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Neuroimaging for drug addiction and related behaviors

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Abstract

In this review, we highlight the role of neuroimaging techniques in studying the emotional and cognitive-behavioral components of the addiction syndrome by focusing on the neural substrates subserving them. The phenomenology of drug addiction can be characterized by a recurrent pattern of subjective experiences that includes drug intoxication, craving, bingeing, and withdrawal with the cycle culminating in a persistent preoccupation with obtaining, consuming, and recovering from the drug. In the past two decades, imaging studies of drug addiction have demonstrated deficits in brain circuits related to reward and impulsivity. The current review focuses on studies employing positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) to investigate these behaviors in drug-addicted human populations. We begin with a brief account of drug addiction followed by a technical account of each of these imaging modalities. We then discuss how these techniques have uniquely contributed to a deeper understanding of addictive behaviors.

Keywords: dopamine; electroencephalography (EEG); event-related potentials (ERPs); magnetic resonance imaging (MRI); positron emission tomography (PET); prefrontal cortex.

Introduction

In the past two decades, we have seen unprecedented advances in studying the human brain. Perhaps the most exciting has been the advent of structural and functional brain imaging techniques, which have revolutionized cognitive and behavioral neuroscience by allowing us a window into the brain activity underlying complex human behaviors. These technological advances have also led to the swift translation of basic neuroscience findings into more targeted therapies for clinical practice.

There is a wide variety of brain imaging techniques, which can be classified into three major categories: (1) nuclear medicine imaging techniques, including positron emission tomography (PET) and single photon emission computed tomography (SPECT); (2) magnetic resonance imaging (MRI) techniques including structural MRI, functional MRI (fMRI), and MR spectroscopy; and (3) electrophysiological imaging techniques, which include electroencephalography (EEG) and magnetoencephalography (MEG). Each of these techniques reveals a different aspect of brain structure and/or function, yielding a breadth of knowledge about the biochemical, electrophysiological, and functional processes of the brain; neurotransmitter activity; energy utilization and blood flow; and drug distribution and kinetics. Together they shed light on complex neuropsychological diseases, including drug addiction.

Addiction is a chronically relapsing disease characterized by drug intoxication, craving, bingeing, and withdrawal with loss of control over drug-related behaviors. This cycle culminates in the escalated preoccupation with the attainment and consumption of the substance. While the compulsion to consume the drug increases, the seeking of other (healthier) rewards (e.g., social experiences, exercise) in the environment decreases leading to detrimental consequences to the individual's well-being (encompassing physical health and other personal, social, and occupational goals). The Impaired Response Inhibition and Salience Attribution (iRISA) model of drug addiction (Goldstein and Volkow, 2002) posits that the cycle is characterized by impairments of two broad behavioral systems – response inhibition and salience attribution. According to the iRISA model, the salience and value attributed to the drug of choice and associated conditioned stimuli is much higher than the value attributed to other non-drug reinforcers, which in turn is associated with a decrease in self-control.

Drugs of abuse increase mesolimbic and mesocortical dopamine (DA) levels, which is crucial for their reinforcing effects (Koob et al., 1994; Di Chiara, 1998). Drugs of abuse exert their reinforcing and addictive effects by directly triggering supraphysiological DA action (Bassareo et al., 2002) and indirectly, by modulating other neurotransmitters [e.g., glutamate, γ aminobutyric acid (GABA), opioids, acetylcholine, cannabinoids and serotonin] in the reward circuit of the brain (see Koob and Volkow, 2010 for a review). With chronic drug use, DA D_2 receptor availability is reduced (Volkow et al., 1990a, 1997c; Nader and Czoty, 2005; Nader et al., 2006), altering function in dopaminergically innervated corticolimbic areas [encompassing the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC)] that mediate processing of reward salience, motivation, and inhibitory control (Volkow et al., 1993a; McClure et al., 2004; Goldstein et al., 2007a).

Here, we summarize PET, fMRI and EEG studies of the brain systems underlying human behaviors that are associated with the drug addiction syndrome. Hundreds of papers were

potentially appropriate for this review and, of necessity, we had to be selective. To provide the reader with a general perspective of the rapid advances, we have chosen to highlight only key behavioral domains, including intoxication, drug craving, bingeing, withdrawal, abstinence, and relapse, with an illustrative blend of neuroimaging studies across several drugs of abuse.

Overview of neuroimaging techniques

Positron emission tomography (PET)

PET is based on the physical principles of (1) positron emission and (2) coincidence detection (Eriksson et al., 1990; Burger and Townsend, 2003). The radionuclides which are used in PET imaging emit a positron (β^+), shortly after their generation by a particle accelerator or a cyclotron. These radionuclides (e.g., ^{15}O, ^{11}C, and ^{18}F) generally have short half-lives (i.e., they degrade quickly) and can be built into biologically active molecules. The radionuclide-labeled molecules (e.g., glucose or water), also known as radiotracers, thus contain a positron emitting isotope, which decays by emitting a positron from its nucleus (Eriksson et al., 1990).

