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Rodent Empathy and Affective Neuroscience

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Abstract

In the past few years, several experimental studies have suggested that empathy occurs in the social lives of rodents. This indicates that rodent behavioral models can be developed in an attempt to elucidate the mechanistic substrates of empathy at levels that have heretofore been unavailable. For example, the finding that mice from certain inbred strains express behavioral and physiological responses to conspecific distress, while others do not, underscores that the genetic underpinnings of empathy are specifiable and that in the future they could be harnessed to develop new therapies for human psychosocial impairments. However, the advent of rodent models of empathy is met at the outset with a number of theoretical and semantic problems that are similar to those previously confronted by studies of empathy in humans. The distinct underlying components of empathy must be differentiated from one another and from lay usage of the term. The primary goal of this paper is to review a set of seminal studies that are directly relevant to developing a concept of empathy in rodents. We first consider some of the psychological phenomena that have been associated with empathy, and within this context, we consider the component processes, or endophenotypes of rodent empathy. We then review a series of recent experimental studies that demonstrate the capability of rodents to detect and respond to the affective state of their social partners. We focus primarily on experiments that examine how rodents share affective experiences of fear, but we also highlight how similar types of experimental paradigms can be utilized to evaluate the possibility that rodents share positive affective experiences. Taken together, these studies were inspired by Jaak Panksepp's theory that all mammals are capable of felt affective experiences.

Keywords

fear; pain; distress; emotion; social behavior; *Mus musculus*; *Rattus Norvegicus*; reciprocity; altruism

1. Introduction

Historically, empathy has been considered a high-level affective/cognitive process that is expressed exclusively by humans. However, recent scientific developments have placed this anthropocentric view into question. Prompted in part by the research and writings of primatologist Franz de Waal, more principled and evolutionary based perspectives on empathy have emerged (de Waal, 2008). For instance, it is now generally accepted that

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many primate species have a capacity for empathy, that empathy can be a proximate mechanism underlying the expression of altruistic behavior, and that empathy is the product of an integrated set of brain processes. Moreover, contemporary views of empathy consider its expression to be a product of several behavioral, affective and cognitive processes, each of which can vary with development, context and species (see below). Deconstructing empathy into specifiable components is highly amenable to employing experimental approaches that aim to elucidate the biological substrates that contribute to impairments in social interaction.

In this paper, we consider one core feature of empathy—the ability to share affective experiences—in rodents. We review and compare the experimental approaches and results of a series of recent papers that explored different aspects of rodent behavior in response to the distress of conspecifics. Rather than attempting to provide a comprehensive review of research on empathy in primates, of which there are several (Davis, 1994; Farrow and Woodruff, 2007; Silk, 2007; Decety, 2010), our goal is to outline how shared affect can be modeled in laboratory rats and mice. In this regard, studies of shared affect in rodents can provide a level of biological resolution that has never been achieved in empathy research.

Several of the studies that we describe employ a fear-conditioning paradigm in which an individual is challenged to learn an association between a conditioned stimulus (CS), such as a tone or context, and an unconditioned stimulus (UCS), such as a delivery of a shock. In a standard fear-conditioning paradigm, a subject learns to associate the CS with the UCS because direct experience with the UCS engenders pain. However, many of the studies described herein utilize a very different UCS, a distress cue that has been generated by the induction of pain in *another* individual (see Section 4). Consistent with the affective neuroscience approach (Panksepp, 1998), we adopt the perspective that such associations can be learned because changes in an animal's subjective state occur while others are undergoing distress. In this scenario, a subject's subsequent responsiveness to a CS thus reflects its previous emotional experiences with a conspecific in pain.

A basic premise of affective neuroscience is that careful behavioral and neuroanatomical manipulations in the laboratory can yield insights into how affective and cognitive processes are distinct both in terms of their overt expression and their respective underlying neural circuitries (Panksepp, 2005). Through the lens of affective neuroscience, we can envision building a robust framework for elucidating the neurobiological substrates that underlie different aspects of empathy in animals.

1.2. Empathy

The study of empathy is heavily influenced by questions about terminology, and there continues to be an imprecise and therefore confusing usage of the term 'empathy' both in the scientific literature and amongst the lay public. In this paper, we will not review this literature or how empathy is expressed in humans (readers are referred to MacLean, 1967; Hoffman, 1981; Davis, 1994; Decety, 2010). Rather, we will point out a few salient definitions that can be useful in developing a concept of empathy in rodents.

The word empathy has undergone a substantial evolution in the last century. Lipps provided the original definition of empathy in 1903 as a process by which "the perception of an emotional gesture in another directly activates the same emotion in the perceiver, without any intervening labeling, associative or cognitive perspective-taking processes." (pp.2, Preston and de Waal, 2002). During the next one hundred years, perspectives on empathy were substantially expanded and refined. Some investigators focused on how individuals perceive and respond to the emotional expressions of others. Such approaches emphasized a role for affective arousal, associative learning and motor mimicry (i.e., imitation). More

cognitive approaches to studying empathy were based on describing how an individual comes to understand the perspective of another by actively projecting into the psychology of their social partners. Within this context, major questions involved discerning when and how an individual can distinguish self from other, and whether there was an ability to recognize that the perspective of another could be different from one's own. At the highest level, cognitive approaches to empathy focused on language-based abstractions in which certain words could activate emotions in others because they were relevant to a past experience. Moreover, some cognitive approaches considered a role for compassion in the empathic response, which allowed individuals to relate with the emotional state of others even though they did not necessarily share the same state (for an excellent review of different definitions of empathy and its historical evolution see Davis, 1994).

Modern theoretical developments in empathy research have centered on an approach that views the expression of empathy as the result of an interaction between several component processes, both affective and cognitive (Hoffman, 1987; Preston and de Waal, 2002; Decety and Jackson, 2004). Preston and de Waal (2002) hypothesized that these processes utilize an ancient perception-action coupling mechanism in which a subject's attention to the 'state' of another can automatically active the same state in the subject. Regardless of the underlying mechanism, this model serves as a very useful heuristic insofar that viewing empathy as a psychological phenomenon which stems from several underlying processes offers a practical strategy for employing biological approaches in empathy research. In the rest of this section, we review what some of these component processes are in attempt to clarify our own hypothesis that rodents are capable of sharing affective experiences.

Emotional contagion is a psychological process that is relevant to empathy and refers to a phenomenon in which the perception of a *behavioral* change in an individual appears to automatically activate the same process in another individual. Emotional contagion is thus a reflexive behavioral process among individuals within the context of a motivationally salient event. By definition, contagion requires that two individuals contemporaneously express a behavior that reflects a common experience. Perhaps the most common examples of emotional contagion in humans are infectious crying among babies and yawning among adults. Although emotional contagion fits within a more generally accepted definition of empathy; "the generation of an affective state more appropriate to the situation of another compared to one's own" (Hoffman, 1975), it is excluded from others, particularly when there is an emphasis on the ability to distinguish self from other. Importantly, emotional contagion does not require an ability to discern whether the source of an affective experience comes from one's self or from another individual (Singer and Lamm, 2009).

The ability to distinguish self from other is a key feature of emotional empathy, in which directed attention to another's emotional state can lead to the same state in a subject. Thus, like emotional contagion, emotional empathy involves 'state-matching' between individuals. However, emotional empathy is exclusively concerned with the *affective* state of individuals. Importantly, because emotional empathy requires an ability to distinguish one's self from another, it can subsequently lead to helping behaviors and also can be engaged by one's personal recollection of an experience (see Davis, 1994; Preston and de Waal, 2002).

