Chapter 2

Neuroimaging Research on Empathy and Shared Neural Networks

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Abstract

Understanding other people's feelings and perspectives is an important part of effective social communication and interaction. Empathy is the phenomenon that enables us to infer the feelings of others and understand their mental states. It aids in social learning and bonding and is thought to be impaired in individuals with social deficits like schizophrenia and autism spectrum disorder (ASD). Advances in neuroimaging technology have allowed social neuroscientists to study brain activity during this complex social process. A growing body of empathy literature demonstrates that multiple brain regions are involved in empathy. Current theories propose that empathy is enabled through the activation of various dynamic neural networks, each made up of several different regions. These networks respond differently depending on specific contexts and available information. This chapter reviews the networks involved in empathy and highlights the current theories and limitations of empathy research.

Keywords: empathy, functional magnetic resonance imaging, mentalizing, mirror neuron system, pain matrix

1. Introduction

Empathy is a complex social phenomenon that broadly refers to the ability to understand and share the feelings of another person. Unlike sympathy, which only requires someone to understand another person's feelings on an intellectual level, empathy is unique in that it is also thought to involve knowing someone's feelings by connecting with those same feelings in one's self. In other words, empathy means having a first-person understanding or emotional response to someone else's experience. This shared understanding can occur in various

ways by employing different emotional and cognitive mechanisms such as affect sharing, simulation, imagination, and theory of mind [1]. Researchers categorize subtypes of empathy as cognitive empathy or emotional empathy. Cognitive empathy refers to perspective taking, while emotional or affective empathy refers to shared emotions and feelings. It is thought that the capacity to empathize requires the activation of different neural networks depending on the type of empathy evoked. Despite the rapid growth in empathy research since Robert Vischer's first English translation of the word, einfühlung, meaning "in-feeling" or "feeling-into," over 150 years ago [2], there are still many questions that remain regarding the neuroscience of the phenomenon.

Social and behavioral psychologists have conducted the majority of empathy research in the last few decades [3]. With the advent of modern neuroimaging techniques, researchers now have the ability to study the neural processes involved in empathy and how different factors such as individual traits, situational context, and even personal experience modulate related neural network activity. State-of-the-art neuroimaging methods and techniques such as functional magnetic resonance imaging (fMRI) allow scientists to investigate how these networks activate when sharing the feelings of another person in controlled experimental environments. Functional MRI studies typically measure blood-oxygen-level dependent (BOLD) changes that occur as a result of precisely timed experimental designs that elicit empathy in participants. These designs allow scientists to compare BOLD responses during different subtypes of empathy and compare them to control conditions that do not require empathy. A link between empathy and brain regions is most often found by statistically correlating the BOLD response evoked in an empathy task with individual differences in empathy traits as measured by questionnaires. The present chapter highlights current neuroimaging research on neural networks thought to enable empathy and the attributes that modulate network activation. Specifically, this chapter will cover prevailing theories of empathy, how it is generated, i.e., through "shared" or "mirroring" networks, and the limitations of current study designs.

2. "Shared" brain networks of empathy

The first question to ask when investigating the neuroscience of empathy is "What parts of the brain are active when people are acting empathically or feeling empathy?" Core brain regions thought to underlie empathy include regions within the "pain matrix," namely the anterior insula (AI) and the middle anterior cingulate cortex (mACC) [4–6]. In numerous fMRI studies, these core regions respond both when experiencing first-hand as well as when observing in others an emotional response or feeling (mostly conducted with the feeling of pain [7, 8]). Therefore, it is thought that we understand the emotions and perspectives of others by utilizing and processing in brain regions that are active both when we ourselves have a sensory, affective, or bodily experience, and when someone else has a similar experience [9]. This theory has become known as the "Shared Network Hypothesis" [10]. For this reason, the AI and mACC, as well as other brain areas that have similar properties, are often referred to as "shared" or sometimes "mirroring" brain regions. Indeed, the activation of many shared brain networks, such as the mirror neuron system (MNS) as well as the pain matrix and some

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emotion-related brain regions, has been linked either directly or indirectly to the genesis of empathy. These shared networks have repeatedly been proposed to underlie the mechanisms that allow people to mentally "share" the feelings of another. The sections below discuss previous and current research related to empathy across these networks.