A positron is the antiparticle of the electron: the two particles have the same mass but different charges; the electron has a negative charge, whereas a positron has a positive charge. When a radiotracer is administered to a subject, a positron is emitted. Upon interaction with an electron from a nearby tissue, the particles 'annihilate' each other and generate two photons, which travel in opposite directions and are detected by a pair of detectors alongside the line of response on two sides of the annihilation event. In the detector, the photons are typically converted into photons in the visible light range, which are then converted into an electrical signal. These electrical signals from opposing detectors enter a coincidence circuit where the coincidence logic selects pairs of photons which are detected within a narrow time window (typically a few ns), which are called coincidence events. These coincidence events are then used to generate a PET image (Wahl and Buchanan, 2002).

PET is a versatile and minimally-invasive imaging technique that can be used *in vivo* to answer mechanistic questions about biochemistry and physiology in animals and humans. Many drugs of abuse, and ligands binding to the neurotransmitters they affect, can be radiolabeled and detected in the body using PET. Bioavailability can be measured and quantified in any organ of interest including the brain. For example, in drug addiction research, [^{11}C]raclopride and [^{11}C]cocaine are radiotracers that have been used extensively; [^{11}C]raclopride to measure D_2 receptors availability and to measure changes in extracellular DA (Volkow et al., 1994a) and [^{11}C]cocaine to measure pharmacokinetics and distribution of cocaine in the human brain and also to assess DA transporter (DAT) availability and their blockade by stimulant drugs (Volkow et al., 1997b). As PET is used *in vivo* and reveals pharmacokinetics and biodistribution. It allows repeated testing and use in awake human participants in whom one can obtain, in parallel, subjective and objective measures of drug effects (Halldin et al., 2004). The outcome variable of this technique is the binding potential (or binding) of the radiotracer or the receptor/transporter availability, which is equivalent to the product of receptor/transporter density and affinity of the radiotracer for the receptor/transporter. PET can also be used to quantify the concentration of enzymes. For example, PET studies have assessed the effects of cigarette smoke on the concentration of monoamine oxidases (MAO A and MAO B) in the human brain and body (Fowler et al., 2005).

Although the intrinsic temporal resolution of PET coincidence events is very high (few ns), it takes a large number of events to provide sufficient counting statistics to generate an image. Moreover, the data acquisition time is often limited by the tracer kinetics, metabolism, and binding, which limit the temporal resolution vis-à-vis the physiological process being measured. For example, the measurement of brain glucose metabolism using [^{18}F]fluorodeoxyglucose averages activity in the brain over a 20- to 30-min period and the measurement of cerebral blood flow (CBF) with [^{15}O] water averages activity over ~60 s (Volkow et al., 1997a). The technique also suffers from a relatively low spatial resolution (>2 mm) compared to that of MRI. However, the major limitation of the feasibility of this technique is that most radiotracers are short-lived and therefore have to be processed in proximity of the imaging facility. The use of radioactivity also limits its application mostly to adults with very few studies having been done in adolescents because of safety concerns despite a relatively low absorbed dose.

Functional magnetic resonance imaging (fMRI)

The creation of an MR image requires that the object is placed within a strong magnetic field. Magnetic strength for human MRI scanners ranges from 0.5 to 9.4 T; however, the strength of most clinical MRI scanners is 1.5–3 T. Within a magnetic field, the nuclear spins of certain atoms within the object are oriented either parallel or anti-parallel to the main magnetic field and precess (spin) about the main magnetic field with a certain frequency called the Larmor frequency. Magnetic resonance occurs when a radio frequency (RF) pulse, applied at the (tissue specific) Larmor frequency, excites the nuclear spins, raising them from lower to higher energy states. This is represented by a rotation of the net magnetization away from its equilibrium. Once the magnetization is rotated, the RF field is switched off and the magnetization once again freely precesses about the direction of original main magnetization. This time-dependent precession induces a current in a receiver RF coil. The resultant exponentially decaying current, referred to as the free induction decay, constitutes the MR signal. During this period, magnetization returns to its original equilibrium state (also known as relaxation), characterized by two time constants T_1 and T_2 (Lauterbur, 1973). These time constants depend on physical and chemical characteristics unique to tissue type and hence are the primary source of tissue contrast in anatomical images (Mansfield and Maudsley, 1977). These T_1 and T_2 differences between different tissue types (e.g., gray matter, white matter, and cerebrospinal fluid) yield a high-contrast MR image.

It was not until the 1990s that MRI was used to map human brain function non-invasively, rapidly, with full brain coverage, and with relatively high spatial and temporal resolution. Belliveau et al. (1990), using gadolinium as contrast agent, was the first to introduce the functional MRI (fMRI). This was then immediately followed by a series of fMRI studies using the 'Blood Oxygen Level Dependent' (BOLD) signal (Ogawa et al., 1990a,b) as endogenous contrast agent for indirect measure of brain activity (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). Recently, work by Logothetis et al. (2001) has explored a causal relationship between the BOLD signal and neuronal local field potentials (see Logothetis, 2003; Logothetis and Wandell, 2004 for reviews).

fMRI has become perhaps the most widely used functional neuroimaging technique because of its non-invasive nature (unlike PET and SPECT, it does not expose participants to radioactivity) and very high spatial resolution (~1 mm). The limitations of this technique include high susceptibility of the BOLD response to several non-neural and imaging artifacts, especially due to its low signal-to-noise ratio and low temporal resolution (~1–2 s) compared to other techniques, such as EEG (although much higher than that of PET). More recently, the use of fMRI at rest has enabled researchers to investigate resting functional connectivity of the human brain (Rosazza and Minati, 2011). Measures of resting functional connectivity have been shown to be reproducible and consistent across laboratories (Tomasi and Volkow, 2010) and to be sensitive to diseases of the brain including drug addiction (Gu et al., 2010).

