

## Stress, social behavior, and resilience: Insights from rodents



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### ABSTRACT

The neurobiology of stress and the neurobiology of social behavior are deeply intertwined. The social environment interacts with stress on almost every front: social interactions can be potent stressors; they can buffer the response to an external stressor; and social behavior often changes in response to stressful life experience. This review explores mechanistic and behavioral links between stress, anxiety, resilience, and social behavior in rodents, with particular attention to different social contexts. We consider variation between several different rodent species and make connections to research on humans and non-human primates.

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### 1. Introduction

The social worlds of animals are filled with many different types of interactions, and social experience interacts with organismal stress on many levels. Social stressors have proven to be potent across a wide range of species, and their study in rodents has led to greater understanding of the role of stressor type, timing, and other factors impacting physiology and behavior. While negative social interactions can be acutely damaging, social interaction can also moderate stressful experiences, buffering potentially adverse impacts and contributing to resilience. In this review we explore the many interactions of stress and social behavior in research on rodents. We consider three main classes of effects: the social environment as a stressor; the effects of stress on subsequent social behavior; and social buffering of stressful experience (Fig. 1). We explore mechanisms that mediate links between stress and social behavior, and consider sex differences in these mechanisms and behavioral outcomes. Finally, we discuss data from a wide variety of rodent species wherever possible, in order to explore the universality and specificity of findings in single species.

#### 1.1. Measuring stress and social behavior

Responses to stress span a spectrum from detrimental immediate and long-term effects to resilience and protection against

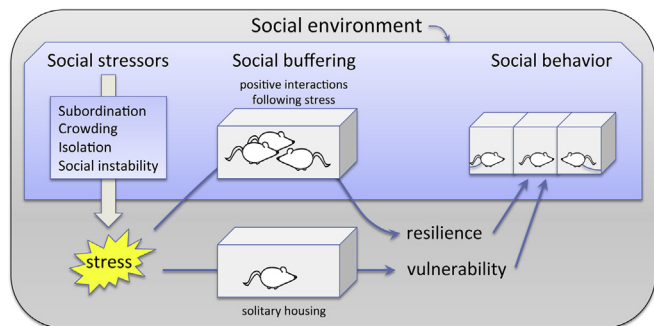
future stressors. The effects of stress exposure and consequent trajectory depend on the nature of the stressor, the severity, duration (acute vs. chronic), sex/gender, genetics, timing of exposure (early life, adolescence, adulthood or aging) as well as the perception of the stressor by the individual—for example, stressor controllability dramatically affects resilience versus vulnerability as an outcome (Maier and Watkins, 2005; Amat et al., 2010; Lucas et al., 2014). Recently it was shown that even the gender of researchers can affect rodent stress levels and influence results of behavioral tests (Sorge et al., 2014).

Stress can be assessed by both behavioral and physiological indicators. One of the most commonly measured immediate physiological responses to stress is activation of the hypothalamic–pituitary–adrenal (HPA) axis. During stressful events, corticotropin releasing factor (CRF, also called CRH) is released from the hypothalamus, and is the primary trigger of adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary. ACTH then triggers systemic release of glucocorticoids (CORT) from the adrenal gland (Bale and Vale, 2004). We describe outcomes related to HPA-axis responsivity, as well as several additional neurochemical players including BDNF, serotonin, and multiple neuropeptides in the text below.

Social behavior is complex and varies with the behavioral test chosen, and whether focal individuals are tested with familiar or novel conspecifics, with same- or opposite-sex individuals, or with familiar or unfamiliar strains. The laboratory setting is a sparse environment compared to the complexity of nature, both physically and socially. Some research aims to quantify social behavior in complex housing areas such as enriched caging with social groups

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**Fig. 1.** Schematic representation of the levels at which the social environment impacts and reflects the individual. To the left and in Section 2 of this review, we consider aversive social environments as potent stressors. This stress has far-reaching impacts on individual physiology as well as on social behavior (Section 3), but these impacts are potentially moderated by social buffering (Section 4).

(e.g., artificial, visible burrow systems (Blanchard et al., 2001; Seney et al., 2006), and large, semi-natural enclosures (e.g. King, 1956; Dewsbury, 1984; Ophir et al., 2012; Margerum, 2013). Other research relies on constrained social interactions in tests designed to measure a few particular aspects of social behavior (Crawley, 2007). For example *social interaction* tests typically measure the amount of time spent in social contact or investigation with a conspecific. *Social choice* tests take place in multi-chambered apparatuses that allow investigation of either a conspecific or a non-living stimulus such as a novel object or empty restrainer (Moy et al., 2007). Variations on this test involve a choice of a familiar versus unfamiliar individual, such as in the *partner preference test* (Williams et al., 1992). *Social habituation/dishabituation* tests are often used to assess social recognition and memory for familiar individuals (Ferguson et al., 2002; Choleris et al., 2003). *Social motivation* may be assessed by measures of effort expended to access another individual (Lee et al., 1999), or by conditioned place preference for a social environment (Panksepp and Lahvis, 2007). Other tests measure specific aspects of social competency, such as memory and social inferences involved in hierarchy (Cordero and Sandi, 2007; Grosenick et al., 2007). Recent studies of pro-social behavior in rats have focused on latency to free a restrained rat under different scenarios (Ben-Ami Bartal et al., 2011, 2014).