2.1. Empathy and mirror neuron system (MNS)

Neurons in motor regions of the brain that respond both to action execution and action observation are called mirror neurons. Mirror neurons were first discovered in macaque monkey's F5 premotor region in the 1990s when scientists noticed the same neuron responded not only when the monkey was performing an action but also when he observing another person performing a similar action (e.g., cracking a peanut or watching someone else crack a peanut). In humans, the mirror neuron system (MNS), first proposed by Gallese et al. [11], is a network of brain areas that respond similarly (see **Figure 1**) [11]. It is composed of the inferior frontal gyrus (IFG; thought to be homologous to F5 area in the macaque monkey), in addition to sensorimotor regions (i.e., the lower part of the precentral gyrus, the rostral part of the inferior parietal lobule). Many models of the MNS suggest that mirror neurons provide a mechanism for automatically translating the actions of others onto our own motor system. In other words,

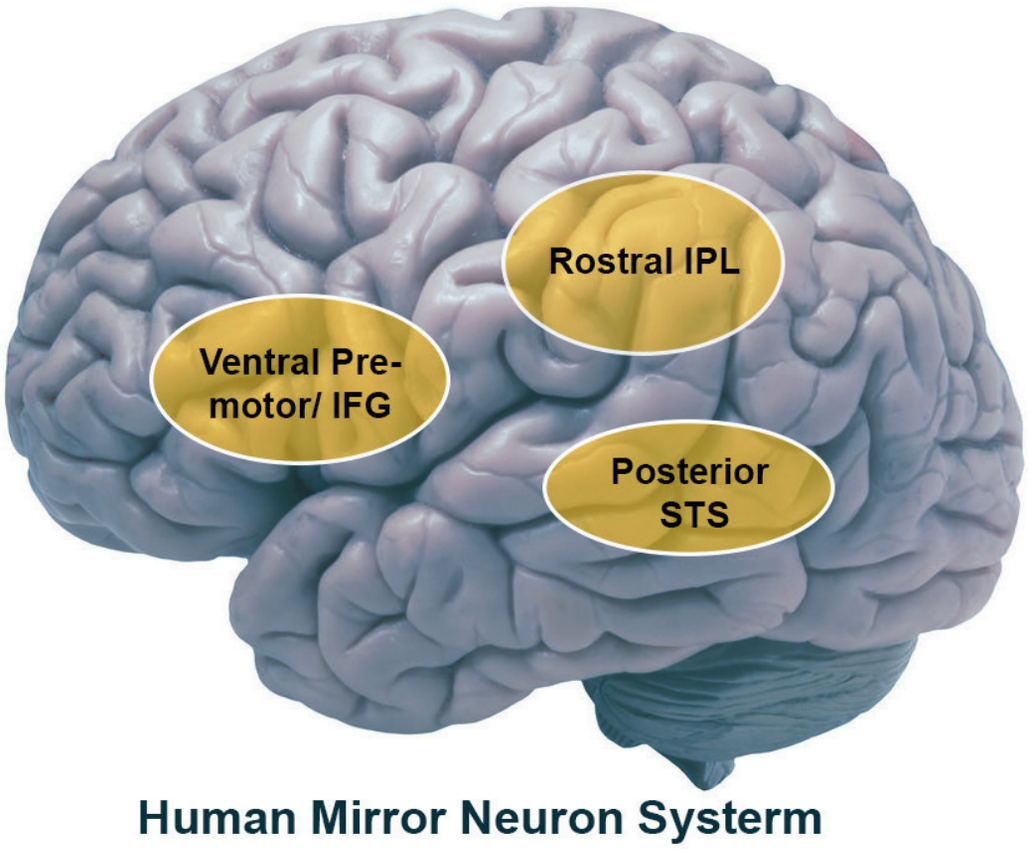

Figure 1. Human mirror neuron on system (MNS). Lateral view of brain with frontal (ventral pre-motor and IFG) and parietal (rostral IPL) labels of the mirror neuron system in addition to the superior temporal sulcus. IFG = inferior frontal gyrus; IPL = inferior parietal lobule; STS = superior temporal sulcus.

whenever one perceives an action of another person, we automatically and covertly "mirror" those actions onto our motor system. Thus, we might understand other people's actions and intentions by covertly simulating them in our motor regions as if we were performing the action ourselves. This form of putting ourselves in someone else's shoes and taking their perspective is thought to be an important component of cognitive empathy [12]. Indeed, several studies have related empathic traits to neural activity in the MNS, indicating that individuals who have higher activity in the MNS also score higher on cognitive aspects of empathy [13–18]. Thus, the MNS may be one neural network involved in perspective taking and cognitive aspects of empathy.

