

SEX DIFFERENCES, GENDER AND ADDICTION

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Abstract

This review discusses alcohol/other drug addiction as both a sociocultural and biological phenomenon. Sex differences and gender are not solely determined by biology, nor are they entirely sociocultural. The interactions among biological, environmental, sociocultural and developmental influences result in phenotypes that may be more masculine or more feminine. These gender-related sex differences in the brain can influence the responses to drugs of abuse, progressive changes in the brain after exposure to drugs of abuse and whether addiction results from drug-taking experiences. The basic laboratory evidence for sex differences in addiction is discussed within the context of four types of sex/gender differences.

Significance

Alcohol/other drug addiction is a major public health concern; understanding the basic mechanisms mediating the path to addiction in both women and men is important for improving prevention and enhancing treatment. In rodents, estradiol in female rats enhances acquisition and escalation of drug taking, motivation for drugs of abuse, and relapse-like behaviors. Nevertheless, even in rats, not all variation between the sexes is due to the biological processes involved, but result from an interaction among genetics, epigenetics, sociocultural factors and environmental conditions that mediate expression of specific traits such as risk and protective factors for addiction.

KEY WORDS: Addiction, Animal Models, Sociocultural Influences, Gender, Sex Differences

Introduction

The theme of this special issue is sex differences in the brain. This article will discuss the topic of gender and sex differences in drug addiction, our field of study, but there are similar gender and sex differences in compulsive behaviors such as gambling (Potenza et al. 2001; Blanco et al. 2006). We define addiction as the chronic, compulsive use of a substance or engagement in a behavior, regardless of negative consequences. We use sex to refer to the characterization of an individual as female or male from biological and morphological features. As discussed below, there are similar sex differences in humans and rodents in addiction or addiction-like behaviors (respectively). This suggests that there are some basic biological differences between females and males that influence how each responds to drugs of abuse and engage in addictive behaviors (Becker et al. 2012; Perry et al. 2013b; Carroll and Anker 2010; Lynch 2006; Kerstetter et al. 2012; Becker and Hu 2008).

Gender is defined as a system of social organization with a set of behavioral prescriptions that are believed to follow from biological sex characteristics. These perceptions of gender are socially constructed and shaped by sociocultural structures and processes over time (Fausto-Sterling 2012). Researchers in the social and natural sciences have demonstrated that addictions and consequences of addictions differ by biological sex and also by gender (Becker et al. 2016). A thesis of this article is that gender and sex differences in addiction are a complicated interaction between sociocultural factors and neurobiological sex differences.

Unfortunately, reports of “sex differences in the brain” means to many people who are not neuroscientists that male and female brains are “hard-wired” to be different from each other. In addition, the conceptualization of addiction as a “brain disease” contributes to the belief that some people’s brains make it almost inevitable that they will become addicts (Meurk et al. 2016; Hall et al. 2015; Johnson et al. 2015). When a scientist describes findings of sex differences that result in women becoming addicted more rapidly than men (Anglin et al. 1987), for example,

many non-scientists assume that there is nothing anyone can do to change this. While it is likely that some individuals are more vulnerable for addiction, as will be discussed below, it is not an inevitable outcome that a vulnerable person will necessarily become an addict. Additionally, for many people the label of 'brain disease' strips them of their agency, so they fail to take responsibility for their addiction (Wiens and Walker 2015). Neuroscientists understand that the human brain is not "hardwired", but it is rare that the nuances are conveyed to the public by the popular press. It is important to do so. Scientific findings need to be presented in a way that does not attribute sex differences in addiction entirely to the brain, and this message conveyed to the media as well. This idea will be revisited at the conclusion of this article.

A third goal for this article is to address a conclusion of an article by Vidal et al (2012), that "The challenge is not to deny that there are brain differences between the sexes, but to find out their origin and to assess their significance in real-life situations" (p. 301). This article discusses reports of "brain, sex and gender" by scientists and the subsequent popular reports. Both scientists and the lay audience may not dissociate the differences between mechanisms mediating biological sex differences (the meaning here is the hormone/genetic-driven differences between males and females) vs. cognitive sex differences (differences between males and females in fMRI images while performing cognitive tasks) (Vidal 2012). These two types of sex differences differ in the extent to which they may be modified by environmental and sociocultural factors, with cognitive sex differences being affected to a greater extent by learning.

