Imaging Visceral Pain

Stuart W. G. Derbyshire, PhD

Corresponding author
Stuart W. G. Derbyshire, PhD
University of Birmingham, School of Psychology,
Edgbaston B15 2TT, UK.
E-mail: s.w.derbyshire@bham.ac.uk

Current Pain and Headache Reports 2007, **11:**178–182
Current Medicine Group LLC ISSN 1531-3433

The application of functional imaging to study visceral sensation has generated considerable interest regarding insight into the function of the brain-gut axis. Brain activation in normal control subjects during visceral sensation includes the perigenual cingulate cortex, which is involved in affective processing and has direct connections to autonomic centers. In contrast, somatic pain rarely activates the perigenual cingulate. This difference in brain activation is highly interpretable because visceral stimuli are experienced as more unpleasant than somatic stimuli. Clinical studies are suggestive of functional changes that may be a consequence or cause of conditions such as irritable bowel syndrome, but the findings are not consistent and are not as obviously interpretable as the differences observed when contrasting visceral and somatic stimulation. Although this is partly because brain imaging is still a relatively new technique, it also reflects weaknesses inherent to the understanding of chronic visceral pain as a biopsychosocial phenomenon. The biopsychosocial concept is very broad and rarely provides for precise predictions or mechanisms that can be directly tested using brain imaging. Future use of brain imaging to examine chronic visceral pain and other pain disorders will be more likely to succeed by describing clear theoretical and clinical endpoints.

Introduction

Visceral versus somatic nociceptive stimuli evoke different perceptions and behavioral responses [1]. Pain from a somatic origin is easy to localize, usually possesses a sharp or other sensory quality (eg, burning or cold), is often escapable, and generally motivates an active motor response such as fight or flight accompanied by tachycardia, hypertension, and increased alertness. In contrast, visceral pain is difficult to localize, is usually experienced as dull, diffuse, or throbbing, is often inescapable, and generally fails to motivate any active motor response, instead resulting in quiescence, bradycardia, and hypotension, with decreased reactivity to the environment. In general, although noxious somatic stimulation readily produces a sharp, precise experience of pain, noxious visceral stimulation produces a sense of unpleasantness that is not always reconcilable with what the subject might refer to as pain.

The different experience after visceral versus somatic nociceptive input is partly due to the very different afferent input [2]. Visceral receptors are largely unresponsive to most somatic stimuli, such as temperature and laceration, but respond readily to changes in pressure. In addition, only approximately 1.5% of all visceral neurons converge on spinal cells and then ascend to the brain [3]. Most visceral neurons perform local regulatory functions that remain below the level of sensory awareness. It is not surprising that visceral stimuli produce diffuse and poorly localized sensory experiences.

Clinical and animal evidence also suggests that visceral afferent pathways to the brain are separate from those that carry noxious somatic information [4]. Somatic pathways include the anterolateral spinothalamic tract, which projects into the lateral and medial thalamic nuclei and then onto the cerebral cortex. Visceral afferent pathways include the dorsal column, which projects into the gracile nucleus and then onto lateral thalamic nuclei.

Brain Responses to Visceral and Somatic Stimuli

The different peripheral anatomy, central projections, and experience of visceral sensation suggest that the brain activation profile during visceral sensation should be different from that during somatic sensation [5]. Activation during somatic pain experience includes the primary sensory cortex (S1), secondary sensory cortex (S2), mid-anterior cingulate cortex (MCC), prefrontal cortices, insular cortex, and the thalamus [6,7•,8]. Figure 1 illustrates regions on the medial and lateral surface that have been activated during the application of various visceral stimuli.

