

## Imaging the pain of low back pain: functional magnetic resonance imaging in combination with monitoring subjective pain perception allows the study of clinical pain states

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### Abstract

Most brain imaging studies of pain are done using a two-state subtraction design (state-related design). More recently event-related functional magnetic resonance imaging (fMRI) has also been used for studying pain. Both designs severely limit the application of the technology to clinical pain states. Recently we demonstrated that monitoring time fluctuations of perceived pain could be used with fMRI to identify brain regions involved in conscious, subjective perception of pain. Here we extend the methodology to demonstrate that the same approach can be used to study clinical pain states. Subjects are equipped with a finger-spanning device to continuously rate and log their perceived pain during fMRI data collection. These ratings are convolved with a canonical hemodynamic response function to generate predictor waveforms with which related brain activity can be identified. Chronic low back pain patients and a normal volunteer were used. In one series of fMRI scans the patient simply lies in the scanner and indicates spontaneous fluctuations of the subjective pain. In other fMRI scans, a straight-leg raising procedure is performed to exacerbate the back pain. In the normal volunteer, fMRI scans were done during painful and non-painful straight-leg raisings. The results indicate the feasibility of differentiating between different pain states. We argue that the approach can be generalized to identify brain circuitry underlying diverse clinical pain conditions. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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A considerable body of literature has accumulated regarding the human brain circuitry underlying pain perception, see reviews [2,14]. Most of these studies examine brain responses to experimental manipulations of painful stimuli. A few studies have examined clinical pain states [9,13] exploring brain activity either indirectly, e.g. by presenting painful stimuli on a body part with ongoing pain [6,10], or after irreversible gross manipulations, e.g. brain activity comparisons before and after cordotomies [7]. The majority of brain imaging studies of pain use state-related comparison approach, although recent functional magnetic resonance

imaging (fMRI) studies have also used event-related approaches [5]. Both state-related and event-related approaches for analyzing brain responses rely on a precise knowledge of the timings of the application of stimuli and the assumption that the subject's responses to these stimuli are stereotypical, reproducible, with a precise temporal relationship to the stimuli. Generally, clinical pain states do not obey these rules. For example, when a neuropathic pain patient continuously rates thermal painful stimuli applied to the affected arm there is a long time delay from the application of the stimulus to the report of pain, and the duration of the perceived pain far outlasts the stimulus [8]. The back pain patients studied here also exhibit similar dissociations between stimulus and perception of pain.

Recently we outlined an alternative approach for analyzing fMRI data [3]. The convolution of the temporal profile

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of pain ratings with the hemodynamic impulse response function (IRF) was used to generate a predictor function for subjective pain perception. The correlation between this predictor function and cortical activations identified cortical areas specifically involved in conscious, subjective perception of pain. Here we demonstrate that individual subject's on-going ratings of fluctuations of the experienced pain can be used to identify cortical areas involved in this subjective perception. Examples are presented from a normal volunteer undergoing an acute pain paradigm, and from patients suffering from chronic low back pain.

fMRI studies were performed in two male right-handed subjects: One was a normal volunteer; the other had chronic low back pain. Pain ratings in another three male right-handed patients with chronic low back pain are also shown. The subjects were informed of the procedures. They signed a consent form, and all procedures were approved by Upstate Medical University Institutional Review Board.

Subjects continuously rate their pain intensity through a logging device. The device is a linear potentiometer attached to the fingers of the hand, opposite to the leg that is in pain or will be in pain during leg raisings, connected to a computer running LabView (National Instruments, Austin, TX). The magnitude of finger span between the thumb and index finger indicates intensity of perceived pain, an analog proprioceptive scale [1,15]. Subjects are instructed that the thumb and pointer finger touching each other corresponds to no pain, and that maximum finger span corresponds to maximum imaginable pain. Moreover, during functional scans they should concentrate on continuously indicating the intensity of their perceived pain by varying the finger span. During fMRI data collection, the computer is triggered from the MR scanner at each image acquisition epoch. With each trigger the potentiometer value is logged together with the acquired fMRI image number. This procedure records the exact temporal relationship between perceived pain and fMRI image acquisition timings. At the beginning and end of functional scans, subjects verbally indicate the level of their current pain, and the maximum pain experienced during the scan, on a 0–10 scale, where 0, no pain and 10, maximum imaginable pain. These values are used to scale the finger span ratings. In control studies where the leg is raised to a non-painful magnitude the subject is instructed to rate the position of the leg rather the pain intensity.

