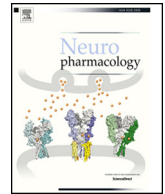


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Invited review

Genetic factors associated with empathy in humans and mice

Sehoon Keum, Hee-Sup Shin*

Center for Cognition and Sociality, Institute for Basic Science (IBS), Daejeon, Republic of Korea

HIGHLIGHTS

- Empathy has evolutionary and neurobiological underpinnings.
- Gene variants are associated with individual differences in empathy behaviors.
- Rodent models become useful for assessing the neurobiological correlates of empathy.

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ABSTRACT

The neurocognitive ability to recognize and share the mental states of others is crucial for our emotional experience and social interaction. Extensive human studies have informed our understanding of the psychobehavioral and neurochemical bases of empathy. Recent evidence shows that simple forms of empathy are conserved from rodents to humans, and rodent models have become particularly useful for understanding the neurobiological correlates of empathy. In this review, we first summarize aspects of empathy at the behavioral and neural circuit levels, and describe recent developments in rodent model behavioral paradigms. We then highlight different neurobiological pathways involved in empathic abilities, with special emphasis on genetic polymorphisms associated with individual differences in empathy. By directly assessing various neurochemical correlates at molecular and neural circuit levels using relevant animal models, we conclude with the suggestion that rodent research can significantly advance our understanding of the neural basis of empathy.

1. Introduction

The way we socially interact is greatly influenced by our understanding of the emotional states of others. Empathy is the ability to identify other people's feelings, thoughts, and intentions and to respond to the mental state of others with an appropriate emotion (Bernhardt and Singer, 2012; de Waal, 2008). Either elevated or reduced empathy can contribute to difficulties in social interactions and mental well-being, and differences in empathic abilities have been observed in many neuropsychiatric conditions including autism, schizophrenia, and major depressive disorder (Baron-Cohen, 2004; Bora et al., 2008).

Empathy is a broad concept that refers to a sense of knowing the experience of another person with cognitive, affective, and behavioral components (Shamay-Tsoory et al., 2009). Empathy occurs when witnessing affective states in others induces shared states in the observer, which necessarily involves components of affective sharing, self-awareness, and self-other distinction (Baron-Cohen and Wheelwright, 2004; de Waal and Preston, 2017). The capacity to share, appreciate

and respond to other's emotions has evolved over time, and ranges from primitive forms such as mimicry and emotional contagion to high-level forms such as perspective taking, sympathy, altruism, and targeted helping (Preston and de Waal, 2002). Recent studies using functional magnetic resonance imaging (fMRI) have identified distinct brain regions implicated in different aspects of empathy. In particular, the anterior cingulate cortex (ACC) and insular cortex are activated when people are engaged in empathic responses of pain or fear (Olsson et al., 2007; Singer et al., 2004).

There are considerable neurochemical and genetic contributions to empathy behaviors in humans. Combined with neuroimaging tools, recent studies have assigned a special role to neurochemicals such as oxytocin, vasopressin, and testosterone in modulating empathic responses (Abu-Akel et al., 2015; Shamay-Tsoory et al., 2013; van Honk et al., 2011). Genetic approaches have identified several genetic variations associated with empathy-related traits (Ebstein et al., 2010; Knafo et al., 2009; Rodrigues et al., 2009). Moreover, recent genome-wide association studies using high-throughput genotyping

* Corresponding author. Center for Cognition and Sociality Institute for Basic Science (IBS) KAIST Bd, E18-3, 291 Daehak-ro, Yuseong-gu, Daejeon, 34141, Republic of Korea.

E-mail address: shin@ibs.re.kr (H.-S. Shin).

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technologies in a large number of subjects have revolutionized direct discovery of genes and variants associated with empathy traits in humans (Warrier et al., 2017). However, in many cases, the specific genes identified as determining individual variability in empathy have not been replicated in other studies, possibly due to genetic heterogeneity and uncontrolled environmental variables. Despite accumulating information about brain regions and biological factors involved in empathy, the underlying neural mechanisms at neurobiological and circuit levels are poorly understood.

Although humans are special in the sense that high-level cognitive abilities are layered on top of phylogenetically older emotional and social capacities (Stone, 2006), empathy is not unique to us as many of the biological mechanisms are shared with other mammalian species. Converging evidence now suggests that empathy has deep neuroendocrine and neurophysiological underpinnings, with evolutionary continuity from rodents to humans (de Waal and Preston, 2017; Decety, 2010). Recent evidence shows that rodents possess a remarkable affective sensitivity to the emotional state of others and show simple forms of empathy-like behaviors such as observational fear, emotional contagion of pain, social buffering, and prosocial helping behaviors (Ben-Ami Bartal et al., 2011; Burkett et al., 2016; Jeon et al., 2010; Langford et al., 2006). In particular, observational fear has been recognized as a useful behavioral model for assessing empathic fear capacity (Keum and Shin, 2016; Kim et al., 2018; Meyza et al., 2017; Panksepp and Lahvis, 2011; Sivaseelvachandran et al., 2016).

