Neural mechanisms necessary for empathy-related phenomena across species

Paradiso, E.; Gazzola, V.; Keysers, C.

DOI
10.1016/j.conb.2021.02.005

Publication date
2021

Document Version
Final published version

Published in
Current opinion in neurobiology

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Neural mechanisms necessary for empathy-related phenomena across species

Enrica Paradiso[1], Valeria Gazzola[1,2,a] and Christian Keysers[1,2,a]

Abstract

The neural basis of empathy and prosociality has received much interest over the past decades. Neuroimaging studies localized a network of brain regions with activity that correlates with empathy. Here, we review how the emergence of rodent and nonhuman primate models of empathy-related phenomena supplements human lesion and neuromodulation studies providing evidence that activity in several nodes is necessary for these phenomena to occur. We review proof that (i) affective states triggered by the emotions of others, (ii) motivations to act in ways that benefit others, and (iii) emotion recognition can be altered by perturbing brain activity in many nodes identified by human neuroimaging, with strongest evidence for the cingulate and the amygdala. We also include evidence that manipulations of the oxytocin system and analgesics can have such effects, the latter providing causal evidence for the recruitment of an individual's own nociceptive system to feel with the pain of others.

Addresses

[1] Netherlands Institute for Neuroscience, KNAW, Amsterdam, Netherlands

[2] Brain and Cognition, Department of Psychology, University of Amsterdam, Netherlands

Corresponding authors: Gazzola, Valeria (v.gazzola@nin.knaw.nl); Keysers, Christian (c.keysers@nin.knaw.nl)

[a] Contributed equally.

Current Opinion in Neurobiology 2021, **68**:107–115

This review comes from a themed issue on **The Social Brain**

Edited by **Hailan Hu** and **Michael Brecht**

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.conb.2021.02.005

Introduction

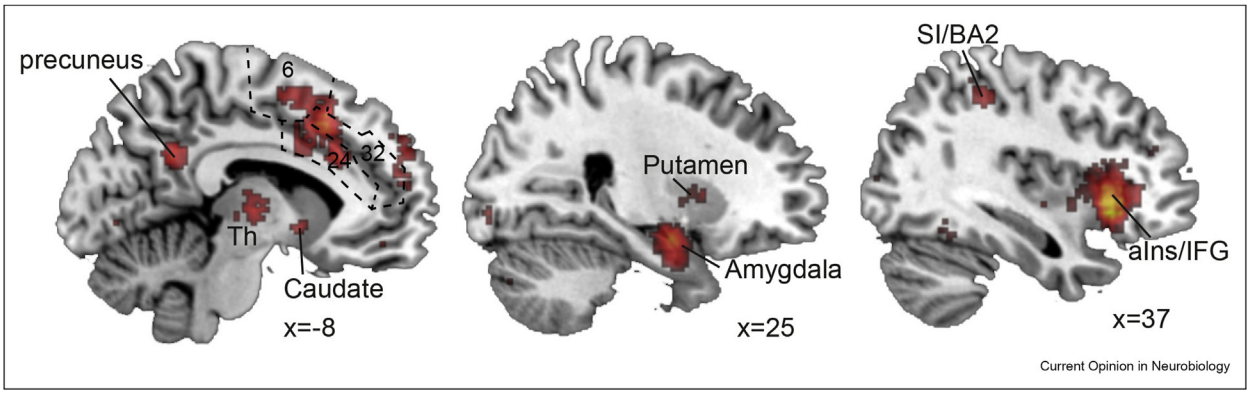
Although people disagree on what empathy exactly is, most agree it includes feeling what another person feels. Over the past two decades, a wave of functional magnetic resonance imaging experiments showed that humans activate a network of brain regions involved in their own actions, sensations, and emotions while witnessing the actions, sensations, and emotions of others [1] (Figure 1), including the insula, inferior frontal gyrus, medial frontal regions around the cingulate cortex (BA24, BA32, and BA6), [2**] as well as the amygdala, thalamus, putamen, caudate, and primary somatosensory area SI (BA2). Activity in these networks is stronger in more empathic [1] and reduced in psychopathic individuals [3], leading many to suspect this network is what is causing us to feel what others feel.

Neuroimaging studies alone however remain correlational and cannot establish that activity in the nodes of this network causally contributes to empathy-related phenomena. The question we must ask is would modifying brain activity in these nodes alter empathy-related phenomena? With most of these nodes too deep to noninvasively neuromodulate in humans, this critical question may thus be close to untestable.

However, over the past years, behavioral neuroscientists have started developing paradigms that make empathy-related phenomena measurable in rodents and primates, in which brain activity can be precisely altered everywhere in the brain [4]. To address the burning question of causality, here we will thus sieve through the literature of the past couple of years in search of studies in humans, rodents, and monkeys that can help us establish whether some of these nodes really do contribute to empathy-related phenomena.

The term empathy is used by different scholars to refer to various reactions to other individual's feelings [5,6]. It may refer to the cognitive ability to perceive other people's thoughts, the affective tendency to experience the emotions of others, or the motivation to help. Importantly, these facets of empathy are subjective experiences (recognition, emotions, and motivations) that are different from the behaviors through which we measure them. For instance, emotional contagion is 'feeling the emotions of another' and the behavior we observe (e.g., freezing in rodents) is only an indirect means to infer such emotion sharing. Such indirect means are all we can often access in rodents and nonhuman primates who cannot verbalize how they feel.

Figure 1



Results of a neurosynth meta-analysis identifying regions with activity in studies including the keyword Empathy (uniformity test). Numbers in green represent the approximate position of three distinct cortical midline structures that include the supplementary motor cortex (BA6) and cingulate cortices (BA24 and BA32) that have homologs in rodents and nonhuman primates (refer the study by van Heukelum et al. [2]). BA, Brodmann area; Th, thalamus; aIns, anterior insula, IFG, inferior frontal gyrus, SI, primary somatosensory area.

Many scholars additionally argue for distinguishing feeling with and for another individual [7*]. If a rat freezes upon witnessing another receive shocks or stops to use a lever shocking another, is it because the witness is scared to be shocked themselves or because they worry about their cage mate [7,8**]? Although some studies have started to explore this distinction [7,9], neuromodulation data remain scarce and the interpretation of that data difficult.

