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# Frontoparietal mechanisms supporting attention to location and intensity of painful stimuli

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Attention can profoundly shape the experience of pain. However, little is known about the neural mechanisms that support directed attention to nociceptive information. In the present study, subjects were cued to attend to either the spatial location or the intensity of sequentially presented pairs of painful heat stimuli during a delayed match-to-sample discrimination task. We hypothesized that attention-related brain activation would be initiated after the presentation of the attentional cue and would be sustained through the discrimination task. Conjunction analysis confirmed that bilateral portions of the posterior parietal cortex (intraparietal sulcus [IPS] and superior parietal lobule) exhibited this sustained activity during attention to spatial but not intensity features of pain. Analyses contrasting activation during spatial and intensity attention tasks revealed that the right IPS region of the posterior parietal cortex was consistently more activated across multiple phases of the spatial task. However, attention to either feature of the noxious stimulus was associated with activation of frontoparietal areas (IPS and frontal eye fields) as well as priming of the primary somatosensory cortex. Taken together, these results delineate the neural substrates that support selective amplification of different features of noxious stimuli for utilization in discriminative processes.



## 1. Introduction

Top-down attentional bias established by the cognitive task affects neuronal activity even before stimulus presentation [5]. During nociceptive processing, such prestimulus effects can be seen in expectation paradigms. Expectation of pain activates brain regions that are known to be activated by painful stimuli alone [46]. Expectations of lower pain not only decrease subjective pain experience but also decrease pain-related activations [31].

In addition to general anticipation, attention to specific dimensions of a sensory event may also dramatically shape processing by producing changes in neural activity before the stimulus has been presented. Spatial cueing in vision experiments frequently increases activity in areas of occipital cortex that retinotopically correspond to the cued location [20,25]. Feature cues, on the other hand, increase activity in areas that are known to process the feature inside and outside spatial spotlight of attention [47,53,56,57]. Finally, direction of spatial attention modulates event-related potentials produced by pain [33,34].

Top-down attention has been shown to engage posterior parietal cortex (PPC) and superior frontal cortex (including frontal eye fields [FEF] and dorsolateral prefrontal cortex [DLPFC]) in both spatial [6,9,11,22,25,51] and feature [21,23,53,54] attention in vision studies. Although brain mechanisms supporting top-down attention to specific stimulus dimensions have been well characterized in visual and auditory modalities, little remains known about the mechanisms that support spatial and feature attention for nociceptive information. Our group has previously shown the existence of the dorsal (consisting of posterior parietal and prefrontal cortices) and ventral (consisting of insula and prefrontal cortex) processing streams engaged by discrimination of location versus intensity of painful stimuli [42,43]. Those studies were designed to isolate activation related to the comparison of specific features of noxious stimuli with information retrieved from memory of a previous stimulus. Attention is critically important for the acquisition of the target features of sensory stimuli and is an integral part of the discrimination process. However, it remains unclear how much of this discrimination-related activation is related to the direction of attention.

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To identify brain activation associated with attention to specific features of pain, subjects were cued to attend to either pain intensity or pain location before the delivery of noxious stimuli. Their attentional performance was assessed by the use of a 2-alternative, delayed match-to-sample task. Functional magnetic resonance imaging (fMRI) was used to characterize brain activity during all 4 phases of the delayed match-to-sample task. These phases include the period following the cue (cue maintenance period), the period in which subjects were acquiring noxious information (acquisition period), the memory period between stimuli, and the discrimination period. We hypothesized that attention-related activation during the cue maintenance phase would be sustained across multiple phases of the discrimination task.

## 2. Methods

### 2.1. Subjects

Both psychophysical and MRI components of the study were completed by 18 right-handed healthy volunteers, 9 male and 9 female (age 20 to 33 years; mean, 27 years). Fifteen subjects were white, 1 Hispanic, 1 African American, and 1 Indian. One additional subject was withdrawn from the study due to extreme sensitivity to the heat stimuli during the training session. All subjects gave written, informed consent acknowledging that they would experience painful stimuli, all procedures and manipulations were clearly explained, and subjects were free to withdraw at any time. All procedures were approved by the Institutional Review Board of Wake Forest University School of Medicine.

### 2.2. Stimulation procedures

A thermal stimulator with a 16 × 16-mm contact surface (Medoc TSA II, Ramat Yishai, Israel) was used for noxious heat stimulation. The probe was placed on a special holder, after which the stimulated body region was positioned on the surface of the thermode. A baseline temperature was 35°C. The stimulus temperature was changed with rise and fall rates of 6°C/s. To minimize sensitization or adaptation, each experimental series was delivered to previously unstimulated skin areas.

