, heroin, morphine, THC, and alcohol (e.g. Chambers et al., 2003). All rewards are reinforcers but not all reinforcers are rewards. For instance, electric shocks reinforce the avoidance response of animals but do not constitute rewards (Maier and Seligman, 1976). Rewards are positive reinforcers, while aversive events, such as electric shocks that elicit an avoidance response, are negative reinforcers. (Aversive events that decrease the probability of responding are called punishers, but they will not be discussed here.)

Numerous brain regions and neurotransmitters are involved in the reward circuit (Fig. 1). The most studied among them in relation to behaviour is undoubtedly mesocorticolimbic and nigrostriatal dopamine. First, the mesolimbic projection connects the ventral tegmental area to the ventral striatum (or nucleus accumbens). This pathway is known to induce neuronal and behavioural sensitisations associated with rewarding and reward-associated stimuli (e.g. Berridge and Robinson, 1998; Depue and Collins, 1999). Contextual stimuli are represented in different limbic areas, such as the basolateral amygdala and the hippocampal formation, whose glutamatergic projections ascend to the nucleus accumbens and to the ventral tegmental area via the medial prefrontal cortex (Jentsch and Taylor, 1999; Everitt and
Robbins, 2005). Second, the mesocortical projection ascends from the ventral tegmental area to the prefrontal cortex; also related to reward processing, it is an essential component of the emotional response network that ensures normal cognitive functioning, in particular working memory and decision making (e.g. Arnsten, 1998; Miller, 2000; Durstewitz and Seamans, 2002). Third, the nigrostriatal projection ascends from the substantia nigra to the dorsal striatum (caudate–putamen), where dopamine is associated with the initiation and execution of habitual behaviour (Sano et al., 1996), although its role in reward has also been shown (Young et al., 1992; Ito et al., 2002). More precisely, recent findings indicate that only the dorsomedial striatum in rats (or caudate in humans) is necessary for the learning of action-outcome associations, the expression of goal-directed actions, and the development of sensitivity to outcome value (Yin et al., 2004; Wikens et al., 2007). As the nucleus accumbens and prefrontal cortex (see below), the dorsomedial striatum seems to be somehow involved in goal expectancy (e.g. Lauwereyns et al., 2002). In contrast, the dorsolateral striatum (or putamen in humans) fails to exhibit such properties and appears crucial for the learning of stimulus–response habits (e.g. Devan et al., 1999), which are controlled by antecedent stimuli and render animals insensitive to outcome devaluation (Yin et al., 2004).

This review examines the role of mesolimbic dopamine in reward. Before considering how drug and natural rewards interact, we need to scrutinize additional aspects of reward mechanisms. In the next section, I argue against the idea that dopamine specifically carries a reward signal because this neurotransmitter also is released in response to other types of incentive stimuli (Section 2.1). Some doubts are also raised concerning the expectation of dopamine’s role in reinforcement because alternative interpretations exist to account for the facts considered critical in supporting this view (Section 2.2). Finally, a way of utilizing both these approaches is suggested (Section 2.3).

2.1. Dopamine nonspecificity

Three significant features of dopamine action point to nonspecific effects in the brain. First, its projections reach a large number of cerebral sites—between 20 and 30 (Le Moal and Simon, 1991; Depue and Collins, 1999). Of course, the cells to which dopaminergic neurons project to are rather limited in scope (Le Moal and Simon, 1991; Rolls, 1999). Nevertheless, this limitation is compensated by the presence of abundant interconnections among dopaminergic subsystems (Le Moal and Simon, 1991). They constitute a network in which powerful feedback loops regulate imbalances arising in some parts of the network. These interconnections enable up to 75% of dopamine neurons to be synchronically activated when animals experience physical contact with a hidden food or liquid during an exploratory phase (Romero and Schultz, 1990) and up to 55–70% by conditioned visual and auditory stimuli (Schultz, 1998). Neuronal synchronisation is thereby strong in relation to reward and reward-associated stimuli.

Many dopamine neurons in the ventral tegmental area and substantia nigra (especially pars compacta) exhibit similar activations and depressions in situations for which the dopamine neurons of other regions do not respond at all (Schultz, 1998). However, in anaesthetized animals, clear heterogeneity appears between the burst firing of mesolimbic/mesocortical dopamine neurons (73%) and that of nigrostriatal dopamine neurons (18%) in response to electrical stimulation (Grenhoff et al., 1988). While the acute administration of antipsychotic drugs, such as haloperidol, increases dopamine levels in the ventral tegmental area and substantia nigra in anaesthetized rats, atypical antipsychotics (e.g. clozapine) activate dopamine neurons of the ventral tegmental area without generally affecting those of the substantia nigra (e.g. Chiodo and Bunney, 1983; for a review, see Gardner and Ashby, 2000). It must be also noted that stimulation of the ventral tegmental area decreases both the amplitude and decay time of EPSPs elicited stimulation of the prefrontal cortex, leading to a reduction of accumbal responding to prefrontal inputs (Brady and O'Donnell, 2004). This attenuation of prefrontal responses by ventral tegmental area stimulation may result from D2 receptor activation, as it is shown that D2 receptors exert a tonic dampening of cortical inputs to accumbens neurons (O'Donnell and Grace, 1994). There are also significant differences in the firing patterns of dopamine neurons in the striatum. For instance, the number of dopamine varicosities per mm³ is greater in the dorsolateral striatum than in the ventromedial striatum, leading to a higher density of dopamine release and more rapid signalling in the former region than in the latter (Wikens et al., 2007). In addition, the quantity of dopamine transporters (DAT) — proteins required for dopamine reuptake — is also higher in the dorsolateral striatum, allowing a more precise temporal control over dopamine release (Wikens et al., 2007). In conclusion, dopamine nonspecificity

Fig. 1. Brain regions and neurotransmitters involved in the reward circuit. The nucleus accumbens (NAc) receives glutamatergic projections (GLU) ascending from important corticolimbic structures (hippocampal formation, basolateral amygdala, and prefrontal cortex) as well as dopaminergic (DA) and GABAergic (GABA) projections ascending from a midbrain structure, the ventral tegmental area. The nucleus accumbens is composed of both core and shell regions that project to motor systems, via the ventral pallidum with respect to the core and via the lateral hypothalamus with respect to the shell (not represented) (for more details, see Robbins and Everitt, 1996; Chambers et al., 2003).
caused by a high synchronicity among dopaminergic neurons should not lead to think that all these neurons respond in a similar way to identical sources of stimulation.

Second, dopamine seems to have similar psychological effects irrespective of the type of reward involved. Initially, the anhedonia hypothesis suggested that dopamine levels in the nucleus accumbens carried the hedonic, or pleasant, effect of rewards (Wise, 1982; Wise and Bozarth, 1987). In contrast to this hypothesis, however, the pharmacological blockade of dopamine receptors does not appear to suppress pleasure, as indicated by some measures (see Berridge and Robinson, 1998; Di Chiara et al., 2004). Currently, many findings support the view that dopamine is released during the appetitive, anticipatory phase of obtaining a reward (Berridge and Robinson, 1998; Robinson and Berridge, 2000). For instance, mesolimbic dopamine neurons in inexperienced monkeys discharge when these animals are permitted physical contact with a novel food item (Apicella et al., 1991; Ljungberg et al., 1992). If this food reward is repeatedly paired with a neutral stimulus (e.g. light), then dopamine neurons stop responding to food and vigorously discharge in response to light as a predictive stimulus of food delivery (Apicella et al., 1991; Ljungberg et al., 1992). In conditioned animals, various studies revealed increased dopamine levels in the ventral tegmental area before the presentation of sucrose (Kosobud et al., 1994), cocaine (Gratton and Wise, 1994), or heroin (Kayakin et al., 1993), compared with levels when these substances are consumed. Ranaldi et al. (1999) claim that ‘the important factor determining the pattern of DA [dopamine] fluctuations is the level of anticipation of the to-be-earned drug reward.’ In humans, PET studies indicate that striatal release of dopamine is correlated with anticipation of a video game (Koepp et al., 1998) or amphetamine-induced drug wanting (de la Fuente-Fernandez et al., 2002; Leyton et al., 2002; Oswald et al., 2005). The core region of the nucleus accumbens seems to play a key role in this anticipatory process. Indeed, several studies demonstrated that lesions of the core region did not affect continuous instrumental responding in rats, whereas they induced deficits when the drug infusions were delayed (Hutcheson et al., 2001; Ito et al., 2004). Such lesions also increase impulsivity by producing a preference for small, immediate rewards over larger, delayed rewards (Cardinal et al., 2004). Similar consequences are observed after lesions of the basolateral amygdala (Whitlaw et al., 1996; Alderson et al., 2000) and of the orbitofrontal cortex (Damasio, 1996), which are massively connected to the nucleus accumbens core (Everitt and Robbins, 2005).

A third argument for dopamine nonspecificity is the observation of its release for rewards as well as for aversive events, such as unavoidable foot shocks (Gray et al., 1997), conditioned signals for foot shocks (Young et al., 1993), administration of anxiogenic drugs (McCullough and Salamone, 1992), and when working to escape from aversive hypothalamic stimulation (Rada et al., 1998). It is not clear whether mild aversive events can elicit mesolimbic dopamine release (e.g. Cenci et al., 1992; Mirennowicz and Schultz, 1996), which is elevated in response to strong aversive events (for a review, see Horvitz, 2000). Characteristically, most aversive events induce some stress, which is known to be correlated with dopamine release (Kalisas and Duffy, 1995), especially when the event’s occurrence is uncontrollable (McLennan and Maier, 1983).

So, dopamine is released during the expression of displacement activities in animals, that is, banal behaviours in the repertoire of a species that individuals perform ‘out of context’ when they are thwarted in achieving a goal or subjected to motivational conflicts (Timbergen, 1951; for a review, Anselme, 2008). While anxiogenic drugs have been shown to increase dopamine levels (McCullough and Salamone, 1992), there is evidence that these drugs – in particular, FG 7142 – facilitate the occurrence of displacement activities in monkeys subject to social conflicts (Schino et al., 1996). Lesions of the lateral hypothalamus, as well as chemical blockade of dopamine receptors, reduce the appearance of such behaviours (Wayner et al., 1991). According to Panksepp (1998), the cause of displacement activities is overarousal of the brain’s SEEKING system, which primarily includes dopamine’s neural network. In a similar vein, Schino et al. (1996) suggested that ‘uncertainty and anticipation of unpleasant events are crucial factors in the causation of displacement activities.’ Finally, dopamine release is also facilitated by salient, novel stimuli irrespective of their motivational value (Horvitz, 2000). For instance, single-unit data showed midbrain dopamine release when subjects exhibited target-directed saccades in response to the novel opening of a door compartment of a behavioural apparatus prior to appetitive conditioning (Ljungberg et al., 1992).

