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Comparative studies of social buffering: A consideration of approaches, terminology, and pitfalls

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Highlights

- Various approaches to studying social buffering are considered and categorized
- A distinction is made between buffering during stress exposure and during recovery
- Buffering is more common when there is a strong relationship between individuals
- Species differences in social and sensory systems affect buffering outcomes
- Underlying neural mechanisms can vary with different subjects and different partners

Abstract

KIYOKAWA, Y. and HENNESSY, M.B. Social buffering of stress responses: A consideration of approaches, terminology, and pitfalls…NEUROSCI BIOBEHAV REV XXX-XXX, .- Over the past decades, there has been an increasing number of investigations of the impact of social variables on neural, endocrine, and immune outcomes. Among these are studies of "social buffering"—or the phenomenon by which affiliative social partners mitigate the response to stressors. Yet, as social buffering studies have become more commonplace, the variety of approaches taken, definitions employed, and divergent results obtained in different species can lead to confusion and miscommunication. The aim of the present paper, therefore, is to address terminology and approaches and to highlight potential pitfalls to the study of social buffering across nonhuman species. We review and categorize variables currently being employed in social buffering studies and provide an overview of responses measured, mediating sensory modalities and underlying mechanisms. It is our hope that the paper will be useful to those contemplating examination of social buffering in the context of their own research.

Keywords: Affiliation; Attachment; Bonding; Maternal buffering; Social buffering; Stress.

Introduction

Over the past several decades, there has been ever increasing awareness by the neuroscience community of the impact that social variables can exert on aspects of neural, endocrine, and immune responses and their regulation (Cacioppo and Berntson, 1992;

Curley et al., 2011; Stephens and Wallen, 2013). Much of the research in this domain has focused on the disruptive and often damaging consequences of removing social partners or disturbing species-typical social relationships (Cacioppo et al., 2015; Meyer and Hamel, 2014). A second emphasis has been on the beneficial effects that social relationships or the presence of social partners can confer on biobehavioral endpoints. Among these are studies of "social buffering"—or the phenomenon by which the presence of affiliative social partners mitigates stress responses. But, as these studies become more commonplace, and additional species, responses, paradigms, and potential mechanisms come to be examined in social buffering studies, more thought will need to be given to the conceptualization of approaches and delineation of terms to preclude the complexity of findings leading to confusion and miscommunication. The intent of the present paper, therefore, is not to offer a complete review of the field of social buffering—reviews are available elsewhere (Gunnar and Hostinar, 2015; Hennessy et al., 2009; Hostinar et al., 2014), but rather, to provide an overview and categorization of the variety of approaches currently being employed in this field and to highlight experimental considerations, potential pitfalls, and general conclusions that have emerged from this work. Coverage in this paper is limited to nonhuman animal studies, as human research introduces numerous cognitive, language, and cultural variables unique to this species. We do, however, note some points of broad similarity and difference of findings in the non-human and human literature. It is hoped that

the paper will be of use to those first contemplating examination of social buffering in the context of their own research.

In the following sections, we first briefly address definition of terms and then general types of procedures utilized in social buffering studies. We then survey the classes of responses that have been measured, variables related to the subject and the partner serving as the buffering agent, and the sensory modalities through which buffering is achieved. Finally, we examine potential underlying mechanisms that might mediate the phenomena observed.

A consideration of terminology

Because the phrase "social buffering" is underpinned by ambiguous concepts—notably "social" and "stress"—it would seem useful to begin with a clarification of some terminology. By its dictionary meaning, "social" implies an affiliative or cooperative association among two or more individuals or the belonging to the same organized community or common group. We are, therefore, limiting our definition to those situations in which the individuals have an affiliative relationship. This definition eliminates any instances in which a stress response is reduced through a distinct agonistic interaction, such as the diminished elevation of circulating adrenocorticotropic hormone (ACTH) levels observed in rats engaged in ritualistic fighting when exposed to electric shock (Conner et al., 1971). Moreover, we should note that "affiliation" is used here in a broad sense to

include classes of partners that have evolved to interact amiably with each other even if the particular individuals are unfamiliar to each other at the time of testing.

While the term social buffering has been extended to general outcomes of health and well-being that do not explicitly involve measures of stress (Balasubramaniam et al., 2016; Sul et al., 2016), we are adhering to the traditional view that reduction in stress responses is integral to social buffering (Cohen and Wills, 1985). This constraint alone, however, does not resolve issues of definition of the term social buffering that derives its meaning from its impact on stress responses. Since its characterization by Selye (see Selye, 1956), the term "stress" has been notoriously difficult to delineate to the satisfaction of all (Koolhaas et al., 2011; Levine, 2005). Yet, most can agree on a broad variety of environmental disturbances (e.g., a painful stimulus, confrontation with a predator, perception of loss of control) that constitute stressors. Further, it is clear that such stressors elicit changes in physiology--notably activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system—and often changes in behavior. We consider these responses, as well as the central nervous system changes that drive them, to be appropriate outcome measures for social buffering studies.

Procedural variables

Timing of stressor relative to social contact

One of the most fundamental ways in which procedures in social buffering studies differ is in terms of when the subject and partner are exposed to each other relative to the

administration of the stressor. Most frequently, the two animals remain together during stressor exposure, though it is not uncommon for the subject to be administered the stressor while alone and then to be housed with the partner immediately following the stressor termination. A useful distinction can be drawn between these two procedures (designated as "exposure-type" and "housing-type" social buffering; Kiyokawa, 2017) since they vary in terms of whether the partner mitigates the initial reaction to, or recovery from, the stressful experience. When individuals with a strong affiliative relationship (e.g., mother-infant pairs, pair-bonded adults) are rehoused together after one member of the pair has been exposed to a stressor, housing-type is often simply referred to as "reunion".

Different control conditions may be required with these two procedures. For exposure-type, controls typically can simply be animals exposed to the stressor in the absence of the social partner. If the two conditions differ only in the presence or absence of this figure, then a reduction in stress responses in the presence of the partner can appropriately be attributed to buffering. Studies can also assess whether some additional factor (e.g., brain lesion, particular early experience) modifies the effectiveness of social buffering. In these cases, it is crucial to distinguish between effects on buffering from those on the stress response. If, for instance, lesioned animals with a partner show larger responses than sham-lesioned controls with a partner, it is possible the brain lesion reduced buffering effectiveness or that it increased the stress response. In such experiments, treated and control animals tested without a partner are needed to make this distinction (Kiyokawa

et al., 2012). In housing-type, an additional control, in which an animal not previously exposed to the stressful stimulus is subsequently housed alone, may be necessary. Depending on the species, duration of post-stress observation period and so on, individual housing may induce its own adverse consequences. If non-stressed animals housed alone are not included, these outcomes may be interpreted as effects due to the previous stressor that are buffered by housing with the partner (de Jong et al., 2005; Ruis et al., 1999).

