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Review

Rodent models for studying empathy

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ABSTRACT

Empathy is the important capacity to recognize and share emotions with others. Recent evidence shows that rodents possess a remarkable affective sensitivity to the emotional state of others and that primitive forms of empathy exist in social lives of rodents. However, due to the ambiguous definitional boundaries between empathy, emotional contagion and other related terms, distinct components of empathic behaviors in rodents need to be clarified. Hence, we review recent experimental studies demonstrating that rodents are able to share emotions with others. Specifically, we highlight several behavioral models that examine different aspects of rodent empathic behaviors in response to the various distress of conspecifics. Experimental approaches using rodent behavioral models will help elucidate the neural circuitry of empathy and its neurochemical association. Integrating these findings with corresponding experiments in humans will ultimately provide novel insights into therapeutic interventions for mental disorders associated with empathy.

1. Introduction

Empathy - the capacity to share the feeling of others - is crucial for social interaction, and it allows us to recognize and relate to the feelings of others. We feel happy when we vicariously share the joy of others and we can share the experience of suffering when we empathize with others in pain (Bernhardt & Singer, 2012; de Waal, 2008).

Despite the blurred conceptual boundaries of empathy due to ambiguous definitions in mechanisms, current evolutionary evidence suggests that there are several systems underlying empathy; phylogenetically early emotional contagion and more advanced cognitive perspective-taking systems (de Waal, 2008; Gonzalez-Liencres, Shamay-Tsoory, & Brune, 2013; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). The basic emotional contagion system is thought to support our ability to empathize emotionally ("I feel what you feel"). Examples include infectious crying among babies and yawning among adults. The higher forms of empathy require more complex cognitive functions, including Theory of Mind and mentalizing (de Waal, 2008), and involves the ability to share another's feelings and to understand another person's perspective ("I understand what you feel"). From a psychological perspective, compassion and altruistic behaviors are included in this form of empathy. Cognitive perspective-taking empathic ability is believed to occur only in great apes and humans that possess self-awareness (de Waal, 2008; Zaki & Ochsner, 2012).

Recently, there has been a growing body of evidence that rodents possess a remarkable affective sensitivity to the emotional state of others, which could be developed into experimental models of mental disorders associated with impaired empathy in humans (Ben-Ami Bartal, Decety, & Mason, 2011; Burkett et al., 2016; Chen, Panksepp, & Lahvis, 2009; Jeon et al., 2010; Langford et al., 2006). This review highlights emerging topics of the rodent models for studying empathic behaviors in the context of capacity to share affective experiences. We discuss recent experiments that examined different aspects of rodent behaviors in response to the distress of conspecifics. Specifically, a series of recent studies have been collectively used to demonstrate that rodents are capable of (1) emotional contagion, (2) observational fear learning, and (3) pro-social/consolation behavior. We also point out several important factors that affects the degree of observers to respond to other's distress in observational fear learning that has served as a foundation for modeling empathy in rodents. Accordingly, this review aims to highlight the role of rodent models for elucidating the neural substrates underlying empathy.

2. Emotional contagion for pain

The ability to share the emotions of someone who is experiencing painful stimuli, broadly referred to as 'empathy for pain' has been widely explored in neuroimaging studies in humans

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(Bernhardt & Singer, 2012; Decety & Jackson, 2004; Keysers & Gazzola, 2007; Preston & de Waal, 2002). In 1959, an experimental study by Church first demonstrated that a trained rat to obtain a food reward by pressing a lever stopped the pressing behavior when it observed another rat in a neighboring cage receive an aversive foot shock (Church, 1959). This seminal study suggested that by seeing conspecific's pain rats are able to recognize and share affective states of others (Church, 1959). Langford et al. have provided robust evidence that mice show emotional contagion of pain (Langford et al., 2006). Using a writhing test (pain-related behaviors after an intra-peritoneal injection of acetic acid) or paw licking behavior after a subcutaneous injection of formalin, the authors found that mice displayed more pain-related behaviors when they were tested together with a similarly injected partner as compared to mice tested alone or tested with a non-treated mouse. Importantly, the hyperalgesia was only found when their test partners were cagemates. This pain-related behavior was not specific to the type of noxious stimulus (acetic acid or formalin) or the resulting behavior (writhing or paw licking). More interestingly, the level of pain experienced by its social partner affected the behaviors of observer mouse. The level of pain-behavior was increased in mice exposed to a low concentration of formalin paired with a cagemate treated with a high dose, whereas the high-dose mouse showed reduced levels of pain while observing a cagemate exposed to a low dose. Taken together, Langford et al. have demonstrated an effect that has no reasonable explanation other than emotional contagion, a primitive form of empathy, wherein one individual is affected by the emotional state of another. Through several control experiments, the authors found that this form of social modulation of pain was communicated by the sensory/perceptual system than by the motor system (Langford et al., 2006). In addition, the authors found an analgesic effect when the observer mouse was paired with an untreated stranger male mouse, suggesting that social threat from an unfamiliar male mouse is responsible for the reduced pain-behaviors (Langford et al., 2006).

