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Empathy circuits

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The social neuroscientific investigation of empathy has revealed that the same neural networks engaged during first-hand experience of affect subserve empathic responses. Recent meta-analyses focusing on empathy for pain for example reliably identified a network comprising anterior insula and anterior midcingulate cortex. Moreover, recent studies suggest that the generation of empathy is flexibly supported by networks involved in action simulation and mentalizing depending on the information available in the environment. Further, empathic responses are modulated by many factors including the context they occur in. Recent work shows how this modulation can be afforded by the engagement of antagonistic motivational systems or by cognitive control circuits, and these modulatory systems can also be employed in efforts to regulate one's empathic responses.

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Introduction

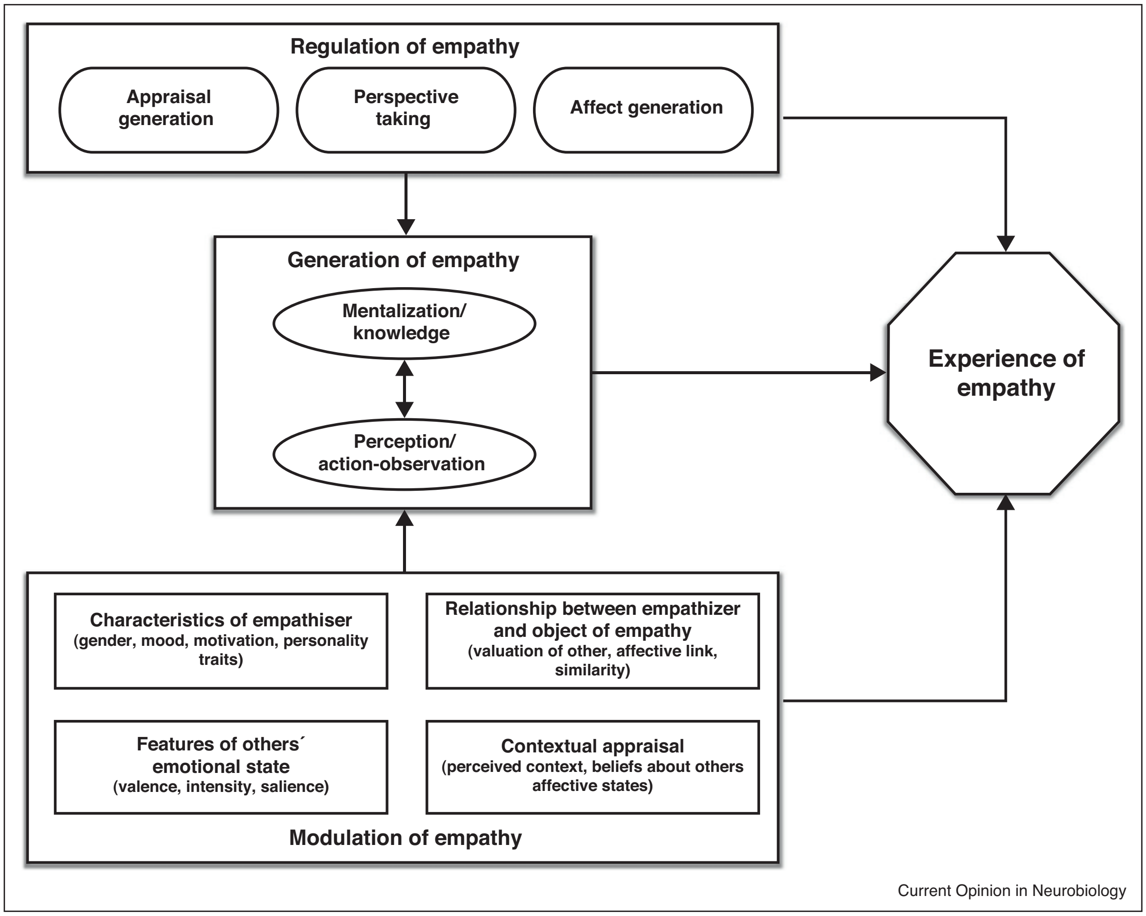
Empathy can be defined as the process by which an individual infers the affective state of another by generating an isomorphic affective state in the self, while retaining knowledge that the cause of the affective state is the other [1,2]. Empathy is an important contributor to successful social interaction, allowing us to predict and understand others' behavior and react accordingly. However, despite its adaptive value empathy is not obligatory: Often, when confronted with the suffering of strangers, it does not affect us, either because we are not motivated to attend to it, because we willfully ignore it, or because our beliefs about the other's feelings override the evidence of our senses. These examples illustrate that empathic resonance is not an automatic response pattern vicariously infusing us with the feelings of others, but that its occurrence is dependent on a series of factors, such as the characteristics of the empathizer, the object of empathy, the social context, and the beliefs and goals we harbor when confronted with emotion in others (see Figure 1). In this review we provide an overview of recent evidence from the neuroimaging literature on empathy that elucidates both the mechanisms allowing us to feel with another, as well as the mechanisms by which empathy can be dynamically modulated, focusing on research showing the interplay of neural networks underlying the representation, generation, modulation, and regulation of empathy.

