Current Rodent Models for the Study of Empathic Processes

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Abstract

Empathy is a complex phenomenon critical for group survival and societal bonds. In addition, there is mounting evidence demonstrating empathic behaviors are dysregulated in a multitude of psychiatric disorders ranging from Autism Spectrum Disorder (ASD), Substance Use Disorders (SUD), and personality disorders. Therefore, understanding the underlying drive and neurobiology of empathy is paramount for improving the treatment outcomes and quality of life for individuals suffering from these psychiatric disorders. While there is a growing list of human studies, there is still much about empathy to understand, likely due to both its complexity and the inherent limitations of imaging modalities. It is therefore imperative to develop, validate, and utilize rodent models of empathic behaviors as translational tools to explore this complex topic in ways human research cannot. This review outlines some of the more prevailing theories of empathy, lists some of the psychiatric disorders with disrupted empathic processes, describes rat and mouse models of empathic behaviors currently used, and discusses ways in which these models have elucidated social, environmental, and neurobiological factors that may modulate empathy. The research tools afforded to rodent models will provide an increasingly clear translational understanding of empathic processes and consequently result in improvements in care for those diagnosed with any one of many psychiatric disorders.

Keywords

Empathy; rat; mouse; perception action model (PAM); emotional contagion; targeted helping; observational fear; oxytocin; neurobiology

INTRODUCTION

Empathy is broadly understood as the capacity to share the feelings of another and generate an appropriate response to those shared feelings (Hoffman, 1975; de Waal, 2009; Lahvis, 2017; Meyza et al., 2017). It is a multidimensional concept that lays the groundwork for cooperation and prosocial altruistic behaviors, both of which are critical for the formation and maintenance of interpersonal relationships and societal cohesion (Decety, 2011; de Waal and Preston 2017). Empathic processes that help shape social behaviors and ultimately guide complex societal norms are therefore critical for reproduction and individual and group survival (Decety et al. 2015; Sivaselvachandran et al., 2016; Adriaense et al., 2020). Further, it is becoming more apparent that empathy is dysregulated in numerous DSM-V-defined

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psychiatric disorders. An increasing number of studies have concluded patients with diagnoses of Substance Use Disorder (McCown, 1989; McCown, 1990; Massey et al. 2018), Major Depressive Disorder (Cusi et al. 2011; Ekinci and Ekinci, 2016; Kupferberg et al., 2016), Autism Spectrum Disorder and alexithymia (Bird and Cook, 2013; Cook et al., 2013; Harmsen, 2019), and Antisocial Personality Disorder (Mealy, 1995; Blair and Cipolotti, 2000; Decety and Moriguchi, 2007), to name a few, have blunted empathic behaviors that are correlated with the severity of the disease (Cusi et al., 2011) and a reduced quality of life (Kronmuller et al., 2011). The role empathy plays in social behaviors and the prevalence of its dysregulation in psychiatric disorders make the behavioral and neurobiological understanding of empathy paramount. Furthermore, the development and use of a translationally relevant rodent model allows for significant advancements in our current understanding of empathic behaviors. Because of the recent explosion of empathy-related research, this review seeks to outline the prevailing theories of empathy, the psychiatric disorders in which empathy is affected, the rat and mouse models of empathy currently used, and the important social, environmental and neurobiological factors that affect empathic behavior discovered using these models. There are numerous recent reviews focused on the evolution (Decety, 2011; Decety et al., 2012) and comparison of empathy across species (Panksepp and Panksepp, 2013; Perez-Manrique and Gomila, 2017), as well as neural correlates of empathy based on fMRI studies (Bernhardt and Singer, 2012; Decety, 2015; Keysers and Gazzola, 2018; Marsh, 2018). There is currently no single agreed-upon rodent model of empathic behavior (Keum and Shin 2016; Uysal et al. 2020), in part because of its complexity. Moreover, specific models evaluate different behavioral outputs of components of what we broadly call empathy. Overall, however, rodent models could advance the treatment of psychiatric disorders through the elucidation of the underlying motivation and neurobiology of empathic behaviors.

THEORIES OF EMPATHY

Despite its ubiquity and importance, empathy has many definitions due to its multidimensional and complex nature (Preston and de Waal, 2002; Sivaselvachandran et al., 2016; Yamamoto, 2017; Uysal et al, 2020). Often, researchers will define the parameters of empathy to best fit their experimental question, and this often leads to discrepancies amongst researchers. Some early definitions of empathy were cognitively focused, putting emphasis on the ability to simulate how others are feeling, like Theory of Mind (Goldman, 2008). Empathy had been described as a "leap of imagination into someone else's headspace" (Baron-Cohen, 2005) or putting oneself in the place of another (Allport, 1937). These definitions, however, do not allow for a full affective description of what occurs during empathically-driven behaviors and was more exclusive to adult humans. In the 20th century, a new theory of empathy grew from the notion that empathy was an involuntary affective response in which individuals were able to "feel into," (Einfülung) without extensive cognition or reasoning (Lipps, 1903; Zahavi, 2008). Although most researchers accept empathy involves both aspects, much of the recent debate surrounding empathy has focused on this distinction between cognitive and emotional empathy (discussed in Preston and de Waal, 2002). Emotional empathy, often used interchangeably with emotional contagion, is a subcortical and evolutionarily conserved process by which one is able to state-match with a

conspecific (Panksepp and Panksepp, 2013; Keysers and Gazzola, 2018). Because of its relative simplicity, forms of emotional empathy have been observed in numerous animal species across the tree of life (Mogil 2012; Sivaselvachandran et al., 2016; Lahvis, 2017; Meyza et al., 2017). Cognitive empathy, on the other hand, is a top-down, cortically-driven process that allows for perspective-taking and targeted helping towards a distressed conspecific (Lamm, et al., 2007; Shamay-Tsoory et al., 2009; Lamm and Majdandži, 2015; Barrett et al., 2016). Historically, cognitive empathy was thought to be exclusive to species with developed forebrains, such as non-human primates (de Waal, 2009; Yamamoto and Takimoto, 2012; Perez-Manrique and Gomila, 2017), and humans (Singer et al., 2004; Shamay-Tsoory, 2011; Bernhardt and Singer, 2012; Zaki and Ochsner, 2012). Although this distinction may be useful for studying similar phenomena across species (Panksepp and Lahvis, 2011) or distinguishing high-order, cognitively-driven empathy tasks in humans versus animals, it may hinder the advancement of translational rodent research of empathic processes. Further, growing evidence suggests behaviors canonically within the spectrum of cognitive empathy, such as targeted helping, are observed in rodents (Bartal et al., 2011; Sato et al., 2015; Bartal et al., 2016; Karakilic et al., 2018; Cox and Reichel, 2019). Therefore, it is likely these forms of empathy are highly interconnected in evolution and across species (de Waal and Preston, 2017). However, theoretical models of empathy continue to be numerous and differ across the research fields. In the next few paragraphs, we will briefly outline some of the current and more prominent theoretical frameworks for understanding empathic behaviors.