Electroencephalography (EEG)

EEG provides a graphic representation of the difference in voltage between two different cerebral locations plotted over time. The fluctuating EEG voltage recorded at the scalp through metallic electrodes is made up of summations of billions of individual postsynaptic potentials (both inhibitory and excitatory) from large groups of cortical neurons (Martin, 1991). Several well-established recurring patterns of rhythmic cycles can reliably be observed in the scalp recorded EEG, and result from complex interplay between thalamocortical circuitry and both local and global corticocortical circuitry (Thatcher et al., 1986). The range of these frequencies in human EEG is commonly (although variably) divided into five bands: delta (<4 Hz), theta (4–7.5 Hz), alpha (7.5–12.5 Hz), beta (12.5–30 Hz), and gamma (<30 Hz). Each of these EEG bands is believed to have some functional significance and have been associated with specific brain states (e.g., working memory, cognitive processing, and quiet relaxation).

Transient EEG changes in frequency and time domains, that are time locked to some external or internal event, are called event-related oscillations (EROs) and event-related potentials (ERPs), respectively (Basar et al., 1980, 1984; Rugg and Coles, 1995; Kutas and Dale, 1997). EROs are spectral changes that can be described by their three parameters: amplitude, frequency, and phase. The amplitude (the total fast Fourier transform measure of electrical power) is a measure of synchrony between local neuronal assemblies, whereas the differences in frequencies at which power peaks most likely reflect neural activity in different cell assemblies (e.g., differing in size/type and/or interconnectivity) (Corletto et al., 1967; Basar et al., 1980, 1984; Gath and Bar-On, 1983; Gath et al., 1985; Romani et al., 1988, 1991; Rahn and Basar, 1993). Phase is related to the excitability of neurons and, thus, to the probability of the generation of action potentials (Varela et al., 2001; Fries, 2005).

The ERP components are generally quantified by their amplitude and latency measures. For example, N200, P300, and the late positive potential (LPP), each reflects unique cognitive brain functions (e.g., attention, motivation, and higher level executive function). Because EEG recordings offer a level of temporal resolution (~1 ms) that exceeds that of other neuroimaging modalities, it provides the flow of information almost in real time (Gevins, 1998). Other neuroimaging technologies cannot achieve such temporal resolution because blood flow and glucose utilization changes are indirect measures of neural activity, and the methods to record them are slow. Thus, PET and fMRI are less well suited for determining the neural chronometry of a certain brain function. Another major strength of EEG technology is its portability, ease-of-use, and low cost. For example, manufacturers are now producing small, light-weight and battery-operated multichannel EEG amplification systems which could be mobilized to study patients in treatment facilities, rural settings, and other removed or restrictive residences (such as prisons). This portability and ease-of-use can lead to rapid translation of laboratory findings to clinical implementations, e.g., in relapse prediction (Bauer, 1994, 1997; Winterer et al., 1998) or recovery assessment (Bauer, 1996).

Major neuroimaging findings of human behavior in drug addiction

Intoxication

Intoxication occurs when an individual consumes a drug dose large enough to produce significant behavioral, physiological, or cognitive impairments. Neuroimaging studies assessing the effects of acute drug intoxication have traditionally relied on single drug exposure. This process of short-term drug administration to induce a 'high' or 'rush' has been traditionally associated with increases in extracellular DA in limbic brain regions, particularly the nucleus accumbens (NAcc); however, there is also evidence of increased DA concentrations in other striatal regions and in the frontal cortex. Stimulant drugs, such as cocaine and methylphenidate (MPH) increase DA by blocking DAT, the main mechanism for recycling DA back into the nerve terminals. The 'high' associated with a stimulant intoxication (e.g., cocaine) is positively related to the level of DAT blockade (Volkow et al., 1997b) and drug-induced increases in DA (Volkow et al., 1999a,c). In fact, DA enhancing effects are directly associated with the reinforcing effects of cocaine, MPH, and amphetamine (Laruelle et al., 1995; Goldstein and Volkow, 2002).