In this review, we discuss recent reports that empathy involves a variety of neurobiological processes, with special emphasis on how rodent models can advance our understanding of the neural basis of empathy. We begin by reviewing neural circuits involved in empathy and discussing several rodent models with different behavioral paradigms. Then, we highlight emerging topics in neurochemical and genetic studies of empathy behaviors, and discuss several genes and polymorphisms associated with individual differences in empathy-related traits in humans. Finally, we conclude by suggesting ways in which rodent research can significantly advance the study of human empathy, particularly by permitting direct access to various neuromodulatory factors at the molecular, cellular, and circuit levels.

2. Empathy and core neural networks

Due to ambiguous definitions in mechanisms, empathy has no universally accepted definition and the nature of empathy has been debatable (Bernhardt and Singer, 2012; Preston and de Waal, 2002). Empathy occurs when witnessing affective states in others induces shared states in the observer, which necessarily involves components of affective sharing, self-awareness, and self-other distinction (Baron-Cohen and Wheelwright, 2004; de Waal and Preston, 2017). Recent evidence supports a model of two systems mediating empathy: affective (emotional) and cognitive (Frith and Singer, 2008; Shamay-Tsoory et al., 2009). Emotional empathy may involve several processes, including emotional contagion and recognition, where one responds to another's mental state with an appropriate emotion. This is thought to be phylogenetically earlier than cognitive empathy. Cognitive empathy is described as cognitive role-taking ability, or the capacity to share another's feelings and to appreciate another's thoughts, intentions, and desires (Bernhardt and Singer, 2012). Cognitive empathy requires perspective-taking and mentalizing, and conceptually overlaps with "theory of mind", the ability to put oneself into someone else's shoes and to imagine their thoughts and feelings (Decety, 2010). When individuals empathize, they (1) vicariously feel others' emotions (emotional resonance), (2) explicitly understand targets' states and their sources, and (3) evoke affective communication (empathic concern, sympathy, or compassion) that may motivate them to remove the source of target's distress and/or provide comfort (Decety, 2011a; Zaki and Ochsner, 2012). Thus, although the two empathy systems may be behaviorally or developmentally dissociable, there could be

interactions between the two systems. Empathic responses evoke both systems to some extent, depending on the social context (Decety and Lamm, 2006).

Recent conceptual work on empathy has greatly facilitated the design and interpretation of empirical studies that assess empathic traits through self-report measures and empathic states through controlled observational experiments. Empathy comprises related but distinct processes through which 'perceivers' (individuals focusing on another person's internal states) relate to 'targets' (individuals who are the focus of perceivers' attention). Preston and De Waal proposed that, in order to identify with the state of another individual (target), the observer (subject) must activate the same neural networks in the brain as the target, a process they called perception-action mechanism (Preston and de Waal, 2002). Indeed, neuroimaging studies mainly using fMRI have demonstrated that observing the affective states of others activates brain networks also involved in the direct experience of these emotional states, confirming that empathy is based on shared neural networks (de Vignemont and Singer, 2006; Keysers and Gazzola, 2007). Specifically, the anterior insula and cingulate cortex played central roles in vicarious responses, particularly the perception of others' distress or pain as trait measures of empathy (de Waal and Preston, 2017; Jackson et al., 2005; Lamm et al., 2011). Activation of the insular cortex is nearly ubiquitous in studies of pain empathy. The insular cortex and its array of projections serve to integrate bottom-up interceptive signals with top-down predictions from high-level cortical areas, which is necessary for the feeling of pain and its emotional awareness (Craig, 2009). The ACC, a region that is integral to negative affect, pain, and cognitive control, contains pain-responsive neurons that are activated by both anticipation of pain and empathic responses (Bliss et al., 2016; Vogt, 2005). In addition, the neural substrate of an individual that sees others in pain involves the pain matrix (Avenanti et al., 2005; Singer et al., 2004) and pain signals are relayed through the thalamus via the lateral and medial pain systems (Price, 2000). The mediadorsal and parafascicular nuclei of the thalamus, which are a part of affective pain systems, were activated during both self-experienced pain and observation of pain of others (Singer et al., 2004; Vogt, 2005). Taken together, these findings support the idea that the observation of others' experiences activates similar neural regions to one's own experiences, which is interpreted as a neural marker of empathy.