Perception-Action Model of Empathy

A major milestone came with Preston and de Waal's Perception Action Model of empathy (Preston and de Waal, 2002; de Waal, 2012; de Waal and Preston, 2017; Preston and de Waal, 2017). The model asserts that attended perception of an individual's affective state automatically activates the observer's representations of the state, situation, and target. Additionally, activation of these representations automatically primes or generates the associated autonomic and somatic responses unless inhibited (Preston and de Waal, 2002). When an observer attends to another's affective state, they are able to access information about them through an associative process evolved from the nervous system's ability to map others' states onto our own (Preston and de Waal, 2017). The PAM lies at the core of empathy and the myriad component parts are built from it, similar to a Russian nesting doll (de Waal, 2012; de Waal and Preston, 2017). Simple empathic behaviors, like emotional contagion and motor mimicry, are nearest the PAM core of the nesting doll, while more complex behaviors, like perspective-taking and targeted helping, are the outermost layers of the doll and require additional cognitive capabilities and emotional self-regulation. However, all of these abilities are reliant and are built upon the PAM (Preston and de Waal, 2002; de Waal, 2012; de Waal and Preston, 2017; Preston and de Waal, 2017). This model allows for an understanding of how affective transfer may then promote helping behavior (Bartal et al., 2011; Meyza et al., 2017). Emotional transfer between a distressed target and an observer occurs, causing shared affect. The now distressed observer must self-regulate to perform an action (e.g. consolation or aid) to reduce the distress of the target and, by a second emotional transfer, themselves (de Waal and Preston, 2017). This model links cognitive and emotional empathy by their underlying process and links behaviors ranging from emotional contagion

to altruistic behavior, as they all require or involve some level of affective transfer. It also sheds light on the fact that, although there is a top-down/bottom-up circuitry distinction, it has been overestimated or, at the very least, perseverated upon. There is empirical evidence to support this theory in numerous species (Perez-Manrique and Gomila, 2007) including rats and mice (described in the Models and Affective Transfer and Models of Targeted Helping sections). The PAM's simplicity and usefulness in the evolutionary development and translational understanding of empathic behaviors makes it one of the most widely cited theories of empathy today.

Three Factor Model of Empathy

While the PAM is a widely accepted model of empathy, there are others that have differing theoretical frameworks. Some argue that the "elegant simplicity" of the PAM may not sufficiently describe the underlying complexity of empathy (Hollis and Nowbahari, 2013; Yamamoto, 2017; Adriaense et al., 2020). Yamamoto suggests that, while many animals do exhibit empathic behaviors, the species differences and the cognitive requirements of the observed behaviors may be interpreted in a way other than a simple, linearly developing model (Yamamoto, 2017; Adriaense et al., 2020). In the PAM, it is assumed that more complex empathic behaviors are built linearly from more evolutionarily-conserved ones (Preston and de Waal, 2002). However, according to Yamamoto, it is not necessarily the case that helping behaviors are present if more simplistic state matching is observed. For example, chimpanzees are highly capable of perspective-taking, but they often do not engage in helping behavior proactively and instead react to begging (Yamamoto and Tanaka, 2009; Yamamoto et al., 2009). For this reason, Yamamoto proposes a re-organization into a combinatorial model. It is therefore suggested that three main component factors of empathy, matching with others, understanding of others, and prosociality, can be present individually or in combination with one another. This theory focuses on the complexities of species-specific differences and cognitive sophistication in empathic behaviors. Yamamoto's theory allows for independent evaluation of, as well as the interaction between, the separate components of empathy, especially through the lens of comparative evolutionary biology.

Dualistic Theories of Empathy

There are other theoretical models of empathy that, based on the research question or model used, focus more specifically on the elucidation of human empathy. As such, a more strict distinction between cognitive and emotional empathy is maintained within each theory. For example, the Dual Route Model of Empathy (Yu and Chou, 2018) was developed to understand the neural mechanisms of affective and cognitive empathy. The authors proposed that empathy, like emotion generally, has a "low road" and a "high road" (LeDoux, 1998). A fast, subcortical, short-latency pathway drives the affective "low road" of empathy that is processed automatically and subconsciously. In contrast, the slower, more complex and conscious process of cognitive empathy is moderated by attention and involves cortical structures more exclusively (Bernhardt and Singer, 2012; Decety 2015; Marsh, 2018). These routes, although separated by their neural substrates, are hypothesized to be interconnected in several ways, such as familiarity with others (Levine et al., 2005; Han and Northoff, 2008; Serino et al., 2009; Liew et al., 2011) and prior experience (Lamm et al., 2011; Meyer et al., 2012,). Further, prosocial behavior, they suggest, flows from both routes because, "people

who share and understand others' mind will finally care about others and generate desires to help others" (Yu and Chou, 2018). Additionally, activity in brain regions that are associated with both affective (e.g. amygdala, anterior insula) and cognitive empathy (e.g. dorsolateral prefrontal cortex, anterior cingulate cortex) in fMRI studies can positively predict the willingness to perform prosocial behaviors (Singer et al., 2008; Rameson et al., 2012; Waytz et al., 2012; Keysers and Gazzola, 2018).

Another framework known as the Self-Other Model of Empathy (SOME), addresses the complexity of "how empathy is shared" or how affective and cognitive systems allow for empathy to be experienced (Bird and Viding, 2014). The SOME is comprised of several subsystems, all of which are required to meet the criteria for an empathic process. These systems are separated into the following: the situation understanding system (which provides information on emotional state of another), the affective representation system (which represents the currents affective state of the self), the affective cue classification system (which allows for emotional pattern matching to signal the affect state of another), and Theory of Mind system (which represents the mental states of self and other) (the mirror neuron system component of the theory is outside the scope of this review but Bird and Viding, 2014 provides an excellent discussion). According to the authors, emotional contagion can occur using these systems once the affective state of one is matched in another and the perceiver understands that state is being experienced by the other. However, empathy only occurs following the self-other switch. In brief, this switch is the process by which the empathizer pays more attention to the other compared to self and the resulting affective state is more appropriate to the conspecific compared to one's own. The self-other switch indicates the empathizer's emotional state matches the other through Theory of Mind. This model puts forth a framework of a more 'advanced' form of empathy directed more towards specifically understanding empathy in human research of psychiatric disorders. In fact, in a study of individuals with alexithymia, researchers concluded enhancing self-other distinction potentiates alexithymics' ability to use advanced empathy, but not primitive empathy (Saito et al, 2016).

Empathy is a highly complex emotional state that can be manifested and measured in many ways. Developing an underlying theoretical framework that is able to incorporate every aspect and nuance of empathy may not be feasible, or warranted, across all fields of study. Some theories, like the SOME, seem to have an anthropocentric understanding of empathy framed to best answer questions derived from human experimentation. On the other hand, the PAM of empathy is more focused on the evolutionary development and comparison of empathic processes across species. We do not wish to take a stance on the validity of any one theory, as we acknowledge the scientific question may inform the theory used. However, because this article describes the importance of evaluating empathic behaviors translationally through rodent models to improve our understanding of empathy and our treatment of psychiatric disorders, some discussions within this article will be framed through the lens of the PAM of empathy.