Depressant drugs such as benzodiazepines, barbiturates, and alcohol increase DA indirectly, in part *via* their effects on

the GABA/benzodiazepine receptor complex (Volkow et al., 2009). Opiates such as heroin, oxycontin, and vicodin act by stimulating μ-opiate receptors, some of which are located on DA neurons and others on the GABA neurons that regulate the DA cells and their terminals (Wang et al., 1997). Nicotine is believed to exert its reinforcing effects in part by activation of the α4β2 acetylcholine nicotinic receptors, which have also been identified on DA neurons. Nicotine (similarly to heroin and alcohol) also appears to release endogenous opioids, and this is also likely to contribute to its rewarding effects (McGehee and Mansvelder, 2000). Finally, marijuana exerts its effect by activating cannabinoid 1 (CB1) receptors, which modulate DA cells as well as postsynaptic DA signals (Gessa et al., 1998). Moreover, there is increasing evidence for the involvement of cannabinoids in the reinforcing effects of other drugs of abuse, including alcohol, nicotine, cocaine, and opioids (Volkow et al., 2004).

Along with mesolimbic DA subcortical brain areas, prefrontal cortical (PFC) regions are also involved in the intoxication process and their response to drugs is in part related to previous drug experiences. Other factors that affect the extent of the 'high' from a drug are the rate of drug delivery and clearance to and from the brain (Volkow et al., 1997b) as well as the severity of use (e.g., magnitude of the increase in DA is reduced with the progression from drug abuse to drug dependence; Volkow et al., 2002). PET studies have revealed that drug intoxication is generally associated with changes in brain glucose utilization, which serves as a marker of brain function. In cocaine abusers acute cocaine administration, and in alcoholics (and controls) acute alcohol administration, decreases brain glucose metabolism (London et al., 1990a,b; Volkow et al., 1990b; Gu et al., 2010). However, these responses are variable and depend not only on the drug administered but also on individual characteristics. For example, acute administration of MPH has been found to increase levels of glucose metabolism in the PFC, OFC, and striatum, in active cocaine abusers with low D_2 receptor availability (Ritz et al., 1987; Volkow et al., 1999b), whereas it decreases metabolism in these prefrontal regions in non-addicted individuals (Volkow et al., 2005). Studies utilizing CBF and BOLD methods generally have shown activations during drug intoxication (Volkow et al., 1988b; Mathew et al., 1992; Tiihonen et al., 1994; Adams et al., 1998; Ingvar et al., 1998; Nakamura et al., 2000) with exceptions for cocaine which is found to lower CBF throughout the brain, including the frontal cortex (an effect considered to result from vasoconstricting effects of cocaine) (Wallace et al., 1996). fMRI studies have also linked the pleasurable experience during drug intoxication with subcortical striatal function after acute drug administration across several drug classes (Breiter et al., 1997; Stein et al., 1998; Kufahl et al., 2005; Gilman et al., 2008).

Prior to these neuroimaging studies, EEG measurements provided some of the first *in vivo* data on the acute effects of drugs in the human brain. For example, acute nicotine administration has been linked to strong increases in scalp-recorded activity shifts from low (delta, theta, lower alpha) to high (higher alpha, beta) frequencies, indicating a state of arousal (Domino, 2003; Teneggi et al., 2004). In contrast, EEG studies indicate that low doses of alcohol produce alterations in theta and lower alpha frequency bands, while effects at higher frequencies tend to depend on individual factors such as drinking history and pre-drug EEG baseline (Lehtinen et al., 1978, 1985; Ehlers et al., 1989). This increase in alpha has also been linked to the elevated feelings of drug-induced euphoria or 'high' in marijuana (Lukas et al., 1995) and cocaine (Herning et al., 1994). In cocaine addiction, increase in beta (Herning et al., 1985, 1994), delta (Herning et al., 1985), frontal alpha (Herning et al., 1994), and global spectral (Reid et al., 2008) activities have also been reported. Acute administration of illicit drugs has been observed to alter different ERP components across all classes of drugs (Roth et al., 1977; Herning et al., 1979, 1987; Porjesz and Begleiter, 1981; Velasco et al., 1984; Lukas et al., 1990). For example, alcohol has been found to attenuate the auditory N100 (Hari et al., 1979; Jaaskelainen et al., 1996) and P200 (Hari et al., 1979; Pfefferbaum et al., 1979; Jaaskelainen et al., 1996) amplitudes. Increased latency and decreased P300 amplitudes have also been reported in response to alcohol intoxication (Teo and Ferguson, 1986; Daruna et al., 1987; Krein et al., 1987; Lukas et al., 1990; Wall and Ehlers, 1995).

Taken together, neuroimaging studies of drug intoxication suggest a role of DA in PFC and striatal functions that is specifically associated with anxiolytic effects of drugs of abuse as quantified by an increase in slower EEG spectral bands. Although numerous animal studies have shown similar DA related dysfunction during drug intoxication, only human neuroimaging studies are able to integrate these findings with behavioral manifestations such as intoxication-induced high and craving.

Craving

The pharmacological effects of a drug are modulated by non-pharmacological contextual factors (e.g., places, people, or paraphernalia associated with drug intake). As these factors are consistently paired with the pharmacological effects of the drug they are integrated into the intense experience associated with drug use, becoming 'motivational magnets' or 'drug cues' through Pavlovian conditioning (Berridge, 2007; Berridge et al., 2008). This conditioning shapes an individual's expectations of the effects of a drug and, in turn, modifies the neural and behavioral responses to the drug. For example, in drug-addicted individuals, attention and other cognitive and motivational processes are biased towards the drug and away from non-drug stimuli culminating in an urgent desire to consume the drug in susceptible individuals (e.g., Johanson et al., 2006).