In summary, the action of dopamine is nonspecific because the consequences of dopaminergic stimulation are synchronised extensively for any kind of incentive stimulus (appetitive, aversive, or novel). From such a viewpoint, dopamine can be considered as ‘a common neural currency’ (Berridge, 2004). Although many studies indicate that dopamine is released in response to stimulus saliency, it cannot be ignored that dopamine also affects stimulus saliency in sensitising the mesolimbic region in the brain (e.g. Berridge and Robinson, 1998). Importantly, dopamine is mainly produced before the stimulus arrival, that is, during the anticipatory phase of behaviour—the term ‘anticipatory’ is preferred here to that of ‘appetitive’ since the stimulus can be unpleasant. On account of this nonspecific, anticipatory aspect of dopaminergic responding, it has been suggested that dopamine acts as a ‘go’ rather than as a reward signal in the brain (Rolls, 1999); hence, this neurotransmitter is the computational substrate of reinforcement rather than of motivation.

2.2. Dopamine and reinforcement

Since the nucleus accumbens is regarded as an interface between limbic structures and the motor system (Mogenson et al., 1980), it is sometimes hypothesized to play a role in reinforcement processes (for a review, see Salamone and Correa, 2002). To date, an extended literature supports the view that dopamine depletion in the nucleus accumbens reduces the efforts animals are disposed to invest in a task to obtain a reward, but without affecting the incentive value attributed to the reward. For instance, when rats with large lesions of the nucleus accumbens have to respond to visual cues indicating the size of an expected reward, their reaction times and response rates depend on the reward magnitude, similar to control subjects (Balleine and Killcross, 1994; Brown and Bowman, 1995). In addition to correctly decoding the meaning of visual cues signalling the incentive value of a reward, lesioned rats placed on a progressive-ratio schedule (where the number of lever presses required to obtain a pellet increases with each successive reward) increased the maximum number of responses emitted for a reward of more than 50%, in comparison with the control rats (Bowman and Brown, 1998). The higher breaking point of lesioned rats seems to be incompatible with the traditional hypothesis, reported by others (e.g. Wise, 1982; Berridge and Robinson, 1998), of a motivational or hedonic decrease following accumbal lesions. Such a performance of rats might result from the development of habitual control over behaviour, which depends on normal stimulation of the dorsolateral striatum: behaviour is no longer goal-directed but controlled by strong, post-training stimulus-response associations (e.g. see Yin et al., 2004).

Also in contrast with this traditional hypothesis is evidence that intra-accumbens injections of dopaminergic antagonists, or the
neurotoxin 6-OHDA, do not suppress food consumption (Bakshi and Kelley, 1991; Ikemoto and Panksepp, 1996; Sokolowski and Salamone, 1998). The use of low doses of dopaminergic antagonists is sufficient to suppress lever pressing, but food and water consumption remains unaffected, or is even sometimes increased in comparison with control animals (Salamone, 1986; Ljungberg, 1990; Horvitz et al., 1993; Cousins et al., 1994; Rusk and Cooper, 1994; Salamone et al., 1996; Koch et al., 2000). Such results indicate that the suppression of lever pressing is not due to appetite reduction; low doses of antagonists would impair the activational ('working to obtain') rather than the directional ('appetite to consume') component of reward-related behaviour (Salamone and Correa, 2002). In a T-maze choice task, one arm obstructed by a 44-cm barrier, for example, contained four food pellets, while the other arm contained only two food pellets freely available (Salamone et al., 1994). When control rats were tested in such a condition, they were observed to climb the barrier on most trials in order to obtain the high-density food. However, when rats received low doses of the D2 receptor antagonist haloperidol (0.1 mg/kg), they chose to climb the barrier less often and preferred to consume the food in the low-density arm. Thus, higher doses of antagonists are necessary to disrupt food intake. Haloperidol suppresses lever pressing at a dose as low as 0.08 mg/kg (Trevitt et al., 1997), whereas it affects feeding only at a dose of 0.2–0.4 mg/kg (Salamone et al., 1990). According to Salamone and Correa (2002), the reinforcing property of dopamine is compatible with the view that dopamine conveys the ‘wanting’ signal of a reward in that both activational and directional components of behaviour are assumed to belong to the ‘wanting’ process, as defined by Robinson and Berridge (1993) (see Section 3.2). Without denying the effects of dopamine depletion on motor systems, it is difficult, however, to determine whether the activational/directional distinction is necessary to account for the data available. In the T-maze choice task reported above, how can we know whether the motor deficits of the rats are due to impairment of the ‘wanting’ to work for food (activational component) or to a reduction of the ‘wanting’ to approach food (directional component)? If the ‘wanting’ to approach food is reduced by low doses of antagonists, then it seems logical that the rats are content with the two pellets, not because they are of easier access but because the rats are not hungry. To this end, it would be interesting to assess the behaviour of haloperidol-injected rats that have no other choice than to climb the barrier to obtain some food. The number of rats climbing the barrier should be greater than expected, and directional components of behaviour are assumed to belong to the ‘wanting’ process, as defined by Robinson and Berridge (1993) (see Section 3.2). Without denying the effects of dopamine depletion on motor systems, it is difficult, however, to determine whether the activational/directional distinction is necessary to account for the data available. In the T-maze choice task reported above, how can we know whether the motor deficits of the rats are due to impairment of the ‘wanting’ to work for food (activational component) or to a reduction of the ‘wanting’ to approach food (directional component)? If the ‘wanting’ to approach food is reduced by low doses of antagonists, then it seems logical that the rats are content with the two pellets, not because they are of easier access but because the rats are not hungry. To this end, it would be interesting to assess the behaviour of haloperidol-injected rats that have no other choice than to climb the barrier to obtain some food. The number of animals climbing the barrier should be greater than described above in the case of a reduced ‘wanting’ to work for food, because the absence of freely available pellets decreases the price to pay for the obstructed pellets. In contrast, a reduced ‘wanting’ to approach food would make the rats weakly hungry and therefore would not significantly compel them to climb the barrier.

In my opinion, it would be preferable to avoid using the term ‘wanting’, which is assumed to designate an unconscious preparatory motivational signal but often refers to a conscious psychological state, as it is in the experiment reported here (for a similar remark, see also Di Chiara, 2002; Robbins and Everitt, 2007). The rats explicitly want or do not want to climb the barrier. In this case, hypothesising a direct action of dopamine on the explicit wanting process is not necessary. Owing to its involvement in anticipation, dopamine might merely boost the anticipatory processes at work in explicit wanting, but not solely as previously mentioned. Dopamine antagonists, such as haloperidol, then would alter the expression of these processes (see Section 2.3).

As a result, organism do not want to commit to an action whose outcome is uncertain – for example, climbing a steep barrier when food is not guaranteed – so they only perform an action with immediate consequences.

An argument in favour of the reinforcement theory is that haloperidol-injected rats continue to consume food in the same proportion as normal animals. However, some findings indicate that a ‘liking’ as opposed to a ‘wanting’ process controls food consumption (Berridge and Robinson, 1998; Berridge, 2007). Animals with dopamine depletion consume nutrients (they continue to ’like’ them) but fail to exhibit approach and appetite behaviours (they no longer ‘want’ to approach them) (Ungerstedt, 1970; Berridge et al., 1989; Cannon and Bseiki, 2004). For instance, genetically dopamine-deficient mice are hypoactive and would die in an environment full of appetizing foods (Zhou and Palmiter, 1995). But once they begin to feed, these animals consume food in a similar way to normal mice, or even at a higher rate. Dopamine-deficient mice have been shown to drink a sucrose solution less frequently than normal mice but to absorb the solution longer and faster (Cannon and Bseiki, 2004). To interpret these data in terms of an explicit wanting suppression, as Cannon and Bseiki (2004) do, may appear to contradict the observation that dopamine-depleted rats, after accumbal lesions, continue to differentiate the cued incentive value of a reward (Balleine and Killcross, 1994; Brown and Bowman, 1995). However, the contradiction disappears if we consider that dopamine depletion reduces the anticipatory capacities of obtaining a reward. Explicit wanting involves both anticipatory and discriminative abilities, so reducing the efficiency of anticipation may leave discrimination intact. As with liking, discrimination does not require anticipating any information, as it entails a sensory event resulting, in this case, from an operant learning procedure. It can therefore be expected that animals continue to like and discriminate rewards depending on their incentive value, even though they no longer are willing to work for a delayed outcome (see Cardinal et al., 2004). Thus, the strong increase in response rates of lesioned rats on a progressive-ratio schedule, as observed by Bowman and Brown (1998), may reflect the inability of the rats to correctly anticipate reward delivery owing to the increasing delay between an action and its expected outcome.

Whishaw and Kornelsen (1993) reported that rats with lesions of the nucleus accumbens consumed food at the same rate as unlesioned rats, except that they never carried food to hoard it. Stern and Passingham (1994) showed that lesioned monkeys worked for peanuts, but there was a reduction in the number of unshelled peanuts they were prepared to collect and hoard. Bowman and Brown (1998) suggested that ‘food-hoarding deficits might arise from an unwillingness to ‘pay the price’ for rewards.’ More experimental investigations are needed to test this prediction, although such results may be explained otherwise: if the nucleus accumbens (especially the core region) plays a role in anticipatory processes, as advanced previously, then its dysfunction would make hoarding behaviours difficult to achieve because of the delay introduced between the action towards food (collect) and its expected outcome (feeding). Several findings are in favour of this latter interpretation (Whitelaw et al., 1996; Alderson et al., 2000; Hutcheson et al., 2001; Ito et al., 2004; Winstanley et al., 2004). For instance, the dopaminergic receptor antagonist pimozide reduces the number of visits by rats to a niche where some food is expected, at doses that do not affect food consumption when food becomes available (Blackburn et al., 1987).

