Imaging the Neurochemistry of Alcohol and Substance Abuse

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Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radiotracers to image molecular targets in the human brain. These techniques have been applied over the last decade to study addiction and provide an important body of knowledge about the neurochemical alterations associated with drug and alcohol dependence.

Although the techniques of PET and SPECT molecular imaging have been reviewed elsewhere, we briefly overview the concepts that are needed to interpret these studies. The PET radiotracers most frequently used in substance abuse research are those that label the dopamine type 2/3 (D2/3) receptors of the striatum, such as the antagonists ^18^F-N-methylspiroperidol (labeled with a positron-emitting fluorine) and ^11^C-raclopride (labeled with a positron emitting carbon). Other radiotracers that are available include those that label the dopamine transporter, serotonin transporter, and other neurotransmitters.

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and receptors, GABA receptor, and opioid receptors. The outcome measure in PET studies is termed receptor availability or binding potential (BP), which is equivalent in pharmacologic terms to the product of receptor density and affinity of the radiotracer for the receptor.

In addition to the BP, PET and the radiotracer \(^{11}\)C-raclopride can also be used to measure striatal dopamine transmission. \(^{11}\)C-raclopride binding is sensitive to the endogenous dopamine in the brain: increases in extracellular dopamine (produced with a psychostimulant such as methylphenidate or amphetamine) decrease \(^{11}\)C-raclopride binding (Fig. 1). In the same individual, therefore, a comparison of baseline (ie, pre-stimulant) and post-stimulant BP provides an indirect measure of dopamine transmission. The mechanism underlying the decrease in radiotracer binding is believed to be competition between extracellular dopamine and the radiotracer for the D\(_{2/3}\) receptor, although other mechanisms, such as receptor affinity state, internalization, or polymerization may also play a critical role [1,2].

Several PET studies in human drug- and alcohol-dependent subjects have been performed using these techniques. Most of these studies have measured dopamine receptors and dopamine release in the striatum, and thus are the focus of this review. In addition, most PET studies of addiction have been performed in cocaine-dependent subjects, so the authors’ review of the literature begins with this disorder.

**Cocaine dependence**

**Dopamine D\(_{2/3}\) receptors and dopamine transmission**

As early as 1990, studies with PET have shown that cocaine addiction is associated with alterations in dopamine receptors. Using PET and \(^{18}\)F-N-methylspiropiperidol, Volkow and colleagues [3] demonstrated that cocaine dependence was associated with a decrease in D\(_{2/3}\) receptor availability in the striatum compared with healthy control subjects. Subsequent studies performed using similar methods have consistently shown decreases of 11% to 15% in striatal D\(_{2/3}\) receptors in this same population using \(^{11}\)C-raclopride [4–6]. In addition, Volkow and colleagues [4] reported that the decrease in D\(_{2/3}\) receptors persisted in a group of cocaine-dependent subjects rescanned after 3 months of inpatient rehabilitation.

Although this decrease in D\(_{2/3}\) receptor BP was first measured in cocaine dependence, a similar decrease has been seen in several other addictions, such as heroin addiction [7], alcohol dependence [8,9], methamphetamine abuse [10], and even obesity [11]. These findings suggest that low D\(_{2/3}\)
receptor availability might be a general risk factor for addiction, and it has been hypothesized that low D<sub>2/3</sub> receptor BP is associated with a low sensitivity to naturally occurring reinforcers and a propensity to depend on pharmacologic stimulation to experience reward [12,13].

In addition to baseline D<sub>2/3</sub> receptor BP, PET studies have been used to investigate dopamine transmission in cocaine dependence. Volkow and colleagues [5] demonstrated that cocaine dependence was associated with less displacement of <sup>11</sup>C-raclopride following methylphenidate (0.5 mg/kg IV) compared with control subjects, suggesting that cocaine dependence is associated with a loss of dopamine transmission. Malison and colleagues [14] reported similar results using SPECT and <sup>123</sup>I-IBZM (which also labels the D<sub>2/3</sub> receptor) using amphetamine (0.3 mg/kg IV) to increase endogenous dopamine. Both studies thus suggest that cocaine dependence is associated with a decrease in presynaptic dopamine function. This hypothesis is supported by a PET study showing that cocaine-dependent subjects (abstinent 11–30 days) had lower uptake of the levodopa analog <sup>6,18</sup>F-fluoro-L-DOPA compared with healthy control subjects, suggesting that cocaine dependence is associated with a decrease in the dopamine stores of the presynaptic neuron [15].

Because of the resolution of PET (and SPECT) cameras, these studies measured dopamine receptors and dopamine transmission in the striatum as a whole. In other words, the resolution did not allow for differentiation of the signal emitted from the caudate, putamen, and ventral striatum. With a higher-resolution device, the substructures of the striatum can be measured separately [16,17]. The authors recently published two studies in human cocaine-dependent subjects and matched healthy control subjects using a high-resolution PET camera [16,18]: one study measured D<sub>2/3</sub> receptors and the other measured dopamine transmission using <sup>11</sup>C-raclopride and a psychostimulant challenge (amphetamine 0.3 mg/kg IV). In these studies, the striatum was subdivided into the ventral striatum (which contains the nucleus accumbens), associative striatum (which includes the caudate and anterior putamen and is largely involved in cognition), and the sensorimotor striatum (which contains the posterior putamen and receives input from motor and premotor areas).

The results of the authors’ study investigating D<sub>2/3</sub> receptor BP showed a significant reduction in all three striatal subdivisions in the cocaine-dependent subjects (decreases of 15% in the limbic and associative striatum and 17% in the sensorimotor striatum) compared with the healthy control subjects [6]. In the study of dopamine transmission, cocaine dependence was associated with a marked reduction in amphetamine-induced <sup>11</sup>C-raclopride displacement in each of the functional subregions [18]. These studies thus demonstrate that in cocaine dependence the deficits in dopamine neurotransmission are similar across the ventral and dorsal subdivisions of the striatum.