In laboratory settings, a craving state is usually achieved by exposing participants to images depicting drug-related stimuli. Using this technique with cocaine users, PET [^{11}C]raclopride studies have revealed that cocaine cue videos can elicit a significant release of DA in the dorsal striatum and this increase is positively associated with self-reported drug craving especially in severely addicted individuals (Volkow et al., 2006, 2008). Another PET study showed that chronic cocaine abusers retain some level of cognitive control when instructed to inhibit

cue-induced craving as quantified by lower metabolism with cognitive inhibition in the right OFC and the NAcc (Volkow et al., 2010). These results are consequential as there is a significant association between DA D_2 receptor binding in the ventral striatum and the motivation for drug self-administration, as measured by [^{11}C]raclopride (Martinez et al., 2005) and [^{18}F] desmethoxyfallypride (Heinz et al., 2004).

Studies measuring CBF, glucose metabolism, or BOLD have also shown that drug cue-induced craving in drug-addicted individuals is associated with activations in the perigenual and ventral ACC (Maas et al., 1998; Childress et al., 1999; Kilts et al., 2001; Wexler et al., 2001; Brody et al., 2002, 2004; Daglish et al., 2003; Tapert et al., 2003, 2004; Grusser et al., 2004; Myrick et al., 2004; McClernon et al., 2005; Wilson et al., 2005; Goldstein et al., 2007b), medial PFC (Grusser et al., 2004; Heinz et al., 2004; Tapert et al., 2004; Wilson et al., 2005; Goldstein et al., 2007b), OFC (Grant et al., 1996; Maas et al., 1998; Sell et al., 2000; Bonson et al., 2002; Brody et al., 2002; Wrase et al., 2002; Daglish et al., 2003; Tapert et al., 2003, 2004; Myrick et al., 2004) insula (Wang et al., 1999; Sell et al., 2000; Kilts et al., 2001; Brody et al., 2002; Daglish et al., 2003; Tapert et al., 2004), ventral tegmental area and other mesencephalic nuclei (Sell et al., 1999; Due et al., 2002; Smolka et al., 2006; Goldstein et al., 2009c). Brain regions that are involved with memory processing and retrieval are also activated during craving, including the amygdala (Grant et al., 1996; Childress et al., 1999; Kilts et al., 2001; Schneider et al., 2001; Bonson et al., 2002; Due et al., 2002), hippocampus, and brainstem (Daglish et al., 2003). Of note is evidence showing that these effects are observed even when controlling for the effects of pharmacological withdrawal (Franklin et al., 2007).

In general, findings from craving studies in drug abusers suggest increased mesocortical (including the OFC and ACC) activation when processing drug cues and that drug expectation plays a significant role in this process. Such evidence in part explains the difficulty for drug abusers to focus on other non-drug related cues. Interestingly, in females but not in male cocaine abusers a PET study showed decreases in metabolism in prefrontal regions involved with self-control following exposure to cocaine cues, which could render them more vulnerable (than males) to relapse if exposed to the drug (Volkow et al., 2011). This finding is consistent with preclinical studies suggesting that estrogen may increase the risk for drug abuse in females (Anker and Carroll, 2011).

EEG has also been used to investigate the reactivity to drug-associated stimuli across different drugs of abuse. For example, increased cortical activation has been reported in response to drug cue exposure in alcohol-dependent patients (quantified by EEG dimensional complexity) (Kim et al., 2003), and in cocaine-addicted individuals (quantified by high beta and low alpha spectral power) (Liu et al., 1998). Another study of cocaine-addicted individuals showed an increase in beta spectral power along with a decrease in delta power while handling cocaine paraphernalia and viewing a crack cocaine video (Reid et al., 2003). This pattern was also observed when comparing these individuals to healthy controls during rest (Noldy et al., 1994; Herning et al., 1997) and this increase in beta was associated with amount of prior cocaine use (Herning et al., 1997). In nicotine addiction, an increase in theta and beta spectral power was observed in response to cigarette-related cues (Knott et al., 2008). Higher cortical activation in response to drug cues has also been reported in ERP studies. For example, increased amplitude of P300 and other P300-like potentials have been reported in response to drug cues in alcohol- (Herrmann et al., 2000) and nicotine- (Warren and McDonough, 1999) addicted individuals. Increased LPP amplitudes have also been reported in response to drug-related pictures compared to neutral pictures in alcohol- (Herrmann et al., 2001; Namkoong et al., 2004; Heinze et al., 2007), cocaine- (Franken et al., 2004; van de Laar et al., 2004; Dunning et al., 2011), and heroin- (Franken et al., 2003) addicted individuals.

