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PET Studies in Nonhuman Primate Models of Cocaine Abuse: Translational Research Related to Vulnerability and Neuroadaptations

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Abstract

The current review highlights the utility of positron emission tomography (PET) imaging to study the neurobiological substrates underlying vulnerability to cocaine addiction and subsequent adaptations following chronic cocaine self-administration in nonhuman primate models of cocaine abuse. Environmental (e.g., social rank) and sex-specific influences on dopaminergic function and sensitivity to the reinforcing effects of cocaine are discussed. Cocaine-related cognitive deficits have been hypothesized to contribute to high rates of relapse and are described in nonhuman primate models. Lastly, the long-term consequences of cocaine on neurobiology are discussed. PET imaging and longitudinal, within-subject behavioral studies in nonhuman primates have provided a strong framework for designing pharmacological and behavioral treatment strategies to aid drug-dependent treatment seekers. Non-invasive PET imaging will allow for individualized treatment strategies. Recent advances in radiochemistry of novel PET ligands and other imaging modalities can further advance our understanding of stimulant use on the brain.

Keywords

animal models; dopamine; D2-like receptors; sex differences; PET imaging; nonhuman primates

1. Introduction

Drug abuse and dependence continue to be a problem worldwide. Recent estimates report between ~4–6% of the population surveyed (155–250 million people worldwide) between

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the ages of 15–64 used some illicit substance in 2008 (UNODC, 2010). In the United States alone, nearly 22 million people reported drug use, of which ~1.6 million were cocaine users (SAMHSA, 2010). In Europe, the number of reported cocaine users doubled in the last decade (UNODC, 2010). Despite significant advances in our understanding of the effects of drugs at a molecular, cellular and behavioral level, successful strategies for treating addiction including stimulants such as cocaine, remain elusive. The goal of the current review is to describe the utility of positron emission tomography (PET) imaging as an *in vivo* research technique to provide a greater understanding of the effects of cocaine on the central nervous system and environmental, physiological, and pharmacological factors that influence drug-related effects in nonhuman primate (NHP) models of addiction. Subsequent sections will highlight recent studies using PET and cocaine self-administration (SA) to examine sex-specific differences and executive function, two areas of research that may lead to novel pharmacotherapeutic approaches to treat addiction.

1.1. Animal models of cocaine abuse

By utilizing animals to model aspects of human addiction, researchers can control for factors that may confound examination of drug-related effects including stress, history and nutrition. Further, baseline assessments prior to drug exposure allow for examination of factors that may influence vulnerability to addiction, an otherwise unethical assessment in humans. For example, as described below, stress and fluctuations in ovarian hormone concentrations affect PET measures of dopamine (DA) D2-like receptor availability and are related to differences in sensitivity to the reinforcing effects of cocaine (Morgan et al., 2002; Riddick et al., 2009; Nader et al., 2012b).

The animal studies described in this review will focus on NHP research conducted in rhesus (*Macaca mulatta*) and cynomolgus (*M. fascicularis*) macaques. Old World macaques and baboons are the closest relatives of humans approved for invasive biomedical research in the United States. Macaques have similar developmental and aging processes, neurotransmitter distribution and neurocircuitry as humans (Berger et al., 1991; Joel and Weiner, 2000; see Weerts et al., 2007 for review). Thus, NHPs provide excellent models to understand the direct effects of drugs administered *in utero*, during early development, adolescence or adulthood, or how drug exposure at one developmental stage influences subsequent neurobiology and behavioral outcomes at a later stage. In addition, compared to rodents, NHPs demonstrate similar drug biodistribution, pharmacokinetic and pharmacodynamic profiles to humans (e.g., Lyons et al., 1996; Roberts et al., 1999; Lile et al., 2003). NHPs can learn complex behavioral tasks and can be studied within a laboratory setting for decades providing an excellent organism for within-subject assessment and longitudinal study designs.

Pharmacological studies in monkeys can be designed to answer a number of questions. Drugs can be administered non-contingently (e.g., by the experimenter) to provide measures of drug-receptor interactions and can result in profound neurobiological adaptations. However, a more translatable model to the human condition is drug SA such that drug delivery is contingent upon a behavioral response emitted by the animal. Drug SA models provide information relative to organism-environment interactions that may directly

influence subsequent drug-related behaviors or influence executive function such as learning, memory, or aspects of impulsivity that may indirectly influence drug-related behaviors. Numerous studies have shown distinct differences in both acute and chronic effects of a drug on neurochemistry or neurobiology dependent on contingent versus non-contingent administration (Dworkin et al., 1995; Bradberry, 2000; Galici et al., 2000; Lecca et al., 2007; Howell et al., 2010). Similar to the human condition, SA paradigms allow animals to titrate rate and total intake individually in contrast to non-contingent experimenter administered drugs that might affect neurobiology differently based on individual sensitivity to reinforcing and aversive effects of a drug.

Drug SA studies have been incorporated for decades to examine the reinforcing effects of compounds and to examine effects of putative pharmacotherapies on established SA (e.g., Johanson and Fischman, 1989; Woolverton and Nader, 1990; Mello and Negus, 1996). Further, chronic drug SA in monkeys produces neurobiological effects that parallel those reported in human drug users including metabolic, structural and functional CNS alterations (e.g., cocaine: Strickland et al., 1993; Volkow et al., 1993; Lyons et al., 1996; Beveridge et al., 2006). In these respects, drug SA studies have strong predictive and construct validity to human drug addiction. This review discusses the use of SA procedures as a model to examine the relationship of cocaine to sex-specific differences in neurobiology and cognition. As described below, the use of *in vivo* imaging allows for individualized treatment strategies.

1.2. CNS targets for positron emission tomography (PET) imaging

PET is an *in vivo* neuroimaging technique that involves injection of a radioactive isotope, typically ^{18}-Fluorine, ^{11}-Carbon or ^{15}-Oxygen (^{18}F, ^{11}C, ^{15}O, respectively) attached to a known molecule of interest. Once injected into an organism, the radioactive decay of the isotope is recorded over time and the location or amount of radiation can be quantified to determine where and to what extent the molecule of interest is interacting within the CNS in a non-invasive manner (see Kegeles and Mann, 1997 for review). Depending on the relative efficacy and affinity of the radiolabeled molecule, PET imaging can be used to identify receptor distribution, ligand-receptor interactions, pharmacokinetics and pharmacodynamics related to a labeled drug or indirectly assess neuronal function via measures of glucose utilization or blood flow. Although we will focus on PET imaging, some molecular imaging studies described in this review utilize single photon emission tomography (SPECT). SPECT is similar to PET because it uses radiotracers labeled to molecules of interest. However, unlike PET in which two photons are emitted (and in opposite directions), SPECT tracers emit a single photon and, consequently, have lower resolution.

One utility of PET imaging is to examine protein expression, notably neurotransmitter receptor availability or changes in availability following an environmental or pharmacologic manipulation. Although cocaine binds with near equal affinity to DA, serotonin (5-HT), and norepinephrine (NE) transporters (DAT, SERT, NET, respectively; Ritz and Kuhar, 1989; Bennett et al., 1995) acutely elevating synaptic concentrations of all three monoamines, the reinforcing effects of cocaine are attributed primarily to elevated synaptic DA levels (e.g., Di Chiara and Imperato, 1988; Bradberry et al., 1993; Florin et al., 1994). Therefore, a

predominant focus of PET imaging has involved the DA system. Dopamine pathways implicated in addiction project from cell bodies in the midbrain, primarily the ventral tegmental area (VTA) to various limbic and cortical brain regions. These mesocorticolimbic pathways innervate extended limbic structures including the striatum (caudate-putamen), amygdala and hippocampus, and cortical structures including the prefrontal cortex and cingulate gyrus mediating actions related to reinforcement, emotion, and executive function (see Beaulieu and Gainetdinov, 2011 for review). Dopamine receptors located pre- and/or post-synaptically on DA neurons are distinguished by their ability to stimulate (D1-like receptors) and inhibit (D2-like receptors) adenylyl cyclase activity. Following release, DA is removed from the synapse through the DAT where it can be repackaged in vesicles by vesicular monoamine transporters (VMAT) or degraded by catechol-O-methyltransferase or monoamine oxidase (COMT and MOA; for reviews of the DA system see Vallone et al., 2000; Beaulieu and Gainetdinov, 2011). PET radiotracers targeting D1- and D2-like receptors, DAT, VMAT, and COMT have been examined in NHP models of addiction (Murnane and Howell, 2011; for an extensive list of radioligands and their targets see Howell and Murnane, 2011). A list of radioligands described in this review is provided in Table 1.

