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Neural mechanisms necessary for empathy-related phenomena across species

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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.

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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
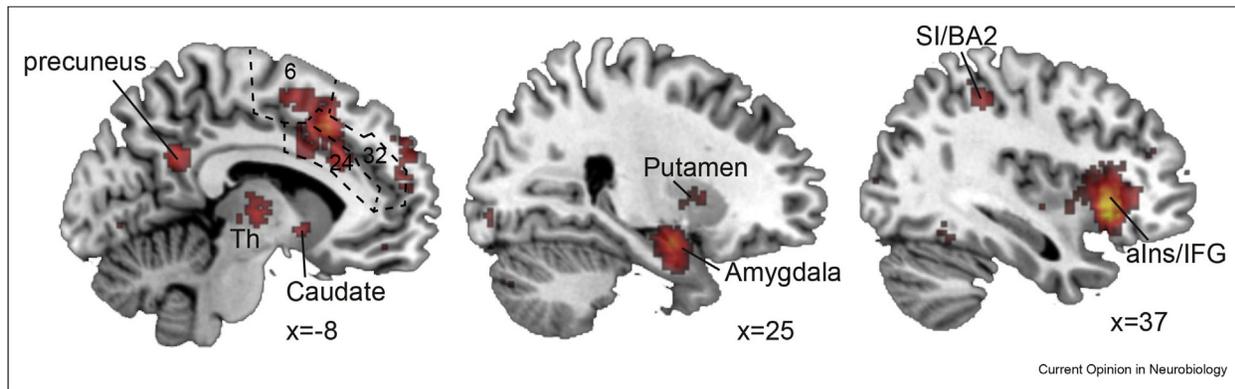
Results of a neurosynth meta-analysis identifying regions with activity in studies including the keyword Empathy (uniformity test). Numbers in green represent the approximate position of three distinct cortical midline structures that include the supplementary motor cortex (BA6) and cingulate cortices (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].

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.

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