Figure 1 shows clear activation during visceral sensation in S2 (probably including insula projected onto the surface), MCC, and prefrontal cortices. These activations are highly comparable with those seen during noxious somatic sensation. S2 contains neurons that code spatial, temporal, and intensive aspects of innocuous and noxious stimuli and is

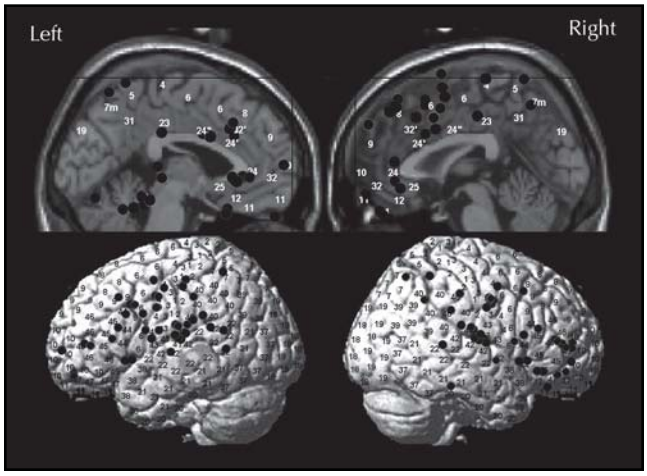

Figure 1. Reported increases in activation on the medial (top) and lateral (bottom) surface of the brain during the experience of visceral sensation, plotted onto the standard Montreal Neurological Institute brain using black dots. The numbers represent Brodmann's areas based on translation from the atlas by Talairach and Tournoux [9], and from reviews by Vogt et al. [8] and Derbyshire [6].

widely considered to provide the predominant sensory representation of visceral stimulation [10,11].

Activation of insula is the most consistent finding during both noxious visceral and somatic sensation [6,7•,12,13]. Insula responses are associated with internally generated emotion, and the insula has been designated as a visceral sensory area by Neafsey et al. [14]. Electrical stimulation of the insula in rats, cats, dogs, monkeys, and humans elicits changes in blood pressure, heart rate, respiration, piloerection, pupillary dilatation, gastric motility, peristaltic activity, salivation, and adrenaline secretion.

The anterior cingulate and insula cortices have long been considered to be components of the limbic (emotional) brain [15,16] and thus involved in the affective motivational dimension of pain. Early functional imaging experiments with noxious somatic stimulation were precisely designed to assess the activation of medial pathway projections to the anterior cingulate cortex [17,18]. These studies, and subsequent reports, have confirmed activation of the anterior cingulate cortex during noxious stimulation.

Prefrontal activation is commonly observed during visceral and somatic stimulation, but the role of the prefrontal cortex is much less certain. Coghill et al. [19] observed prefrontal activity only in response to the transition from no stimulus (rest) to the presence of a stimulus (heat or noxious heat), thus suggesting that prefrontal cortex does not play a direct role in pain perception but is involved in general stimulus detection. Strigo et al. [5] reported significantly more prefrontal activity in response to a noxious somatic stimulus than a noxious visceral stimulus, suggesting prefrontal activity to be especially dominant for somatic events. However, other studies have demonstrated prefrontal cortex activation to correlate with the intensity of a noxious stimulus [20,21], and Figure 1 clearly indicates activation of prefrontal cortex during visceral sensation across several studies. The precise role of the prefrontal cortex may remain uncertain, but in general, the prefrontal cortex is involved in the regulation and organization of behavior and cognition. The prefrontal regions activated (areas 10/45/47/11) receive widespread neural inputs from unimodal areas in all the major sensory modalities, from all other heteromodal regions of the brain, and from many limbic areas [22]. These prefrontal neuronal responses can be specialized, mixed, or multimodal and can integrate vast amounts of information to provide control outputs for varied cognitive and motor operations that are likely to be required during detection of noxious stimuli from visceral and somatic sources.

Regions of Differential Brain Response During Visceral Stimulation

Although both somatic and visceral stimuli activate MCC, there is an additional region of the anterior cingulate cortex around the genu of the corpus callosum, the perigenual anterior cingulate cortex (pACC), which is also activated during visceral sensation but rarely activated during noxious somatic stimulation. The division of the anterior cingulate cortex into MCC and pACC is motivated by the different connections of these regions. These differences are described in detail elsewhere [8,23••]. In summary, pACC receives most mediodorsal thalamic and amygdala afferents, whereas midcingulate has major and reciprocal connections with cingulate premotor areas, the pontine nuclei, and area 46 of the prefrontal cortex. Thus, the MCC is liable to be involved in executive motor function and decisions including response selection during divided attention tasks, whereas the pACC is more likely to be associated with affective responses. The pACC receives substantial direct input from the hypothalamus and amygdala and has direct monosynaptic input to brainstem autonomic centers and the periaqueductal gray (PAG). This circuitry represents a system capable of mediating important autonomic visceral response, affective integration of visceral events, and descending modulation of viscerosensory traffic.