The core network of empathy

Considerable effort has been put into research on the neural substrates of empathic states in situations ranging from the vicarious experience of disgust, pain, reward, and joy [1,2,3,4,5,6•]. An influential hypothesis guiding empathy research is that of shared-networks, which states that empathic experiences are subserved by activation of the same neural networks which are activated in the first-person experience of an affective state [7,8]. Two recent meta-analyses [9•,10•], summarizing mainly the published neuroimaging work on empathy for pain, found strong support for the involvement of the anterior insula (AI), and the boundary area between posterior anterior and anterior medial cingulate cortex (pACC/aMCC; BA 24b) in empathy (Figure 2a). As seen in Figure 2b activations of the AI and pACC/aMCC are also commonly observed in pain processing [11], providing support for the shared-networks hypothesis of empathy. Furthermore, these regions have been implicated in a range of different affect related functions: AI has been shown to be reliably involved in the evaluation and experience of emotion [12,13] and interoceptive awareness [14•]. On the basis of both single cell neuron recordings [15], and fMRI studies [16], the pACC/aMCC region reported has been observed to contain neurons responsive to both felt and observed pain. pACC/aMCC is strongly connected to the AI [17] and has been suggested to play a pivotal role in the integration of pain, negative affect, and cognitive control [18]. AI and pACC/aMCC also have hub-like position in multiple functional networks [14•,18] making them ideally suited to integrate core affective information with contextual input into global feeling states and allowing for the adaptive modulation of behavior by empathic states [19].

The importance of this network in empathy is also shown in several studies showing that it is modulated by person characteristics (e.g. gender [20]) and individual differences in self-reported state and trait empathy [9•]. Interestingly, people who score high on trait questionnaires of alexithymia, a personality trait characterized by difficulties with understanding one's own emotional and bodily

Figure 1



Schematic illustration of the factors have been found to be involved in the generation, modulation, and regulation of empathic experiences and their relationship, as discussed in the current review. Empathic experiences can be generated through perceptual information, where the experience of affectively significant situations for the other leads to a subsequent representation of affective states in the self, or from internal sources of information, where existing knowledge is employed to infer and activate the affective state of the other. While these routes are experimentally dissociable, they work in concert to effect generation. Both modulatory factors and efforts to regulate empathic responses can have their effect by determining whether empathic responses occur through the modulation of generative processes, or by altering the affective quality of the empathic experience itself, such as seen in, for example, Schadenfreude and compassion.