Here, we thus harness that altering brain activity can change the degree to which the behavior of an observer is influenced by the emotional state of another to examine the causal relationship between brain activity and empathy-related phenomena as operationally defined in Box 1. We believe it prudent to remain agnostic to whether changes in targeted brain activity alter responses for or with the other.

Prefrontal and cingulate regions

Emotional contagion and vicarious learning

Inactivation of right but not left anterior cingulate, specifically area 24b (A24b), of observer mice reduces emotional contagion (observers freeze less while witnessing the demonstrator receive foot shocks) and vicarious learning (observers freeze less in the environment in which they had witnessed the demonstrator receive shocks the previous day) [10], while electrostimulation enhances both phenomena [11]. Similarly, deactivating A24a/b in rats reduces freezing while witnessing another rat receive shocks, leaving unaltered freezing while listening to a fear conditioned tone (CS+) [12**], suggesting A24a/b is specifically necessary for the social transmission of danger information [13–15]. Interestingly, A24a/b is also where emotional mirror neurons, activated by both the self-experience of pain and witnessing pain in another, have been found [12,15]. Intriguingly, deactivating A24a/b in a witness rat indirectly also reduces freezing in the demonstrator akin to social buffering [7]. An important role in emotional contagion has also been assigned to a subset of interneurons in the anterior cingulate cortex (ACC), somatostatin-expressing (SST+) interneurons, whose optogenetic silencing increases and activation decreases vicarious freezing [16**]. Another group of studies examined the reaction of rats to witnessing a demonstrator hear a previously shock-associated CS+. In these studies, the witness thus does not directly witness the pain of the demonstrator but its CS+ triggered fear. Deactivating the ACC also reduces this emotional contagion (vicarious freezing while the demonstrator is exposed to CS+) [14] and vicarious learning (freezing when the witness hears the CS+ alone two days later) [13]. Chemogenetic inactivation of A24b also impairs emotional contagion as measured by a change of pain threshold when a witness is exposed to a conspecific undergoing alcohol withdrawal [17]. Moreover, optogenetic inhibition of A24 neurons activated by interacting with a conspecific in pain prevented observer mice from developing mechanical hypersensitivity [18**]. Antagonizing oxytocin receptor and ethanol infusion in A24a, respectively, reduces and enhances observational fear responses [15].

Human patients with damage to the inferior frontal cortex (IFC) report to experience the emotions of others less than controls [19] and noninvasive transcranial direct current stimulation (tDCS) over IFC also alters how much emotion human observers perceive when witnessing people's touch [20].

Box 1. Operational definitions for empathy-related phenomena

Emotional contagion: Emotional state matching between individuals. Test: exposing an observer to a demonstrator in a particular emotional state and showing that the state of the witness comes to resemble that of the demonstrator.

Emotion recognition: The ability to recognize that a demonstrator is in a particular emotional state. Proof: evidence that a witness can differentiate different emotional states in others. Although emotion recognition can occur in the absence of emotion sharing, we include it as a phenomenon of interest because it dovetails with certain understandings of empathy as 'understanding what other people feel'.

Vicarious learning: learning the valence of a stimulus by association with the affective reactions of another. Proof: showing an emotional reaction (e.g., freezing) to a formally neutral stimulus (e.g., tone) that has acquired significance through pairing with the emotional reaction of another.

Social harm aversion: a motivation triggered by causing harm to another individual. Proof: the frequency of a behavior is reduced if the behavior is associated with harm to others.

Other regarding preference: a motivation triggered by causing rewards to others. Proof: the frequency of a behavior is increased if the behavior is associated with rewards to others.

Motivation to liberate: a motivation to freeing another from an aversive situation, often also called 'rescuing behavior'. Proof: an animal repeatedly works to free a trapped other.

Consolation: a motivation to increase positive interactions with a distressed conspecific. Proof: an animal increases grooming toward a stressed compared with a nonstressed conspecific.

Emotion recognition

In mice, optogenetic inhibition of cingulate area 32 (A32) SST+, but not parvalbumin (PV+) neurons, reduced affective state discrimination as measured by a preference for a mouse in a positive or negative affective state over a mouse in a neutral emotional state [21**]. Optogenetic activation of A32 SST+ neurons when a mouse approaches another is sufficient to increase exploration of that mouse [21]. In humans, lesions in a number of prefrontal regions interfere with emotion recognition: in lateral prefrontal areas including the inferior frontal gyrus [22], as well as in ventromedial and orbitofrontal regions [23,24]. Noninvasive manipulations have also been reported to alter emotion recognition, including lateral tDCS [25], anodal tDCS over orbitofrontal or IFC [26,27], and transcranial magnetic stimulation over dorsomedial prefrontal cortex [28].

Harm aversion

If faced with a choice between two levers delivering food, one of which also delivers a shock to another rat, most rats avoid the shock lever, thereby showing evidence of social harm aversion. Deactivating cingulate A24 reduced this harm aversion [8]. Anodal tDCS stimulation over the medial PFC increased human willingness to invest money to prevent pain to someone else [29].

Other regarding preferences

Excitotoxic lesions to areas A24 and A32 reduce the willingness of monkeys to learn to choose options that reward others over option that reward no one [30*], showing this region is important to associate value to the reward of others [31]. On an iterated prisoner's dilemma game, perturbation of the dorsal ACC in monkeys also reduces reciprocation [32]. In humans, focal damage of the ventromedial PFC reduces the amount of money given to a confederate that was suffering compared with one that was not [33], whereas anodal tDCS stimulation of orbitofrontal or dorsomedial PFC increases the repayment ratios in a trust game [34] and altruistic behavior in a dictator's game [35].

Motivation to liberate and consolation

In voles, oxytocin receptor antagonist (OTA) or $GABA_A$ receptor antagonist infusion in ACC impairs consolation behaviors [36,37], whereas OTA administration in A24b delays the acquisition of helping behavior in rats [38].