First, some evidence for sex differences in addiction, in both animals and humans will be briefly reviewed. This has been the topic of a number of detailed reviews recently (Becker and Koob 2016; Carroll and Lynch 2016; Perry et al. 2016), the reader is referred to these articles for additional details. We describe four ways to understand patterns related to sex/gender, and then discuss how findings can be framed in terms of gender influences and sex differences in the brain. The article ends with thoughts about how to discuss results with

scientific and lay audiences in ways that stress the complex interrelationships among biological and environmental factors and challenge assumptions about biological determinism..

Sex Differences in Addiction.

This section provides a brief overview of the state of current knowledge regarding gender, and sex differences in addiction. It is important to note that unexamined assumptions about how women “should” behave have influenced research agendas (Campbell 2000; Campbell and Ettore 2011). As a result, findings remain incomplete and sometimes contradictory, particularly when the LGBT community is considered (Hughes et al. 2016). Nevertheless, humans, monkeys and rodents exhibit similar sex differences in addiction-like behavior (Carroll et al. 2005; Carroll et al. 2016; Becker et al. 2012) and biological sex differences can affect addiction-like behavior differently for males and females (Becker et al. 2012; Perry et al. 2013a). Effects of the environment and positive or negative experience can also affect the brain and influence vulnerability to addiction differently in males and females (Bowman et al. 2004; Thomas et al. 2009; Carroll et al. 2009).

For centuries it has been known that the phenomenon we now call addiction is a progressive condition. Today, we conceptualize addiction as having a series of stages: initiation/acquisition, escalation, maintenance, abstinence or withdrawal, and relapse or reinstatement of use (Table 1). The initial stage involves engagement with the drug, when the person or animal experiences its rewarding aspects after sampling the drug. It is important to note that some individuals never progress past this point, indefinitely using the drug occasionally or even stopping use. During acquisition the individual is not addicted, but for some individuals engagement and drug taking escalates and addiction follows, while others maintain moderate intake indefinitely or even stop using altogether (Deroche-Gamonet et al. 2004; Belin et al. 2008).

Using drugs can be related to social roles; for most of American history, men were much more likely than women to drink alcohol and use illicit drugs recreationally, while women were more likely to be prescribed drugs as medicine (McClellan 2011; Kandall 1999; McClellan 2017). Today, however, in adolescents equal numbers of boys and girls ages 12-17 use illegal drugs (Substance Abuse and Mental Health Services Administration 2014).

Within the general population, individuals differ in their risk for addiction due to a range of factors including genetic and personality traits (Heinrich et al. 2016), experience of trauma or abuse (Boschloo et al. 2011; Stevens et al. 2003; Kachadourian et al. 2014; Lieberman et al. 2016), and sociocultural influences (Felitti et al. 1998; Macleod et al. 2013). Physicians, psychiatrists and social workers have believed since early in the 20th century that women escalate alcohol use rapidly once they start (McClellan 2011; McClellan 2017; Kandall 1999). Still, we do not know what makes some individuals at greater risk for addiction. For those women and men who are vulnerable to addiction (i.e., escalate use after initial drug use and continue to use despite adverse consequences), women tend to progress more rapidly than men from initial experience to addiction (Bobzean et al. 2014; Brady and Randall 1999; Anglin et al. 1987). In contrast, a recent analysis of data from two U.S. national surveys found no evidence that in the general population women exhibit a shorter period of time from first use to alcohol dependence (Keyes et al. 2010). The contradiction may be explained by the fact that the “telescoping” phenomenon was reported for alcoholism in women who were in a treatment program already (Piazza et al. 1989). More rapid escalation after initiation of drug use in women compared with men has been replicated for other drugs of abuse (Richmond-Rakerd et al. 2016; Brady and Randall 1999; Moran-Santa Maria et al. 2014). In the general population only 15-20% are at risk for addiction (Kandel et al. 1997), therefore, it is possible that these differences occur within those individuals who make up the 15-20% of the population most at-risk, and this effect is obscured when the general population is studied. Thus, we are defining vulnerable as those

who show rapid escalation of drug taking. Among this vulnerable group, females exhibit a greater rate of escalation of drug use than males..

