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Contributions of Neuroimaging to Understanding Sex Differences in Cocaine Abuse

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Abstract

A consistent observation in drug abuse research is that males and females show differences in their response to drugs of abuse. In order to understand the neurobiology underlying cocaine abuse and effective treatments, it is important to consider the role of sex differences. Sex hormones have been investigated in both behavioral and molecular studies, but further evidence addressing drug abuse and dependence in both sexes would expand our knowledge of sex-differences in response to drugs of abuse. Neuroimaging is a powerful tool that can offer insight into the biological bases of these differences and meet the challenges of directly examining drug-induced changes in brain function. As such, neuroimaging has drawn much interest in recent years. Specifically, positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) technology have emerged as effective non-invasive approaches for human and animal models. Studies have revealed sex-specific changes in patterns of brain activity in response to acute cocaine injection and following prolonged cocaine use. SPECT and PET studies have demonstrated changes in the dopamine transporter but are less clear on other components of the dopaminergic system. This review highlights contributions of neuroimaging toward understanding the role of sex differences in the drug abuse field, specifically regarding cocaine, and identifies relevant questions that neuroimaging can effectively address.

Keywords

drug abuse; neuroimaging; sex differences; cocaine; MRI; PET; SPECT

1. Introduction

Cocaine is one of the most addictive illicit drugs and its abuse is a significant public health concern, with approximately 1.1 million Americans dependent on or abusing cocaine (Substance Abuse and Mental Health Services Administration, 2010). Several factors have been identified that influence cocaine-related effects, such as environmental context, age and genetic predisposition. However, until the past decade, the influence of sex on the neurobiological and behavioral aspects of drug abuse had been largely ignored. Certain aspects of cocaine use and addiction are more severe in women, including the prevalence of

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cocaine dependence in adolescence (Kandel et al., 1997), speed and age at which they acquire dependence (Robbins et al., 1999; Fattore et al., 2008; Becker and Hu, 2008), severity of use (Robbins et al., 1999) and cocaine-induced craving (Kosten et al., 1993; Robbins et al., 1999). Furthermore, females, both in clinical and preclinical studies, relapse more readily than males (Fattore et al., 2008) and may have a higher vulnerability to cocaine abuse than males (Cotto et al., 2010). To date, the neurobiological basis for these differences is not understood. Thus, a key part of investigating drug abuse and developing treatments is understanding the contribution of sex differences.

Although multiple neurotransmitter systems are involved in mediating cocaine's complex effects, the reinforcing and abuse-related properties of cocaine are primarily due to its ability to increase extracellular dopamine in the mesolimbic dopaminergic system through interaction with the dopamine transporter (DAT) (DiChiara, 1995; Howell and Wilcox, 2001; Wu et al., 2001). Chronic use can cause regulatory changes in the dopaminergic system (Mash et al., 2002). The dopamine system may also be affected by the menstrual cycle (Fattore et al., 2008). Furthermore, men and women respond differently to stimulants (Kuhn et al., 2001; Becker and Hu, 2008), suggesting that sex-dependent differences in underlying neurobiology may modulate drug abuse. These sex-dependent differences may be due to neuroendocrinological modulations of the dopaminergic and related systems (Quiñones-Jenab et al., 2001). However, the role of hormones in the modulation of cocaine-induced behavioral and molecular alterations has been the subject of a limited number of studies. Thus, the sex-specific causes and consequences of cocaine use are not yet well elucidated on a neurobiological level.

Neuroimaging techniques offer the powerful possibility of meeting the challenges of investigating the interaction of sex and cocaine abuse at the neurobiological level. These methods have drawn much interest in recent years as they begin to help clarify the neurobiology of drug abuse. Neuroimaging not only allows the specific effects of drugs upon the brain to be investigated, but is also able to contribute information regarding the neurochemical and physiological adaptations of the brain during recovery from addiction (Gatley et al., 2005). The main focus of this review is to highlight recent contributions of neuroimaging toward understanding the role of sex in the drug abuse field, specifically regarding cocaine, and to identify relevant questions that neuroimaging can effectively address. Further knowledge of the relationship between sex and cocaine abuse is not only important for understanding the basic neurophysiology of cocaine, but may also shed light on the distinct behavioral and neural substrates that underlie the sex-related differences associated with drug abuse. We will first briefly discuss the current knowledge of hormonal involvement and sex differences in drug abuse before discussing the contributions of neuroimaging. Since the dopaminergic system is the main target of cocaine and mediates its rewarding effects and addictive properties, this review will focus on the dopaminergic system.

2. Hormonal influences in drug abuse

Gonadal steroid hormones exert organizational and activational effects within the central nervous system (CNS) (Dluzen and McDermott, 2006), both of which could interact with cocaine abuse. However, only a limited number of studies have focused on the role of hormones in the modulation of cocaine-induced behavioral and molecular alterations. Indeed, since the 1990's, the National Institute on Drug Abuse (NIDA) has actively focused upon the study of issues specific to women and sex differences in drug abuse research in order to draw attention to this area of research. It has been proposed that the sex-specific differences in the pattern of cocaine abuse may reside in neuroendocrine modulations that affect the use of and/or dependence on cocaine (Quiñones-Jenab et al., 2001). Since women

and men respond differently to stimulants (see Introduction), investigation into the biological differences between the sexes may provide helpful insights into the cascade of events that modulate cocaine-induced behavioral and neurochemical adaptations after cocaine administration.

