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Review

Neural Basis of Observational Fear Learning: A Potential Model of Affective Empathy

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Observational fear learning in rodents is a type of context-dependent fear conditioning in which an unconditioned stimulus (US) is provided vicariously by observing conspecific others receiving foot shocks. This suggests the involvement of affective empathy, with several recent studies showing many similarities between this behavior and human empathy. Neurobiologically, it is important to understand the neural mechanisms by which the vicarious US activates the fear circuit via the affective pain system, obviating the sensory pain pathway and eventually leading to fear memory formation. This paper reviews current studies on the neural mechanisms underlying observational fear learning and provides a perspective on future research on this subject.

Conceptual and Empirical Similarities between Observational Fear and Affective Empathy

Human social interactions are greatly influenced by understanding the emotional states of others. Empathy is the ability to identify another person's feelings, thoughts, and intentions and to respond appropriately to these emotions (Bernhardt and Singer, 2012; de Waal, 2008). Empathy occurs when humans vicariously feel the emotions of others (emotional resonance), explicitly understand the target's states and their sources, and evoke affective communications that motivate these individuals to remove the sources of the target's distress and/or provide comfort, such as empathic concern, sympathy, or compassion (de Waal and Preston, 2017; Decety, 2011; Zaki and Ochsner, 2012). Empathy is not unique to humans, as many of its biological mechanisms are shared with other mammalian species. The capacity to share, appreciate, and respond to another'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 (de Waal and Preston, 2017; Panksepp and Panksepp, 2013). Recent evidence shows that rodents possess a remarkable affective sensitivity to the emotional state of others and show various forms of empathy-like behaviors, such as observational fear, emotional contagion of pain, consolation, and prosocial helping (Ben-Ami Bartal et al., 2011; Burkett et al., 2016; Jeon et al., 2010; Langford et al., 2006).

Humans and animals can acquire fears by observing conspecifics being subjected to aversive events. Observational fear is induced by social transmission of the demonstrator animal's affective state and should therefore be dependent on social perception and integrated social cognitive processes (Jeon et al., 2010; Olsson and Phelps, 2007). By definition, this process, in which recognition of the demonstrator's distress triggers fear in the observer, is a form of affective (emotional) empathy and is a critical factor in the transmission of social fear (Jeon et al., 2010; Keum and Shin, 2016; Kim et al., 2019; Olsson and Phelps, 2007; Panksepp and Lahvis, 2011). Indeed, studies in primates and humans have demonstrated that stronger vicarious fear responses were positively associated with trait empathy (Kleberg et al., 2015; Olsson et al., 2016). Similarly, in mice, the fear response in the observer tended to be greater when the demonstrator was a sibling or long-time mating partner than when the demonstrator was an unfamiliar mouse (Gonzalez-Liencres et al., 2014; Jeon et al., 2010; Pisansky et al., 2017). Together, these findings suggest that observational fear may constitute a fundamental feature of affective empathy (Olsson and Phelps, 2007; Panksepp and Lahvis, 2011).

Studies on observational fear are providing significant insight into the architecture and function of neural circuit mechanisms for socially driven emotional resonance (Allsop et al., 2018; Carrillo et al., 2019; Jeon et al., 2010). Importantly, sharing the emotional experiences of others can initiate both learning and empathic processes. In observational fear learning, observing the demonstrator's distress responses can serve as a vicarious unconditioned stimulus (US), resulting in an association between the affective experience of the observer and the specific environmental context (Chen et al., 2009; Jeon et al., 2010). Witnessing the suffering of others due to aversive experiences may evoke emotional contagion and can help the observer avoid potential risks, such as predation or poisoning (Heyes and Dawson, 1990; Kavaliers et al., 2001; Laland, 2004). Accordingly, there are many conceptual and empirical similarities between emotional learning through vicarious experiences and empathy (Debiec and Olsson, 2017), and the two may often be mutually reinforcing, suggesting that empathy and observational fear recruit brain systems that partly overlap.

