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Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective

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Here I argue that addicted people become unable to make drug-use choices on the basis of long-term outcome, and I propose a neural framework that explains this myopia for future consequences. I suggest that addiction is the product of an imbalance between two separate, but interacting, neural systems that control decision making: an impulsive, amygdala system for signaling pain or pleasure of immediate prospects, and a reflective, prefrontal cortex system for signaling pain or pleasure of future prospects. After an individual learns social rules, the reflective system controls the impulsive system via several mechanisms. However, this control is not absolute; hyperactivity within the impulsive system can override the reflective system. I propose that drugs can trigger bottom-up, involuntary signals originating from the amygdala that modulate, bias or even hijack the goal-driven cognitive resources that are needed for the normal operation of the reflective system and for exercising the willpower to resist drugs.

Imagine yourself at a party during the first year in college, your friends offering you alcoholic drinks and drugs. In the back of your mind, you hear the voice of your parents warning you against such activities. What would you do? This is a hard decision, but you are the one who will ultimately decide, with a clear sense of exercising free will. Willpower, as defined by the Encarta World English Dictionary, is a combination of determination and self-discipline that enables somebody to do something despite the difficulties involved. This mechanism enables one to endure sacrifices now in order to obtain benefits later, or vice versa.

There are similarities in behavior between patients with ventromedial prefrontal cortex (VMPC) damage and drug addicts. Both often deny, or are not aware, that they have a problem. When faced with a choice that brings immediate reward, even at the risk of incurring future negative outcomes, including loss of reputation, job, and family, they appear oblivious to the consequences of their actions. (For the purposes of this piece, VMPC is defined as the ventral medial prefrontal cortex and the medial sector of the orbitofrontal cortex, thus encompassing Brodmann's areas (BA) 25, lower 24, 32 and medial aspect of 11, 12 and 10.) After injury to this area, patients tend to recover normal intelligence, memory and other cognitive functions, but emotion, affect and social behavior change completely. The patients begin to make choices that often lead to financial losses, loss in social standing, and even loss of family and friends.

When this syndrome was initially described[1], the decision making deficit seen in these patients was puzzling because their poor decision making and failure to learn from repeated mistakes was obvious in their everyday lives, but there was no laboratory probe to detect and measure their impairment. This challenge was overcome by the development of the Iowa Gambling Task[2]. In this task, subjects choose from four decks of cards, each with a different potential payoff, to maximize their monetary gain. After each choice, subjects receive feedback telling them how much money they won or lost. Through this feedback, normal decision-makers learn to avoid decks that yield high immediate gains but larger future losses down the line. In contrast, patients with VMPC damage and drug addicts persist in making disadvantageous choices despite the rising losses associated with their choices[2].

Early on, abnormalities in the VMPC region were observed in cocaine addicts[3]. These deficits were linked to the decision making impairments of VMPC patients when cocaine addicts were shown to make poor decisions on the Iowa Gambling Task[4]. This linkage energized a new line of research aimed at understanding the relationship between substance abuse and poor decision making (see refs. 2,5–8 for reviews). The aim of this perspective is to highlight the key role of choice in addiction, and to present a broad conceptual framework that brings together several disparate lines of research on addiction. The main purpose is to provide a gross picture of how multiple brain mechanisms come together in addiction, instead of focusing on one specific process of addiction, or one specific brain region. The view I present here is that addiction is a condition in which the neural mechanisms that enable one to choose according to long-term outcomes are weakened, thus leading to loss of willpower to resist drugs. This complements previous proposals that disruption of the VMPC leads to loss of self-directed behavior in favor of more automatic sensory-driven behavior[3].

A neural system for willpower

The somatic marker hypothesis is a systems-level neuroanatomical and cognitive framework for choosing according to long-term, rather than short-term, outcomes[1]. The key idea of this hypothesis is that the process of decision making depends in many important ways on neural substrates that regulate homeostasis, emotion and feeling[8]. The term 'somatic' refers to the collection of body- and brain-related responses that are hallmarks of affective and emotional responses. Both the amygdala and VMPC are critical for triggering somatic states, but as I will explain shortly, the amygdala responds to events that occur in the environment, whereas the VMPC triggers somatic states from memories, knowledge and cognition. In order for somatic signals to influence

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cognition and behavior, they must act on appropriate neural systems. As I will explain, there are several target sites through which somatic (affective) signals modulate cognition and behavior, and I will propose that this modulation is in fact mediated by neurotransmitter systems (**Fig. 1**). Thus, during the process of pondering decisions, the immediate and future prospects of an option may trigger numerous affective (somatic) responses that conflict with each other; the end result is that an overall positive or negative signal emerges. We have proposed that the mechanisms that determine the valence of the dominant pattern of affective signaling are consistent with the principles of natural selection (that is, survival of the fittest)[9]. In other words, numerous and conflicting signals may be triggered simultaneously, but stronger ones gain selective advantage over weaker ones. Over the course of pondering a decision, positive and negative signals that are strong are reinforced, and weak ones are eliminated. This process can be very fast, and ultimately a winner takes all: in other words, an overall, more dominant, pattern of affective signaling emerges that then can act on appropriate neural systems to modulate cognition and behavior.