2.2. Empathy and the pain matrix

Other neural networks are thought to process emotional aspects of empathy. One network that has been indicated to be involved in empathizing with pain experienced by others is called the pain matrix. The pain matrix includes the insula, anterior and middle cingulate gyrus, and somatosensory cortices (SI and SII) [6, 19–21]. Interestingly, like the MNS, the pain matrix is activated both when one experiences pain oneself and when observing another person experiencing pain. In a seminal paper in this area, researchers found significant activity in the pain matrix both when a participant in an MRI scanner experienced pain as well as when someone close to them was experiencing pain (**Figure 2**) [6]. Because this network responds so strongly to both physical pain and to processing the pain of others, the AI and mACC are thought to be involved in processing affective components of empathy [6, 8, 22]. The activation of the core regions of the pain matrix for processing self and others' pain is consistent across numerous studies implementing a variety of experimental paradigms, suggesting that pain mirroring, and perhaps empathy itself, can be investigated with high reliability by social neuroscience [8].

However, some critics have proposed that shared representations for self and other in the pain matrix might not be related to empathy, but instead merely reflect an evolutionary response carried out to prepare a motor response as a self-protection mechanism when a threat is detected [23]. For example, watching someone grimace in pain from stepping on a nail may activate our pain and sensorimotor network to prepare the actions needed to avoid experiencing pain ourselves (i.e., stepping away from the nail). Furthermore, while there is a consensus regarding the core regions in the brain that process pain, there are discrepancies on when and how input from the pain matrix is linked to empathy. Disparate results in pain research, such as the engagement of primary and secondary somatosensory cortices during the observation of pain [6], suggest that the pain matrix as a whole may not respond to all types of pain and that it depends on the contextual environments (see sections below for more detail). The same is true for the recruitment of the MNS during cognitive empathy. One common explanation for aberrant findings in empathy research is that there are distinct networks or routes for different types of empathy. Many research groups are using new imaging paradigms and methodologies to explore this dynamic network theory. More research is needed to better understand how the different circuits involved during pain empathy interact and modulation by context.