Exposure to social partners *prior* to an aversive event also has been found to reduce responsiveness to stressors. In one example, prior exposure of a male subject mouse to an apparently calm male partner mouse in an unfamiliar environment impaired establishment of contextual fear conditioning in the same context (Guzman et al., 2009). In this case, however, the beneficial effect appeared due to observational learning of safety in this context rather than to social buffering by the partner per se because the same procedure did not affect an establishment of auditory fear conditioning (Guzman et al., 2009; see also Mineka and Cook, 1986). In another example, adult female Siberian hamsters showed reduced HPA axis activation in response to restraint if they had been co-housed with other females as compared to if they had been housed individually (Detillion et al., 2004). It should be noted, however, that, in gregarious species, an experimental paradigm such as this may reflect the effect of isolation on HPA responsiveness (Hatch et al., 1965), rather than the effect of social partners. In contrast, in one, and possibly unique, example, adolescent male guinea pigs housed in large, mixed age/sex colonies showed a smaller

cortisol response to a novel environment than did males housed with a female in a standard laboratory cages (Kaiser et al., 2007). A series of experiments revealed that this buffering effect was due to elevated circulating testosterone, which was stimulated by social interactions with older animals (Lürzel et al., 2011a; Lürzel et al., 2011b).

Stressors

Social buffering studies also differ in terms of the stressor. Commonly used laboratory stressors include exposure to a novel environment, immobilization, electric shock, and stimuli conditioned to shock (Hennessy et al., 2009; Kiyokawa et al., 2014a; Sullivan and Perry, 2015). For novel environments, the duration of exposure can be an important consideration, particularly in studies of buffering in altricial infants (e.g., rat and mouse pups). While responses of separated infants during brief exposures to a novel environment can be assumed with some certainty to be stress responses, those emerging after hours of isolation may reflect the removal of physiological regulatory influences provided by the mother (Hofer, 1987). For instance, maternal tactile cues and stimuli associated with feeding maintain typical levels of HPA activity in the preweaning rat pup (Levine, 2002). If the pup is without the mother for a number of hours, glucocorticoid levels gradually rise (Stanton et al., 1988) as the effects of loss of regulatory control become evident. Thus, the presence of the mother does have a suppressive effect on HPA activity during exposure to a novel environment, but the process appears to be

fundamentally different than that seen during exposure to other stressors or to a novel environment for a briefer period.

Naturalistic conditions

The inability to adequately control conditions when one moves outside the laboratory makes the study social buffering in the field a particularly challenging proposition. One approach is to compare the stress response (e.g., fecal glucocorticoid levels) of animals exhibiting differing levels of affiliative social relationships during periods that vary in objective measures of stressfulness (e.g., weather conditions or the number of aggressive acts received from other members) (Wittig et al., 2008; Young et al., 2014). Here, social buffering might be indicated by smaller stress responses in animals with closer social ties during exposure to strong stressors, but a weaker or no relation between social ties and stress responses when conditions are less stressful (Young et al., 2014).

Response variables

Social buffering has been widely studied in the context of the suppression of measures of HPA activity (Hennessy et al., 2009; Kiyokawa et al., 2014a), though the term often is used in studies measuring only behavioral or psychological responses (Aslund et al., 2014; Creswell et al., 2015; Edgar et al., 2015) or other physiological or neural endpoints (Cohen et al., 2015; Moriceau et al., 2010). Given the vagaries of the definition of social buffering and the wide variety of effects that can result from exposure to a stressor, it should not be surprising that different responses have been examined in different

studies or that the responses reported in the literature have not always occurred in unison. Moreover, in contrast to the acute situation, there seems to be no long-term physiological or behavioral alteration widely accepted as a stress response that persists over an extended time frame and can serve as an endpoint in social buffering studies. With these constraints notwithstanding, a number of physiological, behavioral, and neural measures can be useful in assessing social buffering, at least during relatively brief periods of stressor exposure.

Physiological responses

Increased activity of the HPA or sympathetic systems are the most universally accepted stress responses. As such, attenuation of circulating, urinary, or salivary levels of glucocorticoids, circulating levels of ACTH, or the direct mediators of sympathetic activity (epinephrine or norepinephrine) in the presence of a partner, either during exposure to a stressor or during recovery, are preferred indices of social buffering. For the HPA system, glucocorticoid responses offer the additional advantage of requiring several minutes to be expressed so that one has an opportunity to collect a sample before the sampling procedure has a chance to contribute to the glucocorticoid levels in that sample. Still one should also be aware that changes in glucocorticoid levels are sometimes not closely correlated with upstream changes in ACTH (Herman et al., 2016; van der Doelen et al., 2014).

For the sympathetic system, the extremely short latency for increases in epinephrine and norepinephrine in blood requires a catheterization procedure to prevent contamination of the response to the stressor with that to the sampling procedure. This constraint limits the

usefulness of these measures in most studies of social buffering. For this reason, secondary responses stimulated by sympathetic outflow, such as hyperthermia, rapid changes in blood pressure, or alpha amylase secretion, may serve as useful proxies for sympathetic activity, particularly in studies of exposure-type social buffering.

During housing-type social buffering, alteration in circadian rhythms of autonomic activity, such as heart rate and body temperature, might constitute stress responses. Body weight, which may reflect altered autonomic activity, might also be used. In one example, co-housing after a single defeat in rats led to weight loss recovery and reduced alteration in circadian rhythms of heart rate and body temperature (de Jong et al., 2005).

Behavioral responses

Species-typical defensive responses to aversive unconditioned stimuli (e.g., bright lights, open field, elevated platform, or predators and their odors in rats; US) can be useful measures of exposure-type social buffering. Moreover, it is now known that stressors such as electric shock and isolation in novel environments can activate proinflammatory processes of the innate immune system, which then act on the brain to induce so-called "stress-induced sickness behaviors" (Maier and Watkins, 1998), including, for instance, inactivity, a hunched posture, eye-closure, and piloerection. Reduction of such sickness behaviors can also be used as measures of social buffering. Furthermore, if exposure to stressors exacerbates subsequent behavioral responses to an aversive US (e.g., open arms in

the elevated plus maze), remission of this exacerbation may serve as a useful index of housing-type social buffering.

