CHAPTER ONE

Neuroimaging of Addiction

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1. INTRODUCTION

Scientific advances over the past 20 to 30 years have established drug addiction as a chronic brain disease (Leshner, 1997). Key evidence supporting this concept was produced by brain imaging studies of drug abusers obtained during or following various periods of drug exposure. These studies have provided information on drugs' neurobiological effects, helped explain the causes and mechanisms of vulnerability to drug abuse, and yielded important insights into abusers' subjective experiences and behaviors, including their difficulty to attain a sustained, relapse-free recovery. Clinicians may be able, in the not too distant future, to use brain imaging to evaluate the level and pattern of brain dysfunction in their addicted patients, helping them to tailor their treatments and to monitor their response to therapy.

The seven primary brain imaging techniques - structural magnetic resonance imaging (MRI), functional MRI, resting functional MRI, Diffusion Tensor Imaging (DTI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT) - reveal different aspects of brain structure and/or function (Bandettini, 2009; Detre and Floyd, 2001; Duyn and Koretsky, 2011; Johansen-Berg and Rushworth, 2009; Sharma and Ebadi, 2008). Individually, the techniques yield highly complementary information about brain anatomy and tissue composition; biochemical, physiological, and functional processes; neurotransmitter levels; energy utilization and blood flow; and drug distribution and kinetics. Together, and in combination with other research techniques they contribute to continuously improve our understanding of drug abuse and addiction.

2.1. MAGNETIC RESONANCE-BASED IMAGING TECHNIQUES

2.1.1. Structural Magnetic Resonance Imaging

Structural magnetic resonance imaging (sMRI) translates the local differences in water content into different shades of gray that serve to outline the shapes and sizes of the

Imaging of the Human Brain in Health and Disease
http://dx.doi.org/10.1016/B978-0-12-418677-4.00001-4

brain's various subregions. An MRI scanner delivers a specific radiofrequency that excites hydrogen atoms in the water molecule, which return some of this energy in the form of a characteristic nuclear magnetic resonance signal. Not all protons "resonate" in that way, but enough do such that the resulting computer-generated image constitutes a highly detailed map of the brain's tissues and structures. Thus, this tool can be used to discover the presence of abnormal tissue through the changes in tissue density or composition. Scientists examining an sMRI can readily distinguish between gray and white matter and other types of tissue—both normal, such as blood vessels, and abnormal, such as tumors—by their different shading and contrast with surrounding areas.

Such measurements can help scientists and doctors to home in on the regions that are most heavily affected by drugs. Importantly, these initial observations often guide additional investigations, using other research tools and techniques, to determine the reasons for the structural changes as well as their experiential and behavioral consequences. As explained below, sMRI studies have provided detailed evidence that chronic drug exposure can lead to both increases and reductions in the volume of specific brain regions.

Drug Exposure can Trigger Abnormalities in Prefrontal Cortex and Other Brain Regions

Numerous sMRI studies have documented that addictive drugs can cause volume and tissue composition changes in the prefrontal cortex (PFC), a brain region that supports logical thinking, goal-directed behaviors, planning, and self-control. These changes in turn are likely to be associated with drug abusers' cognitive and decision-making deficiencies. Related to this finding, another sMRI study found that individuals with a history of abusing multiple substances have smaller prefrontal lobes than did matched controls (Liu et al., 1998).

These findings add to the growing evidence associating prefrontal abnormalities with the abuse of various substances (Goldstein and Volkow, 2002; Stapleton et al., 1995; Volkow et al., 1991). For example, using sMRI, Schlaepfer and colleagues found that chronic substance abusers' frontal lobe tissues contained a lower proportion of white matter than those of matched controls did (Schlaepfer et al, 2006). Interestingly, similar deficits in white matter content have been found in individuals with other psychiatric disorders that tend to cooccur with substance abuse.

Pertaining to the abuse of stimulants, Kim and colleagues (Kim et al., 2006) documented a reduction in the gray-matter density in the right middle frontal cortex of abstinent methamphetamine abusers (Figure 1). A lower density correlated with a worse performance on a test that measures a person's ability to switch mental gears (Wisconsin Card Sorting Task). Gray matter was closer to normal in individuals who had been abstinent for >6 months than in others with a shorter period of abstinence.

In another sMRI study, cocaine abusers who had been abstinent for 20 days exhibited a reduced gray-matter density in the regions of the frontal cortex. Interestingly, no