Straight leg raising is a routine clinical procedure to document the extent of radicular pain in back pain patients [11]. In functional imaging studies we implement this procedure in the scanner to examine associated brain activity. Subjects are strapped to the scanner gantry, the knee is locked in an extended position, and in normal subjects the heel is dorsiflexed. The leg is moved up and down manually between two positions, one of which may cause pain. In normal subjects large amplitude leg raisings causes extreme stretching of multiple tendons at the heel and the knee, resulting in

an acute deep pain involving joints, muscles and tendons; while smaller amplitude leg raisings are pain free. In back pain patients with significant radicular involvement, the leg raising exacerbates the back pain.

fMRI scans were performed on a 1.5 T General Electric clinical imaging instrument. The subject is positioned on the scanner bed, the head immobilized using a vacuum beanbag, and the body strapped to the table to minimize head movement. The leg to be manipulated is loosely attached to a board, raised by an experimenter. Anatomic images are obtained with conventional spin echo pulse sequences while functional images are obtained using GRE echo planar imaging pulse sequences (TR = 3500 ms; TE = 60 ms; FA = 90°; repetitions per slice = 10), with a voxel size of 3.75 × 3.75 × 8.0 mm [3,4].

The individual pain perception time curves were low-pass filtered and convoluted with the cortical hemodynamic IRF to generate predictor functions for pain perception. Head movement artifacts were corrected using AIR software [16]. Head movement, pre- and post-AIR correction, was calculated by measuring the center of gravity of the brain in all three dimensions taking into account voxel dimensions, at each time point of acquisition. After movement correction, the predictor functions were correlated to the corresponding fMRI data on a per voxel basis. The resulting correlation coefficient maps were converted to Student's *t*-value maps, filtered with a Gaussian FWHM of 6 × 6 × 6

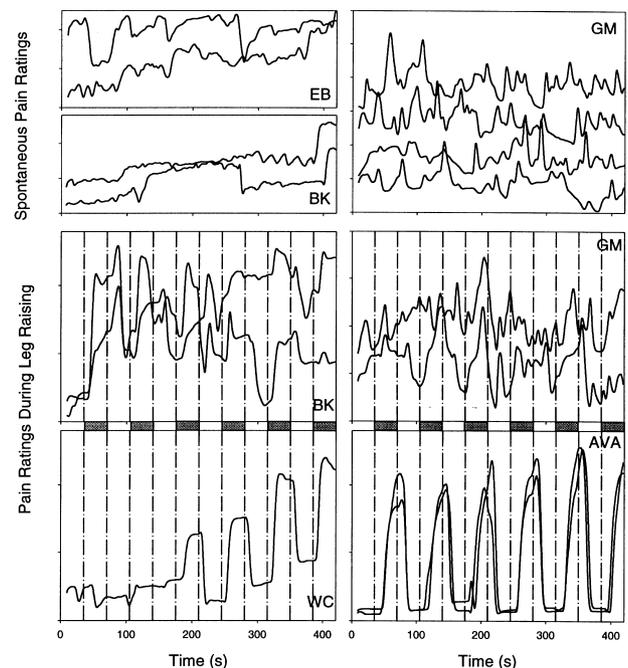


Fig. 1. Temporal variation in spontaneous pain (top panels) and pain exacerbated by leg raisings (bottom panels). Repeat ratings of spontaneous pain are shown in three chronic back pain patients (top panels; EB<sub>S</sub>, BK<sub>S</sub>, and GM<sub>S</sub>). Ratings of pain during leg raisings (every 35 s, dashed lines; gray bars, leg raisings) are shown in the same patients (BK<sub>L</sub>, GM<sub>L</sub>, and WC<sub>L</sub>) and a normal volunteer (AVA<sub>L</sub>).

mm, converted into Fisher's Z-maps, transformed into standard brain atlas space and averaged across scans [3]. The temporal properties of brain responses were examined in relation to pain ratings and to head movement, by identifying clusters of voxels (>10 voxels) with significant fMRI activity normalized to percent change in fMRI signal and averaged over time. The average response was regressed with pain ratings to quantify their relationship.

