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Review article

Sex differences in the brain: Implications for behavioral and biomedical research

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ABSTRACT

Biological differences between males and females are found at multiple levels. However, females have too often been under-represented in behavioral neuroscience research, which has stymied the study of potential sex differences in neurobiology and behavior. This review focuses on the study of sex differences in the neurobiology of social behavior, memory, emotions, and recovery from brain injury, with particular emphasis on the role of estrogens in regulating forebrain function. This work, presented by the authors at the 2016 meeting of the International Behavioral Neuroscience Society, emphasizes varying approaches from several mammalian species in which sex differences have not only been documented, but also become the focus of efforts to understand the mechanistic basis underlying them. This information may provide readers with useful experimental tools to successfully address recently introduced regulations by granting agencies that either require (e.g. the National Institutes of Health in the United States and the Canadian Institutes of Health Research in Canada) or recommend (e.g. Horizon 2020 in Europe) the inclusion of both sexes in biomedical research.

1. Introduction

Considerable interest has been directed towards understanding differences in how male and female physiology can contribute to sex differences in disease incidence, manifestation, and outcome. This review begins with an overview of an evolutionary explanation of why sex differences in different traits may have developed, with an eye towards understanding how studying an evolutionary perspective can aid in our understanding of sex differences in the regulation of social behavior, cognition, and recovery from stroke.

1.1. Brief History of the Evolution of Sex Differences

Species in which two distinct cell types, the gametes, must fuse together to produce offspring (i.e. species with sexual reproduction) are typified by two distinct sexes each producing morphologically different reproductive cells. Further sex differences evolve when different evolutionary pressures exist for each sex, the exact nature of which depends upon a species' particular ecology (recently reviewed in Morrow, 2015). Charles Darwin, in his 1871 two-volume book entitled "The Descent of Man, and Selection in Relation to Sex", formulated the theory of sexual selection to explain the existence of a considerable number of species with behavioral and morphological sexual dimorphisms. According to Darwin's theory of sexual selection, two factors can skew reproductive success towards one sex versus the other. The first, intrasexual competition (often among males) is heightened when access to reproduction is limited to few members of a sex. The second, intersexual choice, drives sex differences when the mating preferences of one sex (often the female sex) cause the evolution of specific traits in the opposite sex. Although sexual selection can explain traits that affect mating success in a number of species including *Homo sapiens* (Geary, 2010, 2016), it is less suitable for explaining sex differences in traits, such as foraging strategies, that may not be directly involved in intrasexual competition or intersexual mating choices. For these traits, differences in the selective pressures acting on the two sexes can better explain the evolution of sex differences (Lande, 1980; Morrow, 2015). In this regard, the evolution of sex differences can be seen as driven by differences in the life history strategies that enable males and females to maximize reproductive success over a lifetime (Morrow, 2015).

A number of proximal mechanisms for the evolution of sex differences have been investigated, including the hormonal or genetic sex-

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dependent regulation of functions (Arnold, 2017), sex-specific epigenetic regulation of genes (e.g. different DNA methylation patterns in males and females; Day and Bonduriansky, 2004; Naumova et al., 2013; reviewed in McCarthy and Nugent, 2013), and alternative splicing of gene transcripts (McIntyre et al., 2006), as well as sex chromosome-linked genes (reviewed in Arnold, 2017; Ellegren and Parsch, 2007; Wyman et al., 2012). When present, sex differences in traits have implications for a number of phenotypes, from physiological to behavioral, as well as for susceptibility to stressors, pathogens, and disease (Hamilton and Zuk, 1982; reviewed in Morrow, 2015; Roved et al., 2017).

1.2. Why Studying Evolutionary causes of Sex Differences in Traits Matters

The evolutionary causes of sex differences may aid our understanding of sex differences in disease and can inform sex-targeted and sex-appropriate medical interventions. The approach of using evolutionary theory to better understand medical conditions has been formulated in the field of medicine often referred to as "Evolutionary or Darwinian Medicine" (Nesse and Williams, 1996; Nesse et al., 2010) and can be applied to the understanding of sex differences in disease, mortality, and lifespan (e.g. Gilks et al., 2014; Kruger and Nesse, 2006).

Sex differences in psychiatric disorders may be rooted in sex differences in brain and behavior that are frequently found in a number of species including humans and rodents (Earls, 1987; see recent meta-analysis in Ruigrok et al., 2014). For example, females of these species tend to be more sensitive and responsive to potential threats, showing enhanced stress responses and defensive behaviors (Blanchard et al., 1991; Craske, 2003; Jolles et al., 2015; reviewed in Palanza, 2001; Shors, 2016). This reaction appears evolutionarily adaptive in view of the greater reproductive and parental investment by mammalian females, whereby greater evolutionary costs (i.e. reduced offspring survival) are associated with the loss of females than the loss of males. The evolutionarily adaptive female advantage in risk aversion in humans (Betzig, 2012; Maner et al., 2007) may explain female predominance in psychiatric disorders related to the activation of the stress systems such as anxiety disorders, phobias, depressive disorders, (Rutter et al., 2003), and post-traumatic stress disorders (Craske, 2003; Klabunde et al., 2016).