2.3. Dopamine, anticipation, and uncertainty

As discussed, dopamine responses often are produced in situations correlated with anticipation. Dopamine release is observed during the appetitive phase of obtaining a reward (e.g. Berridge and Robinson, 1998) and during stress episodes induced
by exposure to an aversive stimulus (e.g. Gray et al., 1997). Interestingly, dopamine depletion disrupts the reactivity of subjects placed in contexts where reward seeking and stimulus avoidance usually are performed (e.g. Berridge et al., 1989; Cannon and Bseikri, 2004) as well as the ability to elicit a reward-seeking action when a delay is introduced (e.g. Hutcheson et al., 2001; Whishaw and Kornelsen, 1993).

Upon initial examination, the hypothesized relationship between dopamine and anticipation might be questioned because there is evidence that both phenomena do not necessarily come together. For instance, unpredicted rewards are known to cause a phasic dopamine response of short latency (50–100 ms) and short duration (100–200 ms) (Schultz, 1998). These phasic response characteristics are remarkably constant across mammalian species, such as rats, rabbits, cats, and monkeys (Feedman, 1985; Horvitz et al., 1997; Schultz, 1998; Guarraci and Kapp, 1999), even when the animals are under anaesthesia (Dommett et al., 2005). However, dopaminergic signalling happens too quickly to be modified by anticipation, or by any stimulus-identification process (Redgrave et al., 2008). In contrast, predicted rewards are, in essence, anticipated, although they do not produce dopamine signalling (Schultz, 1998; Harmer and Phillips, 1999). Dopamine neurons fire in response to novel foods and liquids, but cease responding upon habituation to their presentation after a learning period (Ljungberg et al., 1992) and when conditioned stimuli predict their arrival (Romo and Schultz, 1990).

However, it is important to note that, in nature, events rarely are either totally unpredictable or totally predictable, but rather, their predictability falls somewhere in between: that is, the event has an element of uncertainty. Therefore, uncertain events are predictable (they can be anticipated), with a probability of occurrence greater than zero but less than one, and there is evidence that they stimulate dopamine production in the ventral midbrain area (Fiorillo et al., 2003). Interestingly, it is specifically towards events of an uncertain nature that behaviour is directed when animals seek rewards (appetence), become stressed by an aversive stimulus that they attempt to avoid or to escape, or accept the presence of a delay between obtaining a reward and its consumption. In these three cases, reward obtaining or stimulus avoidance is subject to uncertainty. The observation that dopamine-depleted animals seem to be unprepared to work for rewards, whereas their instrumental actions are unaffected vis-à-vis easily accessible rewards, may be similarly explained: to work for rewards does not ensure that they will be obtained. In this view, dopamine-depleted animals do not work for rewards for the same reason they do not commit to reward-seeking, avoidance/escape, and hoarding behaviours: dopamine depletion renders them unable to deal with uncertainty. Assuming that this explanation is correct, uncertain events might therefore be a key factor in understanding the interrelations among dopamine, anticipation, and motivation. This point will be discussed in more detail in a later section. For now, we need to assess the ability of current theories of addiction to explain the opposite psychological effects of drug rewards on natural rewards.

3. A process not accounted for

To date, several theories attempt to explain addiction by elucidating different brain structures or processes that may play a role in this phenomenon. Each of them is likely to correspond to part of the truth, and further empirical investigations are needed to clarify their precise contributions. Furthermore, a theory of addiction must account for behaviours in relation to natural rewards, in addition to those directed towards a drug. The problem highlighted here with current theories of addiction is their inability to simultaneously explain an increased interest in a drug reward over time and the corresponding inverted-U shape function of interest in natural rewards. I begin by describing two promising theories (i.e. the allostatic and incentive-sensitisation theories) for that purpose, while showing that both exhibit some difficulties that prevent them from satisfactorily capturing the phenomena under consideration (Sections 3.1 and 3.2). Additional theories are then briefly examined (Section 3.3). After this section, I attempt to bridge the gap between the apparent paradoxical effects of drug rewards on natural rewards via a theoretical framework referred to as the anticipatory dynamics model, which is compatible with the incentive-sensitisation theory in many respects. The ADM provides a unified, though hypothetical, model of the psychobiological mechanisms underlying addiction, from moderate to compulsive use.

3.1. The allostatic theory

A few decades ago, Solomon and Corbit (1974) proposed that the dynamics of affective responding is homeostatic; in essence, a stimulus arouses an affective a-process, which is then replaced by an affective b-process of the opposite valence, thereby allowing an individual to return to a neutral affective state. For instance, the happiness (positive emotion) of meeting a friend turns to transient loneliness (negative emotion) when the time to leave comes. The return to a neutral affective state then follows. Homeostasis is a vital mechanism because it maintains the equilibrium of physiological parameters (e.g. blood pressure and hormonal rates) by inducing negative feedback adjustments after any change in these parameters (McEwen, 2000). Interestingly, Solomon and Corbit (1974) observed that when a stimulus is presented repeatedly, the individual’s habituation to that stimulus consists of a gradual decrease in the intensity of the a-process, while the intensity of the b-process is increased and the return to affective neutrality delayed. With regard to addiction, they related the homeostatic effects of affective behaviour to drug tolerance, that is, the reduction of drug effects following repeated administration of a constant dose.

The allostatic theory of addiction (Koob and Le Moal, 2001) addresses the disastrous consequences of chronic drug use on homeostatic regulation. The transition from controlled to compulsive drug use corresponds to spiralling down an ‘addiction cycle.’ At the beginning of moderate drug consumption, neuronal sensitisation to the drug’s effects facilitates preoccupation with the drug, which then leads to binge use of the drug owing to its pleasurable effects (a-process, positive reinforcement). However, as drug consumption is prolonged and intensified, the individual’s intoxication steadily appears and withdrawal symptoms become stronger and stronger during abstinence (b-process, negative reinforcement). These withdrawal symptoms, in turn, cause a stronger preoccupation with the drug, so that subsequent spiralling through the addiction cycle begins at a higher level of intensity. In the end, extended drug consumption constantly shifts the organism’s physiological parameters outside of the normal homeostatic range in order to counter the multiple effects of chronic demands, resulting in a progressive depletion of the organism’s resources. Homeostatic deregulation is assumed to reduce the ability of brain reward systems to regulate the individual’s motivational state regarding a drug. Thus, the individual would develop compulsive behaviour, not to obtain more pleasure with the drug, but because this would be the only means of avoiding the increasingly aversive consequences of withdrawal. For instance, escalation in cocaine self-administration was observed in rats allowed access to the drug for 6 h a day, compared with the stable, moderate consumption of animals with
access to the drug for only 1 h a day (Ahmed and Koob, 1998). The rats also were tested with different doses of cocaine, and self-administration in the rats belonging to the 6-h group was twice as high as in the rats from the 1-h group, regardless of the dose used. This difference is explained by a change in the physiological set-point of the rats.

In contrast with concurrent views of addiction that emphasize sensitisation of the mesolimbic dopamine system in addicts (e.g. Robinson and Berridge, 1993; Robbins and Everitt, 1996; Taylor and Jentsch, 2001; Bradberry, 2000, 2002; Di Chiara, 2002; Leyton, 2007), the allostatic theory implies that addiction results from ‘a hypofunctioning of neurotransmitter systems involved in positive reinforcement and a recruitment of neurotransmitter systems involved in negative emotional states that provide the motivation for negative reinforcement’ (Koob and Le Moal, 2001). Therefore, affective symptoms (dysphoria, depression, irritability, and anxiety), as opposed to the physical ones (sudation, trembling, etc.) caused by withdrawal, can motivate drug taking. These symptoms have been observed during abstinence from chronic use of all major drugs of abuse and seem to be correlated with a reduced functioning of reward systems; the neurochemical changes observed mainly include decreased levels of dopamine and serotonin in the nucleus accumbens during cocaine withdrawal (Weiss et al., 1992; Parsons et al., 1995), increased sensitivity of opioid receptors in the nucleus accumbens during morphine withdrawal (Stinus et al., 1990), decreased GABAergic and increased NMDA glutamatergic transmission during alcohol withdrawal (Fitzgerald and Nestler, 1995; Roberts et al., 1996; Weiss et al., 1996), as well as increased activation of the hypothalamic-pituitary–adrenal axis, the brain stress systems (Koob and Le Moal, 1997), and the corticotropin-releasing factor (Rodriguez de Fonseca et al., 1997).

A number of studies have highlighted a massive reduction in neurotransmitters, usually considered to play a determining role in reward-related brain regions (e.g. dopamine in the nucleus accumbens), during withdrawal from chronic drug use. For example, Ben-Shahar et al. (2004) observed that 14 days after an 8-day protocol of cocaine self-administration, rats having experienced 6 h of daily access to cocaine showed reduced synaptic activity – assessed by c-Fos-positive cell counts – in dopaminergic mesocorticolimbic brain regions, while rats having experienced only 1 h of daily access showed sensitised synaptic activity. Correspondingly, behavioural sensitisation in response to a single intravenous cocaine injection was not shown in the animals of the 6-h access group (where cocaine consumption became uncontrolled), whereas it was observed in the animals of the 1-h access group (where cocaine consumption remained stable and moderate) (Ben-Shahar et al., 2004). These results are consistent with the view that compulsive drug use recruits counteradaptive processes that deregulate brain reward systems, and therefore suppresses the effects of sensitisation, and resets an hedonic set-point upwards (see Koob and Le Moal, 2001). In another study, Lenoir and Ahmed (2007) compared rats allowed to self-administer heroin for 1 or 6 h per day, with respect to locomotion and the reinstatement of drug-seeking behaviour after receiving priming injections. Over a self-administration period of 18 days, heroin-seeking behaviour was subjected to two extinction tests in both groups after a withdrawal period of 24 h. A test consisted of four successive extinction phases of 45 min each, followed by an injection of a non-contingent dose of heroin whose volume was progressively increased. After extinction, it was observed during Test 1 that locomotion was identically stimulated in both groups, but that after the injection locomotion was only sensitised in rats with 1-h access during Test 2. It also was shown that, in both tests, heroin reinstated drug seeking in a dose-dependent manner in the 6-h access rats but not in the 1-h access rats. Therefore, sensitisation of locomotion observed in the 1-h access rats seemed to have a different origin from the priming effects of heroin. As recognized by Lenoir and Ahmed (2007), however, such a conclusion must be drawn cautiously because longer exposure of the 1-h access rats to heroin might have allowed the reinstatement of drug-seeking behaviour, as shown by other studies (e.g. Stewart and Wise, 1992; De Vries et al., 1998; Yao et al., 2005). In addition, the absence of conditioned stimuli paired with heroin injections might have restrained the development of the reinstating effects in these rats (e.g. Shaham and Stewart, 1995; Fattore et al., 2003; Leri et al., 2003). Finally, the development of a compulsive action pattern and the reinstatement of heroin-seeking behaviour in the 6-h access rats do not seem to involve sensitisation. However, it must be noted that a withdrawal period of 24 h is very short; it cannot be excluded that sensitisation would appear after longer drug deprivation (for reviews, see Vanderschuren and Kalivas, 2000; Vezina, 2004).