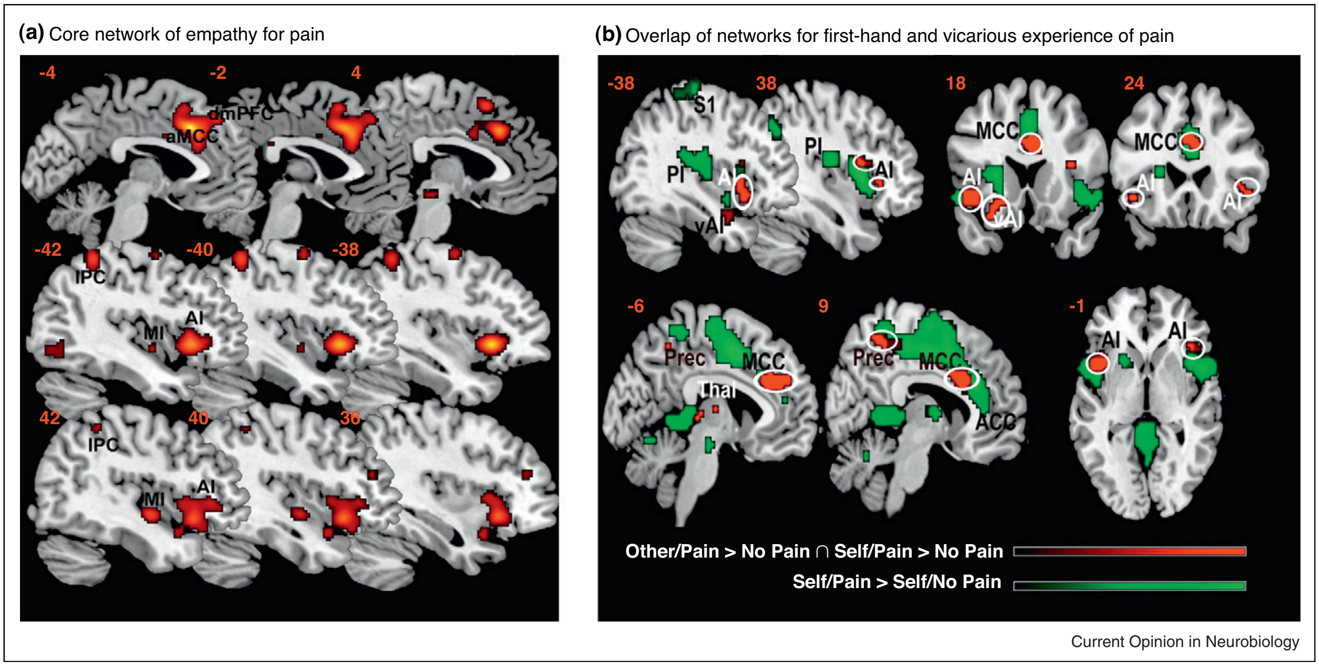
states, show less activation of AI both when interocepting on their own feeling states [21] and when empathizing with the pain of others [22]. Overall, this pattern of findings supports the notion that the formation of first-hand cortical representations about one's own feeling states in interoceptive cortex is a necessary condition to engage in vicarious predictions about the emotions of others.

Networks supporting the generation of empathic responses

A distinction between a stimulus-response, perception-based route and a more abstract, inferential route to the generation of empathic reactions has been suggested [19,23]. This distinction implies that in the presence of concrete visual stimuli depicting, for example, other people or body parts in painful situations, core empathy-related networks in AI and pACC/aMCC can be activated via simulation of the affective state observed via the engagement of action-perception networks [7]. In situations where such direct perceptual evidence is missing, affective states of others can be inferred by the creation of representations of the others potential mental state. In these situations, the generation of an empathic state is dependent on the employment of perspective taking and prior knowledge about the situation and the individual in question to make attributions about the affective state of the other. Accordingly, in such cases activation of core empathy-related networks are consequent upon the activation of networks underlying Theory of Mind and mentalizing [24,25].

Investigation of the neural bases of these two routes to empathy was performed by both of the previously