In their recent, subsequent study, Martin et al. demonstrated that this emotional contagion was prevented by the stress of a social interaction with an unfamiliar conspecific in both mice and humans, and could be evoked by response of stress hormones (e.g., glucocorticoid) (Martin et al., 2015). When the authors tested mice for sensitivity to noxious stimulation, the observer mouse paired with a stranger displayed a higher level of stress than a mouse paired with a cagemate partner or a mouse tested alone. Only the familiar pairs showed increased pain-related behaviors compared to isolated testing. Pharmacological blockage of stress hormone synthesis enabled the expression of emotional contagion of pain in mice and humans (Martin et al., 2015). In a similar experiment using rats, Li et al. also found familiarity-dependent emotional contagion of pain that only the cagemate observer, but not the non-cagemate observer, exhibited mechanical hypersensitivity and enhanced pain-related behaviors following bee venom injection (Li et al., 2014). However, in this study no difference in a stress-related response (serum corticosterone concentration after social interaction) or an anxiety-like behavior was found between cagemate and non-cagemate pairs.

3. Observational fear learning

Fear is a biological response to dangerous, threatening situations or stimuli. Fear can be acquired in two ways: either directly, through exposure to an aversive situation, or indirectly, through social observation of others (Hooker, Germine, Knight, & D'Esposito, 2006; Mineka & Cook, 1993; Olsson & Phelps, 2007). In the classical Pavlovian conditioning experiment, the pairing of a neutral, conditioned stimulus (CS), such as a tone, with an aversive, unconditioned stimulus (US), such as a foot shock, induces learning and memory of an association of the two stimuli in the animal. This association results in expressed fear behaviors (freezing) when the animal is later exposed to the same CS in the absence of the US (LeDoux, 2000).

Fear behaviors also develop vicariously by observational fear conditioning. Observational fear conditioning has been studied in primates and humans, where subjects recognize fear by observing a conspecific suffering from an enemy attack (Hooker, Germine, Knight, & D'Esposito, 2006; Mineka & Cook, 1993; Olsson & Phelps, 2007). Recently, several studies have successfully demonstrated that a brief social exposure with a demonstrator modifies the behavioral performance of an observer in an associative fear learning in rodents. Bredy and Barad demonstrated that the acquisition, retention and extinction of a cue-fear association were influenced by a social interaction with a familiar conspecific that was previously exposed to the same fear-conditioning procedure (Bredy & Barad, 2009). In contrast, Knapska et al. found that conditioned fear was increased in rats when they were exposed to rats that had already been conditioned just before being fear conditioned themselves. (Knapska, Mikosz, Werka, & Maren, 2010). Guzmán et al. also demonstrated that after a social interaction with a non-fearful demonstrator, observer mice showed context-specific impairments of fear memory (Guzman et al., 2009). It is not clear what factors drive the observer's behaviors toward a similar or different response relative to that of demonstrators, but these three studies clearly demonstrated that social interaction with a distressed partner directly altered the emotional responses of the observers to make a new association (Bredy & Barad, 2009; Guzman et al., 2009; Knapska et al., 2010).