When discussing treatment strategies, drugs can either directly affect the DA system or indirectly through a multitude of neurotransmitters. For example, elevating GABA neurotransmission can decrease concentrations of extracellular DA (e.g., Dewey et al., 1992), while elevating glutamate can potentiate some of the behavioral effects of cocaine (see Kalivas and Volkow, 2011). These other neurotransmitter systems can be targeted in imaging studies in order to identify treatments that do not directly affect DA. Because we discuss cocaine-induced changes in cognition (Section 3.0), it is worth briefly highlighting the interactions between acetylcholine (ACh) and DA neurotransmitter systems (see Williams and Adinoff, 2008). There are two primary ACh projection pathways within the CNS. Cell bodies in the basal forebrain project to the amygdala, hippocampus and cortex and have been implicated in various aspects of cognition including attention and memory (for review see Perry et al., 1999; Williams and Adinoff, 2008). As it relates to the DA system, ACh neurons project from the mesopontine nuclei in the midbrain and synapse on DA neurons within the thalamus, ventral tegmental area (VTA) and substantia nigra. In addition, there are ACh interneurons in the striatum that synapse on striatal DA dendrites (see Exley and Cragg, 2008 for review). Nicotinic ACh receptors are ligand-gated cation channels whereas muscarinic ACh receptors are G-protein coupled receptors (see Dajas-Bailador and Wonnacott, 2004, Williams and Adinoff, 2008 for reviews). As a result of their location on DA, GABA and glutamate nerve terminals, nicotinic AChRs can directly influence neuronal excitability and subsequent neurotransmitter release (e.g., Jones et al., 2001; Zhou et al., 2001; Rice and Cragg, 2004).

In baboons, ^{11}C-labeled cocaine was visualized in striatal brain regions of dense DAT distribution. Administration of non-labeled cocaine and other DAT but not NET or SERT blockers prior to PET imaging with [^{11}C]-cocaine reduced striatal binding (Fowler et al., 1989). This seminal study demonstrated the binding site of cocaine *in vivo*, and the pharmacokinetic principles including competition and displacement of the radioligand at the

target receptors that can influence PET imaging studies. Further studies in rhesus monkeys showed an orderly association between receptor displacement in the basal ganglia measured with [^{18}F]-fluoroclebopride ([^{18}F]FCP), a D2-like receptor ligand, and the percent increase in basal DA release following non-contingent administration of various psychostimulants (Mach et al., 1997). These studies reinforce the use of PET imaging as a non-invasive method to assess the neurochemical milieu in the brain and highlight one important caveat when interpreting PET data. Radioligand binding to receptors *in vivo* is dependent on both the number of receptors available and the levels of endogenous substrates competing to bind at those receptors. Therefore, PET imaging assessment of receptor "binding" is more accurately termed receptor "availability" or "binding potential". It is important to keep in mind that the primary dependent variable from PET studies, binding potential or distribution volume ratios, is not the same as measuring receptor density, as is done with *in vitro* receptor autoradiography studies, although some studies have incorporated both techniques in similar animal models of cocaine abuse. For example, in monkeys with a cocaine SA history, lower D2-like receptor availability as determined with PET imaging has been shown to be associated with lower D2-like receptor densities confirmed by *in vitro* receptor autoradiography suggesting a strong association between receptor availability and receptor density (Moore et al., 1998; Nader et al., 2002, 2006). Although PET cannot definitively assess receptor number *in vivo*, it can provide a neurochemical correlate to behavioral assessments. An inverse relationship between the peak uptake of various [^{11}C]-labeled cocaine analogs and the reinforcing effects of these compounds (Kimmel et al., 2008) supports the use of preclinical models of addiction and ligand-based PET imaging as tools to aid in developing novel pharmacotherapies for cocaine abuse.

Another use for PET imaging is to examine changes in blood flow or metabolic activity as an indirect measure of neural activity. [^{18}F]fluorodeoxyglucose (FDG) can be used to examine metabolic rates of cerebral glucose utilization (MRglc). Glucose is delivered to cells in the brain through glucose transporters to maintain or restore chemical gradients. FDG, a glucose analog, competes with endogenous glucose at these receptors, as well as glucose metabolism (Sokoloff et al., 1977). [^{18}F]FDG-PET imaging can be used to compare MRglc between two conditions, typically a baseline condition and a variable of interest such as a specific behavior (e.g. cognitive task, stressor), pharmacological challenge, or consequence of subsequent behaviors (e.g., chronic cocaine SA, diet). Clinically, [^{18}F]FDG-PET studies provide a marker for disease progression such as in Parkinson's or Alzheimer's patients (e.g., Borghammer et al., 2010; Pappata et al., 2011) and this strategy can be employed in NHP PET studies of cocaine abuse.

In this review, we focus on translational research – what animal imaging studies inform us about the human condition of drug addiction. Most NHP imaging studies involve anesthetized monkeys, while most human imaging studies do not involve anesthesia. Howell et al. (2001, 2002) have described the methodology necessary for imaging awake monkeys. Depending on the research question, it is possible to compare PET imaging data from anesthetized monkeys to studies in conscious humans (see Nader and Czoty, 2008). For example, researchers interested in how receptor availability correlates with behavior or changes following some event (e.g., chronic drug treatment, social environmental changes,

etc.) can determine these relationships without the monkey being awake – and the data, as described in this review, appears quite orderly between monkeys and humans (e.g., Nader et al., 2006 and Volkow et al., 1993; Morgan et al., 2002 and Martinez et al., 2010).

2. Sex Differences

The influence of sex differences on the neurobiological and behavioral effects of cocaine has not been fully explored. Despite similar patterns of use (Griffin et al., 1989; Boyd and Mieczkowski, 1990), studies have reported important differences between men and women cocaine users. While more men report illicit drug abuse and dependence (Brady and Randall, 1999), women differ on several aspects of cocaine abuse, including severity. There is a higher prevalence of women dependent on cocaine during adolescence compared to men (Kandel et al., 1997), women enter treatment at an earlier age than men (Griffin et al., 1989) and report greater stimulant use (Pope et al., 2011) upon entering treatment compared to men (Kosten et al., 1993). Women report the onset of comorbid psychiatric disorders (e.g., depression) before the onset of cocaine abuse, while men report the opposite (Griffin et al., 1989; Brady and Randall, 1999). In addition, following drug dependence treatment, men improve on measures of comorbid psychiatric disorders at a faster rate than women (Griffin et al., 1989; Brady and Randall, 1999). However, women may make better use of treatment, as measured by 6-month follow-up interviews (Kosten et al., 1993). These studies suggest women may be more sensitive to the effects of cocaine and may progress to cocaine dependence faster than men, an effect that has been referred to as a “telescoping” effect (Griffin et al., 1989; Brady and Randall, 1999; Becker and Hu, 2008). Taken together, there is a need to better understand sex differences in drug abuse and treatment.