In any case, reliance on behavior alone can potentially lead to erroneous conclusions, especially when the behavior is not a clear defensive response. If the behavioral responses are evoked by the activation of neural defense mechanisms, the activation most likely elicits concurrent physiological responses. In this situation, the behavioral responses can serve as indirect indices of stress responses. However, it is also possible that the observed behavior is elicited by another change in the stimulus environment. For instance, "distress" vocalizations by infants during isolation from the mother have been used to indicate social buffering (Hennessy et al., 1979; Hofer and Shair, 1978). But one might ask, for instance, if the vocalizations of a primate infant in a particular situation necessarily constitute a stress response or rather are they simply a behavioral response elicited by the absence of the clingable surface of the mother that have evolved to reinstate the clingable surface by calling the mother to return (Hennessy et al., 1979)? In such situations, behavioral responses may not reflect the stress status of the animals. Another questionable situation might exist with responses mediated by pain. If interaction with a partner is stressful for the individual during exposure to a painful stimulus, stress-induced analgesia could be misinterpreted as social buffering (Rodgers and Randall, 1985, 1986). Simultaneous measurement of endocrine or autonomic responses in such circumstances can be valuable to clarify these concerns.

Social buffering can also reduce conditioned behavioral responses. If a previously neutral stimulus (conditioned stimulus: CS) that has been associated with an aversive US comes to elicit the reaction originally elicited by the US, then this conditioned response might be attenuated by the presence of a conspecific in the exposure-type paradigm. Once again, however, it is useful to support the behavioral responses with endocrine and/or autonomic measures. It is possible that the partner might reduce the response to the CS by distracting the subject rather than by social buffering. This scenario is particularly likely if the measured response involves a reduction in activity, such as "freezing" in the presence of the CS. Conditioned responses can also be used in the housing-type paradigm by introducing the partner to the subject's enclosure after the initial conditioning has occurred. The subject can then subsequently be exposed to the CS while alone to determine if the conditioned response has been attenuated. Here, there is no concern about the partner affecting the response by distracting the subject. Nonetheless, it is advisable to clarify whether the interactions between the subject and partner appear affiliative. If the interactions are agonistic, the resulting stress could affect central memory consolidation processes (Aubry et al., 2016) and/or disrupt the aversive properties of the US by stress-induced analgesia in the subject (Hishimura, 2015), which would result in a reduced response during later exposure to the CS.

Neural responses

Historically, social buffering has been assessed by examination of peripheral physiological responses (e.g., cortisol, heart rate) or behavior. With the development of increasingly effective means of measuring neural activity in precise brain regions following stressor exposure, neural changes can be included among the responses available for study in buffering studies. Measuring the expression of immediate early genes as markers of neuronal activation by immunohistochemistry or in situ hybridization is a particularly accessible procedure. C-Fos is the most widely used for assessing neural activation, though a variety of others, for instance Arc, c-Jun, Egr-1, FosB can be employed as well, as can the presence of phosphorylated 40S ribosomal protein S6 (pS6). As new procedures continually evolve (e.g., Kawashima et al., 2014), the study of central responses to social buffering will no doubt become progressively more accessible.

But, changes in neural activity during stress exposure may reflect any of a number of functions beyond response to the stressor per se, e.g., shifting attention, perception of distracting stimuli, movement. So, if a partner reduces neural activity in some nucleus other than one directly involved in peripheral physiological stress responses [e.g. paraventricular nucleus of the hypothalamus (PVN)], how does one determine if this represents buffering in any meaningful sense? The concept of "survival circuits" (LeDoux, 2012) may provide a useful framework for making a judgment in this regard. Survival circuits are conceived of as those evolutionarily conserved neural circuits that instantiate functions allowing the animal to survive in the face of environmental threats. Stimuli that activate the defense

survival circuit include predators, alarm calls by conspecifics, loud noise, open space, and harmful conspecifics. Specific nuclei that participate are said to include the medial, lateral (LA), basal, and central amygdala, intercalated cell masses, ventromedial hypothalamus, premammillary nucleus of the hypothalamus, and periaqueductal gray. Thus, reductions in activity of these structures in the presence of a partner might reasonably be considered an instance of social buffering. Another target of social buffering may be the bed nucleus of the stria terminalis based on its importance in responses to ambiguous threats (Davis et al., 2010; Goode and Maren, 2017). Indeed, this nucleus plays an important role in the corticosterone response to such threats (Sullivan et al., 2004). In short, for a change in the activity of some neural structure to be convincingly considered an instance of social buffering, we would argue that the activity of that structure needs to underlie the animal's defensive repertoire or be directly linked to peripheral, physiological stress responses.

Subject/partner variables

Attachment and bonding

Subject and partner variables are often the main focus of social buffering studies. That is, what is it about individuals' age, sex, relationship with the partner and so on that determines whether or not a partner can moderate another's stress response? The relationship with the partner is a particularly crucial variable. In this regard, it is useful to differentiate particularly strong affiliative relationships, often characterized as "attachment" or "bonding". Attachment is used here in the traditional sense, as derived from

psychological theory, to describe the specific and intense relationship that infant mammals of a number of species exhibit to the primary caretaker, typically the mother (e.g., Ainsworth, 1979; Mason and Capitanio, 1988). Bonds are used to refer to attachment-like relationships among different classes of partners, with pair-bonds denoting an attachment-like relationship between the male and female of a breeding pair in monogamous species (Gobrogge and Wang, 2015; Lieberwirth and Wang, 2016). These relationships are inferred from the animal's behavioral, endocrine, and/or autonomic responses to the presence or absence of the partner.