PSYCHIATRIC DISORDERS WITH ALTERED EMPATHIC PROCESSES

The translational study of empathy has garnered increasing attention due to the growing research indicating empathic processes are affected by, or contribute to, a majority of Diagnostic and Statistical Manual (DSM)-V-defined psychiatric disorders (2013). In the following section, we will discuss some of these disorders and how empathy is dysregulated in each.

Substance Use Disorders

To date, only a handful of clinical studies have considered the relationship between empathy and Substance Use Disorders (SUD), yet the consistency of the results is striking. Stimulant users, poly drug users, and those with Alcohol Use Disorder all show impairments in empathy (McCown 1989; McCown, 1990; Massey et al., 2018; Robinson et al., 2018). Further, targeting empathic processes may be a treatment-modifiable risk factor for maintaining drug-free abstinence. For example, higher levels of empathy, as evaluated by questionnaire, in patients participating in twelve-step addiction programs was correlated with enhanced involvement in such programs and prolonged abstinence periods (McCown, 1989; McCown, 1990). These findings, alongside evidence that social support and maintenance of personal relationships via empathy improves the overall success of treatment outcomes in SUD, suggest restoration of empathic behaviors in individuals suffering from SUD may improve treatment outcomes and reduce the chance of relapse (Massey et al., 2018; Robinson et al., 2018).

Major Depressive Disorder

Along these same lines, patients suffering from Major Depressive Disorder display overall lower empathy, emotional accuracy, and affective response compared to control patients (Cusi et al., 2011; Ekinci and Ekinci, 2016; Kupferberg et al., 2016). One conceptual framework posits that empathic dysregulation as a consequence of major depression causes social impairments (Kupferberg et al., 2016), strains interpersonal relationships (Kronmuller et al., 2011), and may be positively correlated to the severity of the disorder (Cusi et al., 2011).

Autism Spectrum Disorder

Many researchers agree that empathy, broadly defined, is altered in those diagnosed with Autism Spectrum Disorder (ASD). The underlying cause of the deficits in empathy is poorly understood, although some posit that children with ASD have difficulties expressing or feeling emotion, which prevents them from engaging empathically with others (Decety and Moriguchi, 2007). Others believe that empathic deficits can be more specifically tied to alexithymia, the understanding and processing of one's own emotions, as opposed to the more heterogeneous spectrum of symptoms that underlie autism. Cook et al. (2013) demonstrated that, in those patients with ASD, the severity of co-occurring alexithymia, not the severity of the ASD, directly correlated to reduced emotional recognition. Focusing on understanding and evaluating changes in empathy could have both diagnostic and therapeutic implications for ASD (Harmsen, 2019) by maintaining a distinction between

social and emotional impairments, with ASD being associated with the former, not the latter (Bird and Cook, 2013).

Personality Disorders

There are numerous personality disorders described in the DSM V that exhibit dysregulated empathic processes. Antisocial Personality Disorder is, by its very nature, defined by a paucity of empathy towards others. This deficit has been postulated to originate from a reduced ability to feel and respond to changes in others' emotional states (Blair, 1995). However, it has been suggested the reduced empathic ability could be related to a disruption in the affective processing of emotion rather than the inability to adopt the emotions of others (Decety and Moriguchi, 2007). Higher-order emotional abilities are also disrupted in Bipolar Disorder. Bipolar individuals have augmented emotional recognition and affective responsiveness, but maintain perspective-taking similar to that of healthy controls. This may suggest they have difficulty identifying emotion on other's faces and identifying emotions they would experience in the same situation, but they may still be able to take the perspective of another, depending on the severity of their symptoms (Seidel et al., 2012). Interestingly, empathic dysregulation in patients with Bipolar Disorder may depend on whether they are experiencing an acute manic or depressive episode. For example, cognitive empathy was attenuated during both manic and depressive episodes, but affective empathy was potentiated during a manic episode while remaining unchanged in a depressive one (Bodnar and Rybakowski, 2017).

Schizophrenia

Finally, studies have consistently demonstrated patients with schizophrenia have blunted cognitive empathy, including Theory of Mind, emotional processing, and affective face processing (Savla et al., 2013; Green et al., 2015; Varcin et al., 2019), the degree of which was correlated to the severity of schizophrenic symptoms (Shamay-Tsoory et al., 2007). However, the changes may be more nuanced as they related to emotional empathy. For example, one meta-analysis concluded affective empathy is disrupted in patients with schizophrenia (Bonfils et al., 2016), and another study demonstrated schizophrenics have blunted emotional expressivity to faces compared to controls (Varcin et al., 2019). In contrast, affective sharing, as defined by the activation of the emotion-related neural substrates in a person observing the emotional expression of another (Green et al., 2015), were comparable between healthy controls and patients with schizophrenia. In some cases, schizophrenics reported significantly higher reactivity to the feelings of others (Achim et al., 2011; Michaels et al., 2014). The subtleties regarding empathic dysregulation in schizophrenia likely means subcomponents of empathy, like emotional processing, should be treated and trained individually (Green et al., 2015). Overall, continual improvement in the understanding of the association between schizophrenia and empathy will improve the social disability and overall quality of life in schizophrenic individuals.

This list, far from extensive, is expanded upon in review articles focused on empathic dysfunction in psychiatric disorders (Decety and Moriguchi, 2007; Farrow and Woodruff, 2007). However, the multitude of disorders with dysregulated empathy demonstrates translational models of empathic behavior are imperative to elucidate its underlying

neurobiology, as well as directly discern the relationship between psychiatric disorders and empathic dysregulation as a potential diagnostic and therapeutic tool to clinical populations.

MODELS OF AFFECTIVE TRANSFER

The study of empathy in rodents began in earnest in the 1950–1960s with two seminal studies. In the first, by Russel Church (1959), rats learned to stop pressing a lever that had previously been associated with an appetitive food reward when it became associated with an aversive shock stimulus to a rat in an adjacent cage. This was the first evidence to intimate rodents were capable of recognizing and sharing the affective state of a conspecific. Soon thereafter, Rice and Gainer (1962) utilized an apparatus in which a rat was hoisted off of the ground to generate distress. A second animal was able to quickly, and without prior training, learn to press a lever to lower the conspecific back to the ground, thereby alleviating its distress. These initial studies spurred a great debate over animal empathy that continues to this day. Because of their seminal work, an exponential number of experiments have been performed to better explain the phenomena observed in their studies. Importantly, they also inspired a myriad of research and novel behavioral models. One such line of research is the evaluation of consolation behavior in prairie voles (*Microtus ochrogaster*) as a proxy for empathy. Prairie voles are uniquely useful for the understanding of social affiliation because they form and maintain monogamous pair bonds (Bosch and Young, 2018; Lee et al., 2019). Recently, research has also determined they are capable of emotional contagion, state-matching, and self-other discrimination (Burkett et al., 2016; Meyza et al., 2018; Stetzik et al., 2018). Moreover, these prosocial behaviors have been shown to be modulated by the neuropeptides oxytocin and vasopressin in a sex-dependent manner (Winslow et al., 1993; Wand and Aragona, 2004; Burkett et al., 2016; Tickerhoof and Smith, 2017). This research has been widely reviewed (Demas and Jansow, 2016; Tabbaa et al., 2016; Bosch and Young, 2018; Meyza et al., 2018; Pohl et al., 2019), and therefore the following sections focus on models that use rats and mice to evaluate empathic behaviors of varying cognitive degrees. The major findings using each of the models discussed below are summarized in Table 1.