Likewise in mice, the activity of the ACC is augmented in observational fear (Allsop et al., 2018; Pisansky et al., 2017a), and its role in the acquisition of vicarious freezing has been demonstrated using neuroanatomical lesions, electrical stimulations and optogenetic manipulations (Jeon et al., 2010; Keum et al., 2018; Kim et al., 2012). Additionally, inactivation of the medial affective pain system, including the ACC, the parafascicular, or the mediadorsal thalamic nuclei by lidocaine injection significantly impaired empathic fear in mice, whereas inactivation of the lateral sensory pain system did not affect observational fear learning (Jeon et al., 2010). However, we still have limited knowledge of how a specific neural circuit in these brain areas integrates social cognitive information in empathy behaviors. Recently, we have identified that a particular subgroup of the cortical neurons within the ACC play a crucial role in controlling the level of empathic fear in mice (Keum et al., 2018). Using optogenetics, we found that somatostatin-expressing (SST+) GABAergic inhibitory neurons in the ACC bi-directionally controlled the degree of socially transmitted vicarious fear. Because the dendrite-targeting SST+ neurons exert distal inhibition to control incoming inputs to excitatory pyramidal cells in the cortex, our finding suggests that specific inhibitory mechanisms in the ACC microcircuit regulate empathic fear responses. Thus, it will be of interest to investigate whether the inhibitory mechanism mediated by SST+ neurons in the ACC controls other types of empathy-related behaviors, such as empathic pain, social buffering, or prosocial helping behaviors (Ben-Ami Bartal et al., 2011; Burkett et al., 2016; Langford et al., 2006).

Table 1
Genetic variations associated with empathy-related traits in humans.

Genes	Description	Variants	Biotypes/Function	Reference
<i>OXTR</i>	Oxytocin receptor	SNP rs53576	intronic	(Gong et al., 2017; Rodrigues et al., 2009; Smith et al., 2014)
		SNP rs2268498	Promotor	Laursen et al. (2014)
		SNPs rs13316193, rs2254298, rs1042778, rs2268494, and rs2268490	all intronic except rs1042778 (3'-UTR)	Schneiderman et al. (2014)
<i>CD38</i>	Cluster of differentiation 38	SNP rs3796863	intronic	Liu et al. (2017)
<i>AVPR1A</i>	Arginine vasopressin receptor 1A	327bp repeat	promotor	Avinun et al. (2011)
<i>SLC6A4</i>	Serotonin transporter	GC-rich, 20-23bp repeat	promotor	(Crisan et al., 2009; Gyurak et al., 2013)
<i>HTR2A</i>	serotonin 2A receptor	SNP rs6313	exon, synonymous	(Gong et al., 2015; Matsunaga et al., 2017a, 2017b; Murphy et al., 2006)
<i>DRD4</i>	Dopamine D4 receptor	48bp coding sequence repeat	exon	Uzefovsky et al. (2014)
<i>DRD5</i>	Dopamine D5 receptor	148 bp microsatellite (18.5 kb upstream)	unknown	Bachner-Melman et al. (2005)
<i>DBH</i>	Dopamine beta-hydroxylase	SNP rs1611115	promotor	Gong et al. (2014)
<i>OPRM1</i>	Opioid receptor mu 1	SNP rs3778151	intronic	Pearce et al. (2017)

3. Rodent models of empathy

Animal research has shown that the ability to share and be affected by the emotional state of another is evolutionarily conserved across organisms, and rodents possess affective sensitivity to their social partners. Like humans, mice and rats exhibit social modulation of pain, observational fear consolation, and prosocial helping behaviors (Atsak et al., 2011; Ben-Ami Bartal et al., 2011; Burkett et al., 2016; Jeon et al., 2010; Langford et al., 2006). This continuity has important implications for the study of human empathy behaviors as it allows for application of animal models to better understand the neurobiological mechanisms underlying empathy (Meyza et al., 2017; Panksepp and Lahvis, 2011).

In one such study, pain sensitivity was modulated in mice by the presence of other mice displaying pain behaviors (Langford et al., 2006). Interestingly, the pain response was conditional upon the relationship of the subject mouse with the target mouse. Observing pain-mediated writhing behavior in conspecifics only influenced pain behavior when the target mouse was a cage mate of the subject mouse. Moreover, when a mouse was injected with the noxious stimulus acetic acid, their pain response was greater when they observed another mouse treated with the same noxious stimulus than when they were placed alone or with a non-writhing mate. This modulation of pain response in the observer mouse is thought to rely on a shared representation of pain. Such vicarious simulation of the emotional and bodily states of another mouse presumably mimics the negative emotional experience associated with pain, which may promote understanding of others' painful feelings (Bernhardt and Singer, 2012).

