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Authors
Petersen, Nicole
London, Edythe D

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Addiction and Dopamine: Sex Differences and Insights from Studies of Smoking

Nicole Petersen[1] and **Edythe D. London**[1,2,3,*]

[1]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA, 90024

[2]Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, CA, USA, 90024

[3]Brain Research Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA, 90024

Abstract

Mesolimbic dopaminergic function influences addiction through effects on reinforcement learning, decision-making, and impulsivity. This review covers sex differences in dopaminergic neurochemistry, their hormonal and genetic determinants, and how differences in dopaminergic tone interact with sex and/or ovarian hormone status to affect cognitive functions. Findings from research on cigarette smoking reveal sex differences in striatal and midbrain dopamine D2-type receptor availability and striatal dopamine release that suggest mechanisms of nicotine dependence, and stronger subjective responses to nicotine and efficacy of nicotine replacement therapies in male smokers than in their female counterparts. Opportunities exist to extend such efforts in studies of how sex and hormone status influence other addictions.

II. Introduction: Sex differences and Dopaminergic Signaling in Drug Use Disorders

The prevalence, course, and consequences of substance use disorders differ in men and women. Although men are approximately 70% more likely than women to have a substance use disorder, more women than men (12–49 years of age) recently initiated the use of marijuana, stimulants, heroin, phencyclidine, and alcohol [1]. Women tend to escalate from initiation of drug use to addiction more rapidly than men [2,3], and are more likely than men to relapse after initiating abstinence [4]. Because substance use increases maternal and perinatal morbidity, women experience addiction-related health consequences that do not affect men [5]. They also are disproportionately affected by other untoward effects of drug

*Corresponding author: Dr. Edythe D. London, Department of Psychiatry and Biobehavioral Sciences, Semel Institute, University of California Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90025, USA, Tel: 310 825 0606, Fax: 310 825-0812, elondon@mednet.ucla.edu.

use, exhibiting a higher relative risk of smoking-related cardiovascular disease [6], and occurrence of cardiovascular [7] and other alcohol-related physical illnesses at lower levels of drinking than men [8].

The National Institutes of Health now has mandated that sex be considered as a biological variable in all biomedical research [9], and sex differences have been evaluated in animal models of addiction and human addiction. This review extends previous syntheses of relevant literature [10,11] on sex differences (and in some cases, similarities) in dopaminergic neurochemistry (for review, see [12]) and addiction. Involvement of dopaminergic systems in the effects of cigarette smoking are highlighted because recent developments and expert recommendations in this research area illustrate an exemplary role for studies of other addictions.

Dopaminergic signaling is central to the etiology and maintenance of substance use disorders by influencing the motivational processes underlying the learning and execution of goal-directed behaviors, as indicated by electrophysiological recordings from midbrain dopamine neurons in monkeys [13,14]. Numerous studies of animal models have implicated striatal dopamine D2-type receptors in vulnerability as well as resilience to addiction [15–22]. These include findings that striatal D2-type receptor availability influences subsequent cocaine self-administration and that striatal D2-type receptors and dopamine transporters show long-lasting neuroadaptations to stimulant administration in nonhuman primates [23,24]. Human studies reinforcing this view show below control striatal dopamine D2-type receptor availability in individuals with addictions to various substances, including stimulants, heroin, alcohol, and tobacco (for reviews, see [25–27]), and (as detailed below) associations of striatal D2-type receptor availability with cognitive functions that affect addiction.

III. Dopamine Signaling, Cognition and Responses to Drugs: Effects of Ovarian Hormones

Cognitive control and adaptive decision-making, functions that are linked to dopaminergic neurochemical markers, influence the course of addictions [28,29]. Impaired cognitive control, measured as impulsivity in personality inventories, has been implicated in the initiation, maintenance, and relapse of drug-seeking behaviors [32]. Stimulant users are more impulsive than healthy control subjects, and show a negative correlation between impulsivity and striatal D2-type receptor availability (e.g., [33,34]). Conversely, cognitive control, measured in tests of motor response inhibition [35–37] and cognitive flexibility [38,39], show weaknesses in substance abusers, and positive correlations of striatal D2-type receptor availability with performance on relevant tests in healthy controls is disrupted in stimulant users [40,41].