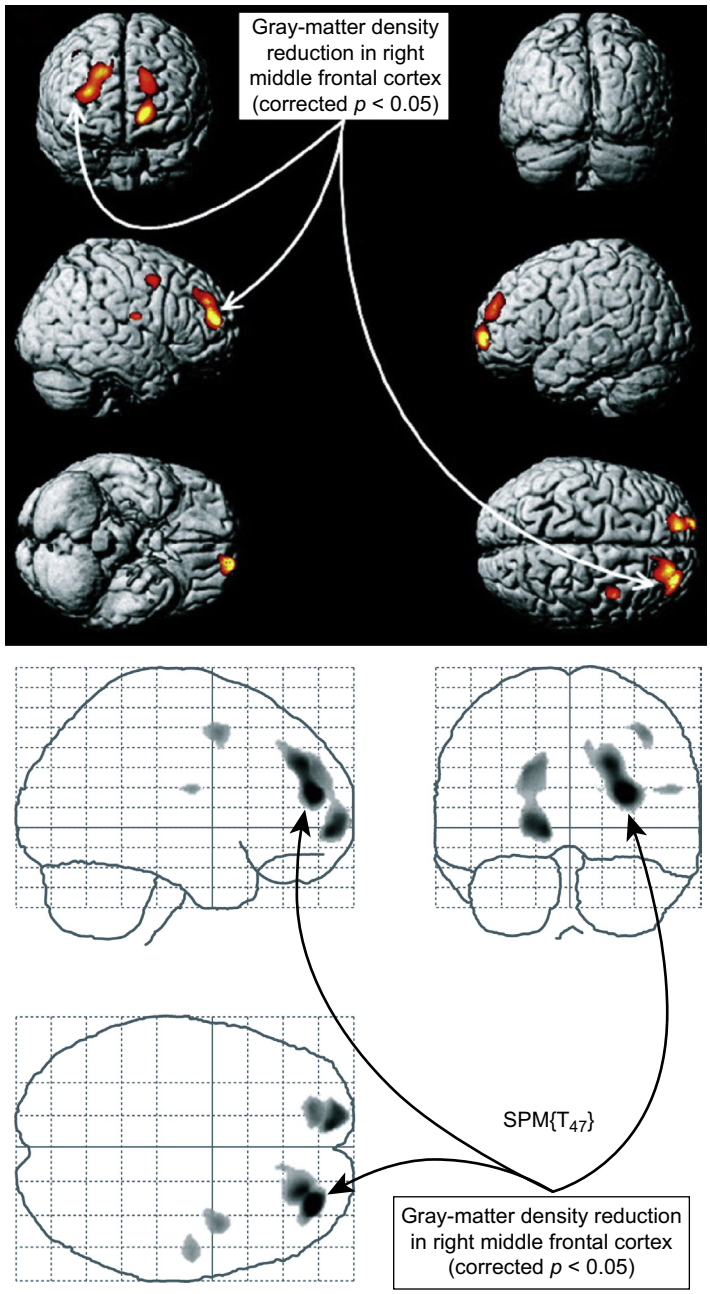


Figure 1 MRI: methamphetamine reduces gray matter. The yellow and red area in the central brain view indicates a reduced gray-matter density in the right middle frontal cortex. The same deficit is shown from other perspectives in the flanking views. *Reprinted with permission from Kim et al. (2006).*

differences were found with respect to white matter density (Matochik et al., 2003). With regards to other brain regions, several sMRI studies have shown an enlargement of the brain's basal ganglia in cocaine-dependent (Jacobsen et al., 2001) and methamphetamine-dependent (Chang et al., 2005; Jernigan et al., 2005) subjects compared with healthy subjects. This is similar to other observations made in schizophrenic subjects who were treated with typical antipsychotics (Gur et al., 1998).

The fact that stimulant drugs, such as cocaine or methamphetamine, and typical antipsychotics that occupy receptors for dopamine in the basal ganglia appear to cause an enlargement of the basal ganglia and are related to psychosis, support the hypothesis that the hyperstimulation of dopamine in basal ganglia structures is involved in psychosis. Finally, an automated morphometric analysis of MR images also showed that a group of chronic methamphetamine abusers had severe gray-matter deficits in cingulate, limbic, and paralimbic cortices. They also had smaller hippocampi than did nondrug abusers of drugs.

The hippocampus is a key site for memory storage, and the volume decrements correlated with a poorer performance on a word recall test (Thompson et al., 2004). Furthermore, sMRI studies have also reported amygdala volume reductions in cocaine addicts (Makris et al., 2004).

Alcohol abuse provides a case study on the utility of MRI to evaluate the structural damage that can result from the chronic use of a psychoactive substance. Investigators using sMRI have reported diminished cortical gray matter, most prominently in the PFC, in alcoholic patients in treatment (Pfefferbaum et al., 1998). In another study, researchers found that alcohol-dependent individuals had reduced whole brain, prefrontal cortical, and parietal cortical gray matter compared with controls (Fein et al., 2002). Two additional studies have shown alcoholics' frontal cortex and other structures beginning to recover their normal volumes within weeks of stopping drinking (Bendszus et al., 2001; O'Neill et al., 2001; Pfefferbaum et al., 1995) [see Mann et al. (Mann et al., 2001), for a comprehensive review on the brain imaging of alcoholism].

Another MRI study indicated that the amygdala, a brain structure that helps shape our emotional responses to experiences, is relatively smaller in children of alcoholics (Hill et al., 2001; Wrase et al., 2008), a finding that might be a clue to brain-dependent vulnerabilities to alcohol abuse disorders.

2.1.2. Functional MRI

Like sMRI, functional MRI (fMRI) produces images by applying a magnetic field and detecting the radiofrequency energy from the excited protons in water molecules. However, fMRI is an ultrafast technique that can image the whole brain in a second and has the ability to detect changes in the ratio of oxygenated to deoxygenated hemoglobin in the capillary bed of the brain by contrasting task and baseline conditions. Since neurons use oxygen as the main fuel source, this measure turns out to be a reliable proxy for brain

activity. In an fMRI image, differences in oxygen content appear as variations in the signal intensity, which is referred to as blood oxygen level-dependent (BOLD) contrast.

In fMRI studies, researchers compare multiple images, which may be of single or different individuals. Images of a single individual taken under varying conditions—for example, at rest and then working on a cognitive task, such as a puzzle, or before and after taking a drug—enable researchers to map which brain regions were activated during the performance of that task or in response to experiences or chemical exposures.

Studies of individuals from different groups—for example, drug-addicted and nonaddicted—can reveal differences in the brain regions that the two groups tap into in order to perform identical tasks or respond to stimuli or exposures. In turn, the differences in brain activity patterns revealed by fMRI provide valuable information on a wide range of issues. For example, studies have correlated regional brain patterns in response to taking a drug with a vulnerability to drug abuse, addictive symptoms and behaviors, and long-term cognitive capacity.

Increasingly, fMRI is being used to investigate the pattern of interactions associated with a given task and how these differed as a function of performance and intersubject variability. This change in the emphasis, from the identification of specific brain region toward the identification of networks (regions working together) reflect the understanding that any given process in the brain results from the complex interactions of dynamic networks that are distributed between and within different brain regions.

Stimulant Effects Correlate with Brain Activity in Several Areas

Researchers have used fMRI to obtain detailed information about the roles of different brain areas in mediating cocaine-induced euphoria and subsequent craving and, more recently, about the involvement of functional networks in drug reward and addiction. In one investigation, volunteers given an infusion of cocaine reported a "high" during the brief period when a set of areas, including the caudate (an area of the basal ganglia), cingulate, and most of the lateral PFC showed higher levels of activity. The participants' reports of craving commenced when the euphoria subsided and persisted as long as a different set of brain areas—including the nucleus accumbens (NAc)—remained activated (Breiter et al., 1997; Breiter and Rosen, 1999). Two more recent studies also saw correlations between craving and NAc activity, although—possibly because of differences in study methods—the "high" was associated with a decreased rather than an increased brain activity in regions including the NAc, inferior frontal/orbitofrontal gyrus, and anterior cingulate. Craving correlated positively with the activity in these regions (Kufahl et al., 2005; Risinger et al., 2005).