Based on these findings, we have previously developed a simple behavioral assay to assess social observational fear learning as a measure of empathy in mice (Jeon & Shin, 2011; Jeon et al., 2010). In this task, instead of receiving direct aversive stimuli, mice are conditioned for context-dependent fear vicariously by observing conspecifics receive repetitive foot shocks. Empathy occurs when an individual (observer) shares the affective state of another individual (demonstrator) and is evoked by observing or recalling the affective state of demonstrators. Familiarity is a crucial factor for empathy in humans. Animals also behave differently depending on the familiarity of their partners in social learning (Kavaliers, Choleris, & Colwell, 2001; Langford et al., 2006). Notably, the fear response of the observer mouse is positively influenced by the animal's familiarity with the demonstrator (i.e., siblings or long-time mating partners as the demonstrator tend to trigger higher fear response in the observer). Since empathy is broadly defined as affective behaviors focused on the response of the observers and familiarity is considered as a factor increasing empathy in observers for the state of the demonstrators, our behavioral assay could be reasonably matched to empathic fear shown in higher primates and humans. Nonetheless, the freezing response itself during observational fear conditioning in our study seems to be consistent with emotional contagion because freezing of the demonstrator and observer mice occurred at the same time. However, when the observer mouse was placed alone back in the same chamber next day, the mouse showed freezing response (contextual fear memory), indicating that observers made a direct connection between the distress state of others and the specific environment where the event happened. This subsequent effect could be distinct from emotional contagion because freezing behavior expressed by the observer took place long after its exposure to the distressed conspecific and the observer had never experienced the foot shocks. Therefore, these findings indicate the social transfer of an emotional state from one mouse to another.

Brain-imaging studies in humans have demonstrated that the ACC is active when people engage in the experience of empathy

for pain (Singer et al., 2004). Intriguingly, ACC neurons are activated when people experience a painful sensory stimulus and also when they see another person experiencing pain (Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999). Activity in dorsal ACC region linked to the experience of pain distress was increased when people were socially excluded in a virtual ball-tossing game (Eisenberger, Lieberman, & Williams, 2003). Thus, it is suggested that ACC neurons could represent a type of 'mirror neuron' for pain empathy (de Waal, 2008, 2012; Preston & de Waal, 2002). In addition, recent studies show that the ACC plays a crucial role in evaluating the behaviors of others and in estimating other's level of motivation and emotion (Apps, Rushworth, & Chang, 2016; Hillman & Bilkey, 2010). Together, the ACC plays a vital role in mediating the affective components associated not only with painful noxious stimulus but also with anticipation of an upcoming pain stimulus, attention, and social recognition of pain (Apps et al., 2016; Shackman et al., 2011). In accordance with these studies in humans, we have also identified that the ACC is required for acquisition of observational fear and functional connectivity between ACC and lateral amygdala is enhanced during the behavior (Jeon et al., 2010). Additionally, we have further provided evidence that the observational fear learning is lateralized to the right ACC (Kim, Matyas, Lee, Acsady, & Shin, 2012). Cortical asymmetry in acquisition of observational fear in mice was congruent with a previous study that negative emotion processing is modulated with a right hemispheric dominance in humans (Adolphs, Damasio, Tranel, & Damasio, 1996).

Different inbred mouse strains show different emotional responses to social stress and such differences have been attributed to genetic differences of the strains (Chen et al., 2009; Hovatta et al., 2005). We have recently found that different inbred mouse strains differ in observational fear learning (Keum et al., 2016). Male mice from five inbred strains, C57BL/6J, C57BL/6NTac, 129S1/SvImJ, 129S4/SvJae, and BTBR T^{+} $Itpr3^{tf}$/J – showed observational fear responses, whereas AKR/J, BALB/cByJ, C3H/HeJ, DBA/2J, FVB/NJ and NOD/ShiLtJ mice exhibited low empathic fear responses. Importantly, innate differences in anxiety, locomotor activity, sociability and preference for social novelty were not significantly correlated with observational fear learning among the 11 strains, indicating that there is genetic factor(s) that modulate the degree to respond to other's distress. Since some individuals are more likely to deploy experience sharing and mentalizing than others and neural systems supporting empathic subprocesses exhibit both contextual and inter-individual variances in human (Singer et al., 2004; Wagner, Kelley, & Heatherton, 2011; Zaki & Ochsner, 2012), this strain-dependent difference may be important in identifying novel genetic pathways and underlying neural mechanisms that modulate empathy.