Is the allostatic theory able to explain the nonlinear effect of drugs on the receptiveness to natural rewards? Conceptually, I believe that the theory can illuminate this issue. First, an increase in the attractiveness of natural rewards during moderate drug consumption can be understood in terms of dopamine nonspecificity. In the next section, it will be shown that nonspecificity can account for the numerous findings that the interest exhibited in a reinforcer is transposed to another reinforcer when circumstances are favourable (e.g. Panksepp, 1998; Cosgrove et al., 2002). Second, the allostatic decrease in brain reward function with prolonged access to drug can explain, in principle, why addicts neglect natural rewards in favour of drug rewards (Ahmed et al., 2003; Lenoir and Ahmed, 2007). Indeed, an excessive preoccupation with obtaining a drug, in order to avoid withdrawal symptoms, should reduce interest in other rewarding events. The allostatic theory is therefore conceptually appropriate to account for the interactions between drug and natural rewards reported in this paper. However, the comments mentioned below imply that the theory fails to reflect important empirical results. In addition, the lack of reliable data before and after the period of time within which neural desensitisation appears, does not permit the conclusion that desensitisation is responsible for compulsive drug use. Thus, the role allostasis plays in the neglect of natural rewards during prolonged drug use currently remains undetermined.

It is now a well-documented fact that sensitisation of dopaminergic neurons develops about 10 days after discontinuation of limited drug use, but is not observed when a drug is consumed at higher doses (Markou and Koob, 1991; Benwell et al., 1995; Wise and Munn, 1995; Ahmed et al., 2002; Crombag et al., 2002; Leri et al., 2003; Ben-Shahar et al., 2004; Ahmed and Cador, 2006; Morgan et al., 2006). According to the allostatic theory, the appearance of withdrawal symptoms during interruption of drug use can elicit a motivation to seek and take the drug again. However, a series of findings directly challenge this view. For instance, drugs such as tricyclic antidepressants and kappa opioid agonists induce strong tolerance and withdrawal symptoms but are never consumed compulsively (Jaffe, 1992). It must also be noted that after extinguishing heroin self-administration in rats, reinstatement of heroin-taking behaviour is easier after a priming injection of heroin in these animals than after the injection of an opioid receptor antagonist whose effect is to cause withdrawal symptoms (Stewart and Wise, 1992; Shaham et al., 1996). Finally, tolerance and withdrawal symptoms always disappear after a few days (e.g. Gawin and Kleber, 1986; Kornetsky and Bain, 1990; Legault and Wise, 1994; Parsons et al., 1995), so that allostasis cannot convincingly explain the relapse of individuals several months after interrupting drug administration (Robinson and Berridge, 2000).
The lack of correlation between the appearance of withdrawal symptoms and drug consumption seems to exclude withdrawal as the primary cause of addiction, although opiate withdrawal has been shown to affect subsequent heroin-seeking behaviour (Helleman et al., 2006). This also casts some doubts on the idea that addiction depends on allostasis rather than on sensitisation. Assuming that withdrawal symptoms are transient and correlated with neural desensitisation, then neural desensitisation should be transient as well. This phenomenon remains largely unobserved because, as Vezina et al. (2007) point out, the assessment of dopaminergic responsiveness in the mesocorticolimbic region is usually systematically conducted at short withdrawal times following repeated drug injections (e.g., Hope et al., 1992; Ennulat et al., 1994). These withdrawal times usually extend from 1 day (e.g., Lenoir and Ahmed, 2007) to 2 weeks (Ben-Shahar et al., 2004). However, they may not be long enough to induce neural sensitisation in animals subject to chronic drug use. Sensitised dopaminergic overflow in the nucleus accumbens has been reported 3 weeks following exposure to nicotine (Schoffelmeer et al., 2002) and even 3 months following exposure to amphetamine (Hamamura et al., 1990) (see also Fig. 2). In summary, the allostatic theory is consistent with the view that sensitisation is a time-dependent phenomenon (Antelman, 1988; Henry and White, 1995; Paulson and Robinson, 1995), but additional experiments are required to better understand the causal and functional significance of transient desensitisation on compulsive behaviour, as well as on the subsequent development of sensitisation observed with many drugs after longer periods of withdrawal.

According to Berridge (2007), incentive salience is a normal, temporary process allowing the sensory or memory representation of a stimulus (food, water, partner, etc.) to be translated into a reward. This predisposes the individual to seek food when hungry, or water when thirsty, until these rewards can be found. Drugs also activate this process although prolonged drug consumption is believed to induce persistent neuroadaptations that progressively sensitize an organism to the drug as well as to contextual stimuli associated with drug taking (Robinson and Berridge, 1993, 2000); ‘incentive-sensitisation’ represents a longer-lasting version of incentive salience.

A core principle of the incentive-sensitisation theory is that reward is not a unified brain mechanism but rather two distinct processes called ‘wanting’ and ‘liking’ (Berridge and Robinson, 1998). Incentive-sensitisation would result in an exaggeration, in terms of duration and intensity, of the ‘wanting’ process, brought about by increased levels of mesolimbic dopamine in the nucleus accumbens. In contrast, ‘liking’ seems to be determined by GABA systems in the brainstem and opiate systems in the nucleus accumbens shell (Berridge and Robinson, 1998). A double dissociation then can be artificially induced between both processes (Berridge, 2007). ‘Liking’ without ‘wanting’ is obtained by neurochemically destroying dopamine projections or blockading dopamine receptors (Berridge et al., 1989; Pecina et al., 1997; Berridge and Robinson, 1998). In this case, animals dramatically reduce their reward-seeking behaviours because they are unable to attribute incentive salience to previously motivating stimuli, while the affective facial reactions they express during the consumption of these stimuli remain unchanged. After the destruction of mesolimbic projections of dopamine using the neurotoxin 6-OHDA, rats develop profound aphagia, although they continue to like food and even learn hedonic associations between food and other stimuli (Ungerstedt, 1970; Berridge et al., 1989). The rats merely stop eating because the food loses its attractiveness. Conversely, electrical stimulation of the lateral hypothalamus in rats produces ‘wanting’ without ‘liking’. The rats adopt reward-seeking behaviours but exhibit negative hedonic facial reactions when they consume a reward (Berridge and Valenstein, 1991; Pecina et al., 2003). Interestingly, such a double dissociation between ‘wanting’ and ‘liking’ also has been recently demonstrated in humans in relation to food (Flinlayson et al., 2007).
In everyday language, both processes are referred to as conscious states: explicit wanting designates the desire to consume a reward; explicit liking is the hedonic reaction to that reward during its consumption. Here, it is suggested that wanting and liking also might function as core psychological processes at the unconscious level: implicit wanting (or ‘wanting’) would consist of attributing incentive salience to a stimulus in order to make it attractive, implicit liking (or ‘liking’) would be an unconscious affective reaction. Such unusual interpretations are supported by a series of empirical findings that revealed the appearance of incentive salience and hedonic reactions for stimuli independently of any subjective awareness (Wyvell and Berridge, 2000; Berridge and Winkielman, 2003; Berridge, 2004; Winkielman et al., 2005). However, several authors protest that the use of such terminology produces ambiguousness (Di Chiara, 2002; Robbins and Everitt, 2007). In particular, it is argued that ‘a state of wanting normally requires an object that is desired and it is unclear how this presumably ‘subconscious’ process of wanting can be linked to representations of such specific goals’ (Robbins and Everitt, 2007). This point highlights an important problem for the incentive-sensitisation theory concerning its ability to explain the nonlinear effects of drugs on receptiveness to natural rewards.

To date, there is general agreement that dopamine is involved in the reward process, even though some differences exist among authors concerning its exact role (e.g. Wise, 1982; Robbins and Everitt, 1996; Taylor and Jentsch, 2001; Koob and Le Moal, 2001; Di Chiara, 2002; Salamone and Correa, 2002; Franken et al., 2005; Vanderschuren and Everitt, 2005). Despite unavoidable theoretical differences, perhaps due to the inextricable relationship between dopamine and brain functions, most of these authors admit that higher levels of dopamine in mesolimbic brain regions increase sensitivity to numerous sources of reward (see Section 2.1). As dopamine is a nonspecific neurotransmitter, a connection between the multiple sources of rewards becomes possible. Carelli et al. (2000) showed that 8% of accumbal neurons activated during water consumption in rats also were activated during cocaine consumption, and a greater percentage of overlap was discovered in other studies. Bowman et al. (1996) recorded neuronal activity in monkeys working in blocks of trials for juice and then working in blocks of trials during which they self-administered cocaine. The in monkeys working in blocks of trials for juice and then working in blocks of trials during which they self-administered cocaine. The in monkeys working in blocks of trials for juice and then working in blocks of trials during which they self-administered cocaine. The in monkeys working in blocks of trials for juice and then working in blocks of trials during which they self-administered cocaine. The

In short, on the one hand, the incentive-sensitisation theory accounts for the nonspecific brain action of drug-induced dopamine, which can stimulate the attractiveness of other reward categories. On the other hand, its explanation that a drug may have a targeted impact on specific brain regions, leading to the development of compulsivity and therefore to a disinterest in natural rewards, remains less convincing, as other authors also noted for different reasons (Di Chiara, 2002; Vanderschuren and Everitt, 2005).