**Functional significance of low D<sub>2/3</sub> receptor binding in cocaine dependence**

The observation of decreased D<sub>2/3</sub> receptor BP in cocaine-dependent subjects raises the question of whether this finding may serve as a risk factor for cocaine dependence. In fact, a series of studies have suggested that a high level of D<sub>2/3</sub> BP may be protective against developing dependence. A recent study reported that nonaddicted siblings of cocaine abusers had a higher D<sub>2/3</sub> receptor BP compared with their cocaine-dependent siblings [19]. Because the siblings presumably had similar risk factors for dependence, this finding suggests that elevated D<sub>2/3</sub> receptor BP may be a neurobiologic marker of resilience. Volkow and colleagues [20,21] reported that high striatal D<sub>2/3</sub> receptor BP in healthy control subjects was predictive of an unpleasant experience following administration of the psychostimulant methylphenidate, and conversely, lower D<sub>2/3</sub> BP was associated with a pleasurable experience. Insofar as a pleasurable experience with a drug indicates a risk for substance abuse, these results indicate that high D<sub>2/3</sub> receptor BP may be protective.

The authors recently investigated the correlation between low D<sub>2/3</sub> receptor BP and the choice to self-administer cocaine in human cocaine-dependent subjects [6]. As described, these subjects had a decrease in D<sub>2/3</sub> receptor availability throughout the subdivisions of the striatum compared with a group of matched healthy control subjects. Following the PET scans, the cocaine-dependent volunteers underwent cocaine self-administration sessions in which participants were given the choice between doses of smoked cocaine and monetary vouchers. This study showed no correlation between D<sub>2/3</sub> receptor BP and the positive effects of cocaine or the choice to self-administer cocaine [6]. Although low D<sub>2/3</sub> receptor availability might be related to a pleasurable psychostimulant experience in control subjects, this phenomenon thus does not seem to be present in addicted subjects. One way to interpret these data is that low D<sub>2/3</sub> receptor BP may correlate with a positive response to a psychostimulant and is thus a risk factor for cocaine dependence. Of the individuals who become addicted (ie, choose to self-administer cocaine), most therefore have lower than average D<sub>2/3</sub>
receptor binding. Within the cohort of cocaine abusers, however, low D_{2/3} Receptor BP does not predict drug-seeking behavior.

**Behavior and dopamine transmission**

Given the consistent finding of low dopamine transmission in cocaine dependence, the authors recently completed a study designed to investigate the correlation between drug-seeking behavior and blunted dopamine transmission. As described, cocaine dependence was associated with a decrease in amphetamine-induced \(^{11}C\)-raclopride displacement compared with healthy control subjects [18]. Following the scans, the cocaine-dependent participants were given the choice between smoked cocaine and monetary vouchers in self-administration sessions. The results of this study showed that blunted dopamine transmission in the ventral striatum was predictive of the choice for cocaine over the choice for money [18]. The self-administration sessions were developed as a laboratory model of relapse based on animal studies showing that a priming dose of cocaine reinstates cocaine self-administration [22–24]. This finding thus suggests that cocaine-dependent subjects who are the most vulnerable to relapse are those with the lowest presynaptic dopamine function. This is in agreement with the hypothesis put forth by Melis and colleagues [13], who have proposed that a hypodopaminergic state in addiction is associated with a decreased interest in nondrug-related cues and excessive interest in drugs of abuse.

**Imaging cue-induced craving in cocaine dependence**

Two recent studies have investigated the effect of drug-related cues on \(^{11}C\)-raclopride binding in cocaine dependence [25,26]. Both studies used a video of persons using cocaine compared with a neutral video (nature scenes). Volkow and colleagues [25] showed a decrease in \(^{11}C\)-raclopride BP in the dorsal striatum (caudate and putamen) following the cocaine video compared with the neutral video. Wong and colleagues [26] showed a significant decrease in BP in the left anterior putamen in the cocaine subjects who craved cocaine, whereas there was no significant change in cocaine abusers who did not crave cocaine. In both studies, the magnitude of \(^{11}C\)-raclopride displacement correlated with craving for cocaine.

In addition, Volkow and colleagues [25] showed that cue-induced changes in dopamine correlated with the severity of addiction, such that greater dopamine release in the dorsal striatum correlated with higher scores of severity. This finding suggests that dopamine release in response to a cue correlates with craving for drug and might thus correlate with a greater risk for relapse. In contrast, the data described demonstrated that subjects with the lowest amphetamine-induced dopamine release are more likely to self-administer cocaine, such that greater deficits in dopamine release may indicate 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 ventral striatum [27]. Dopamine transmission in the ventral versus dorsal striatum may thus play a critical role in relapse.

**Cocaine dependence and the dopamine transporter**

A study using SPECT and the dopamine transporter (DAT) radiotracer \(^{123}I\)-beta-CIT reported a 20% increase in DAT availability in cocaine abusers who had been abstinent for only 96 hours [28]. Two studies using the radiotracer \(^{11}C\)-cocaine to label the DAT, however, showed no difference in BP between healthy control subjects and cocaine abusers who had been abstinent 5±8 days or 42±7 days [29,30]. Together these studies suggest that the DAT is elevated in very early abstinence but does not seem to differ from control subjects after this time point.

**Imaging studies of cocaine dependence and other neurotransmitters**

Despite that cocaine directly affects the serotonin system and that altering serotonin transmission in human subjects modulates the subjective effects of cocaine [31–33], only one SPECT study has been performed to measure the serotonin transporter. This study showed that the transporter was increased in the brainstem in cocaine abusers who had been abstinent for 3.7±3.8 days [34]. The duration of abstinence was brief, and it is not known if this elevation is long-lasting.

Two PET studies of cocaine dependence using the \(\mu\)-agonist receptor radiotracer \(^{11}C\)-carfentanil have been performed. The first of these imaged cocaine-dependent subjects after 1 to 4 days of abstinence and again at 4 weeks of abstinence compared with control subjects [35]. \(\mu\) Receptor BP was increased in the anterior cingulate, frontal and temporal cortex, caudate, and thalamus in the cocaine abusers in early abstinence and increased in the cingulate, frontal cortex, caudate, and thalamus after 4 weeks of abstinence. In a later study, this same group measured \(\mu\) receptor BP in a group of cocaine abusers at three time points: after 1 day, 1 week, and 12 weeks of abstinence [36]. The results showed that \(\mu\) receptor BP was increased in the anterior cingulate, frontal cortex, and temporal cortex after 1 day of abstinence and remained elevated in
the anterior cingulate and anterior frontal cortex up to 12 weeks [36]. In both of these studies, μ receptor binding positively correlated with self-reports of craving for cocaine, suggesting that modulation of the endogenous opioid system may play a role in cocaine addiction and relapse.

