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Review

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Representing Sex in the Brain, One Module at a Time

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Sexually dimorphic behaviors, qualitative or quantitative differences in behaviors between the sexes, result from the activity of a sexually differentiated nervous system. Sensory cues and sex hormones control the entire repertoire of sexually dimorphic behaviors, including those commonly thought to be charged with emotion such as courtship and aggression. Such overarching control mechanisms regulate distinct genes and neurons that in turn specify the display of these behaviors in a modular manner. How such modular control is transformed into cohesive internal states that correspond to sexually dimorphic behavior is poorly understood. We summarize current understanding of the neural circuit control of sexually dimorphic behaviors from several perspectives, including how neural circuits in general, and sexually dimorphic neurons in particular, can generate sexually dimorphic behaviors, and how molecular mechanisms and evolutionary constraints shape these behaviors. We propose that emergent themes such as the modular genetic and neural control of dimorphic behavior are broadly applicable to the neural control of other behaviors.

Introduction

Men and women exhibit sex differences in behaviors that immediately enhance reproductive success as well as in tasks that involve higher cognitive function. It is actively debated whether such sex differences are genetically wired or a byproduct of societal influences. While the jury may be out for the underpinnings of these behaviors in humans, research in model organisms leaves little doubt that such manichean distinctions between nature and nurture are simplistic. Indeed research on diverse animals unequivocally demonstrates the importance of both genes and experience on sexually dimorphic behaviors. Nevertheless, these studies underscore the primacy of genetically programmed mechanisms that control the development and activation of the neural circuits underlying these behaviors.

Sex-typical displays of behaviors such as mating and aggression are genetically hardwired in the sense that they can be displayed by animals without training. The activation of the underlying neural circuits is controlled by sensory cues as well as by physiological signals such as sex hormones. Such external and internal control mechanisms ensure that these social behaviors are displayed in the appropriate context. Many animals, including mice, secrete pheromones, chemosensory cues that signal social and reproductive status to other members of the species, to initiate social interactions (Karlson and Lüscher, 1959). Sex steroid hormones secreted by the gonads are the critical internal signals that control these behaviors in vertebrates (McEwen, 1981). The identity of the pheromone and hormone-responsive neural circuits that drive specific sexually dimorphic behaviors remains elusive. By contrast, we have significant insight whereby chemosensory input and sex hormones control the development or activation of specific neurons that influence these behaviors (Liberles, 2014; Morris et al., 2004; Touhara and Vosshall, 2009; Wu and Shah, 2011).

Our Review discusses the mechanisms that regulate sexually dimorphic behaviors in mammals with a specific focus on mice and the assumption that similar mechanisms are likely to operate in humans. The literature on sexually dimorphic behaviors in other organisms has been reviewed elsewhere (Baum, 2003; Cahill, 2006; Crews and Moore, 2005; Dickson, 2008; Manoli et al., 2006; Moore et al., 2005; Newman et al., 1997; Perkins and Roselli, 2007; Portman, 2007; Wade and Arnold, 2004; Wallen, 2005). We focus largely on sex differences in mating and aggression because the underlying neural pathways have been studied in some detail. We do not list all known cellular or molecular sexual dimorphisms in the nervous system because these have been documented extensively (Cahill, 2006; Cooke et al., 1998; Simerly, 2002; Vries, 1990). Where instructive, we discuss findings in other model organisms, especially flies, that provide insight into the neurobiological basis of sex differences in behavior.

A Framework to Understand How the Brain Can Generate Sexually Dimorphic Behaviors

Males and females transform sensory input into sexually dimorphic behaviors, suggesting that such behaviors are generated by neural circuits that differ between the sexes. This insight has led to a highly successful effort to identify anatomical or molecular sex differences in neuronal populations in order to gain an entry point into the neural circuits underlying gender-typical behaviors (Cachero et al., 2010; Cahill, 2006; Cooke et al., 1998; Jarrell et al., 2012; Liu and Sternberg, 1995; Nottebohm and Arnold, 1976; Raisman and Field, 1971; Simerly, 2002; Vries, 1990; Yu et al., 2010). How these genes or neurons control neural circuit

