Prospective Evaluation

Brain Activity Associated with Chronic Cancer Pain

Asokumar Buvanendran, MD, Amjad Ali, MD, Travis R. Stoub, PhD, Jeffrey S. Kroin, PhD, and Kenneth J. Tuman, MD

From: Rush University Medical Center, Chicago, IL.

Dr. Buvanendran is an Associate Professor, Department of Anesthesiology, Rush University Medical Center, Chicago, IL. Dr. Ali is with the Department of Radiology, Rush University Medical Center, Chicago, IL. Dr. Stoub is with the Department of Neurology, Rush University Medical Center, Chicago, IL. Drs. Kroin and Tuman are with the Department of Anesthesiology, Rush University Medical Center, Chicago, IL.

Address correspondence: Asokumar Buvanendran, MD, Department of Anesthesiology Rush University Medical Center 1653 West Congress Parkway Chicago, IL 60612, E-mail: Asokumar@aol.com.

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Background: The number of neuroimaging studies that examine chronic pain are relatively small, and it is clear that different chronic pain conditions activate diverse regions of the brain.

Objective: Cancer patients presenting for diagnostic positron emission tomography (PET) imaging were asked to rate their spontaneous baseline pain score. Twenty patients with either no pain (NRS = 0) or with moderate to severe pain (NRS ≥ 4) were invited to participate in this study to determine the difference in brain activity in cancer patients with moderate to severe chronic pain versus no pain.

Study Design: Prospective, non-randomized, observational report.

Setting: Academic medical center.

Methods: Patients had a 2-D PET scan with the radionuclide 18F-fluoro-2-deoxyglucose (FDG) at a dose of approximately 20 mCi. Each individual raw PET scan was coregistered and normalized to standard stereotactic space. Differences in regional glucose metabolism were then statistically compared between patients with moderate-to-severe pain and patients with no pain.

Results: The NRS pain score in the patients with moderate to severe pain (n = 11) was 4.5 [4.0-6.0] (median[interquartile range]) versus 0.0 [0.0-0.0] ($p < 0.001$) in the group with no pain (n = 9). Compared to patients with no pain, patients with moderate to severe pain had increased glucose metabolism bilaterally in the prefrontal cortex, BA 9-11. Unilateral activation was found in the right parietal precuneus cortex, BA 7. There were no areas of the brain in which there was decreased activity due to moderate to severe pain.

Conclusions: Our results showing a preferential activation of the prefrontal cortex are consistent with results from studies showing that affective pain perception and negative emotions play an important part in the chronic pain experience.

Limitations: This was not a randomized clinical trial. Patient medication was not controlled.

Key words: chronic pain, cancer pain, positron emission tomography, brain imaging, prefrontal cortex, affective pain, negative emotions

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Neuroimaging represents an innovative method to evaluate brain processing of different pain conditions. Previous brain imaging studies have demonstrated differences between brain activity associated with acute experimental pain in volunteers versus chronic pain conditions in patients (1). Specifically, acute pain preferentially activates the somatosensory cortex (S1,S2), thalamus, insular cortex, and anterior cingulate cortex (ACC). Chronic pain conditions might activate the prefrontal cortex,

a region of the brain associated with emotions. However, the number of neuroimaging studies that have examined chronic pain are relatively small, and it is clear that all chronic pain conditions do not activate the exact same brain regions (2-5).

The present study uses positron emission tomography (PET) imaging to measure alterations in regional glucose metabolism in patients with moderate to severe chronic pain related to cancer. The PET scan reflects energy use associated with neuronal activity coupled to metabolic and vascular responses at the synapse (6). Our study examines baseline spontaneous pain in cancer patients, with no outside stimuli. There is only one early brain imaging study that looks at this patient group (7), and its main finding was a decrease in thalamic blood flow in cancer pain patients. The aims of this study are to characterize how the brain in cancer patients adapts to ongoing pain and to compare this with previous studies of other chronic pain conditions, such as arthritis or low back pain.