On the basis of this neural framework, I propose that willpower emerges from the dynamic interaction of two separate, but interacting, neural systems: an impulsive system, in which the amygdala is a critical neural structure involved in triggering the affective/emotional signals of immediate outcomes, and a reflective system, in which the VMPC is a critical neural structure involved in triggering the affective/emotional signals of long-term outcomes (**Fig. 1**). This framework addresses one important question in drug addiction: of the millions of people who drink alcohol or experiment with drugs, why do only about 10% become addicted? The view I present here challenges the old thinking that people may be equally vulnerable to addiction once drugs are made available, as drug use can induce neuronal changes that lead to addiction. I argue that before one gets to the stage where a certain pattern of drug use can cause changes to the brain, there is a decision by the person to use, or not to use the drug. This mechanism protects most individuals who have used drugs from losing control and succumbing to addiction. For some individuals, however, this decision making mechanism is relatively weak. Such individuals are vulnerable to addiction because the process that enables one to inhibit actions elicited by the impulsive system is dysfunctional. The source of this dysfunction, I will suggest, can be genetic or environmentally induced.

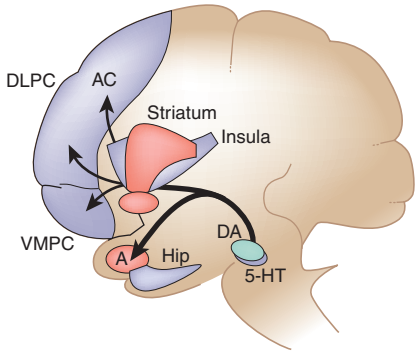

Figure 1 A schematic diagram illustrating key structures belonging to the impulsive system (red) and the reflective system (blue). An emergent dominant pattern of affective signaling can modulate activity of several components of the impulsive and reflective systems. These include regions involved in (i) representing patterns of affective states (*e.g.*, the insula and somatosensory cortices); (ii) triggering of affective states (*e.g.*, amygdala (A) and VMPC); (iii) memory, impulse and attention control (*e.g.*, lateral orbitofrontal, inferior frontal gyrus and dorsolateral prefrontal (DLPC), hippocampus (Hip) and anterior cingulate (AC); and (iv) behavioral actions (*e.g.*, striatum and supplementary motor area). 5-HT: serotonin; DA: dopamine.

The impulsive system

Physiological evidence suggests that responses triggered through the amygdala are short lived and habituate very quickly[10]. Therefore, we have suggested that pleasant or aversive stimuli, such as encountering an object that induces fear (a 'fear object', such as a snake) or a cue predictive of a fear object, trigger quick, automatic and obligatory affective/emotional responses through the amygdala system[11]. According to the somatic marker framework, the amygdala links the features of the stimulus to its affective/emotional attributes. The affective/emotional response is evoked through visceral motor structures such as the hypothalamus and autonomic brainstem nuclei that produce changes in internal milieu and visceral structures, as well as through behavior-related structures such as the striatum, periaqueductal gray (PAG) and other brainstem nuclei that produce changes in facial expression and specific approach or withdrawal behaviors[1].

Unlike food and water, money does not initially have affective properties, but acquires them with learning, such that exposure to monetary reward triggers affective signals through the amygdala system. We have shown that autonomic responses to large sums of monetary gains or losses depend on the integrity of the amygdala, as patients with bilateral amygdala damage fail to show such responses[11]. This is consistent with research showing that the brain can encode the value of various options on a common scale[12], thus suggesting that there may be a common neural 'currency' that encodes the value of different options, thus allowing the reward value of money to be compared with that of food, sex or other rewards.

Similarly, drugs may acquire powerful affective and emotional properties. In addicts, fast, automatic and exaggerated autonomic responses are triggered by cues related to the substance they abuse, similar to the effects of monetary gains[2]. Several lines of direct and indirect behavioral evidence have supported the view that conditioned approach behavior to drug cues relates to abnormal activity in the amygdala–ventral striatum system, thereby resulting in exaggerated processing of the incentive values of substance-related cues[13]. This ascribes a functional role to the striatum in the motivational and behavioral aspects of drug seeking, and it is consistent with the currently proposed framework of addiction.