While emotional empathy inherently requires that two individuals share an affective experience, it's expression also can be modulated by cognitive processes. These cognitive aspects of empathy incorporate changes in the emotional state of one individual that are subsequently experienced by another individual after some degree of additional processing (e.g., top-down processing). Examples of this include contextual appraisals, such as integrating past experiences or familiarity, and high-level cognitive phenomena, such as perspective taking (see below). For instance, in some of the studies described in Sections 2–

4, responsiveness of a subject is altered if they have had previous experience with the UCS, if they have lived with or share kinship with their social partner, or if their social partner poses a concurrent threat. Moreover, in humans, empathic responses are modulated by a subject's perceived fairness of an individual suffering from a painful stimulus, as well as by gender (Hein and Singer, 2008). In some situations and species, a distinct form of cognitive empathy may be operational, which requires an ability to distinguish that another can maintain a perspective distinct from one's own. This ability to recognize that the perspective of another individual is different from one's own is based upon a phenomenon known as 'Theory of Mind' (Farrow, 2007), a form of metacognition (see below). In this form, it is thought that cognitive empathy allows an individual to understand the emotional state of another without necessarily sharing the same emotional state. In several instances, the expression of empathy is therefore determined not just by the ability to share an affective experience, but also by factors that can modulate the empathic experience.

One way of broadly exemplifying the emotional versus cognitive aspects of empathy is through a comparison of two commonly used clinical tests that evaluate psychosocial functioning in humans. The 'feigned distress test' is used to assess whether an individual attends to emotional changes in another. During the assessment, a clinician exclaims surprise in response to an accident, such as dropping papers on the floor or burning her fingers while lighting a candle on a cupcake. Normal children look toward the clinician's eyes and to the vicinity of the accident (i.e., papers on the floor, fingers), whereas some children on the autism spectrum express abnormal responses or fail to respond (Bacon et al., 1998; Dawson et al., 2004; Hutman et al., 2010). The feigned distress test thus identifies whether an individual can detect and respond to an emotional change in another.

Theory of Mind (ToM) is the ability of an individual to understand that another individual can have a separate experience from one's own. In one test of ToM (Wimmer and Perner, 1983), a human subject observes a scenario in which one doll (A) places a marble in a basket and then leaves the room. Then, a second doll (B) enters the room and removes the marble from the basket and places it into an adjacent box. When doll A returns, the subject is asked to predict where doll A will search for the marble. Individuals with a healthy ToM identify the basket, understanding that doll A would not have experienced doll B change the location of the marble. The individual can therefore infer, through cognitive re-representation, the perspective of another and it is thought that this ability is critical for the expression of cognitive empathy.

While empathy can include different levels of cognitive ability that vary across species and according to social, temporal and environmental contexts, emotions are a basic substrate for all empathic capacities. Indeed, a view of empathy that focuses on affective experience brings one closer to the original translation of einfühlung or 'empathy' as a process of 'feeling into' another (Titchener, 1909). Within an experimental context, such as the rodent studies described below in Sections 2–4, it may be useful to examine the features of a very practical definition of empathy proposed by de Vignemont and Singer (2006). In their definition, empathy occurs when an individual (A) experiences an affective state that is isomorphic to the affective state of another individual (B), and is elicited by observing or recalling the respective expression of the affective state by individual B. Within this model, the affective state of individual B is therefore the source of emotional change in individual A (de Vignemont and Singer, 2006). Some investigators would also allow empathy to include anisomorphic emotional responses between individuals A and B (see below). However, the de Vignemont and Singer model provides a useful framework for studies of rodent affective states that are activated during a social exchange.

Emotional empathy requires that individuals share a feeling state based upon the same influence, even if these respective experiences are temporally disconnected (i.e., recollection). This type of empathy can be conceptualized within the context of our understanding of the basic emotional systems of the mammalian brain and how they generate affective feelings (Panksepp, 1998). For instance, an emotional experience of anger can engender behavioral responsiveness (aggression) in a dominant male that subsequently induces an emotional experience in a subordinate, such as fear. Importantly, this example of anisomorphic emotional exchange is compatible with a perception-action mechanism, but particular emphasis is placed on the distinct affective experience of each individual (viz., anger induces fear). Employing an affective neuroscience approach, with its seven basic emotion systems, allows one to identify and differentiate the affective experiences of animals (e.g., fear or happiness in one individual leads to fear or happiness, respectively, in another individual). It is also important to keep in mind that empathy can engender a string of subsequent behavioral phenomena (e.g., escalated aggression, nurturing or consolation behavior).

Observational learning studies serve as a foundation for studying empathy in rodents because they require an individual attend to the behavior of another individual. Numerous studies have demonstrated that mice and rats are capable of learning from others how to perform a specific task (Zentall and Levine, 1972; Collins, 1988; Valsecchi et al., 2002; Carlier and Jamon, 2006). These studies typically involve a task in which an observer experiences a demonstrator acquiring a foodstuff. In these experiments, hunger serves as the putative motivation for both the demonstrator performing the task and the observer attending to the behavior of the demonstrator. Thus, the demonstrator and the observer experience a *common* motivational state that does not necessarily involve a *shared* component. Here, and through out this review, we use the term ‘shared’ to denote a situation in which a UCS that engenders an affective state in one individual (‘demonstrator’) can be communicated to another individual (‘observer’). Importantly, this type of shared experience does not imply that a demonstrator intentionally communicates with an observer. Observational learning (including imitation and social facilitation) can be differentiated from empathy based on differences in expression and behavioral responsiveness. Empathy occurs if a subject expresses a change in affect in response to an affective experience in a conspecific. By contrast, observational learning occurs if changes in behavior represent modifications of task performance in the absence of emotional signals. Readers are directed to excellent reviews by Heyes (1994) and Galef and Giraldeau (2001) for additional perspectives on rodent observational learning.

In this paper, we focus on the affective component of empathy in rodents. This is not to say that rodents are incapable of some psychological processes that are related to cognitive empathy. Indeed, there is evidence that rodents possess the prerequisite skills for this ability, such as some forms of metacognition (Foote and Crystal, 2007). However, we will limit our focus here to the affective aspects of empathy because of the solid framework that affective neuroscience provides for elucidating the basic emotional operating systems of the mammalian brain (Panksepp, 1998). Specifically, a series of very recent studies is described that collectively demonstrate rodents are capable of (1) emotional contagion, (2) social modulation of associative learning, and (3) the shared affect component of empathy. We also describe where attempts have been made to identify the neural substrates that underlie these phenomena. Taken together, these studies underscore that rodents possess a remarkable affective sensitivity to the emotional state of others, which in the future could be developed into robust experimental models of psychosocial dysfunction relevant to disorders such as autism (Bacon et al., 1998; Dawson et al., 2004; Hutman et al., 2010).