The amygdala inputs into pACC are substantial and reciprocal, but the cortical regions receiving the heaviest amygdaloid afferents, with much reduced reciprocal projections, are the medial and lateral orbitofrontal cortex, medial wall of the frontal cortex, and the anterior insula [24,25]. Although the difference is not as obvious as in the pACC region, lateral frontal responses during visceral sensation include the orbitofrontal cortices to a greater degree than in somatic sensation.

S1 activation can be observed during visceral stimulation but is much less apparent than during somatic pain, probably reflecting the very different localization processing of somatic versus visceral pain. Visceral studies

often include the peri-anal and proximal divisions of the gastrointestinal tract that contain a relatively dense spinal innervation and may provide for spinothalamic transmission directly or indirectly via the ventrolateral medulla or midbrain PAG region, into the thalamus [10,11]. Alternatively, or perhaps additionally, there is a dorsal-column projection to the brain-stem gracile nucleus that projects to the ventral posterior lateral thalamic nuclei [26].

Somatic stimulation provides extensive bilateral activation of the thalamus that is almost completely absent during visceral stimulation. This lack of thalamic response from the studies of visceral distension is surprising because information arising from the viscera that reaches conscious perception would be expected to synapse in the thalamus before reaching primary sensory or motor regions. Primary motor and sensory cortices can be observed during studies of visceral sensation, suggesting that the lack of thalamic report may be a false-negative result. Some visceral studies have reported thalamic activation but did not include coordinates to allow a plot on Figure 1 [27,28]. Thalamic activation also has been described in animals during both colorectal and esophageal distension [26,29]. It seems likely that visceral sensations do correlate with some thalamic activation, but this may be less than observed during somatic experience. Further studies will be necessary to clarify the nature of any thalamic differences in processing.

Brain Activity in Clinical Pain States

The persistence, intractability, and apparent absence of peripheral disease to account for the irritable bowel syndrome (IBS) and other functional disorders has led to particular interest in the possibility of a central etiology and the use of functional imaging to test central hypotheses regarding IBS. The dominant themes in the clinical understanding or interpretation of functional disorders such as IBS include hypersensitivity, hypervigilance, hyperalgesia, central sensitization, stress-mediated dysfunction, and encompassing all these themes, the biopsychosocial model of visceral disorder [10,11,30,31].

The suggestion of hypersensitivity follows the observation that patients are more sensitive than control subjects when examined using balloon distension of the esophagus, stomach, small intestine, bile duct, and colorectum. Numerous trials with IBS patients have provided evidence of reduced pain and discomfort threshold during rectal distension (compared with controls), which may be further increased after rapid repetitive stimulation of the sigmoid colon [32]. Somewhat analogously, repetitive distension of the esophagus has been shown to reduce pain threshold in patients with functional dyspepsia, but not in controls [33].

This hypersensitivity can occur as a consequence of inflammation or infection, with secondary hyperalgesia and allodynia following sensitization of peripheral nociceptors and excitability of spinal dorsal horn neurons. This phenomenon has been demonstrated experimentally in patients with non-cardiac chest pain [31]. The role of higher central, psychological involvement is inferred from studies demonstrating development of IBS after a bout of gastroenteritis only in patients with high levels of life stress and hypochondriasis [34]. The suggestion that functional gastrointestinal patients may be hypervigilant toward their organ of distress and symptoms is supported by studies demonstrating selective recall and biased information processing in IBS patients [35,36]. The biopsychosocial model of functional gastrointestinal illness encapsulates the multimodality inputs and processes that can precede and maintain visceral dysfunction and distress [37].