Emotional Contagion

The ability to share an affective state of pain with another has been widely explored in human fMRI studies (Keysers and Gazzola, 2007; Bernhardt and Singer, 2012; Keum and Shin, 2016). In fact, Church's rodent model took advantage of this phenomenon, suggesting for the first time rats are able to recognize and share the affective state of a conspecific (Church, 1959). In a typical model of emotional contagion of pain, animals are subjected to a painful stimulus and placed with an animal that undergoes the same, a different, or no pain treatment, and pain related behaviors like writhing and paw licking are assessed. Mice tested with another animal that also received a painful stimulus (intraperitoneal acetic acid injection or subcutaneous formalin injection) displayed potentiated pain related behaviors as compared to mice that were tested alone or with a non-treated mouse (Langford et al., 2006). A bidirectional modulation of pain behavior occurred in familiar mice; pain behavior was potentiated when the partner received a more noxious stimulus and decreased when the partner received a less noxious stimulus (Langford et al., 2006). However, these effects were

not observed when stranger mice were used. Instead, pain related behaviors were attenuated if the conspecific was unfamiliar (Langford et al., 2006). The apparent analgesic effect of an untreated stranger mouse suggested the social threat of an unfamiliar conspecific may play a role in the reduction of the pain behaviors. These results indicate mice are capable of emotional contagion, a more primitive form of empathy, and the social threat of an unfamiliar animal may attenuate it.

Stress also modulates observed emotional contagion in mice (Martin et al., 2015). Mice subjected to the social stress of an unfamiliar animal significantly reduced emotional contagion to a noxious stimulus. The observer mice paired with a stranger had higher levels of circulating glucocorticoids compared to mice paired with a familiar mouse or tested alone. Further, pharmacological inhibition of stress hormone synthesis enabled the expression of emotional contagion in the presence of an unfamiliar animal (Martin et al., 2015). However, other studies that demonstrate changes in emotional contagion in relation to familiarity do not show the same glucocorticoid-mediated regulation of pain-related behaviors (Li et al., 2014), possibly due to a difference in the type and/or severity of the noxious stimuli used.

More directly related to empathic processes are accounts of emotional contagion of pain even when the experience is not shared. For example, mice will develop corresponding hyperalgesia by observing a conspecific experience pain (Smith et al., 2016). When a "bystander" mouse is housed and tested in the same environment as mice that were subjected to inflammatory (CFA injections) or alcohol or morphine withdrawal-induced pain, the bystander rats will develop corresponding hyperalgesia as measured through mechanical, thermal, and chemical sensitivity tests (Smith et al., 2016). Interestingly, observer rats will exhibit not only emotional contagion, but also prosocial consolation behaviors, like allo-licking and allo-grooming, towards the conspecific that received the painful stimulus (Li et al., 2018; Du et al., 2019).

Social defeat stress also taps into the emotional contagion of fear (Carnevali et al., 2017). In this case, a rat is exposed to a cage mate that was either previously exposed to an aggressive male or simply to a novel cage. Following exposure to a rat that had previously undergone social defeat, observer rats show state matching behaviorally (social avoidance) and physiologically (elevated heart rate and circulating corticosterone). In this version of the model, the social communication of interaction-mediated stress and fear between animals can be easily evaluated (Carnevali et al., 2017; Carnevali et al., 2020).

Emotional contagion is a highly conserved process that provides a rapid assessment and adaptation to social and environmental challenges (Hatfield et al., 1993). This behavior can be easily observed across species, including rats and mice (Meyza et al., 2018). All of the models currently utilized take advantage of the transfer of negatively-valent emotions, such as fear or pain, purportedly due to a difficulty in standardization of models associated with positive affect transfer (Meyza et al., 2018). However, emotional contagion, due to its biological prevalence and importance, makes it a simple model ideal for the exploration of well-defined neuronal pathways of empathy (Meyza et al., 2017; Meyza and Knapska, 2018;

Zaniboni et al., 2018), as well as neurotransmitters involved in normal and dysregulated emotional sharing (Zoratto et al., 2018).

Observational Fear Learning

Fear is an appropriate response to many environmental stimuli, and the acquisition of fear through indirect measures (social observation) is critical for the survival within social groups (Olsson and Phelps, 2007; Keum and Shin 2016; Keum and Shin, 2019). The process of evaluating observational fear learning involves Pavlovian conditioning, in which a conditioned stimulus is paired with an aversive unconditioned stimulus. However, in this case, the fear behaviors, such as freezing, are developed vicariously when an animal observes a conspecific undergoing an aversive stimulus (i.e. foot shock) (Keum and Shin 2016; Kim et al., 2018). Models of observational fear learning have generated several interesting findings. For example, in several rodent studies (Bredy and Barad, 2009; Guzman et al., 2009; Knapska et al., 2010; Jeon and Shin, 2011), social interaction with a familiar conspecific that had previously been exposed to the fear condition modulated the acquisition, retention, and/or subsequent extinction of cue-fear associations of observers. Conditioned fear was significantly increased when observers were pre-exposed to a conditioned animal when testing occurred in a novel context (mice: Guzman et al., 2009; rats: Knapska et al., 2010; Atsak et al., 2011). In contrast, when social interaction between familiar animals occurs in a home cage, observer mice's fear acquisition is impaired when exposed to a recently conditioned familiar mouse (Bredy and Barad, 2009). Together, these findings propose an interesting caveat to this model and suggest a possible context-specific modulation of the social transmission of fear (Bruchy et al., 2010).

In the aforementioned studies of conditioned fear, animals are subjected to conditioning and transferred to safe environment where social interaction occurs with the observer (remote danger) (Jones et al., 2014). In contrast, a shift in the paradigm exposes the rat to an aversive stimulus in an environment without the possibility of escape (imminent danger) and a conspecific views the distressing event (Meyza and Knapska, 2018). This allows for an elucidation of vicarious freezing behavior specifically due to affective transfer. In one example, observer animals viewed demonstrators receiving foot shocks without ever receiving the shocks themselves. Both animals showed simultaneous freezing behavior during the task. Further, when the observers were placed back in the same chamber the next day absent the demonstrators, the observer still exhibited freezing behavior, indicating a contextual fear memory even though they were never shocked (Jeon et al., 2010; Jeon and Shin, 2011). The observers made a connection between the stressed state of the conspecific and the environment in which they were placed. Therefore, this variation of the model seems to test both initial emotional contagion and prolonged affective transfer (Kim et al., 2018). However, there is some discrepancy as to whether observing a conspecific alone is sufficient to induce vicarious freezing behaviors. In one study, a similar protocol showed that observing a conspecific was not enough to generate vicarious freezing (Sanders et al., 2013). Instead, animals had to be subjected to the same foot shock as the demonstrators 24 hour before the test to exhibit a shared affective response. The authors suggest that in naïve observers, a high level of aversive stimuli occurring to demonstrators is required to obtain

freezing, but if observers have had a prior experience with the aversive stimulus, they respond to lower levels of the stimulus (Sanders et al., 2013).