During attempts to quit drug use (abstinence), women exhibit greater unpleasant symptoms than men do (Hogle and Curtin 2006; Becker and Koob 2016). When trying to quit smoking, women also go through more severe withdrawal than men (Hogle and Curtin 2006). Women report greater effects on mood and anxiety as well as a greater stress response, compared to men (Hogle and Curtin 2006). On the other hand, males exhibit greater withdrawal symptoms when quitting alcohol consumption than females do (Devaud et al. 2003)

Most data suggest that women and men have similar outcomes after treatment for substance use disorders (Greenfield et al. 2007) once women have navigated all the barriers to treatment and engagement that they encounter. What has been reported to differ between women and men are the factors related to relapse, which is reported to be more sporadic (occurring without apparent trigger or intent) and related to negative affect as well as previous physical and sexual abuse among women (Greenfield et al. 2007; Walitzer and Dearing 2006; Hyman et al. 2008). This propensity to relapse associated with negative affect could be related to the greater withdrawal responses that women exhibit for some drugs (Hudson and Stamp 2011; Sinha et al. 2006). Alternatively, women might experience greater sensitivity to stress or the cues associated with the drug, as relapse can be triggered by these variables (Hudson and Stamp 2011). Greater stress or cue-induced reinstatement of drug taking by females after abstinence is seen in animal models of drug self-administration (Feltenstein et al. 2011; Anker and Carroll 2010). All of these factors have been reported to be related to relapse in studies of men and women who are addicted and are trying to quit (Becker and Koob 2016). There are also issues related to social support for maintaining abstinence, with men tending to receive more social support at home and on the job and women tending to be more isolated or not supported by their partners in their decision to be abstinent (Gallop et al. 2007; Schuckit et al.

1998; Campbell and Ettore 2011). Additionally, women who are addicted experience greater stigma than do men; this combined with less social support means more isolation and greater risk for relapse for women than men (Becker et al. 2016).

Interim Summary. Sex and gender differences in addiction and relapse can be seen in humans and in animal models. Among the vulnerable populations, females escalate drug use more rapidly than males and relapse is more likely to be triggered by stressful events or drug-related cues. But these differences are not solely determined by biology: sociocultural influences also differentially affect men and women and how they respond to drugs of abuse. In humans, stigma, on-going interpersonal violence, many more barriers to treatment-seeking and engagement, lack of social support for recovery among girls and women. The animal models as well as the clinical research need to take into consideration how contextual and social factors may influence the processes of addiction and relapse differentially in males and females.

Sex Differences in Animals Models of Addiction

The Neurobiology of Sex Differences in Addiction. For this very brief discussion of the neurobiology of sex differences in addiction we will focus on the nucleus accumbens and the dorsal striatum, but other areas of the brain are also involved in the neurobiology of addiction and the reader is referred to recent reviews for more details (Becker and Koob, 2016; (Becker et al. 2012; Perry et al. 2016). One current model for the development of addiction is that the nucleus accumbens is important for engaging in behaviors that are initially rewarding, while the dorsal striatum is involved in escalated drug taking and compulsive behaviors (Clark et al. 2013; Willuhn et al. 2012). When an individual experiences something new and exciting or consumes a new substance, dopamine in the nucleus accumbens and dorsal striatum are important for the development of craving or 'wanting' to experience it again, the endorphins in the nucleus accumbens are important for the pleasure or 'liking' for the new experience (Berridge 2009). In

this model of addiction, when dopamine activation of the dorsal striatum becomes greater than the response to the drug in the nucleus accumbens, there is a loss of pleasure associated with drug taking even though drug taking increases (DiFeliceantonio and Berridge 2016; Castro and Berridge 2014).

The dorsal striatum is important for well-learned patterns of behavior that can operate in the background without intentional control, which is usually exerted by the prefrontal cortex. For some habits such as learning to drive a car with manual transmission, this is an advantage for being able to shift gears when needed without conscious thought. The pattern of behavior, once learned, can be executed without thinking about it and it transfers from one car to another even when the gearshift is in a different position. This flexible pattern of automatic behavior also characterizes addiction. When intake progresses from being a casual pleasure to avid and compulsive intake, the pattern of activation in the brain has also shifted from dopamine activation in the nucleus accumbens to dopamine activation in dorsolateral striatum (Willuhn et al. 2012; Clark et al. 2013; DiFeliceantonio and Berridge 2016).

Among female rats and humans that become compulsive drug takers, there is the tendency to experience the shift in loss of voluntary control of drug intake to compulsive drug intake more rapidly than for males (Becker et al. 2012; Perry et al. 2016; Perry et al. 2013b). There is a reduction in nucleus accumbens dopamine release that is thought to be what allows the dorsal striatum to assume control of the addict's behavior, thereby transforming the drug taking into a compulsive behavior or what we consider addiction (Perry et al. 2015; Volkow et al. 2006; Clark et al. 2013; Willuhn et al. 2012). Female rats tend to exhibit a smaller response in the nucleus accumbens to drug stimulation initially, compared with males, and have a relatively greater and more rapid initial response in the dorsal striatum to drugs, coupled with a decrease in the accumbens response after cocaine taking is well established (Cummings et al. 2014; Cosgrove et al. 2014; Perry et al. 2016). This brain pattern may underlie the sex difference in

escalation of drug taking that leads to addiction. Supporting this notion, women who are smokers exhibit a lower response in the ventral striatum than in the dorsal striatum to nicotine stimulation compared with male smokers (Cosgrove et al. 2014)

