Imaging Neurotransmitter Release by Drugs of Abuse

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Abstract Previous studies have shown that imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) radiotracers that are specific for brain dopamine receptors can be used to indirectly image the change in the levels of neurotransmitters within the brain. Most of the studies in addiction have focused on dopamine, since the dopamine neurons that project to the striatum have been shown to play a critical role in mediating addictive behavior. These imaging studies have shown that increased extracellular dopamine produced by psychostimulants can be measured with PET and SPECT. However, there are some technical issues associated with imaging changes in dopamine, and these are

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D.W. Self and J.K. Staley (eds.), *Behavioral Neuroscience of Drug Addiction,*
Current Topics in Behavioral Neurosciences 3, DOI 10.1007/7854_2009_34,

reviewed in this chapter. Among these are the loss of sensitivity, the time course of dopamine pulse relative to PET and SPECT imaging, and the question of affinity state of the receptor. In addition, animal studies have shown that most drugs of abuse increase extracellular dopamine in the striatum, yet not all produce a change in neurotransmitter that can be measured. As a result, imaging with a psychostimulant has become the preferred method for imaging presynaptic dopamine transmission, and this method has been used in studies of addiction. The results of these studies suggest that cocaine and alcohol addiction are associated with a loss of dopamine transmission, and a number of studies show that this loss correlates with severity of disease.

Keywords PET · SPECT · Neuroimaging · Addiction · Alcohol dependence · Dopamine · Neurotransmission

Abbreviations

BP	Binding potential
D_2	Dopamine type 2 receptor
GABA	Gamma-aminobutyric acid
IV	Intravenous
PET	Positron emission tomography
PO	Per os
SPECT	Single photon emission computed tomography

1 Positron Emission Tomography Radioligand Imaging

Positron emission tomography (PET) uses receptor specific agonists and antagonists that are labeled with a positron-emitting radionuclide, usually carbon-11 (^{11}C) or fluorine-18 (^{18}F) to image these receptors in human brain imaging studies. The specific techniques involved in PET radioligand imaging have been reviewed previously (Carson 1986; Slifstein and Laruelle 2001). Briefly, the radionuclide is incorporated into the receptor-specific molecule, so that as the ligand binds to the receptor in the brain, it can be visualized with imaging. As the positron emitted by the radionuclide encounters an electron, an annihilation event occurs which produces two gamma rays about 180° apart. These gamma rays are detected by scintillators of the PET scanner. Using coincidence detection, an image of the receptor-bound radioligand can be obtained which results in the ability to quantify neuroreceptors in vivo in the human brain. To date, a number of radiotracers are available to image neurochemistry, including the dopamine receptors and transporters, serotonin receptors/transporters, GABA and glutamate receptors, opioid receptors,

and others. In addition to PET, single photon emission computed tomography (SPECT), which uses radionuclides that emit photons, can also be used to image brain receptors and transporters. While SPECT has a lower resolution than PET, it has the advantage of using radionuclides with a longer half-life (usually iodine-123 (^{123}I) for brain receptor imaging) which reduces the need to generate the radiopharmaceutical onsite and allows greater flexibility.

The main outcome measure used in PET and SPECT imaging studies of clinical populations is called "binding potential" (BP), which is the product of receptor density and affinity of the radiotracer for the receptor. BP is usually measured as either BP_P (BP relative to the free fraction of radiotracer in the arterial plasma) or BP_{ND} (BP relative to the free fraction of radiotracer in the brain tissue) (Innis et al. 2007). Since BP is a composite of both receptor density and affinity, most human imaging studies cannot differentiate these two parameters. Thus, a difference in BP seen between two groups could result from either a difference in receptor density or affinity. However, PET studies performed with receptor antagonists, are expected to be less affected by the affinity state of the receptor, whereas PET studies performed with an agonist may provide information regarding receptor affinity state.

2 Using PET to Image Neurotransmitter Release

In addition to the imaging receptors, PET and some radiotracers can be used to indirectly image the change in the levels of neurotransmitters within the brain. The most frequently used radiotracer for this purpose is the radiotracer [^{11}C]raclopride for PET and [^{123}I]iodobenzamide (IBZM) for SPECT, which bind to the D_2 family of receptors (referred to as D_2 for simplicity) and can be used to measure changes in extracellular dopamine in the striatum. Previous imaging studies have shown that radioligand binding to the D_2 receptor is sensitive to changes in the level of endogenous dopamine in the brain and that increases in extraneuronal dopamine decrease [^{11}C]raclopride or [^{123}I]IBZM binding (since fewer D_2 receptors are available to bind to the radioligand). In these studies, dopamine levels are increased by the administration of a psychostimulant (such as methylphenidate or amphetamine), which results in a large increase in extracellular dopamine. Therefore, in the same individual, a comparison of BP prior to and following stimulant administration provides an indirect measure of dopamine transmission. This is depicted in Fig. 1, where an individual subject's scan is shown at baseline (left panel) and following the administration of methylphenidate (right panel). As shown in Fig. 1, [^{11}C]raclopride binding is reduced following methylphenidate due to the reduction in the D_2 receptors available to bind to the radiotracer.

Alternatively, decreases in dopamine levels in the striatum result in increased [^{11}C]raclopride binding, given that more D_2 receptors are available to the radiotracer. This is shown in Fig. 2, where the depletion of endogenous dopamine increases the percentage of receptors available to bind to the radiotracer, by reducing the pool of receptors occupied by dopamine. A paradigm has been

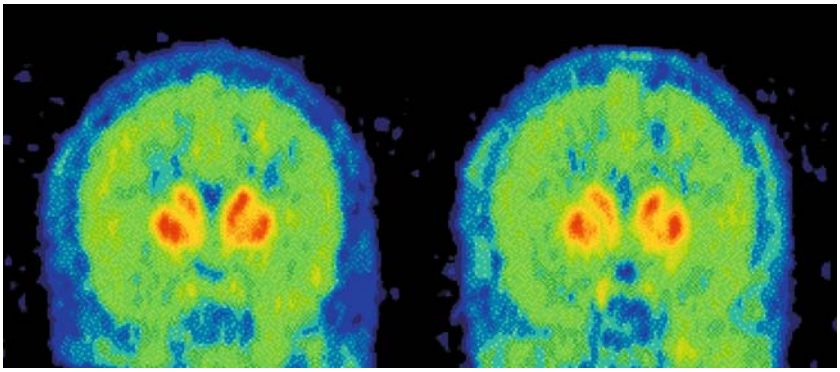

Fig. 1 Using PET and [^{11}C]raclopride to measure changes in endogenous dopamine in the striatum. The *left panel* shows baseline D_2 binding to the radiotracer in a healthy control and the *right panel* shows D_2 binding following the administration of methylphenidate (60 mg PO). Methylphenidate blocks the dopamine transporter on the dopamine nerve terminals in the striatum, resulting in a large increase in extracellular dopamine levels. As a result, fewer D_2 receptors are available to bind to [^{11}C]raclopride. Thus, the decrease in [^{11}C]raclopride binding provides an indirect measure in stimulant-induced increases in endogenous dopamine