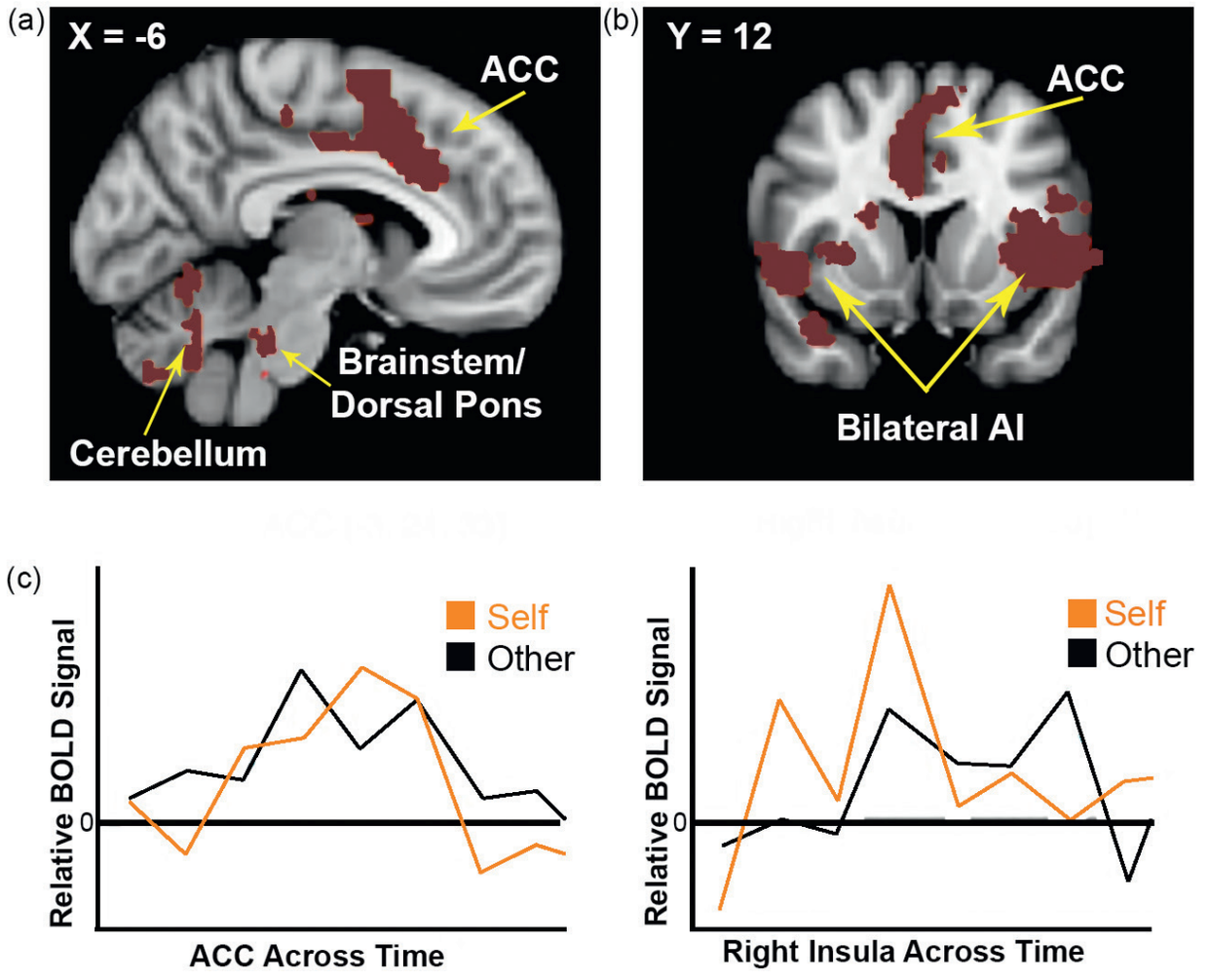

Figure 2. Shared network for self and others' pain. Modified figure from Singer et al. [6]. (a) and (b) illustrate location of increased BOLD signal in brain regions that were significantly active for pain over no pain in both the self and others' conditions as reported by Singer et al. Regions of increased activation to pain in both self and others' conditions included the ACC, cerebellum, brainstem/dorsal pons, left insula, and right anterior insula. (c) Graphs representing the time courses extracted from areas of peak activation in the ACC and right insula for pain greater than no pain in both the self (gray) and other (black) conditions. ACC = anterior cingulate cortex.

2.3. Mentalizing network and cognitive empathy

Mentalizing is a term sometimes used interchangeably with theory of mind (ToM), both typically refer to the cognitive processes involved in understanding the intentions, desires, or beliefs of another person. The "mentalizing network" involves brain regions that have been shown to be activated when someone thinks about another person's mental states. They include the precuneus, ventral parts of medial prefrontal cortex, posterior superior temporal cortex, temporal parietal junction (TPJ), and the temporal poles [24–26]. For example, this network is active when participants are asked to think about the intentions of another person's emotions or actions. Some researchers restrict the definition of mentalizing to only cognitive perspectives when the observer is consciously mentalizing about someone's mental state [27];

however, others include the immediate, automatic, and covert cognitive inference about other people's emotional states [28]. Neuroimaging studies on ToM often do not make this distinction and typically ask participants to consciously mentalize. However, some neuroimaging research distinguishes between cognitive and affective aspects of ToM. Cognitive ToM is required to understand what someone else may be thinking and affective ToM is required to understand how someone might feel given a specific situation. While cognitive and affective components of ToM may be necessary for a fully functioning ToM, individual regions have been shown to play prominent roles in either cognitive (ventral medial prefrontal cortex) or affective (ventral medial frontal lobe) perspective taking [29].

2.4. Emotion-related brain regions and affective empathy

Affective empathy is thought to elicit emotion-related brain regions that are involved in the processing of feelings and emotions. Emotion-related brain regions commonly include the hypothalamus, hippocampus, amygdala, insula, and the cingulate, as well the ventral and medial sectors of the prefrontal cortices [30]. Activity in the insula and amygdala are commonly known to be involved in affective processing and are thought to be related to affective aspects of empathy along with regions of the MNS (i.e., IFG) [31–33]. In particular, the anterior insula, by processing information from the viscera that arise when emotions occur, may be necessary for interpreting body states as affective feelings [34]. Notably, Antonio Damasio et al. have argued that changes in body states and homeostasis (i.e., emotions) are felt as feelings through the representation of these emotions in the brain [35]. So when you feel nervous, this may be because your brain (anterior insula along with other brain areas such as regions of the brainstem) has noticed a quickening in your heartbeat, a clenching in your gut, sweat being produced, and has interpreted that change in body state as nervousness [34]. Damasio has also posited that a physical stimulus is not necessary to experience feelings and that they can be simulated in brain maps when you are empathizing [36]. Indeed, more recent research has been suggested that the insula is involved in integrating subjective feelings, uncertainty, and empathy [10, 37].