The presence of an attachment or bond appears to be the best single predictor of whether social buffering between the subject and partner is likely to occur. Early research established that attachment figures could be powerful buffers of an infant's HPA response (e.g., Hill et al., 1973; Mendoza et al., 1978). Similarly, bonded males and females were found to effectively buffer plasma glucocorticoid responses of each other (Mendoza and Mason, 1986; Sachser et al., 1998; Smith and Wang, 2014; Smith et al., 1998). The shift in the types of partners that buffer HPA responses depending on age supports the importance of an attachment or bond in social buffering. For instance, as young guinea pigs mature, the preferential buffering of the cortisol response by the mother as opposed to other adult females that is characteristic of the preweaning period becomes less selective. And, by the time that males attain an age at which they can successfully compete with other males for breeding females, selectivity of the buffering response re-emerges, though at this age it is

favored breeding females that are most effective (Hennessy et al., 2006). The importance of the intensity or selectivity of the relationship rather than of the particular type of partners (e.g., mothers and infants) is further illustrated in the titi monkey. In this New World primate, the infant shows stronger attachment to the father than to the mother, and the father, not the mother, is most effective in buffering plasma cortisol elevations of the infant (Hoffman et al., 1995). On the other hand, in the laboratory rat, in which mothers will communally nurse (Mennella et al., 1990; Schultz and Lore, 1993) and there is no evidence of a specific filial attachment, the biological mother and other lactating females can be used indiscriminately in social buffering studies (Moriceau and Sullivan, 2006). Further, lactating rhesus monkeys that exhibited typical maternal behavior were found to be more effective in buffering their infants' cortisol response than were mothers that maltreated their infants (Sanchez et al., 2015). These findings in laboratory species parallel those in humans, in which attachment quality (i.e., security) varies among infant-mother dyads, and buffering effects appear stronger in the more-securely attached infants (Gunnar, 2017). Finally, the partner need not even be of the same species. In domestic dogs which can form an attachment-like bond with their human owner, the presence of the owner was found to reduce the HPA response to novelty exposure, while the presence of a long-standing kennel-mate and sibling did not (Tuber et al., 1996).

Additional relationship variables

It is important to note, however, that while buffering commonly is characteristic of attachment relationships, there also are ample examples of buffering of HPA activity, often together with other behavioral and physiological responses, by other, even unfamiliar, conspecifics in species ranging from laboratory rats (Kiyokawa et al., 2004; Kiyokawa et al., 2007; Terranova et al., 1999) and mice (Klein et al., 2015) to guinea pigs (Hennessy et al., 2008; Kaiser et al., 2003), common marmosets (Galvao-Coelho et al., 2012), pigs (Kanitz et al., 2014), sheep (Lyons et al., 1993), goats (Lyons et al., 1988), squirrel monkeys (Stanton et al., 1985), rhesus monkeys (Winslow et al., 2003) and chickens (Jones and Merry, 1988). Subjects and partners in these studies were often the same sex or were tested prior to puberty so that effects cannot be ascribed to sexual activity. In these cases, affiliation to the unfamiliar conspecific may have been strong enough to induce social buffering. Nonetheless, there are cases both in which unfamiliar partners have no buffering effect (e.g., Armario et al., 1983a), and in which familiarity of the partner enhances buffering effectiveness (Hennessy et al., 2008; Kiyokawa et al., 2014b). Yet, familiarity alone has limited explanatory power as highlighted by findings of familiar partners actually augmenting HPA responses to a novel environment (Armario et al., 1983a; Armario et al., 1983b).

Other variables

Beyond aspects of the relationship between subject and partner, there are a variety of experiential, biological, maturational, and situational variables that may determine the

outcome of social buffering studies, as illustrated in the following examples. One critical variable can be the subject's earlier experience. In rhesus macaques, the presence of a male cage mate failed to induce social buffering in nursery-reared males, although mother-reared monkeys showed social buffering in the same situation (Winslow et al., 2003). Similarly, young guinea pigs living with mother and littermates in large mixed age/sex social groups showed social buffering of circulating cortisol levels when subsequently tested with a sibling (Sachser et al., 1998), whereas young guinea pigs reared with just mother and littermates under standard laboratory conditions showed no benefit of the presence of a sibling on the cortisol response (Hennessy et al., 1995; Hennessy et al., 2015; Ritchey and Hennessy, 1987).

Little attention has been paid to genetic influences on social buffering in non-human species. In one study, corticosterone and behavioral responses of adult male rats were buffered by partners of the same or closely related strains, but not by partners of more distantly related strains (Nakamura et al., 2016), suggesting a genetic influence on cues—likely odors—that mediate buffering effects. In humans, polymorphisms in the oxytocin receptor gene have been found to moderate the impact of social buffering on HPA and autonomic outcome measures (Chen et al., 2011; Kanthak et al., 2016), suggesting that such effects deserve closer scrutiny in other species.

As discussions of buffering by the mother vs a mate illustrate, age or developmental state is one of the most obvious influences determining the effectiveness of a buffering

partner. Changes across the life span are perhaps clearest in the male guinea pig, in which buffering by the mother becomes more generalized to other adult females following weaning, can shift to an overall suppression of cortisol responsiveness in late adolescence, and then become selective for the favored mating partner in full adulthood (Hennessy et al., 2006; Maken and Hennessy, 2009; Sachser et al., 1998). In nonhuman primates, studies examining potential buffering by peers at about or shortly following weaning have yielded mixed results, with cortisol levels in the presence of the peer unchanged, modestly reduced or even elevated when the peer was unfamiliar (Gunnar et al., 1980; Hennessy, 1984; Hennessy et al., 1982). By comparison, evidence in humans indicates that buffering by parents wanes at puberty (Hostinar et al., 2015) and, somewhat surprisingly, the presence of a friend at this time can accentuate cortisol elevations (Doom et al., 2017). At older ages, romantic partners acquire the capability to buffer, though men appear to benefit more than women from the verbal support of their partner (Ditzen et al., 2007; Heinrichs et al., 2003; Kirschbaum et al., 1995).

Despite this intriguing difference between men and women, there has been little consistent evidence of sex differences in social buffering in other species. One must keep in mind, however, that the great majority of comparative studies have either examined the buffering of animals prior to puberty—before sex differences would be likely to have developed—tested only animals of one sex, or formed groups of small numbers of animals of each sex so that only very large male-female differences would be detected. Nonetheless,

in the case of the suppression of the cortisol response of adolescent male guinea pigs living in mixed age/sex groups (Hennessy et al., 2006), the effect is mediated by a large, male-specific surge of testosterone (Lürzel et al., 2011a) so that a sex difference may be inferred.

Another factor found to affect buffering effectiveness is the stress status of the partner. Davitz and Mason (1955) and Kiyokawa et al (2004) both observed that a fear-conditioned male rat, i.e., a partner that was fear-conditioned to the same CS as the subject, was less effective than a non-conditioned male rat in reducing stress responses of the fear-conditioned subject to the CS. Further, Klein et al (2015) found that a male mouse that had been acclimated to a test environment was more effective than a naïve male mouse in reducing Fos expression in the PVN of the subject when first introduced to the environment. The number of social partners available may also play a role. When adult male squirrel monkeys housed with 0, 1, or 5 other males were presented with an aversive CS in the home cage, there was a monotonic decline in the plasma cortisol response with increasing numbers of partners (Stanton et al., 1985). These results could reflect natural grouping tendencies of squirrel monkeys, which travel in large bands in the wild. As the number of social buffering studies continues to increase, the number of subject and partner variables found to affect buffering no doubt will increase as well, and likely will often be related to social characteristics of the species in question.