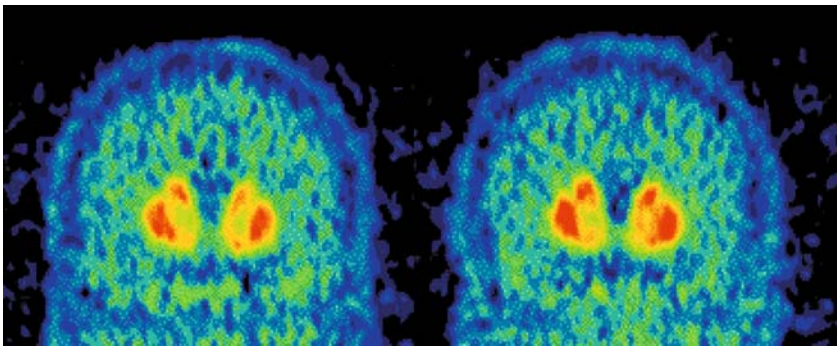

Fig. 2 PET and [^{11}C]raclopride can also be used to measure a reduction in endogenous dopamine, using alpha-methylparatyrosine (AMPT), which inhibits tyrosine hydroxylase and reduces dopamine production. The *left panel* shows baseline D_2 binding in a healthy control and the *right panel* shows D_2 binding following the administration of AMPT (120.7 ± 9.2 mg kg^{-1}). Following 48 h of treatment, endogenous dopamine levels are significantly reduced, resulting in an increase in D_2 receptor availability for the radiotracer

developed for use in human volunteers to acutely deplete dopamine using the drug alpha-methylparatyrosine (AMPT), which inhibits tyrosine hydroxylase and reduces endogenous levels of dopamine in the brain (Laruelle et al. 1997a, b). Using this paradigm, AMPT has been used in both PET and SPECT studies to image the percent of D_2 receptors occupied by endogenous dopamine, and occupancies ranging from 9 to 28% have been reported in control subjects (Laruelle et al. 1997a, b; Abi-Dargham et al. 2000; Verhoeff et al. 2001, 2002). Taken

together, these studies in human volunteers show that pharmacologic manipulations that either increase or decrease endogenous levels of dopamine provide reliable changes in radioligand binding ([^{11}C]raclopride for PET and [^{123}I]IBZM for SPECT) that mirror the change in endogenous dopamine; i.e., radioligand binding decreases in the setting of higher levels of endogenous dopamine and is increased when dopamine levels are reduced.

3 Loss of Sensitivity in Measurement of Dopamine Transmission

Studies in nonhuman primates using this PET technique and microdialysis have shown that there is a linear correlation between the stimulant-induced change in BP and extracellular dopamine (Breier et al. 1997; Laruelle et al. 1997a, b). In other words, the magnitude of the increase in endogenous dopamine is faithfully mirrored by the decrease in radiotracer binding. However, there is a significant loss of sensitivity: each percent decrease in [^{11}C]raclopride BP corresponds to a 54% increase in extracellular dopamine measured with microdialysis (Breier et al. 1997). Thus, in healthy controls the administration of amphetamine (0.3 mg kg^{-1} iv), in general, produces an average decrease in striatal raclopride binding on the order of 10–25% (Drevets et al. 2001; Martinez et al. 2003; Munro et al. 2006) despite the fact that animal studies using microdialysis have shown that amphetamine produced a several 100-fold increase in extrasynaptic dopamine (Breier et al. 1997; Laruelle et al. 1997a, b). Thus, a major limitation of this technique is its comparatively low sensitivity; i.e., relatively large increases in extracellular dopamine are associated with relatively modest effects on D_2 antagonist radiotracer binding. In addition to this low sensitivity, previous studies have shown a ceiling effect of about 40% (Laruelle et al. 1997a, b; Price et al. 1997). In other words, even large doses of intravenous (IV) amphetamine do not result in more than approximately 40% reduction in radiotracer binding, despite the enormous increase in synaptic dopamine. Decreases in [^{11}C]raclopride and [^{123}I]IBZM BP have been measured following a number of challenges in anesthetized animals, and the literature is quite consistent in the range of radiotracer displacement, which is −10 to −48% (Schlaepfer et al. 1997; Dewey et al. 1993; Laruelle et al. 1997a, b; Price et al. 1997; Volkow et al. 1999a, b, c). Thus, less than half of the radiotracer-specific binding is vulnerable to changes in synaptic dopamine.

This low sensitivity and ceiling effect may be related to the fact that D_2 receptors are configured in interconvertible states of high or low affinity for agonists. The high affinity sites (D_{2high}) are G-protein-coupled D_2 receptors, whereas the low affinity sites (D_{2low}) are those uncoupled with G-proteins. In vitro, approximately 50% of D_2 receptors are configured in the high affinity state (Zahniser and Molinoff 1978; Sibley et al. 1982; George et al. 1985; Seeman and Grigoriadis 1987; Richfield et al. 1989). Antagonists, such as [^{11}C]raclopride, bind with equal affinity to both states. The agonist dopamine is not expected to compete efficiently with

[^{123}I]IBZM or [^{11}C]raclopride binding to D_{2low}. This factor would leave less than 50% of the antagonist binding susceptible to endogenous competition by dopamine. These observations suggest that the ideal radiotracer for endogenous competition studies would be a D_2 receptor agonist. Consistent with such a hypothesis are recent imaging studies in anesthetized nonhuman primates and cats that suggest dopamine D_2 agonist radiotracers such as [^{11}C]-*N*-propyl-nor-apomorphine (NPA), [^{11}C]-methoxy-NPA, and [^{11}C]-(+)-propyl-hydroxy-naphthoxazine (PHNO) are more vulnerable to endogenous competition by dopamine relative to the reference D_2 antagonist radiotracers (Narendran et al. 2004; Ginovart et al. 2006; Seneca et al. 2006). A recent study with [^{11}C]PHNO and amphetamine in humans demonstrated that D_2 agonist are vulnerable to endogenous competition by dopamine following an acute amphetamine (0.38–0.45 mg kg^{-1} PO) challenge (Willeit et al. 2008). Unfortunately, this study failed to contrast the vulnerability of the antagonist [^{11}C] raclopride with that of the agonist [^{11}C]PHNO in the same subjects and did not allow for definitive conclusions to be drawn with respect to superiority of D_2 agonists over antagonists in measuring dopamine transmission. The replication of the results previously observed in anesthetized animal studies and in humans will not only allow for the use of more sensitive probes to image dopamine transmission but also allow for the measurement of dopamine D_2 receptors configured in a state of high affinity for the agonists in health and disease.