2.1 Nonhuman primates as a model for sex differences

Despite the significant differences between men and women in several aspects of cocaine abuse and dependence, women have not been traditionally included in drug abuse research. A thorough examination of the interactions of gonadal hormones and menstrual cycle phase on the neurobiological effects of cocaine in women is difficult. For example, a within-subjects design investigating the effects of menstrual cycle phase in cocaine abusers may require an extended stay in a residential unit, which can have implications for both retention and cost. As discussed in the previous section, NHPs are excellent models to study the behavioral (e.g., self-administration) and neurobiological (e.g., PET imaging) effects of drugs of abuse. In addition, macaques, including rhesus and cynomolgus, exhibit a remarkably similar menstrual cycle and gestational period to that of humans. Similar to women, female macaques have a 28-day menstrual cycle with distinct follicular and luteal phases, and have similar fluctuations in estrogen and progesterone across menstrual cycle phases (Jewett and Dukelow, 1972; Goodman et al., 1977; Appt, 2004).

In general, many of the sex differences reported in studies of cocaine abuse have been observed using animal models (e.g., Becker and Hu, 2008; Carroll and Anker, 2010) and gonadal hormones have been implicated in mediating these effects. Two general approaches have been applied in research focusing on the effects of gonadal hormones on stimulant abuse in laboratory studies: 1) investigation of the effects of different menstrual cycle phases on aspects of drug abuse (e.g., acquisition, maintenance, efficacy), and 2) examination of the

effects of direct administration of different hormones (e.g., estrogen, progesterone, testosterone) on behavior.

As with cocaine, estrogen can affect DA neurotransmission (Thilbin et al., 1999; Becker et al., 2001). The effects of estrogen and estradiol on cocaine reinforcement have been mixed in rodent studies, and did not increase cocaine SA in female NHPs (Mello et al., 2008). Studies in humans also have been mixed. Estradiol did not consistently enhance the subjective or physiological effects of cocaine in women across menstrual cycle phase compared to men (Mendelson et al., 1999; Collins et al., 2007). However, in women the subjective responses to cocaine seem to vary across menstrual cycle phase. In the majority of studies, women report more positive subjective ratings of cocaine during the follicular phase, when estrogen and progesterone levels are low, compared to the luteal phase, when estrogen and progesterone levels are high, irrespective of route of cocaine administration (Lukas et al., 1996; Sofuoglu et al., 1999; Evans and Foltin, 2006; for review see Terner and de Wit, 2006). Female NHPs self-administered significantly more cocaine and reached higher progressive-ratio break points, a measure of reinforcing strength, compared to males; however consistent changes in break points across menstrual cycle phase in females have not been observed (Mello et al., 2007). Differences in cocaine metabolism have not been found in women across menstrual cycle phase or in NHPs, suggesting that pharmacokinetics do not account for sex differences in cocaine reinforcement (Mendelson et al., 1999; Evans and Foltin 2004, 2010).

Other possible mechanisms for differences in sensitivity to cocaine observed between males and females and across female menstrual cycle involve concentrations of progesterone and testosterone. Progesterone administration to women in the follicular phase decreased the positive subjective effects ratings of cocaine (Sufuoglu et al., 2002; Evans, 2007; Evans and Foltin, 2010). Similarly, progesterone administration decreased cocaine SA in female NHPs and rodents, but did not attenuate the discriminative stimulus effects of cocaine (Jackson et al., 2006; Mello et al., 2011). Progesterone levels are decreased in the follicular phase when the reinforcing effects of cocaine may be highest, suggesting progesterone may play a role in blunting the effects of cocaine. Less is known about the role of testosterone in cocaine reinforcement in males and females; however, preclinical literature suggest it may decrease the reinforcing effects of cocaine, observed as decreased cocaine sensitization in male rats and decreased cocaine SA in female NHPs (Chen et al., 2003; Mello et al., 2011). Taken together, fluctuations in gonadal hormones during menstrual cycle phase likely contribute to sex differences in the effects of cocaine.

2.2 Use of PET imaging techniques in sex differences

In addition to the research methods discussed above, PET imaging techniques are powerful tools to further investigate the interaction of sex and cocaine abuse with regards to neurobiology. The DA system has been strongly implicated in stimulant abuse and can be influenced by gonadal hormones. The two most commonly utilized imaging targets of the DA system are the DAT and the D2-like receptor superfamily, which consists of three receptor subtypes, D_2, D_3 and D_4 receptors (Sibley et al., 1993). Less research has been done with the DAT compared to the D2-like receptor. Staley et al. (2001) used SPECT

imaging and [^{123}I]β-CIT to measure DAT availability in men and women, some of whom were also cigarette smokers. These investigators did not find any significant effects due to smoking, but they did report sex differences, with higher DAT availability in women compared to men in striatal brain regions (Staley et al., 2001). In another study using the same [^{123}I]β-CIT SPECT tracer,Best et al. (2005) did not find significant effects of menstrual cycle phase on DAT availability in 10 women (age range was 18–40 years). Thus, it appears that there are sex differences in DAT availability, but these differences are not modified by fluctuations in estrogen and progesterone.

A reasonable question would be “what are the functional consequences of sex differences in DAT availability?” One possible answer can be gathered from an imaging technique that assesses synaptic neurotransmission by studying post-synaptic displacement of a PET tracer by administration of indirect DA agonists (Laruelle, 2000).Riccardi et al. (2006) conducted PET studies in six women and seven men using [^{18}F]fallypride, a D2-like receptor ligand. To study DA neurotransmission, the investigators also administered *d*-amphetamine (p.o.), which interacts with the DAT and elevates extracellular DA concentrations, 3 hrs prior the PET study. The increases in extracellular DA compete with [^{18}F]fallypride for D2-like receptors, and the displacement provides an index of DA neurotransmission (Laruelle, 2000). Riccardi et al. (2006) found that *d*-amphetamine resulted in greater DA release in women than men in several cortical brain regions, while men showed greater increases in the dorsal striatum. In both men and women, there was evidence of negative correlations between *d*-amphetamine-induced DA release and sensation seeking, as well as correlations between DA measures and spatial working memory. The investigators concluded that the observed sex differences are likely due to gonadal hormone modulation of central DA neurotransmission.

As it relates to the DA neurotransmitter system, much imaging research has focused on DA D2-like receptors and addiction (Nader and Czoty, 2005, 2008; Gould et al., 2012b), but this has primarily involved male subjects. With regards to the study of sex differences, the first question that should be addressed is how D2-like receptor availability changes with phases of the menstrual cycle. Three human studies have investigated the effects of menstrual cycle phase and D2-like receptor availability in humans with differing results. Nordstrom and colleagues (1998) used [^{11}C]raclopride in five healthy women and found no differences in D2-like receptor binding in the putamen between the luteal and follicular phases. However, Wong et al. (1988) reported decreased striatal uptake of 3-N-[^{11}C]-methylspiperone, a D2-like receptor ligand, in the follicular phase compared to the luteal phase. This pattern indicates that women in the follicular phase either had low D2-like receptor availability or increased DA levels in the striatal regions (see below for further discussion). In contrast to these findings, a third study, also using [^{11}C]raclopride, reported decreased D2-like receptor availability in the putamen during the luteal phase compared to the follicular phase (Munro et al., 2006). These results suggest that menstrual cycle phase may affect D2-like receptor availability (in 2 of 3 studies there were significant effects, but in opposite directions).

These equivocal findings with regard to menstrual cycle phase and D2-like receptor availability may not be surprising if one considers the individual differences in the subject population (e.g., drug history, stress, etc.) which would support the use of animal models to

better understand the role of menstrual cycle and D2-like receptor availability. As mentioned above, female macaques have an approximate 28-day menstrual cycle, so these monkeys are an ideal species for addressing this question. In experimentally naïve female cynomolgus monkeys, D2-like receptor availability, as measured with [^{18}]FCP, varied across menstrual cycle phase (Czoty et al., 2009). For this within-subjects design study, seven monkeys were scanned twice, once in follicular and once in the luteal phase (counterbalanced across monkeys). D2-like receptor availability was significantly lower in the follicular phase compared to the luteal phase. These findings are in line with reports of increased reinforcing effects of cocaine during the follicular phase, when D2-like receptor availability may be low (Lukas et al., 1996; Suofoglu et al., 1999; Evans et al., 2002; Evans and Foltin, 2006). The results with PET imaging of the DAT and the D2-like receptor support the use of experimental designs that monitor menstrual cycle phase in studies involving females.

