Anticipatory coping of pain expressed in the human anterior cingulate cortex: a positron emission tomography study

Jen-Chuen Hsieh a, b, c,*, Sharon Stone-Elander a, d, Martin Ingvar a

a Cognitive Neurophysiology, Department of Clinical Neuroscience, Karolinska Hospital/Institute, S-17176, Stockholm, Sweden
b Integrated Brain Research Unit, Department of Medical Education/Research and Department of Anesthesiology, Veterans General Hospital-Taipei, No.201, Sec.2, Shih-Pai Rd., 11217, Taipei, Taiwan
c Institute of Neuroscience and Department of Medicine, Schools of Life Science and Medicine, National Yang-Ming University, 11217 Taipei, Taiwan
d Karolinska Pharmacy, Karolinska Hospital, S-17176, Stockholm, Sweden

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Abstract

We used positron emission tomography (PET) to monitor the regional cerebral blood flow (rCBF) as an index of brain activity in regions proposed to participate in affective-motivational and cognitive-evaluative dimensions of pain during anticipation of a noxious stimulation. Specifically we were interested in the anterior cingulate cortex (ACC), the ventromedial prefrontal cortex (VMPFC) and the periaqueductal grey (PAG). Anticipating an unpredictable and unlearned pain stimulus activated the right ACC, the VMPFC and the PAG while anticipating a learned pain-stimulus resulted in a decreased activity in the ACC and the VMPFC. These patterns are compatible with two facets of affect-laden cognitive coping: alertness and attention-distraction. The right-preponderant expression of the changes in the ACC supports the hypothesis of a preferential role of the non-dominant hemisphere in negative emotional processing. The data demonstrate an anticipatory coping mechanism and illustrate a neurophysiological process underlying the modulation of attention to pain.

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Most of the events that we experience everyday do not happen unexpectedly. A warning of an upcoming event allows for an anticipatory adaptation, and for us to cognitively engage in anticipatory coping in response to distress of various contents [14]. It is evident that such mechanisms are essential for survival and that they both consciously and unconsciously influence subsequent behavior. Therefore, the occurrence of contingent events should elicit distinct brain responses.

There are accumulating evidence which indicate that the medial prefrontal cortex (including ventromedial prefrontal cortex, VMPFC), anterior cingulate cortex (ACC) and the periaqueductal grey (PAG) are crucial for the anticipatory appraisal of pain [3,7,9,11]. However, functional brain imaging investigation on the neurophysiological processes in these structures has been limited. Of special interest is the ambiguity about the functional implication of the changes of neuronal activity (indexed by the regional cerebral blood flow, rCBF) in these regions. The ACC (area 24) has been demonstrated using positron emission tomography (PET) to be either activated or deactivated in various functional brain imaging studies of pain (for a review, see [7,13]).

To probe the central mechanisms behind the human adaptive behavior to emotional distress, we conducted two experiments with different psychological disposition in order to address the anticipatory modulation of neuronal activity induced by the cognitive appraisal of impending pain stimuli. The expectation of pain can be regarded as an antecedent causal factor in the emotional response. The data show that anticipating an unpredictable and unlearned
pain stimulus activates while anticipating a learned pain stimulus decreases activity in similar structures.

All procedures were approved by the local Ethics and Radiation Safety Committees of the Karolinska Hospital/Institute. Informed consent was given by all the subjects. Participants were well instructed before the experiment to minimize confounding anxiety. In the first experiment, we subjected the volunteer to a situation in which they anticipated a painful event (impending, unpredictable) of unknown identity. The anticipation was achieved by an intracutaneous (i.c.) injection of saline [9]. In the second experiment, the anticipation of a noxious stimulation (inevitable, predictable) was achieved with stress inoculation by explicitly instructing the subjects to psychologically prepare for a painful experience of known quality (calibrated endureable electro-stimulation of preset intensity) [10]. Separate 100-mm visual analogue scales (VAS; anchored with: 0, not at all; 100, the worst imaginable) for rating subjective sensory intensity and unpleasantness for pain per se and anxiety together with the Spielberger state anxiety inventory (SSAI [18]) were employed and recorded immediately after each rCBF measurement was executed. The heart rate was continuously monitored with electrocardiography. Verbal communication was used to assess psychodynamic processing, i.e. the deployment of attention.