Other fMRI studies demonstrated that a cocaine-addicted individual's vulnerability to cocaine-related cues has a neurological basis. For example, Wexler and colleagues

(Wexler et al., 2001) documented the activation of the anterior cingulate cortex (ACG), a region associated with emotional processing, while cocaine-addicted subjects watched videotapes containing cocaine-associated cues, even if they did not experience craving (Figure 2). The finding indicates that addicted individuals' emotional responses to cues have a subconscious component. The subjects also showed less activation in the frontal lobe relative to healthy subjects during the viewing of cocaine-cue tapes, suggesting that their ability to control their cue responses was inhibited.

Research with fMRI has linked chronic stimulant abusers' cognitive impairments to drug-related alterations in brain activation: In one study, methamphetamine dependence

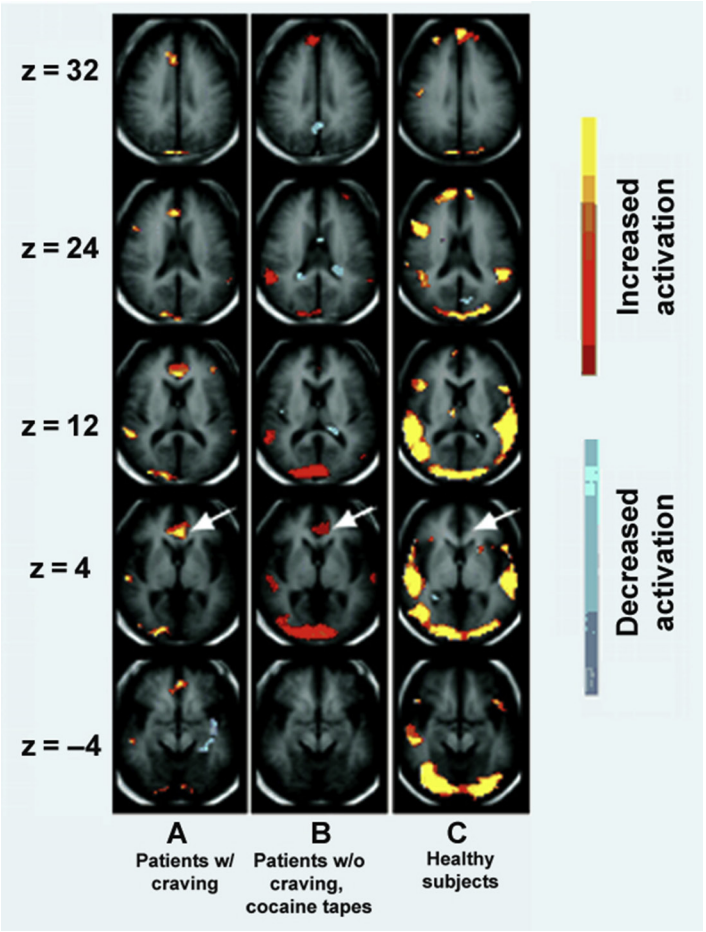


Figure 2 fMRI: The brain's response to cocaine cues. The arrows point to the anterior cingulate area, which activated (yellow) in cocaine-addicted patients (left) but not in healthy volunteers (right). *Reprinted with permission from Wexler et al. (2001).*

and poor decision making correlated with the reduced activation in the PFC (Paulus et al., 2002). In another study, investigators found that chronic cocaine abusers had abnormally low levels of activity in the midline areas of the anterior cingulate that are crucial for cognitive and behavioral control (Kaufman et al., 2003).

Genes Affect Responses to Drugs and Vulnerability to Abuse

More recently, innovative fMRI researchers have begun to explore the role of genes in drug abuse. In one such study, a gene variation that affects the metabolism of neurotransmitters, including dopamine and norepinephrine, appeared to influence the brain's response to amphetamine (Mattay et al., 2003). A similar fMRI study showed that individuals with a particular variation in the serotonin transporter gene experienced a greater activation of the amygdala, a region associated with fear and anxiety, in response to frightening stimuli (Hariri et al., 2002). This particular genetic variation is likely to increase sensitivity to stress and heighten vulnerability to drug abuse.

2.1.3. Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a special application of fMRI that uses different scanner settings. In MRS, the magnetic pulses and radiofrequency energy are precisely calibrated so that they stimulate a specific nucleus of interest (e.g., proton, carbon, phosphorous, or fluorine) in the molecules located in the regions of interest of the brain. The sum of all the returning (resonance) signals is recorded and analyzed using sophisticated computer programs that separate the signals for each metabolite. The result of these signals can then be displayed as various metabolite peaks on a spectrum. Thus, in addition to creating structural (sMRI) and functional (fMRI) maps of the brain, magnetic resonance technology can also be used to detect and measure important chemical compounds in the brain.

To be detectable by MRS, however, a compound must respond in a unique way to magnetization and energy stimulation and it must be present at relatively high concentrations (typically in the millimolar range). If these two conditions are met, MRS scans can reveal the location and concentrations of target chemicals in the brain tissues (Ross et al., 1992). Among chemicals naturally present in the brain, two that can be studied with MRS are *N*-acetylaspartate (NAA), which researchers use as a gauge of neuronal cell health (De Stefano et al., 1995), and myoinositol, which is primarily present in support cells called glia (Brand et al., 1993), thus providing an index of glial health.

Other molecules that can be detected easily are choline compounds, which are involved in the synthesis of cell membranes, and creatine compounds, which are important for cells' energy maintenance. Among substances of abuse that penetrate the brain after being ingested or administered, alcohol is readily detectable with MRS (Hetherington et al., 1999). Researchers have used MRS to identify drug-related biochemical changes

that indicate damage to the health and function of brain cells. Often, these studies focus on brain areas that preclinical models or neuropathology of drug users had shown to be affected. In some cases, biochemical changes have been directly correlated with cognitive and behavioral deficits (Cowan et al., 2009;Yang et al., 2009).