1.3. Foundational studies

Prior to reviewing the more modern studies that are relevant to rodent empathy, it is imperative to briefly discuss two studies that were conducted over 45 years ago. Each of the studies is foundational in that they highlight the extent to which a rodent can be attuned to the affective state of a social partner. In one experiment (Church, 1959), the behavior of well-trained rats was assessed as they preformed a lever-pressing task and were concurrently exposed to a conspecific that was being shocked. Perhaps not surprisingly, the distress cues that were generated by a conspecific had a direct suppressive effect on the rate of lever pressing by subjects. The more intriguing part of the experiment included an 'emotional conditioning' component, during which subject rats and their respective social partners simultaneously received a shock that was paired with a CS (i.e., panel lights in the testing apparatus). Control groups included subject rats that underwent the same procedure, but with shocks that were presented in an unpaired fashion relative to the shocks that were delivered to their social partners, as well as a group of rats that were not conditioned. Following this phase of the protocol, subjects were retested for lever pressing with intermittent co-exposure to conspecific distress and the CS. Subjects that had previously been shocked contemporaneously with their social partner during the conditioning phase of the experiment expressed a robust depression in lever pressing (relative to the other groups) that persisted for 10 days. Subjects from the unpaired group also decreased their lever pressing initially in response to co-presentation of the CS and conspecific distress, however, their responsiveness was much higher than rats from the paired group and it also returned to baseline by the last day of testing. These results are particularly intriguing for 2 reasons: (1) Perception of social distress by a rat substantially disrupted its behavior even though it was depleted of a vital resource (22-hr food deprivation). (2) More importantly, responses of individuals in the paired group indicated that the shared experience of pain was a more potent modulator of behavior than was the consecutive experience of pain and perception of pain in others. Thus, the findings of Church (1959) were seminal because they demonstrated that a rat could identify whether its own emotional experience was temporally coordinated with the same experience in a conspecific.

In another study, Rice and Gainer (1962) asked whether a rat could exhibit directed helping behavior to alleviate the distress of a conspecific. In the first part of the experiment, a subject was trained to depress a lever to avoid delivery of a shock that was signaled by a visual cue. Subsequently, subjects were tested with a distressed social partner that was suspended in the air via a hoist system (distressed conspecifics produced squeals in response to this procedure and their 'wriggling' behavior was visually perceptible to the subject). In this scenario, lever depression by the subject resulted in lowering of the conspecific and alleviation of its distress. Lever-pressing behavior of subjects was compared to a control group of rats that could lower a Styrofoam block that was suspended in the air. Subjects that had previous experience with conpecific distress expressed >10-fold more responses to lower a distressed conspecific compared to controls, whereas subjects that had never experienced conspecific distress expressed >3-fold more responses to lower a distressed conspecific relative to their respective control group. Collectively, these findings demonstrated that rats would actively work (i.e., help) to reduce the distress of conspecifics, another phenomenon that is relevant to empathy.

2. Social modulation of pain

Langford et al. (2006) conducted one of the first studies that assessed empathy in rodents within the context of contemporary neuroscience approaches. Their study adapted several traditional behavioral assays that are used to study pain in mice to include a social component in which a 'partner' also experienced a noxious stimulus. They asked if pain-related behaviors (e.g., writhing after a intra-peritoneal injection of dilute acetic acid or paw

licking after a subcutaneous injection of formalin) are sensitive to the behaviors of a social partner that also experiences pain. Individual mice were subjected to the pain-inducing manipulation, and their subsequent behavior was evaluated in real-time under experimental conditions of social isolation, a painful experience with a non-treated partner or a painful experience with a partner that was in pain at the same time. Their experimental results can be summarized into three key findings: (1) If experiencing pain together, mice expressed greater levels of pain-related behavior (i.e., hyperalgesia) compared to when pain was experienced individually. This effect was not specific to the type of noxious stimulus that was experienced (acetic acid or formalin) or the resulting behavior that was expressed (writhing or paw-licking). (2) If experiencing different levels of pain together (e.g., each partner was simultaneously subjected to a different concentration of a noxious stimulus), the behavior of each mouse was modulated by the level of pain experienced by its social partner. For instance, if the forepaw of one mouse was injected with a high concentration of formalin, it exhibited less intense licking behavior if its partner had received a lower concentration of formalin. (3) Observing a conspecific in pain engendered the same amount of post-stimulus hyperalgesia as the direct experience of a painful stimulus. That is, the typical increase in nociceptive sensitivity that mice undergo after a painful experience was also detected in individuals that had simply observed mice in pain without experiencing the noxious stimulus themselves.

Taken together, the Langford et al. (2006) findings demonstrated that mice are remarkably responsive to the level of pain experienced by other individuals. Control experiments that evaluated different sensory modalities revealed that this form of social modulation of pain was communicated by visual signals. Langford and colleagues argued that their behavioral findings were best conceptualized within the context of emotional contagion, a process in which the behavioral state of an individual automatically activates the same state in nearby conspecifics. An analogous situation to this contagion-type of responding also exists in rats, where freezing by an observer is positively correlated with the amount of freezing expressed by a nearby demonstrator when tested in a fear-conditioning paradigm (Wöhr and Schwarting, 2008). Notably, Langford et al. (2006) found that this process in mice was strongly influenced by the degree of familiarity between social partners (also see D'Amato and Pavone, 1993), a finding that closely matches the human empathy literature. Moreover, the opposite effect (i.e., analgesia) was observed when the mouse in pain was paired with an unfamiliar male that was not in pain (Langford et al., 2006). This result was hypothesized to be due to the social threat that was posed by the unfamiliar male, a finding subsequently confirmed and shown to be dependent upon the hormonal status of the male partner (Langford et al., 2010). While the Langford et al. (2006) study provided strong evidence that a certain component of empathy can be studied in mice, not until recently has the extent to which the distress of others can influence behavior of rodents become clear. In the next section, we describe a series of studies that demonstrate communication between rodents modifies their future ability to learn about emotionally salient events.

3. Social interaction with a recently distressed conspecific modulates subsequent learning about environment signals that predict distress

Four recent papers (2 studies using mice and 2 using rats) revealed that a brief social exposure with a demonstrator modifies how an observer rodent subsequently performs in an associative learning paradigm. Bredy and Barad (2009) demonstrated that the acquisition, retention and extinction of a cued-fear association could be modified by a social interaction with a familiar conspecific that itself was previously exposed to the same fear conditioning procedure. Specifically, an observer mouse experienced a 35-min social exposure in its home cage with an animal that had just received three 2-sec shocks (1mA) that were each paired with a 2-min presentation of white noise (2-min inter-trial interval). Critically, within

this behavioral context, the observer did not directly experience the demonstrator while it was distressed. Rather, the observer mouse interacted with the demonstrator in a familiar environment at a time between fear conditioning of the demonstrator and conditioning of itself. The observer mouse was then subjected to the same conditioning procedure as the demonstrator, and this experience resulted in reduced acquisition of a fear response (freezing), diminished ability to recall the CS-UCS association, and increased extinction of the fearful memory. All of these changes were indexed by reduced freezing behavior in response to presentation of the CS-only relative to observers that had interacted with a fear-naïve mouse. It is important to note that the directionality of the observer responses was somewhat unexpected, as it was predicted that a fearful demonstrator would respectively facilitate acquisition of a fear-induced memory and inhibit its extinction.