What factors then affect the degree of vicarious freezing in observer mice? In a tone-based fear conditioning paradigm, mice that witnessed a demonstrator mouse being presented with a tone and shock pairing subsequently showed increased freezing to presentations of the tone alone (Chen et al., 2009). Observer mice showed 24 h fear memory when they were exposed to the tone that was previously paired with foot shocks applied to demonstrators. In contrast to our observation that individual mouse exhibited freezing during the experience of distress in demonstrators, no appreciable freezing behaviors of observer mice was found in their experimental procedure (Chen et al., 2009). As we and others reported (Jeon & Shin, 2011; Panksepp & Lahvis, 2011; Wohr & Scattoni, 2013), this discrepancy is, in part, due to difference in the strength of foot shocks provided to the demonstrator. We utilized twenty 2-s foot shocks of 1 mA delivered for a 4-min period, whereas Chen et al. provided ten 2-s foot shocks of 0.5 mA delivered for a 20-min period to demonstrators.

Visual cues play an important role in inducing vicarious freezing in observer mice, but we found that there was still residual freezing responses when an opaque black partition prevented the observers from seeing the demonstrators. Thus, these data indicate that other sensory modalities, such as olfactory and auditory cues, may also contribute to the development of the vicarious fear responses (Jeon et al., 2010).

Vocal communication has been shown to affect social transfer of fear in mice in a tone-based observational fear conditioning (Chen et al., 2009). Similarly, the number of ultrasonic vocalizations (USV) emitted by a fearful rat demonstrator is positively associated with the amount of fear expressed in an observer rat (Kim, Kim, Covey, & Kim, 2010; Wohr & Schwarting, 2008). However, Atsal et al., demonstrated that USVs recorded from observer-demonstrator pairs during the training alone did not produce significant vicarious freezing either in naïve nor shock-experienced rats (Atsak et al., 2011). To address this issue further, we have investigated whether various behavioral reactions of different out-group demonstrator strains to foot shocks (i.e. jumping, freezing, running or vocalization) can trigger the differential level of vicarious freezing in observer mice. Despite potential difference in demonstrator's vocalization or social cues between different inbred strains (C57BL/6J, 129S1/SvImJ, and FVB/NJ), we found that C57BL/6J observer mice exhibited similar level of observational fear toward different out-group demonstrator strains (Keum et al., 2016). If demonstrator's vocalization or social cues differ in the details of expression and characteristics between these three inbred strains, these difference might not significantly determine the degree of C57BL/6J observer mice to conspecific's distress.

So far, we have discussed social factors that contribute to the degree of empathic reactions to conspecific's behaviors. Alternatively, a recent study showed that vicarious freezing in observer rats was triggered by the cessation of movement-evoked sound (silence) from demonstrators, suggesting that without any direct awareness of what conspecifics are experiencing, specific sensory cues in the environment could also affect observational fear responses (Pereira, Cruz, Lima, & Moita, 2012). Taken together, familiarity, the strength of the US delivered to demonstrator, social interaction, stress, common experience, or a simple sensory cue have been known to influence the degree of behavioral response to distress in others (Atsak et al., 2011; Chen et al., 2009; Gonzalez-Liencres, Juckel, Tas, Friebe, & Brune, 2014; Jeon et al., 2010; Kim et al., 2010; Langford et al., 2006; Panksepp & Lahvis, 2011; Sanders, Mayford, & Jeste, 2013; Watanabe, 2015a; Yusufishaq & Rosenkranz, 2013), but it is still unclear how these factors modulate observational fear learning.

4. Prosocial and consolation behaviors

Empathy allows individuals to vicariously experience the affective states of others, predict others' actions, and motivate prosocial behavior in humans. Despite a primitive form of empathy (emotional contagion) observed in social lives of rodents, many believe that higher forms of empathy such as sympathetic concern, consolation, targeted helping, or altruistic caring are human-specific abilities. Even the possibility of these social behaviors being present in species other than primates was considered highly unlikely.