On the other hand, the males of many species tend to show greater levels of active patrolling of a territory (Gaulin and Fitzgerald, 1986; Jacobs et al., 1990; reviewed in Geary, 2010), and better spatial ability than females (Spritzer et al., 2005). Those males also tend to display more aggressive behaviors related to defending territories and gaining exclusive or priority access to important resources. This male advantage in social competition, territoriality, and active territory use is common in many species (Wilson and Daly, 1985; reviewed in Ervin et al., 2015a; Geary, 2016; Marlowe, 2005), and may be linked to the higher incidence and/or severity in men of risk-taking disorders, impulsive behaviors, and disorders of social behavior such as autism spectrum disorders (Lai et al., 2013), early onset schizophrenia (Shepherd et al., 2012), and violence and impulsive aggression (Caspi et al., 2014; Rice, 2015).

Steroid hormones such as estrogens, progestins, and androgens are involved in driving the development and subsequent regulation of sexually different structures, function, and behavior throughout life. Developmental (also termed "organizational") actions of hormones lead to the often sexually different life-long epigenetic regulation of genes (reviewed in McCarthy and Nugent, 2013). So called "activational" effects of hormones are also seen at puberty (Schulz and Sisk, 2016) and in adulthood, as hormones continue to regulate and modulate multiple behaviors and cognitive functions (reviewed in Arnold, 2017, Ervin et al., 2013; Gillies and McArthur, 2010). The laboratories of the speakers of the symposium "Sex Differences in the Brain: Implications for Behavioral and Biomedical Research" presented at the 2016 conference of the International Behavioral Neuroscience Society have devoted considerable effort to understanding the activational role of hormones in various behaviors, brain functions, brain health, and the molecular functioning of brain cells. These investigations have often demonstrated sex differences in the way that estrogens, progesterone, and androgens affect those biological systems. Below, Drs. Elena Choleris, Liisa Galea, Karyn Frick, and Farida Sohrabji summarize their findings showing sex differences in, and hormonal regulation of, rodent social behavior, pattern separation and spatial learning, as well as the molecular mechanisms of memory and recovery from stroke. We first review literature on sex differences and hormonal underpinnings of social behavior (Section 2), with a focus on brain regions underlying regulation of key social cognitive skills, social recognition, social learning, as well as known sexual dimorphisms in social interactions and aggression. We subsequently review literature on sex differences in spatial cognition (Section 3), with a focus on the brain plasticity and hormonal mechanisms underlying pattern separation and spatial learning. In Section 4, we focus on the molecular mechanisms through which estrogens and progesterone regulate memory formation in females and discuss emerging data suggesting sex differences in these mechanisms. In Section 5, we present an overview of sex differences in the outcome and therapy of strokes deriving from research with humans and animal models. Finally, this review concludes with some general thoughts about future directions for sex differences research.

2. Sex differences in rodent social behavior: hormonal influences.

Hormones regulate most aspects of social behavior, from reproduction and mate choices, to social cognition, social interactions, and aggression. The regulation of sexual and reproductive behaviors is a well-studied function of androgens, estrogens and progestins (for recent reviews see Georgiadis et al., 2012; Motta-Mena and Puts, 2017). Sex hormones are also involved in regulating the choice of, and preference for, specific mates. Generally, the sex that has the greatest investment in reproduction is also the choosiest when it comes to mating. In mammals, this is typically the female (Edward, 2015; Jennions and Petrie, 1997). Female mating and mating preferences are driven by the phase of the estrous cycle. In rodents, females are sexually receptive and proceptive only when both estrogens and progesterone peak, during the proestrous/behavioral estrous phase (Walmer et al., 1992). In humans, even though mating occurs throughout the menstrual cycle, sex drive and preference for traits linked to "good genes" are increased during the fertile phase, with evidence suggesting this is driven by estradiol as well as androgens (reviewed in Motta-Mena and Puts, 2017). Mating preferences in most non-human animals are also driven by androgens (possibly *via* their estrogenic metabolites) in males and both estrogens and androgens in females (reviewed in Adkins-Regan, 1998, 2009).

The choice of specific mates and/or social partners requires the cognitive function of social recognition. Social recognition can be broadly defined as an animal's ability to distinguish between conspecifics, and is important for the establishment of social hierarchies, social bonds, mate choices, territoriality, and the avoidance of infected or sick individuals (reviewed in Choleris et al., 2009, 2012; Ervin et al., 2015a; Sánchez-Andrade and Kendrick, 2011). Social recognition is regulated by sex hormones, especially estrogens. In addition to social recognition, estrogens regulate social learning, which is defined as, "learning that is influenced by observation of, or interaction with, another animal (typically a conspecific) or its products" (such as odor cues; Box, 1984; Galef, 1988; Heyes, 1994). Social learning is evolutionary adaptive in that by "exploiting the expertise of others" (Russon, 1997), it can allow animals to circumvent the costs that may be associated with trial-and-error individual learning (recently reviewed in Matta et al., 2016; Ervin et al., 2015a).

Social recognition also affects how animals interact with conspecifics, which can be investigated in the laboratory by assessing social interactions between cagemates or strangers. Such social interactions