LETTER TO THE EDITOR

Interoceptive cortex in the posterior insula: comment on Garcia-Larrea et al. 2010 Brain 133, 2528

A. D. (Bud) Craig

Sir, In a recent publication in *Brain*, Garcia-Larrea *et al.* (2010) reported their identification of patients with post-stroke central pain and selective thermosensory dysfunction, but without other somatosensory abnormalities, and they suggested that the basis for such dissociated symptoms might be the presence of a ‘third somatosensory area’ specifically supporting temperature sensation in the operculo-insular region. In actuality, prior findings, which they did not cite, provide solid neurobiological evidence that the dorsal posterior insula contains the primary cortical sensory representation of temperature and pain in humans; indeed, these previous findings explain perfectly well these and other clinical observations by Garcia-Larrea and colleagues.

In a carefully designed positron emission tomography study (Craig *et al.*, 2000), my colleagues and I examined cerebral activation associated with six different innocuous cool temperatures applied to the hand of awake human subjects, and by performing a regression analysis against stimulus temperature across scans, we obtained clear and unequivocal evidence that the only site in the
contralateral cortex with activity directly (linearly) related to stimulus temperature was in the dorsal posterior insula (Fig. 1). We concluded that this site contains the primary discriminative thermosensory representation in the human brain. Subsequent reports directly support our findings (Maihofer et al., 2002; Hua et al., 2005; Stancak et al., 2006).

It was clear 10 years ago that this evidence matched two prior clinical reports of cerebral lesions that produced profound thermosensory dysfunction (Schmahmann and Liefer, 1992; Greenspan et al., 1999), as well as substantial comparative neurobiological evidence. The only ascending neurons capable of supporting human innocuous thermal (cool, warm) sensation are thermoreceptive-specific lamina I spinothalamic neurons (Craig, 2003). In primates, these neurons project to a selective lamina I thalamocortical relay nucleus that has been termed the posterior part of the ventral medial nucleus (Craig et al., 1994, 1999; Dostrovsky and Craig, 1996; Blomqvist et al., 2000).

Double- and triple-anterograde tracing data from macaque monkeys indicate that the posterior part of the ventral medial nucleus maintains its antero-posterior somatotopic organization in its projection to the fundus of the superior limiting sulcus of the posterior insula, which differentiates it clearly from the main somatosensory (mechanoreceptive and proprioceptive) regions in thalamus and cortex. Figure 2 illustrates the projection observed in one case from a large series previously described (Craig, 1995; and, in preparation). Note that it matches exactly the locus identified in our positron emission tomography experiment in humans and the region of interest for Garcia-Larrea et al. (2010).

Recent publications provide accumulating evidence that significantly extend these original findings (e.g. Bjornsdotter et al., 2009). Indeed, the broader and deeper view of this pathway as an interoceptive representation of the physiological condition of the entire body is widely acknowledged as a useful perspective that provides a basis for understanding the role of the insula in

Figure 2 (A) Drawings representing the location of an iontophoretic injection of biotinylated dextran amine in the posterior part of the ventral medial nucleus (VMpo) of a macaque monkey and the resulting terminal labelling in the dorsal margin of the posterior insula. (B) Photomicrographic documentation of the localization of terminal biotinylated dextran amine labelling in a cytoarchitectonically distinct region at the fundus of the superior limiting sulcus of the posterior insula.
human awareness of feelings from the body, as well as all other subjective feelings (Craig, 2002, 2009; Keysers et al., 2010; Lamm and Singer, 2010).

Unfortunately, Garcia-Larrea and colleagues (2010) did not acknowledge any of these additional findings. Perhaps, they regard the existence of the posterior part of the ventral medial nucleus as too controversial (Montes et al., 2005), or their clinical perspective on the operculo-insular region as probative (Mauguier et al., 1999). However, the clinical impact of these additional findings extends well beyond the basic science of identifying the location of the primary thermosensory representation in human cortex. These additional findings strongly support the fundamental hypothesis that a common mechanism (i.e. release from cold inhibition of pain) may underlie all cases of central pain (Craig, 2007), a proposal made initially in Brain (Kendall, 1939) and also recently endorsed in Brain (Ducreux et al., 2006). This hypothesis can explain why the cardinal feature in virtually all patients with post-stroke central pain is dysfunctional innocuous thermal sensation in exactly the region to which ongoing pain is referred (Bowsher, 1996); why central pain is always associated with lesions of the ascending lamina I spinothalamocortical pathway (Leijon et al., 1989); and why the thermal grill illusion of pain (Craig and Bushnell, 1994) was found to be absent in a patient with central pain (Morin et al., 2002). Obfuscating this hypothesis by disregarding these additional prior findings and by dissociating patients with post-stroke central pain and operculo-insular lesions could interfere with the immediate clinical impact, because on the basis of this hypothesis the thermal grill has in fact been recommended as a useful probe for the discovery of pharmaceutical therapies for central pain (Kern et al., 2008).

Funding

The author’s laboratory is supported by funds from the James S. McDonnell Foundation and the Barrow Neurological Foundation.

References