Plasma and brain concentrations of cocaine are the same in males and females after intraperitoneal injection and are unaffected by ovariectomy and castration (Bowman et al., 1999; Evans and Foltin, 2006; Evans and Foltin, 2010), suggesting that the sex-related differences in cocaine responses may result from innate differences in their neural targets, with the most likely candidate being the dopaminergic system (Hu and Becker, 2003). However, relatively little is known about the neurobiological basis for sex differences in motivational processes in general. Considering the marked rise in the percentage of women using drugs, such as amphetamine and cocaine, there is a need for both preclinical and clinical studies that incorporate information regarding sex, hormonal status, and circadian rhythms, in order to appropriately address and design prevention, intervention and treatment strategies in women (Yang et al., 2007; see also Lynch et al., 2002). Addressing the outcomes of drug abuse separately in males and females would expand our knowledge regarding sex differences in drug abuse.

It has been reported that during naturally occurring behavioral estrus, cocaine-induced behaviors are greater than on other days of the estrous cycle, both in humans and in animal models (Sell et al., 2000; Becker et al., 2001; Mello et al., 2008). The stage of the menstrual cycle thus may affect the vulnerability to cocaine addiction, especially at the time of initial cocaine use, by influencing cocaine-induced subjective and behavioral effects and thus altering the chance of progressing from initial to habitual use (Quiñones-Jenab et al., 2001). In addition, Justice and de Wit (1999) observed that the effects of amphetamine were greater during the follicular phase than the luteal phase by assessing the subjective and behavioral effects in women at different stages in the menstrual cycle. In women, the follicular phase is characterized by low (early) or moderate (later) levels of estrogen and very low levels of progesterone, whereas the luteal phase is characterized by moderate levels of estrogen and high levels of progesterone. Higher levels of estrogen were associated with greater amphetamine-induced euphoria, energy, and intellectual efficiency. Together, these and other data suggest that females are at an increased risk for addiction to stimulants, and it is plausible to assume that circulating concentrations of sex hormones may mediate these sex differences in vulnerability, subjective effects, and behavior. However, the neural targets and effects are not yet elucidated, questions which neuroimaging can effectively address.

Both ovarian hormones and stimulant drugs directly or indirectly affect dopaminergic activity in the brain. Estrogen receptors are co-localized on some dopaminergic neurons in the diencephalon (McEwens and Parsons, 1982) and appear to have facilitatory effects on dopamine synthesis and release (Castner et al., 1993). Additionally, it is well-established that progesterone modulates the response to cocaine in women (for review, see Evans, 2007); fluctuations in endogenous progesterone concentrations may account for some of sex differences observed in humans.

Over the last decade, progesterone has been investigated as a possible novel route to the treatment of drug abuse or dependence on stimulants, such as cocaine (McEwen et al., 1997; Hu et al., 2004). Female cocaine addicts in the luteal phase showed attenuated responses to the subjective effects of cocaine compared with females in the follicular phase of their menstrual cycle, or compared with men (Evans et al., 2002; Sofuoglu et al., 1999). Since the luteal phase of the menstrual cycle is associated with higher progesterone levels, progesterone may contribute to the attenuation of cocaine's subjective effects during the luteal phase (Evans, 2007). This is supported by parallel preclinical studies, which

demonstrate that progesterone is able to both counteract estrogen's facilitating effects on cocaine-induced behavior, as well as decrease cocaine-induced reinstatement (Peris et al., 1991; Quinones-Jenab et al., 2000; Anker et al., 2007).

Based on the studies mentioned above, it is clear that ovarian hormones influence responses to cocaine. However, the mechanisms by which they act have not been completely elucidated. In addition to direct effects at receptors and targets, sex hormones may contribute to inherent sex differences in the organization of the brain (Yang et al., 2007). Circulating ovarian hormones may facilitate the acquisition of cocaine dependence in women, while differences in brain organization may keep women in a vulnerable state (Yang et al., 2007). Neuroimaging offers the ability to examine and compare both structure and function of the brain between the sexes over time as a function of menstrual cycle status.

3. Application of neuroimaging

3.1 Techniques

Neuroimaging is a powerful tool that can offer insight into the biological bases of sex differences in drug abuse research. Specifically, positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) technology have emerged as effective non-invasive imaging technologies.

3.1.1 PET and SPECT—PET imaging uses positron-emitting radioactivity to label proteins or molecules of interest. When positrons collide with electrons, dual photons are emitted that can be recognized by detector arrays in the tomography (see Senda et al., 2002 for description). Computer algorithms are then used to map the source and concentration of the radiotracer. Many different molecules can be labeled to function as tracers, allowing examination of many different proteins, such as receptors and transporters. PET imaging can answer questions regarding many topics, from drug occupancy of targets and *in vivo* binding potentials, to processes, such as glucose metabolism or blood flow. PET neuroimaging has defined the *in vivo* biodistribution and pharmacokinetics of abused drugs and related these findings to the time-course of behavioral effects associated with their addictive properties (for review, see Howell and Murnane, 2011). SPECT is very similar to PET imaging, but uses different radiotracers that emit a single photon leading to lower sensitivity and resolution compared to PET imaging. Thus, different tracers are optimal for the two techniques, but they can be used to address similar questions. SPECT cameras have been optimized for use with clinical radiopharmaceuticals (Gatley et al., 2005). Both PET and SPECT imaging also allow functional measures of brain activity through recording the uptake and washout of a radioactive marker that competes with endogenous neurotransmitters (Laruelle, 2000). However, the radioactivity necessary for PET/SPECT is also a potential negative to the technique, both because of possible exposure concerns and because of the high cost of producing the radioactive tracers, which requires specialized equipment such as a cyclotron as well as specialized teams of experts to operate the equipment and manufacture the tracers. Additionally, only one molecular system or target can be examined at any given time, leading to important limitations in assessing sex differences in drug abuse, which involves multiple neurotransmitter systems. However, despite these limitations, PET/SPECT has still provided valuable insights into sex differences alone and in the context of drug abuse.