**Alcohol dependence**

**Dopamine D<sub>2/3</sub> receptor and alcohol dependence**

As with cocaine, most radiotracer imaging studies in alcohol dependence have focused on dopamine transmission using the same techniques as those described. As shown in Table 1, eight PET and SPECT studies have measured D<sub>2/3</sub> receptor BP in alcohol dependence: six showed a decrease in D<sub>2/3</sub> receptor BP [8,9,37–40] and two showed no significant difference between alcohol-dependent subjects and healthy control subjects [41,42]. The studies showing a decrease in D<sub>2/3</sub> receptor BP were performed with PET, and the two earliest studies measured the striatum as a whole [8,9]. The other four PET studies used a high-resolution camera and showed a decrease in D<sub>2/3</sub> receptors of a similar magnitude to that seen in cocaine dependence in the caudate [37,38], putamen [37–40], and ventral striatum [38–40]. The two studies showing no difference between the alcohol-dependent subjects and healthy control subjects for 3 months and found that the subjects who relapsed within this time frame had higher D<sub>2/3</sub> receptor BP compared with those who did not relapse [42].

The studies measuring D<sub>2/3</sub> receptor BP described in this review thus have been limited to measuring the striatum. More recently, high-affinity radiotracers have been used to measure D<sub>2/3</sub> receptors outside the striatum, where the receptor concentrations are low, such as within the temporal lobe. In alcohol dependence, only one group has measured extra-striatal D<sub>2/3</sub> receptor BP using the high-affinity SPECT radiotracer 123<sup>i</sup>-epidepride. In their first report, Repo and colleagues [41] reported no difference in D<sub>2/3</sub> BP between alcohol-dependent subjects and healthy control subjects. In a subsequent reanalysis of these data, Kuikka and colleagues [43] reported that the alcohol-dependent subjects had lower D<sub>2/3</sub> receptor BP values in the left temporal pole compared with healthy control subjects (the reanalysis consisted of measuring the right and left temporal poles separately). Although the alcohol-dependent subjects in this study included

<table>
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<th>Reference</th>
<th>Withdrawal period</th>
<th>Radioligand</th>
<th>D&lt;sub&gt;2/3&lt;/sub&gt; receptor BP (alcohol-dependent versus healthy control subjects)</th>
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<tr>
<td>Hietala et al, [8]</td>
<td>23±62 weeks</td>
<td>1&lt;sup&gt;11&lt;/sup&gt;C-raclopride (PET)</td>
<td>Decreased in striatum (20%)</td>
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<td>Volkow et al, [9]</td>
<td>52±48 days</td>
<td>1&lt;sup&gt;11&lt;/sup&gt;C-raclopride (PET)</td>
<td>Decreased in striatum (22%)</td>
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<td>Repo et al, [41]</td>
<td>1 week to 4 years</td>
<td>123&lt;sup&gt;i&lt;/sup&gt;-epidepride (SPECT)</td>
<td>Nonsignificant decreased BP in striatum (5%)</td>
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<td>Guardia et al, [42]</td>
<td>8 to 10 days</td>
<td>123&lt;sup&gt;i&lt;/sup&gt;-IBZM (SPECT)</td>
<td>Nonsignificant decreased BP in striatum (5%)</td>
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<tr>
<td>Volkow et al, [37]</td>
<td>6 to 20 weeks</td>
<td>1&lt;sup&gt;11&lt;/sup&gt;C-raclopride (PET)</td>
<td>Decreased in caudate (14%) and putamen (18%) in early detoxification (6 weeks), decreased in caudate in late detoxification (1–4 months later)</td>
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<tr>
<td>Heinz et al, [39]</td>
<td>2 to 4 weeks</td>
<td>18&lt;sup&gt;f&lt;/sup&gt;-desmethoxyfallypride (PET)</td>
<td>Decreased in the putamen and ventral striatum</td>
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<td>Heinz et al, [40]</td>
<td>36±22 days</td>
<td>18&lt;sup&gt;f&lt;/sup&gt;-desmethoxyfallypride (PET)</td>
<td>Decreased in the putamen and ventral striatum</td>
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<td>Martinez et al, [38]</td>
<td>14 days</td>
<td>1&lt;sup&gt;11&lt;/sup&gt;C-raclopride (PET)</td>
<td>Decreased in the caudate (21%), putamen (21%), and ventral striatum (17%)</td>
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**Table 1: Comparison of studies investigating D<sub>2/3</sub> receptor availability in alcohol dependence**

*Abbreviation: BP, binding potential.*
subjects who had a wide range of abstinence (1 week to 4 years), this study did not include sufficient subjects at the extremes of the range of abstinence to address the question of whether D2/3 recovers after a prolonged period of abstinence. Of note, in the study of Volkow and colleagues [37], alcohol-dependent subjects were scanned at 6 weeks and again at 1 to 4 months later, with no recovery of striatal D2 receptor BP within this time frame. No studies have been performed investigating the recovery of D2/3 receptor BP after longer periods of abstinence, and this question remains unanswered.

**Behavioral correlates of low D2/3 receptor binding potential**

Several studies have investigated the behavioral significance of reduced D2/3 receptor BP in alcohol-dependent subjects. Heinz and colleagues [39] reported a correlation between low D2/3 receptor BP in the ventral striatum and activation in the medial prefrontal and anterior cingulate cortex in response to alcohol-related cues using functional magnetic resonance imaging (fMR imaging). In addition, this study showed that low D2/3 receptor binding in the ventral striatum also correlated with a greater craving for alcohol. Heinz and colleagues [40] also showed that craving for alcohol at the time of the PET scan correlated significantly with alcohol intake at the 6-month follow-up.

The authors recently demonstrated a significant inverse correlation between 11C-raclopride BP and the average daily quantity of alcohol consumed, suggesting that a low BP may be associated with greater severity of disease [38]. This finding is in agreement with studies showing lower D2 receptor density in the caudate-putamen and nucleus accumbens of alcohol-preferring compared with non-alcohol–preferring rats, before exposure to alcohol [44,45]. In addition, Thanos and colleagues [45] showed that adenovirus-induced overexpression of the D2 receptor in rats trained to self-administer alcohol reduced their intake and their preference for alcohol. Together these data suggest that the low D2/3 receptor BP observed in alcohol-dependent individuals is associated with greater severity of disease (more craving, greater attention to alcohol-related cues, and higher alcohol consumption), and may also be associated with an increased risk for relapse.