Insula

Emotional contagion

In mice, chemical inactivation of the insular cortex reduces the nociceptive response induced by cohabiting with a mouse in chronic pain [39].

Emotion recognition

Rats approach stressed juveniles (that received a foot shock) but avoid similarly stressed adults [40*], suggesting an ability to differentiate emotional states. Photoinhibition of the insula and blocking its oxytocin receptors interferes with this differential affective preference [40]. In humans, lesions encompassing the insula affect emotion recognition [41–43]. Insular gliomas, for instance, interfere with a patient's ability to identify when other people are in pain based on seeing images of body parts in specific situations [44]. Recent studies also suggest that the insula may be particularly important for associating emotional relevance (arousal) to stimuli [42,43].

Motivation to liberate

Rats learn to open doors to free a trapped rat [45,46]. This performance is abolished in rats with a history of heroin self-administration [47]. Chemogenetic activation of the anterior insula reversed this heroin-induced liberation deficit [48]. Whether neuromodulation of the anterior insula alters the motivation to liberate without heroin self-administration remains unknown.

Amygdala

Emotional contagion and vicarious learning

In mice, inactivation of the lateral amygdala (LA) reduces both emotional contagion (reduced freezing while witnessing another mouse receive shocks) and vicarious learning (freezing in the same context 24 h later) [10]. Similarly in rats, LA and medial amygdala (MeA) inactivation reduces emotional contagion and vicarious learning [49]. Inhibition of distinct amygdala subregions reduced freezing upon re-exposure to a cue (MeA and LA) or context (only MeA) that observers learned to associate to a foot shock to the demonstrator [49]. Rodents typically respond to imminent dangers with freezing and to distant threats with risk assessment. This adaptive choice is controlled by the central amygdala (CeA). Targeted expression of enhancer opsins in CeA neurons activated by imminent danger (demonstrator receiving shocks) or distant danger (interacting with a demonstrator previously shocked out of sight) allowed for functional investigation of two separate populations, wherein reactivating the former led to freezing and reactivating the latter to exploration [50*]. This suggests a causal role of the CeA in mapping the experiences of others onto adaptive behavior in a fashion that considers socially inferred distance of danger. The fact that this occurs in the CeA, a structure also involved in processing similar first-hand experiences, and in triggering behavior, is reminiscent of mirror neurons [12].

Emotion recognition

In humans, lesions of the amygdala worsen emotion recognition, fear in particular [42,51,52], which might be attributed to an impaired exploration of facial expressions [53]. Indeed, two studies in monkeys have shown that amygdala lesions reduce the viewing preference for faces [54] and the attentional capture by social threat stimuli [55]. Together, this suggests that the amygdala may contribute to emotion recognition by directing attention toward relevant social signals.

Other regarding preferences

Bilateral lesions of the basolateral amygdala (BLA) reduce a rat's preference for actions that reward themselves and another rat over those that only reward themselves [56]. Human patients with selective BLA damage show more subtle deficits in that they fail to adapt their choices to that of their partner in a trust game [57].

Other regions

Several other regions have been reported to influence empathy-related behaviors but are only represented by a limited number of studies. For instance, deactivation of locus coeruleus [58] and medial thalamus [10,11] impairs emotional contagion in rodents. Consolation behavior in mandarin voles is compromised by inhibition of the dorsal raphe nuclei [59], while modulation of the nucleus accumbens (NAc) in rodents [60] and stroke lesions of the thalamus in humans [61] reduces emotions recognition.

Noninvasive neuromodulation studies in humans have also evidenced the impact of additional cortical regions. Altering activity in the temporal parietal junction influences emotional contagion [62,63] and other regarding preferences [64], whereas modifying primary somatosensory area SI activity influences emotion recognition [65,66] and harm aversion [65]. Finally, transcranial magnetic stimulation over the right motor cortex reduced bodily emotion recognition [67].

From brain regions to connections

Modulating brain activity in a brain region X involved in empathy-related functions changes brain activity in connected brain regions and therefore implicitly probes the entire network the target region is a part of [68]. That perturbing brain activity in region X perturbs behavior B should thus primarily be an invitation to explore how B depends on the computations within the network of which X is a part [69]. As an analogy that breaking the wall plug of a toaster interferes with toasting should not so much invite us to focus on the plug alone to understand toasting. Although it shows that the plug is necessary for toasting, it certainly is not sufficient for it. Instead, we should explore how the circuit starting at the plug and continuing into the toaster and its heating elements makes toasting possible.

Accordingly, rodent neuroscience is recently starting to explicitly investigate the role of distinct neuroanatomical connections across several network nodes. Manipulating brain activity in both the A24 and the amygdala impairs emotional contagion and vicarious learning in rodents. Notably, targeted photoinhibition of the A24- > BLA projection during the vicarious conditioning phase and subsequent recall in response to the tone revealed that inhibition during conditioning slightly reduced freezing at recall but inhibition during the recall phase did not. This suggests that information about the pain of the demonstrator transmitted along the A24- > BLA connection is essential for vicarious learning but not recall [70**]. A recent study demonstrated that A24- > NAc projections are selectively implicated in the social transfer of pain but not of fear, while A24 - > BLA projections are necessary for vicarious learning [18]. Interfering with the connection between LA and MeA impaired emotional contagion and vicarious learning [49], and perturbing projections from ACC to lateral mediodorsal thalamus [11] impaired emotional contagion [14]. Moreover, inhibiting anterior insular inputs to the NAc has been shown to reduce a rat's preference to approach a stressed juvenile over an