In a similar experiment, Knapska et al. (2010) found that the ability of a rat to acquire and retain an active fear-conditioned behavioral response (escape) in a two-way avoidance paradigm was facilitated by previous interactions with a fearful demonstrator. In this behavioral paradigm, a demonstrator rat was exposed to ten 1-sec shocks (1mA) that were delivered across a 10-min period (60 sec inter-trial interval) and then the demonstrator was placed back into the home cage of the observer rat for a 10-min social interaction period. Following the social interaction, observer rats were removed from the home cage and placed into a novel apparatus where they were trained to avoid a foot shock by shuttling back-and-forth between two chambers when cued by presentation of white noise. The results of this experiment demonstrated that when a rat was previously exposed to a distressed conspecific, the experience facilitated both the acquisition of avoidance behavior during the training phase of the experiment and an increased retention of the fear memory, as indexed by increased avoidance behavior 24 hrs later.

Knapska et al. (2010) also demonstrated that interacting with a fear-conditioned demonstrator augmented recall of a passive behavioral response (freezing) in a contextual fear-conditioning paradigm. In this paradigm, demonstrator and observer rats were treated as described above, but observers were subsequently exposed to novel context for 4 min, and received a single 1-sec foot shock (1mA) at the transition between minutes 3 and 4 of the context exposure. Increased freezing behavior by the observer rats upon re-exposure to the context was detected 24 hrs later. The directionality of these results contrast sharply with those of the Bredy and Barad (2009) study, where experience with a fearful conspecific retarded the expression of a fear memory. In developing a possible explanation for this difference, it is important to consider how these two experiments are similar. Careful control experiments by both groups illustrated that changes in the ability of an observer to learn after social interaction with a distressed conspecific could not be explained by alterations in noiceceptive sensitivity or generalized locomotion. For example, both studies demonstrated that interaction with a recently distressed animal did not alter the behavior of observers in a hot-plate test of nociceptive sensitivity. Moreover, the differential ability of an observer to learn after social interaction with a distressed conspecific did not result from an influence on subsequent locomotor arousal. Bredy and Barad (2009) found that interaction with a distressed mouse did not alter the exploratory response of observers to a novel environment, which suggests that the increased freezing of observer mice was specific to the learning experience. Knapska et al. (2010) found that social interaction with a distressed rat engendered faster acquisition of learned behavioral responses that required either an increase (escape) or decrease (freezing) in movement. It therefore appears that an event during the social interaction with the distressed animal directly changed the propensity of the observers to learn a new association. Indeed, Bredy and Barad (2009) identified β-phenylethylamine as a pheromone signal that communicated distress to observer mice. Overall the findings of these two studies demonstrate that for rodents learning about fearful situations *in the future* is sensitive to the social experience of distress in others. The reason for the difference

between mice and rats in terms of the directionality of this influence remains unknown, and warrants further experimental attention.

Knapska and colleagues conducted additional in depth analyses of social interactions with a distressed conspecific. When rats were reunited with a recently distressed conspecific, they directed >10-fold more allogrooming at the individual compared to rats that were reunited with a non-distressed conspecific (Knapska et al., 2010). In rodents, allogrooming is a social activity, in which one individual repeatedly licks the head/neck/mouth/ear area of another. It is intriguing to speculate that the facilitation of this behavior after detecting distress in another is an attempt to comfort the afflicted individual, as has been previously suggested for primates (Preston and deWaal, 2002). Interestingly, Knapska et al. (2006) demonstrated a mutual and heightened induction of the inducible transcription factor c-fos in the amygdala of distressed demonstrator rats and observers following a brief social interaction. Although heightened c-fos activity was detected in several nuclei of the amygdala (e.g., lateral, basal, basal medial, medial and central nuclei) of both distressed rats and the respective observers, increased c-fos induction in the central nucleus of the amygdala differentiated these two groups. This finding suggests that particular sectors of the amygdala are responsive to distress in others. Overall, it appears that a coordinated set of changes in the amygdala, a brain region implicated in numerous emotional processes, occurs following the experience of self-distress and the experience of distress in others.

Using an approach similar to the two studies described above, Guzmán et al. (2009) found that observations of non-fearful demonstrator mice modified subsequent learning about a CS-UCS association. In this study, observer mice were exposed to a novel context (3 min) on two successive days with a demonstrator that had previously received a 2-sec shock (0.7mA) in the same context. The observers were then trained with the same conditioning paradigm. In this behavioral model, observations of fearful demonstrators did not alter subsequent learning of the fear-conditioning association by observers. However, if mice observed a non-fearful demonstrator, it inhibited their ability to recall the CS-UCS association themselves. Previous experience with a fear-naïve demonstrator therefore ‘buffered’ the likelihood that mice would become fear-conditioned. It is also worth noting that the presence of a non-fearful partner during the presentation of CS that predicts application of a painful UCS retards the expression of freezing in fear-conditioned rats (Kiyokawa et al., 2009).

Unlike Bredy and Barad (2009) and Knapska et al. (2010), observer mice in the Guzmán et al. (2009) study were able to derive specific information about the experience of the respective demonstrators. While observers in all of the studies ultimately had to learn an association themselves, mice in the Guzmán et al. (2009) study were sensitized to the appropriate context prior to the learning experience. Thus, while the Bredy and Barad (2009) and Knapska et al. (2010) studies illustrated that experience with social distress can subsequently modify the acquisition of a new behavior, the Guzmán et al. (2009) study extended this finding further by demonstrating that observers can make a direct connection between the distress state of others and the specific environmental signals (i.e., context) that are proximal to its occurrence.

In a related experiment with rats, Bruchey et al. (2010) fear conditioned demonstrators with 0.5-sec shocks (0.7mA) that were each paired with a tone (3 pairings), a protocol that engendered robust freezing responses to presentation of the CS 24 hrs later. By contrast, rats that were subjected to the same fear conditioning procedure, but with a less painful UCS (0.4mA shock), exhibited much less CS-induced freezing behavior. Importantly, if observer rats were allowed to socially interact with demonstrators that were simultaneously expressing conditioned freezing (what was referred to as ‘fear conditioning by-proxy’), and

then subjected to the 0.4mA-conditioning protocol, they expressed freezing responses comparable to individuals that had underwent the 0.7mA-conditioning protocol. Thus, it appears that rats exhibit facilitated learning about cues that predict a painful stimulus if they have previously interacted with a conspecific that expresses fear to the same CS (see below).

Differences between the studies described in this section highlight several important issues that should be addressed systematically in future studies of rodent empathy: To what extent is prior experience with the affect-inducing UCS required for observers to respond? When do observers acquire information about the affective state of demonstrators (e.g., as the demonstrator is becoming distressed by a UCS, after the UCS is removed, or as the demonstrator changes its behavior in response to a CS that predicts fear)? What factors play a role in directing changes in observer behavior towards a similar or different response relative to that of demonstrators?

4. Social transfer of fear

The experiments that have been reviewed thus far illustrate that rodents are immediately sensitive to the distress of others (Section 2), and that experience with conspecific distress can modulate how a rodent subsequently learns about environmental cues and contexts that predict fearful situations (Section 3). A critical question regarding empathy in rodents is whether an individual can respond to a CS associated with the distress of a conspecific *as if* it were paired with the direct experience of a UCS. Below we describe five studies that indicate rodents can be responsive in this way, which suggests that rodents are capable of experiencing shared affect.