Another puzzling observation besides the low sensitivity and ceiling effect is related to the significant temporal discrepancy between the microdialysis measures (peak extracellular DA surge between 10 and 20 min, followed by rapid decrease over 100–120 min) and radiotracer displacement (sustained change in BP for 4–5 h) following amphetamine (Laruelle et al. 1997a, b; Carson et al. 2001). This long lasting decrease in D_2 receptor BP that has been observed for both agonist and antagonist radiotracers has been reported to subside, with BP returning to preamphetamine values in approximately 24–48 h (Cardenas et al. 2004; Houston et al. 2004; Narendran et al. 2007). Thus, the exact mechanism behind the decrease in D_2 radiotracer binding is not known. While competition between extracellular dopamine and the radiotracer for the receptor is often used as the model to explain the decrease in radiotracer binding, other phenomena, such as receptor affinity state, internalization or polymerization may also be involved (Laruelle 2000; Logan et al. 2001).

4 Modulation of Imaging of Dopamine Transmission

Notably, PET imaging studies have also shown that stimulant-induced increases in endogenous dopamine can be modulated. Based on microdialysis studies in animals, these studies show that the administration of medications that are known to modulate presynaptic dopamine release also affect changes in [^{11}C]raclopride binding. Microdialysis studies have shown that the pretreatment of *N*-methyl-D-aspartate (NMDA) receptor antagonists increase stimulant-induced presynaptic

dopamine release, and this same phenomenon has been shown with imaging. An imaging study by Kegeles et al. (2000) used SPECT and the radiotracer [^{123}I] IBZM, which is very similar to [^{11}C]raclopride and also images the D_2 receptor family, to investigate the effect of NMDA antagonism on stimulant-induced dopamine release in the striatum. [^{123}I]IBZM BP was obtained before and after the administration of amphetamine (0.25 mg kg^{-1} iv) in healthy subjects under the control condition and during the infusion of the NMDA antagonist ketamine. The results of this study showed that, in the control condition, amphetamine produced an average $-5.5 \pm 3.5\%$ change in [^{123}I]IBZM binding in the striatum compared to $-12.8 \pm 8.8\%$ in the same subjects who had been pretreated with ketamine (Kegeles et al. 2000). This type of design has also been used in imaging studies of nonhuman primates. Imaging with [^{11}C]raclopride and an amphetamine challenge, one study showed that pretreatment with a metabotropic glutamate receptor group II agonist (which inhibits glutamate transmission) also increased dopamine release, similar to the effect seen with ketamine in human subjects (van Berckel et al. 2006). Alternatively, another PET study in baboons showed that pretreatment with gamma vinylGABA, a irreversible inhibitor of GABA-transaminase which potentiates GABA transmission in the brain, significantly attenuated the ability of cocaine to displace [^{11}C]raclopride, presumably due to GABA-induced increased inhibition of the dopamine neurons (Dewey et al. 1998). Thus, these studies show that mechanisms known to affect dopamine transmission in the striatum modulate radiotracer displacement in the direction predicted by the microdialysis studies, which add support to the theory that radiotracer imaging can be used to measure changes in endogenous dopamine in the human brain.

5 Imaging Changes in Endogenous Dopamine with Other Substances of Abuse

The majority of PET imaging studies investigating changes in endogenous dopamine have been performed using a psychostimulant challenge. Drugs such as cocaine or methylphenidate block the dopamine transporter, which regulates synaptic dopamine by the reuptake of dopamine back into the dopamine neuron. Other stimulants, such as amphetamine, release dopamine by forcing the dopamine transporter (and the vesicular monoamine transporter) to work in reverse, causing cytosolic dopamine to be released into the synapse. Thus, a number of studies in healthy human subjects have shown that the administration of a psychostimulant, including amphetamine, cocaine, methylphenidate result in a reproducible decrease in [^{11}C]raclopride binding. In human studies, the challenges used have included methylphenidate (IV and PO) (Volkow et al. 1994, 2001a, b), amphetamine (Drevets et al. 1999; Martinez et al. 2003), and cocaine (IV and intranasal) (Schlaepfer et al. 1997; Cox et al. 2009). In each of these studies, the decrease in [^{11}C]raclopride following psychostimulant administration was approximately 10% at the level of the whole striatum with some studies showing a preferential effect

(i.e., greater radiotracer displacement) in the ventral striatum (VST) (15–20%), which in humans includes the nucleus accumbens. This selectivity is important, given that dopamine transmission in the nucleus accumbens is closely associated with the reinforcing and rewarding effects of drugs of abuse (Di Chiara and Imperato 1988; Wise and Romprè 1989).

However, microdialysis studies in animals show that most drugs of abuse, not just psychostimulants, increase dopamine levels in the striatum, often with a preferential effect (greater dopamine release) on the VST (Di Chiara and Imperato 1988; Wise and Romprè 1989). For example, ethanol has been shown to increase striatal dopamine in microdialysis studies, although not through a direct effect on the dopamine nerve terminal in the striatum. Ethanol acts to release striatal dopamine by activation of the mu opioid receptors in the ventral tegmental area (VTA) of the midbrain, where the dopamine cell bodies are located (Herz 1997). The mu receptors are located on the GABA interneurons in the VTA, which inhibit the dopamine neurons. Activation of these receptors by alcohol administration results in a decrease in the inhibitory activity of these interneurons, so that the dopamine neurons increase their firing, producing increased levels of dopamine in the striatum (Herz 1997).

Thus, based on these microdialysis experiments, it would be expected that the increases in dopamine levels induced by drugs of abuse other than stimulants could be measured with PET. However, previous studies examining the effect of an alcohol challenge on [^{11}C]raclopride binding in healthy control subjects do not provide consistent results. The first study was performed by Salonen et al. (1997) and it showed no effect of alcohol on [^{11}C]raclopride binding, despite the fact that a high dose of ethanol was administered (1 g kg^{-1} ethanol; 40 vol%). A second study reported that oral alcohol (1 ml kg^{-1} of 95% USP alcohol) produced a 14–15% decrease in [^{11}C]raclopride binding in the VST (Boileau et al. 2003). No displacement was seen in the caudate and putamen outside of the VST. Thus, since the earlier study of Salonen et al. measured dopamine release in the striatum as a whole, it is possible that this study did not see an effect that was limited to the VST (which makes up a small percentage of the whole striatum) (Salonen et al. 1997). However, Yoder et al have performed two studies showing that alcohol does not produce a measurable displacement of [^{11}C]raclopride in the VST (Yoder et al. 2005, 2007). In these studies, alcohol was administered intravenously as a "clamp," which produces a stable breath concentration over the time course of the scan at two different doses (60 and 80 mg%). The results were surprising, given that a high range dose of ethanol was administered to produce a steady state throughout the scan, which produced significant subjective effects. In a more recent study by this group, subjects were presented alcohol-associated cues that were dissociated from the actual administration of alcohol, and showed that the cues for alcohol resulted in a decrease in [^{11}C]raclopride binding, whereas the administration of alcohol in the absence of a cue increased radiotracer binding (Yoder et al. 2009).