The results of functional imaging studies can be brought to bear in support of these concepts. It is evident that visceral sensation produces activation in large and widespread regions of the brain that integrate stress, cognition, and visceral sensory information. Disruption in the processing of these regions may explain some of the symptoms of the disorder. In general, differences in activation of pACC, MCC, and orbito and prefrontal cortices in patients with functional visceral pain might be expected to reflect changes in autonomic response, stress experience, and cognitive processing during stimulation or normal regulatory function. Activation of prefrontal area 10 and pACC during the simple expectation of rectal distension in IBS patients, and the exaggerated MCC response to esophageal distension in subjects primed with a negative affective context, provide evidence that these circuits can be modulated independent of gastrointestinal stimulation [11,38]. Enhanced activation of the pACC and insula cortex in syndrome X patients, who have cardiac pain in the absence of abnormal coronary angiogram, provides further evidence for "top down" processes mediating functional pain [39]. In our laboratory, we have used hypnosis to induce somatic pain experience in normal controls without any physically noxious stimulus and demonstrated activity of the MCC, insula, S1, S2, prefrontal cortex, and thalamus [40•]. Thus there is good evidence from functional imaging studies that the brain, rather than just responding to noxious stimuli, can play an active role in creating pain experience.

Nevertheless, any underlying "neural signature" for functional visceral pain remains undiscovered or incompletely described. There is no single region that has been uncovered as the region responsible for functional visceral pain, and patients with functional visceral pain tend to activate the same brain regions as do normal controls, although often with different intensity. The flow of information from functional imaging studies of visceral sensation is yet to provide closure on the nature of any specific process involved in the dysfunction of the gastrointestinal system. This is not entirely a problem of functional imaging. The concepts adopted to interpret functional disorder are themselves broad, and their relevance and utility have been questioned [41,42].

For example, the prevalence of rectal hypersensitivity in IBS is highly variable across studies, ranging from 20% to 80%, and discovery of hypersensitivity is usually dependent upon repetitive stimulation and has only a weak correlation with current pain ratings. Rectal hypersensitivity does not predict therapy outcome and has yet to contribute to the diagnosis or pharmacotherapy of IBS [41]. The results from functional imaging studies have been inconsistent, with studies of functional disorders revealing less [43], more [18,27], and the same [21] ACC response as in control subjects.

The technique of functional imaging to investigate these currently uncertain disease markers and the use of a broad interpretative framework such as the biopsychosocial model can lead toward a line of reasoning that does not necessarily advance understanding. Interpretation of a set of activations using the biopsychosocial model of disease relies upon a large theoretical construct itself dependent on multiple components often not directly addressed by the functional imaging studies. The result is a set of activations that can be easily integrated into current conceptual thinking while remaining indeterminate as sources of evidential relevance for any component of the disease experience [44]. To state this differently, providing evidence that is only "consistent with" general theoretical claims risks leaving the speculative nature of those claims undisturbed by the passage of experimentation. Theories require explanations of processes, and at least for now, this is critically absent.

Conclusions

Functional imaging studies using visceral and somatic stimuli have demonstrated that a large number of brain regions are involved in the processing of these stimuli. Presumably, the different regions capture the different dimensions of visceral and somatic sensory experience, including the intensity and affective components. Greater involvement of the pACC region during visceral relative to somatic sensation can be explained by the greater affective response to visceral stimuli and by the greater involvement of pACC in affective and autonomic function.

The techniques of functional imaging have been extended to investigation of chronic pain states and have revealed variable differences in comparison with normal control subjects that can be broadly explained as reflecting the biopsychosocial changes that occur in patients with chronic pain or that might cause some chronic pains. More recent studies have begun to directly manipulate the factors that may influence pain experience in chronic pain populations and aim to explain why specific components of the pain matrix may not always be present, or may be over-present, in those populations [45•,46•,47]. These advances in experimental technique are important because they narrow the theoretical framework and thus constrain the results and the interpretation. Broad descriptive studies will remain interesting and useful, but studies that focus on hypothesized regional responses to psychophysically well-controlled stimuli have a better chance of explaining the underlying brain processes that may cause functional pain.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Lewis T: *Pain*. New York: MacMillan; 1942.
2. Janig W: **Neurobiology of visceral afferent neurons: neuroanatomy, functions, organ regulations and sensations.** *Biol Psychol* 1996, **42:**29–51.
3. Cervero F, Laird J: **Visceral pain.** *Lancet* 1999, **353:**2145–2148.
4. Willis WD, Al-Chaer ED, Quast MJ, Westlund KN: **A visceral pain pathway in the dorsal column of the spinal cord.** *Proc Natl Acad Sci U S A* 1999, **96:**7675–7679.