Sensory variables

For social buffering to occur, the subject animal must receive sensory signals from the partner. Hypothetically, a signal of a single sensory modality could directly and reflexively affect neural activity to inhibit stress responses. Given the importance of an emotional affiliation to the partner in social buffering, a more likely scenario—at least in most instances—is that recognition of the presence of a partner alters activity in the neural mechanisms related to affiliation which then activates the neural mechanisms that directly inhibit the survival circuits underlying stress responses. In this case, cues of a single or multiple sensory modalities would effectively mediate buffering to the extent that they unambiguously specify the presence of the partner. In as much as species vary greatly in their reliance on different sensory modalities, we might also expect large species variation in the effectiveness of different modalities of stimulation in mediating social buffering. In this section, we present examples of the approaches taken to identify cues of different sensory modalities that mediate social buffering in different species.

Tactile signals.

Whether tactile cues are *necessary* to promote social buffering can be addressed by placing the partner behind a wire mesh barrier so that contact is not possible. The approach has been used to demonstrate the necessity of maternal contact for fully buffering the corticosterone response of maternally deprived rat pups (Stanton et al., 1987) and the plasma cortisol and vocalization responses of young guinea pigs (Hennessy, 1988). For determining whether tactile cues are *sufficient* to mediate buffering, one needs to determine

the effect of presenting only these cues. However, in practice, it is difficult to isolate tactile from olfactory cues of the partner. An alternate approach is to present tactile stimulation that simulates that of the partner. An example of this latter strategy is provided by study of the buffering by littermates of the ultrasonic vocalizations emitted by rat pups isolated in a novel environment. The sufficiency of tactile cues was demonstrated by finding that the ultrasonic calls were buffered not only by an anesthetized littermate and a dead littermate kept at nest temperature, but also by a flashlight battery wrapped in a sheet of synthetic fur with a texture roughly approximating rats' fur, and even a small piece of synthetic fur on the floor of the cage (Hofer and Shair, 1980). However, the subtlety of the interaction among sensory modalities is illustrated by the additional finding that impairing the pup's main olfactory system with application of zinc sulfate eliminated the ability of tactile cues to buffer vocalizations (Hofer and Shair, 1980). That is, while tactile cues may be sufficient signals to produce buffering of behavior in this situation, it appears that these signals must be presented in the context of a functional olfactory system.

Auditory and visual signals.

There has been limited investigation of the role of auditory and visual stimulation in social buffering. Unlike the case for tactile cues, auditory cues of the partner can readily be presented alone with the aid of recordings. One clear example of this approach is a study of social buffering of adult pair-bonded marmosets. When isolated in a novel environment, both males and females exhibited HPA activation as measured by urinary cortisol levels.

This response was suppressed if the subject was exposed to the signature vocalization of its long-term mate, but not that of another opposite-sex adult (Rukstalis and French, 2005). Thus, auditory cues of the bonded mate were sufficient to reduce the endocrine stress response. Auditory signals have also been found to buffer central neurobiological changes. In pups of the precocial rodent, the degu, several minutes of isolation in a novel environment for several days up-regulated dopamine and serotonin receptors in regions of the cortex, hippocampus, and amygdala. These effects were almost entirely prevented if pups were exposed to maternal affiliative calls during the isolation periods (Ziabreva et al., 2003a; Ziabreva et al., 2000; Ziabreva et al., 2003b).

The fact that visual stimuli have rarely been investigated in social buffering studies is not surprising in as much as many laboratory species have limited visual ability, and rely more heavily instead on other modalities, such as olfaction. Sheep, however, have keen visual ability, which they appear to use extensively in recognition of conspecifics (Kendrick et al., 2001). When a sheep was isolated in a novel environment, a picture of a sheep's face was sufficient to reduce behavioral (protest bleats and activity), cortisol, and heart rate responses relative to a picture of a goat's face or an inverted triangle. The sheep's face also decreased circulating epinephrine levels compared to the inverted triangle (da Costa et al., 2004). Another example is a finding in chicks. When a chick was isolated in a novel environment, its vocalization response was attenuated when mirrors were placed in

the environment (Panksepp et al., 1980). Thus, visual cues of conspecifics appear fully capable of mediating buffering is some species.

Olfactory signals.

For species as highly dependent on olfactory stimulation as laboratory rodents, one would expect odor cues to be important mediators of social buffering. Indeed, olfactory signals are sufficient to induce buffering in adult male rats and mice. When a fear-conditioned subject rat was exposed to the CS in a box that previously held an adult male rat, conditioned fear responses and Fos staining in the PVN and various amygdala nuclei were suppressed (Takahashi et al., 2013). Odor cues also appear to be necessary for buffering in this situation since rendering subjects anosmic abolished the behavioral effect, even if the partner was present (Kiyokawa et al., 2009). Moreover, the olfactory signal appears to be volatile because buffering was induced even if a subject was tested in an area that was separated from the odorized region by a punctured acrylic board partition that allowed the penetration of only volatile signals (Kiyokawa et al., 2014b). Additionally, in mice, Fos expression in the PVN induced by placement in a novel test box was reduced when the test box was previously soiled by other mice (Klein et al., 2015).

Central neural mechanisms of buffering effects.

As we saw in a previous section, different classes of social partners can induce social buffering. Intriguingly, they may do so through distinct mechanisms. For instance, both a dam and a littermate can reduce the ultrasonic vocalizations of isolated rat pups, but

the influence of the mother, not the littermate, is mediated by dopamine receptors (Shair et al., 2009). Similarly, in addition to the mother, an unfamiliar adult male can buffer the HPA response of guinea pig pups to a novel environment. Yet, different mechanisms seem to be involved because while the mere presence of an anesthetized mother is effective, the adult male must engage in vigorous social interactions for cortisol elevations of pups to be suppressed (Hennessy and Ritchey, 1987; Hennessy et al., submitted). Buffering by the active adult male is accompanied by increased Fos immunoreactivity in the prelimbic cortex, whereas the presence of an anesthetized male or the conscious mother produces no increase in Fos expression (Hennessy et al., 2015; Hennessy et al., submitted). Because prelimbic cortex activation can inhibit HPA responses (Jones et al., 2011), these results suggest that interactions with the adult male can induce prelimbic activity, which in turn, acts to inhibit HPA activity, though this hypothesis remains speculative at present (Fig. 1A). In any case, adult males and mothers differ in the means by which they buffer the HPA activity of pups. Based on these findings, it is crucial to specify the type of partner inducing social buffering when discussing the underlying neural mechanisms. Below, we distinguish between buffering by the mother, mates, and other conspecifics and provide an overview of the little that is known regarding neural mechanisms underlying each. We recognize that other classes of partners can also be effective (e.g., infants buffering mothers; human companions buffering dogs), but note that little is known about the underlying mechanism in these cases.