Similar findings have been reported with studies investigating the effects of marijuana and tobacco on [^{11}C]raclopride binding. Animal studies have shown that tetrahydrocannabinol (THC) increases the firing rate of dopamine neurons and striatal dopamine release via indirect excitatory action on the dopaminergic cell

bodies in the VTA (Tanda et al. 1997; Cheer et al. 2004). However, a recent study by Stokes et al. (2009) showed that, in control subjects, THC administration (10 mg PO) did not affect [^{11}C]raclopride binding. A number of studies have investigated the effect of tobacco smoking on extracellular dopamine measured with PET. Using PET and [^{11}C]raclopride, Brody et al. showed that smoking a regular cigarette, compared to baseline or smoking a denicotinized cigarette, results in a decrease in radiotracer binding in the VST in dependent tobacco smokers (Brody et al. 2004, 2009). Similar results have been reported by another group who also compared the effects of nicotine-containing and denicotinized cigarettes on [^{11}C]raclopride binding in smokers (Scott et al. 2007). Another PET study showed that nicotine gum resulted in a decrease in striatal [^{11}C]raclopride binding in smokers, whereas no effect was seen in nonsmokers (Takahashi et al. 2008). However, other studies using similar methods have not shown a significant decrease in [^{11}C]raclopride BP following nicotine administration. These studies include a [^{11}C]raclopride scan following cigarette smoking (in smokers) (Barrett et al. 2004), nicotine administered as a nasal spray in smokers (Montgomery et al. 2007), and a study in monkeys administering high dose IV nicotine (Tsukada et al. 2002).

Taken together, these imaging studies investigating the effects of ethanol, THC, and nicotine suggest that dopamine release by ethanol and THC may be less robust than that seen with tobacco smoking. However, even within the studies examining the effect of nicotine on [^{11}C]raclopride BP, the results show some discrepancies. In contrast, to date, no study has been published using a psychostimulant challenge showing no effect on [^{11}C]raclopride binding. One reason for this may be the magnitude of dopamine release. As described above, psychostimulant administration results in a several 100-fold increase in extracellular dopamine, whereas other drugs of abuse, which indirectly affect the dopamine nerve terminals, generally result in a 100–200% increase in dopamine levels (Di Chiara and Imperato 1988; Wise and Romprè 1989). As described above, there is a loss of sensitivity when measuring dopamine release with PET. Thus, while dopamine transmission may still be altered by drugs of abuse in the human brain, these alterations may not be measured as robustly with PET. In addition, it is interesting to note that the one study imaging both tobacco smokers and nonsmokers showed [^{11}C]raclopride displacement only in the smokers, no change was seen in the nonsmokers, suggesting that dopamine transmission may be altered in addicted subjects compared to controls when administered their drug of abuse (Takahashi et al. 2008).

6 Imaging Dopamine Transmission in the Extrastriatal Regions

Since the introduction of the high affinity D_2 PET radioligands [^{11}C]FLB 457 (Halldin et al. 1995) and [^{18F}]fallypride (Mukherjee et al. 1995), several groups have confirmed their increased signal-to-noise ratio relative to [^{11}C]raclopride (Suhara et al. 1999; Olsson et al. 2004; Slifstein et al. 2004) and reported on their

ability to reliably measure D_2 receptor availability (or binding potential, BP_{ND}) in the human cortex (Vilkman et al. 2000; Sudo et al. 2001; Mukherjee et al. 2002; Cropley et al. 2008). Despite numerous investigations, the question of whether these high affinity D_2 PET ligands can be used to measure dopamine transmission in regions with relatively low D_2 receptor densities such as the dorsolateral prefrontal cortex (3–5% D_2 receptor density than the striatum) is still unresolved (Aalto et al. 2005; Riccardi et al. 2005; Montgomery et al. 2006; Cropley et al. 2008).

Human data with [^{18}F]fallypride, from three different groups, evaluating amphetamine-induced DA transmission concluded that [^{18}F]fallypride can be used to measure DA release not only in the striatum but also in a limited number of extrastriatal regions such as the medial temporal lobe (amygdala and hippocampus) and midbrain (Riccardi et al. 2005; Slifstein et al. 2007; Cropley et al. 2008). However, two of the three investigations reported that [^{18}F]fallypride cannot be used to measure amphetamine-induced DA release (greater than 5% decrease in radioligand binding that is statistically significant) in the cortical regions of interest due to its relatively low signal-to-noise ratio in these regions (Riccardi et al. 2005; Slifstein et al. 2007). The third study by Cropley et al. reported a statistically significant decrease of [^{18}F] fallypride binding ($-13 \pm 4\%$) in the medial OFC, but not in the temporal cortex. Other cortical regions such as the dorsolateral prefrontal cortex, the medial prefrontal cortex, and anterior cingulate were not evaluated in this study either due to relatively low binding potential ($BP_{ND} < 0.5$) or poor reproducibility for BP_{ND}.

A more recent human study contrasted the in vivo binding of [^{11}C]FLB 457 and [^{11}C]fallypride in the cortex with respect to their signal-to-noise ratio and vulnerability to endogenous competition by DA (Narendran et al. 2009). The results of this study demonstrated that the signal-to-noise ratio of [^{11}C]FLB 457 is on average 60% higher than that of [^{11}C]fallypride in the cortical regions of interest (for example, DLPFC [^{11}C]FLB 457 $BP_{ND\ is}$ 0.6 ± 0.3, [^{11}C]fallypride 0.4 ± 0.2). The results of this study also demonstrated for the first time that this higher signal-to-noise ratio of [^{11}C]FLB 457 allows for the successful imaging of amphetamine-induced DA release in the cortical regions of interest. The mean displacement in the cortical regions of interest ranged from -5 to -13%. More exciting was the fact that the amphetamine-induced displacement of [^{11}C]FLB 457 was detected in the prefrontal cortical regions of interest such as the dorsolateral prefrontal cortex (-13%), medial prefrontal cortex (-7%), and anterior cingulate cortex (-9%). If further validation of this technique is successful, this technique would potentially allow for the imaging of prefrontal cortical dopamine transmission in several neuropsychiatric disorders such as addiction, schizophrenia, and ADHD.