Figure 2

		Emotional contagion	Emotion recognition	Vicarious learning	Social harm aversion	Other regarding preferences	Motivation to liberate	Consolation
Region specific studies								
Prefrontal regions	ACC (Area 24)	[7,10–12, 14,16–18]		[10,11, 13,16]	[8]	[30,32]	[38]	[36,37]
	PrlC (Area 32)		[21]			[30]		
	IFC/IFG	[19,20]	[22,27]					
	dlPFC		[25]					
	dmPFC		[28]		[29]			
	vmPFC					[33,35]		
	VMF		[23]					
	OFC		[24,26]			[34]		
Insula	Insula	[39] [44]	[40] [41–43]				[48]	
Amygdaloid complex	Amygdala		[51,52] [54,55]					
	CeA	[50]						
	LA	[10]		[10,49]				
	MeA			[49]				
	BLA					[56] [57]		
Other regions								
LC		[58]						
Thalamus		[10]	[61]	[10,11]				
DR								[59]
NAc			[60]					
TPJ		[62,63]				[64]		
SI			[65,66]		[65]			
M1			[67]					
Connections studies in rodents								
ACC → BLA		[18,70]		[70]				
ACC → MDL		[14]						
ACC → MeA		[49]		[49]				
ACC→NAc								
aIns→ NAc			[60]					
Oxytocin system studies								
Systemic		[74,75]				[78,80]		[36]
ACC		[15]					[38,77]	[36,37]
PVN		[74]						
PVN → CeA			[76]					
Insula			[40]					
BLA						[79]		
Analgesic system studies								
Systemic		[18,84] [85–88]		[90]			[89]	

Rodents
Non-human primates
Humans

Current Opinion in Neurobiology

Summary of studies presented according to operational definitions in Box 1 and brain regions, connections, or system involved. Empty cells represent the lack of studies still needed to understand the function of specific nodes in the network for different empathy-related phenomena across species. Color codes represent studies in rodents (in blue), nonhuman primates (in green), and humans (in magenta). ACC, anterior cingulate cortex; PrLC, prelimbic cortex; IFG, inferior frontal gyrous; IFC, inferior frontal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VMF, ventromedial frontal lobe; OFC, orbitofrontal cortex; CeA, central amygdala; LA, lateral amygdala; MeA, medial amygdala; BLA, basolateral amygdala; LC, locus ceruleus; DR, dorsal raphe; TPJ, temporo-parietal junction; SI, primary somatosensory area; M1, primary motor cortex; MDL, mediodorsal thalamus; aIns, anterior insular cortex; NAc, nucleus accumbens; PVN, paraventricular nucleus of the hypothalamus.

adult conspecific [60], a form of emotion recognition [40]. Finally, serotoninergic modulation of the ACC can reverse consolation deficits induced by dorsal raphe nuclei inhibition in voles [59].

Inhibiting specific connections remains in its infancy but may turn out to be essential to understand the wiring diagram of empathy, as it provides data that can challenge expectations derived from inhibiting individual brain regions. For instance, pharmacological inhibition of A24 or LA reduces freezing [10] not only when witnessing a demonstrator receive shocks but also during recall, highlighting this circuitry as necessary for both emotional contagion and learning. In contrast, selective optogenetic inhibition of A24- > BLA connections only reduced freezing during recall [70]. Whether this discrepancy is due to optogenetic tools being weaker than pharmacology, and thus failing to influence the stronger freezing during emotional contagion, or whether freezing during emotional contagion can use alternative pathways remains to be explored.

Oxytocin

Researchers increasingly consider using oxytocin to treat social deficit [71,72]. The effects of oxytocin administration in humans are complex (refer the study by Marsh et al. [73] for review) and how much inhaled oxytocin reaches brain regions is debated. Here, we will thus focus on rodent and monkey studies for which direct interference with the oxytocin system is possible.

Emotional contagion

Mice normally show low levels of emotional contagion to unfamiliar mice, but intranasal oxytocin increases vicarious freezing to unfamiliar mice close to the levels toward familiar ones [74] and in a mouse model of callousness [75]. OTA injections in A24a and activation of the hypothalamic paraventricular nucleus oxytocin neurons, respectively, reduces and increases observational fear responses to unfamiliar mice [15,74].

Emotion recognition

In mice, inhibiting oxytocinergic paraventricular nucleus neurons projecting to the CeA, but not NAc, mPFC, and hippocampus, impaired the discrimination of fear and relief states without effects on sociability [76*]; and infusion of OTA in the insula reduces the tendency of rats to interact with stressed juvenile over stressed adults [40].

Motivation to liberate and consolation

In voles, injection of an OTA into the cerebral ventricle and in the ACC but not the prelimbic cortex abolished consolation [36,37] Similarly, blocking oxytocin receptors in A24b of rats and oxytocin receptor knockout in prairie voles interferes with the motivation to liberate a trapped conspecific [38,77]. In monkeys, infusion of oxytocin in the BLA, but not the dmPFC, increased their preferences for actions that reward others [78,79]. Intriguingly, inhalation of oxytocin can also reduce sharing [78], most likely via a reduction of anxiety [80].

Conclusions

While functional magnetic resonance imaging flagged regions with activity correlating with empathy (Figure 1), neuromodulation studies (Figure 2) reveal how far we have come in showing that many of these nodes are necessary for emotional contagion, vicarious learning, and some motivations to engage in behaviors that improve outcomes for others. The emergence of animal models of empathy-related phenomena has allowed us to modulate deep regions and specific connections. The evidence converges to show that the anterior cingulate (A24) and the amygdala appear to play a necessary role in emotional contagion and motivations in a way that appears to be conserved across rodents, macaques, and humans, in line with their evolutionary homologies [2]. Together, they could represent a conserved mechanism to extract life-saving information about danger from the social environment [7]. Although much of this field was inspired by the notion that we recruit our own emotions to feel with those of others [81,82], most neuromodulation evidence only shows that brain regions are necessary for empathy-related phenomena, not that the neurons involved in our own pain in these regions are necessary to share the pain of others. The fact that A24 contains mirror neurons for pain [12], is encouraging, but would specifically modulating these neurons change the phenomena of Box 1? Intriguing evidence is emerging from studies that show that analgesics, which modulate pain neurons, also modify the reaction to the pain of others in humans and rodents across several empathy-related phenomena [18,83–85,86**,87–90]. Such promising results call for the need of more studies at the cellular level capable of probing the necessity of emotional mirror neurons for pain in the generation of such empathy-related phenomena. If Alexander the Great wept because there were no more lands to conquer, the many gaps in Figure 2 should make us rejoice: for many of the nodes, we still have key experiments to perform to conquer a true understanding of the mechanisms of empathy.

