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Neural mechanisms of social empathy in the anterior cingulate cortex

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Abstract

Empathy is a prosocial behavior that perceives the emotional state of others, expresses similar perceptions that match those of others, and mediates different social behaviors. Empathic behaviors for pain and fear also exist in primates and rodents. In the past decades, the neural mechanisms of empathy have been defined as a result of various sensations and perceptions, such as visual and hearing stimuli, which cause mirror activations in brain regions, such as the insular, the inferior frontal, and the medial frontal cortices, among which the anterior cingulate cortex (ACC) has been identified as a core region of the neural network that is associated with the empathic activity in mammals. Most studies on the neural mechanisms underlying empathy have been based on rodent models, which allowed for single-cell resolution mapping of neuronal activity; moreover, the application of optogenetic techniques in rodent models has led to a deeper delineation of neural circuits. Here, we review the role of the ACC in two behavioral paradigms, pain and fear empathy, in rodents at the neuronal and neural circuit levels. Understanding how the ACC mediates empathic behavior in the brain will provide new targets in the treatment for neuropsychiatric disorders characterized by empathic disorders.

Keywords: Empathy, Anterior cingulate cortex, Mirror neurons, Somatostatin neurons, Neural circuits

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1. Introduction

Empathy is a cognitive process of perceiving and sharing an animal's emotional state, encompassing both affective empathy (emotional contagion and prosocial behavior), which retains primitive features across species, and higher-level cognitive empathy, which exists in human and nonhuman primates. Emotional contagion and imitative behaviors are considered to be the basis of empathy, including behaviors, expressions, or emotional states that match those of others, whereas cognitive empathy focuses more on the observer's understanding of emotions and the demonstrator's motivation to share[1,2].

The existence of cognitive empathy in rodents has been controversial, and there is no ideal way to analyze it directly. However, it has been argued that empathy can serve as a motivation to drive prosocial behavior among rodents[3-5]. Although it has been proposed that empathy serves as a motivation to drive prosocial behavior among rodents, the same motivation to share among demonstrators may also be based on receiving help from others to relieve their own pain, and thus prosocial behavior may indirectly reflect the animal's understanding of emotions.

Initially, empathy was thought to be unique to humans and primates, but subsequent studies have shown empathic behavior in various other mammals[2,6]. It follows that this conserved empathic behavior is crucial for population survival. In rodents, for example, when observers receive threat signals from the social group, they can react accordingly without experiencing them firsthand through passive defense or active helping behavior, which greatly enhances the survival rate of individuals and the stability of the society as a whole. A study has shown that the presence of social buffers caused stimulated rats to exhibit less freezing caused by fear[7], and thus the ability to empathize, allowing for enhanced social roles in the group and leading to better survival. In addition, many psychiatric disorders exhibited diminished or absent empathic abilities, such as autism and schizophrenia[8,9]. Therefore, the exploration of the neural mechanisms underlying empathic behaviors is gaining significance.

Rodents and other non-primates possess an observational learning capacity similar to that of humans, and this highly conserved ability underlies the retention of emotional empathy among animals across species[10]. As a result, behavioral neuroscientists have established empathic rodent models, which include numerous behavioral paradigms for both pain and fear empathy. In these paradigms, the neuronal activity in the brain can be artificially manipulated to further investigate the neural mechanisms underlying empathy. Many excellent literature reviews in the past have provided a relatively clear picture of the neural mechanisms of empathy[11,12]. These include the insular, inferior frontal cortices, medial frontal regions around the cingulate cortex (Brodmann's area [BA] 24, BA32, and BA6), as well as the amygdala, thalamus, putamen, caudate, and primary somatosensory cortex (SI, BA2), where brain activities are highly correlated with empathic activity.

Empathy depends on these neural networks. Beyond the core brain regions that are typically activated in pain empathy research (the insula and the anterior cingulate cortex [ACC]), other secondary networks with more specific processes may be revealed by the diversity of paradigms used. Pain empathy relies on a core network that is regulated by multiple secondary networks, which improves emotional sensitivity by promoting the integration of internal/external sensory information. These changes may eventually promote empathy in the subjects. The co-activation of the higher visual cortex and core region has been observed during empathy[13]. These evidence shows that the core area of empathy must have the ability to integrate external information, especially visual information. In an experiment based on a model of observational fear, when an opaque partition was used to replace a transparent partition, the freezing of observers significantly decreased[14]. This finding is similar to human beings. The social acceptance of visual stimuli is higher, and painful stimuli are more likely to activate the ACC/medial prefrontal cortex (mPFC)[15]. Some studies have shown dense bidirectional projection nerve fibers between the ACC and the visual cortex (VIS) by using virus tracing technology. ACC and VIS neurons have projections from other regions, and these regions constitute a tightly coordinated anterior cingulate area (ACA)-posterior parietal association cortex (PTLp)-retrosplenial cortex (RSP)-VIS network for visual processing[16,17]. These connection networks are the structural basis for the ACC to collect and process information, and as a result, the ACC becomes the core region of empathy activation. According to several studies, children or adolescents with autism have insufficient functional connectivity between the left anterior insula and bilateral visual cortex, but there is no evidence that insufficient connectivity could directly lead to changes in empathy[18]. In brief, it appears that the ACC is more capable of mediating empathy than the insula in the process of empathy.