7 Imaging Other Neurotransmitter Release Using PET

While the dopamine system has been shown to allow measurement of dopamine release measured with PET radioligand imaging, the same is not true for other transmitter systems. A number of attempts have been made to use PET imaging of

the serotonin system to measure changes in endogenous levels of this neurotransmitter. A previous study in healthy humans using the PET radiotracer [^{11}C] WAY100635, which labels the pre and postsynaptic 5-HT1A receptors, used rapid tryptophan depletion to acutely reduce brain serotonin levels but showed no significant effect (Rabiner et al. 2002). Similar results were seen for the other 5HT1A receptor radiotracer, [^{18}F]MPPF, using methods to alter brain serotonin levels with tryptophan infusion and depletion in addition to fenfluramine administration to induce serotonin release (Udo de Haes et al. 2002). PET imaging studies that label the postsynaptic 5-HT2A receptor, instead of the 5-HT1A receptor, have showed similar results with no change in radiotracer binding following fenfluramine-stimulated serotonin release (Staley et al. 2001; Hirani et al. 2003). Lastly, a PET imaging study in healthy human volunteers using the radiotracer [^{11}C]DASB, which labels the serotonin transporter, showed that using rapid tryptophan depletion to acutely reduce brain serotonin levels, had no significant effect on BP (Talbot et al. 2005). With respect to the GABA system, a recent study has shown that an increase in endogenous levels of GABA stimulated by a GABA transporter blocker drug tiagabine can be detected as an increase in [^{11}C]flumazenil binding (Frankle et al. 2009). The principle underlying this hypothesis is a "GABA-shift" – the enhancement in receptor affinity for benzodiazepine – site substrates resulting from increased GABA transmission in the brain (Tallman et al. 1978; Braestrup et al. 1982). The replication and further validation of this method is likely to allow for the characterization of GABA-ergic abnormalities in addictive disorders.

8 PET Radioligand Imaging in Cocaine Dependence

The most studied addiction using PET radioligand imaging is cocaine dependence, and most of these studies have focused on imaging the D_2 receptor and dopamine release. Studies measuring D_2 receptor binding have been performed using both [^{18}F] *N*-methylspiroperidol and [^{11}C]raclopride, and show that cocaine dependence is associated with a decrease in D_2 receptor binding. The first of these, published in 1990, showed that cocaine dependence was associated with a 35% decrease in D_2 receptor BP in the striatum compared to healthy control subjects (Volkow et al. 1990). Subsequent studies, performed with [^{11}C]raclopride, have shown decreases in D_2 receptor binding of 11–15% in cocaine-dependent individuals compared to control subjects (Volkow et al. 1993, 1997; Martinez et al. 2004). These results have led to the investigation of whether this decrease is reversible. Only one study has been done to address this question in human subjects and showed that the decrease in D_2 receptors persisted in a group of cocaine-dependent subjects who were rescanned after 3 months of inpatient treatment (Volkow et al. 1993). This finding is in agreement with a study in rhesus monkeys, which showed that D_2 receptor availability was decreased by 15–20% within 1 week of cocaine self-administration, and that in some monkeys these decreases persisted for up to 1 year of abstinence (Nader et al. 2006).

The decrease in D_2 receptors was first described in cocaine abusers and was initially thought to result from sustained exposure to cocaine. However, subsequent studies showed a decrease in D_2 receptor binding in a number of other addictive behaviors, such as heroin addiction (Wang et al. 1997), alcohol dependence (Hietala et al. 1994; Volkow et al. 1996), methamphetamine abuse (Volkow et al. 2001a, b), and obesity (Wang et al. 2001). As a result, it has been suggested that low D_2 receptor availability might serve as a biomarker for addiction in general, and may reflect a reduced sensitivity to naturally occurring reinforcers or a propensity to depend on pharmacological stimulation to experience reward (Volkow et al. 2002a, b, c; Melis et al. 2005). Thus, the question that arises is whether low D_2 receptor BP is a risk factor for cocaine dependence, which may be present prior to the onset of dependence. Studies in both rhesus monkeys and human subjects have sought to address this question. In rhesus monkeys exposed to a social hierarchy, social dominance is associated with a higher striatal D_2 receptor binding compared to subordinate animals (Grant et al. 1998; Morgan et al. 2002). In addition, in the rhesus monkeys low D_2 receptor BP was predictive of greater cocaine self-administration (Morgan et al. 2002). A subsequent study in rhesus monkeys also showed that low D_2 receptor binding predicted the choice to self-administer cocaine, but in this case the differences in binding were independent of social stress (Nader et al. 2006). In human volunteers, imaging studies in non-addicted participants have investigated the behavioral significance on D_2 receptor binding in the context of addiction. One of these reported that the nonaddicted siblings of cocaine abusers had higher D_2 receptor binding compared to controls (Volkow et al. 2006a, b). Similar results have been reported in a study of social drinkers, where subjects with a strong family history of alcohol dependence had higher D_2 receptor BP in the striatum compared to social drinkers with no family history of alcoholism (Volkow et al. 2006a, b). Since the family history positive subjects would be expected to have a high risk for alcohol dependence, but are not dependent themselves, these findings suggest that increased D_2 receptor BP may be protective (Volkow et al. 2006a, b). In another study in human volunteers, high striatal D_2 receptor BP in healthy controls was predictive of an unpleasant reaction to the psychostimulant methylphenidate, whereas low D_2 binding was associated with a pleasurable experience, suggesting that high D_2 receptor binding may confer a resilience to the development of addictive behaviors, whereas low D_2 BP may reflect a vulnerability (Volkow et al. 1999a, b, c, 2002a, b, c). However, not all human PET studies show results that are in agreement with this theory, and some have shown no difference in D_2 receptor BP in family history positive and negative social drinkers or in the reaction to psychostimulant administration (Martinez et al. 2003; Munro et al. 2006). In addition, while some studies have shown that low D_2 receptor binding is associated with a risk for addiction and suggest that this neurobiologic marker might occur prior to the onset of addiction, other studies in nonhuman primates have also shown that chronic exposure to cocaine itself also reduce D_2 receptor binding (Farfel et al. 1992; Moore et al. 1998; Nader et al. 2002, 2006).

9 Imaging Dopamine Release in Cocaine Dependence

As described above, PET imaging with [^{11}C]raclopride and a pharmacologic challenge that releases presynaptic dopamine can be used to image changes in the level of endogenous dopamine. Using these methods, Volkow et al. (1997) showed that cocaine dependence is associated with a decrease in [^{11}C]raclopride displacement in the striatum following methylphenidate (0.5 mg kg^{-1} iv) (Volkow et al. 1997). The results of this study showed that the cocaine-dependent subjects had an average of 9% decrease in [^{11}C]raclopride binding compared to a 21% decrease in healthy controls, suggesting that this disorder is associated with a loss of dopamine transmission. The cocaine-dependent subjects also reported a decrease in the positive effects of the stimulant compared to the controls. Using SPECT and an amphetamine challenge (0.3 mg kg^{-1} IV), Malison et al. (1999) performed a similar study in cocaine abusers and controls and reported a 1% change in binding in the cocaine abusers compared to a 10% decrease in controls. These studies suggest that cocaine dependence is associated with a decrease in presynaptic dopamine release, and this hypothesis is supported by a PET study that imaged presynaptic dopamine stores in the striatum. Using the levodopa analog 6-[^{18}F]-fluoro-L-DOPA (FDOPA), which provides a measure of presynaptic dopamine activity, Wu et al. (1997) showed that cocaine-dependent subjects who had been abstinent for 11–30 days had lower uptake compared to controls, although this was not seen in subjects who had been abstinent for only 1–10 days. As noted by Wu et al. (1997), the time frame of the decrease in presynaptic dopamine corresponds with the reported peak time of cocaine craving and dysphoria during abstinence, and a higher risk of relapse (Gawin and Kleber 1986; Satel et al. 1991a, b).