MRS-based Findings

One of the main contributions of MRS studies to the addiction field has been the discovery that drugs affect markers associated with inflammation, brain energy metabolism, and neuronal health. For example, Ernst and colleagues (2000) found that methamphetamine abusers exhibit reduced NAA concentrations in their basal ganglia and frontal white matter, compared to that nondrug abusers exhibit, a finding that could help explain the cognitive difficulties experienced by methamphetamine abusers, since the concentrations of NAA correlate with measures of cognitive function even in nondrug users (Rae et al., 1998).

Cocaine-dependent individuals also exhibit lower NAA levels, suggesting neuronal damage, as well as elevated creatine and myoinositol levels reflecting either increased glial cell activity or inflammation (Chang et al., 1999).

Other MRS research has evaluated possible interactions between human immunodeficiency virus (HIV) and drugs of abuse on brain metabolites. For example, a study found that methamphetamine abuse and HIV decreased brain NAA additively, especially in the striatum, while choline and myoinositol were further elevated in the frontal lobes (Chang et al., 2005). Chronic marijuana use and HIV infection are each separately associated with lower levels of glutamate, but together, they appear to moderate glutamate loss in the frontal white matter while exacerbating it in the basal ganglia (Chang et al., 2006).

Magnetic resonance techniques like MRS are especially useful for studying the effects of drugs in the pediatric population because they do not involve radiation. Smith and colleagues (Smith et al., 2001a, 2001b) conducted MRS studies of children who had been exposed to cocaine or methamphetamine prenatally and found that their total brain creatine levels were elevated, suggesting abnormalities in energy metabolism.

2.1.4. Resting State Functional MRI

Resting state fMRI is a relatively recent development that allows investigators to explore the modular nature of cortical function and to assess resting state functional connectivity (RFC). The images generated through this approach rely on the fact that the spontaneous low-frequency fluctuations in the BOLD signals emerging from some brain regions (at rest) are more highly correlated with one another than with fluctuations emanating from other regions (Raichle and Snyder, 2007). The resulting functional connectivity maps reveal the existence of temporally dynamic linkages within and among

several brain regions that include inhibitory control, visual, auditory, default mode, dorsal attention, and sensorimotor networks (Damoiseaux et al., 2006). Moreover, the nonrandomness of such non-task-related, spontaneous brain activity suggests that its member functional networks are organized in a highly coherent fashion.

It is important to point out that the emergence of large RFC databases, across healthy populations will allow investigators to probe into the involvement of specific genes in the functional organization of the brain. In addition, it could also provide an extremely valuable, normative baseline against which to compare various disordered states of the brain that result from either biological, developmental and/or environmental perturbations as well as a means to monitor treatment effectiveness and predict clinical outcomes (Biswal et al., 2010). For example, early studies have found RFC abnormalities in the PFC (Kelly et al., 2011) and mesocorticolimbic circuitry in cocaine abusers (Gu et al., 2011). If corroborated by future studies, such results could add important information toward improving our understanding of the range of cognitive and behavioral disruptions seen in individuals addicted to cocaine.

2.1.5. Neurofeedback

Real-time fMRI is yet another technological development in the fMRI field that is poised to help expand treatment options. This technique emerged as a result of advances in imaging algorithms that enable very fast image processing, allowing researchers to feed that information back to the subjects while in the scanner. In this way, the real-time signal can be used for biofeedback-mediated retraining of neural circuits, such as the strengthening of frontal executive function (Berman et al., 2011). This approach, which has proven its utility for chronic pain patients, is being investigated as a possible treatment for addiction and other psychiatric disorders.

2.1.6. Diffusion Tensor Imaging

In addition to measuring the location of water molecules in the brain to generate a map of the gross brain structures, a recent MRI technique called diffusion tensor imaging (DTI) detects the directions of the water diffusion in the brain, which in turn reflects the placement of fine tissue structures and connecting tracts. DTI has been used to demonstrate in vivo changes in the brain development across different age groups (Gilmore et al., 2006; Huang et al., 2006) and in many different disease states.

Because this technique is relatively new, few DTI studies of the addicted brain have been performed. However, alcoholics have shown significant brain abnormalities on DTI (Daurignac et al., 2005; Pfefferbaum and Sullivan, 2005). Specifically, fractional anisotropy, a measure of the orientation of the water diffusion that reflects the coherence of the fiber tracks in the brain, was abnormally low in the white matter of alcoholics,

while the apparent diffusion coefficient was higher than normal. These findings suggest increased intracellular or extracellular fluid and the possible disorganization of fiber structure (Pfefferbaum and Sullivan, 2005).

Similarly, Warner and colleagues (Warner et al., 2006) evaluated children (average age 10 years) who had been exposed to cocaine prenatally and found that, relative to unexposed children, they had a significantly higher average diffusion in the left frontal callosal and right frontal projection fibers, which suggests a disrupted or reduced maturation along these frontal white matter pathways. This highly sensitive technique to assess the changes in the microscopic environment of the brain will likely yield new, more informative data regarding drugs' effects on the brain. Because MRI techniques are noninvasive and nonradioactive, they are particularly valuable for monitoring the growth, development, and the effects of treatment over time and for studying children and adolescents since they do not rely on the use of radioactivity (as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) technologies do, see below).

2.2. NUCLEAR MEDICINE IMAGING TECHNIQUES

2.2.1. PET and SPECT

PET and SPECT are referred to as "nuclear medicine techniques" because they involve the injection of molecules labeled with radioactive isotopes (o radiotracers) into the bloodstream of the person being studied. A PET or SPECT image displays the distribution of such radiotracers after they reach their targets in the brain and other organs. The energy emitted by the radiotracer interacts with detectors in the PET or SPECT instrument. The instrument's computers register the location of the radioisotope and use this information to construct a 3D map of the radiotracer's distribution in the brain or body.

Because the half-lives of the PET or SPECT isotopes are short, the net radiation dose is small, in the order of other medical diagnostic procedures; thus, studies can be carried out in healthy volunteers as well as in drug-addicted patients. However, PET and SPECT are not normally used in healthy children. PET and SPECT are actually similar technologies, differing mainly in their use of different types of isotopes in their radiotracers. PET radiotracers incorporate isotopes that emit beta positron ($\beta+$) radiation. One especially important set of PET radiotracers incorporates positron-emitting isotopes of the chemical elements of life, that is, carbon, oxygen, and nitrogen, into organic compounds in place of the naturally occurring nonradioactive elements. Substituting radioactive ^{11}carbon for nonradioactive ^{12}carbon in a drug molecule, for example, does not alter the drug's biochemical properties in the brain, but renders it detectable through PET imaging. ^{11}Carbon has a very short half-life (20.4 min), making it ideal for use in humans.

