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Sex differences in impulsive action and impulsive choice

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HIGHLIGHTS

- In laboratory animals and humans, females tend to discount more steeply than males.
- In laboratory animals, males tend to show greater impulsive action than females.
- In humans, sex differences in impulsive action depend on tasks and subject samples.
- Among heavy drinkers and smokers, women show greater impulsive action than men.

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ABSTRACT

Here, we review the evidence for sex differences in behavioral measures of impulsivity for both humans and laboratory animals. We focus on two specific components of impulsivity: impulsive action (i.e., difficulty inhibiting a prepotent response) and impulsive choice (i.e., difficulty delaying gratification). Sex differences appear to exist on these measures, but the direction and magnitude of the differences vary. In laboratory animals, impulsive action is typically greater in males than females, whereas impulsive choice is typically greater in females. In humans, women discount more steeply than men, but sex differences on measures of impulsive action depend on tasks and subject samples. We discuss implications of these findings as they relate to drug addiction. We also point out the major gaps in this research to date, including the lack of studies designed specifically to examine sex differences in behavioral impulsivity, and the lack of consideration of menstrual or estrous phase or sex hormone levels in the studies.

1. Introduction

Here we review the literature regarding sex differences in behavioral measures of impulsivity, within the broader context of how these differences might relate to drug abuse. Men are generally thought to be more impulsive and men also exhibit higher rates of drug use and abuse. However, the evidence for sex differences in impulsivity using objective behavioral measures is mixed. We first briefly review the evidence for sex differences in substance abuse, as well as associations between impulsivity and drug abuse and the potential modulating effects of sex hormones. We define the specific behavioral components of impulsivity (i.e., impulsive action and impulsive choice) that will be the focus of this review, as well as how these are measured in both laboratory animals and humans. We then review the literature on sex differences in impulsive action and impulsive choice. Within each impulsivity component, we report evidence from laboratory animals and humans. For human studies we report findings from both behavioral and neuroimaging studies, and in healthy individuals as well as substance abusers. Finally, we summarize the findings to date and discuss how these fit within existing theoretical framework regarding impulsivity and sex differences, as well as speculate on potential links between sex differences in impulsivity and sex differences in drug abuse. We then point out the gaps in the literature, as well as propose directions for future research.

2. Sex differences in drug abuse

Men and women differ in several indices of drug abuse, but the differences are sometimes conflicting. Men report higher levels of alcohol, tobacco, and illicit drug use including marijuana, cocaine, and hallucinogens than women (SAMHSA, 2011), and men are twice as likely as women to meet criteria for abuse and dependence. Yet, women progress faster from initiation of drinking to problem drinking and dependence (Piazza, Vrbka, & Yeager, 1989; Randall et al., 1999; although see Alvanzo et al., 2011; Keyes, Martins, Blanco, & Hasin, 2010). In laboratory animals, females acquire drug self-administration more rapidly than males, and exhibit more binge patterns and greater reinstatement of drug-seeking (Becker & Hu, 2008; Carroll & Anker, 2010; Lynch, Roth, & Carroll, 2002). There are numerous potential explanations for observed sex differences in drug abuse, including sex differences in

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pre-existing risk factors for abuse. One such risk factor is impulsivity, described below.

3. Impulsivity and drug abuse

Impulsivity, broadly defined as a tendency to act without thinking and without consideration of future consequences, is strongly implicated in drug abuse (de Wit, 2009; Perry & Carroll, 2008). Greater impulsivity is thought to increase risk for drug abuse, and conversely, drugs of abuse produce acute and chronic changes in impulsivity. Behavioral impulsivity is thought to consist of two distinct components: impulsive action and impulsive choice. Impulsive action (also known as behavioral inhibition) involves difficulty inhibiting or controlling behavior, whereas impulsive choice refers to the tendency to prefer smaller, immediate rewards to larger, delayed rewards. Both of these components have been shown to predict different aspects of drug abuse, and acute or chronic use of a drug can alter both types of behavior (Perry & Carroll, 2008).

4. Role of sex hormones

Sex differences may be due to organizing factors at critical phases during development, as hormones present during development may permanently affect both vulnerability to drug abuse and impulsive behavior. Sex differences may also be attributable to circulating levels of sex hormones, as circulating levels of testosterone, estrogen or progesterone may affect these behaviors at any point in life. In laboratory animals, there is some evidence that circulating levels of the ovarian hormone estrogen affect the reinforcing effects of drugs. Estrogen modulates dopaminergic function by enhancing dopamine release and increasing D2 receptor densities (Bazzett & Becker, 1994; Dazzi et al., 2007; Di Paolo, 1994; Xiao & Becker, 1994) and dopamine is thought to be the primary mechanism through which drugs exert their acute rewarding effects (e.g., Di Chiara et al., 2004; Koob & Volkow, 2010). Both impulsive action and impulsive choice are also linked to the dopamine system (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Dalley et al., 2007; Del Campo, Chamberlain, Sahakian, & Robbins, 2011; Diergaarde et al., 2008), and this suggests a potential mechanism through which sex hormones could modulate impulsivity as well.