Methods

This study was approved by the Institutional Review Board of Rush University Medical Center. Cancer patients presenting for diagnostic PET imaging were asked to rate their spontaneous (no external stimulation) pain score at that time using an 10-point numerical rating scale (NRS), with 0 = no pain and 10 = worst imaginable pain. Those with no pain (NRS = 0) and those with moderate to severe pain (NRS ≥ 4), and who reported a similar pain intensity over the previous weeks, were invited to participate in this study. Patients that agreed to study participation then provided written informed consent, which allowed their PET scan, demographic and medical history data, and medication history to be recorded.

Patients with a history of cancer underwent whole body PET imaging for diagnosis and monitoring of disease status. There was no prior evidence of brain metastases. Patients had a 2-D PET scan with a Siemens ECAT EXACT 47 scanner (Siemens Medical Solutions USA, Malvern, PA) with BGO crystal (5.0 mm thick slices) and focused collimator. Prior to the PET scan, the patient fasted for at least 4 hours. In a quiet dark room, the patient was injected intravenously with the radionuclide 18F-fluoro-2-deoxyglucose (FDG) at a dose of approximately 20 mCi. After waiting 30 minutes, the patents underwent a brain scan (8). The 17-minute scan consisted of a 7-minute transmission phase plus a 10-minute emission phase, which provided sufficient emission counts for analysis (about 30 million).

Prior to initiating the study, 18 regions of interest (9 regions, both left and right side) were chosen to be examined based on published studies of acute and chronic pain brain activation (1,8,9). Those regions were primary somatosensory cortex (S1); secondary somatosensory cortex (S2); thalamus; anterior cingulate gyrus;insular cortex; prefrontal cortex: BA 9, BA 10, and BA 11; and parietal precuneus cortex. After completing an analysis of the pain regions of interest, all other regions with Z-score > 3 were then examined.

Each individual raw PET scan was coregistered and normalized to standard stereotactic Montreal Neurological Institute (MNI) space using the default PET template within the Statistical Parametric Mapping (SPM5) software package (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.1 (Mathworks, Sherborn, MA). The normalization process uses a 12 parameter affine registration with nonlinear warping producing a resampled output of 2 x 2 x 2-mm voxel size. To compare PET scans among different patients, a linear normalization was applied by dividing regional activity by whole brain activity for each scan (10). Differences in metabolic activation were then statistically compared between patients with moderate to severe pain and patients with no pain. The significance threshold for group differences was P=0.001. Regions with statistically significant FDG PET activation between the 2 groups were then displayed using the single subject template in SPM5. Locations of regions of interest were identified according to the MNI coordinates in SPM5 and then converted to Talairach using the mni2tal software (imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Coordinate names were derived using the Talairach Daemon system (11). NRS pain scores were compared by Mann-Whitney U-test, and demographics were analyzed by independent samples t-test.

Results

Twenty patients were consented and recruited into this study. The NRS pain score in the patients with moderate to severe pain (n = 11) was 4.5 [4.0-6.0] (median[interquartile range]) versus 0.0 [0.0-0.0] ($p < 0.001$) in the group with no pain (n = 9). Individual patient demographics and history are shown in Table 1. There were no differences in body weight between the 2 groups. The FDG dose did not differ between groups: 20.5 ± 1.7 mCi in the pain group versus 20.9 ± 1.1 mCi in the no pain group. Lymphoma was the diagnosis of 5/11 patients in the pain group, and 6/9 in the no pain