Buffering by mothers (maternal buffering)

In the 2-week-old rat pup, pairing odor and foot shock induces avoidance learning mediated through the action of rising corticosterone levels acting on the basolateral complex of the amygdala (BLA) during the conditioning (Sullivan and Holman, 2010). When pups were conditioned in the presence of an anesthetized dam, the corticosterone elevation was buffered and preference for, rather than avoidance of, the odor occurred (Moriceau and Sullivan, 2006). This buffering of the corticosterone elevation appeared to be accomplished through inhibition of excitatory norepinephrine inputs from brainstem to PVN because the presence of the dam reduced norepinephrine release in the PVN during the conditioning (Shionoya et al., 2007). Moreover, infusion of a norepinephrine antagonist in pups conditioned alone inhibited the corticosterone-mediated avoidance learning and led to preference, whereas infusion of a norepinephrine agonist induced learning in pups conditioned in the mother's presence (Shionoya et al., 2007). Results in guinea pigs are consistent with these findings. Pups placed alone in a novel environment showed both HPA activation and increased turnover of norepinephrine in the anterior hypothalamus that includes the PVN, whereas pups placed in the novel environment with the mother, or pups left alone in the home cage, showed neither HPA activation nor increased hypothalamic turnover of norepinephrine (Harvey et al., 1994; Maken et al., 2010). Thus, across both species, stressors that activated the HPA axis in isolated pups also increased norepinephrine

activity in the region of the PVN, and the presence of the mother inhibited both HPA activation and the norepinephrine response (Fig. 1A).

Buffering by mates

When female prairie voles underwent 1 hr of restraint and then recovered in the home cage alone for 30 min, they exhibited increased stereotypic route tracing and grooming, as well as elevated circulating levels of corticosterone and anxiety-like behavior on the elevated plus maze at the conclusion of the recovery period. However, these responses were completely abolished if the female recovered with the bonded male partner (Smith and Wang, 2014). Because of evidence that oxytocin acting in the PVN reduces HPA activation and anxiety-like behavior in other conditions (Blume et al., 2008; Neumann and Landgraf, 2012; Smith and Wang, 2012), oxytocin content in PVN was investigated further as a potential buffering mechanism. Indeed, intra-PVN infusion of an oxytocin-receptor agonist in isolated females reduced anxiety-like behavior and corticosterone elevations, whereas intra-PVN infusion of an oxytocin-receptor antagonist blocked the buffering effects of the male (Smith and Wang, 2014). Thus, there is strong evidence for oxytocin serving as a mechanism in housing-type social buffering by the pair-mate in prairie vole females (Fig. 1B). These results confirm the findings in humans suggesting that oxytocin mediates social buffering of the cortisol response in men by their romantic partners (Heinrichs et al., 2003), and that whether a man exhibits this buffering effect varies

with the presence or absence of a common single nucleotide polymorphism of the oxytocin receptor (Chen et al., 2011).

Buffering by other conspecifics

When fear-conditioned male rats were exposed to the auditory CS either alone or with a novel male rat, the presence of the partner completely blocked behavioral responses and HPA axis activation (Kiyokawa et al., 2014a; Kiyokawa et al., 2007). Electrophysiological and immunohistochemical analysis confirmed that buffering by a conspecific was accompanied by suppression of activity in the LA (Fuzzo et al., 2015; Kiyokawa et al., 2014b; Kiyokawa et al., 2007; Takahashi et al., 2013). Given that the full suite of behavioral and physiological responses induced by the auditory CS can be ascribed to LA activation (Duvarci and Pare, 2014), there is strong evidence that the blockade of HPA activation originates from this LA suppression.

Additional analyses have delineated a circuit by which conspecific signals may act on the LA. The subject male detects odor signals responsible for this buffering at the main olfactory epithelium (MOE) because lesion of the MOE blocked the buffering effect (Kiyokawa et al., 2009). Anatomical evidence suggests that the olfactory signals mediating buffering effects are transmitted from the MOE to the main olfactory bulb after detection. From there, the signals appear to be transmitted to the LA via the posteromedial region of the olfactory peduncle (pmOP) because a bilateral lesion of the pmOP, as well as disconnection of the pmOP from the ipsilateral BLA, blocked the buffering effect

(Kiyokawa et al., 2012). Further, only the posterior complex of the anterior olfactory nucleus (AOP) within the pmOP showed increased Fos expression during social buffering by a conspecific (Takahashi et al., 2013). Taken together, these findings suggest that the olfactory signal responsible for this form of social buffering is transmitted from the main olfactory bulb to the pmOP, most likely the AOP region. The AOP then suppresses LA activation to achieve the buffering effects (Fig. 1C). However, if the subject had not been conditioned, the presence of the partner did not increase Fos expression in the AOP (Takahashi et al., 2013). Therefore, detection of olfactory signals responsible for buffering by a conspecific does not inevitably activate the AOP, implying the existence of an additional modifying system dependent on the subject's stress status.

Recent research in mice suggests a related and more-direct means by which olfactory cues may induce buffering by a conspecific. When a mouse was placed in a novel test box either alone or with a novel mouse, the presence of the partner reduced Fos expression in the PVN. Further analyses revealed that just the odor of mice is sufficient to induce this social buffering (Klein et al., 2015). Moreover, anatomical analyses revealed that a specific subpopulation of olfactory receptors that respond to the same odor projects to glomeruli that then have projections to the vasopressinergic neurons in the PVN (Bader et al., 2012). These findings imply the existence of a direct, reflexive system mediated by vasopressin in the PVN (Fig. 1C).