Author contributions

All authors determined the scope of the review. EP performed the literature research. All authors collaborated to organize the evidence into a coherent framework. EP then wrote the first draft, and all authors then worked collaboratively to generate the final manuscript. CK and VG obtained the funding.

Conflict of interest statement

Nothing declared.

Acknowledgements

The authors thank Steven Voges for proofreading the article. This work was supported by the European Research Council Starting Grant 'HelpUS' 758703 to VG, Dutch Research Council (NWO) VIDI grant (452-14-015) to VG, and VICI grant (453-15-009) to CK.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Keysers C, Gazzola V: **Expanding the mirror: vicarious activity for actions, emotions, and sensations**. *Curr Opin Neurobiol* 2009, **19**:666–671.

2. ** van Heukelum S, Mars RB, Guthrie M, Buitelaar JK, Beckmann CF, Tiesinga PHE, Vogt BA, Glennon JC, Havenith MN: **Where is cingulate cortex? A cross-species view**. *Trends Neurosci* 2020, **43**:285–299.
An excellent review that summarizes the state of the art regarding the homologies of cingulate cortices across rodents, macaques, and humans.

3. Meffert H, Gazzola V, Den Boer JA, Bartels AAJ, Keysers C: **Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy**. *Brain* 2013, **136**: 2550–2562.

4. Keysers C, Gazzola V: **A plea for cross-species social neuroscience**. In *Current topics in behavioral neurosciences*. Springer Verlag; 2016:179–191.

5. Yamamoto S: **Primate empathy: three factors and their combinations for empathy-related phenomena**. *Wiley Interdiscip Rev Cogn Sci* 2017, **8**:e1431.

6. de Waal FBM, Preston SD: **Mammalian empathy: behavioural manifestations and neural basis**. *Nat Rev Neurosci* 2017, **18**: 498–509.

7. * Han Y, Bruls R, Soyman E, Thomas RM, Pentaraki V, Jelinek N, Heinemans M, Bassez I, Verschooren S, Pruis I, *et al.*: **Bidirectional cingulate-dependent danger information transfer across rats**. *PLoS Biol* 2019, **17**, e3000524.
A study that introduces quantitative methods for tracking emotional contagion in rodents, shows evidence that Area 24 in the anterior cingulate is necessary for emotional contagion, and that emotional contagion could serve for group danger assessment.

8. ** Hernandez-Lallement J, Attah AT, Soyman E, Pinhal CM, Gazzola V, Keysers C: **Harm to others acts as a negative reinforcer in rats**. *Curr Biol* 2020, **30**. 949–961.e7.
This study introduces a paradigm to measure social harm aversion in rats and shows that Area 24 in the cingulate cortex is necessary for social harm aversion.

9. Schneider KN, Sciarillo XA, Nudelman JL, Cheer JF, Roesch MR: **Anterior cingulate cortex signals attention in a social paradigm that manipulates reward and shock**. *Curr Biol* 2020, **30**: 3724–3735.e2.

10. Jeon D, Kim S, Chetana M, Jo D, Ruley HE, Lin S-Y, Rabah D, Kinet J-P, Shin H-S: **Observational fear learning involves affective pain system and Cav1.2 Ca2+ channels in ACC**. *Nat Neurosci* 2010, **13**:482–488.

11. Kim S, Mátyás F, Lee S, Acsády L, Shin H-S: **Lateralization of observational fear learning at the cortical but not thalamic level in mice**. *Proc Natl Acad Sci USA* 2012, **109**:15497–15501.

12. ** Carrillo M, Han Y, Migliorati F, Liu M, Gazzola V, Keysers C: **Emotional mirror neurons in the rat's anterior cingulate cortex**. *Curr Biol* 2019, **29**. 1301-1312.e6.
This study combines electrophysiology to provide evidence for the existence of emotional mirror neurons in Area 24 and pharmacological deactivation of area 24 to show that it is necessary for emotional contagion in rats.

13. Jones CE, Monfils M-HH: **Dominance status predicts social fear transmission in laboratory rats**. *Anim Cognit* 2016, **19**: 1051–1069.

14. Zheng C, Huang Y, Bo B, Wei L, Liang Z, Wang Z: **Projection from the anterior cingulate cortex to the lateral part of mediodorsal thalamus modulates vicarious freezing behavior**. *Neurosci Bull* 2020, **36**:217–229.

15. Sakaguchi T, Iwasaki S, Okada M, Okamoto K, Ikegaya Y: **Ethanol facilitates socially evoked memory recall in mice by recruiting pain-sensitive anterior cingulate cortical neurons**. *Nat Commun* 2018, **9**:1–10.

16. ** Keum S, Kim A, Shin JJ, Kim J-HH, Park J, Shin H-SS: **A missense variant at the Nrxn3 locus enhances empathy fear in the mouse**. *Neuron* 2018, **98**. 588-601.e5.
An elegant study combining multiple methods to show how SST+ interneurons in the cingulate are responsible for individual differences in emotional contagion in mice. Optogenetic inhibition of right cingulate SST+ interneurons during emotional contagion increased online and 24 h later vicarious freezing, whereas their activation showed the reversed effect.

17. Smith ML, Walcott AT, Heinricher MM, Ryabinin AE: **Anterior cingulate cortex contributes to alcohol withdrawal- induced and socially transferred hyperalgesia**. *eNeuro* 2017, **4**:87–104.

18. ** Smith ML, Asada N, Malenka RC: **Anterior cingulate inputs to nucleus accumbens control the social transfer of pain and analgesia**. *Science (80-)* 2021, **371**:153–159.
This excellent work demonstrates the selective involvement of A24- > NAc connections in the social transfer of pain and analgesia, while vicarious fear learning by witnessing another mouse receive shocks depends on A24- > BLA projections.

19. Shamay-Tsoory SG, Aharon-Peretz J, Perry D: **Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions**. *Brain* 2009, **132**:617–627.

20. Peled-Avron L, Glasner L, Gvirts HZ, Shamay-Tsoory SG: **The role of the inferior frontal gyrus in vicarious social touch: a transcranial direct current stimulation (tDCS) study**. *Dev Cogn Neurosci* 2019, **35**:115–121.