The reflective system

Affective reactions can also be generated from recall of personal—or imagination of hypothetical—affective/emotional events. Affective state patterns develop in brainstem nuclei (such as the parabrachial nuclei) and in somatosensory cortices (for example, insula, somatosensory and posterior cingulate cortices) from prior experiences of reward and punishment[1]. After an affective state has been experienced at least once, a neural pattern for this state is formed. Subsequent evocation of memories of a previous experience reactivates the pattern of affective state belonging to an original experience. Provided that representations of these affective state patterns develop normally, the VMPC is a critical substrate in the neural system necessary for triggering affective states from recall or from imagination[11].

This hypothesis is based on evidence from patients with lesions in the VMPC[11]. However, it is also reasonable to suggest based on this evidence that recalling the experience of a drug reactivates the pattern of affective state belonging to the actual previous encounter with that drug. This mechanism should also bring up the negative consequences associated with drug use. These negative consequences are not simply aversive experiences resulting from the actual consumption of the drug. Rather, they relate to social (such as trouble with the law, family or finances) and psychological harms associated with drug use. The affective state patterns of these negative consequences become represented in the brain when individuals learn from parents or society about

the dangers of drug use. Therefore, one does not need to use drugs in order to fear their consequences; these negative consequences should be there, even before experimenting with drugs. However, having poor mechanisms of decision making renders individuals oblivious to these negative consequences, thus facilitating their escalation of drug use, and vulnerability to succumb to addiction.

Normal functioning of the VMPC is contingent upon the integrity of other neural systems. One system involves the insula and other somatosensory cortices, especially on the right side, that are critical for representing patterns of emotional/affective states[1]. Patients with right parietal damage (encompassing insula and somatosensory cortex) show impairments in decision making[11]; addicts show functional abnormalities in these parietal regions when performing decision making tasks[7]. The other system involves the dorsolateral sector of the prefrontal cortex and the hippocampus, which are critical for memory[11]. Indeed, maintaining an active representation of memory over a delay period involves the dorsolateral sector of the prefrontal cortex, and patients with damage to this structure show compromised decision making[14]; addicts who have deficits in working memory also show compromised decision making[15,16]. Thus, decision making depends on systems for memory as well as for emotion and affect. Damage to any of these systems compromises the ability to make decisions that are advantageous in the long term. The VMPC region links these systems together, and therefore when it is damaged, there are many manifestations, including alterations of emotional/affective experience, poor decision making and abnormal social functioning[11,14].

Several voxel-brain-morphometry studies of brain scans of addicts found varying degrees of structural abnormalities in main components of the reflective system (**Fig. 1**), including the VMPC, anterior cingulate, insular cortex[17], dorsolateral prefrontal cortex and lateral orbitofrontal/inferior frontal gyrus[18]. Abnormalities have also been detected in white matter pathways connecting these structures[19,20]. Convergent results have also been obtained from functional neuroimaging studies (see refs. 3,7,8 for reviews). However, it is difficult to determine whether these abnormalities preceded or were the consequences of drug use. My view is that a degree of abnormality pre-existed the addiction state, by facilitating the progress from experimentation to addiction. However, any subsequent excessive and chronic use of drugs can exacerbate these abnormalities.

Top-down control mechanisms of the reflective system

Decision making reflects a process in which a choice is made after reflecting on the consequences of that choice. The choice between another drug use episode and the potential of losing a job, family breakdown and financial ruin down the line presents a dilemma to an addict, and a decision has to be made. Individuals with a weakness in this process (that is, those who do not reflect on the consequences of their decisions) may be similar to individuals with the personality trait of 'nonplanning impulsivity', a tendency to live for the moment with no regard for the future[21], or individuals that lack the trait of 'premeditation', a tendency to think and reflect on the consequences of an act before engaging in that act[22]. Several tasks are now used to study this decision making processes, including the Iowa Gambling Task and the Cambridge Gamble and Risk Tasks[14,23]. A critical neural region for this mechanism is the VMPC region, but other neural components outlined earlier are also important[11].

Impairments in decision making are evident in addicts, regardless of the type of drug they abuse, which suggests that poor decision making may relate to addiction in general, rather than the effects of one specific type of drugs. Alcohol, cannabis, cocaine, opioid and methamphetamine abusers show impairments in decision making on a variety of tasks[2,5,6,23]. Although the differences in cognitive impairments brought by the use of different drugs remains elusive, we have obtained preliminary evidence suggesting that chronic use of methamphetamine may be more harmful to decision making than use of other drugs[24].