Table 1. *Demographics and history of cancer patients in study*

Patient	Age (y)	Gender	Wt (kg)	Malignancy	NRS	Drugs	FDG (mCi)
1	28	F	107	lymphoma	4	none	21.9
2	50	F	43	lymphoma	6	none	18.1
3	68	F	69	breast cancer	0	none	20.6
4	58	F	77	lymphoma	5	none	17.9
5	79	M	86	lung cancer	4.5	acetaminophen	20.5
6	53	F	53	pancreatic cancer	4.5	morphine/ hydromorphone	21.8
7	72	F	60	lung cancer	8	tramadol	21.9
8	61	F	91	lung cancer	8	morphine	21.8
9	25	F	82	lymphoma	4.5	none	19.6
10	49	F	78	lymphoma	0	none	21.8
11	25	F	68	lymphoma	0	none	18.5
12	18	F	68	lymphoma	0	none	19.9
13	75	F	58	esophageal cancer	4	acetaminophen	21.7
14	46	F	82	lung cancer	0	none	21.1
15	24	F	59	lymphoma	0	none	21.8
16	28	M	83	lymphoma	0	none	21.8
17	73	F	68	lymphoma	0	none	21.9
18	46	F	58	breast cancer	0	none	21.0
19	72	F	52	lung cancer	4	none	21.8
20	53	M	102	lymphoma	6	hydrocodone/ acetaminophen	18.3

group. Within the pain group, the NRS pain score in the patients with lymphoma (n = 5) was 5.0 [4.25-6.0], which was not different (p = 0.852) from the NRS of 4.5 [4.0-8.0] of patients with other types of cancer (n = 6).

Compared to patients with no pain, patients with moderate to severe pain had increased regional glucose metabolism bilaterally in the prefrontal cortex, BA 9-11 (Table 2, Fig. 1). Unilateral activation was found in the right parietal precuneus cortex, BA 7 (Table 2). All regions with Z-scores > 3 are listed in Table 2. No patient evidenced brain metastases in the PET images.

When we reversed the comparison process, to see if there were any areas of increased regional glucose metabolism in the no pain patients versus moderate to severe pain patients, there were no statistical increases. Therefore, there were no areas of the brain in which there was decreased activity due to moderate to severe pain.

Three of the 11 patients with chronic pain were on opioid medication (range 60-180 mg/day morphine equivalents). When the PET scans of the 3 opioid pain patients (median NRS=6.0) were compared to that of the 8 non-opioid pain patients (median NRS=4.5), there were no regions in which regional glucose metabolism differed between these 2 groups. Only one patient (pain group) was diagnosed with depression, and was taking a selective serotonin reuptake inhibitor, sertaline. Another pain patient was taking the benzodiazepine, lorazepam, for anxiety. One of the patients in the no pain group was taking the sedative-hypnotic zolpidem tartrate for short-term treatment of insomnia.

Discussion

The results illustrate that increased regional glucose metabolism associated with moderate to severe chronic cancer pain involves primarily the prefrontal cortex (BA 9-11). This is considered an associative area involved with human cognition and negative emotions (1,12,13), but might also have a more direct role in pain control (14). In an fMRI study, patients with intense spontaneous low back pain have shown the greatest brain activation in the medial prefrontal cortex (2). A

Table 2. *Brain regions with increased activation in cancer patients with chronic pain compared to those with no pain*

Brain Region	BA	Z-score	x	y	z
Pain Regions of Interest					
Prefrontal cortex					
R superior frontal gyrus	9	4.14	8	62	32
R inferior frontal gyrus	9	4.16	63	21	27
L middle frontal gyrus	9	3.83	-60	24	38
L middle frontal gyrus	10	3.83	-32	37	6
L middle frontal gyrus	10	3.66	-46	56	-10
L superior frontal gyrus	10	3.64	-32	69	-9
L medial superior frontal gyrus	11	4.16	0	67	-15
Parietal cortex					
R parietal precuneus	7	3.89	6	-77	44
Additional activated regions					
Supplementary Motor Cortex					
R superior frontal gyrus	6	3.92	28	21	67
R middle frontal gyrus	6	3.66	22	-14	62
Frontal cortex					
L inferior frontal gyrus	45	3.68	-55	28	17
Parietal cortex					
R inferior parietal cortex	40	3.94	52	-42	54
L parietal angular gyrus	39	3.78	-56	-66	38
Cingulate cortex					
L posterior cingulate cortex	30	3.71	-2	-50	17
Temporal lobe					
R superior temporal gyrus	38	4.42	20	12	-41
R superior temporal gyrus	38	4.36	24	16	-31
L superior temporal gyrus	22	3.69	-71	-44	22
R inferior temporal gyrus	20	4.35	57	-19	-29
L parahippocampal gyrus	38	4.44	-16	8	-37
L parahippocampal gyrus	36	4.20	-18	-2	-34
Cerebellum					
R cerebellum		4.09	59	-73	-35
L cerebellum		4.29	-46	-37	-33
L cerebellum		3.96	-6	-92	-22

BA = Brodmann area; x, y, z are Talairach stereotactic coordinates in mm.

meta-analysis of 30 studies of clinical pain conditions revealed that 81% of the studies showed activation in the prefrontal cortex (1).