Investigators have considered whether the long-term changes in the brain induced by exposure to the drug of abuse are what cause an individual to become addicted to that drug. Even though all individuals, both human and animal, will exhibit changes in the brain after receiving a drug of abuse (Leyton 2007; Wegener and Koch 2009; Willuhn et al. 2010; Andersen et al. 2012), as discussed above, only about 15-20% of the population of men become addicted to drugs or alcohol among humans (Brady and Randall 1999). In the laboratory, all rodents will eventually learn to self-administer cocaine or heroin if they are isolated in a self-administration chamber for many hours with a lever to push or a nose poke hole that delivers drug intravenously, but only about 10-16% of male rats will develop drug taking behaviors that are similar to the characteristics of addiction in humans (Belin and Everitt 2008; Deroche-Gamonet et al. 2004; Belin et al. 2008). In these studies animals are considered to exhibit addiction-like behavior if they continue to take a drug when receiving an aversive mild shock, exhibit high levels of responding on a progressive ratio schedule and continue to respond for the drug under conditions when drug is not available. A few studies have examined the proportion of female rats that develop addiction-like behavior in the laboratory; in these studies where males and females are allowed to choose cocaine or a food reward, more females than males choose cocaine and females exhibit higher responding for cocaine than do males (Perry et al. 2013b; Kerstetter et al. 2012; Kerstetter and Kippin 2011).

Not many studies have examined the neural mechanisms for sex differences in drug-taking behavior, and more research is clearly needed. In the studies that have investigated sex differences in addiction-like behavior in the laboratory, female rats tend to exhibit similar patterns of drug taking behavior to those seen for women. For example, female rats acquire

drug self-administration more readily than males (Carroll et al. 2002; Lynch and Carroll 1999; Jackson et al. 2006). This is true for all classes of drugs studied and for both rats and monkeys (Carroll et al. 2005; Carroll et al. 2002; Perry et al. 2007). Female rats also escalate their drug use more rapidly than males, take more drug when they get to maintenance dose and females will work harder to get a dose than male rats will (Roth and Carroll 2004; Westenbroek et al. 2013; Reichel et al. 2012; Anker and Carroll 2011).

There are changes in the brain of all individuals who get a drug, but the changes in the brains of individuals who become addicted are different from those who do not. This is assumed because the behavior of an addict is different from the behavior of a non-addict – if the behavior is different the brains are different. Why the changes in the brain are not the same between addicts and non-addicts is not yet completely known. Individual differences in genetics, personality traits, extent of social support, experiences or trauma during development, and in whether one is male or female are all thought to contribute to how someone responds to drugs of abuse and whether one develops compulsive behaviors associated with an addiction (Cummings et al. 2011; Perry et al. 2013b; Buisman-Pijlman et al. 2014; Becker et al. 2012; Thomas et al. 2009; Perry et al. 2005; Morgan et al. 2005; Carroll et al. 2002). This means that even though individuals can be categorized as male or female, or brought up in an impoverished vs. enriched environment, or other characteristics, these variables all interact within an individual to influence whether or not an individual will be susceptible to addiction.

Studies of rodents show that females exhibit enhanced drug-, cue-, and stress-induced reinstatement in alcohol, cocaine and morphine seeking, compared to males (Feltenstein et al. 2011; Anker and Carroll 2010; Becker and Koob 2016). The laboratory evidence supports the idea that there are biological components to the sex differences. But this does not mean that all women are going to be addicts or that women cannot quit once they have started. In fact,

studies document many barriers for women in traditional treatment programs, and that treatment programs tailored for women tend to be more successful (Campbell and Ettore 2011).