3.3. Theories pointing to the role of conditioning and attention in addiction

Several theories are partially in accordance with the incentive-sensitisation framework, but consider that other processes also are involved in the development of addiction, such as associative learning (Robbins and Everitt, 1996; Jentsch and Taylor, 1999; Di Chiara, 2002) and attention (Sarter and Bruno, 1999). One theory proposed by Di Chiara (2002) is that the basic disturbance of drug addiction takes place as a result of Pavlovian incentive learning. The incentive properties of drug stimuli would be dopamine-independent, but aroused by dopamine transmission in the nucleus accumbens shell following their repeated associations with non-drug stimuli—by this way, accumbal and behavioural sensitisations are mainly observed to occur after response-noncontingent exposure to cocaine (e.g. Ito et al., 2000; Lecca et al., 2007), although they may be also obtained after response-contingent exposure to...
cocaine in rats (Hooks et al., 1994) and mice (Zapata et al., 2003). Any kind of reward has the property of stimulating dopamine in the nucleus accumbens shell and core, and the dopamine released tends to decrease as exposure is repeated with respect to natural rewards. However, this habituation phase does not happen with drug rewards, resulting in a progressive counter-adaptive strength of associations between the drug and contextual stimuli. These associations become particularly resistant to extinction. Therefore, Di Chiara et al. (2004) surmise that the nucleus accumbens may differentially affect addiction and ‘natural’ behaviour. Drug-conditioned stimuli seem to increase dopamine release in the nucleus accumbens shell, while food-conditioned stimuli influence dopamine secretion in the nucleus accumbens core (Di Chiara et al., 2004). Thus, drug- and food-conditioned stimuli do not exert a similar impact on dopamine release and, hence, on behaviour. The overproduction of dopamine in the nucleus accumbens shell during repeated exposure to a drug and conditioned stimuli would cause the typical motivational abnormalities observed in addiction. Such a maladaptive behavioural pattern is also hypothesized to occur as a result of the same process in the case of a pathological relation to food (Di Chiara, 2005). This theory is interesting because it contrasts drug and natural rewards in the explanation of addiction, but unfortunately it does not address the problem of their paradoxical interactions.

Jentsch and Taylor (1999) argued for another theory in which compulsive drug-seeking behaviour results from dysfunctions of two important brain regions. First, amygdalar/limbic dysfunction would increase the incentive motivational qualities of a drug in enhancing the release of mesolimbic dopamine. Repeated exposure to the drug would connect its rewarding qualities with drug-associated stimuli, which then control drug-related behaviour to a greater extent and lead to the development of compulsion. There is indeed evidence that repeated drug administration induces amygdalar neuroadaptations, facilitating the learning of associations between drug and contextual stimuli, a process known to occur during craving (Grant et al., 1996; Childress et al., 1999).

Second, corticofrontal dysfunction would impair behavioural inhibition, but also learning and memory, yielding an abnormal vulnerability, and therefore an increased impulsivity, for drug and drug-associated stimuli (Taylor and Jentsch, 2001). The involvement of the prefrontal cortex in compulsive drug seeking has been highlighted (Berchera et al., 2000; Brown and Bowman, 2002). In short, a growing interest in drug rewards due to amygdalar/limbic alterations is hypothesized to be more and more difficult to inhibit because of corticofrontal impairments.

According to Robbins and Everitt (1996), the basolateral amygdala, the hippocampal formation, and the prefrontal cortex play a central role in addiction due to their afferents to the striatum, which in turn projects to the output systems—via the lateral hypothalamicus from the nucleus accumbens shell and via the ventral pallidum from the nucleus accumbens core. In particular, the amygdala would convey associative information about environmental stimuli that predict the occurrence of reinforcers, the hippocampus would underlie conditioning to contextual stimuli as well as their motivational impact on drug-seeking, and the prefrontal cortex would mainly be involved in the reinstatement of drug seeking (Everitt and Robbins, 2005). This theory indicates that changes occurring from controlled to compulsive drug use result from unidirectional cascades of information processing towards the striatum. While drug seeking primarily depends on the prefrontal cortex during voluntary drug use, this behaviour would become more and more controlled by the striatum as habitual, compulsive drug use develops. Even in the striatum, a transition of control is assumed to progress from its ventral part (nucleus accumbens) to its dorsal part (caudate-putamen) (Belin and Everitt, 2008). The dorsal striatum is logically assumed to precipitate drug abuse because it is involved in habit learning, which is a persistent learning process, even after devaluation of the reward (Dickinson et al., 1983).
compulsive drug seeking. Once again, though, this does not explain why moderate drug experience can make natural rewards more attractive.

4. The anticipatory dynamics model

The anticipatory dynamics model was created to bring a theoretical solution to different psycho-ethological problems that arise as soon as an organism’s behaviour is subject to the simultaneous influence of more than one motivation (Anselme, 2007, 2008). Although the ADM relies on plausible neurophysiological processes, the description of these processes has remained succinct. It is argued here that the ADM may be used to explain the interactions between drug and natural rewards. Before illustrating the ADM’s functioning principles when multiple motivations are involved, it is important to explain how motivational specificity is conceived within the model. As a reminder, motivational specificity was presented as the missing piece of the incentive-sensitisation theory to account for the opposite effects of drug rewards on natural rewards. It must be recognized that the ADM cannot explain habit learning, which yet seems to play a role in the development of addiction (e.g. Everitt and Robbins, 2005). The ADM attempts to account for the effects of drug-induced motivational abnormalities (cf. Di Chiara, 2002) on the attractiveness of natural rewards rather than the appearance of goal-independent stimulus-response patterns. Section 4.1 deals with dopamine’s role in relation to anticipation and uncertainty; Section 4.2 provides an interpretation of motivational specificity on this basis; Section 4.3 shows how motivation is represented in the ADM; and Section 4.4 describes the principle of motivational interactions according to the ADM.

4.1. Dopamine’s role in motivation

The extensive literature on dopamine allows us to draw some conclusions with respect to its role in the brain. First, dopamine has a nonspecific brain action. Indeed, a majority of dopamine neurons synchronically fires for any type of salient stimulus, irrespective of its motivational value (Schultz, 1998; Horvitz, 2000). Second, the phasic dopamine response is correlated with the anticipatory phase of behaviour. It is observed during appetite (Berridge and Robinson, 1998), during stress related to the expectation of an aversive event (Gray et al., 1997), during alert induced by a conditioned stimulus (Ljungberg et al., 1992), when obtaining an outcome is delayed (Whishaw and Kornelsen, 1993; Hutcheson et al., 2001), and upon facing unfamiliar or unpredicted stimuli (Schultz, 1998). Third, anticipation is not, however, the cause of the phasic dopamine response. No dopamine release is recorded for predicted stimuli (Schultz, 1998), and the short latency of the phasic response – about 50–100 ms – cannot result from any prior cognitive processing of information (Redgrave et al., 2008). Finally, it is also important to note that dopamine’s role in motivation is mainly carried out from the core rather than the shell region of the nucleus accumbens. The nucleus accumbens core is essential for directional/discriminative instrumental responding to appetitive stimuli (Everitt et al., 1999; Parkinson et al., 1999), aversive stimuli (Di Chiara, 2002), conditioned olfactory stimuli (Bassareo and Di Chiara, 1997, 1999), and delayed outcome (Everitt and Robbins, 2005). I suggest that phasic dopamine responses are induced by events comprising uncertainty with respect to stimulus arrival. In this respect, conditioned stimuli are often followed by a phasic dopamine response because reward-obtaining behaviour is only contingent on these stimuli—the animal cannot be sure that the reward will be delivered, even though its probability of occurrence is high. Interestingly, a conditioned light also stops causing a phasic dopamine response after animals have learned the delay between its occurrence and that of the reward (Schultz et al., 1993). Repeated exposure to this fixed association results in the reward being represented as almost certain. In contrast, the phasic response continues to occur provided that the interval of time between the light and reward is a randomly variable delay (Schultz et al., 1993).

To deal with uncertainty implies that organisms possess some anticipatory capabilities, but as indicated above, it is unlikely that anticipation is the cause of the phasic dopamine response. I therefore make the assumptions that (i) dopamine is necessary to facilitate anticipation in different corticolimbic areas, notably the basolateral amygdala and prefrontal cortex, owing to ascending projections from the ventral tegmental area, and (ii) the nucleus accumbens, especially the core region, is the convergence zone for anticipatory signals because it receives glutamatergic inputs from these corticolimbic areas as well as direct dopaminergic inputs from the ventral tegmental area. There is indeed evidence for an excitatory role of glutamatergic NMDA receptors in the nucleus accumbens on dopamine efflux (Floresco et al., 2001; Howland et al., 2002). The basolateral amygdala not only sends a dense projection that synapses in close apposition to accumbal dopamine varicosities (Johnson et al., 1994), but also indirectly regulates accumbal dopamine efflux in altering dopamine neuronal firing in the ventral tegmental area via glutamatergic afferents to the medial prefrontal cortex, which in turn projects to this area (e.g. Taber and Fibiger, 1995; Jackson and Moghaddam, 2001). The nucleus accumbens is suitable for centralizing the anticipatory signal owing to its connections with motor systems—allowing animals to reduce uncertainty as soon as possible in adopting an appropriate action. Thus, dopamine is necessary for anticipation to occur. Despite the importance of experimental results collected by Schultz and his colleagues, their interpretation of dopamine’s role in terms of reward-related ‘error prediction signal’ is challenged here. They suggest that dopamine release is observed after a conditioned stimulus because this stimulus predicts reward arrival, whereas the transient absence of dopamine release at the usual time of reward delivery, when this reward is not delivered, signals an error in predicting its occurrence (for reviews, Schultz, 1998, 2000; for a computer model, Montague et al., 1996). One difficulty already mentioned with this interpretation is conceiving anticipation as a prerequisite for dopamine release—no prediction without anticipation. Another difficulty pointed out by Redgrave et al. (1999, 2008) is that, in nature, dopamine would be an unreliable error prediction signal of reward since its phasic release arises in the case of events, such as unpredicted and unfamiliar stimuli, whose rewarding value cannot be known in advance (see also Horvitz, 2000). The idea developed here is compatible with the general principle of the incentive-sensitisation theory that dopamine contributes to the motivational value of a stimulus (Berridge and Robinson, 1998). However, it is not believed that dopamine carries the ‘wanting’ signal, or even any motivation per se. Dopamine is only assumed to facilitate anticipation, allowing for an understanding that it is not specifically involved in rewards, in which the role of anticipation in wanting is regarded as a particular case. On the basis of this view, a theory of motivational specificity is developed in the next section. This theory is the key that enables the ADM to explain motivational interactions.

