The Role of Anterior Insula and Anterior Cingulate in Empathy for Pain

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The understanding of others’ feelings and emotional states is commonly defined by the term empathy. Here, I discuss recent findings regarding the differential contribution of anterior insula and anterior cingulate cortices to this function. For the first time, Gu and colleagues (2010) showed no direct involvement of the anterior cingulate during observation of another’s pain and proposed the anterior insula as the main neural substrate for the mental representation of empathy.

Empathy allows us to predict the emotional experience and behaviors of other people, thereby prompting us to act accordingly. For this reason, an increasing number of studies are attempting to uncover the neural underpinnings of such an important function.

The most useful model for studying empathy is the observation and/or the imagination of pain in others. Indeed, the structures reported to be involved in empathy for pain closely overlap those activated during perception of somatic pain. Although on one hand some studies pinpoint a central role of neural activity arising from the “sensory node” of the so-called pain matrix (i.e., primary and secondary somatosensory cortices [SI and SII]; e.g., Bufalari et al. 2007), on the other hand several authors confirmed the involvement of neural activities arising from the “affective node” (i.e., the frontoinsular cortex [FIC] and the anterior cingulate cortex [ACC]), which were reported to be increased in virtually all neuroimaging studies of empathy (e.g., Singer et al. 2004).

Interestingly, some scholars pointed out that different findings among studies (emphasis on somatosensory rather than on anterior cingulate/insula activity and vice versa) during empathy for pain may be due to methodological-related factors such as passive versus active observation, perspective taking, emotional context, selective attention, and cognitive load (for a review see Fitzgibbon et al. 2010).

In a recent study published in The Journal of Neuroscience, Gu and colleagues (2010) importantly addressed for the first time one of these possible sources of variability: the role of cognitive load during the experimental performance. Gu and colleagues adopted a simple elegant task that required participants to either evaluate whether the person depicted in the photograph was suffering from pain (task pain [TP]) or to assess the laterality of the represented hand/foot (task laterality [TL]). These two tasks were chosen according to their similar level of cognitive load, as assessed using reaction times and accuracy measures in a pilot behavioral study. Their main study results show that, although an effect of stimulus type was evident on accuracy (painful stimuli had lower accuracy than that of nonpainful stimuli; see their Fig. 2), no significant effect of task on both reaction times and accuracy was detected, thus suggesting a consistent matching of cognitive load between TP and TL. Interestingly, although the interaction of task and stimulus was not significant ($P = 0.07$), the authors found a trend toward slower reaction times when judging the laterality of painful stimuli rather than when judging the laterality of nonpainful stimuli (TL—painful vs. TL—nonpainful). This finding was interpreted as the occurrence of a Stroop-type phenomenon—that is, painful stimuli might attract attention and interfere with laterality judgment even when the painful feature of the stimuli is unrelated to task requirements.

Such a behavioral pattern was paralleled by higher FIC activity during the observation of another’s pain, irrespective of the task required to judge pain or laterality (Gu et al. 2010; their Fig. 3), whereas in contrast the ACC was shown to be equally activated across tasks and stimuli. In fact, by conducting a region of interest (ROI) analysis of brain activity the authors revealed that only the FIC, and not the ACC, was involved during the observation of another’s pain. Indeed, pairwise comparisons between painful and nonpainful stimuli under TP (painful $>$ nonpainful) yielded significant activation in bilateral FIC, somatosensory, superior parietal, and occipitotemporal visual areas, but not in ACC (their Fig. 4C).

Therefore these findings suggest that ACC does not seem to represent a crucial node in the brain network subserving empathy, as classically reported in the literature. Conversely, FIC was shown to be active when painful stimuli are observed regardless of task requirements, and even when subjects are not asked to directly evaluate pain (see Fig. 1).

However, it is worth noting that the method used for localizing the ROIs (by using an [all]–[baseline] contrast estimated on the same data set) has the potential to miss regions that show task-related deactivations. An atlas-driven ROI selection (independent ROIs) or a meta-analysis–based selection (see Jackson et al. 2006b) would have provided a confirmatory approach to the data analysis, able to strengthen the observation of experimentally induced deactivations.

The crucial finding of an automatic FIC activation for observation of another’s pain (i.e., even when judging only laterality) made the authors conclude that FIC “provides a neural mechanism for the perception–action model of empathy, which states that the sight of another person’s emotional state directly and immediately elicits a mental representation of that state in the observer” (Preston and de Waal 2002).