Broadly, these data suggest that drug-associated stimuli are related to significantly higher neural activations, suggesting an increase in incentive salience and arousal when drug-associated stimuli are encountered or anticipated by drug-addicted individuals. These results corroborate theories that posit addiction as an alteration to the brain's motivation and reward systems (Volkow and Fowler, 2000; Robinson and Berridge, 2001; Goldstein and Volkow, 2002), where processing is biased towards drugs and conditioned cues and away from other reinforcers as associated with craving (Franken, 2003; Mogg et al., 2003; Waters et al., 2003).

Loss of inhibitory control and bingeing

Inhibitory control is a neuropsychological construct that refers to the capacity to control the inhibition of harmful and/or inappropriate emotion, cognition, or behavior. Critically, the disruption of self-controlled behavior is likely to be exacerbated during drug use and intoxication as modulated by a compromise in an essential function of the PFC: its inhibitory effect on subcortical striatal regions (including NAcc) (Goldstein and Volkow, 2002). This impairment in top-down control (a core PFC function) would release behaviors that are normally kept under close monitoring, simulating stress-like reactions in which control is suspended and stimulus-driven behavior is facilitated. This suspension of cognitive control contributes to bingeing; a discrete period of time during which an individual engages in the repeated and unabated consumption of the substance often at the expense of behaviors needed for survival including eating, sleeping, and maintaining physical safety. These periods usually discontinue when the individual is severely exhausted and/or unable to procure more of the drug.

Neuroimaging studies suggest the involvement of thalamo-OFC circuit and the ACC as neural substrates underlying bingeing behavior. Specifically, it has been reported that addicted individuals have significant reductions in D_2 receptor availability in the striatum (see Volkow et al., 2009 for a review), which in turn is associated with decreased metabolism in the PFC (especially OFC, ACC, and dorsolateral PFC), and that these impairments cannot be fully attributed to impaired behavioral responses and motivation (Goldstein et al., 2009a). As these PFC regions are involved in salience attribution,

inhibitory control, emotion regulation, and decision-making, it is postulated that DA dysregulation in these regions may enhance the motivational value of the drug of abuse and may lead to loss of control over drug intake (Volkow et al., 1996a; Volkow and Fowler, 2000; Goldstein and Volkow, 2002).

Indeed, there is evidence showing that these regions, particularly the OFC, are critical in other disorders of self-control involving compulsive behaviors such as obsessive-compulsive disorder (Zald and Kim, 1996; Menzies et al., 2007; Chamberlain et al., 2008; Yoo et al., 2008; Rotge et al., 2009).

Although it is difficult to test compulsive drug self-administration in humans, clever laboratory designs have overcome some of the practical constraints encountered when studying bingeing in humans. For example, in a recent fMRI study, non-treatment-seeking cocaine-dependent individuals were permitted to choose when and how often they would self-administer intravenous cocaine within a supervised 1-h session. Repeated self-induced high was negatively correlated with activity in limbic, paralimbic, and mesocortical regions including the OFC and ACC. Craving, by contrast, positively correlated with activity in these regions (Risinger et al., 2005) (also see Foltin et al., 2003). Simulating compulsive drug self-administration vis-à-vis other compulsive behavior (such as gambling when it is clearly no longer beneficial) may offer invaluable insight into the circuits underlying loss of control in addictive disorders. Interestingly, oral MPH significantly decreased impulsivity and improved the underlying ACC responses in cocaine-addicted individuals (Goldstein et al., 2010).

Another related construct is the compromised self-awareness in drug-addicted individuals. Dysfunctional self-awareness and insight characterize various neuropsychiatric disorders, spanning classic neurological insults (e.g., causing visual neglect or anosognosia for hemiplegia) to classic psychiatric disorders (e.g., schizophrenia, mania, and other mood disorders), as recently reviewed (Orfei et al., 2008). As a cognitive disorder (Goldstein and Volkow, 2002), drug addiction also shares similar abnormalities in self-awareness and behavioral control that can be attributed to an underlying neural dysfunction. For instance, studies in alcohol abuse have reported that alcohol reduces the individual's level of self-awareness by inhibiting higher order cognitive processes related to (attending, encoding or sensitivity to) self-relevant information, a sufficient condition to induce and sustain further alcohol consumption (see Hull and Young, 1983; Hull et al., 1986 for reviews). Moreover, a recent study has shown that cocaine-addicted individuals manifest a disconnect between task-related behavioral responses (accuracy and reaction time) and the self-reported task engagement, highlighting the disruption in their ability to perceive inner motivational drives (Goldstein et al., 2007a).

Specifically, abnormalities in the insula and medial PFC regions (including ACC and medial OFC), and in subcortical regions (including the striatum), have been associated with insight and behavioral control, and with interrelated functions (habit formation and valuation) (Bechara, 2005). These considerations expand the conceptualization of addiction beyond its association with the reward circuit, neurocognitive impairments in response inhibition, and salience attribution (Goldstein and Volkow, 2002; Bechara, 2005) and neuroadaptations in memory circuits (Volkow et al., 2003), to include compromised self-awareness and insight into illness (see Goldstein et al., 2009b for a review).