As described for cocaine dependence, a recent study suggests that increased D2/3 receptor BP may be protective against alcohol dependence. Volkow and colleagues [19] recently reported that social drinkers who have a strong family history of alcohol dependence had higher D2/3 receptor BP compared with those who had no such family history. In addition, the investigators reported that higher metabolism in the prefrontal cortex (measured with 18F-fludeoxyglucose) was associated with higher D2/3 receptor BP in subjects who had family histories of alcohol dependence [19]. Based on these findings, the investigators postulated that high D2/3 receptor BP is protective for subjects who have a vulnerability for alcohol dependence (ie, family history), and that this protective factor is also represented by an increase in activation of cortical brain regions that mediate behaviors such as inhibition control and restraint over alcohol consumption. Munro and colleagues, however [46], found no difference in D2/3 receptor BP values between social drinkers with and without a positive family history. This study was similar to that of Volkow and colleagues [19] with regard to PET methods, enrollment numbers, and subject demographics (eg, age, alcohol intake). Although there were some differences in the numbers of alcohol-dependent relatives required for the two studies, all subjects who had a positive family in both studies included alcohol-dependent fathers, so that it is unlikely that this factor alone could explain the discrepancy in findings.

**Alcohol dependence and presynaptic dopamine**

Presynaptic dopamine function has been studied in alcohol dependence using three methods: (1) imaging the neuronal uptake of the radiotracer 18F-DOPA, which provides a measure of presynaptic dopamine stores, (2) (18F)-dihydrotetrabenazine, which labels the type-2 vesicular monoamine transporters of the dopamine vesicles, and (3) 11C-raclopride with an amphetamine challenge. Two studies performed with 18F-DOPA reported an increase and no difference between alcohol-dependent subjects and healthy control subjects [40,47]. Tiihonen and colleagues [47] demonstrated an increase in 18F-DOPA uptake in the putamen and caudate in alcohol-dependent subjects compared with healthy control subjects, which suggests that alcoholic subjects have increased presynaptic dopamine function. Alternatively, Heinz and colleagues [40] showed no difference in 18F-DOPA uptake in alcohol-dependent subjects who had been abstinent for 36±22 days. Low 18F-DOPA uptake in the putamen, however, correlated with greater craving for alcohol, suggesting that alcohol-dependent subjects who have deficits in presynaptic dopamine may be more susceptible to the reinforcing effects of alcohol [40].

In a PET study using the radioligand (18F)-dihydrotetrabenazine, Gilman and colleagues [48] reported a decrease in striatal type-2 vesicular
monoamine transporters (VMAT2) in the caudate (6%) and putamen (13%) of alcohol-dependent subjects, although this only reached significance in the putamen. Levels of VMAT2 were not specifically measured in the ventral striatum. These results suggest that alcohol dependence is associated with a loss of presynaptic dopamine stores.

The authors recently completed a study using $^{11}$C-raclopride and an amphetamine challenge to investigate dopamine transmission in alcohol dependence [38]. Dopamine transmission was reduced exclusively in the ventral striatum in the alcohol-dependent subjects compared with healthy control subjects; no differences in the associative and sensorimotor striatum were found between the two groups. In contrast to a study of cocaine dependence that showed a reduction in amphetamine-induced $^{11}$C-raclopride displacement in each of the striatal subdivisions, blunted dopamine transmission was seen only in the ventral striatum in alcohol dependence. It is thus possible that addiction in general is associated with decreased dopamine function in the limbic striatum, whereas stimulant dependence is associated with a more widespread reduction.

**Alcohol dependence and the dopamine transporter**

PET and SPECT studies have been conducted to measure the dopamine transporter in alcohol dependence. Tiihonen and colleagues [49] used SPECT and $^{123}$I-beta-CIT to measure DAT in violent alcoholic subjects, nonviolent alcoholic subjects, and healthy control subjects. This study showed a significant reduction in DAT in nonviolent alcoholic subjects and an increase in DAT binding in the violent alcoholic subjects relative to control subjects. A subsequent study by Laine and colleagues [50] reported that alcohol dependence was associated with a decrease in DAT binding only at 1 to 4 days of abstinence; the same subjects scanned after 4 weeks of abstinence did not differ from control subjects. Using PET and $^{11}$C-d-threo methylphenidate, Volkow and colleagues [9] reported no difference in alcohol-dependent subjects who had been abstinent 52±48 days in comparison with healthy control subjects. Similarly, Heinz and colleagues [51,52] reported no difference in DAT in alcohol-dependent subjects scanned after 3 to 5 weeks of abstinence. It thus seems that DAT binding may be transiently decreased in alcohol withdrawal, but that long-term changes in the dopamine transporter are unlikely to play a key role in alcohol dependence.

**Serotonin and alcohol dependence**

Only three groups have published studies investigating alterations in the serotonin system in alcohol dependence, and they have reported conflicting results. Heinz and colleagues [51,53] reported a 30% reduction of serotonin transporter (SERT) binding in the midbrain in men but not women who were alcohol-dependent using SPECT and the radiotracer $^{123}$I-beta-CIT. SERT binding in men was associated with lifetime alcohol consumption and severity of depression [51,53]. In a subsequent study, Heinz and colleagues [54] reported a decrease in midbrain SERT only in alcoholic subjects who were homozygous for the long allele of the promoter of the SERT gene.

These studies were conducted with the SPECT radiotracer $^{12}$I-beta-CIT, which allows the measurement of SERT in the midbrain, yet this radiotracer has a low ratio of specific to nonspecific binding in other brain regions. In contrast, some PET ligands for SERT produce a better signal-to-noise ratio in other brain regions. The earliest PET ligand that was available to measure the SERT was $^{11}$C-McN5652. Using this radiotracer, Szabo and colleagues [55] reported a significant decrease in the distribution volume (DV) of $^{11}$C-McN5652 in most brain regions (midbrain, thalamus, amygdala, pons, cingulate, orbitofrontal cortex, and cerebellum) studied in alcohol dependence. This outcome measure (DV) differs from BP. BP is a measure of specific binding, whereas the DV is a measure of specific binding and nonspecific binding combined. The region of reference in this study was the cerebellum, with a significant difference in nonspecific binding between the alcoholic subjects and healthy control subjects. When the specific binding of $^{11}$C-McN5652 to SERT alone was measured, the only significant difference seen between the alcoholic subjects and control subjects was in the midbrain [53].