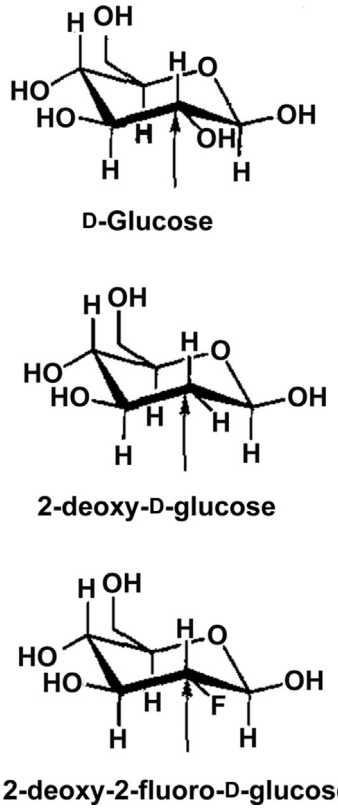


Figure 3 Chemists replace a hydroxyl (–OH) group on the glucose molecule with ^{18}fluorine to make ^{18}FDG, a radiotracer that is used to measure brain glucose metabolism. 18F decays by positron emission resulting in two energetic photons that are detected by a PET scanner to produce an image of glucose metabolism in the brain. *Reprinted with permission from Fowler and Ido (2002).*

One uniquely valuable PET tool is 2-deoxy-2-[18F]fluoro-D-glucose (^{18}FDG), a radiotracer used to measure brain glucose metabolism. ^{18}FDG consists of a glucose molecule in which the radioactive isotope fluorine-18 has been substituted for the naturally occurring hydroxyl group (Figure 3) (Fowler and Ido, 2002). A PET's ability to produce an image of glucose metabolism in the brain using 18FDG is a major advantage, as glucose, along with oxygen, is a major source of the organ's energy. SPECT radiotracers are labeled with single photon emitting radioisotopes. The most commonly used are ^{123}iodine and ^{99m}technetium.

Nuclear medicine techniques are particularly valuable in drug abuse research because they can measure the concentrations of molecules that are extremely low—in the nanomolar and picomolar range, one millionth to one billionth of the minimum amounts necessary for visibility in MRS (Fowler et al., 2003a; Kung et al., 2003). This level of sensitivity enables researchers to study drugs' effects on key components

of cell-to-cell communication, including cell receptors, transporters, and enzymes involved in the synthesis or metabolism of neurotransmitters (Volkow et al., 2003b). In particular, many PET studies have explored the role of the neurotransmitter dopamine in drug abuse and addiction. The radiotracers for these studies piggyback on compounds that bind to various dopamine-interacting proteins on brain cells, including dopamine receptors, dopamine transporters, and dopamine-degrading and synthetic enzymes (Halldin et al., 2001; Rinne et al., 1995; Volkow et al., 1995, 1996a; Wong et al., 1993).

Researchers also use PET to study drug pharmacokinetics: A series of images taken at appropriate intervals provides a stop-action record of a drug's movement into and out of the brain, showing how much of the drug enters the brain, where it binds in the brain, and for how long it lingers (Fowler et al., 1999). This information is crucial because the rate at which a drug enters the brain largely determines its euphorigenic effects and addictiveness. PET can also be used to assess the rates of glucose metabolism, providing an alternative to functional MRI measurement of blood oxygen levels for determining cellular activity. A common use for SPECT is to measure brain blood flow. PET and SPECT brain imaging have perhaps shown their greatest value to date in helping researchers to analyze how drugs affect the neurotransmitter systems that link and coordinate brain cells. Much of this work has focused on the dopamine system, but researchers are also exploring the roles of other neurotransmitters in drug abuse and drugs' effects on cells' energy consumption and health.

2.2.2. PET and SPECT-based Findings

Dopamine Plays Key Roles in Drug Abuse Euphoria and Addiction

The neurotransmitter dopamine is highly concentrated in the striatum, which forms part of the brain's reward circuit. The ebb and flow of dopamine into these areas is the main determinant of how much pleasure we derive from our experiences; it also helps us focus our attention on what is important. PET studies have linked the drugs' presence and action here with their euphorigenic properties and their ability to attract the complete attention of the addicted individual, at the expense of most other natural reinforcers (Di Chiara, 1999; Di Chiara and Imperato, 1988; Leshner, 1997; Volkow et al., 2003a).

In one study, researchers used ^{11}carbon-labeled cocaine and PET imaging to track the movement of cocaine into and out of the cocaine abuser's brain while also recording the intensity of their highs. The results showed that the "high" spiked and subsided in close temporal correlation with cocaine's movement in and out of the striatum (Volkow et al., 1997) (Figure 4). Using the same experimental design with different radiotracers, PET and SPECT investigators established that cocaine, amphetamine, and methylphenidate, when given intravenously, produce their highs by massively increasing the amount of dopamine in the striatum (Drevets et al., 2001; Laruelle et al., 1995;