The insights discussed in this review have been largely attained through recent studies on neural circuit mechanisms and dynamics during observational fear learning, such as the perception and processing of socially driven fear signals as well as their association with environmental cues (Allsop et al., 2018; Carrillo et al., 2019; Jeon et al., 2010; Keum et al., 2018). Focusing on brain structures associated with observational fear learning, including the cortex, amygdala, and thalamus, provides touchstones for comparing and integrating neural circuit data from rodents and humans. These insights into social fear

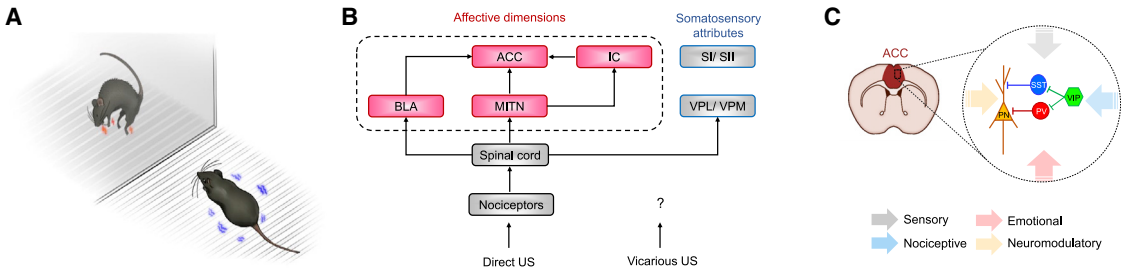

Figure 1. The Neural Circuit Mechanisms Underlying Observational Fear

(A) A diagram of the behavioral paradigm of observational fear. The observer mouse exhibits vicarious freezing behaviors while witnessing a demonstrator mouse receiving foot shocks through a transparent partition.

(B) A simplified scheme of the neural circuitry components involved in affective pain representation. The structures that are expected to be activated in the affective components are in red and those that are thought to represent the sensory attributes of the stimuli are in gray. ACC, anterior cingulate cortex; SI/ SII, cortical somatosensory areas S1 and S2; VPL/ VPM, thalamic ventroposterior lateral and medial nuclei; MITN, midline and intralaminar thalamic nuclei; BLA, basolateral amygdala; IC, insular cortex. The route through which the vicarious US enters the affective pain system is unknown.

(C) A schematic model of the basic ACC microcircuit processing incoming sensory, emotional, nociceptive, and neuromodulatory inputs in observational fear. PN, pyramidal neuron; SST, somatostatin; PV, parvalbumin; VIP, vasointestinal peptide.

transmission can help in understanding social cognition and empathy.

Involvement of the ACC in Empathy, Affective Pain, and Social Information Processing

Empathy and observational fear have been found to share neural substrates. In determining the emotional state of the demonstrator, the observer must activate the same neural networks in the brain as the demonstrator, a process called the perception-action mechanism (Preston and de Waal, 2002). Functional magnetic resonance imaging (fMRI) studies have confirmed that observing the affective states of others activates brain networks involved in the direct experience of these emotional states (de Vignemont and Singer, 2006; Keysers and Gazzola, 2007; Lamm et al., 2011; Singer et al., 2004). This has been interpreted as evidence for embodied models of emotional coding in empathy. In particular, the anterior cingulate cortex (ACC) is activated when observing pain delivered to others (Avenanti et al., 2005; Singer et al., 2004), suggesting that the ACC contains pain-responsive neurons that are activated by both self-pain and empathic responses. In humans, the affective pain processing system, which includes the ACC, the midline nuclei of the thalamus (the limbic thalamus), and the insular cortex, were shown to be involved in processing information about social cues that signal fear (Bliss et al., 2016; Lamm et al., 2011; Olsson and Phelps, 2007; Singer et al., 2004). Similarly, the activity of the ACC in mice is augmented under conditions of observational fear (Pisansky et al., 2017; Sakaguchi et al., 2018), with a well-delineated neural circuit spanning from the ACC to the amygdala apparently being critical for the delivery of information about social cues that signal threat (Allsop et al., 2018; Ito et al., 2015; Jeon et al., 2010). The organization of these vicarious social fear circuits in rodents seems to be similar to the core cortical circuits involved in empathy for pain or distress in humans (Bliss et al., 2016; Bushnell et al., 2013; Debiec and Olsson, 2017). In addition, the social hormone oxytocin was found to enhance vicarious freezing responses in rodents in a manner similar to its effect on empathy-related traits in humans (Abu-Akel et al., 2015; Pisansky et al., 2017; Rodrigues et al., 2009; Sakaguchi et al., 2018; Shamay-Tsoory et al., 2013). These findings support the hypothesis that empathy and observational fear share similar neural circuits, including the affective pain processing system (Figure 1).