Employing a highly innovative and ethologically relevant paradigm, Kavaliers et al. (2003) asked whether a mouse could learn via social observation to avoid a predatory attack. Demonstrator mice were placed in a compartment lined with wood shavings and exposed to ≈50 biting flies for 30 min while an observer resided in an adjacent compartment that was separated by a mesh barrier. During this period, the demonstrator mouse exhibited several defensive behaviors in response to the biting flies and ultimately buried itself under the bedding to avoid further attack. Testing included placing a demonstrator or observer in the same context 24 hrs later and exposing them to flies that had their mouthparts removed, which eliminated the ability to bite. Demonstrators expressed robust burying responses when they were re-exposed to flies, even though the UCS (i.e., biting) was not present. Importantly, observer mice also avoided the non-biting flies by burying themselves, a response that was stimulus-specific because observers did not attempt to avoid non-biting flies of a different species. Thus, the observer mice responded to the CS (i.e., flies) *as if* they anticipated a bite even though they had no direct experience with the UCS. Additional studies by Kavaliers et al. (2003) revealed that exposure to non-biting flies following a single experience with a distressed demonstrator engendered conditioned corticosterone release and analgesia in observers. Moreover, the subsequent behavioral responses of an observer were dependent on visual cues and NMDA-signaling (Kavaliers et al., 2001) during its experience with the demonstrator.

Using a cue-conditioned fear paradigm, Kim et al. (2010) showed that an observer rat can acquire a freezing response by observing fear-conditioned demonstrators, but only if the observer has had prior experience with the UCS itself. In this paradigm, demonstrators were fear conditioned with ten 20-sec tones that co-terminated with a 1-sec shock (2mA). During testing, demonstrators were presented with the CS-only in the presence of an observer rat (i.e., paired testing). The fear conditioning procedure engendered a robust fear response in demonstrators, evidenced by high levels of CS-induced freezing and production of aversive 22 kHz-ultrasonic vocalizations (USVs). Naïve observers did not exhibit fear responses to

presentation of the CS or the conditioned responses (freezing and 22 kHz-USVs) of the demonstrator. However, if the observer had previous experience with a UCS (3 unsignaled 1mA-shocks), then paired testing resulted in robust observer freezing responses. The authors conducted a series of lesion/inactivation experiments that targeted the medial geniculate nucleus (MGN) of the thalamus (i.e., auditory thalamus) and found that MGN activity during the experience of unsignaled shocks was necessary for future observer responses in the paired testing situation. Moreover, during paired testing the largest freezing responses were expressed by observer rats that had produced 22 kHz-USVs concurrently with presentation of the unsignaled shocks. It was hypothesized that rats need to process their own 22 kHz-USVs during a painful experience before they can respond appropriately to the distress state of demonstrators during paired testing. Thus, in this paradigm, a CS triggered a conditioned fear response in demonstrators, which in turn engendered a fear response in 'experienced' observers.

In another experiment, the Bruchey et al. (2010) study (also described in Section 2) found that rats acquire a freezing response simply by observing a demonstrator that is expressing a conditioned fear response to a CS. In this experiment, demonstrator rats were fear conditioned with the same protocol described in Section 2 (e.g., 3 tone-shock pairings). Twenty-four hours later, observers were allowed to interact with demonstrators that were being presented with 3 playbacks of the CS-only. During a testing session 24 hrs later, observer rats expressed appreciable freezing responses when they were presented with the CS-only. Thus, in this experiment, a CS that predicted distress in another engendered a fear response *as if* the observer rat had experienced the UCS itself. Based on the results of the Kim et al. (2010) study, it is intriguing to speculate that the distress of demonstrators was communicated to observer rats via 22 kHz-USVs. Interestingly, Bruchey et al. (2010) found that the responsiveness of observer rats to the CS was positively correlated with the amount of social interaction they had directed at demonstrators during the observation session. The findings of Kim et al. (2010) with rats can be distinguished from those of Bruchey et al. (2010), in which observers did not require prior experience with a UCS nor was the presence of a demonstrator required for the expression of a fear response (i.e., observers responded to the CS-only).

Employing a contextual conditioning paradigm, Jeon et al. (2010) demonstrated that observer mice express freezing behavior when they are adjacent to a fearful demonstrator mouse receiving repeated shocks over a 4-min period. This response by itself is consistent with emotional contagion because freezing of the demonstrator and observer mice occurred at the same time. After the observer was placed back into the specific context where the demonstrator had experienced the UCS 24 hrs earlier (equivalent to a long-term memory test), it also expressed freezing behavior, suggesting that an association had been made between the distress of a conspecific and the CS. This subsequent effect was distinct from emotional contagion because freezing behavior expressed by the observer mouse occurred well after exposure to the distressed conspecific and observers had never experienced the UCS themselves. In other words, the freezing behavior of the observer mouse was expressed *as if* it anticipated initiation of distress in another. Freezing behavior in rodents is a direct, behavioral readout of fear (LeDoux, 2000) and thus this finding reflects the social transfer of an emotional state from one mouse to another.

In earlier work (Chen et al., 2009), we developed a similar experimental procedure in which observer mice experienced distressed conspecifics that underwent a series of tone-shock pairings (Fig. 1). While the demonstrators were receiving the shock, observer mice did not express appreciable freezing behavior themselves, but they immediately oriented towards the demonstrator mice while the shock was being applied (Chen et al., 2009). This finding differs from what was reported for observer mice by Jeon et al. (2010), where individuals

froze during the experience of distress in conspecifics. The discrepancy may be due to the fact that Jeon et al. (2010) provided a very strong UCS to observers (twenty 2-sec shocks [1mA] delivered over a 4-min period) to demonstrator mice, whereas our study utilized a more modest UCS (ten 2-sec shocks [0.5mA] delivered over a 20-min period). Additionally, observers and demonstrators were familiar in the Jeon et al. (2010) study, whereas the mice in our study were unfamiliar (Chen et al., 2009). While the reason for this difference between the experiments is unknown, it does highlight important issues regarding the relationship between the strength of the UCS provided to the demonstrator and the expression of emotional contagion and shared affect.

During the first half of the testing phase, twenty minutes after the last experience with demonstrators (equivalent to a short-term memory test), each observer mouse was individually placed back into the conditioning apparatus and their freezing behavior was examined in response to the CS-only (the CS was not behaviorally salient prior to conditioning; Fig. 2a). Observer mice expressed freezing behavior during playback of the CS *as if* they anticipated the initiation of distress in others (Fig. 2b). Thus, similar to Jeon et al. (2010), the observer mice in our study were responsive to a CS that was associated with the induction of distress in others. Importantly, this behavioral response were readily expressed by observer mice from C57BL/6J (B6) strain, but not in individuals from the BALB/cJ (BALB) strain, which indicates that genetic background can influence the degree to which a mouse is responsive to distress in others. This strain-dependent difference is provocative because heritable impairments in psychosocial functioning often include a component where individuals fail to empathize (Goldenfeld et al., 2007; Hobson, 2007; Silani et al., 2008; Greimel et al., 2010).

During the second half of the testing phase, observer mice were themselves exposed to the CS-UCS contingency and their freezing behavior was evaluated. B6 mice also expressed increased acquisition of the CS-UCS association relative to BALB observers (Fig. 2c). By contrast, without the prior experience of distress in demonstrators, BALB mice expressed increased acquisition of the CS-UCS association relative to B6 mice (Fig. 2d). Thus, a genetic influence on acquisition of a fearful memory (i.e., BALB > B6) was moderated by prior experience with social distress (i.e., B6 > BALB).