As it relates to sex differences in D2-like receptor availability and vulnerability to drug abuse, D2-like receptor availability appears to be inversely related to the reinforcing effects of psychostimulants in males. That is, in men, male monkeys and male rodents, lower D2-like receptor availability is associated with greater reinforcing effects of psychostimulants (Volkow et al., 1999; Morgan et al., 2002; Nader et al., 2006; Dalley et al., 2007). This finding has been well documented in male monkeys. For example, using [^{18}F]FCP,Nader et al. (2006) reported an inverse relationship between baseline D2-like receptor availability and rates of cocaine SA in individually housed male rhesus monkeys.Morgan et al. (2002) manipulated baseline D2-like receptor measures prior to studying cocaine SA and found a similar inverse relationship. In that study, baseline PET scans were conducted in 20 individually housed male cynomolgus monkeys. Next, the monkeys were randomly assigned to social groups of 4 monkeys per pen and then re-scanned with [^{18}F]FCP after 3 months of social housing. Males that became dominant showed an approximate 20% increase in D2-like receptor availability, while subordinate monkeys' D2-like receptor measures did not change (Morgan et al., 2002). When cocaine was made available, subordinate monkeys, with the lower D2-like receptor measures, self-administered cocaine at significantly higher rates and had greater intakes compared to dominant monkeys.

The interaction between D2-like receptors and stimulant abuse in females is less clear. For example, in theMartinez et al. (2004) study in which they reported lower D2-like receptor availability in cocaine abusers compared to controls, women were included with men (for both groups, the controls and the cocaine abusers consisted of 13 males and 4 females); these numbers did not allow for statistical comparisons related to gender differences. In a recent study,Nader et al. (2012b) replicated theMorgan et al. (2002) study using female cynomolgus monkeys. An A-B-A design was employed in which female monkeys were first scanned with [^{18}F]FCP while individually housed, again after social housing and a third time when returned to individual housing (to determine the plasticity of the D2-like receptor measures). As was seen in males, when female monkeys became dominant they showed an approximate 20% increase in D2-like receptor availability, which returned to baseline when the monkeys were again individually housed (Nader et al., 2012b). Interestingly, when cocaine was made available for SA, it was the dominant females (those with the higher D2-like receptor availability) that were more vulnerable to cocaine compared to the subordinate

females. These findings suggest sex differences in D2-like receptor function associated with sensitivity to cocaine reinforcement.

As described in more detail below, a history of cocaine SA resulted in lower D2-like receptor availability in males (Volkow et al., 1999; Martinez et al., 2004; Nader et al., 2006). These effects appear quite orderly –males with low D2-like receptor measures are more vulnerable to cocaine reinforcement and a history of cocaine use further decreases D2-like receptor availability. It is not yet clear how cocaine SA will influence D2-like receptor availability in females. A recent study in male and female smokers (Brown et al., 2012) examined sex differences in D2-like receptor availability using [^{18}F]fallypride. In women, there were no differences in D2-like receptor availability in the caudate nucleus and putamen between smokers and non-smokers, suggesting that a history of chronic stimulant use (in this case nicotine) did not affect D2-like receptor measures in women. In contrast, male smokers had significantly lower D2-like receptor availability in striatal regions compared to male non-smokers and compared to female smokers. These findings suggest sex differences in D2-like receptor function following chronic drug exposure. One limitation of the above study was the acknowledged lack of control for menstrual cycle phase. The use of animal models, beginning with drug-naïve subjects and studying receptor availability over the course of chronic drug exposure and abstinence while controlling for menstrual cycle phase, will provide valuable information as to how D2-like receptor availability in females change with repeated drug use.

In addition to the reinforcing effects of cocaine, imaging techniques can be used to investigate the effects of sex differences on cue-induced craving. Compared to men, women may be more sensitive to cocaine-induced craving in a laboratory setting (Robbins et al., 1999; Elman et al., 2001; but see Avants et al., 1995). Using PET and [^{18}F]-FDG, women cocaine abusers in the follicular phase had greater brain reactivity to cocaine-related cues compared to their male counterparts, but did not report increased subjective ratings of craving (Volkow et al., 2011). Healthy women without drug use had an augmented reactivity to reward in the follicular phase compared to the luteal phase, as measured by event-related fMRI scans investigating brain regions thought to be involved in reward (Dreher et al., 2007).Wong et al. (2006) examined the ability of cocaine-related cues to displace [^{11}C]raclopride from D2-like receptors. The research strategy is similar to what was described earlier using indirect DA agonists to displace post-synaptic D2-like radiotracers except environmental cues are used to elicit DA release.Wong et al. (2006) found that environmental cues associated with cocaine use displaced [^{11}C]raclopride from D2-like receptors. Unfortunately, of the 19 subjects examined, 16 were male and only 3 were female, so the sample size was insufficient to assess sex differences. Volkow and colleagues (1997) examined the ability of methylphenidate to decrease [^{11}C]raclopride binding potential in cocaine abusers (n=20) and controls (n=23) – all males. The investigators reported larger effects in controls compared to cocaine abusers, suggesting a hypodopaminergic state. Future studies should extend these results to systematically examine how males and females respond to cocaine-associated environmental cues. Such information will be critical for developing individualized treatment strategies for cocaine addiction.

3. Cocaine and Cognition

One consistent consequence of cocaine abuse and a factor that may affect treatment outcome is drug-associated disruption of executive function. Broadly defined, executive function includes all processes involved in learning, monitoring and adapting to stimuli to produce complex, goal-oriented behaviors. Delineated cognitive domains include 1) updating, monitoring and adapting to cues relevant to a current goal and discarding/suppressing irrelevant information, 2) shifting, the ability to redirect focus between multiple modalities or tasks, and 3) inhibition, the ability to suppress or withhold a preplanned or impulsive response (see Miyake et al., 2000; Beveridge et al., 2008 for review). Numerous cognitive tests are designed to probe specific subsets within each of these domains. Compared to control groups, chronic cocaine users show impaired cognitive performance across each of these cognitive domains, effects that extend into abstinence, influencing treatment and sensitivity to relapse (Fillmore and Rush, 2002; Bolla et al., 2004; Hester and Garavan, 2004; Goldstein et al., 2007, 2010; Woicik et al., 2009).

While not the main focus of the current review, several rodent studies have demonstrated significant cognitive disruptions following cocaine exposure (e.g., Schoenbaum et al., 2004; Briand et al., 2008; George et al., 2008). Surprisingly, despite similarities in neuroanatomy between human and NHPs and the numerous clinical studies demonstrating cognitive dysregulation in cocaine-experienced humans, few studies have examined the direct effects of cocaine on cognition in NHPs. Of these studies, the cognitive domains frequently assessed are associative learning (updating), measured via a simple discrimination task, behavioral flexibility (inhibition), measured via a reversal learning task, and measures of working memory (updating), assessed by either a delayed alternation task or delayed match-to-sample (DMS) task. Importantly, similar to human cocaine users, NHPs exposed to cocaine demonstrate marked impairments across each of these domains (Jentsch et al., 2002, Liu et al., 2008; Porter et al., 2011). One additional study validated a model of impulsivity, the stop signal reaction time task (SSRT) in a rhesus monkey model and reported increased impulsivity, as measured by long SSRT measures following 18 months of abstinence from cocaine SA (Liu et al., 2009). Recent studies in our laboratory have also shown impaired performance across tasks measuring each of the three subtypes of executive function, reversal learning, attentional set shifting, and working memory in monkeys with an ~5 year cocaine SA history compared to age-matched drug-naïve rhesus monkeys (Gould et al., 2012a). As described below, these cognitive impairments were associated with CNS changes, as assessed with PET imaging.