More recently the radiotracer $^{11}$C-DASB has been used to image SERT because of its improved signal-to-noise ratio [56]. Brown and colleagues [57] used this radiotracer to investigate alterations in SERT in 30 alcohol-dependent subjects (abstinent 14±2 days before scanning) and 18 healthy control subjects. Given the high correlation between alcoholism, aggression, and alterations in serotonin transmission, the alcohol-dependent subjects were divided into two groups based on their scores of hostility. No significant difference in SERT BP was found in any brain region (including midbrain, frontal and medial temporal cortex, striatum, thalamus, and cerebellum) between the two alcohol-dependent groups and healthy control subjects.

Overall the main conclusion from these studies of SERT in alcohol dependence is that two groups have shown a decrease in midbrain SERT in alcoholic subjects, whereas one group has not. The
reason behind this discrepancy is not clear. The studies by Heinz and colleagues [54] suggest that this decrease may be present only in men who have a given serotonin promoter genotype. The study of Szabo and colleagues [55] did not include sufficient female subjects for comparison, and the study of Brown and colleagues [57] reported no effect of gender on SERT binding. No studies outside of that of Heinz and colleagues have looked at the effect of genotype. In addition, the duration of abstinence was varied among studies, from 2 weeks to 27 years. For the duration of abstinence to explain the difference in the study results, it is thus necessary to postulate that SERT availability early in abstinence does not differ from that found in control subjects, but then significantly decreases and remains decreased for many years.

Measures of GABA in alcohol dependence

Although imaging studies have largely focused on a range of neurotransmitter systems in alcohol dependence, GABA<sub>A</sub> receptors probably play a more direct role in ethanol intoxication and withdrawal. To date, the PET and SPECT radiotracers available to image the GABA<sub>A</sub> receptor all label the benzodiazepine site (<sup>11</sup>C-flumazenil for PET and <sup>123</sup>I-iomazenil for SPECT). Seven studies have examined this parameter in alcohol dependence. Three of these studies have shown that alcohol dependence is associated with a decrease in the GABA<sub>A</sub> receptor binding. Gilman and colleagues [58] reported a decrease in the DV of <sup>11</sup>C-flumazenil in the medial frontal lobe and cingulate of nine alcohol-dependent subjects, and a decrease in these same regions and the cerebellum in eight alcoholic subjects who had cerebellar degeneration. Using <sup>123</sup>I-iomazenil, Abi-Dargham and colleagues [59] reported a lower DV in the frontal cortex, anterior cingulate, and cerebellum in alcoholic patients abstinent 1 to 6 months. Finally, Lingford-Hughes and colleagues [60] reported a decrease in GABA<sub>A</sub> receptor binding in the frontal, parietal, and temporal cortices in alcohol-dependent men compared with healthy control subjects using the radiotracer <sup>123</sup>I-iomazenil.

Two studies have reported no difference in GABA<sub>A</sub> receptor binding between alcohol-dependent subjects and healthy control subjects [61,62]. One of these included a small number of subjects [61] and the other study included only women alcohol-dependent subjects [62]. An additional two studies have shown that alcohol dependence is associated with an increase in GABA<sub>A</sub> receptor binding. Jalan and colleagues [63] reported an increase in <sup>11</sup>C-flumazenil binding in the cortex, cerebellum, and the basal ganglia in alcohol-dependent subjects who had cirrhosis and hepatic encephalopathy compared with healthy control subjects. More recently Staley and colleagues [64] studied 23 alcohol-dependent men and 15 healthy control subjects using the SPECT radiotracer <sup>123</sup>I-iomazenil. The alcohol-dependent subjects were scanned at two time points: at 1 week and at 4 weeks of abstinence. At 1 week of abstinence, <sup>123</sup>I-iomazenil uptake was increased in the frontal, cingulate, temporal, insular, parietal, and occipital cortices in the alcohol-dependent subjects who were nonsmokers compared with nonsmoking control subjects and compared with the alcohol-dependent subjects who were smokers. No differences were seen between any of the groups at 4 weeks.

The reasons behind these discrepancies are not entirely clear, but likely relate to differences in sample size and duration of abstinence. Both studies that showed no difference between alcohol-dependent and control subjects included small numbers of subjects, and only the study of Staley and colleagues scanned subjects after a short interval of abstinence. Taken together, these studies thus suggest that GABA<sub>A</sub> benzodiazepine receptor binding shifts across the different stages of alcohol dependence and may be increased in very early abstinence, but more prolonged abstinence may be associated with a decrease in binding [65]. This hypothesis is supported by the finding of Staley and colleagues [64] showing that GABA<sub>A</sub> receptor binding was positively associated with severity of withdrawal and days since the last alcoholic drink. One must keep in mind, however, that the initial increase seems to be present only in alcohol-dependent non-smokers (who tend to be in the minority in this disorder) and the decrease in binding associated with a longer duration of abstinence may be limited to men.

There are also some methodologic issues with imaging studies of the GABA<sub>A</sub> receptor in alcohol dependence. The first issue is that alcohol dependence is associated with a known decrease in cortical gray matter [66], and a loss of gray matter could theoretically result in a decrease in the GABA<sub>A</sub> radiotracer uptake, even without a true difference in GABA<sub>A</sub> receptor availability. For instance, the study of Abi-Dargham and colleagues [59] reported a decrease in the size of the cortical regions studied, and further showed that the group of alcoholic subjects had significantly reduced gray matter in the prefrontal cortex, anterior cingulate, and cerebellum. These were also the brain regions that had a significant decrease in GABA<sub>A</sub> receptor availability. Lingford-Hughes and colleagues, however [60], reported a decrease in binding of <sup>123</sup>I-iomazenil in cortical regions in which gray matter atrophy was absent, suggesting that gray matter loss alone does not explain the decrease in GABA<sub>A</sub> receptor availability.
In addition, because there are no regions of reference for the GABA_A receptor, the outcome measure used in these studies is the DV, which reflects specific binding and nonspecific binding. In other words, none of the studies controlled for possible differences in nonspecific radiotracer binding between alcohol-dependent subjects and healthy control subjects.