### 2.3. Psychophysical training

Initially, all subjects were trained with thirty-two 5-second-duration stimuli (35°C to 49°C) applied to the arm to give them experience rating pain. Subjects then practiced the discrimination task by using 4 of 12 series of stimulations that were subsequently used in the scanner to ensure that they could adequately discriminate the stimuli and also to familiarize them with the task.

### 2.4. Experimental task

A 2-alternative, forced-choice paradigm using pairs of thermal stimuli was used to identify brain regions involved in different parts of a match-to-sample task (Fig. 1). These stimuli were applied to the posterior aspect of the lower left leg, and 2 separate probes remained positioned on a subject for the duration of the series (baseline temperature 35°C). This task (including time intervals for individual periods) was designed to parallel 2 previous studies on spatial and intensity discrimination of pain in our laboratory as closely as possible [42,43]. For each discrimination trial, 20 seconds after task initiation, a sound cue was delivered through headphones instructing subjects to pay attention to location (2 beeps, 200-ms tone with a 100-ms intertone interval) or intensity (1 beep, 200-ms tone). After a 10-second cue maintenance period, the first noxious heat stimulus (48°C) was applied for 20 seconds (T1, acquisition period). A 30-second memory period followed the heat stimulation, after which a second 20-second stimulus was delivered at various temperatures or locations (T2, discrimination period). For intensity-cued trials, subjects received both stimuli at the same location, and for location-cued trials, both stimuli were delivered at the same intensity (48°C). In location trials, T2 could be delivered at the same location (50% of trials) or delivered either 4 cm (25% of trials) or 16 cm (25% of trials) away from T1 using a separate probe. The second probe remained at 4 or 16 cm distance from the first probe for the duration of each MRI series. At the end of each series, both probes were repositioned. In intensity trials, T2 could be 48°C (50% of trials), 49°C (25% of trials), or 50°C (25% of trials).

Approximately 10% of all trials were catch-trials, introduced to monitor whether subjects were performing feature-specific discriminations rather than simply identifying differences among stimuli. In intensity catch trials, subjects were instructed to perform an intensity discrimination, but T2 (48°C) was delivered at a spatially distinct location from T1 (48°C). In spatial catch trials, subjects were instructed to perform a spatial discrimination task, but stimuli of different intensities (T1 = 48°C, T2 = 50°C) were delivered at the same location.

In all tasks, subjects were required to indicate whether T2 was the same as or different from the cued feature of T1 by pressing a button with the index or middle fingers of the right hand, respectively. Subjects were instructed that the determination was to be made as soon as the decision was reached but before the end of the second stimulus. Each 456-second series contained 4 pairs of comparisons, and the experiment contained 12 series per subject. One subject completed only 7 series due to physical discomfort from the head coil (data included). Location and intensity trials were pseudorandomized, and task order was counterbalanced across subjects.

### 2.5. Psychophysical assessment and analysis

For both the training and fMRI acquisition series, subjects' responses to discrimination were recorded using a digital chart recorder (Power-Lab, ADInstruments, Sydney, Australia). These real-time data then were processed using custom-written programs within the IDL software package (Research Systems, Boulder, CO). Response latencies and error rates were examined using repeated-measures ANOVA to identify effects of the stimulus feature (intensity vs location), as well as type of trial (same, different, catch) on the ability to discriminate. The chart recorder data were also used to construct regressors for the fMRI analysis.

Subjective evaluation of task difficulty, pain intensity, and pain unpleasantness were acquired with a visual analog scale (VAS) at the end of each series. The scales had a 0 to 10 range and were 15 cm long. Subjects were instructed that the ratings should reflect the overall experience of all 8 stimuli within the whole series. Ratings of individual stimuli were not obtained to minimize confounds arising from having subjects provide intensity ratings while being instructed to attend to location. Therefore direct comparison of task difficulty between the intensity and location trials was not possible. Also, these ratings do not provide the ability to assess intensity and unpleasantness on a stimulus-by-stimulus basis. At the end of the experiment, subjects were queried regarding the strategy they used during the discrimination and memory in both intensity and location tasks.

### 2.6. Image acquisition and processing

Functional data were acquired on a 1.5-T General Electric echospeed Horizon LX scanner with 1.5-T HD 8-channel high res brain