Direct comparison of the decision making impairments in addicts on the Iowa Gambling Task versus patients with VMPC damage showed that a significantly high proportion of addicts (63%, versus 27% of normal controls) performed within the range of VMPC patients, whereas the rest performed within the range of the majority of normal controls[25]. Further characterization of these decision making deficits, using skin conductance response (SCR) measures as indices of affective states during performance of the task, showed that this small minority of addicts (the 37% of addicts who performed normally) matched normal controls in all respects. However, the remainder of the addicts (the 63% who performed abnormally) had two profiles: one subgroup matched the VMPC patients in all respects (that is, they had abnormal SCRs when they pondered risky decisions), but another subgroup did not match the VMPC patients. This pattern of abnormal physiological responses when making risky decisions in addicts was also obtained with the Cambridge Gamble Task[26]. A minority of normal controls performed like addicts and VMPC patients on the Iowa Gambling Task, and with additional SCR measures, some of them matched the profile of VMPC patients. The remainder of the controls were more like the addicts who did not match the VMPC patients[2,25]. These studies suggest that decision making deficits in addicts, and surprisingly, in some normal controls, are not uniform across all individuals. My view is that attention to individual, as opposed to group, differences in these decision making deficits is the key to understanding the nature of the addiction problem, its prognosis and possible treatment.

There may be more than one mechanism by which the reflective system exerts control over the impulsive system. Besides decision making, there are other mechanisms of inhibitory control, one of which is the ability to deliberately suppress dominant, automatic or pre-potent responses[27]. For instance, acting quickly without an intention to act (as in the case of acting impulsively and using a drug without thinking) reflects an instance of weakness in this mechanism. Poor performance on several laboratory instruments requiring response inhibition reflects deficits in this mechanism of impulse control[27]. A critical neural region for this mechanism seems to be the more posterior area of the VMPC region, which includes the anterior cingulate and the basal forebrain, as patients with lesions in this area demonstrate signs of disinhibition and poor impulse control[11]. Disturbances in this mechanism may relate to the personality trait of motor impulsivity, the tendency to act without thinking[21], or the trait of 'urgency', the tendency to experience strong impulses, frequently under conditions of negative affect[22]. Addicts show poor performance on tasks requiring the inhibition of pre-potent motor responses, and functional neuroimaging studies in addicts with inhibition deficits reveal diminished activity in neural systems involved in these inhibitory control mechanisms[6,8].

Another mechanism of impulse control is the ability to resist the intrusion of information that is unwanted or irrelevant[27]. Difficulties inhibiting particular thoughts or memories, such as thinking about drugs, and shifting attention to something else, reflect instances of weakness in this mechanism. Poor performance on tasks requiring internal inhibition of intrusive information reflects weakness in this mechanism[27], and a critical neural region for this mechanism appears to be the lateral orbitofrontal and dorsolateral (inferior frontal gyrus) regions of the prefrontal cortex. Patients with damage in these areas make perseverative errors and have difficulties shifting attention[28]. Disturbances in this mechanism may relate to the personality trait of 'cognitive impulsivity', the tendency to make up one's mind quickly or have problems concentrating[21], or the trait

of 'perseverance', the ability to remain focused on a task that may be boring or difficult[22]. Addicts show deficits in this mechanism of impulse control, as they demonstrate poor performance on tasks requiring the internal inhibition of an intention to act[28] (E.A. Crone, C. Cutshall, E. Recknor, W.P.M. Van den Wildenberg & A.B., *Soc. Neurosci. Abstr.* **33**,427, 2003).

Bottom-up influence of the impulsive system

The reflective system may generate affective states through top-down mechanisms, but then ascending signals from these affective states can exert bottom-up influence on cognition. Thus, when one is pondering a decision, numerous affective signals that conflict with each other may be triggered simultaneously through both the impulsive and reflective systems. The result is emergence of an overall positive or negative affective state. Ascending signals from this overall affective state can then modulate activity of several components of the impulsive and reflective systems (**Fig. 1**).

We have previously proposed that the key mechanism by which these bottom-up signals modulate synaptic activity at telencephalic targets is pharmacological[9]. The cell bodies containing the neurotransmitter dopamine, serotonin, noradrenaline and acetylcholine are located in the brainstem; the axon terminals of these neurotransmitter neurons make synapses on cells and/or terminals throughout cortex. Anatomically, both the amygdala and VMPC have direct access to these neurotransmitter cell bodies in the brainstem. For affective states and homeostatic signals generated in the body, a number of channels can convey their signals to these neurotransmitter nuclei, but we have suggested that the vagus nerve is the most critical[11].

Changes in neurotransmitter release can modulate synaptic activity in several components of the impulsive and reflective systems. First, changes in representation of patterns of affective states (for example, in the insula and other somatosensory cortices) can lead to an increase in the reward utility of the drug. Second, changes in triggering of affective states (for example, in amygdala and VMPC) can lower the threshold for triggering subsequent affective signals related to drugs. Third, alterations in impulse control and the inhibition of unwanted memories or thoughts (for example, in lateral orbitofrontal, inferior frontal gyrus and dorsolateral prefrontal, hippocampus, and anterior cingulate) can strengthen thoughts about drugs and make shifting attention to other thoughts more difficult. Finally, changes in regions involved in behavior (striatum and supplementary motor area) can translate into drug use (**Fig. 1**).