**Opioids and alcohol dependence**

Recent studies investigating the efficacy of the μ receptor antagonist as an effective treatment for alcohol dependence have shown mixed results [67]. The μ receptor is thus an interesting target for imaging in this disorder. Two PET imaging studies have been performed using the μ receptor selective radiotracer ¹¹C-carfentanil in alcohol dependence. Bencherif and colleagues [68] studied eight alcohol-dependent men after 4 days of abstinence and reported a decrease in μ receptor BP in the prefrontal cortex compared with control subjects. This group of investigators also reported that this finding was associated with a higher score for craving. No BP differences between the two groups were seen in the parietal, temporal, or orbitofrontal cortex. In contrast, a recent study by Heinz and colleagues [69] included 25 alcohol-dependent subjects who were scanned at 1 to 3 weeks and 5 to 7 weeks of abstinence and 10 matched healthy control subjects. In this study, alcohol dependence was associated with an increase in μ receptor BP in the ventral striatum of the alcohol-dependent group at both time points compared with the control subjects, and no difference in BP was seen in the other brain regions studied (caudate, putamen, prefrontal, and parietal cortex). In addition, higher μ receptor BP correlated with a greater craving for alcohol. These studies thus showed opposing findings in different brain regions. Although both studies used PET, however, there were significant differences in the methods. The study of Bencherif and colleagues [68] included a smaller number of subjects, the control subjects were not enrolled specifically for this study (drawn from a pre-existing database), and this group did not report on μ receptor availability in the ventral striatum. As yet, no overall conclusion can thus be made from these imaging studies.

**Heroin dependence**

To date, only four PET studies have been performed measuring neurochemistry in heroin addiction. Two of these imaged opioid receptors. Zubieta and colleagues [70] reported an increase in μ receptor availability in the ventral striatum, inferofrontal cortex, and anterior cingulate in heroin-dependent subjects compared with control subjects using ¹¹C-carfentanil. This was a preliminary study, however, that included three heroin-dependent subjects. Kling and colleagues [71] performed a study using ¹⁸F-cyclofoxy, an opioid antagonist that labels μ- and κ-opioid receptors, in methadone maintained heroin-dependent subjects. This study showed a 19% to 32% decrease in receptor availability in the thalamus, amygdala, caudate, anterior cingulate, and putamen compared with healthy control subjects. Because the subjects were taking methadone at the time of the scan, these results suggest that methadone treatment is associated with a low occupancy of opioid receptors. The heroin-dependent subjects, however, were not scanned at baseline (off medication), and so the actual occupancy is not known. In other words, occupancy is a comparison of radiotracer binding in the baseline scan with radiotracer binding following drug administration. Because the drug binds to the same receptor, the post-medication scan shows lower radiotracer uptake. In this way PET can be used to measure the percent of receptors occupied by a medication at a therapeutic dose. In the study of Kling and colleagues [71], it was assumed that the baseline (off methadone) receptor availability in the heroin-dependent subjects was similar to that of the control subjects. If heroin dependence is associated with a baseline increase in opioid receptor BP, however (as suggested by Zubieta and colleagues), the occupancy of methadone in this study will be underestimated.

In a subsequent study Greenwald and colleagues [72] investigated the occupancy of therapeutic doses of buprenorphine, a partial μ-agonist and κ-antagonist, which has been successfully used to treat heroin addiction. In this study, five heroin-dependent subjects were scanned after maintenance on 2-, 16-, and 32-mg dosages of buprenorphine, which resulted in whole-brain μ receptor occupancies of 41%, 80%, and 84%, respectively. In addition, subjects were given a hydromorphone challenge, and increased receptor occupancy correlated with a decrease in its subjective effects. This study suggests that high μ receptor occupancy is reached with therapeutic doses of buprenorphine, and that this level of occupancy is needed to attenuate the subjective effects of other opioids. In a follow-up study, this group showed that 50% to 60% occupancy of the μ receptor with buprenorphine is effective at blocking symptoms of withdrawal in opiate-dependent subjects [73].

Only one study has been performed to measure the D_2/3 receptorBP in heroin dependence. Wang and colleagues [7] performed PET imaging with ¹¹C-raclopride in 11 heroin-dependent subjects before and after naloxone-precipitated withdrawal.
D2/3 receptor BP in both conditions was compared with healthy control subjects. Heroin dependence was associated with an 18% decrease in D2 receptor availability, and there was no change in 11C-raclopride binding following withdrawal. As described, this reduction in D2/3 receptor BP is of the same magnitude of that seen in other addictions, although the behavioral significance of this decrease in this population is not known.

**Methamphetamine abuse**

In addition to cocaine, alcohol, and heroin-dependent subjects, low D2/3 receptor BP values have been reported in methamphetamine abusers. Volkow and colleagues [10] showed a decrease of 16% in D2/3 Receptor BP in the putamen and of 10% in the caudate in methamphetamine abusers compared with control subjects using 11C-raclopride. In this study, D2/3 receptor BP was not specifically measured in the ventral striatum. Furthermore, low D2/3 receptor BP was associated with a decrease in glucose metabolic rate in the orbitofrontal cortex in the methamphetamine abusers and in the control subjects. This finding is similar to a study showing that low D2/3 receptor BP was associated with low orbitofrontal activity in cocaine abusers [4]. Together these findings suggest that dysregulation of these brain regions may mediate the loss of inhibitory control over compulsive drug-taking in these addictions.

Alterations in DAT also have been demonstrated in methamphetamine dependence. Four notable imaging studies demonstrated significant decreases in DAT binding using PET or SPECT in methamphetamine abusers compared with control subjects. McCann and colleagues [75] reported on six methamphetamine abusers and four methcathinone users using 11C-WIN-35,428, a selective DAT radioligand. The methamphetamine abusers had a decrease in DAT availability of approximately 25% in the putamen and caudate compared with control subjects, and a similar reduction was seen in the methcathinone abusers [75]. Using the same radiotracer, Iyo and colleagues [76] reported decreased DAT binding of 20% in the caudate/putamen (20%) and ventral striatum (26%) in 11 methamphetamine abusers and nine control subjects. A SPECT study by Chou and colleagues [77] showed DAT binding reductions of a similar magnitude. Volkow and colleagues [78] studied 15 methamphetamine abusers who had 2 weeks of monitored abstinence before scanning with 11C-d-threo-methylphenidate. Compared with control subjects, the methamphetamine abusers demonstrated a decrease in DAT availability of 28% in the caudate and 21% in the putamen [78]. The investigators also found that decreased DAT availability correlated with years of abuse and impairment in motor and memory tasks. Despite that these studies used a wide range of methods (ie, different radiotracers, duration of abstinence, and numbers of subjects enrolled), they are largely in agreement, suggesting that the decrease in the dopamine transporter in methamphetamine abuse is a robust finding.