5 Strigo IA, Duncan GH, Boivin M, Bushnell MC: **Differentiation of visceral and cutaneous pain in the human brain.** *J Neurophysiol* 2003, **89:**3294–3303.

6. Derbyshire SWG: **Exploring the pain "neuromatrix."** *Curr Rev Pain* 2000, **6:**467–477.

7.• Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: **Human brain mechanisms of pain perception and regulation in health and disease.** *Eur J Pain* 2005, **9:**463–484.
Most up-to-date review of pain imaging research that includes new comparisons of imaging techniques and some new findings.

8. Vogt BA, Berger GR, Derbyshire SWG: **Structural and functional dichotomy of human midcingulate cortex.** *Eur J Neurosci* 2003, **18:**3134–3144.
9. Talairach J, Tournoux P: *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Georg Thieme; 1988.
10. Aziz A, Thompson DG: **Brain-gut axis in health and disease.** *Gastroenterology* 1998, **114:**559–578.
11. Aziz Q, Schnitzler A, Enck P: **Functional neuroimaging of visceral sensation.** *J Clin Neurophysiol* 2000, **17:**604–612.
12. Derbyshire SWG: **Meta-analysis of thirty-four independent samples studied using positron emission tomography (PET) reveals a significantly attenuated central response to noxious stimulation in clinical pain patients.** *Curr Rev Pain* 1999, **3:**265–280.
13. Derbyshire SWG: **Review and meta-analysis of neuroimaging data reveals differential activation from upper and lower gastrointestinal distension.** *Am J Gastroenterol* 2003, **98:**12–20.
14. Neafsey EJ, Terreberry RR, Hurley KM, et al.: **Anterior cingulate cortex in rodents: connections, visceral control functions, and implications for emotion.** In *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Treatise*. Edited by Vogt BA, Gabriel M. Boston: Birkhauser; 1993:206–223.
15. MacLean PD: **Psychosomatic disease and the 'visceral brain.' Recent developments bearing on the Papez theory of emotion.** *Psychosom Med* 1949, **11:**338–353.
16. Papez JW: **A proposed mechanism of emotion.** *Arch Neurol Psychiatry* 1937, **38:**725–743.
17. Jones AKP, Brown WD, Friston KJ, et al.: **Cortical and subcortical localization of response to pain in man using positron emission tomography.** *Proc Biol Sci* 1991, **244:**39–44.
18. Derbyshire SWG, Jones AKP, Devani P, et al.: **Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography.** *J Neurol Neurosurg Psychiatry* 1994, **57:**1166–1172.

