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Addiction: A Disease of Self-Control

Nora D. Volkow and Ruben Baler

Introduction

Research on the neuroscience of substance use disorders (SUDs) has started to shed light on the ways in which chronic drug abuse changes the brain to cause the profound disruptions we see in the behavior of an addicted person. This is because drugs of abuse impact many neuronal circuits that are crucial for the orchestration of *conscious experience* and hence, for the proper (flexible) functioning in social environments. But the core impairments established during the addictive process have a particularly devastating impact on the interacting circuits of motivational drive (which is enhanced for drug-related stimuli) and of self-control (which is weakened by chronic drug exposure) (Kalivas and Volkow 2005).

For many years, studies of addiction had focused mainly on the role of dopamine and the brain reward circuitry (Di Chiara 1999; Weiss and Koob 2001). However, the drug-induced DA boost fails to fully explain addiction since it happens in naïve animals and its magnitude is decreased in addiction (Volkow *et al.* 1997). Preclinical and clinical studies are revealing neuroadaptations in frontocortical regions of the brain that are likely to underlie compulsive drug-seeking behaviors in addiction (for review, see (Goldstein and Volkow 2002)). Imaging studies have provided particularly compelling evidence for the involvement of the brain's cognitive system (i.e., prefrontal cortex [PFC], including orbitofrontal cortex [OFC], anterior cingulate gyrus [ACC]) in the addiction process (Volkow and Fowler 2000). More recent work has revealed that the PFC plays a crucial role in social cognition and emotions (Forbes and Grafman 2010), which are key to proper social integration including responses to social rewards and punishment. For example, damage to ventral areas, frontal, and striatal regions can interfere with the ability of a person to accurately distinguish right from wrong in a socially acceptable manner, which can lead to socially inappropriate behaviors (Koenigs *et al.* 2007). Similarly, such brain impairments decrease the sensitivity to social rewards or punishments that can lead a person to behave in ways that alienate others and result in social isolation or even incarceration. While repeated drug exposures impair the fronto-striatal circuit there is also evidence that genetics or social adverse environmental exposures during childhood/adolescence can also result in impairments in this circuit that increase the vulnerability of the individual for a substance use disorder.

Drugs' impact on the neural substrate of cognition

Humans addicted to drugs display a significant reduction in dopamine receptor type 2 (D2R) function in the striatum (including the Nucleus Accumbens [NAc] located in the ventral striatum), an effect that has been implicated in impulsive and compulsive behavioral phenotypes (Volkow *et al.* 2012). In the human brain, the reductions in D2R in striatum are associated with decreased activity in the OFC (including the right inferior cortex, which is necessary for inhibition), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) (Volkow *et al.* 2001; Volkow *et al.* 1993; Volkow *et al.* 2007) indicating the impulsive/compulsive phenotypes reflect the impaired modulation by the D2R striato-cortical pathway, which is inhibitory, in PFC. Studies have also shown decreased frontal cortical activity during intoxication from many drugs of abuse (Chang and Chronicle 2007) and disruption of several frontocortical processes with chronic drug use (Table I) (see (Goldstein and Volkow 2012) for a review). Predictably, targeting the frontal impairments in addiction has been proposed as a therapeutic strategy to improve self-control (Goldstein *et al.* 2010; Volkow *et al.* 2013).

Among the frontal regions implicated in addiction, the OFC, ACC, and DLPFC participate in salience attribution, inhibitory control/emotion regulation and error detection, and decision making, respectively. It has been postulated that their improper regulation by striatal D2R-mediated DA signaling in addicted subjects could underlie the enhanced motivational value of drugs and the loss of control over drug intake (Volkow and Fowler 2000). Incidentally, related dysfunctions could also underlie behavioral addictions, like pathological internet use (Yuan *et al.* 2012) and compulsive overeating in some cases of obesity (Volkow *et al.* 2012). In parallel, investigators have also uncovered differential modulation of reward-seeking behavior by D1R versus D2R in the PFC. For example, recent preclinical studies have shown that pharmacologic blockade of mPFC D1R attenuates; whereas D2R increases a tendency for risky choices, providing evidence for a dissociable but complementary role of medial PFC DA receptors that is likely to play a major role in orchestrating the fine balance needed for inhibitory control, delayed discounting, and judgment (St Onge *et al.* 2011).

In addition, because impairments in OFC and ACC are associated with compulsive behaviors and impulsivity, DA's impaired modulation of these regions is likely to contribute to the compulsive and impulsive drug intake seen in addiction (Volkow and Fowler 2000). Clearly, low DA tone in PFC could also represent a preexisting vulnerability for drug use, albeit one that is likely to be exacerbated with the further decreases in striatal D2R associated with drug addiction. Indeed, a study performed in subjects who, de-

spite a positive family history (high risk) of alcoholism, were not themselves alcoholics, revealed a higher than normal striatal D2R availability that was associated with normal metabolism in OFC, ACC, and DLPFC (Volkow *et al.* 2006). This suggests that, in these subjects at risk for alcoholism, the normal prefrontal function was linked to enhanced striatal D2R signaling, which in turn may have protected them from alcohol abuse.

The central role of the PFC among the neural targets of addictive drugs may also help explain why addiction is a developmental disease whose chances of becoming expressed are increased if drug use onset takes place during childhood or adolescence. The heavy bidirectional connectivity between the PFC and limbic regions is instrumental in directing affective and social behaviors and is not fully developed until young adulthood. The maturation of fronto-limbic connectivity is highly sensitive to the deleterious impact of environmental factors such as chronic stress, parental neglect, drugs, and social experiences (Kolb *et al.* 2012). This makes the PFC susceptible to abnormal developmental trajectories, which can increase the risk for addiction and other psychiatric disorders.