The Thalamus-ACC Affective Pain Circuit in Observational Fear

Pain is both a sensory and affective experience. Direct pain experience activates a network called the pain matrix, which is divided into sensory-discriminative and cognitive-affective systems (Mouraux et al., 2011; Price, 2000). The sensory-discriminative system, which includes the lateral thalamus and the primary (SI) and secondary (SII) somatosensory cortices, was thought to process nociceptive input, including its intensity, localization, and quality. In contrast, the ACC and insular cortex are more important for encoding the emotional and motivational aspects of pain (Bernhardt and Singer, 2012; Bliss et al., 2016; Rainville et al., 1997). Ablation of the ACC regions alleviates the emotional suffering of patients with chronic pain, but it does not affect their ability to evaluate the intensity of their own pain (Yen et al., 2005). Similarly, chemical and electrolytic lesions of the ACC in rodents attenuate the affective component of the pain state, as shown by the reduction in conditioned place avoidance induced by a noxious stimulus (Gao et al., 2004; Johansen and Fields, 2004; Johansen et al., 2001; Qu et al., 2011).

Pain signals are relayed through the thalamus via the lateral and medial pain systems, with the thalamus being the essential relay of nociceptive inputs that are transmitted from the spinal cord to the cortex (Bliss et al., 2016; Price, 2000). The ACC receives nociceptive information from the midline and intralaminar thalamic nuclei (MITN) (Dum et al., 2009; Shyu and Vogt, 2009; Vogt, 2005). Electrophysiological studies have demonstrated that the mediodorsal (MD) and the centrolateral (CL) thalamic nuclei have nociceptive response properties that are reflected in neuronal responses of the ACC (Hatanaka et al., 2003; Meda et al., 2019; Vogt, 2005; Wang and Shyu, 2004; Yang et al., 2006). In addition, the parafascicular thalamic nucleus (PF), which forms reciprocal connections with the ACC, has been implicated in the processing and modulation of pain affects (Harte et al., 2011; Vercelli et al., 2003; Vogt, 2005). Ablation of

the PF relieves the emotional suffering associated with chronic pain in humans and reduces affective responses of animals to noxious stimulation (Saadé et al., 2007; Whittle and Jenkinson, 1995). In humans, the midline nuclei of the thalamus are also activated during both self-experienced pain and the observation of pain in others (Singer et al., 2004; Timmers et al., 2018). Studies in rodents have shown that mother-to-infant transmission of social fear is associated with increased neuronal activity in the MITN (Chang and Debiec, 2016). Inactivation of the MD or PF by lidocaine injections was found to impair observational fear learning, whereas inactivation of the lateral sensory pain system had no effect on behavior (Jeon et al., 2010). These findings indicate that social fear transfer depends on the affective, but not on the sensory, component of pain transmission.