These ata are important because it is believed that methamphetamine may be toxic to dopamine neurons. PET and postmortem studies in nonhuman primates have shown that methamphetamine exposure results in a decrease in the DAT in addition to other markers of dopaminergic neurons [79–81]. There is evidence, however, that this phenomenon is reversible. Chou and colleagues [77] used SPECT to scan five methamphetamine abusers in acute withdrawal and again after 2 weeks of abstinence and reported partial recovery of DAT binding. Two studies in nonhuman primates suggest that a reduction in markers of dopamine neuron viability (DAT and 18F-DOPA uptake) seems to be reversible after prolonged abstinence [80,82]. Similarly a postmortem study demonstrated that although there was a reduction in DAT binding in the human striatum, there was no decrease in measures of DOPA-decarboxylase and the vesicular monoamine transporter, suggesting a loss of DAT without frank cell death of the dopaminergic neurons [83]. Nevertheless, PET studies in human subjects raise the concern of neurotoxicity, and these studies demonstrated a reduction in DAT even in subjects who reported a significant time of abstinence.

**Methylenedioxymethamphetamine (Ecstasy) abuse**

To date most imaging studies investigating the effects of 3,4-methylenedioxymethamphetamine (MDMA) on neurochemistry have focused on the serotonin system. Studies in animals have demonstrated the toxicity of MDMA on serotonergic neurons and further have reported that the toxic effects seem to largely occur at the synaptic terminals, leaving the cell bodies of the midbrain intact [84]. Because SERT sites are located on the synaptic terminal of the neurons, imaging of this transporter can be used as a marker of neuronal integrity of the synaptic terminals. SERT can be imaged with PET or SPECT. The SPECT radiotracer 123I-beta-CIT labels the serotonin transporter in the midbrain (in the striatum this radiotracer labels the dopamine transporter) [85,86]. The earliest PET radiotracer available to label the SERT was 11C-(+)-McN 5652, which was followed by 11C-DASB, a ligand with a higher ratio of specific-to-nonspecific binding and shorter scanning time compared with
11C-(+)McN 5652 [87]. Although the SPECT radiotracer only allows reliable measurement of the SERT in the raphe nucleus of the midbrain (and to some extent the thalamus), the PET radiotracers allow measurement of the SERT in midbrain, thalamus, striatum, and cortex (medial temporal lobe and cingulate).

Five studies in human MDMA users have been performed measuring SERT in active MDMA users, as summarized in Table 2. The first of these included 14 MDMA users with a lifetime use of more than 25 tablets [74]. Subjects were scanned with 11C-(+)McN 5652 and 11C-(-)McN 5652 (the inactive enantiomer of the radiotracer) to measure nonspecific binding. The results of this study showed that MDMA abuse was associated with a decrease in radiotracer distribution volumes in the midbrain, thalamus, striatum, pons, cingulate, frontal, occipital, and parietal cortex in addition to the cerebellum. These data, however, showed an unusually high variability, and an unconventional approach to the statistical analysis was used to interpret the results [84]. Two subsequent studies used SPECT and the radiotracer 123I-beta-CIT [88,89] in MDMA abusers. The first of these included a small sample (n=10) of men MDMA users with a lifetime use of more than 50 tablets and matched healthy control subjects [89]. The MDMA abusers demonstrated a significant decrease in 123I-beta-CIT uptake in the occipital, calcarine, and posterior cingulate cortex and no difference in the midbrain and thalamus compared with control subjects [89]. The MDMA abusers demonstrated a significant decrease in 123I-beta-CIT uptake in the occipital, calcarine, and posterior cingulate cortex and no difference in the midbrain and thalamus compared with control subjects. The second SPECT study included a much larger sample divided into three groups: heavy users (reported lifetime use greater than 50 tablets), moderate users (reported lifetime use less than 50 tablets), and ex-users in addition to control subjects [88]. This study showed a significant decrease in 123I-beta-CIT specific binding in the midbrain and thalamus in addition to the frontal, temporal, occipital, and parietal cortex exclusively in heavy women users. There were some methodologic concerns, however, including the use of 123I-beta-CIT to measure SERT in the cortex. At equilibrium, the binding of this radiotracer in the cortical regions is minimally higher than that seen in the region used to estimate nonspecific binding (reference region). The signal of the 123I-beta-CIT binding in the cortical regions that represent SERT is thus too low to provide reliable estimates [86,90,91]. The most robust finding from these studies therefore is the decrease in SERT in the midbrain in heavy women MDMA users.

Subsequently two additional PET studies have been performed. McCann and colleagues [92] studied two SERT radiotracers, 11C-(+)McN 5652 and 11C-DASB, in 23 MDMA users and matched healthy control subjects. A decrease in the DV measure was seen in the amygdala, thalamus, dorsolateral prefrontal cortex, orbitofrontal, cingulate, parietal, temporal, and occipital cortex with both radiotracers. Additional decreases in SERT binding were seen in the hippocampus and striatum with 11C-McN 5652 but not with 11C-DASB. Buchert and colleagues [93] published a large PET study including 117 subjects (30 current users, 29 ex-users, 29 MDMA naïve drug users, and 29 drug-naïve control subjects). In this dataset, SERT BP was significantly reduced in current MDMA users in the midbrain and thalamus, left caudate, hippocampus, posterior cingulate, and occipital and temporal lobes compared with the other groups. No difference in BP was seen in any region between the ex-users and comparison subjects. Notably this decrease was greater in women subjects relative to men. Methodologic concerns included: (1) although the average duration of abstinence in the ex-users was 1.4 years, some had had as little as 29 days of cessation (the current users ranged from 4 to 60 days since last use, so that there was some overlap in time of abstinence between these two groups), and (2) some subjects were scanned after a very short period of abstinence. Reanalysis of the data, however, showed that exclusion of the subjects who had been abstinent less than 14 days did not significantly change the outcome: a decrease in BP was still seen in all the regions mentioned except for the caudate and posterior gyrus.

Subsequently Buchert and colleagues [94] re-scanned 24 of the MDMA users 1 year later; 15 were current MDMA users and 9 were former MDMA users. This study showed that current MDMA users had an increase in midbrain SERT, which the investigators attributed to a decrease in the magnitude of MDMA use over the year-long interval. SERT binding also increased in the thalamus and striatum, although this did not reach significance. In the ex-MDMA users, however, an increase in 11C-McN5652 binding was seen in the thalamus, which the investigators hypothesized was caused by an overshoot in SERT following long-term abstinence. Although this study suggests that the MDMA-induced decrease in SERT may be reversible, it should be kept in mind that the test–retest reliability of these measures of SERT with PET over the course of a year has not been shown.