2.5. Interactions between different neural networks

Recent models of empathy propose that our capacity to understand the affective and cognitive states of others is enabled by different mechanisms or "routes" [9, 38, 39]. Broadly, one route is through the simulating or mirroring networks (e.g., MNS, pain matrix), and the other, the ToM/mentalizing networks (see **Figure 3**). Simultaneous core emotion-related brain regions (ACC and AI) and MNS brain regions are thought to be elicited when empathy is triggered in response to various sensory stimuli such as viewing body parts in pain or hearing action sounds [3, 13, 40]. During conscious intention understanding of others, as well as self-referential thought, it is thought that a second route for empathy is elicited through the theory of mind or "mentalizing" brain regions. Processing in this network enables sharing other's states based upon one's previous experiences and knowledge (see Ref. [41] for review), and it might be particularly important in situations in which externally provided sensory information about the other's mental state is lacking. For example, the mentalizing network might be

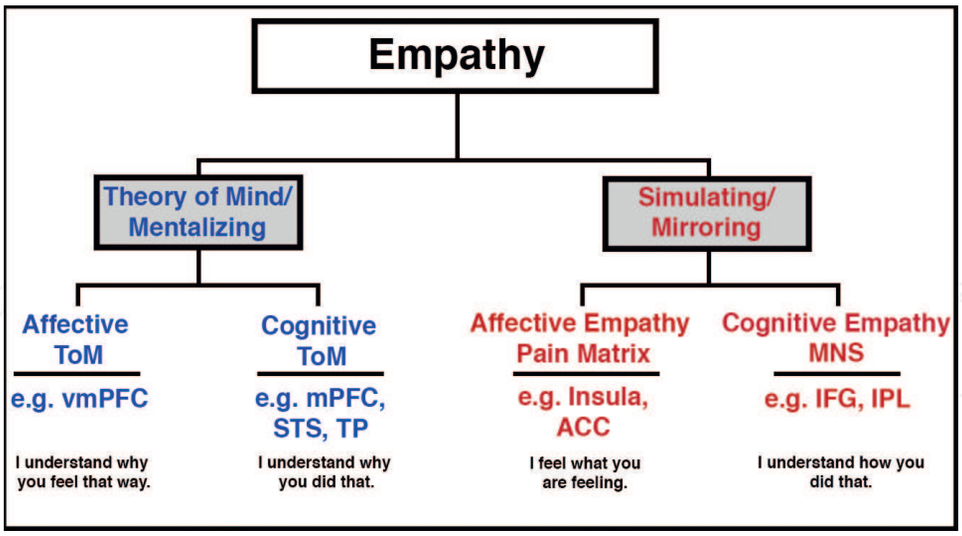

Figure 3. Empathy network. A modified illustration of Dvash and Shamay-Tsoory [42] model of two main systems for empathy, cognitive empathy, and emotional empathy. In addition to Dvash and Shamy-Tsorry's theory of mind (ToM) distinction between cognitive ToM (taking the cognitive perspective of another) and affective ToM (building a theory over what another person feels), a distinction between two types of simulation/mirroring processes is presented. Affective empathy, via regions in the pain matrix/emotional brain regions, refers to the simulation of another's feelings and emotions in oneself is distinguished from cognitive empathy, via regions in the Mirror Neuron System that refers to the simulation of another person's actions. ACC = anterior cingulate cortex; IFG= Inferior Frontal Gyrus; IPL= inferior parietal lobule; mPFC = medial prefrontal cortex; STS = superior temporal sulcus; ToM = theory of mind; TP = temporal parietal; vmPFC = ventromedial prefrontal cortex.

utilized when you listen to lyrics in a pop-song and empathize with the song writer's experience, or when viewing a painting or photo without knowing the events that led up to the event being captured and empathize with the artist or the subject matter.

A similar pattern of dynamic interaction has been proposed for empathic responses in the pain matrix. It is thought that sensory-discriminative attributes (i.e., location, quality, and intensity) and autonomic-affective attributes (i.e., perceived unpleasantness) of a painful experience are coded differently in the network. Singer's research group demonstrated that only self-pain activated contralateral SI, SII/posterior insula, and caudal ACC, while rostral ACC and AI activation enables both self and others' pain. The authors suggest that eliciting different networks for self and others' representations contributes to the better understanding of the subjective feelings. However, contradicting evidence from more recent studies has demonstrated that somatosensory (SI/SII) regions are engaged during both self and others' processing [21, 43]. These disparate findings may be due to the variations in stimulus representation methodology, which again can trigger different neural routes. Viewing body parts in pain, for example, tends to elicit somatosensory regions compared to more abstract pain cues where body parts are not shown [8, 44]. A study that compares both bodily and psychological pain may help detangle and test a multi-route theory.