4.2. Motivational specificity

It is suggested above that dopamine is not the motivational signal in itself but rather an essential causal factor of motivation
owing to its facilitating impact on anticipatory processes. A major issue is to understand how this nonspecific causal factor can lead to the appearance of motivations, that is, psychological states of enhanced receptiveness to specific objects in the world (food, water, partner, cocaine, novelty, etc.). I propose that motivational specificity results from the combined action of dopamine on anticipation, as already seen, as well as on the neuropharmacological processes facilitating task-related attention. Anticipation and attention are indeed two psychological phenomena that, in essence, highlight specific objects. A series of empirical findings indicate that dopamine acts, though indirectly, on attentional processes through what might be called the ‘dopaminergic–cholinergic pathway’ (Sarter and Bruno, 1997, 1999).

Sarter and Bruno (1997, 1999) argued that attentional performance is correlated with the activation of cholinergic neurons of the basal forebrain and of cholinergic projections ascending from the basal forebrain to the cortex. The organization of cortical cholinergic inputs does not reflect a strong topographic pattern; all cortical areas and layers receive cholinergic fibres (Sarter and Bruno, 1997). These inputs have been shown to enhance neuronal responses to stimuli in visual, auditory, somatosensory, and prefrontal cortices (e.g. Müller and Singer, 1989; Metherate et al., 1990; Andrade, 1991; Jacobs et al., 1991). In the visual cortex, for instance, acetylcholine ‘enhances and sharpens the cellular responses to the preferred stimulus characteristics while suppressing the less prominent responses to other features of the stimulus’ (Sarter and Bruno, 1997). Only phasic release of acetylcholine seems to have such cognitive effects (e.g. Richardson and DeLong, 1991; Metherate and Ashe, 1993; Moore et al., 1993). Tonic releases appear to be more correlated with wakefulness and arousal (e.g. Kametani and Kawamura, 1991; Marrosu et al., 1995). The fact that cortical cholinergic inputs facilitate the processing – detection and identification – of sensory stimuli does not mean, however, that they activate selectively specific cortical areas or layers in order to process modality-specific information (Sarter and Bruno, 1997). The cholinergic system’s action is global rather than organized to activate specific local neuronal populations depending on sensory inputs. This property is adaptive since it permits organisms to decide which stimuli are or are not relevant in a situation, probably as a function of their physical or learned salience. Interestingly for our purpose, the basal forebrain’s cholinergic activation depends on dopamine secretion originating in the ventral tegmental area and is stimulated in rats for a variety of tasks utilizing selective, sustained and divided attentional resources (Sarter et al., 1999). As explained, mesolimbic dopamine stimulates the activity of cholinergic neurons in inhibiting the inhibitory GABAergic projection ascended from the nucleus accumbens to the basal forebrain (Zaborszky and Cullinan, 1992; Sarter and Bruno, 1999). In accordance with this, it is the finding that the nonsel ective dopaminergic antagonist cis-flupenthixol (Himmelheber et al., 2000) and the inverse agonist FG 7142 (Moore et al., 1999) reduce the excitability of the cholinergic neurons in that brain region. In human addicts, there is evidence that reducing attentional bias to the levels of accumbal dopamine that are required to stimulate the attention threshold (or A-threshold). The A-threshold corresponds to the levels of dopamine in the basal forebrain. Himmelheber et al. (2000) showed that amphetamine-induced dopamine affected the performance of rats in a sustained attentional task by stimulating cortical cholinergic neurons only, if the perfusion of amphetamine was carried out in the nucleus accumbens core. The performance of rats remained unaffected when the perfusion took place in the nucleus accumbens shell.

Motivational specificity is therefore hypothesized to correspond to the activation of the dopaminergic–cholinergic pathway as a result of the perception or representation of a salient stimulus (Fig. 3). Saliency of the stimulus can be physical (stimulus intensity) or psychobiological (survival- or pleasure-related stimulus). This approach to motivation is original since motivation is conceived as the emergent product of what has already been called ‘anticipatory attention’ (Anselme, 2007, 2008). Anticipatory attention – that is, the psychological state correlated with activation of the dopaminergic–cholinergic pathway – remains nonspecific as long as its source of stimulation is not consciously identified and therefore can be referred to as general arousal (Bindra, 1978), incentive arousal (Di Chiara, 2002) or incentive salience (Berridge and Robinson, 1998), provided that the word ‘salience’ is not applied to a specific object. For instance, a photograph of a happy facial expression presented subliminally, fails to produce any conscious report of an emotion, but increases a person’s subsequent consumption of a fruit drink and its subjective rating, in comparison with a person having subliminally seen an angry face (Berridge and Winkielman, 2003). This experimenter-guided transfer of sensitivity from facial expressions to the fruit drink empirically supports the view that the underlying process of motivation remains nonspecific when it is stimulated by an unconscious event—a notion poorly captured by the word ‘wanting’. However, anticipatory attention is specific when a salient stimulus is consciously perceived or represented and then can be referred to as motivation. In this case, attention is spontaneously oriented toward that stimulus, or related ones. The attentional processes may be either automatic, when attention is suddenly attracted by an unexpected external event, or volitional, when attention is characterised by task demands. Task-related attention may be said to be ‘volitional’ (Bushman and Miller, 2007), although an automatic – involuntary and unintentional – focus of attention on specific stimuli during a task, such as drug seeking, cannot be excluded (Franken et al., 2005). This theory has the advantage of providing a mechanism for relating motivational specificity to the continuum of nonspecific arousal. Neuropharmacologically, both rely on dopamine and acetylcholine as their essential causal factors. Thereafter, the expression ‘causal factors’ will stand for ‘levels of dopamine in the nucleus accumbens’; it will never designate environmental incentives, or cognitive states such as representations, anticipations, or thoughts. We can now envision how the concept of anticipatory attention allows for the representation of motivations and motivational interactions in the ADM.

4.3. Two thresholds of a motivation’s causal factors

To be triggered, all types of behaviour require motivation to reach a given intensity, known as the reactivity threshold (or R-threshold) (Hogan, 1997). This intensity level may vary according to learning or the context (e.g. Balleine, 1992; Hogan and Van Boxel, 1993). However, in a previous paper I showed that another type of threshold also must be taken into account to explain an organism’s behaviour, when several of its motivations are simultaneously activated (Anselme, 2007): the anticipatory attention threshold (or A-threshold). The A-threshold corresponds to the levels of accumbal dopamine that are required to stimulate cortical acetylcholine and spontaneously orient attention to a particular stimulus. It must be noted that attentional processes are multi-determined in the brain and therefore they do not linearly
depend on the dopaminergic–cholinergic pathway emphasized here. For instance, bilateral neurotoxic lesions of the amygdala central nucleus as well as damage to the dorsolateral striatum impair the expression of conditioned orienting responses to sensory cues for biologically significant events (Gallagher et al., 1990; Han et al., 1997). The expression of conditioned orienting responses seems to be mediated by the central nucleus through a dopamine projection to the dorsolateral striatum, which then projects to the substantia nigra pars compacta. As a result, unilateral lesions of the dopamine nigrostriatal system bring about deficits in orienting to stimuli presented contralateral to the site of the lesions (Fairley and Marshall, 1986). This pathway may therefore play a crucial role in the development of addiction.

The ADM's two thresholds are hypothetical constructs. They must be seen as convenient simplifications of complex processes translating nonspecific causal factors into a specific motivation (for the A-threshold) and this specific motivation into an action (for the R-threshold) (Fig. 4). The A-threshold is difficult to define operationally in an experiment, owing to its pre-behavioural expression; however, in a subsequent section I describe an experiment using a procedure of reinforcements in which the A-threshold can be indirectly assessed. The case of the R-threshold is easier since this parameter reflects behavioural expression and traditionally is measured using reaction time tasks (e.g. Baddeley, 1990).

4.4. Motivational interactions

The ADM is a model of motivational interactions in which A-thresholds perform a nonlinear input-output transformation. The

![Fig. 3. Simplified schema highlighting the defining neuropsychopharmacological features of the processes leading to motivational specificity. Salient stimuli (physical or mental) cause phasic dopamine (DA) responses in the ventral tegmental area (VTA). These DA responses sensitise neurons in the nucleus accumbens, notably in the core region (NAc core), and thereby facilitate anticipatory processes in the prefrontal cortex (PFC) and the basolateral amygdala (BLA). The glutamatergic projection (GLU) from the (basolateral) amygdala and the (medial) PFC to the NAc core would amplify the nonspecific sensitisation of accumbal neurons, which code an anticipatory signal. This signal would be conveyed to cholinergic neurons in the basal forebrain (BF) through the GABAergic projection ascending from the NAc core. A large number of cortical areas (visual, auditory, etc.) then receive cholinergic (ACH) inputs from the BF. Phasic ACH release allows for the attentional processing of sensory stimuli (detection and identification), although this release is nonspecific for a given sensory modality. This concatenation of brain mechanisms is assumed to be the substrate of anticipatory attention. Anticipatory attention is hypothesized to increase an individual's receptiveness to specific stimuli in the environment depending on circumstances, and therefore to favour approach or avoidance behaviours. Black arrows: the process of anticipatory attention; white arrows: motivational and behavioural consequences of anticipatory attention; grey arrow: role of context in stimulus-relevance attribution.

![Fig. 4. Motivation is an object-specific psychological state relying on nonspecific causal factors (especially accumbal dopamine). For a given motivation, causal factors (represented in grey) have two thresholds. The A-threshold always designates a smaller intensity of causal factors than the R-threshold. This is a logical postulate: the A-threshold needs to be of weaker intensity than the R-threshold to allow organisms to pay attention to the object of their action before carrying it out. The consequence of this postulate will be explained in Section 4.4.]