Chronic cancer pain patients also had increased regional glucose metabolism in the right parietal precuneus (BA 7). Activation in this region was seen in a PET study of postoperative pain (8). Precuneus activation also accompanied the spontaneous pain of postherpetic neuralgia (4). Studies of acute pain (capsaicin injection in arm) also show precuneus activation (9). The precuneous is an associative cortex involved in a wide range of higher-order cognitive functions (15). The precuneus and prefrontal cortex are strongly interconnected, and so it is not surprising that both areas are activated in patients with chronic cancer pain. Neuroimaging studies have shown the involvement of the precuneus in self-processing tasks, concerning self-awareness and mental imagery, and so precuneus activation might be related to how these pain patients see themselves in relation to the outside world (15).

We did not identify any changes in brain activation with chronic cancer pain in the somatosensory cortexes (S1, S2), thalamus, anterior cingulate cortex, or insular cortex. These brain regions are activated in the majority of acute pain studies, performed on normal subjects (1,9). In addition, 59% of studies in patients with clinical pain conditions report thalamic activation, 58% report insular activation, and 45% report anterior cingulate cortex activation (1). Patients with intense spontaneous low back pain did not show activity in S1 or S2, although there was activity in rostral anterior cingulate cortex (2). However, with the spontaneous chronic pain of postherpetic neuralgia there is activation of S1 and S2 (4), and in osteoarthritis patients experiencing knee pain during the patients' accustomed physical activities, S1, S2, and the thalamus were activated (5).

In an early study of regional cerebral blood flow (PET using $C_{15}O_2$) in 5 cancer pain patients, versus 5 normal subjects, Di Piero et al (7) found that there was less blood flow in the thalamus in the cancer patients than in control subjects. However, we did not see a reduction in thalamic glucose metabolism in the chronic cancer pain group in our FDG PET study. In the earlier study, no change was seen in the S1 cortex, and while there was a small increase in the prefrontal cortex blood flow in cancer patients, it was not statistically significant. Perhaps a larger number of patients would have shown a significant increase in prefrontal cortex blood flow, matching our study.

In addition to the pain-related regions of interest, other areas were activated in the brain of patients with chronic cancer pain. Many of these are motor areas, such as cerebellum and supplementary motor area, which seem to be widely activated in acute pain studies too (9). Regional glucose metabolism was also seen in the parahippocampal gyrus, a region linked to the affective dimension of pain (16), and anxiety-induced pain modulation (17).

