Dissociating Pain from Its Anticipation in the Human Brain

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The experience of pain is subjectively different from the fear and anxiety caused by threats of pain. Functional magnetic resonance imaging in healthy humans was applied to dissociate neural activation patterns associated with acute pain and its anticipation. Expectation of pain activated sites within the medial frontal lobe, insular cortex, and cerebellum distinct from, but close to, locations mediating pain experience itself. Anticipation of pain can in its own right cause mood changes and behavioral adaptations that exacerbate the suffering experienced by chronic pain patients. Selective manipulations of activity at these sites may offer therapeutic possibilities for treating chronic pain.

Intense, noxious stimulation leads to physiological, emotional, and behavioral changes of obvious adaptive significance (1). One is the experience of pain, which minimizes immediate harm by motivating escape (2). A second is the activation of mechanisms to prevent future harm by learning to recognize signals of impending pain (3), allowing future painful events to be expected and thus avoided.

Functional neuroimaging has previously been used to identify cerebral activation patterns associated with the experience of pain (4, 5). Brain areas activated during peripheral painful stimulation included anterior cingulate, insular, prefrontal and somatosensory cortices, and the thalamus (6). Attempts to discriminate between brain responses associated with the expectation of pain and those associated with the direct experience of pain are only now beginning (7). This distinction is important because not only do these two processes have the separate adaptive consequences outlined above, but they also have potentially separate, maladaptive consequences. For example, expectation of pain by itself may be an important factor in the development of chronic pain syndromes (8). A dissection of the functional neuroanatomies of the expectation and the experience of pain could therefore aid development of therapeutic strategies for the treatment of chronic and acute pain.

Twelve healthy volunteers underwent functional magnetic resonance imaging (fMRI) (9) while being presented with a pseudo-random sequence of two intensities of thermal stimulation (painful hot or nonpainful warm). Colored lights signaled in advance the two kinds of thermal stimulation. Subjects learned during the imaging session which color signaled pain and which signaled warmth (10). We identified brain regions involved in the experience of pain by comparing brain activation during pain with activation during warm stimulation. This comparison, denoted "pain," controls for somatosensory input unrelated to pain. In addition, we identified brain regions involved in the anticipation of pain by comparing brain activation during the colored light preceding pain to activation during the colored light preceding warm stimulation. This comparison, denoted "anticipation," controls for anticipatory processes unrelated to pain (11).

Interviews after the experiment confirmed that all subjects were aware of the relation between the light color and the intensity of the thermal stimulation. Subjects rated painful heat significantly higher than nonpainful warmth on two 11-point visual analog scales measuring intensity [mean ± SD, 7.3 ± 1.3 (12)].

Fig. 1. Medial frontal lobe. (A) Group-combined activation map showing volumes selectively activated during pain (red) and anticipation of pain (yellow). (B) Individual subject's activation centers during pain (red triangles) and anticipation of pain (black circles). Centers associated with the anticipation of pain (black circles; mean Talairach coordinates x = 8 mm, y = 38 mm, z = 27 mm) were significantly more anterior than those associated with pain (red triangles; mean coordinates x = 3 mm, y = 4 mm, z = 33 mm (24)) (P < 0.05). (C) Time course of fMRI signal intensity change over the period of the scan averaged across subjects. Epochs related to anticipation of pain are shaded in gray [mean ± SEM]. (D) Time course of fMRI signal intensity change over the period of the scan averaged across subjects [mean ± SEM]. Epochs of pain are shaded in gray.

References:


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www.sciencemag.org SCIENCE VOL 284 18 JUNE 1999 1979

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25. R. M. Perrin, K. Keegstra, N. V. Raikhel, data not shown.

26. Three motifs were found to be conserved among several α,1,2-fucosyltransferases, despite low overall homology. One ([IV][V][H][Q][Y][R][D]N) has been described previously (27) (square brackets indicate that either of the indicated amino acids was found at the indicated position; dots indicate that three or more different amino acids were found at the indicated position). In addition, a second motif [DE][K] [MQ][F][C][E][Q][D]Q and a third region [G][F][G] [N][D][R][C][L][T][S][E][A][S][A][F][W][B][R][Y][A][S][Q][D] [R][L][A][V][D][E] were conserved (29).


