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Review article

How does sex matter? Behavior, stress and animal models of neurobehavioral disorders

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ABSTRACT

Many aspects of brain functioning exhibit important sex differences that affect behavior, mental health and mental disorders. However, most translational neuroscience research related to animal models of neurobehavioral disorders are carried out in male animals only. Based on published data from our laboratory on the House mouse, we discuss the following issues: (1) sex differences in social behavior of wild-derived mice; (2) artificial selection of laboratory strains and its consequences on social and reproductive competition; (3) sex-dependent effects of common experimental procedures; (4) differential effects of developmental events: the case of endocrine disruption; (5) implications for female models of stress and neurobehavioral disorders. Altogether, this review of data outline the marked differences of male and female responses to different social challenges and evinces the current lack of a relevant female mouse model of social stress. Whilst animal modelling is an important approach towards understanding mechanisms of neurobehavioral disorders, it is evident that data obtained in males may be irrelevant for inferring psychopathology and efficacy of pharmacological treatments for females.

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1. Introduction

"A theory has only the alternative of being right or wrong. A model has a third possibility: it may be right, but irrelevant".

Sex differences exist in the vulnerability, incidence, manifestation and treatment of numerous neurological and psychiatric diseases, including the top diseases contributing to the global burden of disease, which in the European Union has been recently calculated as 30.1% in women and 23.4% in men (Wittchen et al., 2011). Many of these disorders exhibit gender bias in frequency, severity, symptomatology, illness course and/or response to treatment (Gobinath et al., 2017). Males are over-represented in neuropsychiatric disorders with origins in development, whereas females disproportionally suffer from disorders with adult onset (Bao and Swaab, 2011). Specifically, women are more susceptible than men to develop dementia, Alzheimer's disease, panic disorder, post-traumatic stress disorder (PTSD), eating disorders, social and generalized anxiety and major depression (Kessler, 2003, 2007; Bekker and van Mens-Verhulst, 2007; Wittchen et al., 2011; Craske and Stein, 2016). Neurodevelopmental disorders such as autism and ADHD, Tourette's syndrome, Parkinson's disease, antisocial personality predominate in boys and men (Van Den Eeden et al.,

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2003; Fombonne, 2009; Werling and Geschwind, 2013; Davies, 2014; Schaafsma and Pfaff, 2014). Major depression, which is the most prevalent mental disorder worldwide according the World Health Organization statistics (WHO, 2015), is twice more common in women than in men and such sex differences extend to the presentation, the course of the illness and the treatment efficacy (Ahnlund and Frodi, 1996; Kessler et al., 1993; Kornstein, 1997; Angst et al., 2002; Gorman, 2006; Kessler, 2007; Wittchen et al., 2011).

Clinical and preclinical research recognize a crucial role of stressful life events in the etiology of several neurobehavioral disorders (Tafet and Bernardini, 2003; Schmidt et al., 2008); specifically, chronic stress has been reported to increase the risk for developing Alzheimer's disease (Wilson et al., 2003), depression and anxiety disorders, often in comorbidity (Kendler et al., 1999; Kessler, 1997; Wang, 2005; Nestler et al., 2002; Belmaker and Agam, 2008; Lupien et al., 2009). Unpredictability, novelty, lack of control, threat to self-esteem are reported as the key factors making people perceive a situation as stressful, and eliciting a physiological and psychological stress response. However, human and animal data clearly indicate that individuals' perception of the stressfulness of a situation as well as the physiological and behavioral responses to stress are strongly dependent on gender, and conditions that are stressful for males are not necessarily stressful for females, and the reverse (Palanza, 2001; Kudielka and Kirschbaum, 2005; Kokras and Dalla, 2014; Bangasser and Wicks, 2017).