The outline of these pharmacological systems given here is very simplistic, mainly because there are many excellent reviews that describe the molecular mechanisms by which neurotransmitters affect synaptic activity in addictive states and that explain how these activities influence cognitive systems such as memory (see refs. 29,30 for reviews). Other excellent lines of research have attempted to differentiate the specific roles of dopaminergic, serotonergic, or noradrenergic systems in decision making, impulse control[31,32] and time delay[33]. Therefore, the main purpose here is not to detail the processes and mechanisms of any one specific pharmacological system. Rather, the goal is to illustrate (i) how one can relate molecular and pharmacological studies on drug addiction to neural systems concerned with mechanisms of affect and emotion and (ii) the influence of drug addiction on cognition. The proposed arrangement provides a way for affective signals to exert a bottom-up influence on the reflective system. If, for instance, the signals triggered by the impulsive system were relatively strong, they would have the capacity to hijack the top-down goal-driven cognitive resources needed for the normal operation of the reflective system and exercising the willpower to resist drugs.

Hyperactive impulsive system

Hyperactivity in bottom-up mechanisms of the impulsive system can weaken control of the reflective system. Evidence suggests that conditions leading to hyperactivity in this system include hypersensitivity, and attention bias, to reward.

Addicts trigger exaggerated autonomic responses to cues related to the substances they abuse (see refs. 2,25 for reviews). Although addicts show blunted affective responses to affective stimuli that are not drug related[34], we have shown that addicts trigger exaggerated autonomic responses when exposed to monetary reward in the Iowa Gambling Task[2,25]. Perhaps money represents a special case, in that it may be automatically linked to buying drugs. Using different versions of the Iowa Gambling Task, combined with SCR measures, we identified a subgroup of addicts that were different from both VMPC patients and the majority of normal controls; this subgroup of addicts was drawn to choices that yielded larger gains, irrespective of the losses that were encountered, and they generated exaggerated SCRs when they won money[2,25]. Direct autonomic responses to wins and losses are blocked in patients with bilateral amygdala damage. In contrast, in VMPC patients, the SCR defect is specific to the anticipatory phase when they are pondering which option to choose[11]. This suggests that addicts suffer from the opposite condition of amygdala lesion patients; that is, their amygdala is overresponsive to reward. This is supported by functional neuroimaging studies showing increased amygdala activity in response to drug-related cues[35,36] and that this exaggerated brain response generalizes to monetary reward[37].

Other studies using tasks in which subjects were required to respond to targets (drug-related stimuli) but not respond to distracters (neutral stimuli) suggested that substance-related cues trigger bottom-up mechanisms in substance abusers, influencing top-down cognitive mechanisms such as motor impulse and attention control[38]. Another approach for studying these attention biases has been to use cognitive models[6] that deconstruct complex behavioral decisions, such as those made in the Iowa Gambling Task, into simpler component processes of decision making. One of the component processes is the tendency of a subject to pay more attention to gains or losses encountered on previous trials in order to make future decisions. Addicts show patterns of high attention to monetary gains (which are more frequent in men than in women[6]) thus providing indirect evidence for the hypothesis that the amygdala system in addicts is hyperactive in response to monetary reward.

Modulating factors

The control function of the reflective system is complex, and even under normal circumstances, several factors can modify the strength of affective signals triggered by the reflective system, thus influencing its control over the impulsive system. Indeed, one of the fundamental questions in decision making research is how humans assign value to options.

Several factors affect the value of a choice, and research has begun to explore the neural basis of these factors. We have proposed a neural framework for how factors that affect decision making—such as time delay, the probability of the outcome or the tangibility of the reward—could be implemented in the VMPC[9]. We have suggested that information conveying immediacy (the near future) engages more posterior VMPC (including anterior cingulate, basal forebrain and nucleus accumbens), whereas information conveying delay (distant future) engages more anterior VMPC (such as frontal pole)[9]. This is on the basis of the finding that major advancement in the size, complexity and connectivity of the frontal lobes in humans has occurred in relation to Brodmann area (BA) 10 (that is, the frontal pole)[39]. Furthermore, the more posterior areas of the VMPC (such as BA 25) are directly connected to brain structures involved in triggering (autonomic, neu-

rotransmitter nuclei) or representing (sensory nuclei in the brainstem, insular and somatosensory cortices) affective states, whereas access of more anterior areas is polysynaptic and indirect[40]. It follows that coupling of information to representations of affective states via posterior VMPC is associated with relatively fast, effortless, and strong affective signals, whereas the signaling via more anterior VMPC is relatively slowed, effortful and weak. This view is supported by recent functional imaging studies addressing how the perceived delay to receiving a reward modulates activity in reward-related brain areas[33]. This discounting mechanism of time is also relevant to addiction, as addicts tend to exhibit a higher temporal discounting rate than normal people; that is, they prefer smaller, sooner rewards over larger, later rewards[23]. Thus, events that are more immediate in time (such as having the drug now as opposed to the delayed consequences) have a stronger capability to influence decision making and hijack cognition in the direction of short-term outcomes.