21. ** Scheggia D, Managò F, Maltese F, Bruni S, Nigro M, Dautan D, Latuske P, Contarini G, Gomez-Gonzalo M, Requie LM, *et al.*: **Somatostatin interneurons in the prefrontal cortex control affective state discrimination in mice**. *Nat Neurosci* 2020, **23**: 47–60.
An elegant study showing that the preference of mice for mice in altered emotional states depends on medial prefrontal SST+ interneurons. Optical SST+ Area 32 neurons inhibition interfered with affective state discrimination, but not general social exploration. The effect was not found in parvalbumin PV+ neurons under the same experimental conditions.

22. Perry A, Saunders SN, Stiso J, Dewar C, Lubell J, Meling TR, Solbakk AK, Endestad T, Knight RT: **Effects of prefrontal cortex damage on emotion understanding: EEG and behavioural evidence**. *Brain* 2017, **140**:1086–1099.

23. Vaidya AR, Fellows LK: **Ventromedial frontal lobe damage affects interpretation, not exploration, of emotional facial expressions**. *Cortex* 2019, **113**:312–328.

24. Willis ML, Palermo R, McGrillen K, Miller L: **The nature of facial expression recognition deficits following orbitofrontal cortex damage**. *Neuropsychology* 2014, **28**:613–623.

25. Conson M, Errico D, Mazzarella E, Giordano M, Grossi D, Trojano L: **Transcranial electrical stimulation over dorsolateral prefrontal cortex modulates processing of social cognitive and affective information**. *PLoS One* 2015, **10**, e0126448.

26. Willis ML, Murphy JM, Ridley NJ, Vercammen A: **Anodal tDCS targeting the right orbitofrontal cortex enhances facial expression recognition**. *Soc Cognit Affect Neurosci* 2015, **10**: 1677–1683.

27. Penton T, Dixon L, Evans LJ, Banissy MJ: **Emotion perception improvement following high frequency transcranial random noise stimulation of the inferior frontal cortex**. *Sci Rep* 2017, **7**:11278.

28. Gamond L, Cattaneo Z: **The dorsomedial prefrontal cortex plays a causal role in mediating in-group advantage in emotion recognition: a TMS study**. *Neuropsychologia* 2016, **93**: 312–317.

29. Liao C, Wu S, Luo Y, Guan Q, Cui F: **Transcranial direct current stimulation of the medial prefrontal cortex modulates the propensity to help in costly helping behavior**. *Neurosci Lett* 2018, **674**:54–59.

30. * Basile BM, Schafroth JL, Karaskiewicz CL, Chang SWC, Murray EA: **The anterior cingulate cortex is necessary for forming prosocial preferences from vicarious reinforcement in monkeys**. *PLoS Biol* 2020, **18**, e3000677.
A rare study showing that altering activity in the cingulate cortex alters the acquisition of other regarding preferences in monkeys. Rhesus monkeys subjected to ACC lesions lost their ability to acquire social preferences, measured as tendency to give a reward to another monkey over neither of them.

31. Chang SWC, Winecoff AA, Platt ML: **Vicarious reinforcement in rhesus macaques (Macaca mulatta)**. *Front Neurosci* 2011, **5**.

32. Haroush K, Williams ZM: **Neuronal prediction of opponent's behavior during cooperative social interchange in primates**. *Cell* 2015, **160**:1233–1245.

33. Beadle JN, Paradiso S, Tranel D: **Ventromedial prefrontal cortex is critical for helping others who are suffering**. *Front Neurol* 2018, **9**.

34. Wang G, Li J, Yin X, Li S, Wei M: **Modulating activity in the orbitofrontal cortex changes trustees' cooperation: a transcranial direct current stimulation study**. *Behav Brain Res* 2016, **303**:71–75.

35. Zheng H, Huang D, Chen S, Wang S, Guo W, Luo J, Ye H, Chen Y: **Modulating the activity of ventromedial prefrontal cortex by anodal tDCS enhances the trustee's repayment through altruism**. *Front Psychol* 2016, **7**.

36. Burkett JP, Andari E, Johnson ZV, Curry DC, De Waal FBM, Young LJ: **Oxytocin-dependent consolation behavior in rodents**. *Science (80-)* 2016, **351**:375–378.

37. Li LF, Yuan W, He ZX, Wang LM, Jing XY, Zhang J, Yang Y, Guo QQ, Zhang XN, Cai WQ, *et al.*: **Involvement of oxytocin and GABA in consolation behavior elicited by socially defeated individuals in Mandarin voles**. *Psychoneuroendocrinology* 2019, **103**:14–24.

38. Yamagishi A, Lee J, Sato N: **Oxytocin in the anterior cingulate cortex is involved in helping behaviour**. *Behav Brain Res* 2020, **393**:112790.

39. Zaniboni CR, Pelarin V, Baptista-de-Souza D, Canto-de-Souza A: **Empathy for pain: insula inactivation and systemic treatment with midazolam reverses the hyperalgesia induced by cohabitation with a pair in chronic pain condition**. *Front Behav Neurosci* 2018, **12**:278.

40. * Rogers-Carter MM, Varela JA, Gribbons KB, Pierce AF, McGoey MT, Ritchey M, Christianson JP: **Insular cortex mediates approach and avoidance responses to social affective stimuli**. *Nat Neurosci* 2018, **21**:404–414.
One of the few studies showing the importance of the insular cortex in social behavior in rats. In this study, both optical inhibition of insular cortex and blockade of insular oxytocin receptors, prevented the natural tendency of rats to interact with stressed juveniles over adult conspecifics.

41. Corradi-Dell'Acqua C, Ronchi R, Thomasson M, Bernati T, Saj A, Vuilleumier P: **Deficits in cognitive and affective theory of mind relate to dissociated lesion patterns in prefrontal and insular cortex**. *Cortex* 2020, **128**:218–233.

42. Tippett DC, Godin BR, Oishi K, Oishi K, Davis C, Gomez Y, Trupe LA, Kim EH, Hillis AE: **Impaired recognition of emotional faces after stroke involving right amygdala or insula**. *Semin Speech Lang* 2018, **39**:87–100.