Figure 2



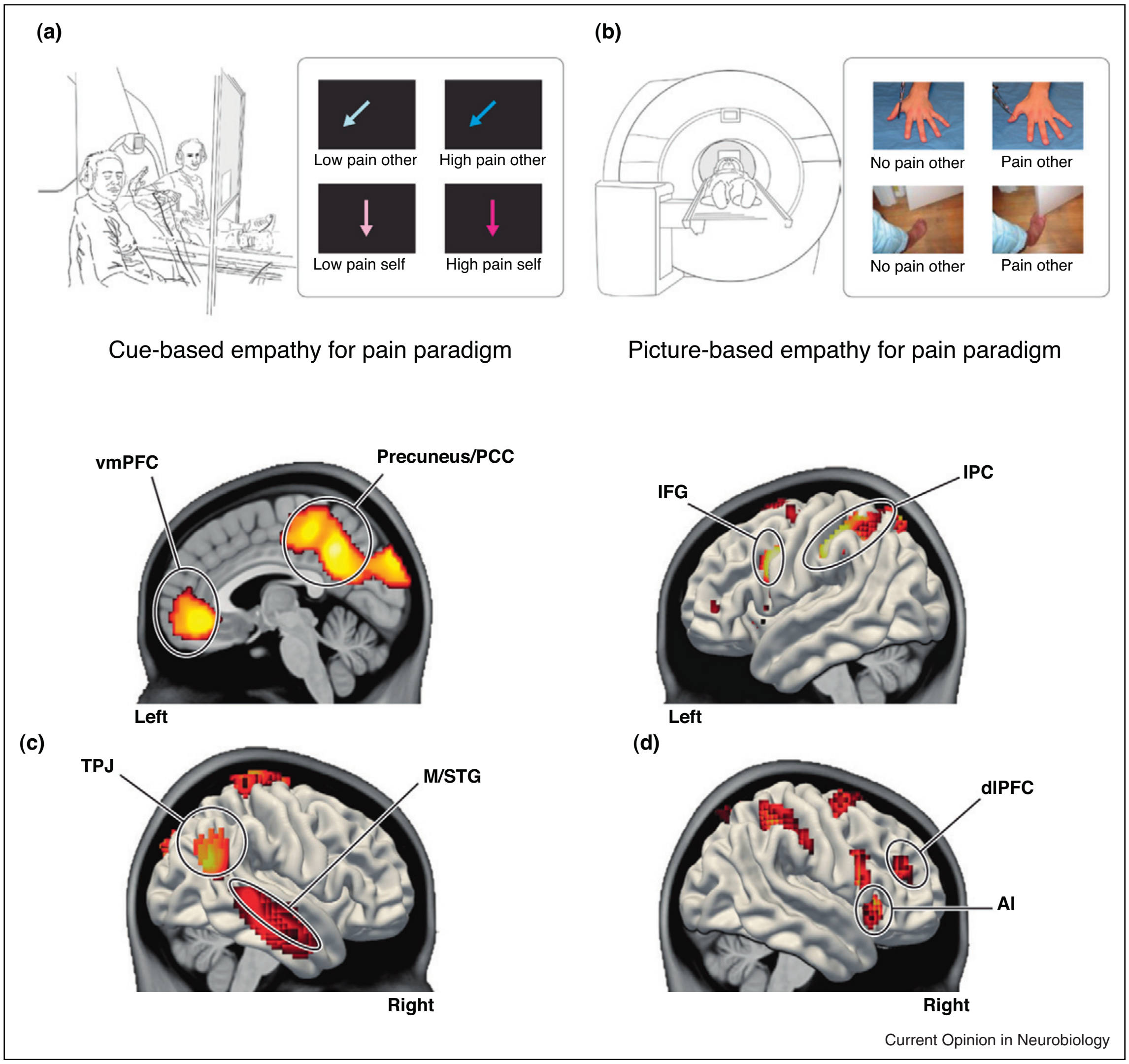
Results from a recent meta-analysis of fMRI experiments investigating empathy for pain [9•]. **(a)** The core empathy for pain network, consisting in dorso-medial prefrontal cortex (dmPFC), aMCC, inferior parietal cortex (IPC), AI, and middle anterior insula. **(b)** Common and distinct activation when observing others in pain, and experiencing pain oneself, supporting the shared networks hypothesis of empathy. Areas of common activation include AI, MCC/ACC, and precuneus (color-coded red) Distinct activations for self-related responses only are observed in posterior insula and SII, primary somatosensory cortex (S1), and in large parts of medial and anterior cingulate cortex (MCC/ACC; color-coded green). Circles indicate regions of strongest overlap. Inset *x*/*z* values indicate a stereotactic coordinate of the shown slice in the MNI space.
Figures adapted with permission from [9•].