Studies employing EEG have reliably reported low-voltage beta frequencies (Kiloh et al., 1981; Niedermeyer and Lopes da Silva, 1982) in alcoholics. This beta activity, which may reflect hyperarousal (Saletu-Zyhlarz et al., 2004), has been shown to correspond to the quantity and frequency of alcohol intake, reliably differentiating between 'low' and 'moderate' alcohol drinkers (determined by pattern of alcohol consumption), as well as familial history of alcoholism (Ehlers et al., 1989; Ehlers and Schuckit, 1990). Simultaneous increases in delta were reported in high-binge drinkers compared to non- and low-binge young adult alcohol drinkers (Polich and Courtney, 2010), and with concomitant increase in theta and alpha frequencies 25 min post-binge-like cocaine dosing (Reid et al., 2006).

Inhibitory control has widely been studied by quantifying N200 and P300 ERP components in go/no-go tasks; these components, thought to measure successful behavioral suppression and cognitive control (Dong et al., 2009) and generate from ACC and associated regions, are increased when a response is withheld (no-go trial) within a series of positive responses (go trials) (Falkenstein et al., 1999; Bokura et al., 2001; Van Veen and Carter, 2002; Bekker et al., 2005). Blunted N200 amplitudes have been reported in individuals with alcohol (Easdon et al., 2005), cocaine (Sokhadze et al., 2008), heroin (Yang et al., 2009), nicotine (Luijten et al., 2011), and even internet (Cheng et al., 2010; Dong et al., 2010) addiction. However, binge drinkers showed larger N200 and smaller P300 as compared to controls, in a sustained attention pattern matching task (Crego et al., 2009) and face recognition task (Ehlers et al., 2007), which may actually be consistent with emotional processing impairment (motivation, salience) more than with loss of control.

Animal models of addiction have provided important clues about the neurobiology underlying bingeing behavior (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004) showing that these behaviors involve DA, serotonergic, and glutamatergic circuits (Loh and Roberts, 1990; Cornish et al., 1999). However, the utility of animal studies rests on the degree to which these behaviors overlap with inhibitory self-control in humans. In particular, it is difficult to ascertain the degree to which such behaviors may be relevant to the putative cognitive deficits that may underlie impaired inhibitory control in humans. Neuroimaging studies circumvent this limitation by investigating the neural substrates underlying these cognitive deficits and by providing a link to the corresponding behavioral manifestations.

Withdrawal and relapse

Drug withdrawal refers to a variety of symptoms including fatigue, irritability, anxiety, and anhedonia that appear when a

drug that causes physical dependence is suddenly terminated (Gawin and Kleber, 1986). These symptoms can vary depending on the type of drug and the length of abstinence from last drug use and are often distinguished by 'early' vs. 'protracted' withdrawal symptoms.

In general, PET studies of drug-addicted individuals suggest durable drug-related adjustments (mostly reduced sensitivity) in regional neural responsiveness during withdrawal. Significantly lower relative CBF in left lateral PFC as well as decreases in glucose metabolism in PFC have been reported in regular cocaine users during early withdrawal (10 days) and more protracted withdrawal from cocaine than in healthy controls (Volkow et al., 1988a, 1991). CBF has also been assessed *via* MR dynamic susceptibility contrast after overnight withdrawal from nicotine, as well as after nicotine replacement. Results of this analysis showed a reduction in thalamic CBF during withdrawal but increased CBF in the ventral striatum with nicotine replacement (Tanabe et al., 2008). Studies of glucose metabolism have shown reduced metabolic activity during alcohol withdrawal throughout the striatal-thalamo-OFC circuit during early detoxification but predominantly lower in the OFC during protracted alcohol withdrawal (Volkow et al., 1992a, 1993a,b, 1994b, 1997c,d; Catafau et al., 1999). In cocaine addiction, studies have reported similar metabolic reductions in ventral striatal activity during drug withdrawal, with greater metabolic activity in the OFC and basal ganglia during early withdrawal (within 1 week of abstinence) (Volkow et al., 1991), and lower metabolic activity in the PFC during protracted withdrawal (1–6 weeks since last use) (Volkow et al., 1992b). Lower striatal DA D_2 receptor binding during withdrawal has been found in cocaine- (Volkow et al., 1993a), alcohol- (Volkow et al., 1996b), heroin- (Wang et al., 1997), methamphetamine- (Volkow et al., 2001), and in nicotine-dependent individuals (Fehr et al., 2008). This effect was associated with lower metabolism in the OFC and ACC in cocaine-addicted individuals and alcoholics and exclusively in the OFC in methamphetamine-addicted individuals (Volkow et al., 2009).

Drug-induced withdrawal also entails the emergence of negative emotional state (e.g., dysphoria), characterized by a persistent inability to derive pleasure from common non-drug-related rewards (e.g., food, personal relationships). This anhedonic state might possibly reflect an adaptive response to repeated DA enhancement by drugs of abuse in the reward circuit rendering the reward system less sensitive to natural reinforcers (Cassens et al., 1981; Barr and Phillips, 1999; Barr et al., 1999) and other non-drug reinforcers (e.g., money; Goldstein et al., 2007a). This adaptive DA-induced response may compromise the function of the PFC, OFC, and ACC in drug-addicted individuals promoting deficits that appear similar to those in non-drug-addicted depressed patients. Indeed, abnormalities in the dorsolateral, ventrolateral, and medial aspects of the PFC including ACC and OFC have been found in studies of clinically (non-drug-addicted) depressed patients (Elliott et al., 1998; Mayberg et al., 1999) during cognitive (e.g., planning tasks) and pharmacological challenges. These drug-induced alterations to the function of the PFC, ACC, and OFC (but also striatal and insula regions) may impair the ability to regulate emotions (Payer et al., 2008) relevant for coping with stress, indeed a strong predictor of relapse (Goeders, 2003) (see Sinha and Li, 2007 for a review).