Empathetic routes are found to exist at even the smallest levels of distinction. There is evidence of distinct empathic routes that are sensitive to emotions at the level of valence. Since pain elicits a robust response in the brain, empathy research has been skewed to favor pain

and negative emotions. It is less known how empathy varies across different emotions in general, and how it is linked to valence (positive or negative feelings). One fMRI study by the Singer group [45] compared pleasant and unpleasant touch in attempts to understand mechanisms for empathy between different valenced emotions. The group found distinct neural pathways for positive and negative valence that were involved in processing empathy. The first-hand and vicarious experience of pleasant touch (e.g., a flower) commonly recruited the medial orbitofrontal cortex (mOFC), while unpleasant stimulation (e.g., rubber maggots) led to shared activation in the right fronto-insular cortex. These findings suggest that different subsystems are engaged when one is mentally sharing positive compared to negative sensations of others. Taken together, these observations indicate that empathy is a dynamic process that elicits multiple subnetworks. Ultimately, further exploration of different emotions in different contexts will bring us closer to understanding the nuances of how empathy is elicited and the subsequent role it plays in influencing one's experience of the mental and emotional states of others. It will also contribute to our understanding of clinical disorders that are characterized by deficits in social processing, such as psychopathy and ASD.

3. Individual differences and empathy in shared brain networks

As discussed above, substantial evidence supports (at least in part) the shared network theory of empathy. However, it is less clear how individual's traits and past experiences modulate these systems. While empathic neural responses often occur automatically, they can also be modulated tremendously by various individual and situational factors [9, 39, 46–49]. Previous experience with particular actions as well as contextual factors, such as the other belonging to an ingroup or outgroup, can influence network activity as well as which subnetworks are invoked. The sections below discuss experience and individual differences related to empathy in the MNS and pain matrix.

3.1. The mirror neuron system

To understand how individual differences relate to neural activity in the MNS, scientists compare brain responses to different actions or changes to the context of an action to individual differences in traits and behavior. For example, one approach has been to try to understand how familiarity with actions modulates MNS activation and empathic processing. One common paradigm is to compare neural activity when observing a familiar action to that of a novel action and correlate the neural activity for each action type to individual differences in trait measures of empathy. Empirical evidence from these studies suggests that while the MNS is engaged for both types of actions (familiar and novel), BOLD signal increases when watching visually or physically familiar actions compared to unfamiliar actions [12, 50–58]. These studies support the general premise of a "like me" hypothesis of action observation function. The "like-me" hypothesis states that we engage with actions that are in our own motor repertoire, or more visually familiar, the more the MNS is engaged [56]. This has led some to propose that experience-driven simulation mechanisms modulate the MNS [54].

On the other hand, some research demonstrates that MNS activity increases when observing novel actions such as a robot dancing [59] or those who are less similar to one's self (e.g., someone with a different cultural or racial background) [60]. Furthermore, one study found that observing a novel limb (the residual limb of an amputee) elicited more activity than observing a typical hand action. However, this effect was modulated by experience with residual limbs [57]. In addition, in that study, it was found that the more empathic participants were, the more they engage their parietal motor regions when viewing the novel limb, but that this correlation was not significant once they were familiarized with the novel limb. This study underscores the notion that regions of the MNS are modulated by familiarity, experience, and individual differences in empathy traits.

3.2. The pain matrix

Various individual and contextual factors modulate the pain matrix as well. Social context such as group bias has been studied in the pain matrix, and similar relationships between BOLD signals in pain-related brain regions and empathy have been found. Relationship dynamics between observer and observee, such as social status or group membership, has been reported to modulate the BOLD signal in regions of the pain matrix while observing pain in others [8–10, 22]. For example, a recent study investigating social status and empathy for pain found that activity in the pain matrix is biased toward self-perceived inferior-status individuals compared with superior-status individuals. When painful stimulation (needle from a syringe penetrating cheek) was applied to inferior-status targets, higher activation in empathy-related brain regions (AI and aMCC) was observed, whereas activity in these same regions was attenuated when observing painful stimulation applied to superior-status targets (**Figure 4**).

In another study, the pain matrix was found to activate more when pain is inflicted on someone from an individual's in-group than out-group [22]. Specifically, activity in the ACC and the insula was found to be greater when participants view pained expressions on the faces of a racial in-group member, while receiving injections to the cheek compared to activity when viewing out-group members. These findings suggest that group biases can modulate empathy and sensitivity in pain-related emotions [22]. In concordance with previous studies, Xu et al. [22] found that empathic activity is a function of individual differences. Participants who showed greater empathic neural responses to in-group members also showed stronger empathic neural responses to out-group members, highlighting the significance of individual differences empathy-related activity [22].