29. Single-letter abbreviations for the amino acid residues are as follows: A; Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Glu; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

30. The authors acknowledge funding from the Department of Energy (grant DE-FG02-91ER20021). C. Wilkerson for assistance with computer analysis, and members of the Keegstra and Raikhel laboratories for helpful discussions.

27 January 1999; accepted 10 May 1999
ANTICIPATION OF PAIN ACTIVATION IN HUMANS

We observed clear activation in brain regions previously reported in neuroimaging studies of pain (6, 12). Crucially, within this network of activation, we identified three brain regions (medial frontal lobe, insular cortex, and cerebellum) where responses to pain could be dissociated from those to the anticipation of pain on the basis of differences in neuroanatomical localization and the time course of the fMRI signal change.

The medial frontal lobe was activated in 7 subjects during anticipation of pain and in 10 subjects during pain itself. Both the group analysis (Fig. 1A) and the individual subject analyses (Fig. 1B) showed that pain activated caudal anterior cingulate cortex, whereas the anticipation of pain activated a more anterior region extending from perigenual cingulate to the frontal pole (“anterior medial frontal cortex”). Time courses of the fMRI signal also differed for pain and for its anticipation. The signal associated with the colored light preceding pain (Fig. 1C, shaded area) increased over successive trials (linear trend, $P < 0.05$). In contrast, painful stimuli (Fig. 1D, shaded area) produced a clear fMRI signal on the first trial that remained constant throughout subsequent testing (no significant trends).

Insular cortex was activated in eight subjects during anticipation of pain and in seven subjects during pain itself. Both the group analysis (Fig. 2A) and separate analysis of data from individual subjects (Fig. 2B) showed that activation related to pain was located in the mid-insula, whereas the activation related to the anticipation of pain was found in the anterior insula. The time courses of fMRI signal were again different for pain and for its anticipation. The signal associated with the colored light preceding pain (Fig. 2C, shaded area) increased over trials (linear trend, $P < 0.05$). In contrast, signal amplitude associated with painful stimuli (Fig. 2D, shaded area) remained constant throughout the scanning session (no significant trends).

The cerebellum was activated in 10 subjects during the anticipation of pain and in 9 subjects during the period of the painful stimulation. The group-combined volume of activation (Fig. 3A) associated with pain was localized to the anterior cerebellum and was bilateral; activation associated with the anticipation of pain was localized in posterior cerebellum and was predominantly ipsilateral for data summed across the entire group. The time courses of fMRI signal were again different for pain and its anticipation. The signal associated with the colored light preceding pain (Fig. 3C, shaded area) increased over trials (linear trend, $P < 0.05$), whereas signal amplitude associated with painful stimuli (Fig. 3D, shaded area) was consistent throughout the scanning session (no significant trends).

Dissociations in these brain regions were specific to pain and its anticipation. They were also seen when comparing brain activation during pain to activation during the colored light preceding pain (13), but not when contrasting warm stimulation with baseline and anticipation of warm stimulation with baseline (14).
Our study demonstrates that the neural substrates of pain and its anticipation can be discriminated both by the involvement of distinct brain regions and the differing response characteristics of these areas (15). This conclusion receives substantial support from our finding that anterior medial frontal cortex, anterior insula, and posterior cerebellum did not activate throughout the entire presentation of the colored light associated with pain, but only during the time before onset of the painful stimulus. The experience of pain activated caudal anterior cingulate cortex, mid-insula, and anterior cerebellum (“pain regions”), whereas anticipation of pain activated anterior medial frontal cortex (16), anterior insula, and posterior cerebellum (“anticipation regions”). Activation in the pain regions was consistent from trial 1 onward (Figs. 1 to 3D), whereas activation in the anticipation regions increased over trials. Such an increase would be expected as subjects learn that the colored light predicts pain. This indicates that fMRI can monitor processes possibly associated with learning cues to painful events.

Each of the anticipation regions has in close proximity a region mediating pain associated with learning cues to painful events. Regions was consistent from trial 1 onward (“anticipation regions”). Activation in the pain bellum (“pain regions”), whereas anticipation the time before onset of the painful stimulus. Receives substantial support from our finding caracteristics of these areas (brain regions and the differing response char-