During cocaine abstinence, EEG studies have reported decreased delta (Alper et al., 1990; Roemer et al., 1995; Prichep et al., 1996), theta (Roemer et al., 1995; Prichep et al., 1996; Herning et al., 1997), but increased alpha (Alper et al., 1990) and beta power (Costa and Bauer, 1997; Herning et al., 1997; King et al., 2000). Increase in alpha has also been reported during early withdrawal in heroin-addicted individuals (Shufman et al., 1996). In contrast to the pattern observed with cocaine abstinence, during nicotine withdrawal, theta power increases while both alpha and beta power decrease (for an overview, see Domino, 2003; Teneggi et al., 2004). This increase in theta power was correlated with drowsiness (Ulett and Itil, 1969; Dolmierski et al., 1983) and the transition from wakefulness to sleep (Kooi et al., 1978), while the decrease in alpha frequency has been associated with slow reaction time (Surwillo, 1963), diminished arousal and decreased vigilance (Ulett and Itil, 1969; Knott and Venables, 1977). These deficits in alpha activity appear to reverse with protracted abstinence suggesting that they may be measuring acute effects of drug withdrawal (Gritz et al., 1975). ERP measurements during withdrawal in alcoholics have demonstrated increases in N200 and P300 latencies and decreases in N100 and P300 amplitudes (Porjesz et al., 1987a,b; Parsons et al., 1990). Reduced P300 amplitude is a consistent finding during cocaine (Kouri et al., 1996; Biggins et al., 1997; Gooding et al., 2008), heroin (Papageorgiou et al., 2001, 2003, 2004), and nicotine abstinence (Daurignac et al., 1998) as normalized after buprenorphine (a μ-opioid receptor partial agonist) administration to addicted individuals withdrawn from heroin and cocaine (Kouri et al., 1996).

Moreover, both EEG and ERP indices have been used to predict relapse. For example, alpha and theta activity in sober alcoholics distinguished, with 83–85% accuracy, between abstainers and relapsers using classification methods (Winterer et al., 1998). Hyperarousal of the central nervous system, as quantified by high-frequency beta activity, was also found to be a reliable classifier between abstinent- and relapse-prone alcoholic individuals (Bauer, 1994, 2001; Saletu-Zyhlarz et al., 2004). ERP studies in sober alcoholics found delayed N200 latency to distinguish between abstainers and relapsers with an overall predictive rate of 71% (Glenn et al., 1993). Comparable relapse prediction accuracy (71%) has also been reported for reduced P300 amplitude in abstaining cocaine-addicted individuals (Bauer, 1997).

Thus, neuroimaging studies have advanced our understanding of drug withdrawal and its associated behaviors by quantifying reduced cortical sensitivity through regional CBF, energy metabolism, EEG frequency band measures, and ERPs across several drugs of abuse. These neuronal markers have also been reported to predict relapse and, therefore, may play a crucial role in treatment development and outcome research.

Conclusion

Neuroimaging technology has had a tremendous impact on the basic knowledge of addiction-related brain circuits and the related behavioral outcomes. It has identified cortically regulated cognitive and emotional processes that result in the overvaluing of drug reinforcers, the undervaluing of alternative reinforcers, and deficits in inhibitory control. These changes in addiction, as represented in the iRISA model, expand the traditional concepts emphasizing limbic-regulated responses to reward by providing evidence for the involvement of the frontal cortex throughout the addiction cycle.

Indeed, animal models of drug addiction have provided a well-informed foundation for studying both the behavioral and biological basis of drug addiction and have also elucidated the neurobiological mechanisms involved in the positive reinforcing effects of drugs and the negative reinforcing effects of drug abstinence. However, a major caveat remains in the uncertainty of the degree to which these behaviors overlap with addiction-related behaviors in humans. Neuroimaging approaches can be instrumental in providing a more 'direct' window into these behaviors in humans with the goal of paving the way for the development of novel and targeted interventions. It is now conceivable that interventions designed to strengthen and remediate brain areas affected by chronic drug use *via* cognitive-behavioral interventions and pharmaceuticals may be highly beneficial to drug-addicted individuals just as they have been for other disorders (e.g., Papanicolaou et al., 2003; Volkow et al., 2007). Neuroimaging tools also enable the investigation of brain phenotypes as a function of genotype, which is crucial for understanding the cerebral processes by which genes affect the vulnerability or resilience of an individual to drug abuse and addiction (e.g., Alia-Klein et al., 2011).

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Notice

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