ACC Activities Respond to Direct Pain and the Pain of Others, but Not to Fear

Despite evidence supporting the involvement of the affective pain system in social fear learning and empathy (Bushnell et al., 2013; Haaker et al., 2017; Jeon et al., 2010; Lamm et al., 2011), it is unclear whether the neural activity of the ACC involved in direct pain experiences supports observational fear. ACC neurons were recently reported to exhibit mirror-like activities and encode the pain of others using a code shared with first-hand pain experience (Carrillo et al., 2019). Using a tone-based observational fear paradigm in primed rats, which had previously experienced foot shocks, the ACC was found to show increased neural firing in rats experiencing their own pain and while witnessing other rats receiving foot shocks. Intriguingly, most of these neurons did not respond to a fear-conditioned sound (CS), but exhibited a maximal increase in spiking in response to distressed squeaking vocalizations and jumping behaviors of demonstrators. Thus, these findings suggest that the vicarious activation of ACC nociceptive neurons may trigger ''nocifensive behaviors'' in observers, such as orienting toward the danger and elevated freezing in response to a demonstrator's distress (Atsak et al., 2011; Carrillo et al., 2019). Further studies are necessary to determine whether the relationship is more causal, such as whether the experimental modulation of these first-hand pain neurons in the ACC drives or changes observational fear responses. However, these vicarious freezing responses could be induced only in shock-experienced, but not in naive, rats. Interpretation of these results on observational fear responses in primed animals is inherently complicated by the socially triggered memory recall of each animal's prior experiences with the same foot shocks. The association of these cellular responses to observational fear induced in naive animals, which would be more relevant to empathy, requires further examination.

Inputs Triggering ACC Activities during Social Fear Learning

The ACC is specialized in that it contains neurons that selectively respond to information pertaining to subjective experiences and the actions of others (Apps and Ramnani, 2014; Apps et al., 2016; Chang, 2013). The ACC is also activated when animals witness a conspecific receiving rewards or being exposed to aversive stimuli (Hillman and Bilkey, 2012; Jones and Monfils, 2016; Kavaliers et al., 2005). Both single-unit recording and neuroimaging studies suggest that this region computes information about other conspecifics (Apps et al., 2013; Behrens et al., 2009). The connection of the ACC with premotor and sensorymotor areas is activated when observers witness the actions of others, which may mediate imitation and mirroring the actions of others (Iacoboni and Dapretto, 2006). The ACC directly receives convergent sensory inputs from widespread areas of the cortex and sensory thalamic nuclei representing all sensory modalities (Fillinger et al., 2017, 2018; Hoover and Vertes, 2007; Mátyás et al., 2014; Zingg et al., 2014), suggesting that multisensory signals contribute to social fear learning. In particular, the ACC neurons form dense reciprocal connections with visual cortical areas, allowing preferential regulation of the perception networks for top-down behavioral control (Zhang et al., 2016; Zhang et al., 2014). Excluding visual cues was found to impair vicarious freezing responses, as when an opaque black partition prevented the observers from seeing the demonstrators (Jeon et al., 2010). Moreover, jumping by the demonstrator was found to be a salient behavior that evoked timely matched increases in ACC neuronal activities (Carrillo et al., 2019). Furthermore, a visual threat, consisting of a light looming overhead, activated the ventral midline thalamic nuclei. Activation of the thalamic nucleus to the ACC and medial prefrontal cortex (mPFC) circuits increased arousal and saliency-enhancing behaviors (Salay et al., 2018). Thus, these findings suggest that vicarious transmission of social fear is associated with activation of the visual system. Auditory information also appears to be an important component of social transmission of fear, with the presence of negative affect vocalizations (Carrillo et al., 2019; Kim et al., 2010; Pisansky et al., 2017) and the sudden onset of silence following the cessation of sound by demonstrators (Pereira et al., 2012) being important indicators of danger in a social setting. Taken together, these anatomical and functional studies further indicate that social information processing in the ACC may not simply reflect general cognitive control processes; they also support the notion that the ACC is implicated in evaluating and computing socially salient information about others.