While several of the studies mentioned above found a relationship between activity levels in the pain matrix and empathy traits, it is unclear if activity levels reflect the depth of pain processing rather than empathic processing per se. For example, in a study by Fox et al. [62], it was found that there was more activity in the pain matrix when viewing disliked others rather than liked others. In this study, Jewish participants showed more activity in components of the pain matrix when they viewed neo-nazis in pain than when viewing neutral likable individuals in pain [62]. Given that the participants did not report feeling more empathy for the neo-nazis than the likable individuals, the authors of that study suggested that perhaps activity levels

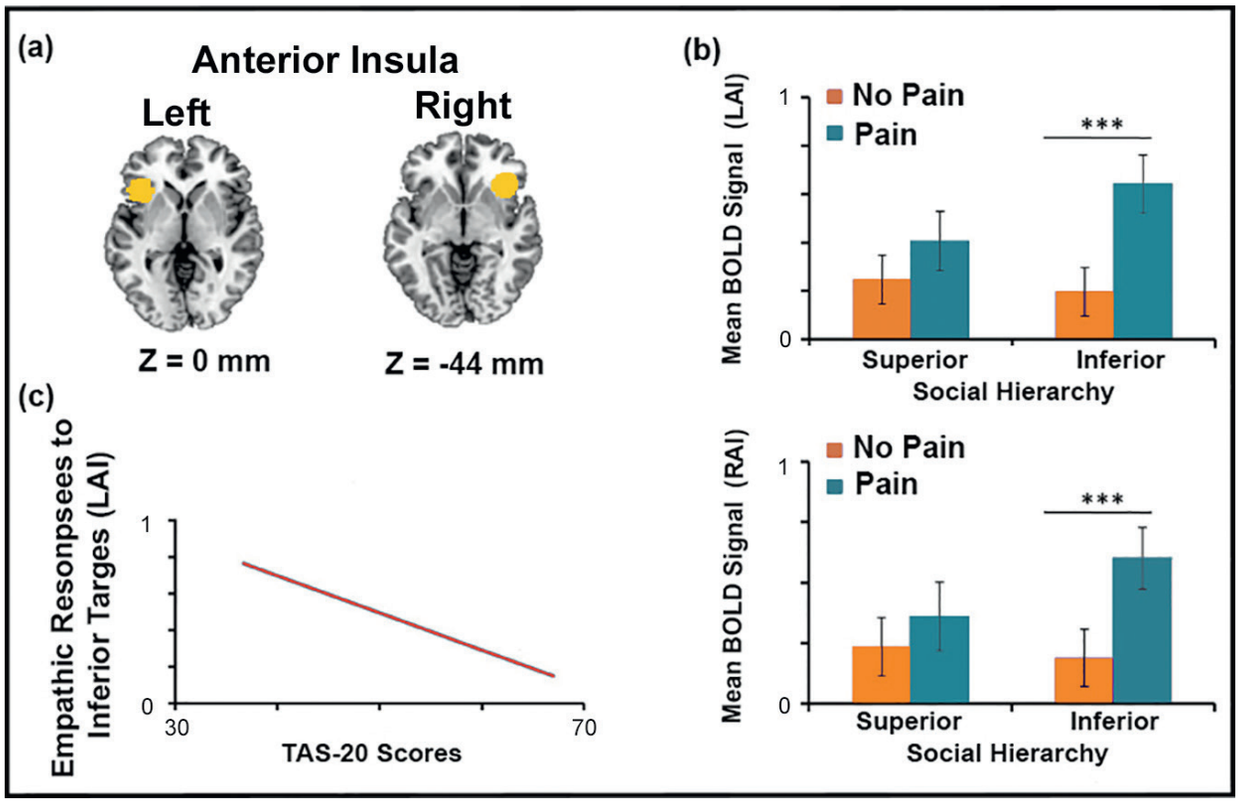

Figure 4. Anterior insula activity and pain. Modified figure from Feng et al. [61]. (a) Representation of the region of interest in the left and right anterior insula used by Feng et al. (b) Graph of mean BOLD signal extracted from the left anterior insula (L, AI) and right anterior insula (R, AI) during pain and nonpain for superior and inferior conditions (error bars indicate one standard error). (c) Graph representing the correlation between TAS-20 scores and empathic responses of the left anterior insula in response to inferior targets during pain compared to no pain.

in the pain matrix do not correspond to the degree of empathy one feels, but instead depth of processing. The authors argue in their study that it was more relevant for the Jewish participants to processes the pain level of their enemy (a neo-nazi) than that of a neutral individual, which was reflected in the increased activity the pain matrix. Thus, it might be that while activity in the pain matrix may contribute to empathic processing, it is not sufficient for empathic processing on its own.