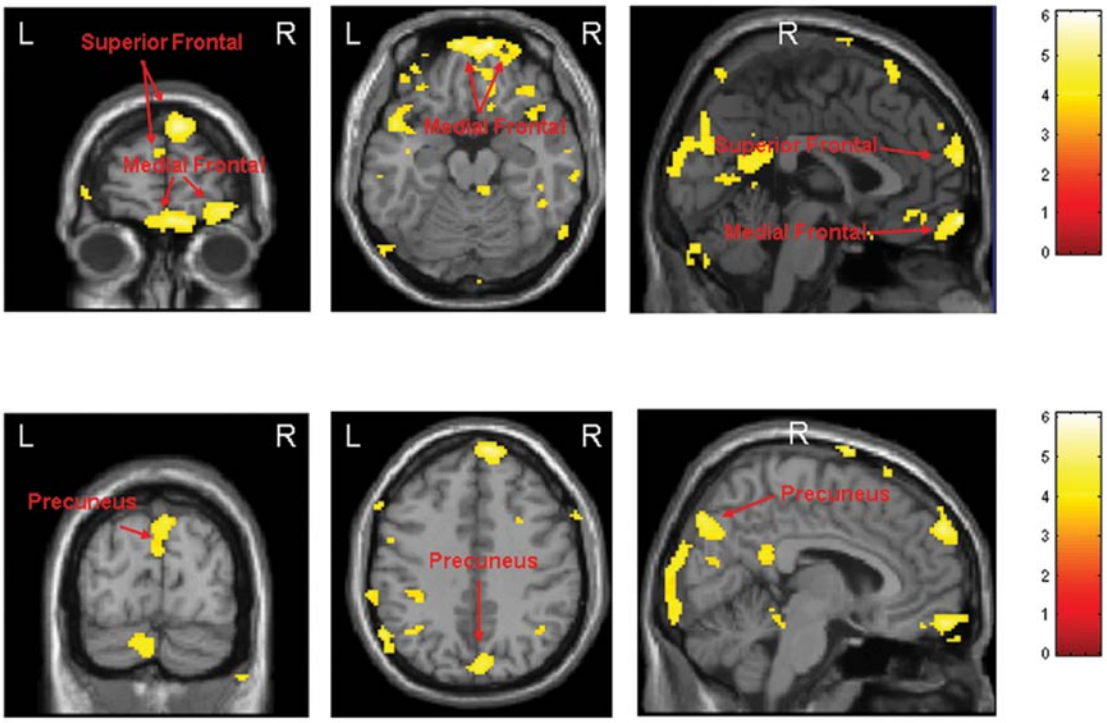

Fig. 1. *Top: Increased brain metabolism in the prefrontal cortex in 11 cancer patients with moderate-to-severe chronic cancer pain compared with 9 cancer patients with no pain. Arrows show regions of interest with increased activation in medial frontal and superior frontal gyrus, in coronal, axial, and sagittal slices. Bottom: Increased brain metabolism in the right parietal precuneus cortex in 11 cancer patients with moderate-to-severe chronic cancer pain compared with 9 cancer patients with no pain. Activity from PET scan is superimposed on a standardized stereotactic space. Color bar represents Z-scores of statistical significance.*

Our study demonstrates that chronic cancer pain preferentially activates the prefrontal cortex, a brain region involved with the affective processing and negative emotions associated with pain (1,2,12,13). While other chronic pain conditions also activate associative, cognitive, and emotional regions, there appear to be anatomical differences in the exact regions of activation. Part of this might involve methodological issues since most chronic pain studies emphasize evoked pain paradigms in their patients (1), rather than spontaneous pain as we have studied. We included many types of cancer patients in our study (mainly lymphoma), because it was felt from psychological studies that the chronic nature of this pain would be the dominant factor in the brain's response to the pain (18). Indeed, the lack of significant activation in many brain regions (S1, S2, thalamus, anterior cingulate cortex) closely associated with acute pain supports this concept.

Since this was not a randomized controlled trial, and there were no interventions, we did not play any role in the prescribing of medications for the patients with moderate to severe pain. A few patients were on opioids, which are known to suppress cerebral blood flow in many regions, including prefrontal cortex (19). However, we did not see a reduction in regional glucose metabolism between moderate to severe pain patients on opioids versus no opioids. Since these patients still had high pain scores even while taking opioids, it is reasonable to conclude that the drugs were not very effective in suppressing brain activation due to pain. With cancer-related chronic pain, there can be depression and anxiety associated with possible reoccurrence or worsening of their neoplasm (20-22). However, in the pain group in our study, only one patient was di-

agnosed with depression, and only one with anxiety. Unlike a research-designed study with a 3-D PET scan, the standard diagnostic protocols use a 2-D scan, which is less sensitive, although an FDG study that directly compared the 2 techniques found no major systematic differences and good agreement between the 2 acquisition modes (23).

Conclusion

Our results showing a preferential activation of the prefrontal cortex are consistent with results from studies showing that affective pain perception and negative emotions play an important part in the chronic pain experience. Understanding the mechanisms of chronic pain in cancer patients using neuroimaging will provide additional insight into the study of future therapies for patients with chronic pain.

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