3.1.2 MRI—MRI and its variants, such as functional MRI (fMRI), structural morphometry and diffusion tensor imaging (DTI), have increasingly been employed to study the consequences of pharmacological manipulations on neurobiology and patterns of brain activity in humans (Schwarz et al., 2004). The spatial resolution of fMRI is better than that of human PET or SPECT, and this is advantageous since regional representation of the

cortex involves areas smaller than the current resolution of most PET or SPECT scanners (Gatley et al., 2005). fMRI is based on blood oxygen level (BOLD) contrast, relying on changes in signal intensity associated with the hemodynamic response, and is recognized as an accessible alternative for the measurement of neuronal activation in response to stimuli (see Huettel et al., 2003 for description). It provides high spatial-temporal resolution, is minimally invasive, and does not involve a radioactive tracer (Xiao et al., 2006). Structural MR images are generated using the difference radiofrequencies resulting from different tissues in the brain and allow determination of different tissue composition and structure within the brain (Fowler et al. 2007). Quantitative measurements of structural morphology can be made using voxel-based analyses. DTI is based on the principle of molecular diffusion by measuring its directionality, which is influenced by the structure of the surrounding brain tissue and can be used to determine tissue microstructure (see Minati et al., 2007 for description). Magnetic resonance spectroscopy (MRS) provides relative measurements of neurotransmitters, metabolites, and neuronal markers by taking advantage of the chemical shift effect (see Minati et al., 2007 for description). The use of MR techniques is limited by the need to restrict movement for extended periods of time, which poses a particular problem for animal settings (although recently there has been some success-see Howell and Murnane, 2011 for review). Furthermore, while the procedures are generally less costly than PET/SPECT, they are still expensive.

3.2 Application of neuroimaging in sex-difference studies

Neuroimaging has been extensively applied to understanding sex differences in brain structure and function and has been reviewed elsewhere (see Cosgrove et al., 2007). Briefly, extensive and varied differences in brain structure have been reported between men and women. For example, studies have demonstrated that females have smaller brains (Rabinowicz et al., 1999; Nopoulos et al., 2000), although this may be due to their generally smaller physical size (Cosgrove et al., 2007). Women also tend to have greater gray/white matter ratios as well as larger relative sizes for the hippocampus, while men have greater white matter, particularly in the corpus callosum, as well as larger relative sizes for the amygdala and hypothalamus (Cosgrove et al, 2007); however, only recently have structural studies begun to control for hormonal or menstrual cycle differences and thus the sex differences in these studies may be confounded.

Protopopescu et al. (2008) examined brain structure within-subject across menstrual cycle, assessed by ovulation tests and confirmed by onset of menses, and reported greater gray matter volume in the lingual gyrus and the hippocampus/parahippocampal region in women following their menstrual period, while before the menstrual period greater gray matter volumes were seen in the superior parietal lobule, globus pallidus/putamen, and medial frontal gyrus/anterior cingulate cortical areas. Pletzer et al. (2010) expanded these results by comparing men, naturally cycling women in both their early follicular and mid-luteal stages, and women on hormonal contraceptives. Men had greater gray matter in the hippocampus, parahippocampal/fusiform gyri, putamen, pallidum, amygdala, and temporal regions compared to all women, and greater gray matter in the cerebellum compared to naturally cycling women, in good concordance with many earlier studies on sex differences (Cosgrove et al, 2007; Witte et al., 2010), although there have been conflicting reports regarding the hippocampus (Pletzer et al., 2010). Women had greater gray matter in the prefrontal cortex, pre-and post-central gyri, supplementary motor area, and inferior parietal lobule. Furthermore, women on hormonal contraceptives had greater gray matter in the prefrontal cortex and pre- and post-central gyri, as well as in parahippocampal/fusiform gyri and temporal regions, than naturally cycling women. Cycle-dependent effects were found in the fusiform/parahippocampal gyri, with larger gray matter in the early follicular phase (Pletzer et al., 2010). Witte et al. (2010) reported associations between circulating levels of

progesterone and testosterone with variation in the middle temporal pole and inferior frontal gyri (respectively). From these studies, it is clear that sex hormones exert great influence on brain structure and plasticity, particularly for women. Furthermore, it appears that hormonal contraception, which elevates the female sex hormones, has enlarging effects on gray matter in sexually dimorphic areas. These widespread sex differences and continual hormonal influences on brain structure may hold great significance for understanding sex differences in drug abuse.

Furthermore, sex differences in structure are present during development. Raznahan et al. (2010) recently created “movies” of brain development in adolescents using longitudinal *in vivo* structural neuroimaging, demonstrating that regionally-specific sex-differences occur during development of the cerebral cortex in adolescence. Time-lapse sequences of cortical maturation in male and female subjects revealed that sex differences in cortical thickness change across adolescence in a highly complex and spatially heterogeneous manner (Raznahan et al., 2010). These sex-specific developmental differences may hold relevance for the understanding vulnerability to illicit drug abuse during adolescence, as well as for understanding the sex-specific consequences of such abuse during a sensitive period in brain development. Further studies are needed to determine the organizational role of sex hormones during development, as well as the short- and long-term effects of cocaine on these processes.