The Influence of Ovarian Hormones on Drug-Taking. For females, the phase of the menstrual/estrous cycle, and the reproductive hormones release that is associated with the cycle, may also affect drug taking and quitting behavior, because the ovarian hormones, estradiol and progesterone, have full access to the brain. The hormone condition of a woman needs to be considered when thinking about sex differences in addiction. The human menstrual cycle consists of follicular, periovulatory, and luteal phases. During the 10-12 day follicular phase, the hormone estradiol is secreted from the ovary as the follicle develops, with concentrations of estradiol increasing daily. Next, during the 2-4 day peri-ovulatory phase, a rapid increase in estradiol triggers the release of luteinizing hormone from the pituitary that induces ovulation. This is followed by the luteal phase that lasts 10-12 days and is characterized by the release of relatively high concentrations of both estradiol and progesterone from the remnant of the follicle that is retained by the ovary (the corpus luteum). Menstruation occurs at the end of the luteal phase, unless pregnancy occurs. During menstruation hormone levels are at their lowest point, indicating the beginning of the next follicular phase (Becker et al. 2005). Rats and mice have a four or five day estrous cycle that consists of a 2-3 day follicular phase called diestrus and a peri-ovulatory phase that is called 'proestrus' during the day of estradiol and progesterone surges and 'estrus' the day following the surges when the female rodent ovulates and is behaviorally receptive. Rats and mice do not have a spontaneous luteal phase (Becker et al. 2005).

The acute subjective effects of drugs of abuse can vary over the menstrual cycle in humans. For example, in women the subjective effects of cocaine and amphetamine tend to be more intense during the follicular phase when estradiol is elevated, relative to the luteal phase of the menstrual cycle when both estradiol and progesterone increase (Justice and de Wit 1999;

Justice and De Wit 2000; Evans et al. 2002). It is not clear, however, that these subjective effects of estradiol and progesterone moderate intake in the cocaine-addicted woman, as exogenous progesterone did not decrease the self-administration of cocaine in this population of women (Reed et al. 2011). On the other hand, women tend to drink more alcohol during the premenstrual phase of the menstrual cycle and women with premenstrual dysphoric disorder have higher levels of alcohol use/abuse (see Becker and Koob 2016 for a complete discussion).

Most of the research on how ovarian hormones influence drug taking behavior in females has been done in rats and mice. In ovariectomized (OVX) female rats, estradiol administration affects behaviors that are induced by cocaine, amphetamine or methamphetamine, including drug self-administration. For example, OVX decreases cocaine-taking behavior. If an OVX rat is given estradiol, the rat will take more cocaine and work harder to get cocaine, just as an intact rat during estrus will work harder for cocaine (Becker and Hu 2008; Roberts et al. 1989).

On the other hand, in males neither testicular hormones nor estradiol affects cocaine-taking (Jackson et al. 2006). This sex difference is attributable to sexual differentiation of the brain during early life (Perry et al. 2013a). Estradiol also enhances the acquisition of opioid self-administration in OVX rats, and intact females acquire morphine and heroin self-administration faster and will work harder to get cocaine, morphine and heroin than will males (Jackson et al. 2006; Carroll et al. 2002; Lynch 2008).

Animal Models of DSM Criteria for Addiction. Most laboratory studies are conducted with rats isolated in the testing chamber for hours. The chamber contains a lever or nose poke hole. The rat may receive an intravenous injection of a drug, such as cocaine, by pressing the lever or poking its nose into the hole. The rats learn to lever press or nose poke and start receiving drug. Most rats self-administer the drug, but not all rats will be highly motivated to get the drug under these conditions as determined by a progressive ratio schedule (where the

number of responses increases exponentially to get a single dose). When criteria are applied that are analogous to the DSM-IV criteria (responding for drug in the presence of adverse consequences; exhibiting high rates of responding for the drug on a progressive ratio schedule; responding for drug even when not available; and loss of motivation for previously valued rewards such as highly palatable food), only a small percentage of male rats exhibit characteristics of addiction (Perry et al. 2013b; Deroche-Gamonet et al. 2004; Belin and Everitt 2008; Belin et al. 2008). These authors argue that these behavioral paradigms are better models of addiction than simply whether the rodent will self-administer a drug, as they identify a specific phenotype of animal that is more susceptible for addiction.

In a choice paradigm a rat can choose whether to receive a banana-flavored sucrose pellet or an injection of cocaine, but only a subpopulation of rats choose cocaine. The initial preference for all of the rats is the sucrose pellets. Over a period of four to eight weeks, some rats choose the cocaine over the pellets, and once a rat makes that shift to cocaine it persists. In this paradigm about 50% of females choose the cocaine (compared with 15-20% of males). The females that choose cocaine also do this sooner than the males that ultimately choose cocaine (Perry et al. 2013b). Other investigators have also shown that more females choose cocaine over a food reinforce compared with males (Kerstetter et al. 2012; Kerstetter and Kippin 2011).

Estradiol plays a role in the acquisition of cocaine-taking behavior (Hu and Becker 2008; Anker and Carroll 2011; Hu et al. 2004). Once the female is avidly self-administering cocaine, however, the ovarian hormones are no longer modulating the motivation for cocaine and cocaine intake does not vary with the estrous cycle in the choice paradigm (Cummings et al. 2011; Perry et al. 2015; Perry et al. 2013b). These results suggest that estradiol is important for the initiation of drug taking, but once the behavior is well established, it is no longer under ovarian hormone regulation.