Maladaptive decision-making also is linked to drug addiction and to dopaminergic function. Individuals with substance use disorders of various types discount monetary rewards as a function of their delay more than healthy individuals [42–45]. Stimulant users exhibit correlation between the steepness of the discounting rate and striatal D2-type receptor availability that is not seen in healthy controls [46]. Methamphetamine users also make

maladaptive choices and fail to show the relationship between risk and activation in the right dorsolateral prefrontal cortex that is exhibited by healthy control subjects during risk taking in a reward-based laboratory test; instead, they show a linear relationship between riskiness of choice and ventral striatal activation [47]. Moreover, association of response in the dorsolateral prefrontal cortex with riskiness of a decision is highly negatively correlated with striatal D2-type receptor availability in controls [48]. Thus, dopaminergic function, especially signaling through D2-type receptors, can influence addiction by promoting disadvantageous behaviors leading to continued drug use.

Circulating levels of ovarian hormones may influence both striatal dopamine signaling and cognitive control. Estradiol levels are correlated with longer reaction time in motor response inhibition [49] and Stroop task performance [50], suggesting that inhibitory control is weaker when estrogen levels are high. This effect may reflect estrogenic effects on striatal dopamine in that local administration of estrogen into the nucleus accumbens decreases K^+-stimulated dopamine release [51], and estrogen administration to the caudal striatum reduces dopamine D2-type receptor density [52]. Circulating progesterone levels also affect inhibitory control, attenuating impulsive action for sucrose pellets in a Go/No-Go task (130) and reducing impulsive action for cocaine in a sex-dependent manner (129; 131). Positron emission tomography (PET) imaging in humans has provided only indirect evidence that ovarian hormones may influence striatal DA receptor availability, specifically that D2-type receptor availability was lower in the putamen during the luteal phase of the menstrual cycle, when estradiol and progesterone levels are relatively elevated [53].

Inasmuch as striatal dopaminergic neurotransmission is an important mechanism of subjective response to drugs, associations of hormone status with responses to drugs of abuse also suggest that the hormones influence striatal dopaminergic function. The subjective responses to a number of drugs - most prominently stimulants - differ as a function of hormone levels in women. As reviewed in [23], subjective responses to cocaine tend to be higher during the follicular phase, when hormone levels are low (except for a brief estrogen surge at the end of the follicular phase), compared to the luteal phase, when estrogen and progesterone are elevated. Consistent with that observation, progesterone administration decreases positive subjective effects of cocaine.

Similar investigations in smokers have also revealed effects of ovarian hormones on effects of nicotine and smoking although the direction of the relationship between ovarian hormones and smoking behaviors is less clear. A systematic review and meta-analysis found that higher progesterone levels were associated with both increased negative and decreased positive subjective effects of nicotine. The same review reported higher levels of withdrawal, and a trend toward higher levels of craving, during the luteal (high progesterone) versus the follicular (low progesterone) phase [54]. In oral contraceptive (OC) users, a high dose (0.25 μg) of norgestimate, a synthetic progesterone analog, reduced smoking satisfaction more than a lower dose (0.18 μg), but high levels of endogenous progesterone were positively related to smoking satisfaction in naturally-cycling women [55]. Studies of abstinence-related symptoms in women using a variety of OCs produced mixed findings, with these women reporting less [56] or more [57] craving than those who were not using OCs. Together, these data suggest a likely relationship between ovarian hormones and smoking-

related behaviors that may potentially be mediated by hormonal effects on the dopamine system, but a great deal more research is needed to confirm or disconfirm this link and to identify the direction of the relationship. Such investigations may help to clarify the mechanism by which sex differences in dopaminergic signaling and addiction emerge.