4. Empathy research limitations

As discussed above, many questions about how, where, and when empathy is generated in the brain remain. Moving forward there are several challenges scientists have to overcome before arriving at a more complete understanding of this dynamic process. Some limitations are the result of neuroimaging techniques. It is difficult to study a complex social phenomenon such as empathy in the sterile, cold, and noisy environment of an MRI. Until a more ecologically valid way of measuring neural activity is found, it is important to keep in mind that findings in the lab may not be generalizable to real, everyday life. Study design, data analysis, and individual differences in samples are also important to consider. The discrepant findings we have examined in this chapter may, in part, be accounted for by differences in these areas. For instance,

using on measures of empathy that rely on subjective, self-reports could be problematic. One of the most commonly used empathy measure is a questionnaire called the interpersonal reactivity index (IRI; [1]). Several studies have found that the higher the participant scores on the IRI, the stronger the response in the aMCC and AI when observing the pain of others [6, 9]. Indeed, individuals who have difficulties identifying and describing their emotions (i.e., alexithymia) show attenuated activation during introspection and while empathizing with others [63, 64]. Therefore, it is very important to relate empathic traits in research participants to research findings. However, self-report measures can be problematic if participants have poor introspection and cannot accurately report on their empathic skills thus resulting in inaccurate data. Alexithymia is prevalent in approximately 10% of the general population [65] and is more common in some socially afflicted disorders such as ASD [66, 67]. Since individuals can vary in their ability to perceive emotion, it should be included as a factor when conducting empathy research, especially when studying social disorders where alexithymia is more prevalent. Understanding the differences between deficits in empathy and deficits in introspection is an important distinction. For example, the long history of research suggesting that individuals with ASD have deficits in empathy has recently been disputed by research investigating alexithymia in ASD. A recent study found that deficits in empathy were related to alexithymia and not ASD severity by comparing individuals with ASD with and without Alexithymia and a typical control group [66]. In this study, ASD individuals without alexithymia did not differ in empathy from the control group. Since ToM deficits are consistently reported in ASD, authors of the study suggest that empathy and ToM are dissociable and are part of different streams of social cognition.

On a similar note, experience and other cultural or biological biases should also be taken into consideration when reviewing empathy literature. Surprisingly, not all studies report on potential gender differences. While a few studies have reported no significant differences between males and females [8, 68], Singer et al. [10] found in men, but not in women, empathic responses are shaped by the evaluation of other people's social behavior, such as participating in fair game play [10]. Gender may potentially be a major factor for some empathy network activation and not others. Relatedly, other biological factors may account for aberrant findings. Oxytocin is a neuropeptide that has been shown to increase social understanding and emotion recognition [69] and may also play an important role in modulating empathy. One large study found that oxytocin receptors were associated with affective empathy, while a second receptor (arginine vasopressin receptor) contributed to cognitive empathy, as measured by the IRI [70]. Genetic variation in oxytocin as well as other receptors may influence empathy-related network activity [71]; therefore, future studies should examine how gender as well as hormones and gene variation modulate empathy.

In addition to individual differences, it is also crucial to note that methodological variation across neuroimaging studies can influence findings. Functional MRI data processing techniques and analysis may affect the robustness, and in some cases, the location of a significant result. For instance, recent studies have found that different segments of the AI respond to various empathic situations [8]. Findings like these require data to be explored with high spatial resolution and thus could be missed or misattributed if the data are preprocessing in such a way that these anatomical boundaries are blurred (i.e., the result of spatial smoothing). Taken together, it is important to consider empathy research in the context of its participants, paradigm, and data analysis before interpreting results.

5. Conclusions

Social neuroscience has rapidly progressed in its understanding of shared representations in the brain since the discovery of mirror neurons. There is little doubt that research on shared networks has been integral to understanding and mapping empathy in the brain; nevertheless, questions remain regarding how empathy is elicited from the myriad social and contextual situations that generate it. The most current research literature indicates that the human brain engages multiple networks when sharing emotions and perspectives of others. Moreover, these networks vary in activation based on individual differences that make each person unique. As scientists continue to study the many connections between what is perceived and what is felt, it will expand previous models of empathy from a single network engagement to more tailored context-specific network activation. This chapter has discussed how core and complementary systems that respond to self and others play a significant role in our ability to empathize. As future work continues to map empathy in the brain and ultimately improve our understanding of social cognition, we will take one step closer to understanding what makes us uniquely human.

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