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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