IV. Sex differences in the functional genetics of dopamine synthesis and degradation

Sex differences in the physiology of the dopamine system can be traced back to chromosomal differences between men and women. The male-determining gene *Sry,* located on the Y chromosome and found only in (phenotypic) males, is expressed in dopaminergic neurons of the substantia nigra, and influences expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in the biosynthetic pathway to dopamine [58,59]. Estrogen is a regulator of TH activity [60,61], suggesting that different pathways to a similar endpoint are important for regulation of dopaminergic function in males and females.

Catechol-O-methyltransferase (COMT) catalyzes the degradation of dopamine (and other catechols), and a single nucleotide polymorphism at codon 158 encodes either valine (Val) or methionine (Met), the latter of which produces COMT that is more thermolabile. COMT activity in the prefrontal cortex of Met^{158} homozygotes, therefore, is 35–50% lower than in Val^{158} homozygotes [62], and Met^{158} carriers have greater concentrations of extracellular cortical dopamine than Val^{158} homozygotes. This is not the case regarding striatal dopamine [63], where the dopamine transporter rather than COMT determines intrasynaptic dopamine concentrations. Independent of genotype, women have significantly lower COMT activity in the dorsolateral prefrontal cortex [62], and higher D2-type receptor availability in the frontal cortex compared to men [64]. These findings broadly suggest that women have greater cortical dopaminergic tone than men.

Recent investigations have capitalized on the discovery that COMT influences prefrontal dopaminergic tone to investigate dopamine / behavior relationships, and many have revealed significant sex differences in effects of COMT genotype (see Table 1).

<InlineShape1>Estrogen levels interact with COMT genotype to affect cognition in women. Higher estrogen improves working memory, measured by the N-back task, in val/val homozygotes, but impairs this ability in met/met homozygotes [65], and a significant negative correlation between change in estradiol and change in delay discounting is observed only in Val carriers [66]. While these findings provide behavioral evidence that estrogen shifts cortical and/or striatal dopaminergic tone, such a shift has not yet been demonstrated directly in humans. A model describing the effects of sex and estrogen levels on dopaminergic tone and cognitive task performance is depicted in Figure 1, building on previous evidence [67] and models [68], and describing an inverted-U-shaped relationship between dopaminergic tone and cognitive performance. The model proposes that cortical dopaminergic tone is higher in women than men, and under conditions of high vs. low estrogen.

Variance introduced by normal hormonal fluctuations may partially explain a finding of a stronger relationship between genotype and brain function in men compared to women. A composite “gene score” reflecting additive effects of five genes related to dopamine function (DRD2, DRD3, DRD4, DAT1, and COMT) was negatively related to the modulation of activation of the left dorsolateral prefrontal cortex during the decision to take risk in a laboratory decision-making task, but the relationship was significantly stronger in male compared to female participants, and hormone levels were not measured [48].

Dopamine signaling plays an important role in nicotine addiction (for review, see [69]), and predictably, COMT genotype influences responses to nicotine and smoking. Compared to heterozygotes and met/met homozygotes, val/val homozygotes are more likely to be smokers [70], to show greater brain activation to a reward processing task while undergoing transdermal nicotine administration [71], and to experience greater negative subjective effects in response to intravenous nicotine [72]. A reasonable interpretation is that val/val homozygotes have greater cortical COMT activity, less tonic dopaminergic activity, and therefore a greater response to phasic release of dopamine in the striatum. The next section discusses sex differences in dopamine signaling, smoking and links between the two.

V. Sex Differences in Striatal Dopamine: Cigarette Smoking and Implications for Addiction

One area of research that has recently provided mechanistic information regarding dopaminergic function concerns Tobacco Use Disorder. Among its other well-known actions, nicotine is an aromatase inhibitor [73], reducing the aromatization of testosterone to estrogens both peripherally [74] and in the brain [75]. Accordingly, female smokers have higher levels of adrenal androgens than nonsmoker females, and experience symptoms of estrogen deficiency, including early menopause [76].