At the time these imaging studies were performed, the resolution of the PET (and SPECT) scanners that were available only allowed measurement of the striatum as a whole, and the signal from the caudate, putamen, and VST could not be differentiated. However, with higher resolution scanners, the substructures of the striatum may now be measured separately (Drevets et al. 2001; Mawlawi et al. 2001). Using a higher resolution camera, we previously published studies in cocaine-dependent subjects and matched healthy controls investigating both baseline D_2 receptor binding and the dopamine transmission using [^{11}C]raclopride and a psychostimulant challenge (amphetamine 0.3 mg kg^{-1} iv). In these studies, the striatum was subdivided into subregions based on its anatomy, function, and connections to other brain regions, as shown in Fig. 3. Animal studies have shown that dopamine transmission in the nucleus accumbens is most closely correlated with the addictive properties of drugs (Di Chiara and Imperato 1988; Wise 1996), and in higher primates, the nucleus accumbens is part of the VST, which includes the nucleus accumbens, in addition to the ventral caudate and ventral putamen (Lynd-Balta and Haber 1994a, b). The VST (also called the limbic striatum) receives most of its glutamatergic input from the amygdala, hippocampus, orbitofrontal and anterior cingulate cortex (Kunishio and Haber 1994; Lynd-Balta and Haber 1994a, b; Haber et al. 2000). The associative striatum includes the caudate and anterior putamen

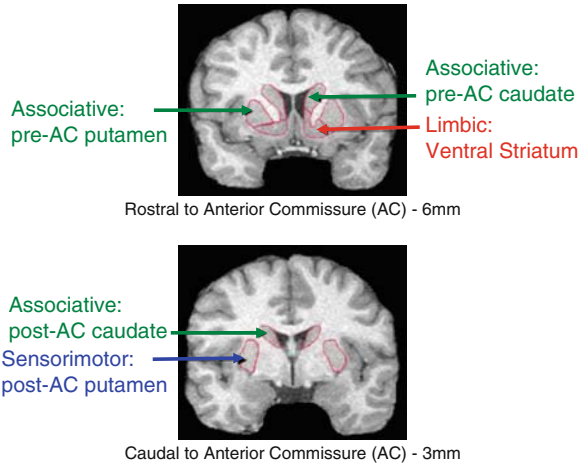

Fig. 3 Subdivisions of the striatum. With greater resolution of PET scanners, it has been possible to measure the signal emitted from the substructures of the striatum. As a result, anatomic markers, including the anterior commissure (AC), are used to divide the striatum into subregions. These include the caudate and putamen rostral to the AC (pre-AC caudate and pre-AC putamen), the caudate and putamen caudal to the AC (post-AC caudate and post-AC putamen), and the ventral striatum which includes the nucleus accumbens. Based on the connectivity of these regions, they have been grouped into the following functional subdivisions: limbic (ventral striatum), associative (pre-AC caudate, post-AC caudate, and pre-AC putamen), and sensorimotor (post-AC putamen)

(rostral to the anterior commissure), is largely involved in cognition, and receives excitatory input from the dorsolateral prefrontal cortex and other associative cortices (Haber et al. 2000; Joel and Weiner 2000). The sensorimotor striatum consists of the posterior putamen (caudal to the anterior commissure), which mostly receives input from motor and premotor areas (Haber et al. 2000; Joel and Weiner 2000).

More recent studies have imaged baseline D_2 receptor binding and stimulant-induced dopamine release separately in the limbic, associative, and sensorimotor striatum. The investigation of baseline D_2 receptor binding showed that cocaine dependence was associated with a decrease in all three striatal subdivisions (15% in the limbic and associative striatum and 17% in the sensorimotor striatum) compared to the healthy controls (Martinez et al. 2004). The study that imaged dopamine transmission, using amphetamine as the challenge, showed that cocaine dependence was associated with a marked reduction in [^{11}C]raclopride displacement in each of the functional subregions (-12% in HC vs -1% in CD for the limbic striatum, -7% for HC and -3% for CD in the associative striatum, and -14% for the HC and -4% for the CD in the sensorimotor striatum) (Martinez et al. 2007a, b). Thus, the results of these studies confirm the findings of the previous studies showing that cocaine dependence is associated with both a decrease in D_2 receptor BP and a blunted dopamine response to a psychostimulant

challenge. In addition, these alterations in D_2 binding and dopamine release were similar across the subdivisions of the striatum in cocaine dependence. However, as discussed below, while there were no differences in the neurochemistry across these subregions, there were regional differences in the behavioral correlates of dopamine transmission.

10 Functional Significance of Low D_2 Receptor in Cocaine Dependence

Overall, these imaging studies have consistently shown that cocaine dependence is associated with both a reduction in D_2 receptor BP and a decrease in dopamine transmission. The next question is what behavioral significance do these findings have?

As described above, studies in nonaddicted human subjects have suggested that high levels of D_2 receptor binding may be protective against the development of addiction and, in animals, low D_2 BP was shown to be associated with a propensity to self-administer cocaine. Our group recently performed a study investigating the correlation between D_2 receptor binding and the choice to self-administer cocaine in human cocaine-dependent subjects (Martinez et al. 2004). In this study, cocaine-dependent subjects were scanned with [^{11}C]raclopride and were shown to have a decrease in D_2 receptor availability compared to a group of matched healthy controls. In addition to the PET scans, the cocaine-dependent volunteers underwent cocaine self-administration sessions. Two types of sessions were performed, sample sessions and choice sessions, and each type was performed three times (total of six sessions) with doses of 0, 6, and 12 mg of smoked cocaine. In the sample sessions, the participants self-administered a single dose of smoked cocaine and were asked to rate the subjective effects of cocaine as described previously (Foltin et al. 2003). The three choice sessions began with a response-independent or "priming" dose of cocaine followed by five opportunities to choose between the same dose of cocaine and a $5.00 voucher. Notably, in the sample sessions, the positive effects of the 6-mg dose did not differ from that of the 0-mg dose, whereas the 12-mg dose was rated as having higher positive subjective effects than either 0 or 6 mg. In other words, the 6-mg dose, which is a low dose, was perceived as not differing from placebo. Despite this, in the choice sessions, the 6-mg dose was self-administered more frequently than the placebo (0 mg). These findings show that the reinforcing effects of drugs of abuse are more complex than simply the pleasurable or euphoric effects they produce, and previous studies have shown similar results. Fischman (1989) studied a group of chronic cocaine abusers presented with a dose of cocaine that was too low to produce subjective effects, yet still chose cocaine over placebo (Fischman 1989) and Lamb et al. (1991) showed that opiate-dependent subjects would work to self-administer a dose of morphine that was indistinguishable from placebo.