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The ADM is a model of motivational interactions in which A-thresholds perform a nonlinear input-output transformation. The...
intensity of the A-threshold is close to zero for one motivation when this motivation is the only one to be activated at a time in the organism (e.g. the search for food is the single thing of interest at the time), so that the A-threshold of this motivation’s causal factors can normally be reached with low mesolimbic dopamine levels. However, this motivation makes the appearance of concurrent motivations in raising the A-threshold of concurrent causal factors more difficult. Indeed, according to the ADM, motivation involves attentional processes with limited resources. This attentional limitation of organisms means that they can barely allocate resources to more than one thing at a time. The limiting features of attention have been documented in humans (e.g. Noble et al., 1981; Shallice et al., 1985; Hirst and Kalmar, 1987) as well as in animals (e.g. Maki and Leith, 1973; Zentall et al., 1997; Lejeune et al., 1999; Dukas and Kamil, 2001). Such a constraint has an immediate, automatic repercussion on the organism’s other motivations. When a motivation increases, because the anticipatory attention process boosts it, this causes the inhibition of the organism’s other motivations due to a rise in their A-threshold. Conversely, when a motivation decreases because its object is of weaker interest, there is a disinhibition of the organism’s other motivations due to a lowering of their A-threshold. Fig. 5A and B show schematically the general principles of inhibition and disinhibition. (A mathematical formulation of the model is found in Anselme, 2007.)

When two motivations are involved, we can depict the consequence of the ADM’s postulate stated above that, for a given motivation, the A-threshold always designates a smaller intensity of its causal factors than the R-threshold. Given this postulate and the mechanism of inhibition/disinhibition, it can be predicted that when a motivation’s causal factors raise their A-threshold, this in turn raises the R-threshold of concurrent causal factors. As shown in Fig. 5A, the R-threshold of concurrent causal factors is in a way ‘pushed’ by the increasing A-threshold. The rise of the r-threshold of a motivation explains why people’s reaction times are slowed down when they do two tasks simultaneously (Baddeley, 1990). Similarly, a tame bird will be willing to eat close to human beings even if it is not very hungry, whereas a wild bird will stay away despite strong hunger. In the case of the tame bird, the R-threshold of the feeding motivation is low because this motivation can be expressed without any constraints, that is, the A-threshold remains low. In contrast, the wild bird exhibits a fear of humans that conflicts with its feeding motivation. This fear is assumed to inhibit the feeding motivation by raising its A-threshold and therefore inhibiting the bird’s reactivity in raising this motivation’s R-threshold. Empirical findings by Weinstein et al. (1998) support the model’s predictions in the field of opiate and alcohol addictions.

It might be said that representing two different motivations on the same scale of intensity (as we do) is nonsense. After all, do motivations such as the one to feed or copulate have anything in common with motivations such as to play or take drugs? Such criticism would be warranted when comparing the environmental and physiological causal factors of two motivations. These are qualitatively so different from one motivation to another that it would be unrealistic to make such a comparison. In contrast, those difficulties seem to disappear, or at least are dramatically reduced, when the causal factors of motivations are considered at a neuropharmacological level. Mesolimbic dopamine and cortical acetylcholine are pharmacological common currencies (Sarter and Bruno, 1997; Berridge, 2004) thereby allowing different motivations to be compared with each other on the same scale of intensity (in the same vein, see Cabanac, 1992). In my opinion, a strong argument for this approach is the existence of a possible substitution between two reinforcers, as mentioned above (e.g. Cosgrove et al., 2002). If consuming one reward (for instance, a rat’s game in a running wheel) alleviates the need to consume another (such as cocaine self-administration), then both rewards presumably are expressed in the same ‘language,’ and comparing their intensities therefore is a reasonable solution.

5. How the ADM explains the interactions between drug and natural rewards

If motivations are object-specific psychological states that depend on nonspecific causal factors, then it becomes possible to understand how different motivations can interact by means of their causal factors. So according to the ADM, what does happen when drug consumption is recent and moderate? Drug use elicits an addictive motivation of a relatively low intensity. Thus, this motivation moderately and temporarily raises the A-threshold of the motivations for natural rewards. For instance, cocaine consumption in rats temporarily causes a dose-dependent inhibition of hunger for approximately 1 h (Cooper and van der Hoek, 1993). The neuroadaptations due to drug consumption remain limited, so the subjects continue to search for food and eat. In turn, it is probable that a subject’s motivations for natural rewards also moderately and temporarily inhibit the addictive motivation by raising its A-threshold (e.g. Cosgrove et al., 2002). However, since the rise in the A-threshold of both types of motivations remains weak, they can continue to express themselves. What kind of relationship does the subject have with natural rewards under these conditions? Taking into account that mesolimbic dopamine and cortical acetylcholine are nonspecific for a given reward type, dopamine release induced by drug taking should therefore stimulate their attractiveness. Despite the rise in their A-thresholds, the motivations for natural rewards are increased by drug-induced dopamine release. A recent and moderate addictive motivation thereby explains why drug consumption sensitises an individual to natural rewards. Fig. 6A schematically depicts this process.

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**Fig. 5.** (A) Inhibition of a motivation M2 after the increase of a motivation M1. (B) Disinhibition of M2 after the decrease of M1. The dotted arrows represent the consequences for M2 of an increase or a decrease (continuous arrows) of M1. CF = causal factors. Here, inhibition and disinhibition are represented as total but they may be only partial.

**Fig. 6.** (A) When drug consumption is recent and moderate, it sensitises the individual to natural rewards due to the contribution of mesolimbic dopamine (DA). (B) When drug consumption is prolonged and/or is excessive, it desensitises the individual to natural rewards in spite of a massive contribution of dopamine: causal factors of their motivations can no longer (or rarely) reach their A-threshold. The R-thresholds are not represented.
This point of view is corroborated by the fact that a drug increases the interest of organisms in natural rewards when its dosage is moderate and especially when the administration period is short: on average, animal subjects received no more than 10 injections. For instance, Taylor and Jentsch (2001) facilitated the sexual behaviour of rats by administrating cocaine (15–20 mg/kg, i.p.), α-amphetamine (2.5 mg/kg, i.p.) or MDMA (2.5 mg/kg, i.p.) once or twice a day for 5 days. Fiorino and Phillips (1999) injected rats with amphetamine (1.5 mg/kg, i.p.) once every 2 days over 20 days and also observed the facilitation of sexual behaviour. These animals showed shorter latencies to mount as well as an increased rate of copulatory acts. Harmer and Phillips (1998) facilitated Pavlovian learning in rats with injections of α-amphetamine (2 mg/kg, i.p.) once per day for 5 days. Finally, Wyvell and Berridge (2001) sensitised rats to sucrose using amphetamine (3 mg/kg, i.p.) administered once a day for 6 days.

When drug consumption is excessive and/or sustained, the resulting addictive motivation is intense. It strongly elevates the A-threshold of motivations for natural rewards, causing a total (or quasi-total) inhibition of their attractiveness in the long term. Indeed, a prolonged period of drug taking induces long-lasting neuroadaptations ‘that may be similar to those seen in other neural systems in association with other forms of experience-dependent plasticity’ (Robinson and Berridge, 2000). The ADM represents these neuroadaptations as a progressive maintenance of the A-threshold for natural rewards at a much higher level than usual. Their A-threshold is prevented from lowering due to drug-induced changes in the mesocorticolimbic systems, which constantly enhance drug attractiveness. No re-equilibration of attention is then possible, so a constant attentional bias exists vis-à-vis the drug. As a result, if motivational inhibition for natural rewards is complete, the interest in these rewards becomes unable to affect the addictive motivation’s A-threshold in turn; no rewarding activity can alleviate the individual’s wanting of the drug. If the inhibition is quasi total, the rise in the addictive motivation’s A-threshold remains too weak to play a significant role in reducing drug attractiveness, which may account for compulsivity. Dopamine release induced by the drug effects remains insufficient to stimulate the attractiveness for natural rewards when their A-thresholds have been elevated so strongly. Here, drug consumption desensitises the individual to natural rewards, as illustrated in Fig. 6B.

Although there are only a few studies on compulsive drug-related behaviour in animals, these studies show the importance of a prolonged period of drug exposure in its development. For instance, Heyne (1996) used the opiate etonitazene (2, 4, and 8 mg/l) over a 30-week period 30. According to Deroche-Gamonet et al. (2004), 3 months of cocaine self-administration (0.8 mg/kg) were necessary for rats to develop an addiction. There is evidence that ‘personal’ vulnerability is an explanatory factor for the limited proportion of individuals suffering from this behavioural disorder (e.g. Laviola et al., 1999; Duka et al., 2000; Gordon, 2002; Chambers et al., 2003). However, as pointed out by Deroche-Gamonet et al. (2004), vulnerability is not solely responsible: it interacts with time exposure to the drug, which is also a key factor leading to addiction (see also Wolffgramm and Heyne, 1995; Robinson and Berridge, 2000; Vanderschuren and Everitt, 2004).

The prevalence of drug rewards over natural rewards is not a defining property of their interactions but a description of what is generally observed. In contrast, Lenoir et al. (2007) show that a 20-s access to water sweetened with saccharin (0.2%) is always preferred by rats to doses of cocaine (0.25 mg, i.v.), even in animals with a long drug history (6 h a day during 3 weeks). This preference is strong and stable and appears very quickly. Increasing the ‘price’ to pay – i.e. the number of lever presses – for saccharin does not induce a shift in preference, as sometimes reported in the case of other substances (for a review, see Bickel et al., 1995), but rather reinforces the attractiveness of saccharin. Although most studies indicate that animals prefer drugs to natural rewards (e.g. Woolverton and Balster, 1979; Nader and Woolverton, 1991), Lenoir et al. (2007) suggest that this may result from the absence (or modest concentrations) of sweet tastants in the rewards used. The reversed preference observed in their study does not therefore reflect a general tendency but constitutes an interesting, unexpected particular case—about which the ADM is totally permissive. Perhaps more problematic for the ADM is the evidence that intravenous cocaine self-administration seems to be more potent than sucrose or saccharin consumption in increasing dopamine levels in the nucleus accumbens (e.g. Pettit and Justice, 1991; Hajnal and Norgren, 2002). Sweet rewards would rather activate striatal opioid receptors, whose role in pleasure is well documented (e.g. Kelley et al., 2002; Pecina et al., 2006). However, whether these receptors can take over dopamine signalling in the control of behaviour is currently unknown (Lenoir et al., 2007). It cannot be excluded that sweet rewards, though less efficacious in presynaptic regions, may generate an overall postsynaptic dopamine signal more intense than cocaine due to the short-term receptor desensitisation and tolerance induced by cocaine (Lenoir et al., 2007).

In summary, by means of a single, simple mechanism, the ADM is able to explain the appearance of sensitivity to natural rewards as well as the subsequent desensitisation to these same rewards as a result of time exposure. In addition, the ADM represents other properties of compulsive behaviour: inflexibility and specificity of drug-seeking behaviour, as well as the origin of the inhibitory interaction among the motivations involved. Finally, the next section presents some findings showing, as the ADM predicts, that an individual’s strong addictive motivation increases the R-threshold of the individual’s other motivations.