mentioned meta-analyses. Lamm and colleagues [9•] contrasted experiments that used implicit induction of empathy via abstract cues indicating that another person present would receive painful stimulation (Figure 3a) with experiments that employed affectively provoking pictures or videos (Figure 3b). Fan and colleagues [10•] contrasted paradigms in which subjects were asked to passively perceive visual stimuli depicting others' emotional or sensory experience with paradigms where the subjects were explicitly asked to actively infer others' emotional states. Paradigms employing inferential processes (Figure 3c) were associated with activations of regions previously implicated in Theory of Mind or mentalizing [25–27], such as ventromedial prefrontal cortex (vmPFC), superior temporal sulcus (STS), temporo-parietal junction (TPJ), and posterior cingulate cortex/precuneus (PCC/PCU). Perception-based paradigms (Figure 3d) were associated with activation of regions previously implicated in action observation [28•] and bottom-up generation of emotion [29], such as the dorsolateral and dorsomedial PFC, inferior parietal cortex (IPC), IFG, pars opercularis, and midbrain. Thus, the theoretical distinction between perception-based and inference-based routes of empathic generation appears to be borne out by a similar division of the brain networks involved. That said, it should be noted that although these two routes are neuroanatomically distinct, they commonly work in concert to allow accurate representation of others affective states [30••] and have been shown to compensate for each other in cases of pathology [31••].

Networks supporting the contextual modulation of empathic responses

The occurrence of empathy can be modulated by a multitude of different factors, such as features of the empathic emotion (e.g., intensity, saliency, and valence), features of the empathizer (e.g., gender, personality, and mood), the relationship between empathizer and target (e.g., familiarity, affective link, and valuation of the other), and the appraisal of the situation [1,32]. The importance of one's valuation of the other as a modulatory factor is illustrated by two recent studies that investigated how empathic responses were modulated by ingroup/outgroup distinctions [33•] and the perceived fairness of others [20]. Both studies found reduced empathy-related activation of the AI to another's suffering when the object of empathy had aberrant characteristics, such as perceived unfairness displayed in economic exchange games or membership of a disliked outgroup (i.e. a fan from a rival football team). This reduction of AI activation was correlated with increased activation of the ventral

Figure 3



Meta-analytic evidence for the differential engagement of networks associated with mentalization and perception-simulation in the generation of empathy as a function of paradigm employed. **(a)** In cue-based paradigms, pain in others is signaled via abstract cues. In the example stimuli, colored arrows indicate whether the other or the self will receive a nonpainful sensation or a painful shock. This paradigm type does not explicitly provide depictions of painful situations, thereby requiring the employment of inferential processes to generate empathic responses. **(b)** In picture-based paradigms, pictures or videos that depict limbs of target persons in painful situations are shown to the observer. In the example stimuli, one image indicates pain in the other, whereas the other image does not. **(c)** Stronger activations in cue-based relative to picture-based studies were found in so-called mentalizing or Theory of Mind networks, including temporo-parietal junction, ventromedial prefrontal cortex, middle/superior temporal gyrus, precuneus and posterior cingulate cortex. **(d)** Stronger activations in picture-based relative to cue-based paradigms were found in so-called mirror-neuron networks, such as the inferior-parietal cortex and opercular IFG, as well as in AI and dorsomedial and dorsolateral prefrontal cortex. Adapted with permission from [3].