Observational fear is a rodent behavioral model for assessing empathic fear (Keum and Shin, 2016; Kim et al., 2018; Meyza et al., 2017; Panksepp and Lahvis, 2011; Sivaselvachandran et al., 2016). In observational fear, mice were vicariously conditioned to experience fear by observing a conspecific receive aversive foot shocks, even though they had never experienced the shock themselves (Jeon et al., 2010). Similarly, mice that witnessed another mouse in a fear-conditioning task consisting of a tone coupled with a foot shock showed freezing in response to the tone alone (Chen et al., 2009). This phenomenon, referred to as emotional state-matching or affect sharing, has been measured as socially transmitted fear response (vicarious freezing) in the behavioral paradigm. The vicarious freezing response in the observational fear model is positively influenced by the animal's familiarity or kinship with the demonstrator. The fear response in the observer tended to be higher when the demonstrator was a sibling or long-time mating partner than when it was an unfamiliar mouse (Gonzalez-Liencrez et al., 2014; Jeon et al., 2010; Pisansky et al., 2017a). Importantly, human performance in a similar observational fear process was correlated with trait measures of empathy, suggesting that observational fear may contain a fundamental feature of empathy that is conserved across

species (Haaker et al., 2017; Olsson and Phelps, 2007; Panksepp and Panksepp, 2013).

Despite a primitive form of empathy observed in social lives of rodents, there is still debate as to whether the emotional state-matching observed in rodents indicates empathy, as it is not clear whether rodents are capable of self-awareness, which is crucial for empathy. Many believe that higher forms of empathy such as sympathetic concern, consolation, targeted helping, or altruistic caring are human-specific abilities. However, multiple studies with rodents provide evidence that affective arousal and emotional contagion prompt efforts to alleviate the distress of a conspecific (Ben-Ami Bartal et al., 2011; Burkett et al., 2016; Church, 1959). In one such study, a rodent species, prairie vole, detects the stress of conspecifics and expresses empathy-based consolation behaviors (Burkett et al., 2016). When demonstrators that experienced foot shocks were reunited with naïve observers, the observers displayed partner-directed grooming behaviors toward the distressed familiar conspecifics (but not strangers), providing social buffering. Because consolation behavior is defined as an increase in affiliative contact toward a distressed individual to ameliorate stress responses, these allogrooming behaviors in prairie voles may indicate empathy-based social buffering. In addition, rats showed prosocial helping behaviors in response to the distress of conspecifics. Empathy allows individuals to vicariously experience the affective states of others, predict others' actions, and motivate prosocial behaviors in humans. Similarly, rats learned to release a cagemate locked in a restrainer, even when they received no explicit rewards (Ben-Ami Bartal et al., 2011). This behavioral paradigm for targeted helping behavior further support that rodents demonstrate empathy-related behaviors to ameliorate aversive stress of conspecifics. Since both human and animal studies have revealed that the perception of distress in others activates a highly conserved neural circuit in the observer (de Waal and Preston, 2017; Decety and Michalska, 2010), empathic responses in current rodent models share similarities at the behavioral and neural circuit levels with empathic responses in humans (Kim et al., 2018).

4. Neurobiological factors associated with empathy-related traits

Using candidate gene association studies there has been a growing body of research dedicated to investigating the neurobiological factors associated with empathic responses (Table 1). Here, we discuss several neurochemical systems that are involved in the empathy-related behavioral traits; neuropeptides (oxytocin and vasopressin), serotonin, dopamine, testosterone, and opioid.

4.1. Neuropeptides

Oxytocin and arginine vasopressin play a crucial role in vertebrate

social signaling (Donaldson and Young, 2008). Oxytocin increases the salience and reinforcing the value of social stimuli, and recent research has examined the role of this neuropeptide in empathy (Young, 2015). Oxytocin is a neuropeptide that modulates a wide range of social behaviors in humans and animals, including sexual behavior, childbirth, maternal bonding, in-group and out-group relationships, and social stress response (Meyer-Lindenberg et al., 2011). Oxytocin is produced in the hypothalamus and released via axons projecting to the pituitary and axons collateral to the nucleus accumbens and other brain regions (Landgraf and Neumann, 2004).

Although the administration of exogenous oxytocin can often produce no effect, more recent work shows that oxytocin increases empathy traits (Abu-Akel et al., 2014; Shamay-Tsoory et al., 2013). For example, participants' empathy ratings were associated with a level of oxytocin and a subsequent increase in generosity towards strangers, and women had a higher empathy-related oxytocin response than men (Barraza and Zak, 2009). Moreover, intranasal administration of oxytocin increased emotional empathy in men to a level comparable to that in untreated women (Hurlemann et al., 2010). However, the administration of exogenous oxytocin can produce contradictory results, and the effects of oxytocin are variable and condition-dependent (Singer et al., 2008). Oxytocin has the potential to increase empathy or induce prosocial behavior, but it does not exclusively act in a beneficial way to enhance empathy, suggesting that its effect may be dependent on individual differences and social, contextual, or genetic factors.