Thus, we investigated the correlation between D_2 receptor BP and the results from the self-administration sessions (Martinez et al. 2004). No correlation was seen with either the positive effects of any dose of cocaine nor was there a correlation with the choice to self-administer cocaine. These results show that while low D_2 receptor availability is associated with cocaine dependence, this parameter does not predict the choice to self-administer cocaine in human cocaine-dependent subjects. Thus, while studies in monkeys show that low D_2 receptor binding is predictive of the choice to self-administer cocaine prior to cocaine exposure, our results show that once addiction is established, D_2 receptor binding does not correlate with self-administration. In addition, while low D_2 receptor availability has been shown to correlate with the pleasurable response to psychostimulants in control subjects, this phenomenon does not seem to be occurring in addicted subjects. Taken together, the results of these imaging studies show that low D_2 receptor BP may correlate with a positive response to a psychostimulant and serves as a risk factor for cocaine dependence. Of the individuals who become addicted, most would be expected to have lower than average D_2 receptor binding. However, within the population of cocaine abusers, BP does not predict drug-seeking behavior.

11 Dopamine Transmission and Cocaine-Seeking Behavior

As described above, PET imaging can be used to measure dopamine transmission in addition to D_2 receptor binding. Thus, our group has also investigated the correlation between dopamine release and the choice to self-administer cocaine, using the sessions described in the previous section. Twenty four cocaine-dependent participants and matched healthy controls underwent two scans with [^{11}C]raclopride, under a baseline condition and following 0.3 mg kg^{-1} iv amphetamine administration. As described, cocaine dependence was associated with a blunted dopamine response compared to the controls. However, this study also showed that, within the cocaine-dependent subjects, blunted dopamine transmission in the VST was predictive of the choice for cocaine over money (Martinez et al. 2007a, b). In other words, within the cocaine-dependent subjects there was a range of dopamine release, and those with the greatest blunting of [^{11}C]raclopride displacement were more likely to choose cocaine over the monetary reinforcer. The self-administration sessions were developed as a laboratory model of relapse and are based on animal studies showing that a priming dose of cocaine reinstates cocaine self-administration (Self et al. 1996; Khroyan et al. 2000; Shaham et al. 2003). Thus, the results of this study suggests that the cocaine-dependent subjects who are the most vulnerable to relapse are those with the lowest presynaptic dopamine function.

Thus, two studies have been performed showing that cocaine dependence is associated with a decrease in dopamine release, this one (Martinez et al. 2007a, b) and that of Volkow et al. (1997). Both of these found no correlation between the subjective effects of the psychostimulant administered (methylphenidate in the study of Volkow et al. and amphetamine in our study), cocaine and dopamine release

measured with PET. In contrast, studies in healthy controls have shown a significant association between psychostimulant-induced euphoria and psychostimulant-induced radiotracer displacement in the striatum (Volkow et al. 1999a, b, c; Drevets et al. 2001; Abi-Dargham et al. 2003; Martinez et al. 2003). In addition, the studies in cocaine dependence reported that these participants experienced less of a positive effect in response to the psychostimulant compared to controls (Volkow et al. 1997; Martinez et al. 2007a, b), again suggesting that there is a significant separation between the positive euphoric effects of drugs of abuse and its reinforcing effects.

12 Sensitization and Chronic Cocaine Exposure

It is striking that three independent studies in human cocaine-dependent subjects have demonstrated a blunted dopamine response to a psychostimulant when much of the preclinical animal literature suggests the opposite: that chronic cocaine exposure should produce an exaggerated dopaminergic response to a stimulant. In the preclinical studies, long-term exposure of an animal to cocaine results in sensitization, which is an enhanced or exaggerated dopamine response to a psychostimulant (Pettit et al. 1990; Kalivas and Duffy 1993; Bradberry 2000; Vezina 2004). Sensitization occurs when an animal chronically administered cocaine (which acutely increases extraneuronal dopamine) undergoes a period of abstinence. Following this period of abstinence, a subsequent dose of a psychostimulant (such as cocaine or amphetamine) results in an exaggerated release of dopamine. In these studies, sensitization has been shown to be long lasting and animals exposed to cocaine have been shown to cross sensitize to amphetamine (i.e., a dose of amphetamine following cocaine exposure also elicits an exaggerated dopamine response) (Pierce and Kalivas 1995). In light of this research, it would be expected that cocaine abusers administered a psychostimulant would show an excess of DA release rather than a blunted effect. The study of Volkow et al. (1997) and our study were performed on participants who had been abusing cocaine for prolonged periods of time and the scans were performed following a period of abstinence (3–6 weeks in the study of Volkow et al. and 14 days in our study), such that sensitization should have been elicited. Therefore, these studies show that chronic cocaine exposure in humans is associated with a decrease rather than an increase in striatal DA transmission, and suggest that sensitization may not be present in humans who have been exposed to cocaine for several years. The reason for this discrepancy between the human and animal studies is not known. In a recent review, Bradberry et al. addressed this issue and concluded that sensitization can be elicited when animals are exposed to a recreational schedule of cocaine, but that a chronic regimen of cocaine self-administration at a higher dose did not produce sensitization (Bradberry 2006).

In humans, sensitization has been difficult to demonstrate and has largely been investigated behaviorally. Early studies in chronic stimulant abusers reported that these subjects developed psychosis more readily when reexposed to drug (Sato et al.

1983; Satel et al. 1991a, b) but more recent studies that measure sensitization (by measuring motor behaviors, vital signs, or subjective effects) have produced mixed results (Rothman et al. 1994; Strakowski et al. 1996; Gorelick and Rothman 1997). However, a recent PET study using the radiotracer [^{11}C]raclopride demonstrated sensitization to amphetamine in nondependent human subjects. In this study, 10 healthy men with limited past exposure to stimulants were administered oral amphetamine (0.3 mg kg^{-1}) on five occasions followed by a period of 14 days of abstinence. In the presensitization condition, amphetamine produced an 18% decrease in raclopride BP, whereas the sensitization dose of amphetamine produced a 28% decrease in the VST. Seven of the subjects returned for PET scans at 1 year, and sensitization was still detected (24% [^{11}C]raclopride displacement).

Together, the preclinical and human studies suggest that sensitization can be elicited with limited lifetime exposure. The studies in human cocaine abusers were performed in subjects who had chronic exposure to cocaine. Thus, it can be hypothesized that early on in cocaine use there is a sensitized dopamine response. In the early stages of drug use, the degree of dopamine release correlates with the euphorigenic effects of the drug, as shown in the studies of the control subjects. However, once addiction is established, one of the most significant changes in neurochemistry appears to be a blunted dopaminergic response. A more in-depth review of this topic has been previously published by Narendran and Martinez (2008).