Some evidence suggests that smoking is driven more by affect in women than in men, although these findings are somewhat equivocal. Women experience stronger negative affect than men during abstinence, and unlike men, show improvement in affect upon resumption of smoking [77,78]. However, studies of smokers who were not asked to remain abstinent have produced somewhat different findings. When affect was decomposed into more specific domains, sadness was more closely associated with smoking in men vs. women, and the association between happiness and smoking was stronger in women vs. men [79]. Similarly, ecological momentary assessment of smoking did not find a stronger link between negative affect and smoking in women than in men [80].

Male smokers are more sensitive to the rewarding effects of nicotine than women [81], in whom smoking may theoretically be sustained more by conditioned reinforcement from smoking-related cues [82,83] - although notably, men are more influenced by social smoking cues than women [84]. Consistent with these predictions, in a study of cigarettes in which nicotine levels varied but other smoking-related sensorimotor cues did not, men but not women reported liking cigarettes more with higher nicotine yields, and reported greater relief of craving from cigarettes with higher nicotine yields, whereas women reported no

dose effects on any self-report measures of craving, withdrawal, affect, or cigarette characteristics [77].

These sex differences in responses to smoking and nicotine sensitivity presumably reflect underlying differences in the primary and downstream neurochemical targets affected by smoking. Male but not female smokers have greater availability of β2-containing nicotinic acetylcholine receptors (nAChRs) in the striatum, cortex, and cerebellum compared to non-smokers [85], consistent with animal studies finding nAChR upregulation in response to nicotine administration in male rats only [86]. These findings suggest that males are more susceptible than females to upregulation of nAChRs. Inasmuch as nicotine promotes dopamine release [87,88] and other indices of dopaminergic function, greater upregulation of nAChRs in men may promote greater reliance on nicotine in a cigarette through an enhancement of the dopaminergic response to smoking. In this regard, women show significantly less ventral and more dorsal striatal dopamine release in response to smoking than do male smokers [89].

Moreover, sex differences in dopaminergic signaling in the brain can influence the response to nicotine in cigarettes and replacement therapies. Although D2-type receptor availability is similar in healthy men and women, evidence suggests that striatal dopaminergic tone is higher in women [12]. Lower striatal D2-type receptor availability measured using [^{11}C]raclopride may reflect higher competing endogenous dopamine concentrations in women compared to men [90], and higher striatal [^{18}F]fluorodopa uptake has suggested greater dopamine synthesis capacity in women vs. men [91].

Although male smokers have lower striatal D2-type receptor availability than corresponding nonsmokers, female smokers do not [92,93]. This difference may reflect a protective effect of midbrain dopamine D2-type autoreceptors. Female smokers have higher D2-type receptor binding potential in the midbrain (substantia nigra/ventral tegmental area), where autoreceptors may contribute to reduced dopamine release and therefore reduced D2-type receptor downregulation in female vs. male smokers [94]. Reduced dopamine release in the striatum also can contribute to a relatively smaller subjective response to nicotine. Midbrain D2-type receptor binding potential is negatively correlated with nicotine dependence in women only, suggesting a protective mechanism: higher densities of midbrain autoreceptors may prevent striatal D2 receptor downregulation, thereby reducing nicotine dependence in women [94].

Another influence on intrasynaptic dopamine and thereby on response to dopamine release is the dopamine transporter (DAT). A preliminary study using single photon emission computed tomography indicated that regardless of smoking status, uptake of [^{123}I]beta-CIT was higher in the striatum, diencephalon, and brainstem in females than in males [95]. Higher DAT concentration can limit the smoking-induced change in intrasynaptic dopamine, thereby reducing both the subjective response to smoking and the downregulation of D2-type receptors by nicotine (or other abused drugs). In addition to the aforementioned note of a sex difference in striatal dopamine release due to smoking [89], men show more dopamine release than women in the ventral striatum in response to amphetamine challenge [53], and throughout the striatum in response to drinking alcohol [96]. These findings suggest that in

men, addressing the rewarding effects of drugs may be a more important therapeutic target than in women.