Animal models are widely used to study the neurobiology of psychiatric disorders and much of our understanding of disease processes and treatments begins with preclinical studies. Notwithstanding the notion that an animal model has validity inasmuch as it is similar to a modeled human disease (Belzung and Lemoine, 2011), most preclinical biomedical research does not take into consideration sex as an experimental variable (Beery and Zucker, 2011; Yoon et al., 2014; McCullough et al., 2014; Klein et al., 2015). The evident paradox is that although women are more vulnerable to several stress-related mental disorders, such as major depression and general anxiety, the vast majority of animal studies (both behavioral and neurochemical) related to models of mental disorders are carried out in male animals only (Blanchard et al., 1995a,b; Palanza, 2001; Zucker and Beery, 2010). Females as experimental subjects in translational neuroscience are often neglected because they are thought to be too "variable", and it is easier and cheaper to use only males, as one does not have to take into account and control for stages within the estrus cycle. Apart this pragmatic approach, an often unsaid reason for not using females is that results from studies on stressed female are conflicting or even "anomalous" relative to male data (Willner, 2005). Even good articles on how to improve animal models of human disorders tend to ignore the pervasive problem of exclusively using male animals to model disorders that affect mostly women, despite being evident that findings cannot often be generalized from male to female animals (e.g., Cryan and Slattery, 2007; Nestler and Hyman, 2010; Pollak et al., 2010). This unfortunately reflects a traditional, albeit false, assumption that biological sex does not matter all that much when studying neurobiological functions. However, to understand psychobiological mechanisms of disease it is indeed crucial to unravel the factors contributing in sexual differences that confer differential vulnerabilities to diverse mental health problems. Sex represents one of the most evolutionarily well-conserved differences in biology. Once sexual reproduction evolved (about one billion years ago), sex became a fundamental evolutionary force that through sexual selection shaped male and female reproductive and behavioral strategies and their underlying neural substrates.

1.1. Sexual Selection and sex differences in behavior

Darwin (1871) introduced the theory of sexual selection to account for the evolution of phenotypic characteristics on the basis of a direct reproductive advantage, as opposed to survival advantage (natural selection, *sensu* Darwin, 1859). Sexual selection predicts that the behavioral strategies in coping with social and non-social environment challenges would differ in males and females when a discrepancy in parental investment exists – as it is in all mammalian species. Therefore males and females will be the same or similar in all those domains in which the sexes have faced the same or similar adaptive problems but will differ in domains in which they have faced different adaptive problems over their evolutionary history. Each sex possess mechanisms designed to deal with its own adaptive challenges. It seems reasonable to suppose that behavioral systems related to the way animals cope with stressful or potentially threatening situations, have indeed been a target of sexual selection and are differently expressed in males and females, which are also likely to have different social roles and attitudes. Sexually reproducing animals thus exhibit sex differences in behavior that are not limited to sexual dimorphisms in mating strategies (intra- and inter-sexual selection, sensu Darwin, 1871) but also to non social behaviors as well as other social interactions (aggression, sociability, parental cares) that increase survival, social competition and ultimately the chance of reproductive success, and that can be labelled as social selection (West-Eberhard, 1983; Lyon and Montgomerie, 2012).

Indeed, the analysis of non reproductive behavior of several mammalian species show sex differences in infant play, aggression, learning, exploration, activity level, behavioral circadian rythms, food intake and preference, novelty seeking, impulsivity, emotional behavior, cognitive ability and many more (Archer, 1975; Brain et al., 1991; Palanza, 2001; Alexander and Hines, 2002; Dalla and Shors, 2009; ter Horst et al., 2012; Lonsdorf et al., 2014; Argue and McCarthy, 2015; Krizo and Mintz, 2014; Fukushima et al., 2015; Carroll and Smethells, 2015) However, sex differences are not identical across species, as they depends upon specific, socio-ecological selective pressures that had acted during evolution. For example in laboratory rats and mice, females are more active and less anxious in several tests than males, but such a sex difference varies depending upon context, strain and age (Johnson and File, 1991; Palanza et al., 2001; An et al., 2011; ter Horst et al., 2012; Gioiosa et al., 2007, 2013), while in other species of rodents, such as meadow voles, males are more active than females (Perrot-Sinal et al., 2000). Thus, even between rodent species traditionally used as experimental models there is a differential bias on sex differences in behavior due to their evolutionary history.

Sex differences in behavior reflect sex differences in proximate mechanisms such as brain structure, neurochemistry, neuroendocrinology and neurobiology (Cahill, 2006) and result from chromosome effects, organizational effects of sex hormones during development of the brain and/or activational effects of sex hormones (Goy and McEwan 1980; McCarthy and Arnold, 2011). Apart from genetic factors, epigenetic mechanisms across the lifespan, such as DNA methylation and histone modifications, are involved in the control of sexual differentiation of the brain and play an important role in determining and maintaining sex differences in behavior (McCarthy and Nugent, 2015). Therefore, when addressing the question of sex differences in behavior, in stress perception and response, in susceptibility to disease and treatment, we should consider both the proximate mechanisms (e.g., genetic and hormonal basis) and the adaptive significance of such behavioral diversity (i.e., ultimate causation).