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Distinct brain mechanisms support spatial vs temporal filtering of nociceptive information

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ABSTRACT

The role of endogenous analgesic mechanisms has largely been viewed in the context of gain modulation during nociceptive processing. However, these analgesic mechanisms may play critical roles in the extraction and subsequent utilization of information related to spatial and temporal features of nociceptive input. To date, it remains unknown if spatial and temporal filtering of nociceptive information is supported by similar analgesic mechanisms. To address this question, human volunteers were recruited to assess brain activation with functional magnetic resonance imaging during conditioned pain modulation (CPM) and offset analgesia (OA). CPM provides one paradigm for assessing spatial filtering of nociceptive information while OA provides a paradigm for assessing temporal filtering of nociceptive information. CPM and OA both produced statistically significant reductions in pain intensity. However, the magnitude of pain reduction elicited by CPM was not correlated with that elicited by OA across different individuals. Different patterns of brain activation were consistent with the psychophysical findings. CPM elicited widespread reductions in regions engaged in nociceptive processing such as the thalamus, insula, and secondary somatosensory cortex. OA produced reduced activity in the primary somatosensory cortex but was associated with greater activation in the anterior insula, dorsolateral prefrontal cortex, intraparietal sulcus, and inferior parietal lobule relative to CPM. In the brain stem, CPM consistently produced reductions in activity, while OA produced increases in activity. Conjunction analysis confirmed that CPM-related activity did not overlap with that of OA. Thus, dissociable mechanisms support inhibitory processes engaged during spatial vs temporal filtering of nociceptive information.

1. Introduction

Sensory information undergoes substantial transformation during afferent processing by differential recruitment of inhibitory vs excitatory processes. For example, afferent input can be transformed in the spatial domain by processes such as lateral inhibition and spatial summation. Similarly, afferent input can be transformed in the temporal domain by processes such as adaptation and temporal summation. In the nociceptive system, inhibitory processes contribute substantially to the processing of afferent information in both the spatial and temporal domains.

One mechanism involved in the spatial transformation of nociceptive information is the diffuse noxious inhibitory control (DNIC), which is mediated via the spino-bulbo-spinal loop [17]. The DNIC phenomenon is manifested as a decrease in pain sensation to a noxious stimulus during or after application of another spatially remote noxious stimulus. This "pain inhibits pain" phenomenon is suggested to involve a spatial filtering of pain that helps to extract nociceptive signals from the background noise [18]. Similar spatial regulation of nociceptive processing can also be accomplished solely at the spinal level without recruitment of descending inhibition [9]. Both forms of heterotopic inhibition are measured psychophysically in the laboratory by the conditioned pain modulation (CPM) paradigm [39].

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Another inhibitory processing mechanism is offset analgesia (OA), which reflects temporal filtering of sensory information [11,43]. OA describes a phenomenon in which a small decrease in noxious stimulus intensity produces a robust change in perceived pain intensity that is disproportionally large relative to the actual decrease in temperature. The OA effect is time locked and lasts for approximately 10 s before pain ratings begin to increase toward values that would be predicted from a constant temperature stimulus of the same duration [11,43].

Although both CPM and OA evoke pain inhibition, it remains unclear if they engage similar brain mechanisms. Functional imaging studies of CPM have identified reduced activity in several pain-processing areas including the thalamus, primary somatosensory cortex (SI), and secondary somatosensory cortex (SII), as well as the anterior and middle cingulate cortex (ACC and MCC) and insula (INS) [28,30]. In contrast, OA reduces activity in SI but produces greater activity in the periaqueductal gray (PAG), anterior INS, dorsolateral prefrontal cortex (DLPFC), and MCC [7,42]. Because different noxious stimuli were applied across these different studies, it remains unclear if CPM and OA engage similar brain mechanisms of pain modulation. Moreover, if both CPM and OA rely on similar inhibitory mechanisms, we would predict that the magnitude of inhibition produced by CPM would be strongly correlated with the magnitude inhibition produced by OA. Thus, the aim of the current study was to determine whether spatial filtering of nociceptive information is accomplished by mechanisms that are similar to those engaged by temporal filtering of noxious information.

2. Materials and methods

2.1. Subjects

Sixteen healthy subjects were enrolled into the study. Three subjects were excluded from the study either because they could not tolerate the stimuli or they had an unusual response to the OA paradigm (3 SD above the mean). Thus, our final sample included 13 right-handed subjects (5 men, 8 women) with a mean age of 25.6 ± 2.8 years (range, 21–33 years), with race distribution of 10 white subjects, 1 African American, 1 Hispanic, and 1 Asian. Subjects had no history of chronic pain or neurological disorders and no magnetic resonance imaging (MRI) contraindications. All female subjects reported using a reliable method of birth control and were not pregnant while participating in this study. The institutional review board at Wake Forest University School of Medicine approved all procedures used in this experiment. Before participating in the study, every subject provided written informed consent acknowledging that they understood all methods and procedures used in the experiment, that they would experience painful stimuli, and that they were free to withdrawal from the study at any time.