Advancing the field further, observational fear behaviors were evaluated when the observer was directly responsible for the delivery of the harm to their conspecific (Hernandez-Lallement et al., 2020). Here, a preferred lever (developed from sucrose training) became paired with foot shock for a conspecific in an adjacent compartment and rats had to learn to stop pressing the lever to avoid inflicting harm on the target (i.e. instrumental harm aversion). Both males and females learned to switch levers over time, but pre-exposure to the shock makes the harm aversion effect stronger. Interestingly, this effect was limited by effort. For example, rats would readily avoid pressing the lever if that meant not receiving a single pellet of sucrose, but they would not stop if it meant reducing the number of sucrose pellets from three to one (Hernandez-Lallement et al., 2020). Overall, observational fear models of emotional empathy have been correlated with trait measures of empathy (Olsson et al., 2007; Kleberg et al, 2015), which suggests this model evaluates a fundamental feature of empathic behavior (Panksepp and Panksepp, 2013) and can help offer insights into more basic and conserved forms of human empathic processes (Kim et al., 2018).

MODELS OF TARGETED HELPING

Because empathy allows for the sharing of affective states between individuals, it can also motivate prosocial behaviors like targeted helping. This phenomenon has historically been considered specific to humans and non-human primates. However, in recent years, several groups have demonstrated that rodents will release a distressed conspecific from an aversive situation such as being trapped in a restraint tube (Bartal et al., 2011; 2014; 2016) or a pool of water (Sato et al. 2015; Kandis et al., 2018; Karakilic et al., 2018; Cox and Reichel, 2019; Yamagishi et al., 2019). The following section will describe these models of targeted helping behavior, along with the proposed advantages and limitations of each. We also discuss the influence of social contact on these tasks and how this potential issue can be overcome. In accordance with the PAM model of empathy, the rat charged with rescue or helping is termed as the "observer" throughout and the distressed conspecific is termed the "target". This nomenclature removes any preconceived biases connoted by the other terms.

Restraint Stress Model

In a restraint stress model, rats (Bartal et al., 2011) and mice (Ueno et al., 2019a) exhibited targeted helping toward a conspecific trapped inside a Plexiglas tube. Specifically, an observer learned to release the target from the restraint tube, and this release behavior is maintained even if direct physical contact is blocked following a training period. Further, when given a choice of opening a restrainer with chocolate chips inside or releasing a distressed cage mate, the observers' latency to open either restrainer was not significantly different from one another. The authors conclude from these data that the value of the helping behavior is roughly equivalent to that of palatable food reward (Bartal et al., 2011).

In accordance with primate studies showing that neither likeness nor kinship was required for prosocial behavior (Horner et al., 2011, Baden et al., 2013), social experience modulates targeted helping. For example, rats pair-housed with an animal of their strain or cross-

fostered with a different strain helped the trapped conspecific with which the observer was familiar. In fact, cross fostered rats helped unfamiliar animals from the strain with which they were raised but not an unfamiliar rat of their own strain, suggesting targeted helping, as with other empathic behaviors like fear contagion (Jeon and Shin, 2011), is modulated by social experience and familiarity rather than genetic relatedness (Bartal et al., 2014). Reliance on social experience as opposed to kinship alone can allow for more behavioral flexibility in adapting to various social circumstances (Dugatkin et al., 2002).

Helping behavior can also be modulated pharmacologically. Midazolam (a benzodiazepine) administered to observer rats before the session in which the target was restrained reduced door openings (Bartal et al., 2016). Further, this effect was not due to gross sedative or cognitive effects of the drug, because rats retained the same door opening latency when the restrainer was instead filled with chocolate chips. These findings suggest that affective processing and transfer are required for targeted helping behavior (Bartal et al., 2016).

Whether the restraint stress model extends to empathic process in mice is less clear. For example, mice will open a clear restrainer to release a cagemate (Ueno et al., 2019a) and not a ball of yarn resembling a mouse (Ueno et al., 2019b). However, mice will also open an opaque tube with no animal in it when given the opportunity. In fact, mice show so much interest in the tube after releasing a cagemate that they prioritize its investigation over releasing another cagemate placed in a second restrainer (Ueno et al., 2019b). As such, lid-opening behavior in mice may be more driven by social interest and curiosity with the lid apparatus itself (Ueno et al., 2019b) rather than empathy as previously hypothesized (Ueno et al., 2019a).

Helping behavior in rats is also shaped by other variables. For example, release behavior is subject to the contents of the container (Blystad et al., 2019). Rats pre-trained to open a tube for food and subsequently tested with an empty restrainer had shorter release latencies in response to the trapped conspecific compared to an empty restrainer, but longer compared to a restrainer filled with food (Blystad et al., 2019). Therefore, helping behavior may be reinforcing, but less so than appetitive rewards. Another example intimates selfless behavior may not take precedence over behaviors that directly improve the outcome for the observer. Providing the rats an opportunity to escape from a well-lit arena (which is inherently distressing) into an adjacent dark compartment instead of releasing a distressed conspecific from a restraint tube placed in the lit arena significantly delays the latency of release behavior (Carvalheiro et al., 2019). This alteration elucidates the motivation of rescue behavior if an escape alternative was present for the observer rat. One can conclude from these data that self-benefit may supersede empathically-driven behaviors, or perhaps helping behavior itself may be directed toward increasing self-welfare compared to another (Batson et al., 1983).

Social contact may also be a driving force behind the observed rescue behavior because, in a modified version of the restraint stress paradigm, rats did not learn to release a conspecific into a separate compartment if they were not first trained on the task in which social contact was permitted (Silberberg et al., 2014). Additionally, rats show equal preference for conspecifics in a closed restraint tube (distressed) or in an open one that allows for social

contact (Hachiga et al., 2018). Overall, while the motivation and nuances behind the behavior need to continue to be explicated and replicated, the restraint stress targeted helping task is a very promising model of a higher-order helping behavior that can help elucidate more cognitively driven empathic processes.

Soaked Conspecific Model

In another model of targeted helping, a rat is placed in a pool of water to incite distress. An observer rat is placed in an adjacent dry chamber of the apparatus separated by Plexiglas and given access to a movable door. The observer must open the door to release the wet target into a dry chamber of the apparatus (Sato et al., 2015; Cox and Reichel, 2019). Observer rats quickly learn to release the target over subsequent trials. Latency to door opening increased or was eliminated in response to an empty pool of water, when the target was replaced by an inanimate object, and the water was removed entirely following acquisition of the task (Sato et al., 2015; Cox and Reichel, 2019). Further, observers did not open the door for access to the pool of water alone or when a rat was placed on the opposite side of the Plexiglas partition absent any water (i.e. absent any distress). However, when water was omitted from the task and targets were placed in a dry compartment, observers still executed the chain pull response, indicating that social interaction is a factor in the soaked conspecific model (Cox and Reichel, 2019). In a choice task between releasing the soaked target and receiving a palatable food reward (chocolate cereal), releasing the cage mate had a higher value than the food reward (Sato et al., 2015). Finally, acute and repeated acetaminophen given to observers reduced door openings to release the target (Kandis et al., 2018). Interestingly, a reduction in empathic behaviors due to acetaminophen is also observed in clinical research (Mischkowski et al., 2016).

