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Invited review

# 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.

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## 1. Introduction

Drug abuse and dependence continue to be a problem worldwide. Recent estimates report between ~4 and 6% of the population surveyed (155–250 million people worldwide) between the ages of 15 and 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 (*Macaca fascicularis*) macaques. Old World macaques and baboons

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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 (i.e., 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-maintained 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), 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

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