19. Coghill RC, Sang CN, Maisog JMA, Iadorola MJ: **Pain intensity processing within the human brain: a bilateral, distributed mechanism.** *J Neurophysiol* 1999, **82:**1934–1943.
20. Derbyshire SWG, Jones AKP, Gyulai F, et al.: **Pain processing during three levels of noxious stimulation produces differential patterns of central activity.** *Pain* 1997, **73:**431–445.
21. Derbyshire SWG, Jones AKP, Creed F, et al.: **Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls.** *Neuroimage* 2002, **16:**158–168.
22. Mesalum MM: **Behavioral neuroanatomy. Large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations.** In *Principles of Behavioral and Cognitive Neurology,* edn 2. Edited by Mesalum MM. New York: Oxford University Press; 2000:1–120.
23.•• Vogt BA: **Pain and emotion interactions in subregions of the cingulate gyrus.** *Nat Rev Neurosci* 2005, **6:**533–544.
Comprehensive review and overview of cingulate function, especially with respect to pain.
24. Van Hoesen GW, Morecraft RJ, Vogt BA: **Connections of the monkey cingulate cortex.** In *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Treatise*. Edited by Vogt BA, Gabriel M. Boston, MA: Birkhauser; 1993:249–284.
25. Amaral DG, Price JL: **Amygdalo-cortical projections in the monkey (Macaca fascicularis).** *J Comp Neurol* 1984, **230:**465–496.
26. Willis WD, Al-Chaer ED, Quast MJ, Westlund KN: **A visceral pain pathway in the dorsal column of the spinal cord.** *Proc Natl Acad Sci U S A* 1999, **96:**7675–7679.
27. Mertz H, Morgan V, Tanner G, et al.: **Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distension.** *Gastroenterology* 2000, **118:**842–848.
28. Lotze M, Wietek B, Birbaumer N, et al.: **Cerebral activation during anal and rectal stimulation.** *Neuroimage* 2001, **14:**1027–1034.
29. Horn AC, Vahle-Hinz C, Bruggemann J, et al.: **Responses of neurons in the lateral thalamus of the cat to stimulation of urinary bladder, colon, esophagus, and skin.** *Brain Res* 1999, **851:**164–174.
30. Mayer EA, Gebhart GF: **Basic and clinical aspects of visceral hyperalgesia.** *Gastroenterology* 1994, **107:**271–293.
31. Sarkar S, Aziz Q, Woolf CJ, et al.: **Contribution of central sensitisation to the development of non-cardiac chest pain.** *Lancet* 2000, **356:**1154–1159.
32. Munakata J, Naliboff B, Harraf F, et al.: **Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome.** *Gastroenterology* 1997, **112:**55–63.
33. Paterson WG, Vanner SJ: **Increasing pain sensation to repeated esophageal balloon distension in patients with chest pain of undetermined etiology.** *Dig Dis Sci* 1995, **40:**1325–1331.
34. Gwee KA, Leong YL, Graham C, et al.: **The role of psychological and biological factors in postinfective gut dysfunction.** *Gut* 1999, **44:**400–406.
35. Gomborone JE, Desnap PA, Libby GW, Farthing MJG: **Selective affective biasing in recognition memory in the irritable bowel syndrome.** *Gut* 1993, **34:**1230–1233.
36. Gibbs-Gallagher N, Palsson OS, Levy RL, et al.: **Selective recall of gastrointestinal-sensation words: evidence for a cognitive-behavioral contribution to irritable bowel syndrome.** *Am J Gastroenterol* 2001, **96:**1133–1138.
37. Drossman DA: **Gastrointestinal illness and the biopsychosocial model.** *J Clin Gastroenterol* 1996, **22:**252–254.
38. Naliboff BD, Derbyshire SWG, Munakata J, et al.: **Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation.** *Psychosom Med* 2001, **63:**365–375.
39. Rosen SD, Camici PG: **The brain-heart axis in the perception of cardiac pain: the elusive link between ischaemia and pain.** *Ann Med* 2000, **32:**350–364.
40.• Derbyshire SWG, Whalley MG, Stenger VA, Oakley DA: **Cerebral activation during hypnotically induced and imagined pain.** *Neuroimage* 2004, **23:**392–401.
Direct demonstration that the brain is involved in generating pain experience rather than merely registering nociceptive information.
41. Camilleri M, Coulie B, Tack JF: **Visceral hypersensitivity: facts, speculations, and challenges.** *Gut* 2001, **48:**125–131.
42. Derbyshire SWG: **Burning questions about the brain in pain.** *Pain* 2006, **122:**217–218.
43. Silverman DH, Munakata JA, Ennes H, et al.: **Regional cerebral activity in normal and pathological perception of visceral pain.** *Gastroenterology* 1997, **112:**64–72.
44. Bub DN: **Methodological issues confronting PET and fMRI studies of cognitive function.** *Cogn Neuropsychol* 2000, **17:**467–484.
45.• Gracely RH, Geisser ME, Giesecke T, et al.: **Pain catastrophizing and neural responses to pain among persons with fibromyalgia.** *Brain* 2004, **127:**835–843.
First demonstration that catastrophizing can influence neural pain responses.
46.• Lorenz J, Casey KL: **Imaging of acute versus pathological pain in humans.** *Eur J Pain* 2005, **9:**163–165.
Describes efforts to demonstrate the active role of the brain in creating allodynia and hyperalgesia.
47. Tracey I, Ploghaus A, Gati JS, et al.: **Imaging attentional modulation of pain in the periaqueductal gray in humans.** *J Neurosci* 2002, **22:**2748–2752.