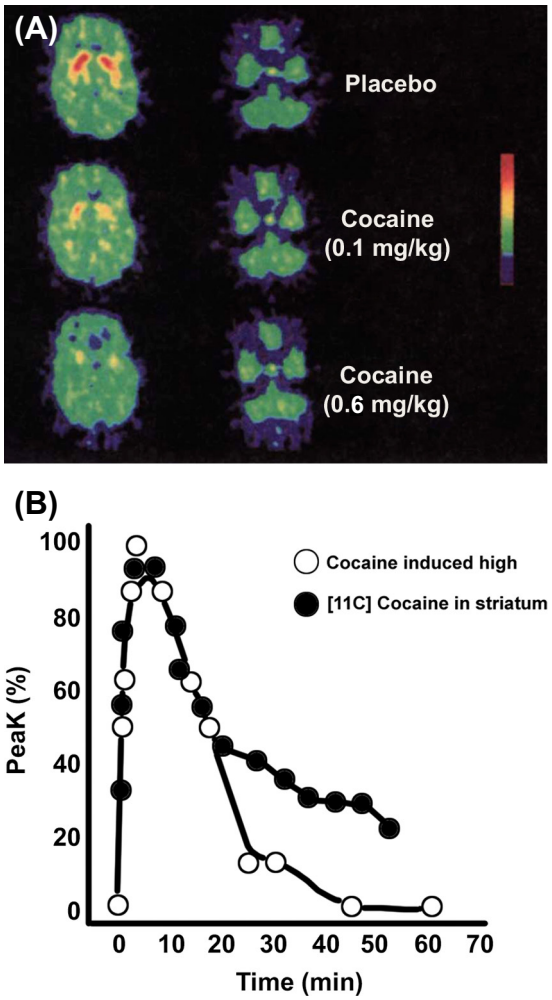


Figure 4 PET: Cocaine activity in the striatum underlies the cocaine high. (A) Study subjects were given a cocaine radiotracer that homes in toward the striatum, where dopamine D2/3 receptors are expressed at high concentrations. (B) PET showed that their reports of how high they felt rose and fell in very close parallel with the passage of the drug in and out of the brain's striatum. *Reprinted with permission from Volkow et al. (1997).*

Volkow et al., 1999). Previous studies with animals had suggested that this was probably the case, but nuclear medicine imaging enabled researchers to noninvasively document the correlation as it actually occurred in living human beings. Still, other PET studies have shown that the abuse liability of any drug actually depends on both the magnitude of the dopamine spike it produces and the speed with which dopamine rises and falls back to normal levels.

PET experiments have identified how one drug, cocaine, causes dopamine to surge: The drug interferes with the normal activity of a molecule called dopamine transporter that is expressed on the cell surface of the presynaptic neuron (Volkow et al., 1997). By doing so, it disrupts the equilibrium of dopamine release and reuptake that maintains the levels of this neurotransmitter within normal limits.

Chronic Methamphetamine Abuse Depletes Dopamine Function

PET studies have also shown that while acute methamphetamine temporarily hyperactivates the dopamine system, chronic exposure to the drug reduces the availability of dopamine transporters, which may indicate a loss of dopamine cells (Volkow et al., 2001b). Study participants with fewer dopamine transporters had a poorer memory and a slower motor function and another study reported that the loss of dopamine transporters was associated with psychoses (Sekine et al., 2003).

Stimulants Reduce the Cellular Activity in Brain Areas that Affect Judgment

PET studies have also been used to explore cocaine's impact on brain structures and activity, and their relationship to the addicted individuals' ability to regain function during and after treatment. Among the most significant results in this line of study are those that showed that cocaine (Volkow et al., 1993) and methamphetamine (Bolla et al., 2003; Volkow et al., 2001a) reduce the cellular activity in the orbitofrontal cortex (OFC), a brain area we rely on to make strategic, rather than impulsive, decisions. Patients with traumatic injuries in this area of the brain exhibit diverse cognitive deficits—aggressiveness, poor judgment of future consequences, inability to inhibit inappropriate responses—that are reminiscent of those seen among substance abusers (Bechara et al., 1994, 2001; Eslinger et al., 1992). The radiotracers used in these studies were 18FDG and oxygen-15 water, which measure the brain's consumption of its two main fuels, glucose and oxygen (Raichle et al., 1983).

In fact, a link between a lower metabolism in the OFC and poor judgment has been found in cocaine abusers (Bolla et al., 2003). The researchers took serial PET images, using oxygen-15 (^{15}O) water as the radiotracer, while cocaine abusers who had been abstinent for 25 days played a card game on a computer. Players who had used more cocaine prior to being abstinent exhibited a lower OFC activity and a poorer performance during the game.

Dopamine Receptor Levels May Determine Vulnerability to Abuse and Addiction

PET studies have demonstrated that abusers of alcohol (Volkow et al., 1996b), cocaine (Volkow et al., 1993, 1990), heroin (Wang et al., 1997), and methamphetamine (Volkow et al., 2001a) all have reduced levels of brain dopamine D2 receptors—one of the cell

surface proteins activated by dopamine. These and other findings have given rise to the hypothesis that people with low levels of dopamine D2 receptors, as a result of genetic variability, life experience, or both, may present a higher risk for drug abuse and addiction. Scientists speculate that such individuals derive suboptimal levels of dopamine-mediated pleasure from ordinary activities and accomplishments and are therefore more susceptible to wanting to repeat the euphoria that follows the massive, drug-induced increase in striatal dopamine.

The μ-Opioid System Plays a Role in Cocaine Craving

PET studies have suggested that the symptoms of cocaine dependence and craving may be caused at least in part by the drug's effects on another neurotransmitter system, the one driven by the μ-opioid peptide. In one study (Zubieta et al., 1996), cocaine-addicted individuals who entered a clinic to quit the drug and remained there for a month of monitored abstinence filled out assessments of their mood and craving symptoms and underwent PET scans, once during their first 4 days in the clinic and again toward the end of the month. Using a potent opioid agonist as the radiotracer (^{11}carbon carfentanil), researchers found that the participants' symptom severity correlated with μ-opioid receptor levels in several brain areas. In interpreting their findings, the researchers suggested that cocaine may have depleted the body's natural opioids, stimulating either a compensatory production of more opioid receptors or increasing the avidity of existing receptors toward opioid molecules.

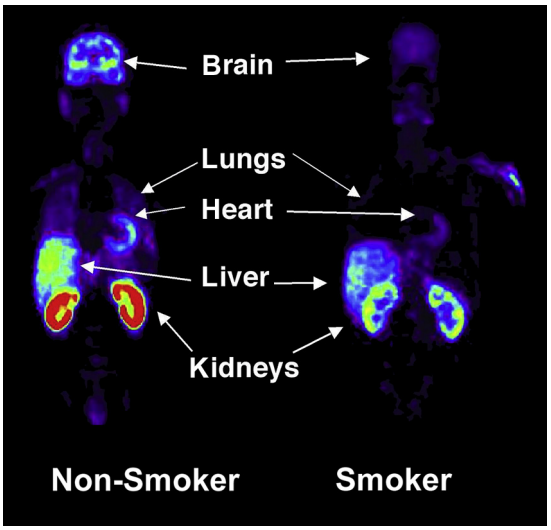


Figure 5 PET: Smoking reduces an important enzyme. In these composite PET images of smokers versus nonsmokers, the arrows demonstrate lower concentrations of the enzyme MAO in many of the smokers' organs. *Reprinted with permission from Fowler et al. (2003c).*