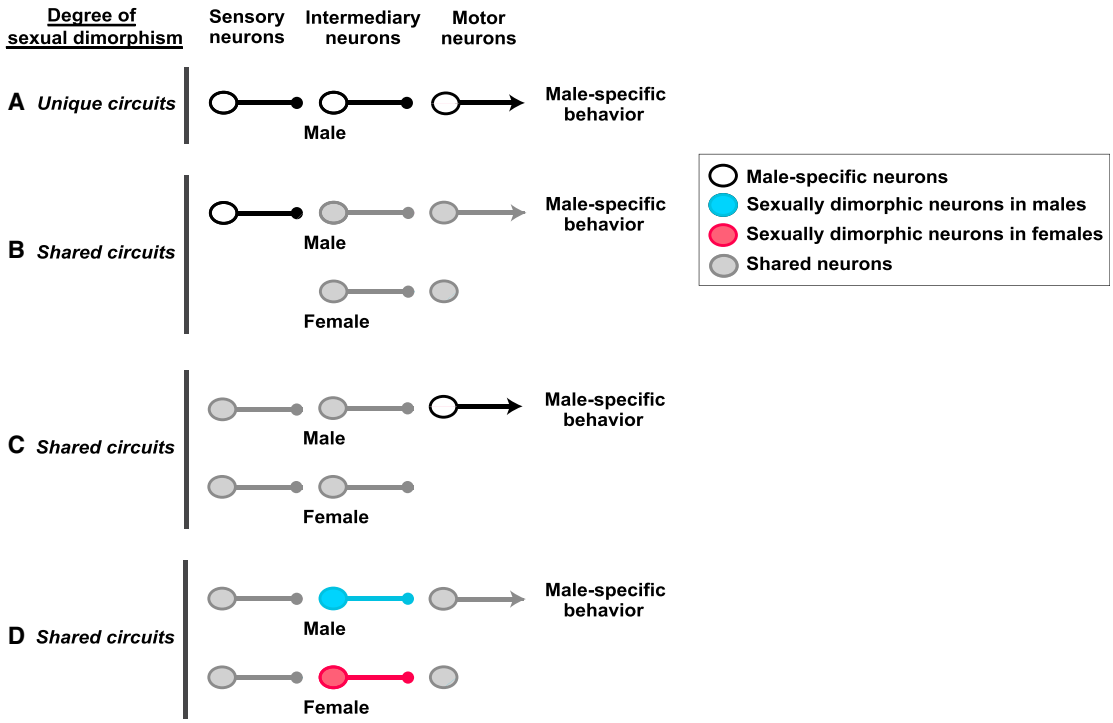

Figure 1. Neural Circuits that Can Generate Sexually Dimorphic Behaviors

Simplified wiring diagram of some neural circuit configurations that can generate sexually dimorphic behaviors. Although only circuits driving male-specific behaviors are shown for clarity, similar circuits will exist for female-specific behaviors. The axon termini of all neurons except those of motor neurons end in small solid circles to show that they may transmit effectively excitatory, inhibitory, or neuromodulatory output. Termini of male motor neurons are shown as arrows to illustrate stimulation of the muscle groups required for the behavioral display. By contrast, female motor neurons are not shown to have termini to depict lack of activation of the male-specific behavioral program.

(A) The entire neural circuit for generating a male-specific behavior is only present in males.

(B) Sensory neurons unique to males feed into a shared neural circuit to activate a male-typical behavior.

(C) Motor neurons unique to males are regulated by a shared neural circuit to activate a male-typical behavioral response.

(D) Sensory and motor neurons are shared between the sexes but there are sex differences in intermediary neuronal populations. Most sex differences in intermediary neurons appear to be quantitative rather than qualitative in mice; in other words, the comparable neuronal population is shared between the sexes, but it displays cellular or molecular sexual dimorphisms that permit activation of the behavior only in males.

function is unclear because a neural circuit that controls a sexually dimorphic display has yet to be delineated from sensory input to motor output.

Absent the complete delineation of such a neural circuit, we envision several mutually nonexclusive neural circuit wiring diagrams that enable sexually dimorphic output (Figure 1). In the most extreme case, such a neural circuit is unique to one sex. One example may be the circuit for penile muscles involved in coitus, which are controlled by motor neurons in the spinal nucleus of the bulbocavernosus (SNB), a population of neurons largely absent in females (Breedlove and Arnold, 1980). Given that wild-type females of many species can display some male-type mounting behavior (see later), if the neural pathway controlling these penile muscles is one component of a singular male sexual behavior circuit then at least some neural centers presynaptic to the SNB are likely to be shared between the sexes. In this scenario, the gender dimorphism in SNB neurons represents an example of a shared neural circuit that differs between the sexes at the level of motor neurons. Sex differences at the level of sensory input can also drive sexually dimorphic behaviors. One example of a neural circuit with well-defined sensory sex differences is that underlying female pheromone-elicited chemotactic flight in the male moth *Bombyx mori* (Nakagawa et al., 2005; Sakurai et al., 2004; Touhara and Vosshall, 2009). Male but not female moths express chemoreceptors for the pheromone mixture emitted by females, and the antennal sensory neurons expressing these receptors project to unique targets in the male antennal lobe. However, the chemotaxis elicited by the presence of the female pheromone engages output pathways that control flight, a behavior shared between the two sexes.

Given that most behaviors are common to the two sexes, males and females probably share many components of a neural circuit that drives a behavior of the opposite sex. For example, biting during intermale aggression, feeding, and maternal retrieval of a wandering pup all entail locomotion and coordinated jaw movements. In such instances, sexually dimorphic behavior is likely to emerge from sex differences in neuronal populations inserted (intermediary neurons in Figure 1) within shared neural circuits. Consistent with this notion, most cell or molecular sex differences in neuronal populations are quantitative rather than all-or-nothing qualitative sexual dimorphisms. We anticipate that real world circuits underlying dimorphic behaviors are

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