In addition to sex differences in gray matter, sex differences in white matter have also been reported. Men generally have greater white matter than women (Cosgrove et al., 2007). Furthermore, differences in white matter microstructure have been reported. In particular, women show decreased fractional anisotropy in the corpus callosum, thalamus, and cingulum compared with men (Shin et al., 2005; Menzler et al., 2011). Menzler et al. (2011) further reported higher radial diffusivity in women in these areas, suggesting that differences in myelination may underlie the observed sex differences.

Sex differences have also been reported in function, with women generally having higher resting cerebral perfusion rates and a tendency for higher glucose metabolic rates than men (Cosgrove et al, 2007). Additionally, regional variation in metabolic rate across menstrual cycle in women has also been demonstrated, possibly due to the natural fluctuations in estrogen (Cosgrove et al, 2007). Furthermore, the BOLD response to negative or stressful stimuli varied across menstrual cycle in women compared to men (Goldstein et al., 2010). Women in the early follicular stage did not differ in brain activation as compared to men, whereas the same women in late follicular or mid-cycle stages had lesser activation in multiple brain areas implicated in stress response circuitry, including the anterior cingulate gyrus, areas of the prefrontal cortex, amygdala, and hippocampus compared to men. These findings suggest that hormonal status influences stress response regulation (Goldstein et al., 2010), which can play a role in drug abuse and relapse.

Importantly for the study of sex differences in drug abuse, sex differences have been demonstrated in the response to non-drug reward. Dreher et al. (2007) showed that during reward anticipation, the hippocampus and frontal gyrus were activated in women while the putamen was activated in men. Furthermore, at reward delivery, women also activated prefrontal and cingulate cortex, among other areas, more strongly than men, who activated a prefronto-parietal network and supplemental motor areas more strongly than women (Dreher et al., 2010). Women in the follicular phase also had greater activation in the midbrain, striatum, amygdala, and orbitofrontal cortex at the time of reward delivery than they did during the luteal phase (Dreher et al., 2007), suggesting that estrogen augments the responsiveness of the reward pathway while progesterone counteracts this effect and clearly demonstrating the modulation of the reward pathway by sex hormones. This is consistent

with the data reviewed by Cosgrove et al. (2007), suggesting higher dopaminergic tone and extrastriatal dopamine receptor availability in women compared to men.

3.3 Application of neuroimaging in cocaine abuse

Neuroimaging techniques have been extensively applied to the question of drug abuse and are reviewed elsewhere (see Fowler et al., 2007 for general overview of neuroimaging and drugs of abuse; see Howell and Murnane, 2008, 2011 for animal studies; Aron and Paulus, 2007 for fMRI findings; Gatley et al., 2005 for PET); for this reason, we will only briefly review the findings. Over the last two decades, SPECT, and especially PET, have proven to be increasingly effective imaging techniques in the study of human psychopharmacology (Gatley et al., 2005). Both methodologies have been used to help understand various aspects of the pharmacokinetics and pharmacodynamics of illicit drugs. Imaging studies have identified several brain regions that are activated by cocaine, including the basal forebrain, caudate, nucleus accumbens, ventral tegmentum, and prefrontal cortex (Breiter et al., 1997). Furthermore, it has been shown that drug-addicted subjects commonly have lower levels of dopamine D2 receptor availability (Volkow et al., 1990, 1993, 1997). fMRI studies have revealed that cocaine abusers (both females and males) demonstrated widespread abnormalities in the pattern of brain activation, including hypoactivation in regions where dopamine nuclei are located (mesencephalon) and the thalamus, deactivation in dopamine projection regions, and hyperactivation in the cortical regions involved with attention (prefrontal and parietal cortices) (Tomasi et al., 2007). DTI data have revealed that cocaine users (both sexes) had lower fractional anisotropy than controls, specifically in inferior frontal white matter (Lim et al., 2008). Furthermore, impaired white matter integrity has been significantly correlated with poorer abstinence-based outcomes (Xu et al., 2010).

However, these studies did not provide any insights into differences between the sexes. The majority of imaging studies have been carried out only using men, while fewer studies have examined a mixed-sex sample (Kilts et al., 2004). Neuroimaging is well able to address the questions and role of sex differences, structural, hormonal, and activational, in the brain and how they relate to drug abuse. Thorough investigation of these sex-related differences may be relevant to understanding the differential drug-related characteristics in men and women addicted to cocaine.

3.4 Application of neuroimaging in sex differences and cocaine abuse

3.4.1 Activation and perfusion studies

Distinct activational patterns in response to cocaine and cocaine cues: Differential brain activation has been reported between men and women in response to cocaine or cocaine cues, suggesting that the neural circuitry underlying drug abuse may differ between the sexes (see Table 1). Using SPECT imaging, Adinoff et al. (2003) reported that male and female addicts display different patterns of regional cerebral blood flow (rCBF) changes in response to a procaine challenge when compared to age- and sex-matched controls. Furthermore, when compared with the male addicts, the female addicts displayed lesser rCBF reductions in the orbitofrontal cortex.

Kilts et al. (2004) found differences in CBF using [O15]-labeled water, following presentation of cocaine-related imagery between cocaine-dependent men and women, with less activation in the amygdala, insula, OFC, and ventral cingulate cortex in women than men. Conversely, greater activation was seen in the central sulcus and frontal cortical areas in women than in men. Similarly, Li et al. (2005) reports that female cocaine users displayed greater activation in the left anterior and right posterior cingulate, left insula, and middle and inferior frontal cortex during stressful imagery as measured with fMRI, although these differences may not be entirely specific to cocaine abusers (Price, 2000; Phillips et al.,

2003). These studies suggest that women form distinct conditioned associations with drug use when compared to the men, and this difference resulted in distinct conditioned neural responses to cocaine or stress cues in the two sexes.