To summarize, hormones of the menstrual or estrous cycle may enhance the initial reinforcing effect that a female gets from a drug of abuse. But once the addictive behavior is established, the hormones do not continue to play as important a role in rats or humans. Thus, the menstrual cycle may contribute to the more rapid escalation of drug taking seen in women and female rats compared with males, by increasing the positive effects of drugs of abuse during the initial stages of acquisition. This phenomenon is most likely greater in the sub-population of women who are more vulnerable for addiction.

Types of Sex Differences

The brains of males and females can differ from each other in more than one way (Becker et al. 2016; McCarthy et al. 2012). Not all sex differences in the brain develop in the same way and they are expressed in different ways. Males and females are sometimes referred to as “opposites,” or it is implied that there is a bimodal distribution of traits that typify “males” and “females”, but for most differences between males and females this is not true. There are four types of sex differences (Becker and Koob 2016; McCarthy et al. 2012) and more than one of these types of sex difference may be involved when we see variation on a given trait between males and females (Table 2). The most obvious sex differences relate to reproduction, for example women ovulate and have babies while men produce sperm and don't get pregnant. These types of sex differences are called **qualitative sex differences**. Then there are more subtle sex differences, here the average or mean is different for males and females but the neural mechanisms are the same (**quantitative sex difference**). We see this is the psychomotor activation induced by amphetamine, where females exhibit a greater initial response to the same dose of the drug and greater behavioral sensitization (Hu and Becker 2003; Camp and Robinson 1988; Camp et al. 1986).

There are also sex differences where males and females exhibit the same response, but the mechanism underlying the trait is different (**convergent sex difference**). In this case there is convergence of function while the mechanisms mediating the trait are different for males and females. We think that some aspects of addiction are mediated by convergent sex differences as discussed above. For example, both males and females progress to compulsive drug taking and addiction, but in females estradiol is hypothesized to facilitate this transition by enhancing dopamine in dorsal striatum (see discussion above).

Finally, there can be sex differences where the proportion of males and females that exhibit a trait is different (**population sex differences**). The difference in the rate of escalation of drug taking is likely a population sex difference. Prenatal stress causes male rats to escalate drug taking so they resemble females (Thomas et al 2009). Experience interacts with the developing brain, in this example, to shift the proportion of male rats that show rapid escalation of drug taking to be comparable to females. In one retrospective study, family violence in childhood, especially directed against the child, was associated with increased risk of injection drug use for both men and women (Macleod et al. 2013). So the population of individuals with drug abuse problems may be increased by childhood abuse or trauma. In a prospective study, abused and neglected girls were more likely than boys from comparable backgrounds to abuse illegal drugs as adults (Wilson and Widom 2009). As this example shows, the number of men and women with drug abuse problems depends on the developmental experiences of both boys and girls and the outcome measure. In some cases a population sex difference may appear to be quantitative sex difference if only the means of the dependent variable for males and females are considered – rather than looking for variation within males and females.

Each type of sex difference contributes to the overall phenotype of an individual; while all four types of sex differences are acting within each person, and individual types of sex

differences may shape the phenotype of an individual in different ways. This makes the continuum of masculine-feminine traits even richer in terms of the variety that can be produced.

Sex Differences and the Scientist's Obligation to the Public

Research on the differences between females and males can be controversial, especially in societies like ours where gender roles are in flux, and because assumptions about immutable biological differences have been used to justify unequal opportunities for women compared to men. That is exactly why the issue must be approached with rigorous scientific methods, and scientists must be aware of the political and social contexts surrounding their work. The bodies of men and women have many elements that look and function essentially in the same way (e.g., we all have arms and legs, lungs and a liver, etc.), yet we tend to be defined by our different sexual organs. The first question we ask a new parent is: Is it a boy or a girl? We ascribe essential differences to individuals based on whether they are male or female, without knowing if a particular trait is present in a particular individual (Fausto-Sterling 2012).

When scientists say that the brains of men and women are different, the intent is to convey that our brains have some regions that look and function the same in men and women and others that look and function differently (Cahill et al. 2001; Cahill 2014; Cahill 2006). There is variation in masculine and feminine traits due to variations in genes expressed, the hormones secreted during development, the intra-uterine environment, as well as influences of maternal nutritional status, stress and the hormones of puberty (McCarthy and Arnold 2011; Sisk and Zehr 2005; Bale and Epperson 2015). These biological processes are further modified by individual experience and sociocultural factors that can differentially affect females and males (Figure 1).