VI. Implications, Future Directions, and Conclusions

Despite temptation to speculate that sex differences in behavior affect reproductive activities only, there are sex differences in dopaminergic signaling that are related to addiction, a maladaptive disorder that does not explicitly facilitate reproduction except insofar as sexual engagement may be a byproduct of drug taking (e.g., links between methamphetamine use and risky sex [97]). Therefore, sex differences related to addiction generally are not adaptations to facilitate reproduction. Genetic and hormonal differences between men and women produce significant differences in dopamine function, which may alter the course of drug consumption and cessation. As initially reviewed in [12], “higher dopaminergic tone in women may protect against the development of ... diseases with established disturbances in dopamine function.” Research in the past decade has supported this observation, especially with respect to substance use disorders, which are less prevalent in women than in men.

Clinical trials that fail to consider male and female patients independently may obscure the value of interventions that would succeed in one sex but not the other. Reducing the nicotine content in cigarettes to non-addictive levels is being considered as a national policy to improve public health [98], an action supported by a large-scale clinical trial [99]. Low nicotine cigarettes have also been tested as a smoking cessation aid [4,100–104]; however, a secondary analysis of one such trial indicated greater efficacy in women than men [105]. Conversely, nicotine replacement therapies show lower efficacy in smoking cessation for women quitting smoking compared to men ([83,106]; but see also [107]). These findings are consistent with evidence from two key studies, demonstrating that women are less sensitive to nicotine than men [77,108]. Faulkner et al. (2017) found that women do not report differences in perceived nicotine levels after smoking cigarettes that ranged in doses of 0.027 to 0.763 mg nicotine delivered, a difference of 28X. Similarly, Jensen et al. (2016) found a statistically significant dose-dependence in intravenous nicotine self-administration in men (doses ranging from 0.1 to 0.4 mg), while women self-administered all doses at the same rate.

Upregulation of D2-type receptors has been suggested as a potential therapeutic target for addictive disorders [26,109], and a recent study found D2 upregulation in female but not male rats following treatment with methylphenidate, which blocks DAT [110]. Varenicline, a partial agonist of $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) and full agonist at $\alpha 7$ nAChRs, currently FDA-approved as a smoking cessation therapy, upregulates striatal D2-type receptors in rats [111,112], and is a more effective smoking cessation aid for women than men in the intermediate (24-week) term of abstinence [113]. Sex-specific analyses also indicate that varenicline is a more effective smoking cessation aid for women than bupropion or transdermal nicotine [114]. However, whether the sex difference in varenicline efficacy is related to sex differences in dopaminergic signaling is unknown, and is an important question for future investigations.

Future directions may include a focus on how neuroendocrine factors that differ between men and women may influence addiction. For instance, high endogenous progesterone is associated with better efficacy of transdermal nicotine patch replacement therapy for relief of smoking urges [115], and administration of exogenous progesterone reduces positive subjective effects of smoking cigarettes [116] and cocaine [117]. Smoking cessation therapies may potentially be able to leverage menstrual cycle phase to reduce relapse by identifying the optimal cycle window in which to initiate abstinence; however, findings to date have been mixed, with some studies showing no effect of cycle phase on cessation [118–120], others showing better outcomes when cessation is initiated in the low progesterone follicular phase [121,122], and still others showing better outcomes when cessation is initiated in the luteal phase [123–125] or when progesterone levels are high [126,127]. Expert recommendations to clarify these findings have been made [128], and can be adapted from the smoking literature to inform evaluations of ovarian hormone effects in other substance use disorders.