Involvement of the ACC in Classical Fear Conditioning

The role of ACC in affective pain processing during fear conditioning (Bissière et al., 2008; Johansen and Fields, 2004; Tang et al., 2005) suggests that pain can result in the expression of conditioned fear, which is induced by the context or specific cues associated with the painful aversive stimuli. Bilateral microinjection of selective gamma-aminobutyric acid-A (GABA-A) receptor agonists or N-methyl-D-aspartate (NMDA) receptor antagonists into the ACC reduced the formation of conditioned fear memory (Bissière et al., 2008; Tang et al., 2005; Zhao et al., 2005), suggesting that ACC neurons are involved in pain-related fear memory (Bliss et al., 2016). In contrast, many other studies have shown that the ACC is not involved in the expression of fear in rodents. For example, no significant change in ACC activity was observed during the 24-h contextual fear memory (Frankland et al., 2004), and conditioned fear responses were normally expressed when ACC activity was suppressed by chemical or optogenetic manipulation (Allsop et al., 2018; Frankland et al., 2004; Goshen et al., 2011; Jeon et al., 2010; Jhang et al., 2018; Kim et al., 2012). Moreover, animals with ACC lesions showed normal expression of place aversion (Johansen and Fields, 2004), and the ACC was shown to be necessary for

the acquisition, but not the retrieval, of fear memory in observational fear learning (Jeon et al., 2010; Kim et al., 2012). Although the reasons underlying these discrepancies in ACC function remain unclear, several possibilities have been suggested. For example, because the cingulate cortex is a large structure, with multiple functions associated with distinct parts of its anatomical structure (Apps et al., 2016; Jones et al., 2005; Nevian, 2017), the discrepancies in ACC function may be due to targeting of different segmental regions in the ACC.

Involvement of the Amygdala Circuits in Social Fear Learning

The BLA in Emotional Valences and CS-US Associations

Studies in both humans and animals studies have shown that information about social signaling threats reaches the amygdala through distinct sensory pathways, suggesting the importance of the amygdala in acquiring fears through social learning (Debiec and Sullivan, 2014; Jeon et al., 2010; Knapska et al., 2006; Meffert et al., 2015; Olsson et al., 2007). The amygdala is activated when an individual observes another person experiencing negative consequences, similar to that expected when an individual directly experiences the same negative outcomes (Janak and Tye, 2015; Olsson et al., 2007). Animal studies of direct fear learning have shown that the amygdala is critical for the acquisition, storage, and expression of conditioned fear (LeDoux, 2000). The amygdala is also thought to be the site at which information about an emotionally neutral conditioned stimulus (CS), such as a tone or context, becomes associated with information about the aversive unconditioned stimulus (US). Specifically, the basolateral nucleus of the amygdala (BLA) is regarded as one of the most fundamental neural structures for encoding negative and positive affective valences (Janak and Tye, 2015; Olsson and Phelps, 2007). The BLA is important for processing and encoding social recognition memories (Debiec and Olsson, 2017; Debiec and Sullivan, 2014; Felix-Ortiz and Tye, 2014; Tanimizu et al., 2017). Furthermore, the BLA exhibits increased activity during social transfer of information (Debiec and Sullivan, 2014; Knapska et al., 2006).

The ACC-BLA Circuit during Observational Fear

The ACC and BLA are reciprocally connected, and their frontal projections to the amygdala have been extensively studied in their "top-down" regulation of behavioral responses to emotionally relevant stimuli (Apps et al., 2016). Coactivation of the ACC and the amygdala supports the processing of vicarious rewards and emotional resonance in rats (Amemiya et al., 2016), monkeys (Livneh and Paz, 2012), and humans (Seara-Cardoso et al., 2016). In mice, the neuronal activities of the ACC and lateral amygdala (LA) during observational fear conditioning were highly synchronized at theta rhythm frequencies of 4–8 Hz (Jeon et al., 2010). Although, whether this synchronized oscillation is indeed related to the hippocampal theta rhythm or plays any role in the acquisition of observational fear remains to be determined, this finding suggests that an interactive communication through the cortico-amygdalar connection may be critical for social fear transmission. Subsequent pharmacological inactivation showed that ACC activity was required for acquisition, but not for recall, of vicarious fear, whereas LA activity was necessary for freezing during both observational fear conditioning and contextual recall (Jeon et al., 2010). These findings indicate that the ACC encodes affective and cognitive information required to induce social fear, but not for retrieval of its fear memory. How the ACC interacts with and drives the BLA to express fear response needs to be studied further.