For example, if a mother rat undergoes restraint stress during the last week of gestation, the period when the fetal testes are normally masculinizing the brain, there are permanent effects on brain and behavior (Kerchner and Ward 1992; de Souza et al. 2013). Both male and

female offspring will show the effects of their mother's stress, but in different ways. The males in the litter will be less aggressive, more prone to addiction and will have learning deficits as adults (Thomas et al. 2009; Bowman et al. 2004). On the other hand, the females will exhibit greater anxiety and depressive-like symptoms as adults (Thomas et al. 2009; Bowman et al. 2004; Van den Hove et al. 2013; Ward and Stehm 1991).

Other types of activities or events can also affect development of the brain in different ways for males and females. Events and experience during development can have the same or different effects on males and females (Juraska 1984; Juraska 1998). The direction of the effect depends on what type of event it is (e.g., good vs. bad nutrition would have different types of influences than enriched environments). Furthermore, even though gendered experiences during development (e.g., playing trucks or hitting a ball vs. playing with dolls or jumping rope) may be influenced by prenatal hormones, these experiences also contribute to greater sex differences in the brains of adults than would be there without these variations in experience (Hines 2011).

For many sex differences in the brain, male-typical and female-typical traits could be considered to be represented along a continuum, rather than a bimodal distribution (Figure 1). Each human's brain is the result of an intricate interplay between biology and environment across the life span. This means that not all areas of a given brain are "masculine" (displaying characteristics more likely to be seen in males) in all men or "feminine" (with features more strongly associated with females) in all women. In fact, it is suggested that the human brain tends to be a mosaic of sexually differentiated brain regions, some of which tend to be more "masculine", and others more "feminine" (Cahill 2006). The brains of women and men develop through complex interactions among the biology (the brain developing in response to genetic and hormonal signals), the physical environment, and sociocultural experiences of an individual,

all of which shape the development of the brain throughout life (Hines 2011; Wallen 1996). As a result, customs and practices contribute to sex differences in the brain.

It is important to remember that even for laboratory animals there are behavioral and experiential effects interacting with the biology to differentially affect females and males. Not only is there variation among females and males, as discussed above, but also different types of sex (and gender) differences emerge from these various processes. In this time of individualized medicine, sex differences are important, but not as a bimodal characteristic of an individual, or discussed separately from environmental influences, and scientists have a responsibility to convey these nuances to the general public. Sex differences are important as a biological factor that interacts with genetics, epigenetics and environmental conditions to mediate developmental pathways for expression of specific traits.

Authorship:

JBB, MM, and BGR were all involved in the conception of this manuscript. JBB drafted the original manuscript. All provided critical revisions of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

The authors confirm they have no conflict of interest.

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Figure Legends

Figure 1. The sexual differentiation of the bi-potential brain is not bimodal – ending up either all male or all female. Instead the adult brain exists on a continuum that can be influenced by events during embryonic development and postnatal life. Events prior to puberty will tend to have a greater effect on the adult brain than events after puberty.

- A. Sexual differentiation of the brain is a result of testosterone produced by the developing testes in the male acting on the bi-potential brain to induce sexual differentiation of target brain regions. At puberty hormones from the testes and ovaries induce additional developmental events throughout the brain that further enhance or diminish sex differences in the brain. In the figure the bipotential brain is depicted in lavender that becomes more blue (masculine) or red (feminine) during development. The red arrows depict the female typical path and the blue arrows the male-typical path. Prior to puberty the brains are not fully formed and the hormones at puberty influence development further to result in the final phenotype. The bar at the bottom indicated that the sexual differentiation of the brain exists along a continuum from feminine to masculine.
- B. Experiences during prenatal development Influence sex differences in the brain (large green 'Experience' arrows). Events and experience during development can have the same or different effects on males and females. The direction of the effect depends on what type of event it is and when it happens during development. In the example here, prenatal experience, such as maternal stress can make both male and female fetuses less masculinized. Resulting in offspring that are both shifted in the same direction along the continuum. Other developmental events could have different effects.
- C. Experiences during post-natal development prior to puberty, such as playing with trucks by boys (blue 'Experience' arrow) vs. dolls by the girls (red 'Experience' arrow), can lead to greater sex differences in the brains of adults than would be there without these

variations in experience. If boys and girls have the same experiences, both would potentially be affected by the experience, but the direction of the effect would depend on the brain at the time the experience occurs.