In experiment 1, subjects (n = 5, mean age 38 ± 7 years, all right-handed) underwent nine rCBF investigations (Scanditronix PC-2048, 25–30 mCi [15O] butanol, and a 100-s scan). The PET scanning was commenced (subjects’ eyes closed) simultaneously with the injection of [15O]butanol. Regional brain tissue radioactivity was measured, which reflects rCBF. The first two studies consisted of saline (20 μL, 0.9%) injection (i.c.) with explicit assurance that they were non-pain control studies (control). The subjects were then informed that during the subsequent studies a noxious stimulation would sometimes be given during the scan without prior information. To maintain the tone of anticipation, a minute amount of ethanol (20 μL, 70%; immediate pain, peak intensity latency 7–10 s, duration 40–45 s) was semi-randomly injected (i.c.) during the course of the study. Subjective rating of pain (burning sensation) intensity was 58 ± 24% (mean ± SD) by VAS. Ethanol and saline (anticipation state) were consecutively studied once and thereafter twice in a randomized manner followed by another control measurement. Saline was injected 20 s while ethanol was administered 10 s after the injection of butanol [9]. All injections were adjacent to each other at the lateral aspect of the right upper arm. The intracutaneous saline injection in both control and anticipation was chosen to exclude the injection response per se. The data on the central processing of the ethanol-elicited traumatic pain was reported previously [9].

In experiment 2, reproducible thresholds of perception, pain, and tolerance (defined as 100% VAS) over the right dorsolateral wrist were carefully established (using ascending method of limits) for each subject by means of transcutaneous electrical stimulation (5 Hz, 200 μs). Five volunteers (n = 5, mean age 36 ± 8 years, all right-handed, eyes closed) were scanned nine times using the aforementioned bolus [15O]butanol method under three conditions: (1) rest control, (2) pain, electro-stimulation delivered 10 s before the butanol injection until the time of peak cerebral radioactivity, aimed at eliciting a rating of 80% pain intensity by 100-mm VAS and (3) anticipation. They were given instructions pertinent to the paradigm at the beginning of each investigation. (1) Control: the subjects were assured that the session would be simply a resting control study; (2) pain, the subjects were informed that the experimental session would be a pain study; (3) anticipation, the subjects were instructed in the anticipation paradigm that the electric shock (280% VAS) would be delivered sometime within the scanning period after the tracer administration. The longer the delay, the more painful the shock would be, but they were assured that it would remain within their previously established limit of tolerance. Electric shock (10–15 s) was delivered immediately after the rCBF measurement in order to maintain the credibility of the instruction during the repeated scans. The three paradigms were consecutively studied once and thereafter twice in randomized order. PET scanning (Scanditronix PC-2048, 25–30 mCi [15O] butanol, and an 80-s uptake image) commenced with the tracer administration. The central processing of pain elicited by this high-intensity electro-stimulation has been previously reported [10].

The image analysis and statistical treatment have been described [9,11]. Stereotaxically reformatted (Computerized Brain Atlas procedure, CBA [6]) normalized and smoothed with 16 mm full-width-at-half-maximum images were contrasted pixel-by-pixel for each experiment. The omnibus significance maps (uncorrected p-maps, thresholded at P < 0.01) were generated and color-coded into four levels defined by: 0.001 ≤ P < 0.01 (increase, red; decrease, blue) and P < 0.001 (increase, yellow; decrease, light blue). The final designation of significant change was based on the calculated local Z-score Maximum (Z-max) [4].

Three regions-of-interest (ACC, VMPPC, PAG) were pre-selected for analysis based on previous pain studies in the literature [8,9,11]. Anatomical structures and Brodmann areas were designated according to the brain database implemented in the CBA [6]. Stereotaxic coordinates [19] of peak activation are expressed in millimeters and refer to medial-lateral position (x) relative to midline (positive = right), anterior-posterior position (y) relative to the anterior commissure (positive = anterior), and superior-inferior position (z) relative to the commissural line (positive = superior).

In the first experiment, anticipating an impending/unpredictable pain increase rCBF in the caudal portion of the ACC (area 24; x = 5, y = 2, z = 28, Z-max = 4.01, P < 0.001, %ΔrCBF = 2.7%) and the VMPPC (area 12; x = 6, y = 52, z = 10, Z-max = 3.79, P < 0.001, %ΔrCBF = 4.2%).
F = 2.6%) in only the right hemisphere (Fig. 1a) as compared to the assured pain-free control. Also activated was another focus of the right medial prefrontal cortex (area 9/32, x = 11, y = 29, z = 31, z-score = 3.83, P < 0.001, %ΔrCBF = 2.3%) and the PAG (x = −4, y = −29, z = −6, z-Max = 3.69, P < 0.001, %ΔrCBF = 4.0%).

In the second experiment, the anticipation of an inevitable/predictable pain resulted in a decrease of rCBF, as compared to the assured pain-free control, in the caudal portion of the ACC (area 24; x = 3, y = 11, z = 30, Z-max = 3.75, P < 0.001, %ΔrCBF = 4.3%) and VMPFC (area 12; x = 4, y = 45, z = −9, Z-max = 3.73, P < 0.001, %ΔrCBF = 5.3%) (Fig. 1b) in only the right hemisphere.

