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Visceral pain and the black box called brain

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Neuroimaging studies have uncovered a network of brain structures, sometimes referred to as the “pain matrix”, that process pain-related information [1,3]. This network for pain consistently includes the insular cortex, anterior cingulate cortex, somatosensory cortices, and thalamic nuclei. Prefrontal cortical areas and the amygdala also contribute to this network [1, 2,6,8]. Since these brain areas are not exclusively concerned with pain but are also related to bodily functions and affective states, the term “homeostatic afferent processing network” was introduced [7]. Apart from differences in the location of activation within these regions and a greater affective (unpleasant-aversive) rating of visceral pain stimuli, a consistent difference in the activation pattern and brain processing of visceral and somatic stimuli has yet to emerge [4,7].

Neuroimaging of metabolic or hemodynamic activity in the human brain in correlation with pain indices provides valuable quantitative and objective markers of visceral pain and drug effects. However, detailed mechanistic analysis and preclinical evaluation of therapeutic targets requires animal models. Visceromotor reflexes evoked by colorectal distension (CRD) are most commonly used to probe visceral pain processing. Though often referred to as “pseudo-affective responses” the predictive value of visceromotor reflexes for the complex visceral pain experience in humans is not clear.

The significance of the study by Wang et al. in this issue of *Pain* [10] lies in the conceptually innovative attempt to bridge the gap between preclinical and clinical approaches to the study of visceral pain. An elegant, relatively novel telemetric technique was used to measure CRD-evoked visceromotor responses in awake, freely moving rats. The commercially available radiotelemetry system included an implanted transmitter with recording electrodes and an external receiver platform connected to a data acquisition and analysis system for electromyography (EMG) of abdominal muscle contractions. Nociceptive behavior was monitored with a videotracking system. Importantly, CRD-evoked EMG signals and behavior were correlated with regional cerebral blood flow (rCBF) that was measured by autoradiography in brain tissues obtained from the same animals. This is likely the first study to map rCBF-like changes related to visceral stimuli in freely moving animals, which is particularly important when analyzing brain areas concerned with bodily functions and affective state.

Important and exciting findings of this animal study include CRD-related activation in brain areas that are associated with visceral pain in humans and correlation of brain activity changes with visceromotor responses and pain behavior. CRD-related activations were detected not

only in the usual suspects of the “pain network” such as insular, anterior cingulate, and somatosensory cortices, but also in prefrontal areas and subcortical structures, including the amygdala and striatum. Activity changes in most of these areas showed positive correlations with visceromotor responses and nociceptive behavior. Less straightforward correlation patterns were observed in prefrontal cortical areas and some nuclei of the amygdala. Cortical activations were seen throughout the different layers suggesting that not only cortico-cortical but also cortico-subcortical output was enhanced. It will be important to correlate activity levels between cortical and subcortical structures and determine the contribution of ascending and descending loops in visceral pain.

An increasing body of evidence links prefrontal cortical areas to the brain network for pain [1,7]. The role of the prefrontal cortex in cognitive functions, such as planning, decision-making and detection of unfavorable outcomes, avoidance of emotion-based risky choices, and goal-directed behaviors, is well established. An interface between ascending and descending systems, this brain area may also be important for the reciprocal interaction between cognitive and affective aspects of pain. Changes in prefrontal cortical activity could be the basis of well-documented cognitive impairments in pain but may also reflect the cognitive assessment of pain and cognitive control of emotional responses to pain that are organized at subcortical levels.

Subcortical regions with CRD-related activity increases included the amygdala and dorsal caudate-putamen whereas thalamic nuclei, lateral caudate-putamen, and hippocampal areas showed decreased rCBF. The amygdala regulates emotional-affective pain behavior and may also contribute to emotion-based cognitive aspects of pain through interactions with prefrontal cortical areas [2,8]. A clear correlation of rCBF with EMG and pain behavior was detected in the lateral amygdala (LA), which receives nociceptive inputs through the thalamus. Some discrepancies were found for the basolateral (BLA) and central (CeA) nuclei. Associative processing in the LA-BLA network is believed to attach emotional significance to sensory stimuli. The CeA serves as the output nucleus for major amygdala functions and receives additional thalamus-independent nociceptive input from the brainstem and spinal cord. The correlation analysis suggests that visceromotor nociceptive information reaches the LA whereas heavy processing in the LA-BLA-CeA network adds a layer of complexity to the relationship between activity and nociceptive behavior. Individual subnuclei may also contribute differentially to visceral versus somatic pain and/or to brief versus prolonged pain. Pharmacologic deactivation of the amygdala inhibits pain behaviors in the arthritis pain model [8]. Adaptive changes in the amygdala network may occur with relatively brief stimuli such as in CRD model. The fact that visceral pain-related activity changes were detected in these subcortical structures and in the prefrontal cortex emphasizes the sensitivity and usefulness of the authors’ approach to analyze pain mechanisms outside the canonical pain system.

Quite surprisingly decreased activation was observed in several thalamic nuclei, including ventroposterior medial, ventroposterior lateral, posterior and parafascicular nuclei, but neither the mechanisms nor the significance of these decreases is clear. They may reflect neuronal inhibition [9]. If so, decreased activity in thalamic nuclei may result from descending inhibitory cortico-thalamic modulation and/or local network inhibition involving the reticular thalamic nucleus. Pain-related inhibition of brain activity could indicate a shift of the balance of activity levels between subsystems of the pain network. Stimulus-induced deactivation could enhance “contrast”, emphasize the “painful” stimulus, and free up resources for the processing of attention-demanding information [5]. Thalamic inhibition might also reflect a compensatory protective mode. Understanding the significance and mechanisms of intrinsic deactivation could lead to novel therapeutic strategies.

In summary, the study by Wang et al [10] demonstrates the usefulness and relevance of the CRD animal model of visceral pain because it engages brain areas that have been identified as part of a pain network in humans. Activation of the “homeostatic afferent processing network” emphasizes the “pseudoaffective” nature of CRD-evoked visceromotor responses. Pain-related activity changes in similar brain areas in humans and animals also validate the use of brain imaging in animals to evaluate therapeutic agents. It will be important to determine differences between acute and prolonged pain states. Finally, the results of this study emphasize the need for a detailed analysis of brain areas outside the traditional pain system to determine if pain-related changes indicate collateral damage or compensatory mechanisms.

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