Ben-Ami Bartal and colleagues have provided the first robust paradigm to study pro-social behavior in rats. The author demonstrated that rats learned to release cagemates trapped in a restrainer, even when they received no explicit rewards (Ben-Ami Bartal et al., 2011). Once learned, this behavior was performed quickly and consistently. Surprisingly, the rats liberated a cagemate equally well when there was another restrainer containing a

preferred food item, chocolate chips, and even shared the chocolate with the newly freed cagemate. Consistent with gender difference in empathy and social perception in humans, female rats performed better in this door-opening task. Taken together, these findings indicates that rats share a mechanism for mobilizing pro-social motivation in response to the distress of others and thus, a rodent form of empathy is the main motivation for this helping behavior (Ben-Ami Bartal et al., 2011).

In a recent subsequent study, Ben-Ami Bartal et al. reported that familiarity did not affect the occurrence of the helping behavior (Ben-Ami Bartal, Rodgers, Bernardez Sarria, Decety, & Mason, 2014). Although movement velocity was greater for rats tested with cagemates compared to those tested with strangers, the free rats consistently released the trapped strangers, just as they helped familiar cagemates. However, intriguingly, the author found that the rats helped cagemates of a different strain but not strangers of a different strain. The albino Sprague-Dawley (SD) rats did not help strangers of a different black-hooded Long-Evans (LE) strain, unless they were housed for 2 weeks before the test. More intriguingly, the albino rats helped strangers of different strains that they were raised with, but they did not help strangers of their own strain. Thus, these results suggest that strain identity without social experience is not crucial for pro-social behaviors in this test. These findings raised a key question regarding the nature of the rat's motivation.

Importantly, it should be noted that empathy-relevant social interaction can modify an animal's response to various stimuli, and this amelioration of aversive stimuli through social interaction is called social buffering (DeVries, Glasper, & Detillion, 2003). Recent studies by Watanabe demonstrated that social interaction influenced the intensity of stress and stress had a memory-enhancing effect on aversive experience in mice (Watanabe, 2011, 2015b). Consistent with these studies, rats tested in groups exhibited less freezing behaviors after aversive foot shocks when compared to rats tested alone (Davitz & Mason, 1955), indicating that rodents demonstrate social buffering behaviors.

Burkett and colleagues have demonstrated that a rodent species, prairie vole, detects the stress of conspefics and expresses empathy-based consolation behaviors (Burkett et al., 2016). When demonstrators that experienced footshocks were reunited with naïve observers, prairie vole observers displayed licking and grooming behaviors toward a distressed demonstrator partners. Since consolation behavior is defined as an increase in affiliative contact toward a distressed individual to ameliorate stress responses, these allogrooming behaviors may indicate that observers provide social buffering to the demonstrators. Notably, observers directed consolation behavior only toward familiar demonstrators (cagemates or siblings) and not toward stressed strangers. The author further demonstrated that exposure to the stressed cagemate demonstrators increased activity in the ACC and the oxytocin receptor is required for the expression of consolation behavior. Although this type of social buffering behavior was observed only in highly social and monogamous prairie vole, but not in a closely related meadow vole, the presence of this consolation behavior suggests that evolutionary shared neural substrates of empathy exist in social lives of rodents. To further address whether any innate difference contributes to pro-social or consolation behaviors, performing similar experiments using genetically diverse multiple inbred mouse strains would be interesting.

Summary

We have described that rodents are capable of empathy, a process where the affective feelings of one are transferred to another and generate the same emotions in that individual. A critical consideration regarding future studies is to clarify whether empathic response in rodents arises from higher cognitive or lower affective brain functions, or a combination of both (Panksepp, 2011). Perspectives on empathy in rodents should be driven by an integration of behavioral, neural, and genetic approaches that will be continuously updated based on experimental evidence. Importantly, different inbred mouse strains show different emotional responses to social stress, and such differences have been attributed to genetic differences of the strains. Although CaV1.2 calcium channel gene (*Cacna1c*) is required for observational fear learning (Jeon et al., 2010) and consolation behavior is mediated by oxytocin receptor in the ACC (Burkett et al., 2016), genetic factors regulating empathy are largely unknown. Since the manipulation of a single gene and neurochemical signaling in a specific brain region or cell-type is feasible in mice, future studies at the levels of functional analysis will significantly contribute to the identification of novel neural circuits underlying empathy.

Declarations

The authors declare no competing interests.

Author's contribution

SK and HSS wrote the manuscript. All authors read and approved the final manuscript.

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