3.1 Dopaminergic regulation of executive function

Both D1- and D2-like DA receptors have been implicated in mediating executive function. However, the effects of DA modulation appear to be dependent on a number of variables including cognitive task, brain region examined, DA receptor subtype, and most notably basal DA function. For example, D1-like receptors in the PFC appear to be implicated in mediating tasks focused on goal-relevant stimuli such as working memory performance (for review see van Schouwenburg et al., 2010). In contrast, D2-like receptors may be more influential in mediating cognition relevant to updating and shifting tasks when there is

competition between task-relevant and irrelevant stimuli, possibly through which the striatum filters relevant from irrelevant information between cortical circuits (see van Schouwenburg et al., 2010; Cools, 2011).

In rodents, D2-like receptor binding in the striatum and hippocampus was directly correlated with accuracy in the radial-arm maze, an assessment of working memory (Levin et al., 1997). In monkeys, D2-like receptor availability was directly correlated with performance on a reversal-learning task measuring behavioral flexibility (Groman et al., 2011). In both studies, lower D2-like receptor availability was associated with poorer cognitive performance. Further, DAT binding in the striatum of humans correlated with functional changes in response to increasing cognitive demand in the frontal and posterior cortical areas (Tomasi et al., 2009). These examples, paired with studies from our laboratory demonstrating an inverse relationship between cocaine intake and D2-like receptor availability (e.g., Nader et al., 2006) support the notion that dysregulation within the DA system may be an underlying cause of cocaine-associated cognitive impairments. Thus, one avenue for therapeutic development is to explore mechanisms to increase DA function.

Effects of pharmacological agents on cognition are dependent on both baseline cognitive function and neurotransmitter tone. Often, equivocal results of DA modulation in human (and animal) studies are attributed to individual differences without an assessment of DA function. Cools and D'Esposito (2011) described the balance between DA function and working memory performance as an inverted-U-shaped curve such that at an optimal dopaminergic tone performance is most accurate, least likely to be enhanced, and most likely to be disrupted. In healthy individuals at the peak of this curve, either increases or decreases in DA function can inhibit cognitive performance through over-stimulation or DA depletion, respectively. The majority of clinical data showing cognitive-enhancing effects of DA modulation involve patients with Parkinson's Disease (PD) or ADHD and preclinical animal models of these conditions are associated with hypodopaminergic function (see van Schouwenburg et al., 2010). With regards to treatments for drug addiction, it would be hypothesized that the cognitive-enhancing effects of DA agonist administration would also occur for individuals with chronic cocaine histories because of the reported hypodopaminergic state.

3.2 Cognitive enhancement as a therapeutic strategy

Cocaine-related cognitive deficits extend into periods of abstinence (e.g., Volkow et al., 1992; Matochik et al., 2003; Tomasi et al., 2007; Hanlon et al. 2011) and are correlated with treatment retention and success (Aharonovich et al., 2006; Turner et al., 2009; Moeller et al., 2010). Therefore, improving CNS function and cognitive performance during addiction treatment may improve overall treatment success (for review, see Sofuoglu, 2010). For example, in one study that showed lower activity measured via fMRI, and poorer cognitive performance in cocaine users compared to controls, methylphenidate, an indirect DA agonist, increased activity in hypoactive brain regions, including the ACC, and improved cognitive performance in the cocaine-dependent individuals compared to control groups (Goldstein et al., 2010). In a PET study utilizing [^{18}F]FDG, Grant et al. (1996) reported increased glucose metabolism in cortical and limbic regions of cocaine abusers when

cocaine-related cues were presented. The authors concluded that mechanisms mediating memory are critical to understanding drug craving and future therapeutic interventions.

Given the longitudinal, within-subject assessment of cocaine SA and repeated PET imaging afforded by NHP research, rigorous and simultaneous assessments of cognition and underlying neurobiological changes will greatly extend our understanding of cognitive deficits associated with cocaine exposure. For example, PET studies in NHPs have been used to identify neurobiological correlates mediating cognitive behavior in much the same way that fMRI studies are conducted in humans. FDG-PET was utilized to identify brain regions associated with increases in glucose utilization, including the hippocampal region, dorsal striatum, and the dorsolateral prefrontal cortex, during a DMS task assessing working memory in NHPs (Porrino et al., 2005). In a related study, cocaine was substituted for juice as the reward during specific DMS trials and resulted in a dose-dependent decline in performance associated with increased activation in the dorsolateral PFC (Hampson et al., 2011). Recently, treatment with the GABA agonist baclofen reversed acute cocaine-induced deficits on a DMS task and alterations in PFC metabolic activity using FDG-PET (Porrino et al., 2012). Our laboratory has recently used FDG-PET to assess glucose utilization during shifting between different attentional sets in cocaine-naïve monkeys as well as monkeys with an extensive (~5 yr) cocaine SA history (Gould et al., 2012a). Importantly, similar to chronic cocaine users, the ability to shift between attentional sets was impaired and FDG-PET demonstrated markedly less activity in the hippocampus, prefrontal cortex, anterior cingulate cortex, and striatum, regions collectively involved in error-detection, reward, learning and memory (Gould et al., 2012a). These data show that cognitive deficits are similar in NHPs and humans following cocaine SA and that similar neurobiological sequelae underlie these cognitive deficits, providing an excellent model with face and construct validity to the human condition for testing putative therapeutic strategies, such as cognitive enhancement for addiction treatment (e.g. Sofuoglu, 2010).

4. Long-Term Consequences of Cocaine Exposure

It has been over two decades since the first reports using PET imaging and [^{18}F]FDG showed lower glucose utilization and [^{18}F]N-methylspiroperidol ([^{18}F]NMSP) showed lower DA D2-like receptor availability in human cocaine users compared to cocaine-naïve controls (London et al., 1990; Volkow et al., 1992, 1993). However, at that time the underlying causes were undetermined (genetic predisposition, environment, or direct pharmacological effects of cocaine) largely due to variables outside the scope of control in human retrospective studies. Further, brain changes are difficult to examine during extended periods of abstinence in humans due, in part, to the high rate of relapse within the first few months (e.g., Gawin and Kleber, 1985, 1986). Since then, numerous preclinical assessments involving PET and *in vitro* receptor autoradiography have characterized the consequences of accumulating cocaine intake and abstinence on the brain and evaluated potential treatment strategies including both environmental and pharmacological manipulations.

4.1 Dopaminergic system changes

The use of NHPs is particularly advantageous in modeling chronic drug use and relapse, two hallmark characteristics of addiction because monkeys can be used in intravenous drug SA

studies for many years, and can self-administer extremely high doses of drug. It is important to note that direct dose comparison is not the critical comparison – reinforcing doses in animals (rats or monkeys) are modeling human addiction. The fact that monkeys can be studied for years allows for examination of receptor changes over time and during abstinence, as well as the ability to study behavior and whether tolerance or sensitization occurs to some of the behavioral effects of cocaine (e.g., Nader et al., 2006). In addition, beginning with cocaine-naïve subjects allows for examination of trait variables associated with vulnerability to substance abuse. For example,Volkow et al. (1993) noted that cocaine abusers had lower D2-like receptor availability compared to controls, but hypothesized that this could be a predisposition rather than a consequence of cocaine use. To test the relationship between D2-like receptor availability and cocaine reinforcement, PET studies using [^{18}F]FCP were conducted in twelve cocaine-naïve rhesus monkeys prior to initiating cocaine SA (Nader et al., 2006). There was an inverse relationship between D2-like receptor availability and rates of responding maintained by cocaine injections. That is, monkeys with lower D2-like receptor measures at the start of the study, responded at higher rates than monkeys who began the experiment with higher measures of D2-like receptor availability. These animals were rescanned following 1-week, 3-, 6- and 12-months of cocaine SA. Following only 1 week of cocaine SA, D2-like receptor availability was reduced by 15–20%. Following 3 months of cocaine SA, maximal reductions in dopamine D2-like receptor availability were still reduced by 20% demonstrating that long-term cocaine SA produced robust decreases in D2-like receptor availability (Nader et al., 2006).