A study of a tone-based observational fear conditioning in mice primed with prior foot shocks of its own found that ACC neurons in observer mice responded to auditory cues that signaled shocks to demonstrator mice (Allsop et al., 2018). This study demonstrated that, during the conditioning, BLA-projecting ACC neurons exhibited earlier firing rate changes when compared to the BLA, which was interpreted to mean that BLA neurons were dependent of ACC inputs. However, the function of those ACC neuronal activities is not clear because their article inhibition of the ACC-BLA circuit during conditioning did not affect the observational fear response, and an interpretation of its effect on the recall was limited due to a high baseline freezing in the mice. Hence, it needs to be tested whether the increased firing of the BLA-projecting ACC neurons has a role in this observational fear paradigm utilizing mice with a prior foot shock as an observer.

In addition to the neuronal activities elicited during observational fear conditioning or immediately afterward, lasting neuronal adaptations between the ACC and BLA were found after observational fear conditioning. Observational fear learning enhanced the NMDA receptor-mediated synaptic transmission in the mPFC (prelimbic/ACC) to BLA synapses (Ito et al., 2015). The synaptic transmission was measured 24 h after observational fear *ex vivo* by recording postsynaptic responses in BLA neurons during optogenetic stimulation of ACC axons expressing channelrhodopsin. Similarly, when synaptic response was evoked by blue light stimulation of the mPFC axons and recorded from BLA principal neurons, an enhancement of long-term potentiation (LTP) was observed 18 h after observational fear learning (Ito and Morozov, 2019). However, the enhanced LTP was occluded when the mice were tested for passive avoidance behaviors the next day after observational fear conditioning. The passive avoidance behavior assay is also dependent on the recall of context fear memory (Malin and McGaugh, 2006). Since the ACC is not required for recall of fear memory (Goshen et al., 2011; Jeon et al., 2010; Jhang et al., 2018; Kim et al., 2012), as discussed above, it is yet to be determined what role this plasticity change in the ACC-BLA synapses plays in observational fear learning.

A neuronal population in the BLA was recently found to encode the aversive qualities of pain perception (Corder et al., 2019). This BLA nociceptive ensemble transformed emotionally inert nociceptive information into affective signals necessary for motivational protective pain behaviors. Since the evidence supports the involvement of the affective pain processing in observational fear, further studies are required to determine whether BLA neurons provide the ACC with aversive information gathered from social cues by the demonstrators during the acquisition of observational fear in naive observer mice with no prior shock experience.

Other Amygdala Circuits Involved in Observational Fear

In rodents, chemosensory pathways transmit the largest proportion of social information. Although the main and accessory

olfactory bulbs do not project to the ACC, their downstream targets send axons to the ACC, but these are relatively sparse (Fillinger et al., 2017; Hoover and Vertes, 2007). Olfactory information from the accessory olfactory bulb is sent directly to the medial nucleus of the amygdala (MeA), where it is further processed and relayed to hypothalamic regions that control innate emotional, reproductive, and social behavior (Choi et al., 2005; Lehman et al., 1980; Li et al., 2017). During observational fear learning, the MeA was required for a social cue emitted by a conspecific demonstrator, with the BLA-MeA circuit mediating the ability to link the affective content of social cues with other external and environmental predictive cues (Twining et al., 2017).

Involvement of the Insular Cortex in Fear Conditioning and Pain Perception

The range of overt behavioral similarities in observational fear has suggested that direct and social fear partially share neural mechanisms (Debiec and Olsson, 2017; Olsson and Phelps, 2007). However, despite some overlap in brain regions involved in direct and observational fear conditioning, the flow of information in the brain differs between the two (Lindström et al., 2018). A direct comparison of information flow and connectivity within this aversive learning network showed that the amygdala was the input area to the network for direct fear conditioning, whereas the insular cortex was the most likely input region for social US processing (Lindström et al., 2018). The insular cortex is involved in the evaluation and experience of emotion and interoceptive awareness, and its activation is nearly ubiquitous in studies of pain (Craig, 2009; Lamm et al., 2011; Peltz et al., 2011; Singer et al., 2009). Nociceptive information is also conveyed to the ACC through the insular cortex (Bliss et al., 2016; Tan et al., 2017). Insular cortex activity was necessary for the aversive properties of an US during direct fear conditioning and insular-amygdala circuits played a role in evaluating aversive painful events (Berret et al., 2019). Furthermore, inhibition of the insular cortex or blockade of insular oxytocin receptors disrupted the social affective behaviors during social affective preference tasks in rats (Rogers-Carter et al., 2018).