We have discovered that the spontaneous pain of back pain is significantly modulated, in the 7 min time interval required for fMRI scans, when such patients simply lie in a supine position on the scanner bed. The top panels of Fig. 1 show individual patients ratings of spontaneous pain, during functional scans. These time curves are distinct for each patient and vary unpredictably between repetitions. There are abrupt increases and decreases in the intensity of back pain with no external manipulation. The pain ratings of patient GM (Fig. 1 right panel, four ratings) increase and decrease in an apparently random fashion in relation just by lying in the scanner.

When the back pain includes a significant component of radicular pain then the straight leg raising further exacerbates the pain. Fig. 1 bottom panels show pain ratings when the leg is manipulated. The ratings in patients BK, GM, and WC illustrate the dissociation between leg position and perceived pain because only a few of the leg raises result in repeated patterns of pain modulation. When the same procedure is performed in a normal subject (AVA, Fig. 1 bottom right) leg raising and pain ratings are time locked, and both pain intensity and timing are highly reproducible.

Fig. 2A,B show brain fMRI activations for patient GM for spontaneous ratings of back pain (A) and for pain during leg

raisings (B). Fig. 2C,D show fMRI activations in a normal subject (AVA) when the leg raisings are painful (C) and when they are not painful (D).

Pain ratings in relation to temporal changes in brain activity and in relation to head movement is shown in Fig. 3 in one functional scan for a back pain patient during leg raisings. Head movement artifacts are important confounders in such studies. The top panel shows that the large head movements were usually related to the pain ratings or leg raisings. Prior to correcting head motion, the head rarely moved more than 1 voxel ( $1.77 \pm 0.7$  mm movement before correction). The mean and standard deviation of head movement was significantly reduced following AIR correction ( $0.66 \pm 0.13$  after correcting with AIR). More importantly the correlation between head movement and pain ratings was small ( $R_2 = 0.012$  and  $0.039$  pre- and post-AIR correction), and even smaller in relation to mean fMRI response ( $R_2 = 0.0006$  for both pre- and post-AIR correction). The average time course of fMRI activity in the brain (Fig. 3

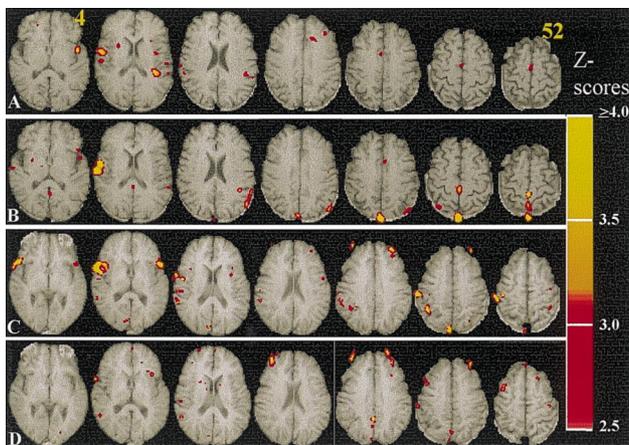


Fig. 2. fMRI activation maps are shown in a chronic back pain patient (GM in Fig. 1), for spontaneous pain (A) and when the back pain is exacerbated by leg raisings (B), and in a normal volunteer when the leg is raised to a level causing pain (C) and when the leg is raised to a level just below the perception of pain (D). Activations in A–C are more similar than in D. Every 4th slice is shown, +4 mm to +58 mm superior to anterior commissure. Color bar shows Z-scores, 2.5 corresponds to  $P = 0.006$ , and 4.0 to  $P < 0.0001$ .