Human neuroimaging experiments have shown that the ACC is activated when people experience distress or witness the distress of others and that the intensities of ACC activation are higher in individuals with greater empathy but lower in those with mental illnesses[19-21]. Studies in rodent models have shown that rodents without prior experience of footshock exhibited stronger freezing behaviors when they observed other rats receiving the same footshock[22]. In addition, increased expressions of immediate early proteins have been observed in some ACC neurons, and a decrease in passive defense behaviors has been observed following either destruction or functional inhibition of the ACC[14]. Therefore, the ACC might be considered as a core brain region in the neural network of empathy.

In the present review, we summarize the neural mechanisms at the neuronal, neural circuit, and synaptic plasticity levels in the ACC based on two different behavioral

paradigms: pain and fear empathy in rodents. The study of the neural mechanisms in the ACC during empathic behavior is of great importance for the exploration of new therapeutic targets for patients with psychiatric disorders.

2. Anatomical division of the anterior cingulate cortex

The human ACC is located in the anterior third of the cingulate cortex, surrounding the cephalic end of the corpus callosum (area [A]24a–c, A25, A32, and A33), while the midcingulate cortex (MCC) is located in the middle third of the cingulate cortex (A24a–c', A32', and A33'). The ACC can be divided into posterior ACC (pACC) and subgenual ACC (sACC) (Figure 1A). For rodents, there is a gradual shift in the nomenclature of the cingulate region. The cingulate cortex was initially divided into cingulate area 1 (Cg1) and Cg2, with Cg1 containing A24b and A24b' and Cg2 containing A24a and A24a'. However, a problem exists, in which the boundaries of the conventional cingulate cortex partition in rodents are perpendicular to those between ACC and MCC in primates[23], suggesting that Cg1 and Cg2 cover parts of what would be considered the ACC and MCC in other mammalians. It has been shown that there is a significant gap between rodent ACC and MCC in terms of anatomical structure, cellular architecture, connections to different brain regions, and the functions involved[24]. However, to the extent of differentiation, rodent ACC and MCC are functionally complementary and coordinated[25]. Therefore, in the last decade or so, some researchers have re-delineated the cingulate cortex of rodents by using a method that follows the distinction between the cingulate cortex of other mammals (MCC and ACC) to facilitate the study of brain function across species homologies. Rodent ACC ranges from A24a–b, A25, A32, and A33 (A33 is present in rats only), with A25 corresponding to subgenual ACC and A32 and A24a and b roughly coinciding with pACC.

Although the extent of the brain regions corresponding to rodent ACC has been re-normalized, there is still no way to clarify the boundary between the ACC and the PFC, especially the mPFC, because the prefrontal lobes of primates and rodents are fundamentally different in development. In general, the lateral prefrontal lobes of rodents, that is, prefrontal lobes with the granular layer, are underdeveloped[26], and researchers tend to use rodent PFC to refer to primate mPFC. It has been found that the ACC is homologous to the granule-free cellular structures in the mPFC, and therefore primate ACC is often treated as a subregion of the medial prefrontal lobe[27]. A large part of the current data on rodent prefrontal lobe comes from studies of the prelimbic (PL), infralimbic (IL), and cingulate regions[28]. Therefore, the definitions of the cingulate cortex, PFC, and mPFC remain ambiguous. As mentioned earlier, a nomenclature change has redefined these two regions and the anterior part of the cingulate cortex as the ACC, but because of the controversy, PL and IL are