The decreased response to cocaine and cocaine cues seen in women as compared to men (Kilts et al., 2004; Adinoff et al., 2003) may be due to the influence of estrogen. Febo et al. (2005) investigated the effects of estrogen treatment on cocaine-induced brain activation in the female rat using fMRI. Ovariectomized females treated with estrogen had decreased BOLD responses in the mesolimbic dopamine system to a single cocaine challenge compared to ovariectomized females not treated. However, following repeated exposure to cocaine, the ovariectomized females treated with estrogen showed an *enhanced* response to cocaine challenge when compared to acute cocaine challenge as well as compared to animals not treated with estrogen. This enhancement is not in accordance with the previously mentioned clinical reports (Kilts et al., 2004; Adinoff et al., 2003), but may be due to either the phenomenon of sensitization (Hu and Becker, 2003) reported in rats or to the limited number of repeat exposures in the protocol used by Febo et al. (2005) as compared to chronic cocaine abusers.

Distinct perfusion changes following chronic cocaine use: Chronic cocaine use can cause reductions in cerebral perfusion. Levin et al. (1994) reported that cocaine-dependent women were less likely to experience abnormalities in rCBF as measured by SPECT, both in the number of regions changed per patient and the number of patients affected. However, changes in rCBF were more frequent in anterior brain structures, such as the frontal and temporal cortex and the basal ganglia, all of which are known to be involved in drug abuse. Ernst et al. (2000) expanded these results, reporting a significant increase in rCBF in the frontal and temporo-parietal white matter of female, but not male, cocaine users. Similarly, Tucker et al. (2004) reported increased perfusion in the posterior cingulate of cocaine-dependent women while men showed decreased perfusion in the anterior cingulate/frontal regions. However, Adinoff et al. (2006) reported decreased perfusion in the medial orbitofrontal cortex as well as the superior frontal gyri, as well as increased perfusion in the middle frontal, anteriolateral temporal and anterior cingulate cortices in women, while men showed decreases in the OFC, anteriolateral temporal cortex, and anterior cingulate. Furthermore, men showed rCBF increases in several areas, including the caudate, which women did not display. These sex-differences in resting state changes following chronic cocaine use may contribute to the sex-differences in the response to acute cocaine or cocaine-cue challenges.

Overall, these studies clearly indicate different changes in rCBF between male and female cocaine users, which may result from differing distribution of neural targets for the drug. Over prolonged periods of use, these differences may result in the development of the distinct patterns of alterations observed in these perfusion studies. Women and men addicted to cocaine have been shown to respond differently to treatment (Weiss et al., 1997), which could be due, in part, to these sex-related differences in cerebral perfusion changes (Levin et al., 1994; Ernst et al., 2000; Tucker et al., 2004). This highlights the importance of evaluating potential treatment strategies in both men and women.

Menstrual cycle-mediated changes in the response to cocaine: Dynamic susceptibility contrast MRI was used to investigate cocaine-induced cerebral blood volume changes in healthy women who occasionally used cocaine at the follicular and luteal phases of the menstrual cycle (Kaufman et al., 2001). Cocaine did not alter cerebral blood volume in the follicular phase (high estrogen/low progesterone), but reduced cerebral blood volume during the luteal phase (high estrogen/high progesterone) indicating vasoconstriction. Furthermore, the effect of cocaine on cerebral blood volume did not differ between women in the luteal

phase and men. Collectively, these data suggest estrogen reduces cocaine's vasoconstrictive effects. Furthermore, lower levels of circulating estrogen in males could result in less estrogen-mediated vascular protection, whereas high testosterone concentrations may impair vascular reactivity and sensitize men to cocaine's vasoconstrictive effects (Kaufman et al., 2001). It is interesting to note that these vasoconstrictive effects of cocaine are associated with the phases of the menstrual cycle during which the subjective effects of cocaine are diminished. Furthermore, it is important to consider these menstrual cycle-sensitive global alterations in blood flow in response to cocaine when considering data generated by other imaging methods that are dependent on blood flow, such as BOLD fMRI and SPECT imaging of rCBF.

3.4.2 Binding studies—The DAT is a target of cocaine and important in mediating its abuse-related effects. Several studies have employed SPECT to focus on the relationship between sex and the integrity of the dopaminergic system through striatal DAT (see Table 2). However, conflicting data have been obtained. Van Dyck et al. (1995) reported no effect of sex on DAT binding in the striatum, and no interaction with their reported age-related decreases, while later studies have reported greater DAT binding in female subjects in the caudate across age (Lavalaye et al., 2000; Mozley et al., 2001) and in the putamen with (Mozley et al., 2001) or without an interaction with age (Lavalaye et al., 2000). Kuikka et al. (1997) also detected sex differences in DAT, with women exhibiting higher heterogeneity in both the left and the right striatum when compared with males. Collectively, these studies suggest that gender is an important factor in determining DAT, although none of these studies examined the influence of menstrual cycle or controlled for its potential effects.