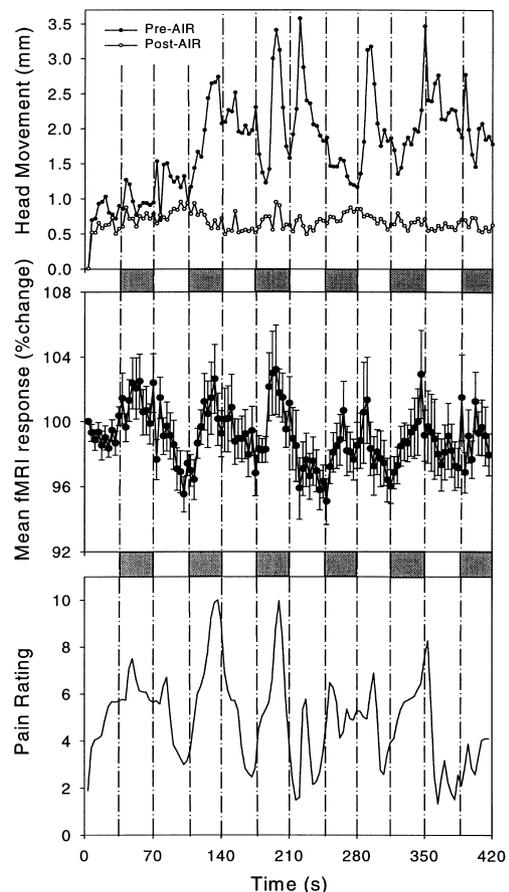


Fig. 3. Temporal relationships between reported pain (bottom panel), mean fMRI response (middle panel) and head movement (top panel: filled circles, pre-motion correction; open circles, post-motion correction). fMRI response is the normalized mean and SEM (average of 11 clusters; first time point is assigned 100%). The correlation between the middle and bottom curves is highly significant.

middle) is more similar to the pain ratings (Fig. 3 bottom;  $R_2 = 0.29$ ,  $F(1, 117) = 48.0$ ,  $P < 0.001$ ). The average pain rating in this case was  $4.9 \pm 1.9$  over the 7 min. Regressing the pain rating with the mean fMRI response resulted in a slope of 0.49, indicating that for every unit change in pain perception brain fMRI signal changed by 0.5%.

The results demonstrate that the neural correlate of back pain can be studied with fMRI as long as the subjective ratings of the pain are used as predictor functions. The temporal dissociation between the perceived pain and leg movements highlights the need for such a design. The approach is general enough that as long as one has a means of manipulating any given clinical pain state the same approach can be used to identify the neural correlates to that pain state. For example, in migraine patients exposure to loud noises or to bright lights, or in neuropathic pain patients with allodynia applying tactile stimuli to the sensitive body part, modulate the clinical pain. Such maneuvers combined with the patients continuously rating the modulation would then be used in functional scans to study their neural correlates.

The reporting of the spontaneous or exacerbated pain is performed by a motor task, the finger span. This should result in activating the hand portion of the sensorimotor cortex, which depends on the rate of finger movement [12]. Since the pain modulation is relatively slow, subjects move the fingers at an approximate rate of 0.01 Hz, it results in minimal activity in the sensorimotor cortex. In contrast when a subject performs the finger movements at a higher rate (self paced at 2–4 Hz) then the activation in this region is much more intense. Since the brain regions involved in the motor performance are well defined the simplest method for removing this confounder is to exclude these brain regions from analyses. Another approach would be to use a regression analysis where finger movement is treated as a confounder. The other confounder is head movement. Since leg movements and increases in pain can both cause head motion, proper control of this parameter is crucial. We have limited head movements mechanically and by measuring and correcting for head movements. The lack of activity along the rim of the brain and the minimal correlation between head movement and brain activity show the adequacy of the approach.

Given that the hemodynamics response function is in the same time-scale as variations in clinical pain, fMRI combined with subjective reports of pain seems to be an optimal methodology for studying clinical pains. The brain responses presented are mainly for illustration purposes and remain to be determined in a large cohort. The outlined methodology illustrates that brain activity patterns can be systematically studied and quantified relative to subjective pain ratings. Since the approach is non-invasive it can be used repeatedly to identify the neural networks underlying individual patients clinical pain states.

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