43. Motomura K, Terasawa Y, Natsume A, Iijima K, Chalise L, Sugiura J, Yamamoto H, Koyama K, Wakabayashi T, Umeda S: **Anterior insular cortex stimulation and its effects on emotion recognition**. *Brain Struct Funct* 2019, **224**:2167–2181.

44. Chen P, Wang G, Ma R, Jing F, Zhang Y, Wang Y, Zhang P, Niu C, Zhang X: **Multidimensional assessment of empathic abilities in patients with insular glioma**. *Cognit Affect Behav Neurosci* 2016, **16**:962–975.

45. Sato N, Tan L, Tate K, Okada M: **Rats demonstrate helping behavior toward a soaked conspecific**. *Anim Cognit* 2015, **18**:1039–1047.

46. Ben-Ami Bartal I, Decety J, Mason P: **Empathy and pro-social behavior in rats**. *Science* 2011, **334**:1427–1430.

47. Tomek SE, Stegmann GM, Olive MF: **Effects of heroin on rat prosocial behavior**. *Addiction Biol* 2019, **24**:676–684.

48. Tomek SE, Stegmann GM, Leyrer-Jackson JM, Piña J, Olive MF: **Restoration of prosocial behavior in rats after heroin self-administration via chemogenetic activation of the anterior insular cortex**. *Soc Neurosci* 2020, **15**:408–419.

49. Twining RC, Vantrease JE, Love S, Padival M, Rosenkranz JA: **An intra-amygdala circuit specifically regulates social fear learning**. *Nat Neurosci* 2017, **20**:459–469.

50. * Andraka K, Kondrakiewicz K, Rojek-Sito K, Ziegart-Sadowska K, Meyza K, Nikolaev T, Hamed A, Kursa M, Wójcik M, Danielewski K, *et al.*: **More than a feeling: central amygdala mediates social transfer of information about proximity of danger**. *bioRxiv* 2020, https://doi.org/10.1101/2020.02.28.969113.
A sophisticated study that shows through optogenetics in behaviorally activated neurons that rats select appropriate defensive strategies in a novel environment depending on cues from the conspecific, and that the central amygdala plays a key role in that process.

51. Adolphs R: **Neural systems for recognizing emotion**. *Curr Opin Neurobiol* 2002, **12**:169–177.

52. Boucher O, Rouleau I, Lassonde M, Lepore F, Bouthillier A, Nguyen DK: **Social information processing following resection of the insular cortex**. *Neuropsychologia* 2015, **71**:1–10.

53. Kennedy DP, Adolphs R: **Impaired fixation to eyes following amygdala damage arises from abnormal bottom-up attention**. *Neuropsychologia* 2010, **48**:3392–3398.

54. Taubert J, Flessert M, Wardle SG, Basile BM, Murphy AP, Murray EA, Ungerleider LG: **Amygdala lesions eliminate viewing preferences for faces in rhesus monkeys** 2018, **115**:8043–8048.

55. Dal Monte O, Costa VD, Noble PL, Murray EA, Averbeck BB: **Amygdala lesions in rhesus macaques decrease attention to threat**. *Nat Commun* 2015, **6**:1–10.

56. Hernandez-Lallement J, van Wingerden M, Schäble S, Kalenscher T: **Basolateral amygdala lesions abolish mutual reward preferences in rats**. *Neurobiol Learn Mem* 2016, **127**:1–9.

57. Rosenberger LA, Eisenegger C, Naef M, Terburg D, Fourie J, Stein DJ, van Honk J: **The human basolateral amygdala is indispensable for social experiential learning**. *Curr Biol* 2019, **29**. 3532-3537.e3.

58. Lü Y-F, Yang Y, Li C-L, Wang Y, Li Z, Chen J: **The locus coeruleus–norepinephrine system mediates empathy for pain through selective up-regulation of P2X3 receptor in dorsal root ganglia in rats**. *Front Neural Circ* 2017, **11**:66.

59. Li L-F, Zhang L-Z, He Z-X, Yuan W, Ma H, Xun Y-F, Hou W-J, Li Y-T, Lv Z-J, Jia R, *et al.*: **Dorsal raphe nuclei to anterior cingulate cortex 5-HTergic neural circuit is implicated in consolation-like behaviors and sociability in Mandarin voles**. *bioRxiv* 2020, https://doi.org/10.1101/2020.09.21.307280.

60. Rogers-Carter MM, Djerdjaj A, Gribbons KB, Varela JA, Christianson JP: **Insular cortex projections to nucleus accumbens core mediate social approach to stressed juvenile rats**. *J Neurosci* 2019, **39**:8717–8729.

61. Wilkos E, Brown TJB, Slawinska K, Akucharska K: **Social cognitive and neurocognitive deficits in inpatients with unilateral thalamic lesions – pilot study**. *Neuropsychiatric Dis Treat* 2015, **11**:1031–1038.

62. Miller JG, Xia G, Hastings PD: **Right temporoparietal junction involvement in autonomic responses to the suffering of others: a preliminary transcranial magnetic stimulation study**. *Front Hum Neurosci* 2020:14.

63. Coll MP, Tremblay MPB, Jackson PL: **The effect of tDCS over the right temporo-parietal junction on pain empathy**. *Neuropsychologia* 2017, **100**:110–119.

64. Soutschek A, Ruff CC, Strombach T, Kalenscher T, Tobler PN: **Brain stimulation reveals crucial role of overcoming self-centeredness in self-control**. *Sci Adv* 2016, **2**, e1600992.

65. Gallo S, Paracampo R, Müller-Pinzler L, Severo MC, Blömer L, Fernandes-Henriques C, Henschel A, Lammes BK, Maskaljunas T, Suttrup J, *et al.*: **The causal role of the somatosensory cortex in prosocial behaviour**. *eLife* 2018, **7**.

66. Paracampo R, Tidoni E, Borgomaneri S, di Pellegrino G, Avenanti A: **Sensorimotor network crucial for inferring amusement from smiles**. *Cerebr Cortex* 2017, **27**:5116–5129.