Estrogen replacement therapy in healthy postmenopausal women led to a significant (although modest) increase in DAT availability in the left anterior putamen after four weeks of treatment, and in both the left and right anterior putamen when medroxyprogesterone acetate was added to the regimen for an additional two weeks (Gardiner et al., 2004). Best (2005) examined the effect of menstrual cycle phase on DAT availability in the striatum. Plasma estradiol and progesterone levels were used to confirm menstrual phase at the time of SPECT imaging. The results showed that in the menstruating subjects, the availability of DAT in the striatum was not correlated with changes in plasma hormones and did not differ between the follicular and luteal phases. Moreover, DAT availability in the striatum or brainstem-diencephalon did not differ from a previously collected sample of males. However, this study did not control for age, which appeared to be an important factor in previous studies of DAT and sex (van Dyke et al., 1995; Lavalaye et al., 2000; Mozley et al., 2001). Clearly, regulation of DAT expression is complex and influenced by many factors, including sex and age, based on these studies. Future studies should continue to address the influence of menstrual cycle in age-matched groups. Despite the conflicting evidence, it is recommended to further examine and control for sex differences in future studies of DAT. Furthermore, additional studies should focus on whether cocaine, known to influence DAT regulation, exerts different effects in cocaine-dependent males versus females. These studies may potentially help explain the sex differences in perfusion and activation observed in cocaine users.

The dopamine receptor D2 has also been implicated in cocaine's reinforcing effects. A small number of studies have used PET to examine D2 receptor sex differences (see Table 2). One study of the effects of menstrual cycle on D2 receptor binding in the caudate showed that there was a tendency for the binding rate constant (k_3) to be lower in the follicular phase and higher in the periovulatory and luteal phases. However, no analyses of hormonal levels were included in this study (Wong et al., 1988). Nördstrom et al. (1998) examined whether sex steroids were associated with variations in D2 receptor density in the putamen during the menstrual cycle in healthy women. No significant variations in D2 receptor density were

found across cycle. PET studies that have examined sex differences in D2-like receptor binding potentials or densities have reported higher values in the female anterior cingulate cortex (Kaasinen et al., 2001), but not in the female striatum (Farde et al., 1995). This is in contrast to preclinical studies using cynomolgus monkeys, which report significantly higher D2-like receptor binding potentials in the caudate and putamen during the luteal phase than during the follicular phase (Czoty et al., 2009). However, the same group reported no difference in D2-like binding between male and female rhesus macaques following prenatal cocaine exposure (Hamilton et al., 2010).

PET has also been used to evaluate sex differences in dopamine release. Munro et al. (2006) and Riccardi et al. (2006) both reported that men had more dopamine release than women in the striatum in response to amphetamine as evaluated by [¹⁸F] fallypride binding, although women had greater dopamine release in extrastriatal areas (Riccardi et al., 2006), consistent with the conclusions of Cosgrove et al. (2007). However, Munro et al. (2006) further reported no differences in basal D2 binding between men and women, but did find differences across menstrual phase with lower binding in the luteal phase. This is difficult to interpret, as it may signify either higher basal dopamine release or lower receptor levels. Similar studies examining sex differences in the dopamine response to cocaine are needed, particularly as DAT regulation may be influenced by sex and menstrual cycle.

3.4.3 Spectroscopy studies—Using proton MRS, Chang and coworkers (1999) non-invasively measured several cerebral metabolites as indicators of structural integrity in cocaine-dependent men and women (see Table 2). The authors found that while cocaine use was associated with markers of neuronal injury, such as decreased N-acetyl compounds and increased glial activation, in the frontal cortex in both sexes, cocaine-dependent women exhibited fewer markers of neuronal damage than cocaine-dependent men. This study demonstrates that ¹H-MRS can be used non-invasively to evaluate *in vivo* neurochemical changes that might occur in cocaine users. The results of this study, combined with studies indicating fewer alterations in rCBF (Levin et al., 1994; Adinoff et al., 2006) suggests that females may be less susceptible to cocaine-induced neuronal damage.

3.4.4 Structural studies—Structural MRI can be used to compare anatomy of brain structures implicated in drug abuse and craving between sexes. For example, the amygdala has been shown to be involved in processes that relate to cocaine consumption, including reward and drug craving (Makris et al., 2004). When compared to healthy controls, the volume of the amygdala (but not the hippocampus) was significantly reduced in the cocaine-dependent subjects. Furthermore, the right-left amygdala asymmetry observed in controls was not observed in the cocaine-dependent subjects. It has been suggested that this decrease in the volume of the amygdala may be a developmental trait that increases the risk of drug dependence. However, the study did not examine differences between men and women. Future studies should address this, as developmental structural differences could help explain the differences in the patterns of cocaine use and abuse between men and women. Additionally, Schlaepfer et al. (2006) reported decreased white matter in the frontal cortexes of male drug abusers, but did not examine women or specific drug effects. There is a distinct lack of studies investigating the sex-specific differences in the impact of cocaine abuse on the structural integrity of both gray and white matter in the brain. Studies of this nature could help explain differences in the pattern and progression of cocaine abuse once initiated in men and women, as well as differences in relapse rate.

4. Conclusions

During the past decade, there has been increased attention upon hormonal involvement in drug abuse. These studies have been motivated by the increased number of women addicted

to psychostimulants, which has become a growing public health concern. Furthermore, compelling data indicate the existence of a role for ovarian hormones in drug addiction. Men and women addicted to cocaine display distinct profiles in incidence, onset, and progression of addiction, in addition to their response to treatment (Adinoff et al., 2003). Preclinical and clinical studies have demonstrated that there are sex-specific differences in the biological response to cocaine, as well as to other stimulants. While there are some differences among specific classes of abused drugs, the general pattern of sex differences is the same for all drugs of abuse (Becker and Hu, 2008).