Genetic variations in the oxytocin receptor (*OXTR*) are associated with empathy-related social behaviors (Feldman et al., 2016). Individuals homozygous for the G allele of the single nucleotide polymorphism (SNP) rs53576 (GG) showed greater empathic ability (Gong et al., 2017; Rodrigues et al., 2009), had higher levels of sociability, and were more prosocial than AG or AA genotypes (Kogan et al., 2011; Tost et al., 2010). Individuals with the rs53576-GG genotype also exhibited larger hypothalamus volume and greater amygdala activation than AA or AG genotypes when observing emotionally salient social cues. The GG genotype also showed greater sympathetic arousal and self-reported empathic concern to pictures of others' pain (Smith et al., 2014). The *OXTR* promoter SNP rs2268498-CC carriers displayed higher empathic accuracy correlated with stronger superior temporal sulcus response to others' pain (Laursen et al., 2014). In addition, allelic variations on five *OXTR* SNPs rs13316193, rs2254298, rs1042778, rs2268494, and rs2268490 were associated with empathic communication at the early stages of romantic love (Schneiderman et al., 2014). Intriguingly, individuals with the genotypes (AA/AC) for a SNP rs3796863 in the *CD38* (cluster of differentiation 38) gene that regulates plasma oxytocin levels showed stronger empathic responses than the CC genotype (Liu et al., 2017), further suggesting that oxytocin signaling pathway is linked to empathy-related prosocial behaviors (Chang et al., 2014).

Animal models have allowed the study of the mechanisms underlying the effects of oxytocin in empathy behaviors. A recent study examined the involvement of oxytocin in observational fear in mice (Pisansky et al., 2017a). Both acute and chronic intranasal oxytocin administration increased vicarious freezing in response to the distress of unfamiliar demonstrators. Chemogenetic activation of hypothalamic oxytocinergic neurons enhanced also observational fear in mice paired with unfamiliar demonstrators. Systemic injection of an oxytocin receptor antagonist reduced vicarious freezing response to familiar conspecifics. Similarly, in a separate study, infusion of an oxytocin receptor inhibitor within the ACC abolished empathy-based consolation behaviors in prairie voles (Burkett). Although further cell type-specific or circuit-based investigations are necessary to understand the underlying neural mechanisms, these two rodent studies clearly suggest that oxytocin increased empathy-like behaviors in association with elevated neuronal activity in the ACC.

Arginine vasopressin (AVP), which is structurally similar to oxytocin and diverges by only two amino acids, has also been associated with a wide range of social behaviors, including protective aggression,

anxiety, bond formation in males, social communication, and social recognition (Donaldson and Young, 2008; Insel, 2010; Johnson and Young, 2017; Walum et al., 2008). In humans, a specific 327bp allele in the promoter region of the AVP receptor gene (*AVPR1A*) has been associated with altruistic behaviors (Avinun et al., 2011; Knafo et al., 2009). Additionally, a microsatellite polymorphism (RS3_334bp allele) in the *cis*-regulatory regions of the *AVPR1A* gene was associated with differential activation of the amygdala when viewing threatening faces, suggesting a role of AVP in emotional arousal and social behavior (Meyer-Lindenberg et al., 2009). AVP increased affiliative behavior in women, and its effects on the perception of emotional states were sex-specific (Thompson et al., 2006). However, compared to the genetic polymorphisms in the *OXTR* gene associated with empathy-related traits (Rodrigues et al., 2009; Schneiderman et al., 2012), the role of the *AVPR1A* gene are largely unexplored in empathic responses.

4.2. Serotonin

Serotonin (5-hydroxytryptamine) is a monoaminergic neurotransmitter that plays a central role in the regulation of emotion, mood, and social behaviors (Meneses and Liy-Salmeron, 2012). Administration of a selective serotonin reuptake inhibitor, citalopram, had prosocial effects (Crockett et al., 2010), and a serotonin 2A receptor agonist increased emotional empathic ability, feelings of happiness, trust, and closeness to others (Dolder et al., 2017). Disruption of the serotonergic system can result in heightened irritability and aggression and lead to antisocial behaviors (Lesch and Merschdorf, 2000). This type of serotonergic dysfunction is observed in a variety of neuropsychiatric disorders, including schizophrenia and autism. However, a relation between serotonergic dysfunction and deficits in empathy has yet to be identified.