There is no peripheral hormonal indicator of sociability, but two neuropeptides have been highly implicated in many aspects of mammalian social behavior: oxytocin (OT) and arginine vasopressin (VP). Oxytocin is produced in the hypothalamus and facilitates a wide variety of processes related to social behavior, including maternal behavior, trust, anxiolysis, and sexual pair-bond formation (reviewed in Ross and Young, 2009; Young et al., 2008; Neumann, 2008; Donaldson and Young, 2008; Carter et al., 2008; Anacker and Beery, 2013). Vasopressin activity has been associated with aggression, anxiety, and social behavior (reviewed in Kelly and Goodson, 2014), as well partner preference formation in male prairie voles (Cho et al., 1999; Young and Wang, 2004). The locations and densities of oxytocin receptors (OTR) and vasopressin type 1a receptors (V1aR) have been associated with species variations, as well as with individual variations in social behavior from affiliation to aggression (e.g. Everts et al., 1997; Young, 1999; Beery et al., 2008a; Campbell et al., 2009; Beery and Zucker, 2010; Ophir et al., 2012; Calcagnoli et al., 2014). Many studies have also investigated the role of the mesolimbic dopamine system and opioid regulation of rewarding social behaviors such as pair-bonds between mates (Aragona, 2009; Resendez et al., 2012); we describe these and additional research avenues throughout.

## 1.2. Species diversity and the comparative perspective

In addition to considering how social behavior is assessed, we must consider the significance of the behavior to the species in which it is assessed. Social behavior encompasses skills from social recognition to social memory, as well as many distinct types of interaction, including with peers, potential reproductive partners, competitors, and offspring. Some of these interactions are better studied in some species than others; for example biparental care is only present in a few rodent species that have been studied in laboratories, namely prairie voles (*Microtus ochrogaster*), California mice (*Peromyscus californicus*), and Djungarian hamsters (*Phodopus campbelli*). Monogamous pairing with mates is similarly rare among rodents, and is most studied in prairie voles and California mice. Mechanisms supporting group living have been explored in colonial rodents including naked mole-rats (*Heterocephalus glaber*), tuco-tucos (*Ctenomys sociabilis*), seasonally social meadow voles (*Microtus pennsylvanicus*), and others (Anacker and Beery, 2013). The idea that some problems are best studied in particular species is far from new; this principle was promoted in 1929 by the late physiologist and Nobel laureate August Krogh (Krebs, 1975). In contrast to Krogh's assertion that species should be selected for their suitability for studying particular problems, modern biological research is strongly biased towards rats and mice; in 2009 rats and mice made up approximately 90% of mammalian research subjects in physiology, up from 18% at the time Krogh's principle was articulated (Beery and Zucker, 2011 supplementary material). Lab strains of mice and rats are highly inbred and in many ways quite different from their wild peers.

Use of multiple species allows researchers to compare and contrast mechanisms across the phylogenetic tree. While the depth of mechanistic information available for non-model organisms is much less than for rats and mice, the comparative perspective is essential for understanding to what extent mechanisms underlying social behavior are unique to particular species, common across broader groups, or are variations on a theme (Phelps et al., 2010; Katz and Lillvis, 2014; Hofmann et al., 2014). In this review we focus on rats and mice for which data on stress and social behavior are most abundant, but incorporate findings from other rodent species whenever possible. And although laboratory research in rodents is heavily male-biased (Beery and Zucker, 2011), we review a substantial body of findings on the interrelationship of stress and social behavior in females.

## 2. The social environment as a stressor

All mammals interact with other individuals. In the wild, rodents may encounter competition for resources such as territory, food, and access to mates, and even solitary species interact with conspecifics and their chemical cues, if only to avoid them in the future. Both aversive and positive interactions are relevant features of the social environment. Widely used models of social stress in rodents include social subordination, crowding, isolation, and social instability (Fig. 1, left side). While most studies have been conducted in mice and rats, prairie voles and other social rodent species provide an opportunity to study the role of identity of the social partner, and how separation from a mate differs from isolation from a same-sex peer.

### 2.1. Social defeat/subordination

In humans, social rejection is used as a potent experimental stressor (Kirschbaum et al., 1993), and decades of work in humans and non-human primates have demonstrated that an individual's position in the social hierarchy has profound implications for

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