We were able to reproduce the strain-dependent effect on freezing behavior in response to the CS-only and acquisition of the CS-UCS association by exposing observer mice to pairings of the CS and playbacks of conspecific distress vocalizations (Chen et al., 2009). This finding suggests that vocal communication plays a crucial role in the social transfer of fear among mice. A similar finding has been demonstrated in rats, where the number of 22 kHz-USVs emitted by a fearful demonstrator was positively associated with the amount of fear that was expressed by an observer (Wöhr and Schwarting, 2008). Importantly, both BALB and B6 observers oriented to the distress vocalizations of demonstrator mice (Chen et al., 2009), and age-matched mice from these strains exhibit comparable thresholds for evoked auditory brainstem responses to stimuli that are presented at frequencies similar to the CS (1kHz) and the distress vocalizations (≈20kHz) (Zheng et al., 1999; Willott et al., 1998). Furthermore, BALB mice were able to acquire the CS-UCS association when they were directly administered the UCS. Thus, it appears that a difference in the hearing ability of mice from these two strains does not account for the difference in their sensitivity to conspecific distress.

The BALB and B6 mouse strains have been developed as an experimental model of sociability by several laboratories (Sankoorikal et al., 2006; Moy et al., 2007; Panksepp and Lahvis, 2007), and it has been suggested that the BALB mouse may be a valid mouse model of autism (Brodkin, 2007). By contrast, B6 mice express high levels of gregariousness and

social reward following social isolation, and are behaviorally sensitive to the induction of distress in others (Panksepp and Lahvis, 2007; Panksepp et al., 2007; Chen et al., 2009). In this regard, it is interesting to note that a positive association between measures of empathic responsiveness and personality-trait indices of sociability is a common finding in the human empathy literature (Eisenberger et al., 2006). Thus, further assessments of the inter-relationships between these social variables in B6 mice are warranted and may yield insights into the mechanisms underlying such phenotypic associations.

In addition to behavioral responsiveness, studies from both our lab (Chen et al., 2009) and the Shin lab (Jeon et al., 2010) demonstrated that observer mice exhibit physiological correlates of empathy while they experience conspecific distress. For instance, the heart rate of observer mice from the B6 strain increased immediately at the beginning of the experience of conspecific distress and then decreased below baseline with repeated exposures to distressed conspecifics. BALB mice also exhibited heart rate acceleration upon the induction of distress in conspecifics, but there was no ensuing heart rate deceleration with repeated exposures to conspecific distress. These results were particularly intriguing because a series of studies in humans has demonstrated a relationship between heart rate deceleration and empathic concern for others (Zahn-Waxler et al., 1995, also see Anastassiou-Hadjicharalambous and Warden, 2008).

Jeon et al. (2010) examined neuronal activity, specifically the theta rhythm frequency (≈6Hz) in the anterior cingulate cortex (ACC) and the lateral amygdala (LA), and found that observing conspecific distress synchronizes these oscillations. When these investigators used lidocaine to locally inactivate discrete brain regions, they revealed that ACC activation was required to engender freezing to demonstrator distress, but not subsequent context-specific freezing behavior in observers. By contrast, LA activation was essential for both freezing responses during the experience of conspecific distress and the subsequent expression of context-specific freezing behavior by observers. Thus, Jeon et al. (2010) proposed that the ACC was an essential brain region for the perception of conspecific distress in mice, whereas the LA was crucial for recalling this experience. As far as we know, the Jeon et al. (2010) study is the first of its kind in that it identified a neuronal substrate underlying a phenotype relevant to empathy in mice. Their findings are especially important because the ACC, a brain region long implicated in the regulation of social processes (Panksepp, 2003; Eisenberger and Lieberman, 2004), has been shown to activate when humans detect distress in others (Singer et al., 2004; Jackson et al., 2005).

The experiments in this section are distinct from other studies described in this review because they demonstrated that rodents do not require direct experience with a CS-UCS contingency in order to express a behavior that reflects an affective response to presentation of the CS-only. Rather, observers gained an explicit understanding of the CS-UCS association through a shared social experience. Many questions remain regarding the extent to which this type of empathy is expressed in rodents. The studies that have been considered in this review implicate several key variables that appear to modulate rodent sensitivity to distress in others; these factors include familiarity with the demonstrator, prior experience with the UCS and the strength of the UCS delivered to the demonstrator, among others. For the sake of clarity, we summarize the key points of similarity and distinction among the studies in Table 1. In our view, it is likely that the expression of shared affect among rodents in any given behavioral paradigm is influenced by a dynamic interaction between these factors.

5. Synopsis and Conclusions

The field of rodent empathy research is in its infancy. Although it has been speculated for years (Darwin, 1872; Crowcroft, 1966), only recently has it become accepted, largely through Jaak Panksepp's contributions, that all mammalian species are universally equipped with brains capable of generating felt, emotional experiences (Panksepp, 1998). With this as a foundation, it becomes almost axiomatic that rodents are capable of empathy, a process where the affective feelings of one are conveyed to another and then generate the same feelings in that individual. Consistent with the affective neuroscience approach, this argument is nevertheless a working hypothesis that can be falsified. Perspectives on empathy in rodents should derive from an integration of behavioral, psychological, neural and evolutionary approaches that are continuously updated based upon the available experimental evidence.

Essentially all of the mouse studies described in this review utilized individuals that were derived from the C57 line and it will be interesting to see if these findings generalize to mice from additional strains. If empathy manifests itself on a phenotypic continuum (see Decety et al., 2007 for a review), than we would anticipate that a graded empathy response should be found when comparing several strains. Such a finding would be highly amenable to employing forward genetic approaches to understand mouse endophenotypes that are relevant to empathy. On a related note, an association between sociability and empathic responding (Chen et al., 2009; Bruchey et al. 2010; Knapska et al., 2010) has not been thoroughly studied in rodents and this too could be evaluated via assessments of multiple strains. Another impending question entails how the affective components of empathy in rodents can be modulated by environmental and pharmacological factors. Several of the studies described above demonstrated that greater familiarity between partners enhances empathic responding in mice (Langford et al., 2006; Jeon et al., 2010), a finding that is consistent with the human empathy literature (reviewed by Davis, 1994; Preston and de Waal, 2002). Moreover, given that many mental illnesses include heightened or diminished abilities for empathy, including schizophrenia (Derntl et al., 2009, Haker & Rossler, 2009), obsessive compulsive disorders (Fontenelle et al., 2009), anorexia-nervosa (Kucharska-Pietura et al., 2004), the neurochemical basis of empathic responding in rodents should be explored and candidate molecules from a class of drugs termed 'empathogens' (Valea and Hautefeuille, 2007) should be evaluated in rodents.