2.2. Study sessions

Subjects first participated in a familiarization session in the psychophysical assessment laboratory. During the familiarization session, subjects first received a standard set of heat stimuli to give them experience rating pain. They then experienced the CPM and OA stimulus paradigms to be used during the imaging session in order to ensure that these stimuli were tolerable. These familiarization data are not presented further. After successful completion of this session, subjects participated in an MRI session on a separate day. In both sessions, the CPM and OA paradigms were delivered in a random order.

2.3. Heat stimulus delivery

Noxious heat stimuli were delivered using an MRI-compatible thermode with a contact area of 16 × 16 mm (TSA II, Medoc, Israel). The temperature increase and decrease rate was 5°C/s from a baseline temperature of 35°C.

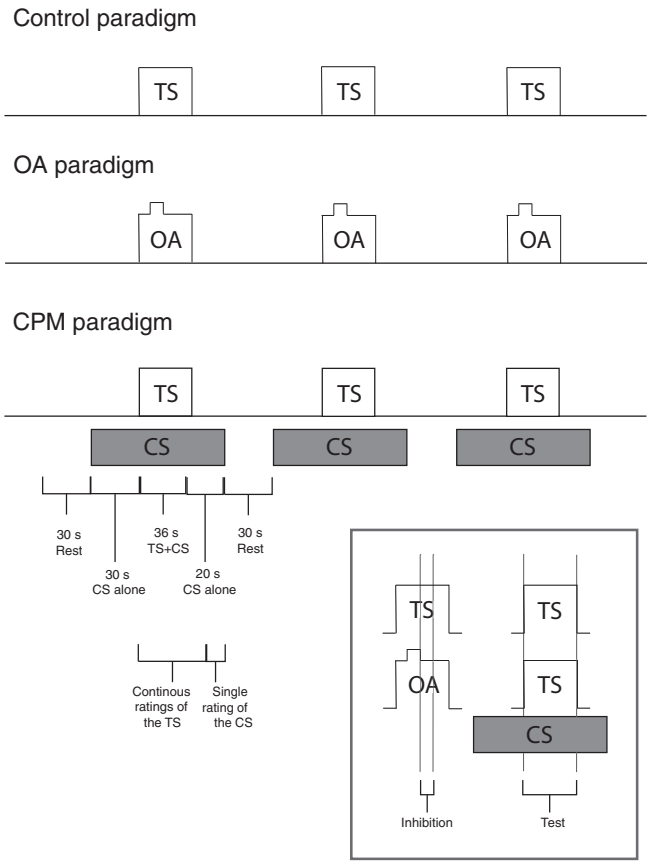

Fig. 1. Study design indicating time course of test-alone, OA, and CPM paradigms. CPM was produced by immersion of right foot into cold water bath (10–12°C), and its effect on noxious heat stimulus (49°C) to lower left leg was assessed. OA was assessed using 3 temperature stimulus paradigm (49–50–49°C) in which 1°C decrease after second temperature (T2) was used to evoke OA. Magnitude of both CPM and OA was assessed by comparisons with control stimulus (49°C). Continuous ratings of pain intensity of TS or OA stimulus were acquired in all paradigms, while single rating of CS was additionally acquired during CPM paradigm. Regressors were constructed to analyze brain activation during 36 s of TS during both CPM and control paradigms (test phase). Because duration of OA is shorter than that of CPM, brain activation was analyzed during the 10 s window after T2–T3 temperature decrease (inhibition phase) during OA and control paradigms. TS, test stimulus; CS, conditioning stimulus; OA, offset analgesia; CPM, conditioned pain modulation.

Table 1
Mean ratings of pain intensity during control, OA, and CPM paradigms.[a]

Characteristic	First repetition	Second repetition	Third repetition
Control (10 s)	4.68 ± 1.14	4.20 ± 1.15	4.22 ± 1.37
OA	4.15 ± 1.36	4.62 ± 1.38	4.62 ± 1.51
Control (30 s)	3.85 ± 1.04	3.04 ± 0.87	3.06 ± 1.04
CPM	3.25 ± 1.28	2.78 ± 1.15	2.96 ± 1.16
CPM response	−0.60 ± 0.65	−0.27 ± 0.57	−0.10 ± 0.51
OA response	−0.53 ± 0.78	0.42 ± 0.87	0.41 ± 0.79

OA, offset analgesia; CPM, conditioned pain modulation.

[a] For CPM and control (30 s) paradigms, the presented pain ratings are averaged across the entire 30 s of the test stimulus. For control (10 s) and OA paradigms, the presented pain ratings are averaged across the 10 s after 2.25 s of the decrease from T2 to T3. Pain ratings are in a scale between 0 (not painful) to 10 (the most intense pain sensation imaginable).

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