Similarly, we have suggested that information conveying higher certainty (or higher probability) engages posterior VMPC, whereas information conveying lower certainty engages anterior VMPC[9]. Functional imaging studies implicating the parietal cortex and anterior cingulate cortex in computing the probability of outcomes on the basis of available options (see ref. 7 for a review) are supportive of this view. This mechanism for processing probabilities is also relevant to addiction, as cocaine addicts show abnormalities in the activity of neural structures critical for decision making in proportion to the degree of certainty (or uncertainty) that they have about receiving their drug at the end of a brain scanning session[3].

Finally, reward values are processed by the VMPC region, and representations of these values are modulated by homeostatic factors such as hunger[41]. Given the view that neural systems supporting drug reward have evolved to subserve natural motivational functions, such as feeding[42], drug withdrawal can be viewed like hunger[43] in that once it is present, it increases the utility of drug reward, and, in doing so, it influences the decision to use drugs. This suggestion is consistent with the incentive motivational view of drug addiction proposing that although physical withdrawal signs are neither necessary nor sufficient for taking drugs, they exaggerate the incentive impact of drugs, thereby increasing the motivation to use drugs[42]. Thus in the presence of withdrawal, the capacity of bottom-up homeostatic signals to hijack control mechanisms of the reflective system is increased.

Implications for treatment and directions for future research

Most addicts show behavioral signs of poor decision making, but in the profiles of their physiological responses, some addicts match VMPC patients, and some do not (see above). We have suggested that addicts who match VMPC patients are characterized by insensitivity to future consequences; that is, they are oblivious to future positive or negative consequences, and instead they are guided by immediate prospects. Addicts who partially match VMPC patients are suggested to be hypersensitive to reward, so that the prospect of drugs outweighs the prospect of future consequences. These differences may have implications for prognosis, and they provide testable hypotheses that could be addressed in future research: addicts who match VMPC patients may have a harder time recovering from addiction and remaining abstinent in comparison with addicts who partially match the VMPC patients.

One subgroup of addicts appeared normal and did not show behavioral or physiological signs of decision making deficits. This suggests that not every drug user has impaired decision making. We have described these addicts as 'functional' addicts, because a closer inspection of their everyday lives has shown that they have suffered minimal social and psychological harm as a consequence of their drug use: for example, they manage to keep their jobs[2]. Therefore, my view is that poor decision making in addiction is evident only when individuals persist in escalating their drug use in the face of rising adverse consequences. According to this view, people described as addicted to coffee, sweets, the internet and so on do not necessarily have impaired decision making, unless their choices bring increasing social, physical or psychological harms. However, an alternate possibility is that the lack of evidence for decision making deficits in this subgroup of addicts is a limitation of the proposed somatic marker framework, in that it does not capture all instances of addiction.

Finally, one subgroup of normal controls shows behavioral and physiological profiles that matches VMPC patients. This raises the question of whether these individuals are predisposed, or at higher risk, for addiction than individuals with normal decision making capabilities. This suggestion is reasonable in light of the evidence that one predisposing factor to addiction is heredity, and genes can act in general fashion (such as the serotonin transporter gene) to predispose individuals to multiple, as opposed to specific, drug addictions[44]. Future research using functional imaging methods could focus on relationships between (i) genotypes related to specific neurotransmitter systems (for example, the serotonin transporter gene) (ii) the level of neural activity in specific neural circuits, and (iii) quality of choice, as shown by complex laboratory tasks of decision making. This will reveal whether genetic factors lead to suboptimal function in specific neural systems, which then leads to behaviors reflecting poor decision making.