By definition, empathy requires that an individual be attuned to the potential for an emotional experience in another. While the studies described in this review, as well as most work with humans, have focused on empathy within the context of negatively valanced emotions (e.g., pain, sadness), the capacity for empathy should also be considered when rodents experience positive emotions. The induction of negative emotional states has been easier to study in animals because they have an immediate impact on the likelihood for survival. However, 'positive empathy' happens everyday. A good example of this in human life is when an individual answers a phone call and immediately, through the vocal prosody of a friend or colleague, the individual becomes invigorated by excitement, even though he or she does not yet possess a propositional knowledge of what underlies the excitement. The positive aspects of empathy have been difficult to document in non-human animals, but there are some provocative recent examples that could be developed into rodent models of positive empathy. For example, a recent study demonstrated that adolescent B6 mice become 'pseudosensitized' to the locomotor-activating effect of morphine simply by observing other mice that had been treated with the drug (Hodgson et al., 2010). Thus, mice were exposed to demonstrator mice that were subjected to a typical morphine-sensitization protocol across multiple days. On the test day, mice that had received repeated treatments of morphine expressed the expected hyperlocomotion phenotype in response to a standard dose

of morphine. Remarkably, observer mice exhibited an enhanced locomotor response to the same morphine dose *as if* they had previous experience with the drug. The doses of morphine used by Hodgson et al. (2010) were within that range that is typically used to measure reward in conditioned place preference studies. Since locomotor sensitization is thought to reflect a state of reward, it is intriguing to speculate that the observer mice shared the reward state with demonstrator mice during the sensitization protocol, and that the enhanced locomotor response of observers during testing was a reflection of this shared experience. It is important to note that the actions of a pharmacological compound, such as morphine, in the brain may be quite different than a more natural stimulus, and the mechanisms underlying pseudosensitization may thus be very different than those described in Sections 2–4.

Another case where positive empathy might come to play is in an experimental paradigm where rats are trained to cooperate to pull in a baited platform to their cage to procure an oat flake (Rutte and Taborsky, 2007). A subject would pull for an unfamiliar conspecific that was adjacent to its cage as long as the act had been previously performed for the subject; it did not matter whether the specific individual adjacent to the rat was a prior altruist, just that the subject had been a prior recipient of helping behavior from any other individual. Rutte and Taborsky (2007) referred to this process as ‘generalized reciprocity’ and suggested that positive affect might be a mechanism underlying this phenomenon. In our view, it is conceivable that positive social affect results from both the act of helping and receiving, and thus shared pleasure might be a psychological consequence of this type of cooperative behavior for rats (also see Schuster and Perelberg, 2004; de Waal et al., 2008).

Rough-and-tumble play is a robust and rewarding form of social activity that is expressed among young rats. In studies of rat play behavior, pharmacological or environmental manipulation of the state of one rat in a dyad drastically alters the behavior of the other within this behavioral context (Poole and Fish, 1979; Humphreys and Einon, 1981; Varlinskaya et al., 1999; Deak and Panksepp, 2006), which suggests that playful rats are very attuned to the state of their partners. Indeed, adolescent rats prefer to be in the company of social partners that express greater amounts of 50 kHz-USVs (Panksepp and Burgdorf, 2003), which are a vocal reflection of positive social affect (Knutson et al., 2002). Thus, rats have a preference for socially positive partners and appear to modulate their play behavior accordingly when the behavior of their partner is discordant with their own. Taken together, these findings imply that rats enjoy play bouts with individuals that are able to share a similar experience with them within the context of social interaction.

A final and critical question regarding empathy in rodents is associated with its underlying neural circuitry. It will be interesting to see how future brain studies involving rodent empathy correspond to the human counterpart experiments. Indeed, the initial comparisons are promising (Jeon et al., 2010). However, rodent brains can also be studied at levels of analysis that are either difficult or unavailable in humans, apes and monkeys (e.g., brain region-specific manipulation of neurochemical signaling, high-throughput genetic approaches including altering the activity of single genes). It will be critical to integrate findings regarding the neural substrates of empathy in rodents with what is known about this process in humans. Consistent with the pioneering work of Jaak Panksepp in affective neuroscience, as more sophisticated models of rodent empathy emerge (including models of positive empathy), it will be crucial to assess the extent to which the neural underpinnings of empathy overlap with the basic emotional operating systems of the mammalian brain (Panksepp, 1998). In other words, do the emotional components of empathy involve the affective neural circuitries that Panksepp has described?

The possibility of empathy in rodents beckons several additional issues. First, if empathy exists in rodents, then it immediately offers an opportunity to study this process at levels of analysis that heretofore have been impossible. The field of mouse genetics is continually evolving, but with the technologies that are currently available, it is realistic that the genetic substrates underlying the ability to detect and respond to distress in others can be discovered and eventually developed into targets for pharmacotherapeutic intervention. At a still greater level, Panksepp's approach to affective neuroscience has provoked us to consider that several basic affective states can be experienced by all mammalian species. If some of these emotional experiences can be induced in animals via other individuals (i.e., shared affect) then many of us will be forced to reconsider our own worldview of animal nature. Similarly, the recognition that rodents possess a capacity for empathy will require scientists to carefully evaluate their own research practices in attempt to reduce the potential for excessive communication of pain or fear between individuals.

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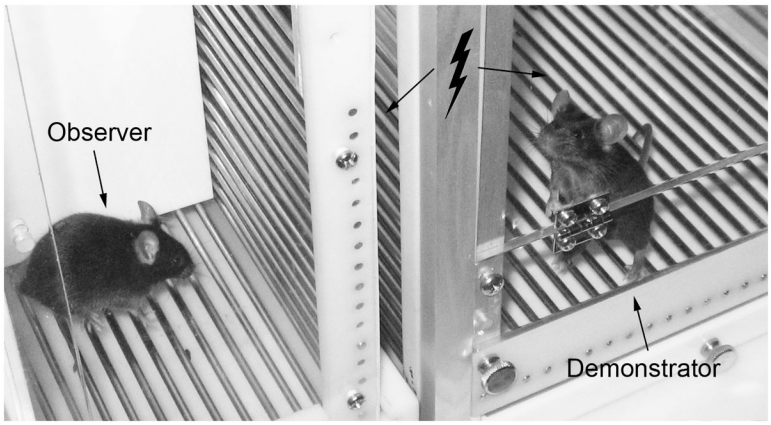

Figure 1.
Conditioning apparatus to assess social transfer of fear among mice. Mice are habituated to the apparatus and then an observer (left) is exposed to a demonstrator (right) receiving 10 consecutive forward-pairings of a 30-sec tone and a 2-sec shock (90-sec inter-trial interval). After 2 days of conditioning, the observer is placed on the side of the apparatus where the demonstrator was conditioned and it is then exposed to 5 presentations of the CS-only followed by 5 presentations of the CS-UCS contingency. The steel bars on the demonstrator side of the apparatus deliver electrical current whereas the bars on the observer side are inactive. Conditioning and testing are conducted during the dark phase of the circadian cycle under dim red illumination.