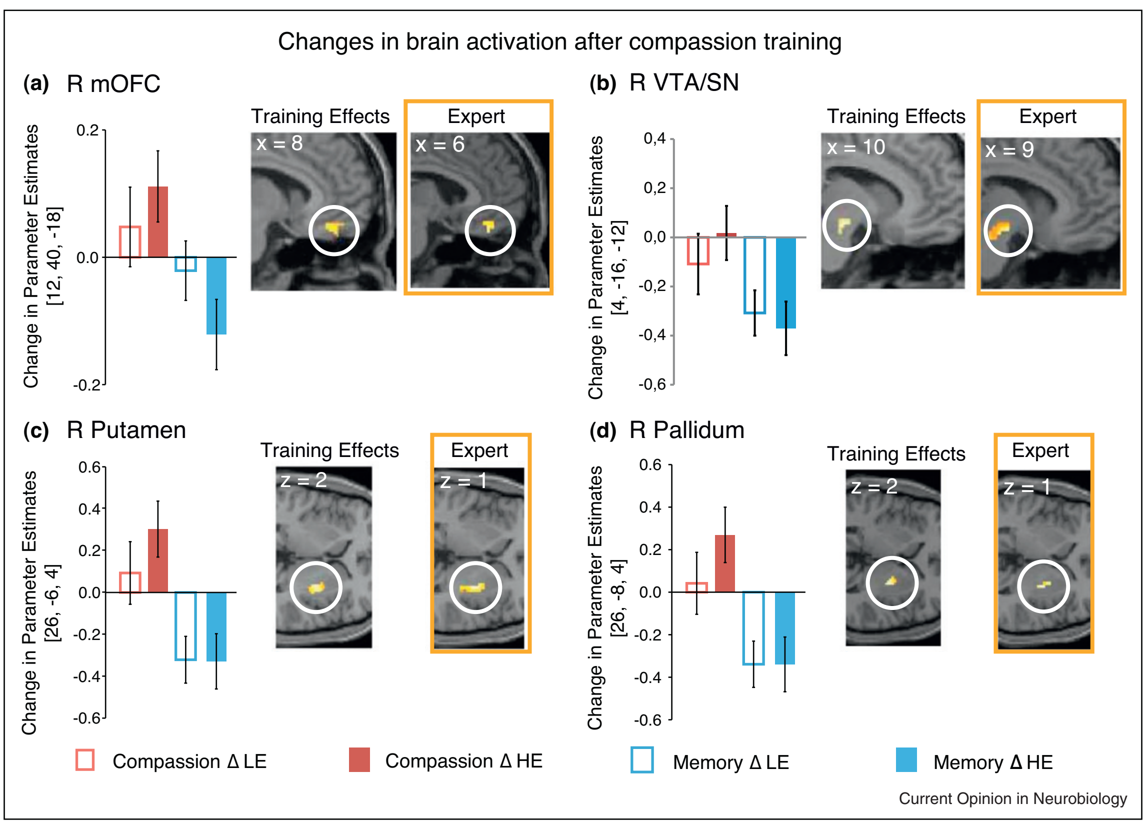
striatum/nucleus accumbens (NAcc) [20], areas often implicated in reward processing [34] and associated with desire for revenge and Schadenfreude [35,36]. The study by Hein and colleagues [33•] elaborated on the functional significance of this relationship by showing that costly helping of ingroup members was best predicted by empathy related AI activity, whereas *not* helping the outgroup member was best predicted by NAcc activity. This demonstrates both that empathy is important in motivating prosocial behavior, and that empathy can be counteracted by activation of antagonistic motivational systems.

The importance of beliefs in determining how one reacts to others' affective states is shown in studies focusing on how contextual appraisal alters empathic responses [37–39]. In these studies subjects were given information about how the object of empathy actually experienced depicted painful situations, finding that activation of the core empathy AI/midcingulate network was modulated as a function of different interpretational contexts. These modulations were associated with activation of a number of regions implicated in mentalizing (e.g. TPJ, vmPFC/orbitofrontal cortex), and executive control and emotion regulation (e.g. lateral Middle Frontal Gyrus, genual ACC, orbital IFG) [26,40–42]. Considering that these experiments in effect supplied subjects with perspective-based reappraisals of the empathy-inducing stimuli, it is tempting to speculate that the activation of these networks reflects engagement of automatic emotion regulation processes [43,44] that supplant the immediate emotional content of the stimulus with context appropriate appraisals. Thus, these studies show that our preconceptions about others' emotional states modulate the quality of empathic responses, and that these modulations are afforded in a similar fashion to that which is seen in emotion regulation research.