Cognitive and behavioral implications

Through a fascinating but sinister process, drugs disrupt the very neurobiological systems underpinning the assessment of what's *important* in a person's life. From a biological perspective, we think much of the addictive behavior phenotype can be explained by the ability of chronic drug exposure to cause neuroadaptations in brain reward and control systems, including the emergence of conditioned associations that link the rewarding experience from the drug to the multiple cues that surround it. In this way, drug addicted individuals suffer from a profoundly distorted system of value placement, which can devastate their self-determination capacity. The structural and functional changes that accompany these drug-induced dysfunctions are long lasting, and can persist even after years of drug discontinuation, which is one of the main reasons why we define addiction as a chronic and relapsing disease of the brain.

Furthermore, while the value that an addicted individual places on drug reward becomes unsustainably exaggerated, the potential impact of deleterious consequences (e.g., familial dislocation, becoming the target of drug-related violence, or incarceration) becomes progressively devalued. The establishment of such a severe imbalance in how an addicted individual attributes value to both rewarding and aversive situations and stimuli has a profound and negative impact on the individual's social competence. His/her behaviors are now governed by the uncontrollable overvaluing of

the drug (enhanced expectation of a positive reward) and by a growing insensitivity to the deterrent value of potential punishments (reduced fear of a negative reward). The problem is further compounded by the tendency of many substance abusers, more so than nonusers, to routinely choose immediate rewards over delayed gratification (e.g., choose $20 dollars now rather than wait 1 week in order to get double that amount) an impairment associated with dysfunction of ventral prefrontal regions (Ernst and Paulus 2005). This inability to appropriately weigh delayed rewards can be devastating to an addicted person who may be willing to sacrifice future gains or incur major losses in exchange for instant gratification. An individual in this situation may not think twice about the risk of losing his or her freedom tomorrow in order to chase the high from the drug today. This knowledge helps explain why the prevailing social system that dangles some future threat of imprisonment over an addict's head seldom deters immediate substance abuse-related behaviors in addicted subjects. It also highlights the need to provide addicted individuals with alternative reinforcers as a strategy both for the prevention of SUD as well as for its treatment.

Implications for treatment and social policy

Behavioral inhibition is fundamental to the success of social intercourse, which is critically dependent on a person's ability to control impulsive behaviors whenever this is needed. For most people, the combination of biological (e.g., individual-level characteristics) and environmental (e.g., culture, laws, religion) factors build up a sufficiently robust mechanism to inhibit or at least help manage internally or externally generated temptations. But the system is not fail-safe and some individuals at one extreme of the impulsivity spectrum, as is the case in addiction, are the constant victims of powerful, unstoppable urges. By perturbing the function of the PFC, the addiction process degrades the very substrates that enable an individual to make appropriate decisions, exercise self-determination and exert free will. This is actionable knowledge that can and should be parlayed into more effective treatments. Therapeutic interventions should create incentives for the substance abusers to engage and stay in treatment; including strategies that help strengthen social ties with family and community, for social interactions are powerful reinforcers that can provide the addicted individual with alternatives that could help counteract the high-reward value of drugs.

An important consequence of the long-term brain adaptations discussed above is that most addicted patients will require a long period of treatment, during which relapse is likely to occur, thus relapse must be considered a predictable setback and not a failure of the treatment. This also explains

why the best treatment outcomes are reported by programs that offer continuity of care for a 5-year period (McLellan *et al.* 2008). It is equally important to recognize that social isolation is a well-recognized risk factor of mental illness including addiction (Karelina and DeVries 2011; Seo and Huang, 2012; Simoni-Wastila and Yang 2006). Yet, by most accounts, stigmatization and/or incarceration have been society's prevailing responses to addicted individuals. Such stigmatization impedes the search for treatment and further isolates addicted individuals and their families.

Finally, the implications derived from the current understanding of addiction could be easily misconstrued as advocating a sort of moral relativism at the expense of individual responsibility. Yet nothing could be farther from the truth; for the addicted individual is responsible for the management and

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

Table 1. Processes associated with the prefrontal cortex that are disrupted in addiction. Orbitofrontal cortex (OFC) includes Brodmann area (BA) 10-14 and 47, and inferior and subgenual regions of anterior cingulate cortex (ACC) (BA 24, 25 and 32) in the ventromedial prefrontal cortex (vmPFC); ACC includes rostral ACC (rACC) and dorsal ACC (dACC) (BA 24 and 32, respectively), which are included within the medial PFC (mPFC). The mPFC also includes BA 6, 8, 9 and 10; dorsolateral PFC (DLPFC) includes BA 6, 8, 9 and 46; and the inferior frontal gyrus (IFG) and ventrolateral PFC (vlPFC) encompass inferior portions of BA 8, 44 and 45. These various processes and regions participate to a different degree in craving, intoxication, bingeing and withdrawal. lOFC, lateral OFC; mOFC, medial OFC; PFC, prefrontal cortex. Reprinted with permission from (Goldstein and Volkow 2012).

treatment of this disease. But at the same time, the fact that addiction is a brain disease that impacts the very neural fabric that enables self-monitoring, self-determination and complex social functioning indicates that a fundamental revisiting of society's conventional responses to the problem of substance use disorders is long overdue.

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