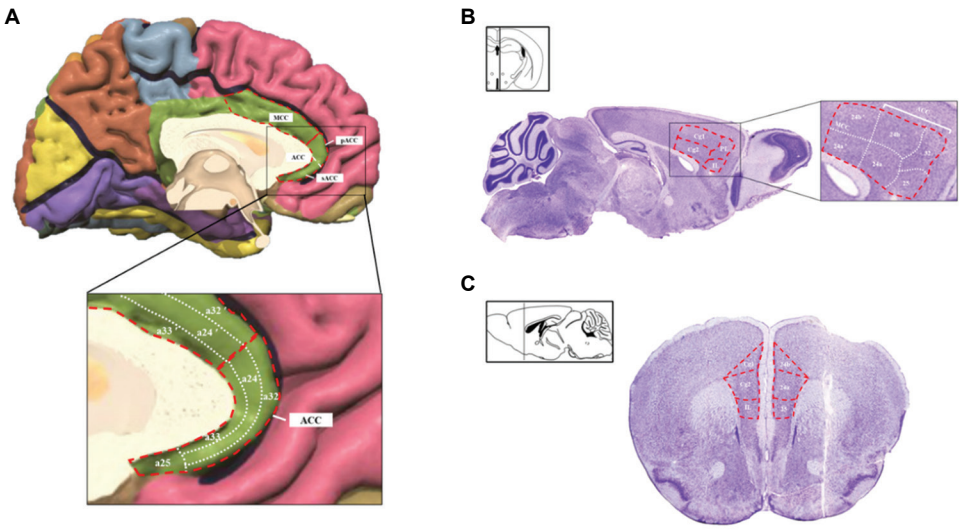

Figure 1. Anatomical division of the ACC. **(A)** The human ACC is located in the anterior third of the cingulate cortex, surrounding the cephalic end of the corpus callosum (area [A] 24, A25, A32, and A33), while the midcingulate cortex (MCC) is located in the middle third of the cingulate cortex (A24', A32', and A33'). The ACC can be divided into posterior ACC and subgenual ACC. **(B and C)** For rodents, the cingulate cortex was initially divided into Cg1 and Cg2, with Cg1 containing A24b and A24b' and Cg2 containing A24a and A24a'. Meanwhile, we define the ACC, IL, PL, and other areas of the mPFC as the ACC.

ACC: Anterior cingulate cortex; Cg1: Cingulate area 1; Cg2: Cingulate area 2; IL: Infralimbic cortex; MCC: Midcingulate cortex; pACC: posterior ACC; PL: Prelimbic cortex; sACC; subgenual ACC.

still considered by many as dorsomedial prefrontal cortex (dmPFC) and ventromedial prefrontal cortex (vmPFC)[27]. Regardless of the change in nomenclature, the ACC is a part of the prefrontal lobe according to anatomy and three-dimensional (3D) stereoscopic imaging. The whole prefrontal lobe is composed of several areas, including the ACC, secondary motor cortex (M2), PL, IL, orbital cortex (ORB), and agranular insular cortex (AI)[29-31]. Since the boundaries between the ACC and the surrounding adjacent areas are unclear and the localization of the ACC varies from experiment to experiment, the ACC, IL, PL, and other areas of the mPFC are defined as the ACC (Figure 1B and C).

3. Involvement of the anterior cingulate cortex in empathy

3.1. Anterior cingulate cortex and pain empathy

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. It is significantly influenced by environmental and psychosocial factors and a social cue that can be recognized and understood by others through emotional contagion in social interactions, thus inducing a corresponding state in oneself, which plays a positive role in self-defense or in triggering prosocial behaviors, such as empathy and helping[32,33]. Therefore, the social transmission of emotional information encoded by painful stimuli may be an important behavioral paradigm for studying the neural mechanisms of empathy. Pain empathy in mice, other than humans and nonhuman primates, has gradually gained recognition[34]. A study in mice has demonstrated that cagemates similarly exhibited pain sensation without pain stimuli under social conditions[35-37]; however, the underlying neural and molecular mechanisms of pain empathy are still largely unknown. The existence of pain empathy among rodents resulted in mechanical nociceptive sensitization in observers.

With the advancement of neuroimaging technology, the ACC has been accepted as the core brain region activated by pain empathy in humans, and its alternative pain production is positively correlated with ACC activity[38]. Although the lateral prefrontal lobe is neurodevelopmentally underdeveloped in rodents, the mPFC, including the ACC, is homologous across species, and therefore, combined with neuroimaging studies in humans, it would be inferred that the core region of pain empathy in rodents is still the ACC. In addition, when mechanical pain sensitivity is observed, neurons in the ACC are activated, and the activity of neurons in the dorsal horn of the spinal cord increases accordingly, suggesting that pain is real, rather than simply imitated. These experiments show that the ACC plays an important role in rodent pain empathy through a top-down regulatory mechanism during pain empathy[37,39].

Witnessing pain in others can produce or reinforce behavioral signs of injurious pain. However, individuals who are innately insensitive to injurious pain show a delayed response to empathic pain. This suggests that there may be overlapping neural representations between injurious pain and empathic pain[40]. The previous studies have suggested that pain-activated brain regions form a complex neuromodulatory network with different regions. The ACC is primarily involved in the production and modulation of the emotional component of direct pain[41].

3.2. Anterior cingulate cortex and fear empathy

In fear empathy, the perception of the emotions of others may further trigger empathic experiences of the self. Rodents have been found to acquire vicarious fear by sharing and perceiving threatening information in the environment, and many studies have also shown that the brain regions activated in empathic pain are also recruited in vicarious experiences associated with other aversive stimuli[42]. This observational fear can help mice avoid risks, and the presence of social buffers that allow for post-fear freezing in stimulated mice is behaviors that could better sustain the population.