Understanding the neurobiological substrates involved in drug-taking behavior is a central challenge in addiction research. Neuroimaging has contributed substantial insight into this issue, as well as into the neurobiological basis for sex differences, but it has been less applied to questions of sex differences in drug abuse. The studies reviewed here suggest a complex influence and interplay between sex differences and drug abuse. PET, SPECT, and fMRI all point to differences in activation of the amygdala, insula, cingulate cortex, and frontal cortex between male and female cocaine users, as well as distinct changes in resting state between the sexes. These changes may be related to greater DAT availability in women as well as less susceptibility to drug-induced neuronal damage.

Neuroimaging offers the unique ability to investigate sex differences in the composition, development, and function of brains of current drug users over time. Furthermore, multiple imaging techniques can be used to address the questions of where and how these sex differences come into play. Parallel studies in animals and human subjects should be able to provide a powerful translational approach, allowing phenomena observed in humans to be investigated in animals, and then translated back into treatment strategies and approaches. In particular, animal models offer the opportunity for longitudinal designs in order to address neurobiological mechanisms underlying chronic cocaine use. Imaging techniques such as PET can help identify target brain structures and receptors in both the male and female brains. Furthermore, neuroimaging should be applied to understanding the developmental differences in anatomy between the sexes, how these differences interact with cocaine use, and how cocaine use differentially affects brain activation, connectivity, and receptor regulation between males and females.

Overall, there is an obvious lack of animal neuroimaging studies addressing the role of sexes in drug abuse. Animal models offer the ability to tightly control and design experiments to address complicated questions in a systematic, thorough manner, and have the potential to answer many questions when combined with the versatility of neuroimaging techniques. For instance, a set of longitudinal neuroimaging studies across the life-span in animals of both sexes to verify whether hormones exert a role in the predisposition to, acquisition of, and maintenance of cocaine use would prove most interesting and informative. Furthermore, such studies could illuminate the role of sex hormones in the neural adaptations caused by cocaine use.

In order to apply these powerful imaging techniques to determining the role of hormones in sex-specific differences in drug abuse, additional measures and controls, such as hormonal assays, are still required to aid interpretation of the results. There is a strong need for further studies investigating sex differences in both animals under carefully controlled conditions and in drug abusers. Reliable radiotracers for dopaminergic targets have been developed and should be utilized to map out any baseline differences between males and females in dopaminergic receptor and transporter distributions and densities, as well as different metabolic responses to initial and prolonged cocaine exposure, and any changes in dopaminergic structure that may differ between males and females following stabilization

of cocaine use. These studies would help guide individual treatment strategies that could target the particular neurobiology of cocaine abuse in women.

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Table 1

Activation and perfusion studies.

Technique	Subjects	Challenge	Main Finding		Reference
			Female	Male	
SPECT	Cocaine- dependent males vs healthy male controls	Procaine		↑ brainstem ↑ insula (right) ↑ OFC (left)	Adinoff et al., 2001
SPECT	Cocaine- dependent females vs healthy female controls	Procaine	↓ anterior cingulate ↓ OFC (bilateral) ↓ temporal regions ↓ caudate (right) ↑ superior frontal (bilateral) ↑ posterior hippocampus ↑ posterior thalamus		Adinoff et al., 2003a
SPECT	Healthy males and females (before and after challenge)	Procaine	↑ amygdala (bilateral) [‡] ↑ anterior cingulate ↑ anterior temporal (bilateral) ↑ mesial temporal (bilateral)	↑ amygdala (bilateral) ↑ anterior cingulate ↑ insula (bilateral) ↑ mesial temporal (left)	Adinoff et al., 2003b
PET	Cocaine- dependent females and males	Cocaine imagery	↑ precentral gyrus ↑ superior temporal gyrus ↑ postcentral gyrus ↑ dorsal anterior cingulate ↑ posterior cingulate gyrus ↑ superior temporal gyrus ↑ nucleus accumbens ↑ fusiform gyrus ↓ cerebellum ↓ amygdala ↓ cuneus ↓ middle occipital gyrus	↑ amygdala ↑ nucleus accumbens ↑ inferior frontal gyrus ↑ caudate ↑ periamygdaloid cortex ↑ anterior cingulate ↑ insula ↓ precuneus ↓ angular gyrus ↓ middle frontal gyrus ↓ precentral gyrus	Kilts et al., 2004
fMRI	Cocaine- dependent females vs males	Stress imagery	↑ middle frontal gyrus ↑ cingulate gyrus ↑ inferior frontal gyrus ↑ insula (stress) ↓ insula (neutral)		Li et al., 2005
fMRI	OVX female rats with estrogen treatment vs without estrogen treatment	Cocaine	Single cocaine injection: ↓ Δ prefrontal cortex ↓ Δ nucleus accumbens ↓ Δ hippocampus ↓ Δ ventral tegmental area Repeated cocaine injection (with estrogen): ↑ Δ nucleus accumbens ↑ Δ striatum ↑ Δ hippocampus ↑ Δ ventral tegmental area Repeated cocaine injection (without estrogen) ↓ Δ hippocampus		Febo et al., 2005