Additionally, the periaqueductal gray (PAG) has also been implicated in both nociceptive and social fear learning (Chang and Debiec, 2016; Haaker et al., 2017). Blocking the endogenous opioid circuits, which relieves self-experienced pain, was found to enhance observational fear learning through changes in activity within the amygdala, midline thalamus, and PAG (Haaker et al., 2017). Taken together, human neuroimaging data and rodent models of empathy suggest that the medial affective pain system involving the ACC, insular cortex, amygdala, and MITN is active during both self-experienced pain and the observation of pain. These overlapping activities are thought to enable inference of another's pain, facilitating empathy (Craig, 2009; Decety, 2011; Haaker et al., 2017).

Cortical Microcircuitry in Observational Fear

The cortex possesses various neuronal properties due to the presence of numerous types of excitatory glutamatergic and inhibitory GABAergic classes. The three main functionally distinct classes of interneurons consist of neurons expressing vasoactive intestinal peptide (VIP), somatostatin (SST), and parvalbumin (PV) (Huang and Zeng, 2013; Kepecs and Fishell, 2014). Different interneurons constitute important elements of dynamic circuit motifs, enabling input-output transformations and distinct computational operations in the cortex (Tremblay et al., 2016). Cortical inhibitory neurons display behaviorally activated responses and have been described as functional units (Bandler et al., 2017; Harris and Shepherd, 2015). SST interneurons in the ACC bi-directionally control the degree of socially transmitted vicarious fear (Keum et al., 2018). Vicarious freezing responses were enhanced by decreasing the inhibition of ACC pyramidal neurons via the optogenetic suppression of SST neurons and impaired by activation of SST neurons. In contrast, reduced inhibition of pyramidal neurons via the photoinhibition of PV neurons had no effect on behavior. Because PV neurons generally target the somas of pyramidal neurons, whereas dendrite-targeting SST neurons exert distal inhibition to control incoming inputs to pyramidal neurons (Gentet et al., 2012; Tremblay et al., 2016), these findings suggest that SST neuron-specific inhibitory mechanisms in the ACC microcircuit are responsible for vicarious transmission of social fear. Following observational fear learning, *ex vivo* slice recording showed that the inhibitory drive was shifted from the soma to the distal dendrites of pyramidal neurons in the ACC (Liu et al., 2017). It is yet to be determined what physiological function this plasticity has.

The cortex is modulated by its own local microcircuit dynamics as well as by the characteristics of long-range inputs that fine-tune local circuits for types of information processing (Harris and Shepherd, 2015). GABAergic microcircuits are therefore likely to mediate input and output connectivity with other brain areas. Retro-tracing circuit mapping analysis using rabies virus showed that all types of inhibitory and excitatory neurons in the ACC receive monosynaptic excitatory inputs from the BLA and MITN (Ährlund-Richter et al., 2019; Zhang et al., 2016). Whereas BLA output neurons are predominantly glutamatergic (Ährlund-Richter et al., 2019), BLA stimulation typically silences pyramidal neurons in the mPFC by exciting PV neurons, indicating that feed-forward inhibition regulates the flow of information from the BLA to the mPFC (Dilgen et al., 2013). In addition, SST neurons in the mPFC were shown to be robustly activated by BLA inputs, providing a parallel interneuron pathway for feed-forward inhibition (McGarry and Carter, 2016). Thalamic MD neurons directly excite PV neurons in the ACC (Delevich et al., 2015), with this MD-ACC circuit playing a modulatory role by enhancing state-specific coding of noxious stimuli in the ACC during chronic pain (Meda et al., 2019). Moreover, the ACC is innervated by dopaminergic, serotonergic, cholinergic, and adrenergic fibers that originate in subcortical regions (Chandler et al., 2013). Intriguingly, dopamine D2-receptors in the ACC were found to be necessary for observational fear learning, whereas experimentally increased serotonin levels disrupted vicarious freezing responses in mice (Kim et al., 2014). Altogether, because distinct cell types build local circuitry structures, enabling computational operations in cortical networks (Harris and Shepherd, 2015), differential functional connectivity of long-range inputs from the BLA, MITN, or neuromodulatory subcortical regions to ACC microcircuits appear to be crucial for emotional or cognitive operations during observational fear.