Alternative fear is highly correlated with the characteristic empathy in humans[43]. Therefore, the rodent model of observational fear has become another important approach to further study the neuronal, circuit, and molecular mechanisms of empathy. In this model, the freezing behavior of observer mice was enhanced after observing the painful state of the demonstrator experiencing footshock and was consistent with that of the demonstrator, suggesting that the social transmission of fear or fear empathy does exist between rodents in this observational fear model. Further experiments revealed that the neural activity of the ACC increased during this observational learning process and the electrical stimulation of the ACC promoted alternative freezing behaviors; conversely, damage to the ACC reduced alternative behaviors[44]. All the above studies suggest that the ACC plays a very important role in fear empathy.

The development of optogenetic techniques has greatly facilitated the underpinnings of empathy mechanisms at the neuronal and neural circuit levels. It has been found that both ACC internal neurons and projection neurons play important roles in the formation of fear empathy and the ACC plays a dominant role in the neural circuitry. The downstream regions are still dependent on the ACC for encoding social information[45], indicating that the ACC

plays an important role in perceiving social fear as well as receiving and encoding social cues.

4. Neuronal types associated with empathy in the anterior cingulate cortex

Considering the versatility of the ACC and the universality of its connections with various brain regions, the neural mechanisms underlying empathy need to be further studied from the perspective of specific neurons. The previous studies have only focused on the functional connections between brain regions, neglecting the classification of neurons. Here, two types of neurons that mediate empathy in the ACC are discussed: Mirror neurons and somatostatin (SST) neurons (Table 1). As for whether there are other types of neurons that mediate empathy, more in-depth research is needed.

4.1. Mirror neurons in empathy

The ACC has proven to be important not only in the generation and processing of painful, negative emotions, but also in recognizing and perceiving the painful states in others. It has been speculated that the ACC might be the intersection for processing both empathic and painful emotions[46,47]. With the advancement of single-cell resolution techniques, a class of emotional mirrors has been identified within the ACC in A24 extending toward M2 and A32[19]. According to several studies, the specific types of ACC neurons are responsive to both the observation and the experience of overlapping emotions[48-50]. Similarly, the subtype ACC neurons can be activated by observational fear and classical fear[40,51]. More than 50% of the neurons that are activated by observational fear have mirror image properties, that is, they can be activated by both observational fear and pain[48]. Only a very small proportion of this group of neurons can be activated by both nociceptive and conditioned fear responses at the same time. The peaks of neurons have been shown to correspond to different conditions. In an algorithmic analysis of the peaks of neurons in the ACC after pain and observational fear tests, the alternative pain induced by observational fear did have the same code as the pain experience[52,53], but with an asymmetry of coding overlap, where neurons encoding ShockObs signals also encoded signals for pain, whereas neurons encoding pain signals did not necessarily encode signals for ShockObs[48]. The alternative activation of mirror neurons, which can also elicit pain behaviors, is explained through the results. The difference in the peak of mirror neurons under different signal stimuli provides greater selectivity in the activation of downstream neurons. These experimental results suggest that mirror neurons may be the biological basis for the overlap of the ACC in processing painful emotions and emotional empathy functions. Some experiments have even observed mirror neuron properties in ACC-basolateral nucleus of amygdala (BLA) neural pathway, with previously pain-activated neurons being

Table 1. Specific neurons and neural circuits associated with empathy

Neurons and neural circuits	Empathic behaviors	Methods and mechanisms	References
Mirror neurons	Pain empathy Fear empathy	A mirror neuron system located in A24b.	[48,54,55]
SST+neurons	Fear empathy	Associated with the recognition of emotional states Reducing inhibitory synaptic transmission in Nrxn3-dependent SST neurons enhances alternative fear responses	[46,58]
ACC-NAc pathway	Pain empathy	A neural circuit from the ACC to the NAc that mediates the rapid transfer of pain sensitivity and analgesia. A familiar social environment is important for pain empathy	[36,65,66]
ACC-BLA pathway	Fear empathy	ACC neurons rapidly alter basal firing rates during social fear transmission ACC input dominates the BLA encoding of social cues and subsequent behaviors	[44,45,71]
ACC-MDL pathway	Fear empathy	The optogenetic activation of the ACC to MDL reduces freezing behavior The destruction of ACC-MDL projection neurons delays the onset of the alternative behavior	[22,77]
ACC internal microcircuits	Fear empathy	Abnormal connections of interneurons induce severe deficits in social functioning SST + neurons in the ACC in the social transfer of fear	[46,94]

A24b: Area 24b/cingulate cortex 1; ACC: Anterior cingulate cortex; BLA: Basolateral nucleus of amygdala; MDL: Mediodorsal thalamic nucleus; NAc: Nucleus accumbens, Nrxn3: Neurexin 3; SST: Somatostatin

recruited preferentially in the social transmission of fear that follows[54], suggesting that mirror neurons may be directly involved in the presence of empathically activated neural circuits.

