The pain matrix and neuropathic pain

Two articles published in this and a recent edition of Brain (Iadarola et al., 1998; Peyron et al., 1998) raise some issues about what functional imaging studies can teach us about nociceptive and non-nociceptive processing in the brain. Both papers address whether brain structures activated during neuropathic and acute experimental nociceptive pain are different. In Peyron et al.'s paper, the neuropathic pain is clinical mechanical allodynia resulting from a brainstem lesion, and in Iadarola et al.'s paper it is capsaicin-induced allodynia in normal volunteers. Both studies suggest similar brain structures are involved in processing the two types of pain. However, Iadarola et al.'s study suggests that inferior prefrontal cortex may be 'uniquely' involved in processing allodynic pain.

Until relatively recently, our understanding of the functional anatomy of human cerebral nociceptive processing was based on post-mortem anatomical studies (Bowsher et al., 1957), effects of cortical and subcortical stimulation during craniotomy procedures, and lesion data (Penfield and Boldrey, 1937; Foltz and White, 1962; Gybels and Sweet, 1989). On this basis, Albe-Fessard et al. (1985) postulated a lateral pain system based on the cortical projections of the lateral thalamic nuclei to the primary somatosensory cortex and a medial pain system based on the medial thalamic group of nuclei with unspecified cortical projections. He proposed a division of function in which the lateral, fast and somatotopic system processes acute nociceptive inputs and the medial system processes chronic nociceptive inputs. However, failure to elicit anything resembling pain during stimulation of the somatosensory cortex, Penfield and Boldrey (1937) raised the possibility that pain was not processed cortically at all. In 1992, Sikes and Vogt identified a nociceptive region of Brodmann area 24 of the anterior cingulate cortex, and suggested that this was one of the main cortical projections of the medial pain system. Since then the key role of the cingulate cortex in the integration of sensory, affective and motivational processes has been recognized (Devinsky et al., 1995).

Human PET studies have confirmed Vogt and colleagues' original finding and suggest that the cingulate cortex is involved in nociceptive processing related to both acute phasic and tonic experimental and chronic pain (Jones et al., 1991, 1992; Talbot et al., 1991; Casey et al., 1994; Hsieh et al., 1995; Vogt et al., 1996). The other brain structures involved are the periaqueductal grey, thalamus, lentiform nucleus, insula, anterior cingulate (areas 24, 25, 32 and 24', 32') and prefrontal cortex (areas 9, 10, 44), inferior parietal cortex (area 39/40) and, somewhat variably, primary and secondary somatosensory cortices.

How do these areas contribute to the experience and behavioural consequences of pain? At first glance it appears that the original division of function proposed by Albe-Fessard is untenable because one of the main components of the medial pain system, namely the anterior cingulate cortex, is involved in both chronic and acute pain processing (Jones et al., 1991; Hsieh et al., 1995). Recent clinical studies suggest that the anterior cingulate responses to nociceptive stimulation are highly context dependent, enhanced in patients with psychogenically maintained pain and reduced in patients with inflammatory pain (Derbyshire et al., 1994; Jones et al., 1997). Thus the anterior cingulate may be concerned with the affective and attentional components of pain experience, and recent experimental evidence lends some support to this concept (Rainville et al., 1997). Because the cingulate cortex is involved in many other higher cognitive processes, it has been suggested by Iadorola et al. (1998) in this issue that cingulate responses to nociceptive stimuli are a non-specific attentional phenomenon. However, other studies suggest that discrete non-contiguous circuitry subserves nociception and attention, and that the cingulate nociceptive responses cannot be described under the general rubric of attention (Derbyshire et al., 1998). Nociceptive specific responses have also been recorded in the anterior cingulate cortex in awake humans and anaesthetized animals, suggesting that non-specific attentional processing is unlikely to explain nociceptive responses in the anterior cingulate cortex (Lenz et al., 1998).

The primary and secondary somatosensory cortices have been variably implicated in acute nociception. The nociceptive projections to these cortical regions are sparse (Kenshallo et al., 1983) and functional imaging results need to be interpreted with some caution. However, it seems that if the stimulus is kept still and the experiment is weighted to reduce the sensory discriminative components of the stimuli except for intensity, somatosensory cortical responses may be difficult to detect (Jones and Derbyshire, 1996). When all the sensory discriminative components are included, significant somatosensory responses are seen and somatotopically mapped (Andersson et al., 1997). Interestingly, no somatosensory responses to chronic pain have been documented (Derbyshire and Jones, 1998). In this context it is interesting that Iadorola et al. demonstrate clear somatosensory cortical responses to capsaicin pain but not to subsequent induced allodynic pain in the same subjects. Unfortunately, the necessary design of the experiment does not allow us to conclude whether this is due to habituation to the sensory discriminative components of the stimulus or whether it is
due to the different nature of the allodynic pain. The intensity of the latter experience was also considerably less than the acute capsaicin-induced pain. Increasing the intensity of pain experience results in progressive recruitment of the pain matrix (Derbyshire et al., 1997), which makes the latter observation difficult to interpret.

The other main difference in brain areas activated in Iadarola et al.’s study was the increased responses in the orbitofrontal cortex. The design of the experiment necessitates the intense capsaicin induced pain preceding the allodynic pain. This represents another example of context-dependent alteration of frontal responses to a nociceptive stimulus, the significance and specificity of which has yet to be determined.

Peyron et al.’s paper describes the pattern of cerebral responses to experimental and neuropathic pain in a group of patients with Wallenberg’s syndrome. They compared the response to allodynic pain on the affected side with induced experimental pain on the non-affected side. The same structures were activated, but interestingly decreases in regional cerebral blood flow rather than increases were seen in the anterior cingulate cortex. Such decreases in regional cerebral blood flow have been observed previously in the anterior cingulate cortex in response to nociceptive stimuli (Vogt et al., 1996). The authors correctly avoid over-interpretation of these increases and decreases in regional cerebral blood flow in terms of excitation or inhibition, but conclude that such quantitative differences are likely to result from altered connectivity or modulation of nociceptive inputs to the cingulate cortex. The challenge now will be to understand the neurochemical basis for the modulation of these inputs.

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References