Possible indirect mechanisms

Although we have focused on neural mechanisms that appear to directly inhibit survival circuits as social buffering mechanisms, neural mechanisms related to affiliation with the partner may also affect social buffering indirectly. Opioid systems appear to be one of example. Early work in leghorn chicks found that opioid-receptor antagonists reduced social buffering of vocalizations by other chicks in a novel environment (Panksepp et al., 1980), whereas opioid-receptor agonists enhanced this social buffering effect (Panksepp et al., 1980). However, the role of opioids is not specific to this type of social buffering because opioid-receptor antagonists also reduced social buffering of vocalizations by the mother (Carden and Hofer, 1990). In addition, opioids can be released during positive social interaction (Panksepp et al., 1985). Together, it may be more reasonable to assume that opioids indirectly mediate social buffering by affecting neural mechanisms related to affiliation. Dopamine appears to be another example because dopamine not only mediates buffering of vocalizations by mothers (Shair et al., 2009), but it also is released centrally during mating (Wang et al., 1999) and non-sexual social interactions (Matthews et al., 2016) and underlies social reward and social memory (Gobrogge and Wang, 2015; Lieberwirth and Wang, 2016).

Of course, contribution to one neural mechanism does not preclude a role in another. For example, analyses of pair-bond formation in prairie voles revealed that vasopressin in the lateral septum (Liu et al., 2001) and ventral pallidum (Pitkow et al., 2001) and oxytocin in nucleus accumbens (Young et al., 2001) play crucial roles in the

neural mechanisms related to affiliation in the male and female brain, respectively. These neurochemicals in the PVN also appear to play important roles in social buffering mechanisms, as we saw in previous sections. Therefore, specifying the target brain region is crucial to understand the role of neurochemicals in social buffering.

Summary and future directions

In this article, we noted early on the ambiguity of concepts such as "stress" and "social" upon which the notion of social buffering is based. In addition, the variety of approaches to the study of social buffering precludes any strict standardization of procedures. These factors and even the backgrounds of the researchers themselves will continue to promote ambiguity and differences of opinion. In drafting this paper, the two authors were themselves surprised by how differences in cultural background led to differences in how a term like "affiliation" can be viewed. For these reasons, it is always crucial to consider the specific circumstances of testing and characteristics of the participants when drawing conclusions from a particular study. Beyond describing the range of conditions that constitute the buffering phenomenon, we may uncover distinctions that a broad categorization of effects would obscure. For instance, different partners can, as illustrated above, buffer the same stress response of the same individual through different processes. Likewise, we may find that whether the effect of a particular stressor can be buffered will depend on more than broad distinctions such as the stressor's intensity of whether it is psychogenic or physical in nature, but instead on whether there has been some

adaptive value for this particular class of partner to buffer this particular stressor under these specific conditions at some point in the evolutionary past of the species. In short, variations in when social buffering does and does not occur may prove to be among the more meaningful of results.

Consistent with the bulk of the literature, we restricted our definition of social to those situations in which individuals have an affiliative relationship, and we emphasized the response of physiological stress-responsive systems, particularly the HPA axis. Behavioral buffering effects were reviewed and limitations of behavioral measures in the absence of supportive physiological data were noted. The activity of upstream drivers of peripheral stress responses, i.e., the survival circuits in the brain, were also identified as appropriate endpoints for social buffering studies. A focus on such outcomes is a trend that no doubt will increase as means of measuring moment-by-moment changes in the neuronal activity continue to advance. We also reviewed and categorized the variables currently employed in social buffering studies. It was suggested that a useful distinction can be made between studies in which the partner is present during the stressful episode (exposure-type) and those in which the partner is present during recovery (housing-type). A particularly crucial variable in determining when buffering will occur is the relationship between the subject and partner. The presence of an attachment or bond appears to be the best single predictor of whether social buffering between the subject and partner is likely to occur,

though many other examples exist, including robust buffering effects in pairs of unfamiliar adult male rats.

The signals that mediate social buffering exhibit large between-species differences, varying largely with the sensory modality dominant for that species. In most cases, it appears that sensory cues serve to identify the partner, and it is the partner's relationship vis-à-vis the subject that determines whether the subject's stress response is reduced. However, social buffering in mice will be the first instance in which a direct neural link between sensory (olfactory) input and stress-response inhibition exists (Klein et al., 2015), if the role of vasopressinergic neurons in social buffering is clarified. What is known about the neural mediators of social buffering effects was then reviewed. Undoubtedly, these systems are only beginning to be understood. Thus, while individual systems have been implicated in different forms of buffering, it is entirely possible, if not probable, that multiple systems interact in ways that currently remain obscure.

Achieving a better grasp of underlying mediators of buffering seems to be the most obvious future direction for this field. The "promise" of oxytocin as a mediator of social buffering provides one example. Despite widespread interest by the neuroscience community, strong evidence for oxytocin as a mediator of buffering has been obtained only for one situation: housing-type buffering by mates in female prairie voles (Smith and Wang, 2014). Yet, hints abound that oxytocin may be involved in other forms of buffering, particularly between mothers and infants. For instance, suckling has been shown to elicit

central oxytocin release in mother (Kendrick et al., 1986; Moos et al., 1989) and at least peripherally in the young (Lupoli et al., 2001). Administering an oxytocin receptor-antagonist to the young was found to reduce rewarding properties of maternal contact (Kojima and Alberts, 2011) and immediate preference for the mother (He et al., 2017). These findings, together with the known calming and anxiolytic effects of oxytocin (Uvnas-Moberg et al., 2014), certainly suggest that oxytocin is somehow—if indirectly—involved in buffering between mothers and infants, though the lack of clear evidence to date suggests the role may be more complicated than commonly assumed. Moreover, potential mediators of buffering are known to interact in complex ways. For instance, social interactions can lead to release of oxytocin in the ventral tegmental area, which then stimulates reward-specific dopamine neurons terminating in nucleus accumbens. (Hung et al., 2017). Likewise, oxytocin can reduce opiate tolerance (Kovacs et al., 1985), which may prolong opioid-mediated reinforcement of social partners. Thus, a deeper understanding of the mediators of social buffering may prove to require the parsing of the interplay of numerous neurochemical systems.

More research designed to directly evaluate male-female differences in social buffering are needed. Intriguing findings in buffering studies with both human (Ditzen et al., 2007; Kirschbaum et al., 1995) and nonhuman (Ishii et al., 2016) species, as well as known sex differences in the neural substrates of bonding (Kelly and Goodson, 2014; Tabbaa et al., 2016), suggest that this would be a fertile area for future study. Interestingly,

a greater focus on sex differences has also been identified as a primary need for studies of buffering in humans (Hostinar et al., 2014). Another area in which it would seem studies would readily advance the field is the developmental origins of individual differences in susceptibility to buffering effects. Human studies implicate polymorphisms in the oxytocin receptor gene in affecting positive social behavior (Krueger et al., 2012) and susceptibility to buffering effects (Chen et al., 2011). We also know that early social deprivation during institutionalization affects children's sensitivity to buffering (Hostinar et al., 2015). These findings suggest that there is much to be learned about the effect of early-life stress or early experience with social buffering on later sensitivity to a partner's presence, and how these effects might vary with genotype. These questions could be readily addressed in laboratory rodents.