The activated/deactivated regions of VMPFC (area 12 by the CBA) in both experiments were stereotactically equivalent to area 11 in the Talairach atlas [19]. The anxiety ratings using 100 mm-VAS were 4.3 ± 5.6 and 5.8 ± 7.6 (mean ± SD) for experiments 1 and 2, respectively. The mean SSAI score as well as the unchanged mean heart rate during anticipation as compared to the control state, but yet did not achieve statistical significance. Subjects self-reported either promptly attended to (experiment 1) or intentionally alienated attention from (experiment 2) the source of distress upon questioning. In experiment 2, most of the subjects actively used imagination strategy (e.g. imaging dancing with girl friend) to distract their attention from pain during the pre-pain period.

It has been demonstrated that receiving instructions, preparation, and anticipation of the cognitive task, rather than the task-related processing itself, may be responsible for the increased activity in the ACC noted in many PET-studies of simple cognitive tasks [15]. Hypnotic suggestions have also been demonstrated to effectively modulate the expression of the ACC on affective encoding of pain [17]. In the current study, it is unlikely that anxiety could explain the modulation of activity in the medial prefrontal cortex and the ACC. The anxiety was minimized by the familiarization procedure as was confirmed by the low VAS rating, the unchanged mean SSAI score as well as the unchanged mean heart rate during anticipation as compared to the control state.

A key factor in coping effectiveness is whether or not the choice of mental adjustment and strategy, contingent upon how a subject constitutes his view of the situation, fits the possibilities for coping an encounter. This cognitive evaluation, referred to as appraisal, is a dynamic process that changes according to the person’s perception of the consequences of an event [14]. The activation and deactivation of the medial prefrontal cortex and the PAG (possibly subserving arousal [9] in experiment 1) here can be viewed as a neurophysiological modulation imposed by the cognitive appraisal and concurrently reflects two facets of ‘emotion-oriented’ anticipatory coping strategy; alertness (vigilance to the encounter in experiment 1) and distraction (averting attention from the source of distress in experiment 2), respectively [9]. Our data suggest that the expression in the medial prefrontal cortex depends on the pain-relevant psychological disposition.

The right-sided cerebral preponderance to anticipation of pain lends support to the hypothesis that the non-dominant hemisphere is preferentially involved in the negative emotion of pain [2,11]. The regions involved in the ACC and the VMPFC (regions bridging between the autonomic nervous system, the limbic system and the prefrontal cortex [3]) are crucial in pain-laden central processing. As evidenced by the clinical observations that limbic forebrain surgery (e.g. cingulotomy, frontolobotomy) alleviates the affective impact, attention and cognitive appraisal of intractable pain while preserving the perception of pain [3], these structures subserve the affective-motivational and cognitive-evaluative dimensions (e.g. attributing emotional valence and attention) of pain. The caudal area 24 involved in this study corresponds anatomically to the subdominant area 24′ (a proposed cognition region of the ACC pertinent to nociception/pain [3]), according to a modified nomenclature which was rooted in an elaborate cytoarchitectural map in humans [20]. Our data has demonstrated that the medial prefrontal cortex, particularly the cingulate cortex, may play a role in attentional modulation in response to the appraisal of an unpleasant distress.

Anticipating an impending but unpredictable painful event (experiment 1) also activated another focus of the
right medial prefrontal cortex (area 9/32) (Fig. 1a), an area previously demonstrated to be involved in willed attention [16]. Prominent activation was also observed in the PAG (Fig. 1a), a neural substrate which coordinates stress coping and arousal [1,11]. Thus, the anticipation of an unpredictable encounter (novel pain) engaged brain structures involved in warning and defensive behavior [1,11]. The increased activity in these medial prefrontal structures and the PAG indicates the activation of the attentional mechanisms which may facilitate the detection of a potentially harmful input. Decreased activity (experiment 2) in these areas may reflect a functional inhibition leading to a diminished attention to an inevitable painful event.

The transactional models of stress have emphasized coping as a process that is both determined by, and alters appraisals of control [14]. This study reveals cerebral structures involved in an anticipatory coping mechanism. The central modulation encodes painful distress and attentional arousal that pertains to the adaptive mechanisms of the individual. The engagement/disengagement of only the MLPFC and the ACC of the right hemisphere during the pre-pain anticipation lend support to the hypothesis that the right hemisphere is preferentially involved in emotional arousal [5,12]. The findings corroborate the results from our previous PET studies on chronic ongoing neuropathic pain [7], cluster headache [11] and painful trigeminal neuropathy [8].

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