Reversing the role of the observers and targets demonstrated that previous experience with the distressing condition enhanced learning of the release behavior compared to the distress-naïve rats (Sato et al., 2015; Cox and Reichel et al., 2019). While it is true rats learn by observing the behavior of others (Heyes and Dawson, 1990), the modulation of learning through experience also suggests the behavior observed is empathically driven. According to the PAM, prior exposure to the same stressor could more readily enable the reversed observer to state match with its target (Preston and de Waal, 2002; Mogil, 2012; Sanders et al., 2013; de Waal and Preston, 2017), perhaps by activating salient emotional memories that drive empathic behavior. Overall, these data suggest that first-hand experience enhanced acquisition of the helping behavior and supports that the measured behavior is based on empathic processes (Sato et al., 2015; Cox and Reichel, 2019).

The debate as to whether rescue behavior is driven primarily by empathic processes or other confounding variables continues for this targeted helping model. Based on a series of control experiments, it has been postulated that the behavior may be driven by social contact or interest in the presence of a water-filled compartment (Schwartz et al., 2017; Cox and Reichel, 2019). Therefore, it is necessary to consider these alternative motivators when interpreting the results from this model. Although empathy as driver of the outcome cannot be ruled out, using Lloyd Morgan's canon, according to the authors, the simpler behavior

should be the preferred explanation over the complexity introduced in empathy (Schwartz et al., 2017).

Targeted Helping Independent of Social Interaction

It is likely the restraint and soaked conspecific models of helping behavior discussed above are driven, in part, by empathy; however, data from our lab and others (Silberberg, et al., 2014; Schwatrz et al., 2017; Hachiga et al., 2018; Hiura et al, 2018; Cox and Reichel, 2019), suggest that these models are also driven by the opportunity for social reward. Social contact, whether through play fighting (Vanderschuren et al., 2016), maternal care of pups (Lee et al., 2000), or sexual behavior (Trezza et al., 2011) is reinforcing and activates circuits associated with reward (Preston, 2017). In addition, animals readily exhibit preference to social interaction in conditioned place preference (CPP) paradigms (Calcagnetti et al, 1992; Thiel et al., 2008; Fritz et al 2011; Peartree et al., 2012), and they have been shown to value social contact above both natural rewards (palatable foods) (Ikemoto and Panksepp, 1992) and drugs of abuse (Normansell and Panksepp, 1990; Yates et al., 2013). In fact, volitional social reward reliably attenuated both methamphetamine and heroin self-administration in rats in an operant choice model (Venniro et al, 2018a, b; 2019; 2020b). This methodological consideration does not render the current models inadequate in the evaluation of targeted helping behavior. On the contrary, they have strong ethological validity, as empathically-driven behavior can certainly be driven by or include social contact (Decety et al., 2016; Lahvis, 2017). Further, these models could lend great insight into more complex empathic behaviors directed at aiding a distressed conspecific.

Some effort has been made to parse apart the effects of social reward and direct empathic behavior. For example, Bartal and colleagues (2011) demonstrated rats will release a target from a restraint tube into a separate compartment, but only after they had been trained to release into the same environment. Our laboratory has recently shown rats will release a target from a pool of water independent of social contact (Cox and Reichel, 2019). In this task, observers learned to pull a chain that opens an automated guillotine door, thereby releasing the target from a pool of water into a different compartment from the observer, preventing physical contact during the task (Cox and Reichel 2019). The release behavior was also retained over time, and previous experience increased the rate of task acquisition (Cox and Reichel, 2019). However, removing water from the apparatus, thus removing the distress, prevented rats from learning the chain pull response. We concluded that, in this three-chamber task, the absence of a distressed conspecific removes the motivating force of state matching in order to drive the helping behavior. Moreover, there is no prior affective experience or reward (social interaction) that allows for enhanced state matching in the absence of the distressing event, making this model a more direct evaluation of an empathically-driven targeted helping behavior (Venniro and Golden, 2020b).

The release of a distressed conspecific is sensitive to other factors like familiarity and motivation. For example, replacing a familiar target with an unfamiliar one significantly increased door opening latency in the initial trials of the experiment, but subsequently returned to baseline with repeated trials, indicating rats can adjust their empathic behavior to help an unfamiliar, distressed conspecific (Cox and Reichel, 2019). In our paper, we also

compared the motivation to perform a socially-reinforced task with an empathy-driven task. In the socially-reinforced task, observers maintained the chain pull response on a fixed ratio 5 (FR 5, guillotine door was raised after 5 chain pulls) (Cox and Reichel, 2019). However, observers in the empathy-driven task did not maintain responding past an FR1. This comparison indicates that social reinforcement can aid in maintaining prosocial behaviors, and empathy is modulated strongly by effort. This notion seems to be confirmed in studies in which rats often chose to alleviate their own distress over a conspecific's when given a choice (Carvalheiro et al., 2019) or will not aid a conspecific if it means sacrificing a high reward alternative (Hernandez-Lallement et al., 2020). Further, clinical studies found that empathy in human subjects decreased when the effort to help increased (Lockwood et al., 2017) and engaging in empathy was avoided because it was considered more effortful compared to an alternative strategy (Cameron et al., 2019). Overall, we can surmise empathic behaviors, especially those requiring more than minimal effort, are significantly less motivating when compared to a behavior that ultimately leads to a personal reward like social interaction (Cox and Reichel, 2019). This model was developed in order to allow for an elucidation of complex social behaviors driven directly by empathy that has applicability for researchers evaluating neuropsychiatric disorders (Heilig et al., 2016; Venniro and Golden, 2020b).

SOCIAL & ENVIRONMENTAL FACTORS THAT CONTRIBUTE TO EMPATHIC BEHAVIORS

In both humans (Bowen et al., 2014; Gunnar and Hostinar, 2015) and non-human primates (Sanchez et al., 2015) social interaction with a familiar conspecific helps to ameliorate the effects of aversive or stressful stimuli. This phenomenon, known as social buffering (DeVries et al., 2003; Kikusi et al., 2006), also occurs in rodents, in which social contact modulates stress-related behaviors (Davitz and Mason, 1955; Kiyokawa et al., 2004; Watanabe, 2011, 2015). Social buffering of a conditioned fear response is potentiated when the conspecific is familiar as opposed to unfamiliar (Kiyokawa et al., 2014). Interestingly, the presence of fear-expressing partners (those exposed to the same fearful stimulus) also reduce fear-induced hyperthermia and freezing behavior, just less so compared to non-fearful partners (Kiyokawa et al., 2004). A slight variant is pro-active social buffering (Meyza et al., 2018), in which interaction with a conspecific occurs prior to an aversive event compared to following it. In this case, pre-exposure to a non-fearful conspecific reduces long term (but not short term) contextual fear memories in mice (Guzman et al., 2009). Social buffering is therefore common in situations where social interaction takes place before and after an aversive stimulus (Morozov, 2019). Its effects must be noted during the use of some of the models described above, and additional research on its effects would aid in our understanding of emotional transfer.