67. Borgomaneri S, Gazzola V, Avenanti A: **Transcranial magnetic stimulation reveals two functionally distinct stages of motor cortex involvement during perception of emotional body language**. *Brain Struct Funct* 2015, **220**:2765–2781.

68. Valchev N, Gazzola V, Avenanti A, Keysers C: **Primary somatosensory contribution to action observation brain activity—combining fMRI and cTBS**. *Soc Cognit Affect Neurosci* 2016, **11**:1205–1217.

69. Keysers C, Paracampo R, Gazzola V: **What neuromodulation and lesion studies tell us about the function of the mirror neuron system and embodied cognition**. *Curr Opin Psychol* 2018, **24**:35–40.

70. ** Allsop SA, Wichmann R, Mills F, Burgos-Robles A, Chang C-J, Felix-Ortiz AC, Vienne A, Beyeler A, Izadmehr EM, Glober G, *et al.*: **Corticoamygdala transfer of socially derived information gates observational learning**. *Cell* 2018, **173**:1329–1342.e18.
Through a combination of electrophysiology and the manipulation of connections, the study shows that ACC- > BLA pathway is necessary for vicarious learning.

71. Erdozain AM, Peñagarikano O: **Oxytocin as treatment for social cognition, not there yet**. *Front Psychiatr* 2020, **10**.

72. Shamay-Tsoory S, Young LJ: **Understanding the oxytocin system and its relevance to psychiatry**. *Biol Psychiatr* 2016, **79**:150–152.

73. Marsh N, Marsh AA, Lee MR, Hurlemann R: **Oxytocin and the neurobiology of prosocial behavior**. *Neuroscience* 2020, https://doi.org/10.1177/1073858420960111.

74. Pisansky MT, Hanson LR, Gottesman II , Gewirtz JC: **Oxytocin enhances observational fear in mice**. *Nat Commun* 2017, **8**:2102.

75. Zoratto F, Sbriccoli M, Martinelli A, Glennon JC, Macrì S, Laviola G: **Intranasal oxytocin administration promotes emotional contagion and reduces aggression in a mouse model of callousness**. *Neuropharmacology* 2018, **143**:250–267.

76. * Ferretti V, Maltese F, Contarini G, Nigro M, Bonavia A, Huang H, Gigliucci V, Morelli G, Scheggia D, Managò F, *et al.*: **Oxytocin signaling in the central amygdala modulates emotion discrimination in mice**. *Curr Biol* 2019, **29**:1938–1953.e6.
This study shows how oxytocin projections to the central amygdala are involved in the approach behavior towards mice in altered emotional states. Inhibition of this specific projection elicits deficit in emotion discrimination, leaving unaltered social exploration.

77. Kitano K, Yamagishi A, Horie K, Nishimori K, Sato N: **Helping behavior in prairie voles: a model of empathy and the importance of oxytocin**. *bioRxiv* 2020, https://doi.org/10.1101/2020.10.20.347872.

78. Chang SWC, Barter JW, Ebitz RB, Watson KK, Platt ML: **Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (Macaca mulatta)**. *Proc Natl Acad Sci USA* 2012, **109**:959–964.

79. Chang SWC, Fagan NA, Toda K, Utevsky AV, Pearson JM, Platt ML, Gazzaniga MS: **Neural mechanisms of social decision-making in the primate amygdala**. *Proc Natl Acad Sci U S A* 2015, **112**:16012–16017.

80. Leverett K, Heyler C, Flemming T, Talbot CF, Zak PJ, Essler JL, Dougall P, Brosnan SF: **Oxytocin reduces food sharing in capuchin monkeys by modulating social distance**. *Behaviour* 2015, **152**:941–961.

81. Gallese V, Keysers C, Rizzolatti G: **A unifying view of the basis of social cognition**. *Trends Cognit Sci* 2004, **8**:396–403.

82. Keysers C, Gazzola V: **Towards a unifying neural theory of social cognition**. *Prog Brain Res* 2006, **156**:379–401.

83. Langford DJ, Crager SE, Shehzad Z, Smith SB, Sotocinal SG, Levenstadt JS, Chanda ML, Levitin DJ, Mogil JS: **Social modulation of pain as evidence for empathy in mice**. *Science (80-)* 2006, **312**:1967–1970.

84. Nazeri M, Nezhadi A, Shabani M: **Role of opioid system in empathy-like behaviours in rats**. *Addict Heal* 2019, **11**:216–222.

85. Rütgen M, Seidel EM, Silani G, Riečanský I, Hummer A, Windischberger C, Petrovic P, Lamm C: **Placebo analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain**. *Proc Natl Acad Sci U S A* 2015, **112**:E5638–E5646.

86. ** Rütgen M, Seidel E-M, Pletti C, Riečanský I, Gartus A, Eisenegger C, Lamm C: **Psychopharmacological modulation of event-related potentials suggests that first-hand pain and empathy for pain rely on similar opioidergic processes**. *Neuropsychologia* 2018, **116**:5–14.
An elegant study showing that placebo analgesia in humans reduces pain ratings and pain-related EEG components for both self and other, and that this effect can be canceled using Naltrexone, an opioid receptor blocker.

87. Rütgen M, Seidel E-M, Riečanský I, Lamm C: **Reduction of empathy for pain by placebo analgesia suggests functional equivalence of empathy and first-hand emotion experience**. *J Neurosci* 2015, **35**:8938–8947.

88. Mischkowski D, Crocker J, Way BM: **From painkiller to empathy killer: acetaminophen (paracetamol) reduces empathy for pain**. *Soc Cognit Affect Neurosci* 2016, **11**:1345–1353.

89. Kandis S, Ates M, Kizildag S, Camsari GB, Yuce Z, Guvendi G, Koc B, Karakilic A, Camsari UM, Uysal N: **Acetaminophen (paracetamol) affects empathy-like behavior in rats: dose-response relationship**. *Pharmacol Biochem Behav* 2018, **175**:146–151.

90. Haaker J, Yi J, Petrovic P, Olsson A: **Endogenous opioids regulate social threat learning in humans**. *Nat Commun* 2017, **8**:15495.