Limitations

Despite these important behavioral and neurobiological similarities, comparisons of affective empathy in humans and mice remain challenging. Although there is significant conservation of brain structures and genes across species, empathic abilities in humans, which are characterized by emotional, cognitive, and/or social context, may possess some aspects unique to humans, making them difficult to model in laboratory animals. It is unclear whether the vicarious social fear observed in rodents is indicative of affective empathy, as it has not been determined whether rodents are capable of self-awareness. Thus, vicarious freezing behaviors in rodents may be emotional contagion without implicit knowledge of the source of distress. However, empathy arises from bottom-up processes that are shared across species, such as motor mimicry, emotional contagion, and state matching (de Waal and Preston, 2017; Decety, 2011). Furthermore, affective arousal and emotional contagion prompt efforts in rodents to alleviate the distress of a conspecific, such as consolation or prosocial helping behaviors (Ben-Ami Bartal et al., 2011; Burkett et al., 2016). Therefore, emotional contagion and its related bottom-up, sensory-driven "primitive" forms of empathic processes may be the basis for building more advanced empathic behaviors (de Waal and Preston, 2017; Decety et al., 2012; Goubert et al., 2005; Panksepp and Panksepp, 2013).

Further Questions

The neural substrate for empathy seems to overlap with neural circuits for observational fear. During observational fear learning, social information appears to be processed in the ACC and transmitted to the BLA, where it substitutes for the representation of the US. Social information can feed into these circuits at several different "entry points," such as the affective pain networks, which include the insular cortex and the MITN (Bliss et al., 2016; Bushnell et al., 2013; Haaker et al., 2017; Lindström et al., 2018). Thus, the content of the social information appears to be more pain-related than fear itself. The vicarious pain experience may mobilize the affective pain matrix, with activation of this pathway feeding into the emotion of fear.

A more detailed, mechanistic understanding is needed of how these brain areas integrate social cognitive information during observational fear behaviors. Future studies are required to determine the flow of social US information among the multiple functional neural circuits involved in observational fear. One immediate question may be the mechanism by which social information obtained through, for example, the visual system-mediated perception network, feeds into the affective pain matrix (Zhang et al., 2016, 2014). Despite the involvement of the ACC in an organism's ability to learn socially transmitted information, it is unclear whether the ACC contains a pain-specific sub-circuit and how the affective pain signal is integrated with other US information to drive socially evoked vicarious fear responses. Recently developed molecular and genetic tools enable the recording and manipulation of endogenous neural activity patterns associated with behaviors in selected neuronal populations. Because complex information is likely to be obtained from multiple brain regions during observational fear behaviors, recently developed *in vivo* tools for synchronous multi-site recording or circuit-specific neural ensemble imaging are likely to provide information about the broader circuitry (Cai et al., 2016; Kim et al., 2016). Additionally, little is currently known about the neuronal and synaptic mechanisms mediating behavioral factors that promote social transmission of fear. Both human and animal studies of empathy need to take into account many factors that affect a subject's emotional responses, including social stress, hierarchy, prior experience, the nature of the stimulus, and the familiarity (Atsak et al., 2011; Gonzalez-Liencres et al., 2014; Keum et al., 2016; Sanders et al., 2013; Yusufishaq and Rosenkranz, 2013). Future studies should establish neural mechanisms underlying how these factors affect socially transmitted empathic fear.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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