At the single-cell level, specific neuronal populations in the ACC have shown to create shared neural representations between direct pain and pain empathy, and the shared neural representations depend on a mirror neuron system (MNS) located in A24b, which is activated both when an action is actively performed and when it is observed[48,55]. Therefore, it has been hypothesized that mirror neurons might be involved in the encoding of painful emotional states transmitted during social interactions and might be the biological bases for the shared neural mechanisms of direct pain and pain empathy[56]. However, it is still uncertain whether mirror neurons are capable of encoding the emotional component of pain. Furthermore, although the neurons that are co-activated by empathy and pain have been identified in the ACC, the exact location of the overlapping neurons and whether they are involved in specific neural circuits remain unclear.

4.2. Somatostatin neurons in empathy

SST neurons release gamma-aminobutyric acid (GABA) ergic transmitters and affect the excitability of neighboring neurons to regulate the cortical state of certain regions[57]. Studies have shown that SST neurons in the ACC are associated with the discrimination of emotional states and the optogenetic inhibition of these neurons would eliminate social discrimination[58]. Therefore, it has been hypothesized that specific SST neurons in the ACC may be responsible for the emotional states of others in empathy and that social cognitive function depends on an intact balance of cortical neuronal excitation and inhibition[59]. Other experimental studies have shown that neurexin (Nrxn)3-dependent SST interneurons in the ACC can control the degree of socially transmitted fear in mice. SST neurons contribute to the hyperactivity of ACC pyramidal neurons by decreasing inhibitory synaptic transmission, thus driving enhanced alternative fear responses[46]. Therefore, the inhibition of ACC neurons through SST neurons can be said to regulate empathy-related behaviors. However, the molecular mechanisms underlying the mediation of SST neurons in the occurrence of fear empathy are unclear. Previous studies have shown that SST neurons with different molecules at different levels or in the same region may result in different function and distribution[60,61]. Therefore, further investigations are required to determine whether there are co-expressed molecules that dictate the specific roles of SST neurons in empathy.

5. Neural circuits associated with the anterior cingulate cortex in empathy

Both neural circuits from the ACC projecting to other nuclei and from other nuclei projecting to the ACC underly the neural mechanisms for social empathy. The neural circuits from the ACC projecting to other nuclei include ACC-nucleus accumbens (NAc), ACC-mediodorsal thalamic nucleus (MDL), ACC-BLA, and local neural circuits in the ACC (Figure 2). ACC appears to have a top-down regulation mechanism in the sensitization of social pain, but the mechanism in which sensitivity is regulated at the spinal cord level remains unclear. According to research, when noradrenergic neurons in the locus coeruleus (LC) are activated, the concentration of norepinephrine in the circulation increases, and alpha-1 adrenergic receptor blockers can be used to block mechanical pain hypersensitivity[62]. The previous studies have shown a bidirectional synaptic connection between the LC and the ACC, and the excitability of its neurons is regulated by the ACC[63,64]. Although it has been suggested that ACC-LC might mediate the top-down regulation of social pain, this hypothesis needs to be further investigated with photogenetic technology. In addition, a study has found that the inactivation of the lateral amygdala (LA) and the medial amygdala (MeA) can decrease emotional transmission and alternative learning in rats[12]. The LA-MeA circuit can connect social cues with environmental cues and use these environmental cues to guide social behaviors in fear conditioning. The stronger the functional connection of the neural circuit, the more the conditional freezing of social fear. According to Allsop *et al*., the inner amygdala path between the LA and the MeA might be the basis for linking the emotional content of social cues with other external prediction cues[45]. Since previous studies have observed a dense projection between the ACC and the amygdala, it is speculated that the ACC-MeA may be a potential neural mechanism for the ACC to adopt corresponding social behaviors after decision-making empathy. Furthermore, the MNS in the ACC may be the biological basis of the neural mechanism shared by pain and pain empathy; this remains to be further investigated.

5.1. Anterior cingulate cortex-nucleus accumbens pathway

Recent studies have shown that the neural circuit from the ACC to the nucleus accumbens (NAc) mediates the rapid transfer of pain sensitivity and analgesia in bystanders, but not the expression of mechanical pain sensitivity[35]. In a study, pain empathy was not detected in unfamiliar mice, which suggested the importance of a familiar social environment for pain empathy[65]. In addition, the

social transfer of pain was found to be more dependent on olfactory perception[36], while visual and auditory sensations contributed equally to the social onset of pain[66]. This is very different from the social transfer of fear, which relies on visual and auditory sensations[67]. Although the ACC encodes our own pain emotions and the emotional states of others[68], further research in rodents is needed to determine whether social cues transmitted through multiple sensory inputs can mediate pain empathy.