However, not all predisposing factors are necessarily genetic; other factors could be environmental (such as drug neurotoxicity), or the product of gene-environment interactions. Although the evidence for neurotoxicity resulting from drug use remains questionable[45], the potential for harm remains relatively higher if drugs were abused during adolescence. Indeed, evidence suggests that the functions of the prefrontal cortex may not develop fully until the age of 21, and until such a time, the development of neural connections that underlie decision making, and the control over powerful temptations, is still taking place[46–48]. Therefore, exposing the prefrontal cortex to drugs before its maturity could be harmful to decision making, just like exposing the fetus to drugs during pregnancy. However, the fact remains that not every adolescent who tries drugs ends up addicted; it takes more than mere exposure to drugs to become addicted. Therefore, my hypothesis is that poor decision making in addiction is not the product of drug use; rather, poor decision making is what leads to addiction. Future systemic and longitudinal studies on decision making in young adolescents should test this hypothesis and determine whether neurocognitive development can serve as a marker predictive of addictive disorders. This research should also take into consideration models of addiction that describe a progressive dysregulation of reward brain circuitry concomitant with a spiraling path from controlled drug use to addiction[49] and should examine whether drug users undergo a slow and gradual hijacking of their willpower as they move from controlled use to addiction. However, my proposal is that not every individual who tries drugs ends up on this down-spiraling path; those with poor decision making capabilities are more vulnerable, and those with normal decision making capabilities are more resistant. These are testable hypotheses with clear predictions that can be addressed in future research.

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COMPETING INTERESTS STATEMENT

The author declares that he has no competing financial interests.