Gold-standard brain imaging studies to determine effects of ovarian hormone status on striatal dopamine receptor availability and release are also needed, as existing findings are mixed. In the first such investigation, Wong et al. (1988) reported a trend toward lower D2-type receptor binding potential measured with 3-N-[^{11}C]-methylspiperone during the follicular phase compared to the luteal phase [137], and Munro et al. (2006) reported lower binding potential measured with [^{11}C]raclopride in the putamen during the luteal compared to follicular phase [52]. However, Czoty et al. (2009) found higher binding potential measured with [^{18}F]fluoroclebopride in cynomolgus monkeys [135], and Nordstrom et al. (1998) found no statistically significant effect of menstrual phase on binding potential in five women who were scanned twice during varying menstrual cycle phases [136]. All studies involved small *N*s (<10 per group), wide menstrual phase windows, and in some cases, a cross-sectional design. Evidently, a larger study with careful monitoring of menstrual phase and a longitudinal design to control for inter-individual variation is needed.

In addition to the focus on sex differences recommended above, attention to endogenous hormone levels, exogenous hormone administration, and genotype may improve efficacy of pharmacological and other therapies that target the dopamine system. Findings from the smoking literature may be useful in developing new hypotheses to evaluate sex differences in dopamine function, and ultimately in tailoring treatments to improve abstinence rates across all addictive disorders.

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HIGHLIGHTS:

- Sex differences in substance use disorders are related to dopaminergic dysfunction.
- Genes underlying dopamine function produce different behaviors in men and women.
- Hormone interactions with the dopamine system are a priority for future investigations.
- Smoking research provides insight into sex differences in therapeutic targets.

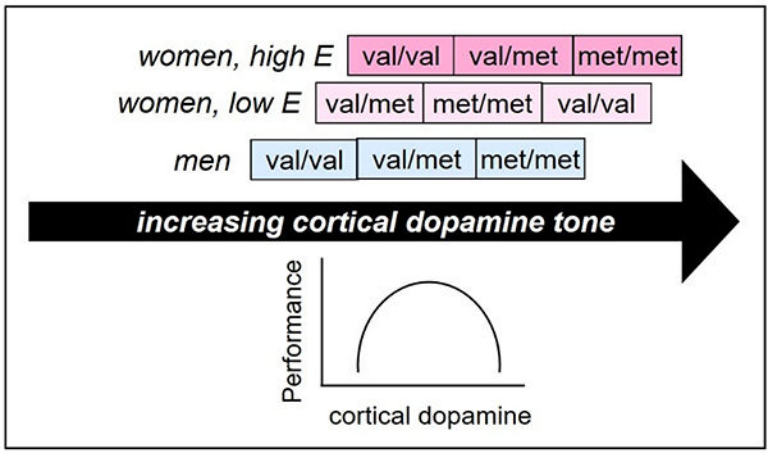

Figure 1. COMT genotype, sex, and estrogen (E) effects on cortical dopaminergic tone and cognitive task performance.

Cortical dopamine tone is higher in women than men, and in individuals with the met/met vs. val/met, and val/met vs. val/val genotypes. Cortical dopamine levels affect task performance in a parabolic, task-dependent manner: performance improves with increases in dopamine tone up to an optimum that depends on task demands, and then declines.

Table 1:

Sex differences in the effect of COMT polymorphisms on behavior. Depending on task demands and participant sex, additional cortical dopaminergic tone provided by val/met polymorphisms may improve or impair performance.

Reference	Task	Finding
Gurvich and Rossell, 2015	Continuous performance task	Female: val/val > val/met > met/met Male: val/val = val/met = met/met
Costa et al., 2016	Iowa Gambling Task (risk but not ambiguity trials)	Female: val/val > val/met = met/met Male: met/met = val/met = met/met
Lamb et al., 2016	Facial recognition	Female: val/val = val/met = met/met Male: val/val = val/met < met/met