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Table 1. Sex Differences in Stages of Addiction

	Acquisition	Escalation	Maintenance	Withdrawal	Relapse
Women	Initial exposure to drug, food or activity. May experience more pleasurable responses to drugs than men (cocaine, amphetamine). More likely to self-medicate than men.	Increase in amount and frequency of drug taking. For those at risk for addiction, escalation is more rapid than for men (gambling, alcohol, drugs).	The addictive behavior is established and stabilizes. Females stabilize at higher doses of drug than do males. Side effects of drug use are greater for women.	Female smokers report increased negative affect during withdrawal and experience a greater stress response than men do.	Women are more likely to relapse than men and do so more sporadically.
Men	Initial exposure to drug, food or activity. Take drugs and engage in risky behaviors to be part of the group more than women do.	Slower escalation than for women (gambling, alcohol, drugs).	The addictive behavior is established and stabilizes. Males stabilize at lower doses of drug than do females.	Men exhibit greater symptoms of withdrawal from alcohol than women.	Men have longer periods of abstinence than women.

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Table 2. Types of sex differences

Type	Qualitative sex differences	Quantitative sex differences	Convergent sex differences	Population sex differences
How males and females differ	Females exhibit one behavior and males exhibit a different behavior on a given test. The traits cannot be measured on the same scale.	One sex exhibits a greater response than the other in the same conditions. The event can be measured on the same scale.	Males and females exhibit the same behavior, but the underlying processes that mediate the trait are different.	The proportion of males and females with a trait differs.
Example	Women ovulate once every 28 days, males produce sperm continuously (24/7). Most qualitative differences are directly related to reproduction. Pair housing decreases motivation for cocaine in female rats but not males ¹ could be argued to be a qualitative difference, <u>- also a quantitative difference</u>	Women have greater verbal fluency (talk faster and say more words) than men do and men do better on tasks of spatial functions than women ² . Female rats exhibit greater rotational behavior after amphetamine than do male rats ³ .	Memory associated with emotionally arousing material is equivalent in men and women, but men and women use different areas of the brain to perform the task ⁴ . Male and female rats both exhibit locomotor activity and stereotyped behaviors after treatment with amphetamine, but the areas of the striatum that exhibit c-fos activation are different ⁵ .	More men are mathematicians than women and this is mediated by sociocultural factors related to gendered expectations ⁶ . More female <u>rats</u> rapidly escalate drug use and acquire a preference for cocaine <u>over palatable pellets</u> than males ⁷ .

¹(Westenbroek et al. 2013); ²(Hampson and Kimura 1988); ³(Robinson et al. 1980); ⁴(Cahill et al. 2001); ⁵(Castner and Becker 1996); ⁶(Watt et al. 2012); ⁷(Perry et al 2013b; 2015)

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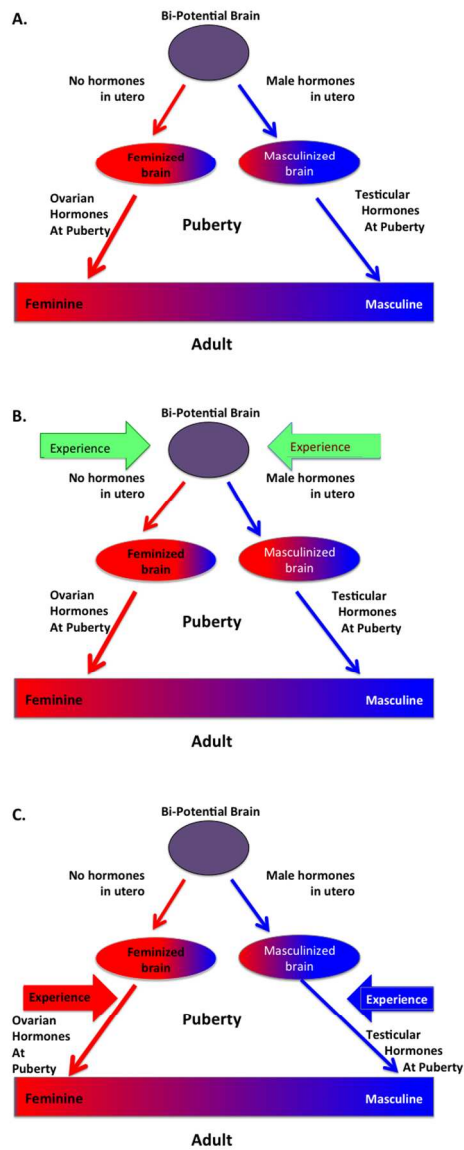


Figure 1

254x564mm (72 x 72 DPI)