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1. Damasio, A.R. *Descartes' Error: Emotion, Reason, and the Human Brain* (Grosset/Putnam, New York, 1994).
2. Bechara, A. Neurobiology of decision making: risk and reward. *Semin. Clin. Neuropsychiatry* **6**, 205–216 (2001).
3. Volkow, N.D., Fowler, J.S. & Wang, G.J. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology* **47**, 3–13 (2004).
4. Grant, S., Contoreggi, C. & London, E.D. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* **38**, 1180–1187 (2000).
5. Rahman, S., Sahakia, B., Rudolph, N.C., Rogers, R.D. & Robbins, T.W. Decision making and neuropsychiatry. *Trends Cogn. Sci.* **6**, 271–277 (2001).
6. Garavan, H. & Stout, J.C. Neurocognitive insights into substance abuse. *Trends Cogn. Sci.* **9**, 195–201 (2005).
7. Ernst, M. & Paulus, M.P. Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. *Biol. Psychiatry* published online 10 August 2005 (doi:10.1016/j.biopsych.2005.06.004).
8. Goldstein, R.Z. & Volkow, N.D. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry* **159**, 1642–1652 (2002).
9. Bechara, A. & Damasio, A.R. The somatic marker hypothesis: a neural theory of economic decision. *Games Econ. Behav.* **52**, 336–372 (2005).
10. Büchel, C., Morris, J., Dolan, R.J. & Friston, K.J. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* **20**, 947–957 (1998).
11. Bechara, A. Disturbances of emotion regulation after focal brain lesions. *Int. Rev. Neurobiol.* **62**, 159–193 (2004).
12. Montague, P.R. & Berns, G.S. Neural economics and the biological substrates of valuation. *Neuron* **36**, 265–284 (2002).
13. Everitt, B.J. *et al.* Associative processes in addiction and reward: the role of amygdala and ventral striatal subsystems: the role of amygdala-ventral striatal subsystems. *Ann. NY Acad. Sci.* **877**, 412–438 (1999).
14. Clark, L., Cools, R. & Robbins, T. The neuropsychology of ventral prefrontal cortex: decision making and reversal learning. *Brain Cogn.* **55**, 41–53 (2004).
15. Bechara, A. & Martin, E. Impaired decision making related to working memory deficits in substance addicts. *Neuropsychology* **18**, 152–162 (2004).
16. Martin, E.M. *et al.* Delayed nonmatch-to-sample performance in HIV-seropositive and HIV-seronegative polydrug abusers. *Neuropsychology* **17**, 283–288 (2003).
17. Franklin, T.R. *et al.* Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol. Psychiatry* **51**, 134–142 (2002).
18. Matochik, J.A., London, E.D., Eldreth, D.A., Cadet, J.L. & Bolla, K.I. Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study. *Neuroimage* **19**, 1095–1102 (2003).
19. Bartzokis, G. *et al.* The incidence of T2-weighted MR imaging signal abnormalities in the brain of cocaine-dependent patients is age-related and region-specific. *AJNR Am. J. Neuroradiol.* **20**, 1628–1635 (1999).
20. Lim, K.O., Choi, S.J., Pomara, N., Wolkin, A. & Rotorsen, J.P. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biol. Psychiatry* **51**, 890–895 (2002).
21. Patton, J.H., Stanford, M.S. & Barratt, E.S. Factor structure of the Barratt impulsiveness scale. *J. Clin. Psychol.* **51**, 768–774 (1995).
22. Whiteside, S. & Lynam, D. The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Pers. Individ. Dif.* **30**, 669–689 (2001).
23. Monterosso, J., Ehrman, R., Napier, K., O'Brien, C.P. & Childress, A.R. Three decision making tasks in cocaine-dependent patients: Do they measure the same construct? *Addiction* **96**, 1825–1837 (2001).
24. Martin, E.M. & Bechara, A. Decision making and drug of choice in substance-dependent individuals: a preliminary report. *Biol. Psychiatry* **53**, 97S (2003).
25. Bechara, A. Risky business: Emotion, decision making and addiction. *J. Gambl. Stud.* **19**, 23–51 (2003).
26. Fishbein, D. *et al.* Cognitive performance and autonomic reactivity in abstinent drug abusers and nonusers. *Exp. Clin. Psychopharmacol.* **13**, 25–40 (2005).
27. Friedman, N.P. & Miyake, A. The relations among inhibition and interference control functions: A latent variable analysis. *J. Exp. Psychol. Gen.* **133**, 101–135 (2004).
28. Aron, A.R., Robbins, T.W. & Poldrack, R.A. Inhibition and the right inferior frontal cortex. *Trends Cogn. Sci.* **8**, 170–177 (2004).
29. Hyman, S.E. Addiction: A disease of learning and memory. *Am. J. Psychiatry* **162**, 1414–1422 (2005).
30. Nestler, E.J. Molecular basis of long-term plasticity underlying addiction. *Nat. Rev. Neurosci.* **2**, 119–128 (2001).
31. Clarke, H.F., Dalley, J.W., Crofts, H.S., Robbins, T.W. & Roberts, A.C. Cognitive inflexibility after prefrontal serotonin depletion. *Science* **304**, 878–880 (2004).
32. Rogers, R.D., Lancaster, M., Wakeley, J. & Bhagwagar, Z. Effects of beta-adrenoreceptor blockade on components of human decision making. *Psychopharmacology (Berl.)* **172**, 157–164 (2004).
33. McClure, S.M., Laibson, D.I., Loewenstein, G. & Cohen, J.D. Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507 (2004).
34. Aguilar de Arcos, F., Verdejo, A., Peralta, M.I., Sanchez-Barrera, M. & Perez-Garcia, M. Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. *Drug Alcohol Depend.* **78**, 159–167 (2004).
35. London, E.D., Ernst, M., Grant, S., Bonson, K. & Weinstein, A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb. Cortex* **10**, 334–342 (2000).
36. Childress, A.R. *et al.* Limbic activation during cue-induced cocaine craving. *Am. J. Psychiatry* **156**, 11–18 (1999).
37. Breiter, H.C., Aharon, I., Kahneman, D., Dale, A. & Shizgal, P. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron* **30**, 619–639 (2001).
38. Noel, X., Van Der Linden, M., Verbanck, P., Pelc, I. & Bechara, A. Deficits of inhibitory control and of shifting associated with cognitive bias in polysubstance abusers with alcoholism. *Addiction* **100**, 1302–1309 (2005).
39. Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K. & Van Hoesen, G.W. Prefrontal cortex in humans and apes: A comparative study of area 10. *Am. J. Phys. Anthropol.* **114**, 224–241 (2001).
40. Ongur, D. & Price, J.L. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex* **10**, 206–219 (2000).
41. Kringelbach, M.L. & Rolls, E.T. The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. *Prog. Neurobiol.* **72**, 341–372 (2004).
42. Wise, R.A. & Bozarth, M.A. A psychomotor stimulant theory of addiction. *Psychol. Rev.* **94**, 469–492 (1987).
43. Nader, K., Bechara, A. & van der Kooy, D. Neurobiological constraints on behavioral models of motivation. *Annu. Rev. Psychol.* **48**, 85–114 (1997).
44. Goldman, D. & Bergen, A. General and specific inheritance of substance abuse and alcoholism. *Arch. Gen. Psychiatry* **55**, 964–965 (1998).
45. Ricaurte, G.A., Yuan, J., Hatzidimotriou, G., Cord, B.J. & McCann, U.D. Retraction. *Science* **301**, 1479 (2003).
46. Eslinger, P.J. Conceptualizing, describing, and measuring components of executive function. in *Attention, Memory and Executive Function* (eds. Lyon, G.R. & Krasnegor, N.A.) 420–441 (Paul H. Brooks, Baltimore, 1999).
47. Crone, E.A., Jennings, J.R. & Van der Molen, M.W. Developmental change in feedback processing as reflected by phasic heart rate changes. *Dev. Psychol.* **40**, 1228–1238 (2004).
48. Overman, W.H. *et al.* Performance on the IOWA card task by adolescents and adults. *Neuropsychologia* **42**, 1838–1851 (2004).
49. Koob, G.F. & Le Moal, M. Drug abuse: Hedonic homeostatic dysregulation. *Science* **278**, 52–58 (1997).