Nicotine is Not the Sole Culprit in Tobacco Addiction

PET imaging studies have confirmed the importance of dopamine signaling in nicotine abuse and addiction (Brody et al., 2004) while also highlighting the need to investigate the role of other chemicals present in tobacco smoke. For example, studies have found that one or more components of tobacco smoke can reduce the levels of monoamine oxidase A and B (MAO A and B), an enzyme that breaks down dopamine in the brain and throughout the body (Fowler et al., 1996a, 1996b, 2003b, 2003c, 2005) (Figure 5). This activity may lead to the exacerbation of the nicotine-induced dopamine dysregulation that reinforces the desire to smoke as well as to abuse other substances. In fact, recent preclinical studies show that the inhibition of MAO A enhances nicotine self-administration in animals (Guillem et al., 2005). While MAO A, rather than MAO B, inhibition increases nicotine reinforcement in rats (Guillem et al., 2006), a recent trial using the selective MAO B inhibitor selegiline (at a dose of 10 mg/day) safely enhanced smoking cessation rates compared with placebo in nicotine-dependent cigarette smokers (George et al., 2003).

The PET finding that smokers have relatively lower levels of MAO may help explain why smokers have a reduced risk of Parkinson's disease (Morens et al., 1995). When MAO metabolizes dopamine, a byproduct is hydrogen peroxide, a potential source of free radicals that can damage nerve cells. MAO-inhibiting compounds have been isolated from tobacco (Khalil et al., 2000) and have shown to be protective in a rodent model of Parkinson's disease (Castagnoli et al., 2002).

2.3. CLINICAL APPLICATIONS OF IMAGING

2.3.1. Medication Development and Imaging Studies

The information that magnetic resonance and nuclear imaging studies have yielded on the brain dynamics of addiction has become a primary source of medication development strategies. Direct clinical applications are still few, but recent studies suggest that the techniques may in the future enhance patient assessment and monitoring. Such studies, together with other research, overwhelmingly indicate that drug addiction is a disease of the brain, and thus, it must be viewed as a bona fide behavioral disorder. To be effective in the long term, treatments should focus on enhancing and restoring the disrupted dopamine function and processing among a widely distributed network of brain circuits (Figure 6), and take advantage of effective pharmacologic and/or behavioral approaches.

In the area of pharmacologic interventions in particular, imaging findings have suggested many possible new approaches. One strategy under active investigation takes its cue from the PET finding that stimulant drugs produce euphoria by causing a rapid dopamine spike and, in doing so, reduce abusers' ability to feel pleasure when their other, non-drug-related

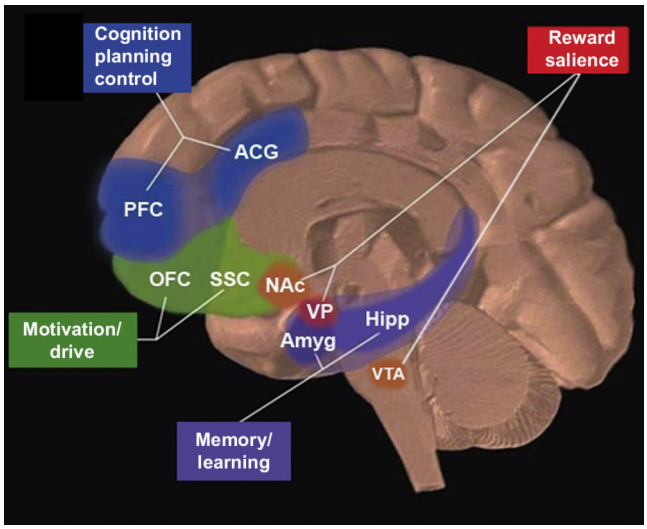


Figure 6 Major brain regions with roles in addiction. The prefrontal cortex (PFC) and the anterior cingulate cortex (ACG) are focal areas for cognition, planning, and inhibitory control. The orbitofrontal (OFC) and somatosensory cortex play key roles in supporting the motivation for goal-directed behaviors. The ventral tegmental area (VTA) and NAc are key components of the brain's reward system. The VTA, NA, amygdala, and hippocampus are the major components of the limbic system, which coordinates drives, emotions, and memories.

activities cause more modest, natural neurotransmitter elevations (Volkow et al., 2007). Researchers are identifying and testing medications that slightly increase the amount of dopamine that cells release when a person engages in normally rewarding activities in the hope that the boost will enable addicted individuals to once again begin to feel pleasure from them. For example, MAO B inhibitors and other medications fitting this criterion have been used successfully to treat smoking addiction (George et al., 2003).

Another medication strategy that stems from imaging evidence that dopamine spikes underlie drug euphoria seeks to reduce the stimulant high and the desire to repeat it by inhibiting the initial dopamine response to these drugs. In one form of this strategy, researchers are testing compounds that enhance the neurotransmitter gamma-aminobutyric acid, which has been shown to inhibit dopamine-releasing cells' response to drug-related cues (Di Ciano and Everitt, 2003). Preliminary clinical trials of this approach have yielded promising results (Brodie et al., 2003, Brodie et al., 2009, 2005). Still other medications interfere with the responses of dopamine-receiving cells and thereby attenuate the reinforcing effects of abused drugs. For example, selective cannabinoid receptor (CB1) antagonists have been shown to modulate both dopamine-releasing and dopamine-receiving cell responses in preclinical studies (De Vries et al., 2001; Julian et al., 2003).