Gene association studies have provided evidence to support the involvement of the serotonin system in empathic ability. A functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR, *SLC6A4*) was linked to individual differences in emotional reactivity (Gyurak et al., 2013). Individuals with the *s/s* genotype (two short alleles) of 5-HTTLPR showed greater levels of empathic responses than participants harboring long alleles (*s/l* or *l/l*). Similarly, individuals with *s/s* genotype showed greater observational fear response than individuals who were homozygous for the long alleles (Crisan et al., 2009). The serotonin 2A receptor gene (*HTR2A*) has also been associated with empathy-related social communication abilities (Murphy et al., 2006). In a large sample of Chinese people, the SNP rs6313 of *HTR2A* was significantly associated with cognitive empathy, supporting the involvement of serotonin neurotransmission in the process of empathic perspective taking (Gong et al., 2015). In addition, salivary serotonin levels were associated with empathic abilities, and the polymorphism was associated with individual differences in happiness-related empathy (Matsunaga et al., 2017a). In support of this finding, individuals with the *HTR2A* GG genotype exhibited greater activity in the right temporal pole than individuals with other genotypes (Matsunaga et al., 2017b). However, the SNP was also shown to be associated with depressive symptoms and increased reactivity to emotional stimuli, and the amygdala in individuals with the AA genotype was activated more intensely in response to sad facial expressions than it was in G-allele carriers (Lee and Ham, 2008). The cellular and molecular mechanisms underlying the link between the *HTR2A* functional polymorphism and empathic responses are unknown.

In mice, blockade of serotonin receptors in the ACC did not affect the observational fear response. However, an experimentally induced increase in serotonin in the ACC reduced vicarious freezing, and extracellular application of serotonin to ACC slices reduced the excitability of ACC neurons (Kim et al., 2014). Similarly, activation of the serotonin 1A receptor (*Htr1a*) within the prefrontal cortex inhibited neuronal activity (Hajos et al., 1999). Thus, it is possible that an increased level of serotonin results in activation of the HTR1A, which

may lead to downregulation of affective and emotional behaviors. Taken together, serotonin certainly modulates empathy-related traits, but since it also influences all psychobehavioral systems, its specific role in neural circuitry mediating empathic ability is unknown. Further investigation to elucidate neural circuit mechanisms underlying the serotonin-mediated reduction in observational fear is necessary.

4.3. Dopamine

Dopamine may mediate social cognition, especially when mentalization is involved (Brunet-Gouet and Decety, 2006; Skuse and Gallagher, 2009). Dopamine-neuropeptide interactions are known to play an important role in social cognition, and a dysfunctional oxytocinergic-dopaminergic system may cause inappropriate salience processing (Rosenfeld et al., 2011). Gene association studies have linked genetic polymorphisms in the dopaminergic systems to prosocial or altruistic traits. There is converging evidence that *DRD4* is linked with cognitive empathic ability (Uzefovsky et al., 2014). A polymorphic region in the third exon of the dopamine D4 receptor (*DRD4*) has been associated with a range of social behaviors such as aggression (Schmidt et al., 2002) and negative affect in infants (Holmboe et al., 2011). The 148bp microsatellite variant in the *DRD5* gene was also significantly associated with self-report measures of altruistic traits (Bachner-Melman et al., 2005). Genetic variation in the *DBH* gene, encoding dopamine beta-hydroxylase that converts dopamine to norepinephrine, was associated with empathic perception and response (Gong et al., 2014). Individuals with the CC genotype of SNP (rs1611115) in the *DBH* gene manifested greater empathic ability than those with one or two copies of the T allele. Inhibiting *DBH* activity increased dopamine levels and decreased norepinephrine levels (Robertson et al., 1986). Given the negative relation between dopamine level and social behaviors, the dopaminergic-noradrenergic system may modulate empathic ability and empathy-related behaviors. A previous animal study showed that mice lacking the *Dbh* gene failed to discriminate familiar and unfamiliar mice, suggesting the important role of dopamine-norepinephrine signaling in social recognition (Marino et al., 2005). Altogether, dopamine certainly affects empathy-related traits, but since its signaling is involved in all psychobehavioral systems, further investigation to elucidate its specific role in neural circuitry mediating empathic ability is necessary.

4.4. Testosterone

Despite general beliefs regarding a link between testosterone and aggressive behaviors such as mate and territorial guarding, testosterone has social effects in humans. Testosterone is released in response to contextually appropriate behavioral responses (Logan and Wingfield, 1990). Administration of testosterone decreased facial mimicry related to affective and cognitive empathy (Hermans et al., 2006; van Honk and Schutter, 2007). In young adult women, testosterone administration significantly impaired performance of a cognitive empathy task (van Honk et al., 2011). Importantly, there is considerable empirical evidence that testosterone negatively affects social cognition and intelligence during fetal programming of the brain. High levels of fetal testosterone have been associated with deficits in cognitive empathy skills and affective empathy (Chapman et al., 2006; Knickmeyer et al., 2006). As male fetuses are exposed to higher levels of prenatal testosterone than female fetuses, testosterone levels during the development of empathy circuits in the brain may influence the gender difference in empathic ability (Baron-Cohen et al., 2009). Additionally, testosterone appears to enhance amygdala and orbitofrontal activity in response to threatening stimuli (Hermans et al., 2008). Thus, these findings suggest that testosterone have an effect on empathy by programming initial organization of neural circuitry during development or by directly affecting the functional connectivity of empathy-related circuits in adults.