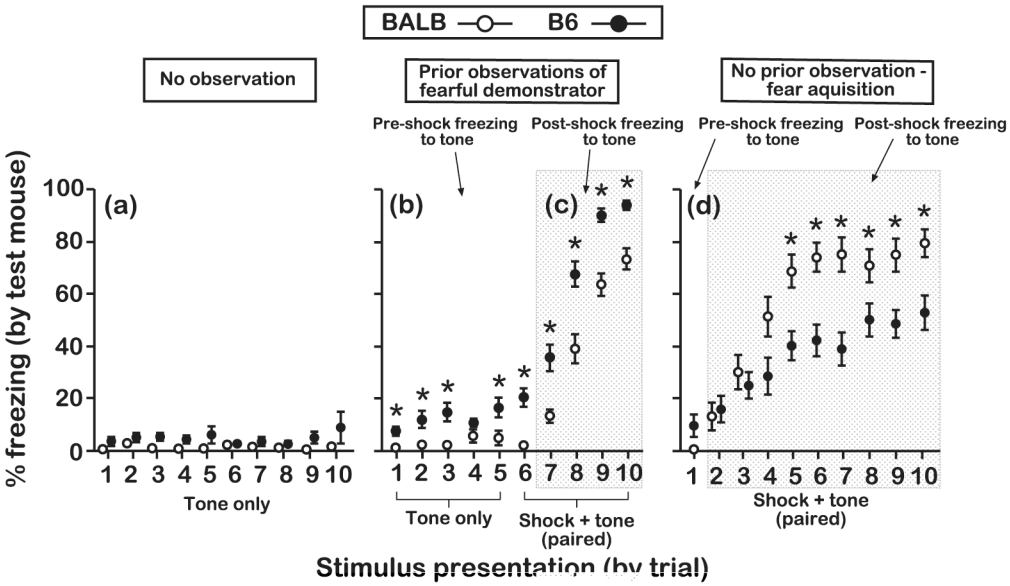

Figure 2.

Freezing behavior of mice. (a) Without conditioning or observations of fearful demonstrators, mice from both the BALB and B6 genetic backgrounds expressed minimal freezing responses to the tone. Freezing was measured for 30 sec during each CS presentation. (b) B6 mice expressed more freezing behavior than BALB mice to the CS if they had prior experience with fearful demonstrators. Freezing was measured for 30 sec during each CS presentation on trials 1–5 and for 28 sec on trial 6. (c) B6 mice that had previous experience with distressed demonstrators also expressed increased acquisition of freezing behavior relative to BALB mice when they were exposed to the CS-UCS contingency. Freezing was measured for 28 sec during each CS presentation on trials 7–10. (d) BALB mice that did not have previous experience with distressed demonstrators expressed more freezing behavior than B6 mice to the CS when it was paired with a UCS. Freezing was measured for 28 sec during each CSP presentation on all trials. Asterisks represent a significant difference ($P<0.05$) between the two genetic backgrounds. All data are presented as the mean ± standard error and were originally reported in Chen et al. (2009).

Table 1

Summary of key variables from recent studies that focused on the detection and response of rodent observers to conspecific (demonstrator) distress. Except for experiments 1 and 2 from Langford et al. (2006), and the first observer responses in Chen et al. (2009) and Jeon et al. (2010), demonstrator pain experiences occurred prior to testing of the observer rodent. Demonstrators expressing a conditioned fear response were present during the testing of observers in Kim et al. (2010). Non-fearful demonstrators were present during the testing of observers in Kiyokawa et al. (2009). [+] refers to a concurrent experience. [ITI] refers to inter-trial interval. [⇒] refers to a transition between experiences. [↑] and [↓] refers to an increase and decrease in behavioral responsiveness of the observer, respectively. [↑↑] refers to an increase in the behavioral responsiveness of the observer relative to the first experiment in the study.

Study (Experiment)	Species	Demonstrator Experience	Observer Experience	Observer Response	Observer Pain Experience Required?	Familiarity Required?	Sensory Modality
Kavaliers et al. (2003)	Mouse	Exposure to biting flies	Demonstrator distress ⇒ Exposure to non-biting flies of the same species	↑ avoidance to non-biting flies of the same species	No	No	Visual
Langford et al. (2006) (1)	Mouse	0.9% acetic acid injection	0.9% acetic acid injection+ Demonstrator distress	↓ writhing	Yes	Yes	Visual
Langford et al. (2006) (2)	Mouse	1% formalin injection	5 % formalin injection + Demonstrator distress	↓ paw licking	Yes	Not tested	Not tested
Langford et al. (2006) (3)	Mouse	0.9% acetic acid injection	Demonstrator distress	↑ thermal pain behavior	No	Not tested	Not tested
Bredy & Barad (2009) (1)	Mouse	2-sec shock (1mA) + cue × 3, 120-sec ITI	Social interaction w/ demonstrator ⇒ 2-sec shock (1mA) × 3, 120-sec ITI	↓ freezing to cue	Yes	Not tested	Olfactory
Bredy & Barad (2009) (2)	Mouse	2-sec shock (1mA) + cue × 3, 120-sec ITI	2-sec shock (1mA) × 3, 120-sec ITI ⇒ Social interaction w/ demonstrator ⇒ Extinction training	↓ freezing to cue (i.e.,↑ extinction)	Yes	Not tested	Olfactory
Bredy & Barad (2009) (3)	Mouse	2-sec shock (1mA) + cue × 3, 120-sec ITI ⇒ 10 extinction trials	2-sec shock (1mA) × 3, 120-sec ITI ⇒ Social interaction w/ demonstrator ⇒ Extinction training	↓ freezing to cue (i.e., ↑ extinction)	Yes	Not tested	Non- olfactory
Chen et al. (2009)	Mouse	2-sec shock (0.5mA) + cue × 10 (2 sessions), 118-sec ITI	Demonstrator distress + cue	↑ orientation to demonstrator distress, ↑ freezing to cue that predicts demonstrator distress	Not tested (observers had 1 prior experience w/shock)	No	Auditory
Guzmán et al. (2009)	Mouse	Exposure to context	Non-fearful demonstrator in context (2 sessions) ⇒ 2-sec shock (0.7mA) + context	↓ freezing to context	Yes	Not tested	Visual
Kiyokawa et al. (2009)	Rat	No experience	0.5-sec shock (0.7mA) × 7, 30–180-sec ITI ⇒ Non-	↓ freezing to cue	Yes	No	Olfactory

Study (Experiment)	Species	Demonstrator Experience	Observer Experience	Observer Response	Observer Pain Experience Required?	Familiarity Required?	Sensory Modality
			fearful demonstrator present during testing				
Knapska et al. (2010) (1)	Rat	1-sec shock (1mA) + context × 10, 60-sec ITI	Social interaction w/ demonstrator ⇒ Active avoidance training to 5-sec shock (1mA) + cue	↑ cue-based avoidance behavior	Yes	Not tested	Not tested
Knapska et al. (2010) (2)	Rat	1-sec shock (1mA) + context × 10, 60-sec ITI	Social interaction w/ demonstrator ⇒ 1-sec shock (1mA) + context	↑ freezing to context	Yes	No	Not tested
Jeon et al. (2010)	Mouse	2-sec shock (1mA) + context × 20, 10-sec ITI	Demonstrator distress + context	↑ freezing to demonstrator distress, ↑ freezing to context that predicts demonstrator distress	No	Enhanced by	Visual
Bruchey et al. (2010) (1)	Rat	0.5-sec shock (0.7mA) + cue × 3, 180-sec ITI	Demonstrator conditioned response to cue x 3	↑ freezing to cue	No	Not tested	Not tested
Bruchey et al. (2010) (2)	Rat	0.5-sec shock(0.7mA) + cue × 3, 180-sec ITI	Demonstrator conditioned response to cue × 3 ⇒ 0.5-sec shock (0.4mA) + cue × 3, 180- sec ITI	↑↑ freezing to cue	Yes	Not tested	Not tested
Kim et al. (2010)	Rat	1-sec shock (2mA) + cue × 10, 120-sec ITI	1-sec shock (1mA) x 3, 60-sec ITI ⇒ Demonstrator response to cue (8 min continuous) during testing	↑ freezing to cue	Yes	Not tested	Auditory