5.2. Anterior cingulate cortex-basolateral nucleus of amygdala pathway

The ACC and the amygdala are associated with observational learning and social decision-making. Studies have shown that the pharmacological inhibition of both the ACC and the BLA significantly decreased freezing behavior in observer mice[14,44,69] and there was a synchronous increase in the theta rhythm between the ACC and the BLA during the transmission of social fear in rodents[44,70]. In addition, ACC neurons have been observed to rapidly alter basal firing rates during social fear transmission[45,71]. Kim *et al.* have shown that the optogenetic inhibition of ACC-BLA projections did not affect the freezing behavior of observational fear but the inhibited fear memory in observational fear the next day[72]. The above findings suggest that the neural circuit from the ACC to the BLA is involved in the transmission and encoding of social fear information (Table 1), where ACC input dominates BLA encoding of social cues and subsequent observational fear memory but does not affect the re-expression of memory[14,45,71]. Post-long-term potentiation (LTP) activation depends on the de-silencing of silent synapses in the ACC-BLA pathway that occurs after observational fear[73]. However, no experiments have been conducted to demonstrate the extent to which this change in synaptic plasticity after observational fear affects behavior. Instead, combining observational fear experiment with inhibitory avoidance experiment (IA) has revealed a rapid disappearance of LTP after the IA test, along with observed rapid maturation of silent synapses and enhanced excitatory synaptic transmission, which facilitated the ACC-BLA circuit[74]. This is in contrast to previous studies, which found that the maturation of silent synapses is able to promote the expression of post-LTP[73].

5.3. Anterior cingulate cortex-mediodorsal thalamic nucleus pathway

Recent studies have found that the optogenetic activation of ACC to lateral MDL circuit reduces the occurrence of freezing behavior (Table 1), suggesting that ACC-MDL can modulate alternative freezing behavior. Studies have also found that rats that experienced foot stimulation were more likely to induce alternative freezing behavior[22,75,76]. In addition, resting state-functional magnetic resonance imaging (rs-fMRI) has revealed significantly enhanced regional connectivity of the ACC after electric shock, suggesting that the plasticity of ACC neurons may also be altered in rodents with the same painful experience[77]; similar to the preferential recruitment of hippocampal neurons in learning and memory with synchronous excitation in recall, there may also be a preferential recruitment of neurons activated by previous painful experiences when reactivated by observational fear. Determining the subpopulation of ACC-MDL projection neurons is thus necessary to further explore the mechanisms of empathy at the neuronal level.

Experiments in which rats were under observational fear stimuli followed by conditioned fear experiments have revealed enhanced conditioned fear, and the dynamic tracking of neurons activated by both types of fear has revealed that conditioned fear preferentially activated neurons in the CA1 region of the dorsal hippocampus, which were also activated by observational fear, suggesting that the overlapping activated neurons may have the ability to integrate both types of fear learning[78]. This may also be the neuronal basis of the alternative freezing behavior that is more likely to be evoked in foot-stimulated rats, suggesting that there may be a bidirectional positive feedback neural mechanism between observational and conditioned fears. As mentioned in the previous section, mirror neurons in the ACC have the dual property of encoding signals for pain signals and observational fears[48]. Mediodorsal (MD)-ACC projections, in turn, are involved in the development of pain emotions and sensations as well as in the enhancement of pathological states[79-81]. Although there is still no experimental confirmation of an overlapping relationship between activated ACC neurons and mirror neurons in this circuit, the speculation that the mechanism by which the formation of observational fear shares a neural loop with affection pain awaits further investigation.

Another interesting phenomenon is that the destruction of ACC-MDL projecting neurons delays the onset of alternative behavior but does not completely prevent it, so there may be other neural loops mediating alternative freezing behavior in rodents[77]. Uncertainty surrounds the ability of ACC interneurons and ACC neurons projecting to the MDL regulating alternative freezing behavior and whether there is a more precise microcircuit mechanism between projecting neurons and interneurons.