Stress and voluntary exercise can also influence empathic behavior. In a recent study with male mice, low levels of observed emotional contagion was correlated to reduced circulating corticosterone following restraint stress, suggesting adequate HPA reactivity is required for empathic behaviors (Laviola et al., 2017). Additionally, a mild stressor (low intensity foot shock) increased rats' latency to release a conspecific in the soaked conspecific model

(Karakilic et al., 2018). Finally, in male and female mice, 8 weeks (6 alone and 2 with a cage mate) of voluntary wheel running improved empathy responses (Yuksel et al., 2019). Given these studies, it is clear many social and environmental factors are involved in empathic processing and subsequent prosocial behaviors, and with the help of animal research, we are beginning to explore an ever-increasing number of variables, from genes (reviewed in Kim et al., 2018), sex (Bartal et al., 2011), strain (Keum et al., 2016), and even the intestinal microbiome (Sgritta et al., 2019).

NEUROBIOLOGY & PHARMACOLOGY OF EMPATHIC BEHAVIORS

Neurobiology of Empathic Behaviors in Rats and Mice

A large library of fMRI studies exists that have evaluated the neurobiology of multiple components and cognitive levels of empathy. Brain regions that have been correlated with aspects of empathy include those involved in emotional salience and interoceptive valence, specifically the amygdala and insula (Adolphs et al., 2002; Singer et al., 2004; Fusar-Poli et al., 2009; Keysers and Gazzola, 2018; Marsh, 2018), as well as substrates necessary for perspective-taking, motivation, and cognition, like the prefrontal (PFC), anterior cingulate (ACC), and orbitofrontal (OFC) cortices (Jackson et al., 2005; Singer and Lamm, 2009; de Waal and Preston, 2017; Decety, 2015; Cerniglia et al., 2019; Uysal et al., 2019). More causational and region-specific research using rats and mice are beginning to corroborate some of these imaging studies, and these findings are discussed in detail in other review articles (Panksepp and Panksepp, 2013; Sivaselvachandran et al., 2016; Meyza and Knapska, 2018; Meyza et al., 2018). Below, we will briefly discuss some neural underpinnings of rodent empathy that have translational importance.

In an emotional contagion paradigm, amygdala and PFC activity, as indicated by *c-fos* staining, in non-stressed rats generally mirrored that of stressed conspecifics (Knapska et al., 2006). Interestingly, the central amygdaloid nucleus was activated to a higher level in unstressed observer rats, suggesting it is likely specific subnuclei of the amygdala are sensitive to the distress of others (Meyza et al., 2018). Additionally, bilateral lesions of the prefrontal cortex, but not the amygdala, were sufficient to inhibit empathy for pain in rats (Li et al., 2014). Overall, these results point towards the amygdala and PFC contributing to emotional contagion, but likely the amygdala playing a more direct role in the salience of another's pain.

The ACC, a region known for its role in pain, affect, and emotional motivation (Keum et al., 2016), is necessary for the acquisition of observational fear learning. More specifically, the deletion of the Cav1.2 Ca^{2+} calcium channel within the ACC was adequate to impair social fear learning in mice (Jeon et al, 2010). Further, ACC dopamine D_2, but not D_1 receptors are required for vicarious fear (Kim et al., 2012). And while inactivation of the ACC led to disrupted fear learning, lateral amygdala inactivation led to impairments in both fear learning and fear expression (Jeon et al, 2010). Pharmacologic deactivation of the ACC abolished harm aversion in a model in which rats were directly responsible for a conspecific's harm, which also helps corroborate the ACC's role in affective transfer (Hernandez-Lallement et al., 2019). One of the more intriguing findings comes from an elegant study of neuronal populations within the ACC by Carrillo and colleagues (2019), in

which they were able to identify neurons that respond to pain of self and pain in others, but not from another emotionally-salient emotion (fear from a conditioned stimulus). Deactivating this region of the ACC reduces freezing in rats observing a conspecific receiving footshocks, but not while hearing a conditioned stimulus. The authors concluded mirror-like neurons are present in the rat ACC that encode the pain of others into a similar or overlapping ensemble for personal experiences of pain (Carrillo et al., 2019)

Lastly, increasing research points to the insular cortex, a region in humans known for its role in predicting the valence of both self and others (Gogolla, 2017). Pharmacological inactivation of the insula was shown to cause an alteration in emotional contagion of pain (Zaniboni et al., 2018). Also, chemogenetic activation of the anterior insula restored a heroin- induced decrease in targeted helping (Tomek et al., 2019; Tomek et al., 2020), indicating this brain area may be a potential translationally-relevant therapeutic target for individuals suffering from SUD. Overall, the volume of research is expanding in regard to the neurobiology of empathy using rodent models. There is still much to understand, including the interaction and circuitry between these regions of interest (Jeon et al., 2010), as well as the role of the emotional processing neural networks in different empathic behaviors and how they communicate with one another (Panksepp and Panksepp, 2013).

Oxytocin's Role in Empathy

There is overwhelming evidence in human studies linking oxytocin (OT) to several components of empathy (Domes et al., 2007; Hurlemann et al., 2010; Decety, 2011; Theodoridou et al., 2013; Christov-Moore et al., 2014; Rilling et al., 2014; Jones et al., 2017; Ebert and Brüne, 2018; Uysal et al., 2020). While rodent studies have focused on the importance of OT in areas such as maternal care (Arletti and Bertolini, 1985; Borrow and Cameron, 2012) and mating (Pederson et al., 1982; Champagne et al., 2001), they have only recently begun to explore its importance in prosocial behaviors (Burkett et al., 2016). For example, mice that were identified as having low levels of empathic behaviors, as measured by emotional contagion of fear, showed potentiated neural OT levels absent any changes in receptor density (Laviola et al., 2017).

Additionally, the OT system plays a role in observational fear learning, as well as the social buffering of observational fear. Intranasal OT, both acute and chronic, enhanced vicarious freezing in mice in response to an unfamiliar conspecific that had undergone a foot shock test. What's more, chemogenetic stimulation of hypothalamic OT neurons caused mice to become sensitive to distress of unfamiliar demonstrators (Pisansky et al., 2017). Systemic OT injection bolstered socially transmitted fear from a familiar animal (Pisansky et al., 2017), while direct infusion of OT into the lateral septum (important in fear responses) accelerates the social buffering effect on observational fear learning, as measured by a reduction in the exposures with the conspecific needed to decrease the contextual freezing (Guzman et al., 2014).