13 Imaging Cue-Induced Craving in Cocaine Dependence

Instead of a pharmacologic challenge to release dopamine, some recent studies have used a sensory stimulus to release dopamine. Two studies have investigated the effect of drug-related cues on [^{11}C]raclopride binding in cocaine dependence (Volkow et al. 2006a, b; Wong et al. 2006), using a video of persons engaged in cocaine use compared to a neutral video (nature scenes). The study of Volkow et al. (2006a, b) showed a decrease in [^{11}C]raclopride binding in the dorsal caudate and putamen following the cocaine video compared to the neutral video, with no effect in the VST (Volkow et al. 2006a, b). Wong et al. showed a decrease in BP in the left anterior putamen in the cocaine subjects who craved cocaine, while no significant change was seen in cocaine abusers who did not crave cocaine (Wong et al. 2006). In both studies, the magnitude of [^{11}C]raclopride displacement correlated with increased craving for cocaine.

In these studies, the magnitude of cue-induced [^{11}C]raclopride displacement was low and similar to that seen in our study using IV amphetamine (5% for the video vs 3% with amphetamine in the caudate and 6% for the video vs 1% for amphetamine in the putamen). In addition, Volkow et al. showed that cue-induced changes in dopamine correlated with severity of addiction, such that greater dopamine release in the dorsal striatum correlated with higher scores of severity (Volkow et al. 2006a, b). This finding suggests that dopamine release in response to a cue correlates with craving for drug and might thus correlate with a greater risk of relapse. Our

data demonstrates that cocaine-dependent subjects with the lowest amphetamine-induced dopamine release are more likely to self-administer cocaine, and thus greater deficits in dopamine release may be indicative of risk for relapse. The reason for this difference is not clear, although it has been suggested that set-shifting depends on dopamine transmission in the dorsal striatum and reversal learning is mediated by dopamine in the VST (Voorn et al. 2004). Thus, dopamine transmission in the ventral vs dorsal striatum may play a critical role in relapse.

14 Imaging Dopamine Transmission in Other Addictions

As mentioned above, cocaine dependence is the most studied addiction and fewer studies imaging presynaptic dopamine release have been published in other addictions. For example, methamphetamine abuse has been shown to be associated with dopamine neuronal injury, such that blunted dopamine release would be expected in this setting. Previous studies have shown that this disorder is associated with reduced levels of the dopamine transporter (which serves as a marker for dopamine neuronal integrity), reduced D_2 receptors, and a reduction in the Vesicular Monoamine Transporter 2 (a marker for presynaptic stores of dopamine), which provide strong evidence that this addiction is also associated with reduced dopamine transmission (Martinez et al. 2007a, b).

Alcohol dependence has also been studied using PET to investigate both baseline D_2 receptor binding and presynaptic dopamine release. A number of studies have been performed investigating baseline D_2 receptor binding: six of these showed a decrease in D_2 receptor BP while two showed no significant difference between alcohol-dependent subjects and healthy controls (Martinez et al. 2007a, b). The studies showing a decrease in D_2 receptor BP have shown that this decrease occurs in the striatum measured as a whole in addition to each of the subdivisions of the striatum. The two studies showing no difference between the alcohol-dependent subjects and healthy controls were performed measuring the striatum as a whole only and were performed with SPECT rather than PET, although these differences in imaging methodology are unlikely to explain the differences in the results (Repo et al. 1999; Guardia et al. 2000; Kuikka et al. 2000). Notably, one study has been performed imaging baseline D_2 receptors following 1–4 months of abstinence and showed that no recovery of D_2 receptors occurred within this time frame (Volkow et al. 2002a, b, c).

14.1 Behavioral Correlates of Low D_2 Receptor BP in Alcohol Dependence

Previous studies have investigated the behavioral significance of reduced D_2 receptor BP in alcohol dependence. In a seminal study, Heinz et al. showed that low

D_2 receptor BP in the VST is associated with greater alcohol craving and greater cue-induced activation of the medial prefrontal cortex and anterior cingulate using functional magnetic resonance imaging (fMRI) (Heinz et al. 2004). These findings led the authors to hypothesize that dopaminergic dysfunction in the VST may attribute incentive salience to alcohol-associated stimuli, such that alcohol cues elicit craving and excessive activation of the networks associated with attention and behavior control (Heinz et al. 2004).

14.2 Alcohol Dependence and Presynaptic Dopamine

Presynaptic dopamine function in the striatum has been investigated in alcohol dependence using a number of PET imaging methods, including scanning with the radiotracers [^{18}F]DOPA (neuronal uptake of this tracer provides a measure of presynaptic dopamine stores), (+)[^{18}F]dihydrotetrabenazine (labels the type 2 vesicular monoamine transporters of the dopamine vesicles), and [^{11}C]raclopride with an amphetamine challenge. Two studies have been performed using [^{18}F]DOPA; one reported an increase in uptake and the other reported no difference between alcohol-dependent subjects and healthy controls (Tiihonen et al. 1998; Heinz et al. 2005). Tiihonen et al. reported an increase in [^{18}F]DOPA uptake in the putamen and caudate in alcohol-dependent subjects compared to healthy controls, a finding that suggests that alcoholics have increased presynaptic dopamine function (Tiihonen et al. 1998). Alternatively, Heinz et al. showed no difference in [^{18}F]DOPA uptake in alcohol-dependent subjects, although uptake in the putamen negatively correlated with craving for alcohol, suggesting that alcohol-dependent subjects with reduced dopamine stores may be more susceptible to the reinforcing effects of alcohol (Heinz et al. 2005). One study has been performed with the PET radioligand (+)[^{18}F]dihydrotetrabenazine, which provides a measure of presynaptic dopamine vesicles in the striatum, and reported a decrease in the caudate and putamen of alcohol-dependent subjects compared to controls (Gilman et al. 1998). However, levels of VMAT2 were not specifically measured in the VST.

Two studies have been performed using [^{11}C]raclopride and a stimulant challenge to investigate dopamine transmission in alcohol dependence. In a study of recently detoxified alcohol-dependent volunteers, our group showed that dopamine transmission was reduced in the VST only in the alcohol-dependent subjects compared to healthy controls: no differences were seen in the associative and sensorimotor striatum between the two groups (Martinez et al. 2005). In a subsequent study, Volkow et al. used [^{11}C]raclopride and methylphenidate to increase dopamine levels and showed that alcohol dependence was associated with a decrease in presynaptic dopamine release in the VST and putamen (Volkow et al. 2007). This study investigated the brain glucose metabolism of the prefrontal with [^{18}F]fluorodeoxyglucose in addition to dopamine transmission, and showed that in controls, but not in alcoholics, metabolism in orbitofrontal cortex was negatively associated with methylphenidate-induced dopamine increases in VST.

This finding supports the hypothesis that the orbitofrontal cortex modulates the value of a reward by regulating the magnitude of dopamine release in the VST, and that this regulation is disrupted in alcohol dependence (Volkow et al. 2007).

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