6. Evidence for the rise of R-thresholds in addicts

The ADM postulates that when one motivation increases in intensity, this raises the A-threshold as well as the R-threshold of causal factors of the other motivations. Next, I present empirical findings illustrating this principle in addicted human subjects (see Weinstein et al., 1998). After a weekend of abstinence, opiate-dependent subjects were waiting in a hospital for 30 min to receive a dose of methadone. During this time, they were invited to participate in a computerized contextual priming task. They were presented with sentences whose content referred to an ardent desire for a drug (craving condition), avoidance of withdrawal (withdrawal condition), or a non-drug related topic (neutral condition). Each sentence was followed either by a drug-related word or by a neutral word. The subjects had to decide as quickly as possible whether or not the word was correct. The situation was said to be congruent when the target word was related to the priming sentence and incongruent in the opposite case. Weinstein et al.’s (1998) results showed that opiate-dependent subjects processed the congruent sentences referring to craving or withdrawal avoidance more quickly than the neutral ones. In contrast, control subjects processed all types of sentences in a similar amount of time. These data agree with evidence that addicted individuals pay more attention (and thus become more reactive) to drug-related stimuli than to other stimuli. However, when mean reaction times were examined in both groups, the opiate-dependent subjects were slower in responding than the control subjects (Fig. 7A).

Weinstein et al. (1998) demonstrated that the same phenomenon occurs when testing alcoholic subjects, where the priming
sentences and target words were adapted to their addiction. Fig. 7B indicates that alcoholic subjects do not process information in the same way as opiate-dependent subjects: they reacted faster to neutral sentences than to those semantically associated with alcohol. However, their mean reaction times also were longer than those of control subjects. It might be concluded that slower reaction times in addicts are predictable because of drug-induced neurotoxicity as well as possible nutritional deficits compared with healthy individuals. Although this argument must be considered, it does not account for two observations. First, neurotoxicity and nutritional deficits do not explain why mean reaction times in opiate and alcohol addicts are different for drug and neutral stimuli in these experiments. If the reactivity of addicts was affected here by such problems, it should be expected that addicts exhibit similar difficulties in processing any type of stimulus. The ADM does not explain the observed difference either, but contrary to the hypothesis above, the model remains permissive about its occurrence. Second, it has to be explained why a slower response pattern is also observed in individuals who do not suffer from addiction problems, such as phobic individuals confronted with words whose content arouses anxiety (e.g. Williams et al., 1996). Why do addicted individuals react less quickly to drug-related stimuli than non-addicted ones? As their attentional resources are strongly solicited in relation to these stimuli, it would have been logical for their performance to be better than that of control subjects. After all, decreased reaction times are observed in healthy individuals carrying out a classical associative priming task. For instance, in supraliminal conditions, a prime such as BREAD facilitates the lexical decision for a semantically associated word instance, in supraliminal conditions, a prime such as BREAD facilitates the lexical decision for a semantically associated word instance, in supraliminal conditions, a prime such as BREAD facilitates the lexical decision for a semantically associated word instance. The ADM does not explain the observed difference either, but contrary to the hypothesis above, the model remains permissive about its occurrence. Second, it has to be explained why a slower response pattern is also observed in individuals who do not suffer from addiction problems, such as phobic individuals confronted with words whose content arouses anxiety (e.g. Williams et al., 1996).

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The ADM posits an explanation for this behavioural phenomenon, as represented in Fig. 8. Addicted subjects’ motivation for a drug is strong after a weekend of abstinence, especially because they are ready to receive a dose of methadone. Thus, this motivation is beyond its A-threshold while remaining below its R-threshold because methadone is not available yet. Consequently, the A- and R-thresholds of the other motivations, including the one for the computerized priming task, are raised. The scheme is different in control subjects, whose addictive motivation is null and thus no motivation reaches the intensity of that for the drug in addicted subjects at that time: the A- and R-thresholds for the priming task are at their normal levels, hence much lower. A significant difference is therefore observed in mean reaction times between addicted subjects and control subjects. The former respond more slowly than the latter in the priming task because the R-threshold for this task has been raised by the addictive motivation.

7. Empirical test of the ADM

To find facts that corroborate some predictions of a theoretical model does not suffice to scientifically support the model; this model has to be the only coherent way of interpreting the facts in question. The previous section aimed to demonstrate that the ADM may be the best way of interpreting different results, especially those of Weinstein et al. (1998). In this section, I would like to briefly describe a possible experimental test of the ADM using a procedure of reinforcement in rats. The rewards used should be intravenously administered cocaine and standard food pellets. Optimally, a behavioural recording of their consumption should be combined with a microdialysis study of dopamine levels in the nucleus accumbens core, in order to be able to croscheck the two sources of information.

![Graph showing reaction times in a contextual priming task of opiate-dependent human subjects in relation to controls in three priming conditions.](Image 1)

Fig. 7. (A) Reaction times in a contextual priming task of opiate-dependent human subjects in relation to controls in three priming conditions. (B) The same task tested with alcohol-dependent subjects. Modified presentation, after Weinstein et al. (1998).

![Graph showing reaction times in alcoholic and control subjects in a priming task.](Image 2)

Fig. 8. The ADM’s graphic representation of Weinstein et al.’s (1998) empirical results. The R-threshold elevation clearly appears in addicts as opposed to controls, with the consequence of an increased reaction time for any non-drug stimulus.
Behaviourally, the two hypotheses to be tested are as follows: (i) cocaine doses received randomly – hence, uncertain – on an operant schedule reduces food consumption in rats compared with cocaine-administered rats on a yoked schedule, where cocaine is obtained passively; (ii) cocaine-administered rats on a yoked schedule exhibit increased food consumption compared with saline-administered rats on a yoked schedule, where no cocaine is provided. In all groups, the animals have an unlimited access to food and water during the test period (this should allow the cocaine-yoked rats to consume more food pellets than the saline-yoked ones, in case these latter would eat a maximal number of pellets in an interval schedule). Confirming the first hypothesis is important for the ADM because this would provide strong evidence for the inhibitory role of the anticipation of a given reward (cocaine) on the consumption of – hence, the motivation for – another reward (food). Although nothing is said here about attention, this process is supposed to be at the origin of the attentional bias in addicts. The second hypothesis, in combination with additional microdialysis results, would support the conclusion that cocaine-induced dopamine levels of the nucleus accumbens core can nonspecifically stimulate an individual’s interest in a reward, such as food, depending on the individual’s opportunities to act. This process may elucidate why drug rewards are temporarily able to increase the attractiveness of natural rewards.

To test both these hypotheses, three groups of rats should be rendered cocaine-dependent and food-deprived following appropriate training periods. In the first (test) group, the rats should be subject to a reinforcement procedure allowing them to get access to cocaine by pressing a lever. Cocaine delivery should correspond to doses whose arrival is certain but their exact moment unknown; a procedure operationalised by means of a random-interval schedule of 60 s (RI60): the rats obtain a dose of cocaine when pressing the drug lever after a random delay whose average is 60 s. In the other two (control) groups, the rats should receive cocaine or saline injections, respectively, in a passive way through a yoked schedule—allowing these animals to obtain the same doses of cocaine or saline at the same times and rhythm as the test rats.

The predicted results presented in Fig. 9 imply that the rats are not made sick by cocaine or anaesthesia, the latter necessary to place a catheter for subsequent cocaine and saline injections. In both these cases, the rats are expected to barely eat and the observation of significant effects is compromised. Such biases should be avoided via moderate doses of cocaine (e.g. 0.25 mg/kg, i.v.) as well as a sufficiently long convalescence period (e.g. 10 days) after surgery. Evaluating these biases is the role of the additional control groups that are not discussed here.

A third parameter could explain the absence of a significant difference between both experimental groups, and it is much more critical for the ADM’s veracity: the rats of the first two groups might eat in a similar proportion because the explicit wait for cocaine in the test rats is compensated by a sort of ‘diffuse’ wait in the yoked rats. At first glance, this result would seem to corroborate the ADM predictions since anticipation is assumed to inhibit food intake in both groups. Unfortunately, the hypothesis is impossible to test: nobody has access what happens in a rat’s head! There is, however, a good reason to think that such a scenario will not occur. A ‘diffuse’ wait for cocaine should affect feeding significantly less than an explicit wait because obtaining cocaine is independent from what the animals are doing. In contrast, an explicit wait elicits the requirement to a lever after an undetermined period of time; if the rats do not try to press, they receive nothing. In a sense, it is here reasonably supposed that the explicit wait of animals results from the requirement to press a lever because both phenomena cannot be operationally dissociated from each other. The test rats, subject to an explicit wait, should then be more preoccupied by obtaining cocaine than the yoked rats, subject to a ‘diffuse’ wait. Assuming that the ADM is correct, a statistically significant difference should therefore be observed between both groups of rats. If a difference did not appear, the conclusion to be drawn would be that anticipation has no effect on feeding and thus the ADM should be refuted. Other experiments examining the impact of anticipation on attention and combining behavioural and electrophysiological data could be run to test further predictions.

8. Conclusion

The ADM was initially constructed with the aim of explaining motivational interactions in any animal species, including humans (Anselme, 2007). It is presented here as a possible theoretical solution to the apparent paradox between drug and natural rewards: the evidence that many drugs begin by increasing the interest of individuals in natural rewards (sensitisation) but that this interest decreases when the period of drug consumption is prolonged (compulsion). The notion is advanced that traditional theories of addiction exhibit difficulties in establishing a transition between both facets of this paradox because they cannot explain how motivational specificity can emerge from nonspecific causal factors. Beyond this specific problem, the ADM can be seen as a general framework for the study of motivation. First, it constitutes a coherent articulation of different phenomena which play a central role in behaviour: anticipation, attention, motivation, causal factors of motivation and reactivity. All these phenomena are known but often remain undifferentiated within theories that do not really explain how behaviour can emerge from their interconnections. Second, the ADM relies on a concept of motivation that contains the principles of motivational interactions: the anticipatory attention threshold is not only the defining feature of motivation, but its existence is also the cause of inhibitory/disinhibitory influences among motivations. This concept of motivation is therefore parsimonious and might help to envision new, testable hypotheses.
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