Thus, it appears that D2-like receptor availability is a trait variable associated with sensitivity to the reinforcing effects of drugs, with individuals having low D2-like measures being more vulnerable and that exposure to cocaine further decreases D2-like receptor levels, perhaps perpetuating drug use (Koob and Le Moal, 2000). Several questions can be asked of these animal models that will impact treatment strategies. (1) How “plastic” are these receptor changes? That is, will there be recovery during abstinence or are these changes long-lasting? (2) Related to this question is what accounts for the changes in D2-like receptor availability? Is it a down-regulation in D2-like receptor density, an increase in extracellular DA or both? And finally, (3) can environmental variables impact these measures, both in terms of sensitivity (i.e., vulnerability) and during maintenance?

Plasticity of D2-like receptor availability—In the Nader et al. (2006) study, monkeys were given access to cocaine and rescanned beginning one week after initiating cocaine SA. In this case, there was an approximate 15% reduction in D2 receptor availability. If these monkeys were not permitted to self-administer cocaine and rescanned after 1 week of abstinence, there was complete recovery of D2 receptor measures. Was this recovery due to D2 receptor densities first being down regulated by cocaine-induced increases in DA followed by recovery in receptor numbers or was the initial reduction measured with PET simply due to increases in extracellular DA? Using *in vitro* receptor autoradiography, Porrino and colleagues have determined that one week of cocaine SA, with intakes ranging between 4.5–50 mg/kg does not result in lower D2-like receptor densities compared to control monkeys (Nader et al., 2002). This suggests that the initial reductions in [^{18}F]FCP

availability and the subsequent recovery were not due to receptor changes, but more likely due to initial increases in extracellular DA (see below).

Assessment of cocaine-induced receptor availability made early in the cocaine SA history of the subjects are related more to vulnerability than to eventual treatment outcomes. The study of long-term cocaine use provides a better indication of treatment outcomes related to the molecular target under examination, in this case D2-like receptors. In the Volkow et al. (1993) study, lower D2-like binding potentials were reported in cocaine users following 3–4 months of abstinence compared to control subjects. Further assessment following extended abstinence was not possible due to relapse. In addition to examining the effects of long-term cocaine SA, the use of NHPs permits the study of abstinence beyond the 4 months reported in human cocaine abusers. In the same study described above (Nader et al., 2006), five monkeys self-administered cocaine for 1 year with similar response rates and cocaine intake (range 703–1011 mg/kg) and showed an ~20% reduction in D2-like receptor availability. Of these five, in three monkeys there was complete recovery of [^{18}F]FCP signal within 3 months of abstinence. Interestingly, there was no recovery of D2-like receptor availability following 1 year of abstinence in two monkeys. Consistent with the theme of this review, simply assessing total cocaine intake and assuming robust and consistent changes in DA receptor function leaves out individual differences and environmental context. As will be described in more detail below, environmental stimuli can also profoundly impact DA receptor function.

What are the effects of cocaine on extracellular DA concentrations?—Two groups of investigators have combined measures of *in vivo* extracellular DA with cocaine SA in NHPs. Bradberry (2000) trained four rhesus monkeys to self-administer cocaine under conditions described as “recreational”. For this study, monkeys responded under an FR schedule of reinforcement to deliver 0.5 mg/kg cocaine, followed by a 100-min timeout; monkeys could receive 2 injections per session. Bradberry (2000) reported that 0.5 mg/kg cocaine significantly elevated extracellular DA concentrations in the striatum and that the second injection resulted in smaller effects. That is, acute tolerance to cocaine-induced elevations in extracellular DA was observed with cocaine. Over 6 months of this modest exposure to cocaine even larger increases in cocaine-induced elevations in extracellular DA were observed. Howell’s group (Henry et al., 2009) began with cocaine-naïve rhesus monkeys and then exposed them first to limited-access (1 hr SA sessions) for 10 weeks followed by extended-access (4 hr SA sessions) conditions for 10 weeks of 0.1 mg/kg/injection cocaine. Microdialysis studies were conducted at the end of each phase. Limited-access conditions (i.e., 1 hr sessions) resulted in average intakes totaling 82 mg/kg, while extended access conditions (i.e., 4 hr sessions) resulted in average intakes of 245 mg/kg. Microdialysis studies involved cocaine-elicited increases in extracellular DA concentrations. Under both SA conditions, the effects of cocaine on DA concentrations were blunted by cocaine history; there was no difference between the two conditions. Thus, just as Bradberry (2000) reported with lower doses, tolerance develops to the effects of cocaine on extracellular DA concentrations.Henry et al. (2009) suggested that cocaine SA results in a hypodopaminergic condition.

The microdialysis results suggest that the cocaine-induced decreases in DA D2 receptor availability are not due to long-term elevations in extracellular DA concentrations competing with the PET radiotracer. In an attempt to better understand the dynamics of cocaine-induced changes in extracellular DA,Kimmel et al. (2012) used squirrel monkeys and combined PET imaging of the DAT with *in vivo* microdialysis studies. These investigators examined cocaine and three cocaine analogs and reported a lack of concordance between the kinetics of drug occupancy at the DAT and increases in extracellular DA concentrations. One possible reason involves D2 autoreceptor stimulation, which will affect the concentration of DA released. However, it is difficult to assess pre-synaptic D2 receptors from post-synaptic receptors. One method that may work is to conduct a PET study using a DAT ligand and challenge the subject with direct-acting D2-like receptor agonists, in a manner similar to *ex vivo* voltammetry studies to measure DAT function (Mateo et al., 2005). While DAT blockers have been administered to displace D2-like PET tracers (e.g., Mach et al., 1996), to our knowledge, studies using DAT tracers and administration of D2-like agonists to indirectly affect DAT availability have not been conducted. *In vitro* receptor autoradiography studies in monkeys with cocaine SA histories suggest that cocaine-induced changes in DAT and D2-like receptor densities vary in opposite directions (DAT increase: Letchworth et al., 2001; D2-like decrease: Moore et al., 1998). Clearly, there is much work to be done to better understand the dynamics between chronic cocaine exposure and the consequences on DA neurotransmission.

Environmental manipulations impacting D2-like receptor availability and DA concentrations—An interesting observation reported in theVolkow et al. (1993) study was that D2-like receptor binding potential was more closely associated with years of drug use and not the estimated total amount of cocaine used. This suggests that environmental variables can impact D2-like receptor availability. The use of different schedules of reinforcement allows for the study of “drug seeking” while keeping total cocaine intake low. For example, 1 month of cocaine SA under a fixed-interval (FI) 3-min schedule of reinforcement resulted in approximately 16% reduction in D2-like receptor availability (Nader et al., 2006). Was this due to cumulative cocaine intake, which in these monkeys averaged approximately 90 mg/kg or was it due to 1 month of engaging in behaviors leading to cocaine injections? To address this, cocaine-naïve rhesus monkeys were scanned with [^{18}F]FCP and then trained to self-administer cocaine under an FI 30-min schedule of 0.03 mg/kg cocaine; monkeys could receive 2 injections per session (Czoty et al., 2007). After 9 weeks of 5 days/week cocaine SA in which total cocaine intakes were < 5 mg/kg, D2-like receptor availability was not significantly different from baseline in any monkey.