Networks supporting volitional regulation of empathy

While the fields of emotion regulation [41] and empathy research have been developed without much crosstalk, the above-mentioned studies suggest a direct link between these capacities, affording a route by which one can exercise control over one's empathic responses. One line of evidence for the controllability of empathy comes from studies in which subjects were instructed to take the perspective of either themselves or others when viewing stimuli depicting painful situations [37,45]. A recent study [45] found evidence for a SFG/TPJ network involved in the modulatory effects of intentional perspective-taking on the generation of empathic responses. When taking the perspective of a close loved one, increased activation of AI and mid-cingulate regions was observed — presumably reflecting increased empathic engagement. Taking the perspective of a stranger was associated with increased activation and connectivity of both SFG and TPJ, and decreased connectivity between TPJ and AI, a pattern of activations similar to what has been reported in emotion regulation through the regulatory strategy of distancing [46,47]. Thus, this study demonstrates the possibility of employing perspective taking as a

Figure 4



Effects of short-term compassion and memory training on neural responses to videos depicting others in distress. Compassion training was associated with activations in **(a)** the right mOFC, **(b)** the right VTA/SN, **(c)** the right pallidum, and **(d)** the right putamen. Orange boxes show neural activations of an expert practitioner during compassion meditation, showing that compassion training was associated with spontaneous activation of the same brain regions as engaged during the active generation of compassion. These results suggest that a relatively short-term intervention can train one how to actively upregulate positive social emotions, changing the affective quality of distressing empathic experiences. Inset *x/z* values indicate a stereotactic coordinate of the shown slice in the MNI space.
Adapted with permission from [50••].

regulatory strategy to increase and decrease empathic responses.

Further evidence for the possibility of strategic regulation of empathic responses comes from two recent studies that required subjects to actively generate appraisals of stimuli in an effort to attain empathic states. One study [48] contrasted passive responses to affective and neutral pictures of others with active attempts to empathize with them, and found that opercular and pars triangularis portions of the IFG were selectively involved in intentional, effortful empathy, regardless of the affective state portrayed by the other. Another study [49••], found that the pars orbitalis and triangularis of the IFG were activated when subjects had to overcome a mismatch between their own and others' implicit appraisals of affective stimuli to accurately represent and empathize with the other. Intriguingly, these regions have been shown to play an important role in reappraisal [42], an emotion regulation strategy that involves the active generation of alternate appraisals of emotionally salient stimuli. While speculative, these findings can be taken as support for the possibility that the employment of emotion regulation networks can underlie active appraisal-based generation of empathy.

A further strand of evidence for the intentional modulation of empathy comes from a recent study showing that it is possible to qualitatively alter one's negative empathic responses toward witnessing distress in others via training oneself to engage alternate social emotions [50••]. In this study subjects underwent training allowing them to respond with compassionate positive affect when confronted with the distress of others. Before training, subjects responded to video stimuli depicting the distress of other with self-reported negative affect and activations of the core AI/midcingulate empathy network. After training, subjects responded with increased self-reported positive affect and activation of regions associated with positive affect and affiliation, such as medial OFC, putamen, pallidum, and the ventral tegmental area (Figure 4). These results suggest that one can learn how to actively upregulate positive social emotions, changing the affective quality of a distressing empathic experience. Thus, the available evidence indicates it is possible to exercise control over the occurrence, strength and quality of empathic responses, and that the neural correlates of this control are similar to those seen in emotion regulation.

Conclusion

Over the course of the past decade research into empathy has resulted in extensive knowledge of its neural architecture. This research has been essential in expanding our understanding of empathy as a dynamic, malleable, and potentially controllable phenomenon. Future research will now have to work toward formulating detailed mechanistic models for how these different components interact in the generation, modulation, and regulation of vicarious feelings. One promising route for the developments of such models is to integrate the study of empathy with that of general models of social cognition as well as emotion regulation, the latter also promoting an understanding of how the dynamics of the processes of generation and modulation dynamically interact to allow or disallow us to understand and feel what others are feeling. Other promising avenues are found in employing other methodologies such as TMS or pharmacological interventions to gain more precise insight into the functions served by the different components of the extended empathy network, and the neurotransmitter systems governing these different affective states.

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This small-scale intervention study provides interesting evidence on the malleability of empathic responses by way of training, and the possibility of employing the cultivation of compassion as an effective coping strategy in the face of others' distress. Compassion training was shown to increase positive emotion when witnessing others in distress, while not altering negative experience. Neurally, this change was associated with activation of brain regions involved in positive affect and affiliation.