Together the results of these imaging studies suggest that MDMA use is associated with a decrease in SERT binding, and that this decrease is more significant in women users. In addition, the studies that included ex-users showed no difference
between this group and control subjects, suggesting that the decrease in SERT is reversible with cessation of use. This hypothesis is supported by the follow-up study of Buchert and colleagues [94], which showed that SERT increased in subjects who decreased their MDMA use. In addition, several studies showed a correlation between SERT and duration of abstinence, also supporting that the MDMA-associated decrease in SERT may be reversible with time.

### Table 2: Comparison of studies measuring the serotonin transporter in MDMA abuse

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Extent of use (MDMA users)</th>
<th>Abstinence</th>
<th>SERT binding</th>
<th>Correlation of radiotracer binding with MDMA use</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCann et al, [74] PET (+/−)</td>
<td>[11C]McN5652</td>
<td>14 (9 M/5 F) current users; 15 MDMA naïve (9 M/6 F)</td>
<td>&gt;50 tablets</td>
<td>19 weeks (range, 3–147)</td>
<td>Decreased in all brain regions studied (including midbrain) in males and females</td>
</tr>
<tr>
<td>Buchert et al, [93] PET</td>
<td>[11C]McN5652</td>
<td>30 current users, 29 ex-users, 29 MDMA naïve drug users, and 29 drug naïve control subjects</td>
<td>&gt;50 tablets</td>
<td>4–60 days (MDMA users), 1.4 years ex-users</td>
<td>Decreased in midbrain, thalamus, and cortical regions</td>
</tr>
<tr>
<td>Semple et al, [89] SPECT</td>
<td>[123I]beta-CIT</td>
<td>MDMA: 10 (10 M) HC: 10 (10 M)</td>
<td>&gt;50 tablets,</td>
<td>18±8 days</td>
<td>Significant decrease in some posterior cortical regions; no difference in midbrain.</td>
</tr>
<tr>
<td>Reneman et al, [88] SPECT</td>
<td>[123I]beta-CIT</td>
<td>Heavy users:</td>
<td>Heavy: &gt;50 tablets</td>
<td>21 days</td>
<td>Decreased in female heavy users only (midbrain and cortical regions); no difference in other groups</td>
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<tr>
<td></td>
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<td>Light: &lt;50 tablets Ex: &gt;50 tablets, but not in the last year</td>
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<td>23 (12M/11F)</td>
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<td></td>
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<td>Moderate users:</td>
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<td>15 (9M/6F)</td>
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<td></td>
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<td>Ex-users: 16 (8M/8F)</td>
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<td></td>
<td></td>
<td>HC: 15 (7M/8F)</td>
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</tbody>
</table>

**Abbreviations:** F, female; M, male; MDMA, methylenedioxymethamphetamine; SERT, serotonin transporter.
Although MDMA also affects the dopamine transmission, only two studies have looked at dopamine transmission and both measured the dopamine transporter. Reneman and colleagues [95] used 123I-beta-CIT to measure striatal DAT in MDMA abusers who used the drug alone and MDMA users who also used amphetamine. DAT binding was lower in the MDMA-amphetamine group relative to control subjects but higher in the MDMA-only group compared with the control subjects. Using the same radiotracer, Semple and colleagues [89] showed no differences in DAT binding between MDMA users and control subjects in the striatum.

**Hallucinogens**

There is a paucity of literature investigating alterations in neurochemistry in hallucinogen abusers. One study used the PET radiotracer 11C-NNC 112 to measure D1 receptor BP in chronic ketamine users and reported a 25% increase in D1 receptor availability in the dorsolateral prefrontal cortex compared with healthy control subjects [96]. No significant differences were seen in other cortical regions or the striatum. In addition, the increase in D1 receptor BP correlated with the number of vials of ketamine used per week. This finding is consistent with the animal literature suggesting that repeated exposure to N-methyl-D-aspartic acid (NMDA) antagonists leads to reduced prefrontal dopaminergic function and a compensatory upregulation of the D1 receptor, which is the main dopaminergic receptor in the cortex [97]. Because decreased dopamine transmission in the dorsolateral prefrontal cortex is associated with deficits in working memory and executive function, neurocognitive function was examined in these subjects. No difference was seen in tests of working memory and executive function between the ketamine users and healthy control subjects, and no correlation was seen with D1 receptor BP.

**Summary**

There is convergence from multiple lines of evidence that addiction is associated with low D2/3 transmission in the striatum, including reduced D2/3 receptors, dopamine release, and dopamine synthesis, all in the presence of normal DAT, and furthermore that this decrease may predominantly affect the ventral striatum. This trait seems to be common to multiple drugs of abuse but has been most extensively studied and documented thus far for cocaine and alcohol. Low dopamine transmission stems from presynaptic and postsynaptic factors, is present in the chronic stages of addiction, has been observed during abstinence, and may represent a mixture of vulnerability and toxicity factors, although more research is needed to better characterize the relative contribution of these variables to the development of addiction.

Methamphetamine use has been consistently associated with low DAT levels in the striatum that seem to be long-lasting, suggesting an additional component of neurotoxicity that may not be shared with other drugs of abuse. Alternatively, although ecstasy use may be associated with low SERT in different brain regions, this decrease may be reversible with cessation of use.

Imaging of other neurotransmitter systems, such as the GABA, serotonergic, and opiate systems, has contributed some interesting insights into the pathophysiology of alcohol abuse and dependence but has not yet yielded a consistent picture.

Finally, preclinical research has suggested a prominent role for the glutamatergic system in the establishment of compulsive addictive behaviors by strengthening certain frontostriatal synapses that may underlie the perseverative aspects of drug-taking behaviors. No tracers are available at this point to explore this system in the human brain, and much progress in ligand development is needed to provide the tools necessary for such investigations. In addition, some drugs of abuse have not been studied with radioligand PET imaging, such as marijuana, prescription drugs, inhalants, and most of the hallucinogens. So although much work has been done, we are at the beginning of an exciting phase in the field in which exponential progress will be made with the availability of a wider range of radiotracers for different molecular targets implicated in addiction. We need to better understand the pathophysiology and the longitudinal course of addiction, with studies targeting different phases of addiction taking into account particular genetic risk factors to develop better preventive and therapeutic interventions.

**References**


[60] Lingford-Hughes AR, Acton PD, Gacinovic S, et al. Reduced levels of GABA-benzodiazepine receptor in alcohol dependency in the absence