The findings fromCzoty et al. (2007) suggest that the initial reductions in D2-like receptor availability are due to the pharmacology of cocaine, not to the behavior leading to cocaine injections. However, this should not imply that environmental variables do not impact current drug use. In fact, PET studies have nicely highlighted the importance of environmental stimuli on DA receptor function in models of drug abuse (e.g., Boileau et al., 2007). In one study (Schiffer et al., 2009), cocaine conditioned place preference (CPP) was established in male rats using 5.0 mg/kg cocaine. Once the CPP was established, each animal was subsequently injected with [^{11}C]raclopride and placed into either the cocaine- or

saline-associated compartment for 25 min and then scanned for an additional 25 min. [^{11}C]Raclopride binding potential was significantly lower when animals were in placed in the cocaine-associated compartment compared to the saline side, supporting the hypothesis that cues associated with cocaine elicited DA release.

4.2 Ex vivo assessments and other neurotransmitter systems

Similar to PET studies in recent cocaine users that showed lower glucose metabolism in the PFC compared to cocaine-naive control groups, and a correlation between low metabolic activity and D2-like receptor availability in the striatum (Volkow et al., 1993), NHP studies noted a similar relationship between D2-like receptor availability using PET and glucose metabolism in the PFC using a 2-[^{14}C]deoxyglucose (2DG) method and *in vitro* autoradiographic analysis (for reviews see Porrino et al., 2007 and Beveridge et al., 2008). Similar *ex vivo* assessment of glucose metabolism has also shown a progressive expansion of cocaine's effects on glucose utilization from reward-related limbic regions to cortical regions associated with inhibitory control and executive function over the course of 100 days of cocaine SA (for review see Beveridge et al., 2008). *In vivo* assessment using FDG-PET also showed a progressive involvement of limbic and cortical brain regions following acute and extended cocaine SA (Henry et al., 2010). Together, these studies support cocaine-related changes in brain regions underlying reward and cognition that may perpetuate drug use and hinder attempts at remaining abstinent.

Recent chemical and radiological advances have provided the drug addiction field with numerous opportunities to characterize other neurotransmitter receptor systems using PET. In female cynomolgus monkeys, DAT availability measured with [^{18}F]fluorobenzylchlorotropane ([18F]FCT; Nader et al., 2012b) was associated with reduced sensitivity to cocaine reinforcement. In male rhesus monkeys, however, DAT availability was not affected by acquisition of cocaine reinforcement (Czoty et al., 2007). SERT availability in rhesus monkeys measured with [^{11}C]-3-amino-4(2-dimethylamino-methyl-phenylsulfanyl)-benzonitrile ([^{11}C]DASB; Banks et al., 2008; Gould et al., 2011) and NET availability in humans measured with (S,S)-[^{11}C]O-methylreboxetine ([^{11}C]MRB; Ding et al., 2010) were greater in groups with a cocaine SA history compared to control groups. Together, these studies demonstrate cocaine-related differences across all three monoaminergic transporters, corroborating *ex vivo* assessments, and highlight the use of PET imaging to understand mechanisms of action mediating potential treatments.

PET imaging studies examining the effects of cocaine on other neurotransmitter systems may also aid pharmacotherapeutic development given the recent trend towards targeting neurotransmitter systems that indirectly affect the DA system (for review see Karila et al., 2008). For example, DA and acetylcholine systems are intimately linked (for review see Williams and Adinoff, 2008). In baboons, nicotinic acetylcholine receptor (nAChR) availability increased and decreased following D2-like receptor antagonist and agonist administration, respectively, assessed via PET and the ligand norchloro[^{18}F]fluroepibatidine ([^{18}F]NFEP; Ding et al., 2000). Given the strong influence of acetylcholine neurotransmission mediating reward and cognition, further examination of this neurotransmitter system is warranted. In fact, abstinent cocaine users showed a differential

effect of nicotinic or muscarinic agonist administration on cerebral blood flow compared to non-cocaine users as assessed via SPECT imaging, although the direct influence of cocaine on this measure was confounded by a history of nicotine use (Adinoff et al., 2010). Male rhesus monkeys with an ~5 year cocaine SA history were less sensitive to the effects of nAChR agonists across different cognitive assays, and showed higher nAChR availability using [^{11}C]-nicotine and PET (Gould et al., 2013). Novel radiotracers designed for specific nicotinic and muscarinic acetylcholine receptor subtypes (e.g. Muhkin et al., 2008, Yamamoto et al., 2011) are now available. For example, 2-[^{18}F]fluoro-A-8530 (2FA) and has been used in squirrel monkeys to show an inverse relationship between α4β2* nAChR availability and the reinforcing strength of nicotine (Le Foll et al., 2009), and has shown a greater α4β2*-nAChR distribution in smokers compared to non-smokers (Muhkin et al., 2008). A similar relationship may exist between α4β2* nAChR distribution and sensitivity to addiction, or similar changes following chronic use of other addictive substances such as cocaine, a hypothesis that has yet to be tested. Recently,Sawyer et al. (2012) examined changes in SERT and 5-HT2A receptor availability using [^{18}F]FEmZIENT and [^{11}C]M100907, respectively, in a NHP model of cocaine abuse, before and after treatment with an SSRI. They reported that chronic fluoxetine (an SSRI) treatment blunted cocaine-induced reinstatement; the potential mechanism of action, however, may be related more to 5-HT2A receptors than SERT. The investigators reported that chronic fluoxetine resulted in increases in 5-HT2A receptor binding potential, but had no effect on SERT availability. Lastly, strong evidence implicates the glutamatergic system in addiction (e.g., Chiamulera et al., 2001; Beveridge et al., 2011; see Kalivas and Volkow, 2011 for review). While PET tracers for various glutamatergic receptors are available and have been utilized in NHP Parkinsonian models (e.g., Sanchez-Peraulte et al., 2008), none to our knowledge have been applied to cocaine-related studies. Similar to advancements in our understanding of dopaminergic changes associated with cocaine SA, changes in other neurotransmitter systems and displacement studies would aid therapeutic development.

Advances specifically in ligand development for the DA system can be utilized to further our understanding of the chronic effects of cocaine. Dopamine D1- and D2-like superfamilies are subdivided into D_1 and D_5, and D_2, D_3, and D_4 receptors, respectively and are expressed in relatively different densities across cortical and limbic regions lending to differential pharmacological treatment strategies. The predominant ligands for the D2-like receptors (e.g., FCP, raclopride, fallypride) are antagonists and do not distinguish between high- (G-protein coupled) and low-affinity (G-protein uncoupled) receptors. Recently [^{11}C]N-propylnorapomorphine ([^{11}C]NPA), a radiolabeled agonist, was compared with [^{11}C]raclopride (Narandran et al., 2011). Although there were no differences in binding potentials between these two ligands in cocaine users compared to controls, suggesting no significant changes in the ratio of high to low affinity state receptors, this development helps to elucidate receptor-affinity status related to addiction (Narandran et al., 2011). More recent studies have involved newer tracers for both DA D1-like and D_3 receptors.Martinez et al. (2009) did not find differences in D1 receptor availability between cocaine-dependent and control subjects using the PET tracer (+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-[^{11}C]methyl-2,3,4,5-tetrahydro-1H-3-benzazepine ([^{11}C]NNC 112). However, within the cocaine-dependent individuals, there was an inverse relationship between D1-like receptor

availability in the ventral striatum and cocaine self-administration. DA D_3 receptors, a subtype of the dopamine D2-superfamily are a promising target for psychostimulant pharmacotherapies given their specific localization within limbic brain regions, higher density in cocaine overdose victims (see Heidbreder and Newman, 2010 for review) and behavioral data showing increased sensitivity to D_3-selective compounds in monkeys with a cocaine SA history (Hamilton et al., 2010; Blaylock et al., 2011). Recent findings have shown that D_3 receptor availability, assessed using [^{11}C]-(+)-propyl-hexahydro-naptho-oxazin ([^{11}C]PHNO) is higher in methamphetamine users compared to controls (Boileau et al., 2012), suggesting that changes in the ratio of D_2/D_3 receptors may play an important part in addiction and addiction treatment. Similar PET studies have not yet assessed D_3 receptor availability as an effect of cocaine exposure.