5. Behavioral measures of impulsive action and impulsive choice

In humans and laboratory animals, impulsive action, or the ability to inhibit inappropriate responses, is typically assessed with stop signal and go/no-go tasks (Logan, Schachar, & Tannock, 1997; Newman, Widom, & Nathan, 1985). These measures involve a reaction time task in which subjects must respond as quickly as possible to 'go' stimuli, while inhibiting responses when no-go targets are presented or when a stop signal (e.g., an auditory tone) occasionally occurs. The major dependent measures derived from these tasks include number of commission (i.e., inhibitory) errors, and stop signal reaction time (SSRT), an estimate of the time necessary to inhibit a response. More commission errors and longer SSRTs are indicative of greater impulsive action. Another procedure commonly used in laboratory animals is the 5-choice serial reaction time test (5-CSRTT; Robbins, 2002) in which animals are trained to respond when 'go' signals are presented, and to inhibit such responses when 'go' signals are not presented. Responses that are made before the 'go' signal are considered premature responses, or inhibitory errors, and these are indicative of greater impulsive action.

Impulsive choice is typically assessed in both humans and laboratory animals using discounting tasks in which subjects make choices between small rewards delivered immediately or with 100% certainty, or larger rewards delivered after a delay or with less than 100% certainty (Richards, Zhang, Mitchell, & de Wit, 1999; Thiebot, Le Bihan, Soubrie, & Simon, 1985). A curve is plotted based on the subject's points of indifference between immediate and delayed rewards, and steeper discounting curves indicate greater impulsive choice. Human subjects perform these tasks for either real reward, usually money, in which they have a chance to actually receive one of their choices or for hypothetical monetary rewards. In laboratory animals, animals respond on one lever for a small, immediate reward (e.g., a food pellet), and respond on a different lever for a large, delayed reward (e.g., several food pellets after 30 s). Discounting curves are plotted, or the reward delay is adjusted and the mean adjusted delay (MAD) is calculated. In both humans and nonhumans, steeper discounting curves and shorter MAD are indicative of greater impulsive choice, or greater discounting of delayed reward.

6. Sex differences in impulsive action

6.1. Laboratory animals

There is mixed evidence for sex differences in impulsive action in laboratory animals (see Table 1 for a summary). Papaleo et al. (2012) found no sex differences in mice on 5-CSRTT acquisition or performance during the challenging task condition (although males learned to perform less impulsively than did females over repeated testing). However, when mice were no longer food-restricted or exposed to a mild stressor, males displayed greater premature responses than females. Using a simpler version of the task (the 2-CSRTT), Burton and Fletcher (2012) found no sex differences in either young or adult rats in task acquisition, but adult females made more premature errors than did adult males in the challenging task condition. Finally, Anker et al. (2008) found no sex differences in premature responding for a food reward on a go/no-go task, but reported that female rats made more premature responses when responding for a cocaine drug reward. Thus, the direction of sex differences in impulsive action depends in part on the species studied (mice vs. rats), the task used (5-CSRTT vs. 2-CSRTT), and the reinforcer (food vs. drug).

Studies that have taken sex hormones into account provide more consistent evidence of greater impulsive action in male laboratory animals compared to females. Jentsch and Taylor (2003) examined sex differences in normal and gonadectomized rats on a modified version of the 5-CSRTT. In intact animals, males made more premature responses both during task acquisition and in a challenging task condition (i.e., longer inter-trial intervals). Gonadectomy decreased impulsive action in males, suggesting that the difference was related to circulating levels of testosterone, but ovariectomy increased impulsive action in females, suggesting that ovarian hormones also play a role. Bayless et al. (2012) compared 5-CSRTT performance of male to female rats tested only in the proestrous phase of the estrous cycle (when estradiol levels are high, as verified by vaginal smears). In this study, male rats committed more premature responses in the challenging task condition, indicating greater impulsive action. In sum, males show greater impulsive action in studies that take sex hormones into account, whereas studies that do not account for hormones provide mixed evidence regarding the presence and direction of sex differences. This suggests that circulating hormones contribute to the greater impulsivity observed in males, and emphasizes the importance of taking sex hormones into account when assessing sex differences in impulsive action in laboratory animals.

6.2. Humans

Investigations of sex differences in impulsive action in humans have produced mixed results (see Table 1). On go/no-go tasks males commit more inhibitory errors than females in samples of both adults (Saunders et al., 2008) and children (Liu et al., 2013). Similarly, a meta-analysis of 8 studies using the continuous performance task (CPT, in which impulsive action is assessed by errors of commission) in children and adolescents