5.4. Local neural circuits in the anterior cingulate cortex

In the cerebral cortex, information processing relies on a highly interconnected microcircuit that is composed of excitatory glutamatergic pyramidal neurons and GABAergic inhibitory neurons[82]. The ACC is no exception; as a center of social interaction and information integration, the activation and inhibition of its internal pyramidal neurons depend not only on the direct projections of superior neurons, but also on the dynamic modulation and filtering of information by intermediate neurons[83]. The interaction of different neurons allows the ACC to process the input and output signals differently. Inhibitory interneuron dysfunction is more likely to cause dysregulation of neural homeostasis, thus resulting in psychiatric symptoms[84]. This includes both parvalbumin (PV)+ and SST+ neurons[85]. Results of a viral bundle pathway tracing have shown that both PV+ and SST+ neurons receive monosynaptic excitatory inputs from the BLA and midline and intralaminar thalamic nuclei (MITN)[16,86]. Fast-spiking PV+ neurons in the ACC mainly receive information filtered by the thalamus[83,87] and mediates feed forward inhibition around L2/3 pyramidal cells to control excitatory inputs to pyramidal neurons[88]. SST+ interneurons, on the other hand, target the distal dendrites of pyramidal cells and play a prominent role in regulating distal dendritic excitability[89]. SST+ interneurons also receive direct projections from L5 pyramidal neurons or the cortex. There is also a reciprocal inhibitory effect between these two interneurons[89,90]; an increase in PV neuron-mediated perisomatic feed forward inhibition of pyramidal neurons leads to a compensatory decrease in (SST+ neuron-mediated) dendritic inhibition[83,91]. The modulation of pyramidal neurons by interneurons is seen to be a dynamic balance[83,92]. However, less dendritic inhibition decreases the threshold at which pyramidal neurons are activated, lowering the neurons' capacity to filter information, and thus causing behavioral abnormalities. However, the effect of these two modes of inhibition differs in that an increase in input from PV+ neurons significantly decreases E/I, whereas the input from SST+ neurons to the distal dendrites of pyramidal neurons significantly increases E/I. As a result, the modulation of pyramidal neurons by interneurons is more flexible and dynamic, thus facilitating the processing of information from different brain regions. Recent studies have found that oxytocin can bind to postsynaptic oxytocin receptors on fast-spiking interneurons in the ACC and enhance inhibitory input to pyramidal neurons by lowering the action potential (AP) threshold and resting membrane potential of interneurons, and thus promoting depolarization of interneurons and inducing a decrease in the E/I ratio[93]. Therefore, the modulation of social cognition in rodents by ACC relies heavily on the modulation of these interneurons, that is, receiving remote projections from cortical or subcortical areas or receiving local neurotransmitter modulation to achieve a shift in excitatory or inhibitory effects on pyramidal neurons following information integration. This ability to dynamically regulate interneurons is necessary for social interaction, and deficits or abnormal connections of interneurons within the ACC can cause severe deficits in social functioning in animals, as shown in a study in which participants with high autistic traits showed elevated observational fear responses[94]. In contrast, when PV+ neurons are absent, there is a deficit in information filtering in the cortex that leads to autism[83,95]. This is consistent with the neuroanatomical findings of autistic individuals or model rats exhibiting PV+ neuron deficits[96,97]. Past experiments have revealed a unique role for specific SST+ neurons in the ACC in the social transfer of fear in rodents, but the inhibition of PV+ neurons did not alter the level of alternative freezing in experimental animals[46]. The possible reason for this is that PV+ neurons in the ACC have a weaker direct modulation of pyramidal neurons and are more involved in the modulation of SST+ neurons. However, it is undeniable that the microcircuits composed of PV+ neurons, SST+ neurons, and pyramidal neurons will be an important neurobiological basis for decoding social cues in the ACC and the balance of microcircuits homeostasis within the ACC is crucial for decoding the behavior of social cues, such as empathy (Table 1).

There appears to be a top-down regulatory mechanism in the ACC for social pain sensitization. More and more neural circuits are likely to be identified in the involvement of empathy with the development of neural modulations.

6. Clinical studies

Numerous clinical studies have confirmed that there are variations in the empathic abilities of patients with different neuropsychiatric disorders[98-100]. Patients with Alzheimer's disease (AD) and Parkinson's disease (PD) have significantly lower social emotion recognition ability than their respective caregivers; meanwhile, changes in emotion perception and empathy in patients with AD and PD have an impact on the perceived burden and depression among caregivers. Therefore, an early identification of the changes in empathic abilities in those patients may be effective for interventions in both patients and their caregivers[98]. As an other-oriented form of emotional empathy, empathic concern was found to be higher in AD patients than in controls. fMRI can be used to assist in the assessment of functional changes in empathy-related brain areas. A higher connectivity between the ACC

and periaqueductal gray matter predicts a longitudinal increase in empathic concern in AD patients. These results suggest that the acquisition of empathic concern may be a very early feature of AD pathophysiology, involving hyperconnectivity in a system that supports emotion generation and perception[101]. Therefore, an early identification of changes in empathic abilities may help in the early detection of neuropsychiatric disorders in some patients.

Patients with autism spectrum disorder (ASD) tend to exhibit reduced empathic abilities and impaired emotional empathy[102,103]. Imaging studies have demonstrated structural defects in the core empathic network in autism, such as reduced volumes of gray matter in bilateral superior temporal gyri (STG) and disturbances in resting-state functional connectivity between the ACC and prefrontal lobes[99]. However, another study has shown that patients with autism lack the ability to recognize, understand, and describe their own emotions. On that account, while ASD patients with alexithymia may experience emotional empathy differently, it should not be described as a lack of ability to empathize with emotions[104]. Since there is no standard, consistent definition of empathy, controversial views have emerged. Although there are consistent assessment scales and evidence of reduced empathy in people with autism from the data on Empathy Quotient (EQ), a 60-item self-report measure[8], the questions in such measures may be vague and imprecise as it is not clear to whom or which group one should be comparing with[105]. Further grouping of individuals with autism, and thus individualizing treatment, will be necessary. The use of different behavioral paradigms combined with neurophysiological markers measured by fMRI-based blood oxygen level dependent (BOLD) response for the assessment of ASD patients might be a good way[106]. As mentioned earlier, the MNS plays an important role in the perception of emotions and the imitative behaviors of individuals with ASD, which would further help to mediate empathic behaviors[107]. Future studies examining the effects of specific treatments on specific neurophysiological markers of MNS may reveal diagnostic subgroups of patients with ASD, with each subgroup requiring a specific treatment approach[106].