However, this interpretation should not easily be drawn due to the lack of trait/state empathy measures and due to a lack of correlation between personality trait and neural activity in this study. In addition, there is no strong evidence of a causal relationship between the well-known insular activation functions (e.g., interoceptive representation) and their hypothesized higher-level functions (empathy and shared representation),

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neither in this study nor in the literature (for a critical review see Decety 2010). Therefore the call for caution when using the mirror neuron theory to make inferences regarding human behaviors is mandatory. Indeed, this theory has not yet been validated (Hickok 2009) and its application to typically human functions, such as empathy, is importantly less straightforward than its application to action understanding in monkeys.

Thus one might reinterpret the observed differences as rather associated with a process of pain recognition rather than with the subjective feeling of empathy itself (see Morrison et al. 2007). The higher the saliency of the stimulus condition (noxious vs. neutral), the higher the attentional resources to be allocated, especially in those areas related to the understanding of another’s experience (both emotional and cognitive evaluation). Noteworthy is that pain recognition may be necessary, but not sufficient, for empathy and may occur independently of it. Recently, other authors suggested an even more conservative scenario (Lamm et al. 2007): when the subject knows in advance that the hand’s owner is not going to feel pain (e.g., due to medical anesthesia), the vision of a hand inflicted by a syringe elicits activity in a set of structures (including FIC and ACC) similar to that recruited when the subject is certain that the effector will provoke a painful percept in the model. Therefore Lamm and colleagues concluded that such an activity might not be specific to pain as such, but to the exposure to aversive and potentially threatening situations in general.

A compelling research strategy relies on a more scrupulous approach that addresses the complexity of empathy. Indeed, it is well known how empathy depends on other subfunctions such as “mimicry,” “emotional contagion,” “perspective taking,” “sympathy,” “concern,” and “compassion” for it to take place (for a review see Singer and Lamm 2009). Therefore researchers isolate those subfunctions that are thought to shape the neural correlates of empathy to reduce the complexity of their observations, thus increasing the experimental power and the heuristic value of their interpretations (e.g., Kim et al. 2009; Lamm et al. 2008; Li and Han 2010).

On the basis of results reported by Gu et al. (2010), at least four crucial issues remain to be addressed in future studies (see Fig. 1B). First, can we exclude that FIC activity is a specific correlate of empathy for pain (or of its subfunctions) rather than being a more general nonspecific correlate of potential threat and harm detection in the peripersonal space? Future studies should compare the observation of another’s pain to the observation of other categories of aversive and potentially threatening situations, possibly measuring the impact of automatic activity on brain functioning (e.g., heart rate), especially in view of Critchley’s findings about insula activation being related to interoceptive awareness (Critchley et al. 2004). Well-controlled studies are needed both to dismiss the specific involvement of anterior cingulate activity as empathy processor and to discard a possible interpretation of insula activity as a general sensory and affective magnitude estimator not specifically mediating the function of empathy. Second, Gu and colleagues did not report any information on the connectivity between FIC and ACC during empathy or its subfunctions. Third, the same set of stimuli used in the reviewed study by Gu and colleagues significantly activated somatosensory cortices in the previous two studies where it was applied (Jackson et al. 2005, 2006a). Thus the lack of significant somatosensory activation reported by Gu et al. was likely due to task requirements. An alternative version of cognitive load control task may ask the subjects to judge whether the body part showed is a foot or a hand, rather than judging laterality. According to data reported by Gu and colleagues, during this version of the task we may expect a heightened activation of SI and SII following the observation of body parts being harmed. Such an extension of the paradigm may help researchers to further investigate the role of somatosensory cortices during empathy-like brain activities, when the subject’s attention is directed to somatic features of another’s pain. Fourth, the functional interaction between sensory and affective structures may be crucial during the assessment of homeostatic meaning of a stimulus (both during self-referred and other-referred experience). At present, we do not have a clear-cut picture of what constitutes the interaction between anterior insula and somatosensory cortices (especially SII) when a subject is asked to focus on different sensory aspects of the observed noxious experience. For instance, anterior insula may interact with somatosensory cortices (especially SII) in assessing intensity of vicarious pain experience, whereas it may be deactivated during evaluation of other sensory features, such as spatial localization and duration of pain experience.

Gu and colleagues introduced an elegant and sensitive experimental paradigm able to characterize the different contributions of anterior cingulate and anterior insula cortices during observation of another’s pain. This methodological improve-
ment will possibly pave the way to a series of neuroimaging and electrophysiological studies aimed at addressing the representation of empathy and its subfunctions in the brain.

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