A third strategy to counter drug-induced euphoria and its hold over individuals is based on a medication that activates the same neurotransmitter system coopted by an

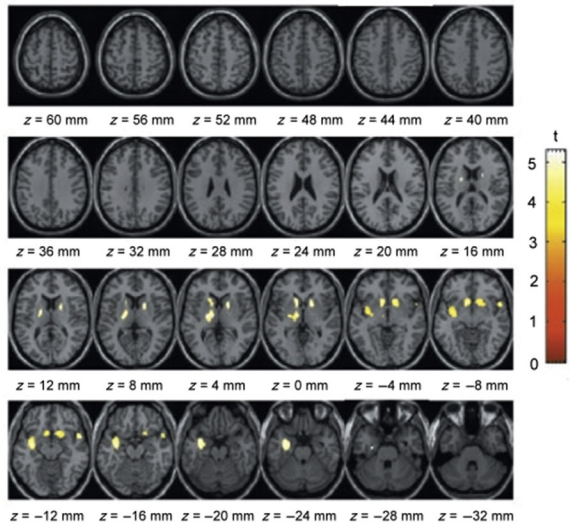
abused drug, but produces no sharp dopamine spike. Treatment of heroin addiction with methadone and buprenorphine exemplifies this approach (Kreek et al., 2002). Similar attempts to treat stimulant addiction have yet to produce positive results (Shearer, 2008). For example, replacement of cocaine with oral methylphenidate or oral amphetamine did not decrease cocaine consumption when compared with placebo in most drug-addicted individuals. However, treatment with oral methylphenidate did decrease drug consumption by patients suffering from comorbid addiction and attention deficit hyperactivity disorder (Grabowski et al., 1997).

2.3.2. Patient Assessment and Monitoring

Recent studies suggest that imaging has the potential to help clinicians determine the most appropriate level of treatment for individual patients and monitor their progress toward recovery. Results of a recent fMRI study performed on a group of men entering treatment for methamphetamine addiction revealed two contrasting patterns of brain activity (during a psychological task that required decision making) that predicted with a 90% accuracy which of the men would relapse within 1–3 years after completing treatment (Paulus et al., 2005). Those who relapsed exhibited less activity in the prefrontal lobe and also in regions not previously thought to play a role in addiction. Another study found that a more rapid response of the posterior cingulate to cocaine cues distinguished relapsers from nonrelapsers, even though both groups reported similarly intense cravings (Kosten et al., 2006).

Imaging researchers have also been documenting changes that appear to represent brain healing in response to treatment. One group has applied MRS to evaluate the effects of methadone maintenance therapy on heroin-addicted individuals (Silveri et al., 2004). The subjects' levels of certain metabolites involved in cellular energy production, which were abnormal at the beginning of the treatment, began to change over the first month. The researchers interpreted the metabolite changes as evidence that the switch from heroin to methadone might have improved the neurons' oxygen supply. This explanation may account for the findings from another study by the same research group that individuals' cognitive abilities improve during their first 2 months of methadone therapy (Gruber et al., 2006).

Similarly, studies have shown that, while detoxified methamphetamine abusers have fewer dopamine transporters than do drug-naive, age-matched individuals, those who remained abstinent for 9 months recovered a significant fraction of transporters (Volkow et al., 2001b; Wang et al., 2004). Unfortunately, they did not exhibit a concomitant recovery from the cognitive and motor deficits associated with low transporter levels. PET studies with 18FDG also showed a significant recovery in brain glucose metabolism in methamphetamine abusers after protracted abstinence (Wang et al., 2004) (Figure 7).



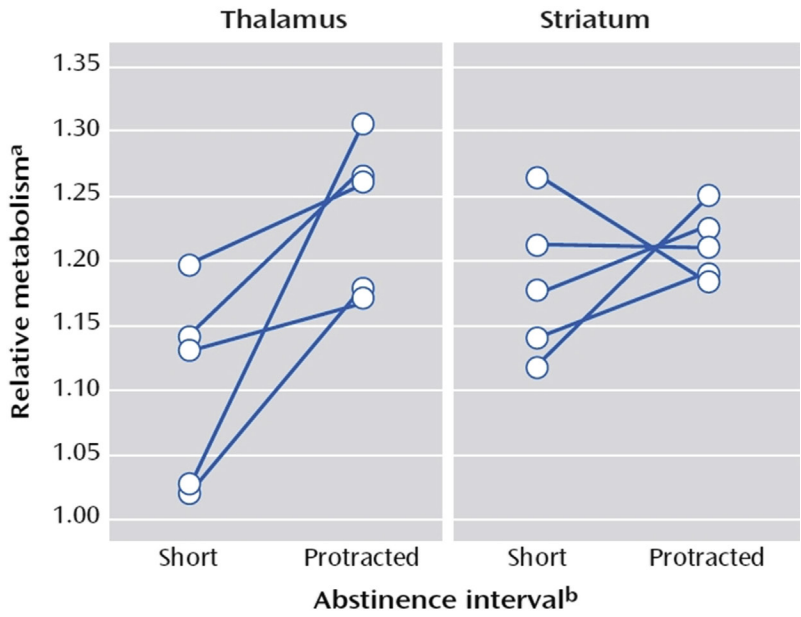


Figure 7 PET: Brain recovery occurs with methamphetamine abstinence. A. PET studies in methamphetamine abusers show that brain metabolism is depressed in the thalamus and striatum shortly after quitting methamphetamine. Protracted abstinence can lead to partial recovery, particularly in the thalamus. *Reprinted with permission from Wang et al. (2004).*

3. CONCLUSIONS

Brain imaging techniques enable researchers to observe drug effects while they are occurring in the brain and compare brain structure, function, and metabolism in drug-abusing and nonabusing individuals. The results to date have firmly established that drug addiction is a disease of the brain, causing measurable perturbations in many areas, including pathways affecting reward, inhibitory control, motivation, interoception, memory/learning, and emotion/stress. Ongoing studies continue to broaden our understanding of the dynamics underlying the development, symptoms, and consequences of addiction, as well as recovery.

While there is yet no clinically approved application for the imaging tools described here in ways that will improve outcomes for substance-abusing individuals, the translational opportunities created, offered, and presented by this suite of imaging technologies are incredibly exciting and represent a very active and potentially transformative area of research. Indeed, the impact of most of these advances on addiction research has been remarkable, and there is little doubt that, at the current rate of technological progress, the translation of these and emerging new imaging applications into the clinic is only a matter of time.

ACKNOWLEDGMENTS

Some of the work described in this article was performed at the Brookhaven National Laboratory under contract DEAC02-98CH10886 with the US Department of Energy and was supported by its Office of Biological and Environmental Research and by the National Institute on Drug Abuse (K24-DA16170 and Ko5-DA020001) and NIH GCRC (MO1RR10710).

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