Testosterone modulates affiliative behaviors in rodents, particularly

through its relation to other systems. For example, early exposure to testosterone was necessary for AVP-triggered partner preference behavior in male voles (Cushing et al., 2003). However, despite evidence supporting the role of testosterone in empathy, the neural mechanisms underlying the link remain unknown. Testosterone played a crucial role in the development of neural pathways that were activated during male-specific aggressive territorial behaviors in mice (Wu et al., 2009). Thus, testosterone signaling might be also involved in development of neural circuitry important for modulation of empathy-related affiliative behaviors.

4.5. Opioid receptor

The μ -opioid receptor (MOR) has been of particular interest because the endogenous opioid system is intimately involved in the modulation of pain and emotions (Fields, 2004; Nummenmaa et al., 2008). Human positron emission tomography (PET) studies have shown that noxious stimuli activate the MOR system, and the magnitude of MOR activation in the thalamus and ACC correlates with negative emotional experiences associated with pain (Scott et al., 2008; Smith et al., 2006; Zubieta et al., 2003). Since brain circuits involved in nociceptive processing are also engaged in vicarious pain (Jackson et al., 2005; Lamm et al., 2011; Singer et al., 2004), the opioid system may therefore affect our emotional abilities to perceive others in pain. Indeed, administration of the opioid antagonist, naltrexone, increased pain ratings and unpleasant experiences while witnessing others in pain (Rutgen et al., 2015). Hemodynamic responses during empathic pain depended on cerebral MOR availability in a brain region-selective manner (Karjalainen et al., 2017): MOR availability was negatively correlated with activity in sensorimotor regions and the emotion circuit (insula, thalamus), but positively correlated with activity in the orbital frontal cortex, which is involved in mentalizing and social bonding.

Gene association studies combined with PET have linked the A118G polymorphism (rs1799971) of the MOR gene (*OPRM1*) with sensitivity to social rejection and early maternal care on fearful attachment (Troisi et al., 2012; Way et al., 2009). The *OPRM1* SNP rs3778151 was significantly associated with individual differences in attachment, the ability to identify emotional facial expressions, and a self-report measure of empathy (Pearce et al., 2017). Evidence also suggests that β -endorphin, a primary endogenous ligand for the MOR, was involved in the creation and maintenance of social relationships and the *OPRM1* variation was previously linked to the extent to which individuals experience social rewards rather than to pain (Dunbar, 2010; Troisi et al., 2012). Together, these findings suggest that MOR signaling correlates with the capacity to read the emotional states of others (Bonnenberger et al., 2015; Way et al., 2009). Further study is necessary to understand how *OPRM1* signaling controls empathy-related traits at the level of neural circuits in the brain.

4.6. Genes mediating empathic responses in mice

In observational fear, the vicarious freezing response was highly variable among different inbred mouse strains (Chen et al., 2009; Keum et al., 2016). Using forward genetics combined with the CRISPR/Cas9 genome editing, we have recently found that a missense variant in the *Nrxn3* gene selectively enhances observational fear without altering classical fear conditioning (Keum et al., 2018). More importantly, NRXN3 protein was required for inhibitory synaptic transmission in SST + interneurons in the ACC and dysfunctional inhibitory circuits in the ACC of SST + neuron-specific *Nrxn3* knockout (KO) mice caused hyperactivity of excitatory pyramidal neurons, resulting in elevated observational fear. Thus, this study has identified a novel role of *Nrxn3*-dependent SST + neurons in the ACC in controlling the affective capacity in empathy fear behavior in mice (Keum et al., 2018). Neurexins are known to play crucial roles in neurotransmission and synaptic connectivity in multiple brain regions (Sudhof, 2017). In the tone-based

observational fear paradigm, a previous study showed that *Nrxn1* KO rats showed impaired vicarious freezing and 48hr social fear memory caused by reduced synaptic transmission in an intra-amygdala circuit (Twining et al., 2017).