One should also consider the behavior exhibited to the stressed animal by its partner. Recent studies in rodents have documented so-called prosocial "consolation" behaviors that appear motivated to benefit unrelated conspecifics. For example, rats have been observed to release another rat trapped in a restrainer (Ben-Ami Bartal et al., 2011; Ben-Ami Bartal et al., 2014; Ben-Ami Bartal et al., 2016) and to choose to secure food for itself and a partner rather than just for itself (Marquez et al., 2015). Given that consolation behaviors have been observed concurrently with behavioral social buffering in pair-bonded voles (Burkett et al., 2016; Smith and Wang, 2014), it would be interesting to examine whether and how consolation behaviors may contribute to social buffering and whether

differences among dyads in the occurrence of consolation behaviors predict differences in social buffering. Furthermore, it would also be worth analyzing whether individuals that exhibit relatively more consolation, and which presumably are more sensitive to the social cues of distressed companions, are more sensitive to social buffering effects themselves.

Continuing study of the social buffering phenomena is valuable for at least two broad reasons. First, the ability of social partners to reduce the stress responses of each other may shed light on the origins and benefits of sociality. Having one's stress response reduced by another may have promoted gregariousness and living in groups, which, in turn, can offer additional benefits, such as the protection from predators and more efficient utilization of environmental resources. Similarly, changes with development in the ability of different classes of partners to serve as buffering agents may facilitate the transition from social interactions adaptive for one stage of development (e.g., infancy) to another (adolescence or adulthood). Second, since stress, particularly chronic stress, appears to promote, enhance, or trigger any number of human diseases and disorders (Cohen et al., 2007; Salleh, 2008), a better understanding of conditions that favor stress buffering and the mechanisms that underlie it has enormous translational value. Comparative studies of stress buffering can serve as a guide for, and complement to, human studies in this pursuit.

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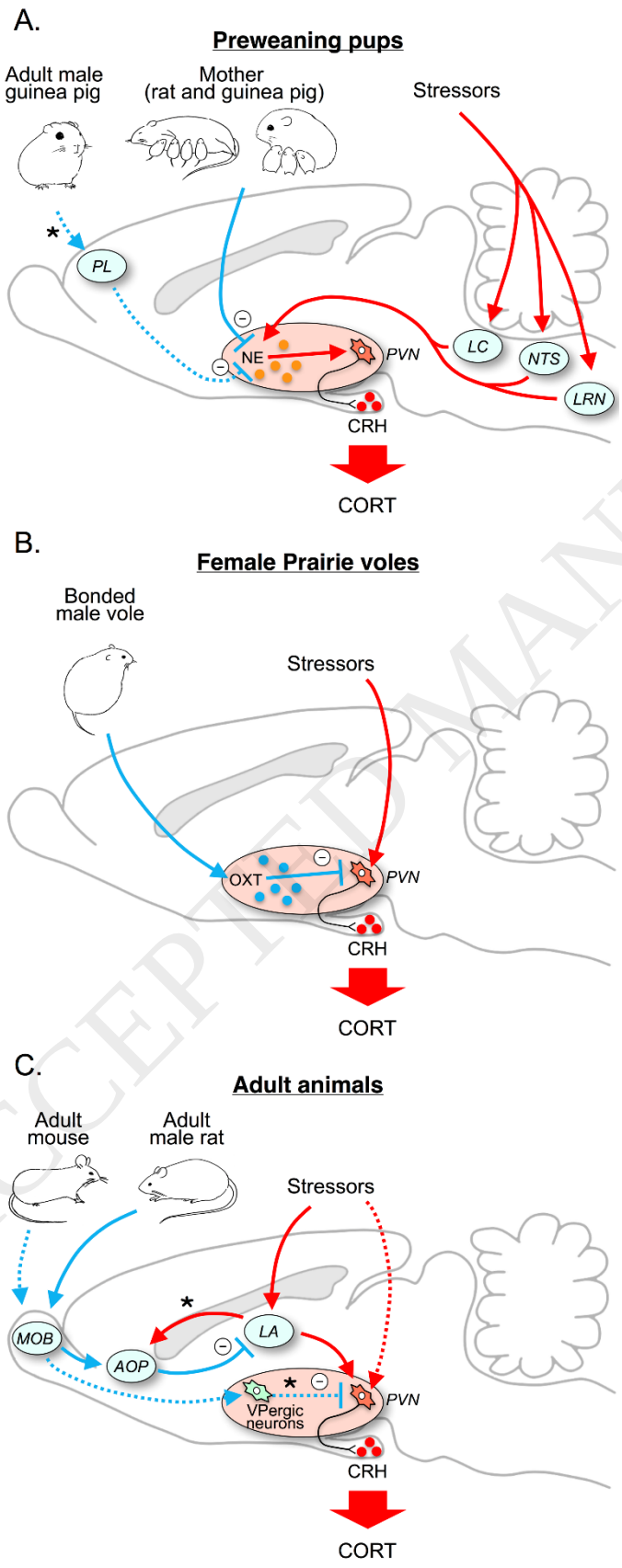
Figure legends

Fig. 1. Summary of the findings in neural circuits underlying social buffering. (A) Possible neural mechanisms underlying social buffering in rodent pups. Solid and dashed lines represent pathways proposed in each experimental model. (B) Presumed neural mechanisms underlying social buffering by mates in female prairie voles. (C) Possible neural mechanisms underlying social buffering by adult conspecifics other than mother and

mates. Solid and dashed lines represent pathways proposed in each experimental model. However, the pathways do not necessarily imply direct anatomical connections. Hypothetical buffering pathways are marked by asterisks. AOP, posterior complex of the anterior olfactory nucleus; CORT, corticosterone or cortisol; CRH, corticotropin releasing hormone; LA; lateral amygdala; LRN, lateral reticular nucleus; MOB, main olfactory bulb; NE, norepinephrine; NTS, nucleus of the solitary tract; OXT, oxytocin; PL, prelimbic cortex; PVN, paraventricular nucleus of the hypothalamus; VP, vasopressin.



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