Technique	Subjects	Challenge	Main Finding		Reference
			Female	Male	
MRI + DSC	Healthy females during follicular and luteal phases and males	Cocaine	No Δ (follicular) $\downarrow$ 10% cerebral blood volume (luteal)	$\downarrow$ 20% cerebral blood volume	Kaufman et al., 2001
fMRI	Healthy females during follicular and luteal phases and males	Monetary reward	Reward delivery: $\uparrow$ Δ anterior medial prefrontal cortex $\uparrow$ Δ subgenual gyrus $\uparrow$ Δ amygdala $\uparrow$ Δ hypothalamus <i>Follicular vs luteal</i> $\uparrow$ Δ amygdala $\uparrow$ Δ caudate $\uparrow$ Δ inferior frontal gyrus $\uparrow$ Δ fronto-polar cortex $\downarrow$ Δ intraparietal region $\downarrow$ Δ inferior temporal cortex Uncertain reward anticipation: $\uparrow$ Δ hippocampus $\uparrow$ Δ middle frontal gyrus <i>Follicular vs luteal</i> $\uparrow$ Δ amygdala $\uparrow$ Δ superior orbitofrontal cortex $\downarrow$ Δ dorsolateral prefrontal cortex $\downarrow$ Δ anterior cingulate cortex	Reward delivery $\uparrow$ Δ prefronto-parietal network $\uparrow$ Δ supplementary motor area $\uparrow$ Δ inferior temporal region Uncertain reward anticipation $\uparrow$ Δ ventral putamen	Dreher et al., 2007
Perfusion	Subjects	Challenge	Female	Male	
SPECT	Cocaine- dependent males and females vs healthy controls	None	Fewer perfusion abnormalities (2 ± 2.52) compared to controls (0.69 ± 1.32)	More perfusion abnormalities (6.06 ± 5.98) compared to controls (1.23 ± 1.74)	Levin et al., 1994
SPECT	Cocaine- dependent males and females vs healthy controls	None	$\uparrow$ posterior cingulate gyrus	$\downarrow$ precentral gyrus (right) $\downarrow$ superior gyrus (right) $\downarrow$ frontal and anterior cingulate gyrus (middle)	Tucker et al., 2004
SPECT	Cocaine- dependent vs healthy males and females	None	$\downarrow$ medial OFC $\downarrow$ superior frontal gyri $\uparrow$ middle frontal $\uparrow$ anterior lateral temporal (bilateral) $\uparrow$ anterior cingulate	$\downarrow$ lateral OFC (bilateral) $\downarrow$ anterior lateral temporal $\downarrow$ anterior cingulate $\uparrow$ caudate (right) $\uparrow$ medial OFC $\uparrow$ superior frontal $\uparrow$ middle frontal $\uparrow$ posterior cingulate	Adinoff et al., 2006
SPECT + MRI	Cocaine- dependent males and females vs healthy controls	None	$\downarrow$ parietal gray matter $\uparrow$ frontal white matter $\uparrow$ temporo-parietal white matter	$\uparrow$ thalamus	Ernst et al., 2000

[‡]: indicates significantly greater than males in the same study;

Δ : change; OFC: orbitofrontal cortex; OVX: ovariectomized; DSC: dynamic susceptibility contrast.

Binding and spectroscopy studies

Table 2

	<i>Subjects</i>	<i>Target</i>	<i>Main findings</i>	
SPECT	Healthy females vs males	DAT	No significant differences	Van Dyck et al., 1995
SPECT	Healthy females vs males	DAT	Greater heterogeneity in the female striatum compared to male	Kuikka et al., 1997
SPECT	Healthy females vs males	DAT	Female>male (caudate and putamen) Interaction with age (greater difference when young)	Mozley et al., 2001
SPECT	Healthy females during follicular and luteal phases; healthy females vs males	DAT	follicular DAT=luteal DAT female DAT=male DAT (striatum and brainstem)	Best et al., 2005
SPECT	Healthy females vs males	DAT	Female>male (striatum)	Lavalaye et al., 2000
PET	Healthy females during follicular and luteal phases	D2 receptor	follicular D2=luteal D2 female D2=male D2	Nordstrom et al., 1998
PET	Healthy females vs males	D2 receptor	Female D2=male D2	Pohjaleinen et al., 1998
PET	Healthy females vs males	D2-like receptors	Female D2>male D2 (general binding, frontal cortex [‡] , anterior cingulate [‡])	Kaasinen et al., 2001
PET	Healthy males and females (before and after amphetamine challenge)	D2 receptor	Female D2=male D2 Male>female amphetamine-induced dopamine release (ventral striatum, anterior putamen, and caudate nuclei) follicular D2>luteal D2 (putamen only)	Munro et al., 2006
PET/MRI	Healthy males and females (before and after amphetamine challenge)	D2 receptor	Female>male amphetamine-induced dopamine release (right globus pallidus, right inferior frontal gyrus, temporal cortex, and parietal cortex) Male>female amphetamine-induced dopamine release (dorsal striatum)	Riccardi et al., 2006
PET	Drug-naïve female cynomolgous monkeys (follicular vs luteal)	D2-like receptors	follicular D2 > luteal D2 (caudate and putamen)	Czoty et al., 2009
PET	Female and male rhesus macaques	D2-like receptor	Female D2=male D2 (caudate, putamen, amygdala)	Hamilton et al., 2010
Spectroscopy	<i>Subjects</i>	<i>Target</i>	<i>Main findings</i>	
H-MRS	Cocaine- dependent female and males vs healthy controls	Markers for neuronal damage	Frontal white matter: Male cocaine users creatine>female cocaine users creatine (+5.7%) Female cocaine user myoinositol/creatine ratio > male cocaine users myoinositol/creatine ratio (+17.1%) (increased myoinositol=indicative of glial activity) Female cocaine users N-acetyl/creatine ratio>male cocaine users N-acetyl/creatine ratio (+6.6%) (less N-acetyl=indicative of neuronal loss)	Chang et al., 1999

H-MRS: Proton magnetic resonance spectroscopy.