Lastly, PET imaging may be used in the future to predict treatment success. Volkow and colleagues (1999) first showed that D2-like receptor availability was inversely correlated with the subjective rating of intravenous methylphenidate (MP). Men with lower D2-like binding potentials found MP “pleasant”, whereas men with higher D2-like binding potentials found the same dose to be “noxious”, suggesting that men with low D2-like receptor binding potential would be more vulnerable to stimulant abuse than individuals with high D2-like measures. Recently, using a similar premise, a group of treatment seeking cocaine-dependent people were scanned using [^{11}C]raclopride before and after acute MP treatment (Martinez et al., 2011). Interestingly, following a 12 week community reinforced behavioral treatment approach, the patients that completed treatment with a greater number of drug-free urines (greater treatment success) were those that had higher baseline striatal D2-like receptor binding potential, and had a greater percent change from baseline following MP administration (Martinez et al., 2011). This study suggested that higher baseline D2-like receptor binding potentials and a greater response to MP were associated with greater success following 12 weeks of behavioral treatment. Predicting success of behavioral or pharmacological treatment strategies using PET prior to initiation may produce individualized treatment strategies with a greater overall success rate.

5. Summary

The studies described in this review focused primarily on changes within the DA system, assessed via PET imaging that directly influenced sensitivity to acquire cocaine SA or the long-term consequences of chronic cocaine SA. Environmental factors such as socially derived stress and environmental enrichment (see Nader et al., 2012a for review) can influence vulnerability to the reinforcing effects of cocaine (Morgan et al., 2002; Martinez et al., 2010). Further, although social rank had similar effects on DA D2-like receptor availability in male and female monkeys, such changes reflected opposing influences on the sensitivity to acquire cocaine SA, suggesting treatment strategies may be sex-specific (Nader et al., 2012b). Chronic cocaine SA in humans and animal models is associated with structural, neurochemical, functional, and cognitive deficits. PET imaging has complimented cognitive assessment by providing information about changes in neurobiology on a global scale following chronic drug SA, as opposed to inferential analysis based on lesion studies attributing single brain regions to impaired cognition. While preclinical assessments utilizing cocaine SA techniques and PET imaging have contributed substantially to our

understanding of dopaminergic function, broadening this assessment to other neurotransmitter systems and other drugs of abuse, will further our understanding of drug effects on the brain. An important aspect for future translational research involves the study of adolescent monkeys. A recent series of studies found that chronic methylphenidate or dl-amphetamine treatment to adolescent rhesus monkeys did not significantly affect age-related changes in dopamine D2/D3 receptor and DAT availability (Soto et al., 2012; Gill et al., 2012).

PET imaging may be used in the future to optimize individualized treatment strategies. Two strategies for addiction treatment that can incorporate PET include identification of 1) drugs that directly reduce cocaine SA; and 2) behavioral or pharmacological means to reverse neurobiological deficits, such as reduced D2-like receptor availability. Howell and colleagues have used PET to examine relationships between receptor occupancy and the ability of drugs to decrease cocaine SA (e.g., Lindsey et al. 2004; Howell et al. 2007; Kimmel et al., 2008). Various drugs that bind to the DAT were examined for their ability to decrease cocaine SA and to substitute for cocaine in rhesus monkeys. PET studies were then conducted using behaviorally active doses administered during a PET study with 2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-[18F]-fluoroethyl)-nortropane ([^{18}F]FECNT). These DAT inhibitors required high DAT occupancy (between 50–90%) to reduce cocaine SA and to function as reinforcers (Lindsey et al., 2004). This information is critical for the development of compounds that reduce cocaine use and that have low abuse liability. Alternately, our laboratory has shown that systemic administration of the DA D2-like receptor antagonist raclopride for one month significantly increased D2-like receptor availability in drug-naïve monkeys (Czoty et al., 2005). This PET study demonstrates one way to increase D2-receptor availability, a measure consistently shown to be low in male cocaine users and animal models of addiction, providing a pharmacological means to reverse cocaine-induced neurobiological deficits. Whether the opposite strategy should be employed for females is an empirical question that has not yet been tested.

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Highlights

- The use of nonhuman primate models of cocaine abuse with PET imaging provides an excellent animal model for the study of addiction.
- PET imaging has identified sex differences and menstrual cycle differences in brain function and the consequences of cocaine exposure.
- Chronic cocaine use affects cognitive performance and brain function in monkeys.
- Studying brain changes with PET imaging during maintenance and abstinence of cocaine use can help identify novel treatment strategies.

Table 1

Selected Imaging Tracers Used in Cocaine Abuse Research

Name	Target	Selected outcome	References
[11C]cocaine	dopamine transporter (DAT) blocker	DAT, but not SERT or NET blockers displace radiotracer Inverse relationship between peak uptake and reinforcing effects	Fowler et al. (1989) Kimmell et al. (2008)
[18F]fluorobenzylchlorotropane (FCT)	DAT blocker	Does not change following acquisitioon of cocaine reinforcement	Czoty et al. (2007)
[123IJIJ-CIT	DAT blocker (SPECT tracer)	Is not different in smokers vs. non-smokers	Staley et al. (2001)
(+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-[11C]methyl-2,3,4,5-tetrahydro-1 H-3-benzazepine (NNC112)	D1-like receptor antagonist	No differences in cocaine-dependent and control subjects. In cocaine-dependent individuals, an inverse relationship between D1 receptor availability and cocaine reinforcement	Martinez et al. (2009)
[11C]raclo pride	D2-like receptor antagonist	Inversely related to stimulant reinforcement in males Lower D2-like receptor availability associated with a cocaine conditioned place preference compared to saline-associated compartment	Volkow et al. (1999) Schiffer et al. (2009)
[18F]fluoroclebopride (FCP)	D2-like receptor antagonist	Inversely related to stimulant reinforcement in males	Morgan et al. (2002); Nader et al. (2006, 2012b)
[18F]fallypride	D2-like receptor antagonist	Male smokers had significantly lower binding potentials compared to non-smokers; no differences in women	Brown et al. (2012)
3-N-[11C]-methylspiperone or methylyspiroperidol (NMSP)	D2-like receptor antagonist	Lower D2-like receptor availability in cocaine abusers compared to controls	London et al. (1990); Volkow et al. (1992, 1993)
[11C]-(+)-propyl-hexahydro-naptho-oxazin (PHNO)	D3 receptor subtype agonist	D3 receptor availability higher in methamphetamine users compared to controls	Boileau et al. (2012)
[18F]flurodeoxyglucose (FDG)	metabolic rates of glucose utilization	Increased glucose metabolism in cocaine abusers shown cocaine-belated cues less glucose metabolism in the hippocampus, PFC, ACC and striatum of cocaine-history monkeys compared to controls during a cognitive task	Grant et al. (1996) Gould et al. (2012)
[11C]-3-amino-4(2-dimethylamino-methyl-phenylsulfanyl)-benzonitrile (DASB)	Serotonin transporter (SERT) blocker	Higher SERT availability in cocaine-history monkeys compared to controls in several brain regions	Banks et al. (2008); Gould et al. (2011)
[18F]-2β-carbo(fluoroethoxy)-3β-(3'((Z)-2-iodoethenyl)phenyl)-nortropane (FEmZIENT)	SERT blocker	no change following 6 wk fluoxetine Tx in cocaine-experienced rehsus monkeys	Sawyer et al. (2012)
(S,S)-[11C]O-methylreboxetine (MRB)	Norepinephrine transporter blocker	Higher NET availability in cocaine abusers compared to controls in several brain regions	Ding et al. (2010)
[11C]-M 100907	Serotonin 2A receptor antagonist	increased BP following 6 wk fluoxetine Tx in cocaine-experienced rhesus monkeys	Sawyer et al. (2012)
[11C]-nicotine	nicotinic acetylcholine receptor agonist	higher availability in hippocampus in monkeys with a ~5 yr cocaine history compared to cocaine-naive male rhesus monkeys	Gould et al. (2013)