Oxytocin has also been shown to modulate targeted helping in a socially-dependent manner. Single-housed rats that received OT injections (1 mg/kg, 5 days) had faster door opening latencies at the beginning of task acquisition compared to animals that were pair-housed and received OT injections (Yamagishi et al., 2019). This may suggest OT reduces social anxiety

or improves prosocial behavior in certain social contexts. In contrast, OT administration had no effect on targeted helping behaviors in mice, which was another indicator to the authors that rescue behavior in mice may not be mediated directly by empathic processes (Ueno et al., 2019b). With the field's continued advancement of translationally-relevant models, there is little doubt other neurotransmitters will receive growing attention. There is already bourgeoning research to discern the role of serotonin (Kim et al., 2014) and dopamine (Lichtenberg et al., 2018) as other critical neurotransmitters involved in empathic behavior.

CONCLUSIONS AND FUTURE DIRECTIONS

Empathy is a process critical for group cohesion and social development. Further, empathic dysregulation is extremely prevalent in psychiatric disorders, ranging from personality disorders, substance use disorders, and schizophrenia. And although the study of the underlying neurobiology of empathy has gained increasing attention in humans, there are inherent limitations to human research. The current neuroimaging techniques do not provide high temporal or spatial resolution that would allow for the study of specific circuits underlying the observed behavior. That is why rodent models of empathic processes have become increasingly important; with these paradigms, we are able to utilize technologies such as chemo- and optogenetic tools that offer precision in deciphering specific neural substrates and mechanisms underlying various empathic processes (Meyza and Knapska, 2018). With the increasingly prodigious library of genetic tools to study neuropsychiatric diseases in rodents, these models can assess the impact specific genetic modifications have on empathic behaviors directly. This field is advancing rapidly and there has been extremely promising research using rodent models. It is important we do not anthropomorphize the findings or over-extend a particular theory of empathy. However, multiple theories describing empathy can be parsimonious, granted the research questions being studied have an appropriate scope. Further, as it has been pointed out previously (Mogil, 2012), the accumulating evidence of rodents sharing or responding to the emotional state of a conspecific makes repudiating their empathic abilities a form of anthropodenial. It is imperative that models like these are replicated, validated, and focused on translating their findings to understand the underlying neurobiology of empathy to improve the outcomes for those with neuropsychiatric disorders.

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Table 1.

Rodent models of empathy, along with species tested, main behavioral findings, as well as any other manipulations performed and neurobiology discovered with each model.

Model of Empathic Behavior	Species Studied	Outcome
Emotional Contagion - Behaviors		
Church et al., 1959	rats	Attenuation of operant behavior once it became associated with aversive shock to a conspecific
Langford et al., 2006	mice	Potentiation of pain-related behaviors tested in the presence of a familiar conspecific that also received painful stimulus
Smith et al., 2016	mice	Hyperalgesia observed in a "bystander" animal tested in the same environment as a conspecific that received painful stimulus, even without the shared experience of the stimulus
Carnevali et al., 2017	rats	
Li et al., 2018	rats	Prosocial behaviors (allo-licking and -grooming) made by "bystander" directed at conspecific that received noxious stimulus
Du et al., 2019	rats	
Li et al., 2014	rats	Expression of emotional contagion may be modulated by circulating glucocorticoid levels, depending on the type/severity of noxious stimuli used
Martin et al., 2015	mice	
Laviola et al., 2017	mice	Low levels of emotional contagion (paw licking) correlated with potentiated oxytocin and vasopressin levels in behaviorally-relevant brain areas absent any changes in receptor density. Low emotional contagion also associated with impaired reactivity to external stressors
Emotional Contagion – Brain Areas Associated		
Li et al., 2014	rats	Prefrontal cortex (PFC)
Knapska et al., 2006	rats	PFC and amygdala
Zaniboni et al., 2018	mice	Insula
Observational Fear Learning - Behaviors		
Bredy and Barad, 2009	mice	Context-dependent modulation of the social transmission of fear learning to an observer from a conspecific
Guzman et al., 2009	mice	
Bruchy et al., 2010	rats	
Knapska et al., 2010	rats	
Atsak et al., 2011	rats	
Jeon and Shin, 2011	mice	
Sanders et al., 2013	mice	
Jeon et al., 2010	mice	Vicarious freezing behavior due to affective transfer to observer from conspecific receiving footshocks
Jeon and Shin, 2011	mice	
Hernandez-Lallement et al., 2020	rats	Instrumental harm aversion tested when observers became directly responsible for the footshock of the conspecific. This behavior was shown to be subject to effort
Guzman et al., 2009	mice	Social buffering, both passive and active, modulated observational fear learning in observer. This phenomenon is dependent on the level of familiarity with the fearful conspecific
Watanabe 2011; 2015	mice	
Kiyokawa et al., 2014	rats	
Pisansky et al., 2017	mice	Oxytocin administration, or chemogenetic activation of oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVN), causes enhanced sensitivity to distress of the conspecific
Guzman et al., 2014	mice	Oxytocin infusion into Lateral septum (LS) accelerated social buffering of observational fear
Observational Fear Learning - Brain Areas Associated		
Pisansky et al., 2017	mice	PVN

Model of Empathic Behavior	Species Studied	Outcome
Guzman et al., 2014	mice	LS
Jeon et al., 2010	mice	Anterior cingulate cortex
Carrillo et al., 2019	rats	
Restraint Stress Model - Behaviors		
Bartal et al., 2011	rats	Animals learn to release a conspecific from a restraint tube
Ueno et al., 2019a	mice	
Bartal et al., 2014	rats	Release of a conspecific is modulated by social experience and familiarity
Ueno et al., 2019b	mice	Underlying motivation for release behavior in mice is less clear and may be driven by social interest and curiosity with the apparatus
Blystad et al., 2019	rats	Release behavior may be modulated or dependent on contents of the container
Silberberg et al., 2014	rats	Release behavior may be modulated or dependent on social contact
Carvalheiro et al., 2019	rats	Release behavior may be modulated or dependent on alternative choices afforded to the observer
Bartal et al., 2011	rats	
Bartal et al., 2016	rats	Midazolam administered to observers before the session reduced door openings
Restraint Stress Model – Brain Areas Associated		
Tomek et al., 2020	rats	Insula
Soaked Conspecific Model - Behaviors		
Sato et al., 2015	rats	Animals learn to release a "soaked conspecific" into a dry chamber. Release behavior specific to presence of conspecific, and previous experience in the distressing condition potentiates the helping behavior
Cox and Reichel, 2019	rats	
Karakilic et al., 2018	rats	Mild stress (footshock) reduces latency to release distressed conspecific
Yuksel et al., 2019	mice	8 weeks of voluntary wheel running improved door opening latency in females
Yamagishi et al., 2019	rats	Oxytocin injections enhanced early acquisition of helping behavior in single-housed, but not pair-housed rats
Ueno et al., 2019b	mice	Oxytocin had no effect on door opening
Kandis et al., 2018	rats	Dose-response relationship observed between acetaminophen concentration administered and reduction in door opening latency
Targeted Helping Independent of Social Interaction-Behaviors		
Cox and Reichel, 2019	rats	Rats will release distressed conspecific from a pool of water independent of social interaction. Release behavior is specific to a distressed conspecific, modulated by previous experience, and is dependent on effort