We have previously demonstrated that L-type calcium channel gene, *CaV1.2* (*Cacna1c*), in the ACC is required for observational fear (Jeon et al., 2010). Mice with an ACC-limited deletion of the *CaV1.2* gene exhibited impaired observational fear and reduced pain responses to formalin and acetic acid, suggesting that *CaV1.2* in the ACC is critical for affective or emotional dimension of noxious or aversive stimuli. Nonetheless, it is still not clear how the *CaV1.2* channel in the ACC modulates observational fear at cellular and molecular levels. Further cell-type specific electrophysiological experiments will reveal the role of *CaV1.2* in observational fear. A recent study showed that the chromodomain helicase DNA-binding 5 (*Chd5*) gene, a chromatin remodeling protein involved in neuronal differentiation, was involved in the acquisition of observational fear learning (Pisansky et al., 2017b). Interestingly, despite no behavioral deficit in conditioned fear, the *Chd5* KO observer mice failed to show enhanced observational fear response to familiar cagemate demonstrators. Because the KO mice exhibited altered vocalization and reduced sociability, the authors suggested that failure to respond to familiar conspecifics in *Chd5*-deficient observer mice could be due to impaired social recognition.

It is interesting to note that all these genes involved in observational fear in mice we discussed above have been also implicated in autism spectrum disorder (ASD). Deletions or copy number variations of the neurexin genes (*NRXN1* and *NRXN3*) were directly implicated as risk factors for ASD (Kim et al., 2008; Vaags et al., 2012). The *CHD* gene family and dysregulated neuronal Ca^{2+} signaling via *CACNA1C* were associated with autism (Bader et al., 2011; Chenier et al., 2014; Gompers et al., 2017; Pisansky et al., 2017b). Disturbance of empathy is a salient feature of ASDs and many patients show impaired emotional processing with deficits of social recognition and empathy (Baron-Cohen and Wheelwright, 2004; Bird et al., 2010). However, in some ASD patients, emotional empathy is preserved or even stronger (Bernhardt et al., 2014; Hadjikhani et al., 2014). This heterogeneity suggests a more general affective imbalance in neurocognitive capacity in ASDs, resulting from a complicated matrix of genes, brain regions and behavioral correlates (Bird et al., 2010; Markram et al., 2007). Dysfunction of these genes (*Nrxn1*, *Nrxn3*, *Chd5*, and *Cacna1c*) may likely perturb the neural circuitry underlying social cognition at different nodes in ASD patients (Courchesne and Pierce, 2005; Sahin and Sur, 2015). Similarly, a previous study showed that pain-related empathic approach behaviors may not be mediated by oxytocin in mice (Langford et al., 2010). Despite the well-documented roles of oxytocin in social recognition, pair bonding, and affiliative behaviors, female *Oxtr* KO mice showed no difference in ability to distinguish and respond to the pain states of familiar conspecifics in the empathic pain behavioral paradigm. Therefore, although certain features of affective empathy can be modeled in rodents, finding a common underlying molecular mechanism that is functionally relevant to other social behaviors and empathy will require additional studies.

4.7. Conclusion and future directions

Considerable evidence now exists to suggest that empathy has deep evolutionary and neurobiological underpinnings. A substantial body of research in humans has documented the neurochemical correlates of empathy, and several genetic variations in candidate genes have been identified. Collectively, it appears that a variety of neurobiological factors participate in the formation and modulation of empathy. Cognitive empathy appears to be associated with dopamine and testosterone. By contrast, the social neuropeptide oxytocin and vasopressin, serotonin, and opioids seem to be more strongly implicated in affective aspects of empathy (Moul et al., 2018). However, the neurochemical correlates of empathy have not been replicated across

different human studies, possibly due to genetic heterogeneity and uncontrolled environmental variables. Moreover, empathy is dependent upon various social and contextual factors that moderate its induction and expression. Different brain regions appear to be associated with affective empathy (amygdala and ventral areas) and cognitive empathy (prefrontal cortical regions) (Bernhardt and Singer, 2012; de Waal and Preston, 2017; Decety, 2011b). Accordingly, the same neurochemicals may act very differently depending on the social context and the targeted brain areas (McCall and Singer, 2012). Using genome-wide association studies with a large number of cohorts (749 twin individuals), a recent study has identified a single genetic locus significantly associated with cognitive empathy in females, measured using the eyes test (Warrier et al., 2017). The closest gene to this SNP locus (rs7641347) is *LRRN1* encoding neuronal leucine-rich repeat protein 1. The *LRRN1* gene is highly expressed in the striatum but its role is largely unknown. Future research needs to investigate the functional significance of *LRRN1* in brain development and neural circuitry mediating empathy-related behaviors.

Relevant rodent behavior models have major advantages, allowing for the precise manipulation of neural circuits and single-cell resolution mapping of neuronal activity *in vivo*. Moreover, model organisms such as inbred mouse strains and isogenic lines enable experimental interventions that can establish causal mechanisms of gene action (Keum et al., 2018). To improve our understanding of the neurobiological bases of empathy, the behavioral phenotypes in the model systems should be addressed by integrating and re-evaluating current knowledge gained from human studies. Future studies using rodent models will offer insights into novel biological mechanisms of mammalian empathy that may be also shared by humans.

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