Central or peripheral oxytocin injections are clinically used to treat diminished empathic abilities in patients with neuropsychiatric disorders[108-110]. Previous studies in rodent models of observational fear have shown that intranasal oxytocin enhanced freezing behavior following observational fear transmission[54,111]. Recent studies have also shown that intranasal oxytocin administration might act on the MSN in the sensorimotor circuit of

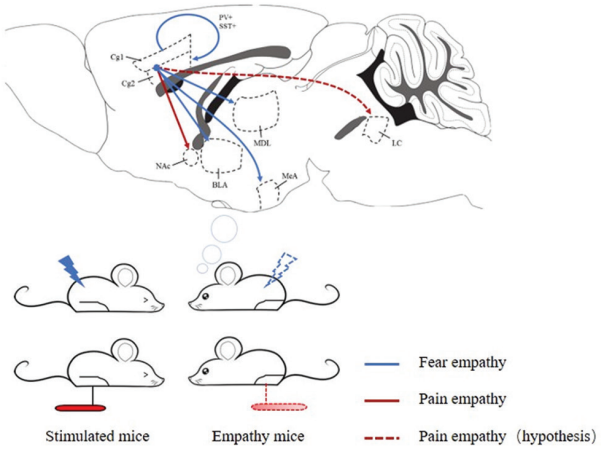

Figure 2. Neural circuits of ACC neurons projecting to the neural nuclei in pain and fear empathy. When empathy mice observe stimulated mice receiving click and mechanical tingling stimuli through visual, olfactory, and auditory sensory organs, there is activation of ACC neurons projecting to downstream nuclei through the stimulation of ACC-BLA, ACC-MDL, and ACC-MeA neural circuits as well as ACC internal microcircuits in fear empathic behaviors (blue arrows), while the ACC-NAc and the ACC-LC neural circuits mediate pain empathic behaviors (red arrows). The neural circuit from the ACC to the LC has been proposed to mediate pain empathy.
ACC: Anterior cingulate cortex; BLA: Basolateral nucleus of amygdala; Cg1/2: Cingulate cortex 1/2; LC: Locus coeruleus; MDL: Mediodorsal thalamic nucleus; MeA: Medial amygdala; NAc: Nucleus accumbens.

social perception and behavioral understanding[112]. Therefore, further investigations are required to determine whether oxytocin contributes to prosocial behavior by acting on ACC mirror neurons. In addition, it has been proposed that oxytocin release is potentially environment-dependent and might be involved in stress response, with a potential synchronous activation with cortisol; however, the two hormones are secreted independently, and stressor exposure is not the primary trigger for oxytocin secretion[113,114]. Oxytocin may bind to postsynaptic oxytocin receptors in fast-spiking interneurons in the ACC, significantly decreasing the action potential threshold and resting membrane potential of interneurons, promoting the depolarization of interneurons, resulting in a decrease in the E/I ratio, as well as enhancing the input from inhibitory to pyramidal neurons[93]. The above studies suggest that the modulatory neural circuitry of oxytocinergic projections to the ACC from other brain regions or subcortical nuclei may be involved in the treatment of neuropsychiatric patients with impaired empathic abilities.

7. Perspective significance

The development of fMRI has greatly facilitated the understanding of the neural basis behind empathy and depicted a vast neurofunctional network of various

neural circuits of the brain associated with empathy and brain areas that are causally associated with empathic behaviors, such as the ACC. Over the years, a wealth of data has been accumulated, which include not only the emotional states of their conspecifics, but also the prosocial behaviors driven by such shared experiences in rodents. The establishment of rodent empathy models has provided more possibilities to precisely modulate neural networks and delineate the connected neural circuits underlying empathic behaviors using techniques that monitor and manipulate neural activities at higher resolution. It also allows for thorough preclinical screening of potential therapeutic agents. This gives an opportunity to explore pharmacological treatments for certain psychiatric disorders with diminishing empathic capacity.

The current research still faces some challenges; although the development of optogenetic techniques is accompanied by a proliferation of studies on neural circuits, the majority of these studies still focus on inter-regional connections and are inactive in tracing the specific neurons behind the neural circuits. This may be a hindrance to the study of inter-brain regions. Therefore, future studies should focus on the neural representation of emotional state perception and behavioral decision in empathic behavior at the single-cell and population levels; further differentiate the neuronal types and map neuronal connectivity networks to further characterize the neural circuits underlying empathic behaviors.

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Conflict of interest

The authors declare that they have no competing interests.

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