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Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain

A. Vania Apkarian[a,*], P. Sebastian Thomas[b], Beth R. Krauss[c], Nikolaus M. Szeverenyi[d]

[a]Department of Physiology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL 60611, USA
[b]Department of Anesthesia, SUNY Upstate Medical University, Syracuse, New York, NY 13210, USA
[c]Department of Neurosurgery, SUNY Upstate Medical University, Syracuse, New York, NY 13210, USA
[d]Department of Radiology, SUNY Upstate Medical University, Syracuse, New York, NY 13210, USA

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Abstract

Chronic pain continues to impose a large burden of suffering, yet its neural correlates remain poorly understood. In sympathetically mediated chronic pain (SMP), peripheral sympathetic blockade temporarily relieves this pain, so that related neural activity can be studied without perturbing sensory inputs. We used functional magnetic resonance imaging and thermal painful stimuli applied to the chronically painful body site, before and after sympathetic blockade, to examine the cortical network of chronic pain. The chronic SMP state was associated with a widely spread prefrontal hyperactivity, increased anterior cingulate activity and decreased activity in the thalamus contralateral to the body side suffering from SMP, but was unrelated to sensorimotor activity. Ineffective sympathetic blocks, i.e. blocks that did not diminish the SMP pain, did not change the cortical responses to the painful thermal stimulus; while effective placebo resulted in similar responses to those of effective blocks. These findings provide evidence for abnormal brain responses to pain in patients with chronic SMP, which engages prefrontal/limbic networks more extensively than in acute pain-states.

Keywords: Brain imaging; Functional magnetic resonance imaging; Chronic pain; Sympathetic blocks; CRPS I; Acute pain; Cognition; Gambling

Chronic pain is a major health problem about which very little is known, partly because of an inability to manipulate such pain either pharmacologically or by more invasive approaches [3]. We have chosen to study the cortical pathophysiology of a specific chronic pain syndrome with properties uniquely suited for brain imaging. Chronic sympathetically mediated pain (SMP) is a subcategory of reflex sympathetic dystrophy (CRPS type I). The symptoms arise after injury to an extremity and include spontaneous burning pain, and other dysfunctions [12]. The sensory dysfunctions include allodynia, and/or cold or heat hyperalgesia, i.e. painful cold or heat stimuli feel more painful. When sympathetically maintained, SMP, blocking sympathetic efferents can relieve the pain without interfering with the sensory afferent fibers. We use this property of SMP to study its cortical pathophysiology. In most patients with reflex sympathetic dystrophy the body areas in chronic pain do not respect dermatomal boundaries, and may expand in time to include the opposite corresponding limb. Given the loose temporal association between injury and symptoms, and the lack of correspondence between the pain and the anatomy of peripheral sensory innervation, it is suggested that the syndrome may be a confabulation imagined by the patient and reinforced by naive physicians [10]. Here we report brain responses to thermal painful stimuli, in SMP patients and in normal volunteers. We find that brain responses to painful stimuli are abnormal in SMP patients while the patients are in their usual chronic pain. Following blockade of the chronic pain their responses are normalized.

The institutional review committee approved all procedures used, and all participants signed a written consent form. Seven SMP patients (32–48 years old, six female one male, with chronic pain for $>$ 1 year, each previously

* Corresponding author. Tel.: +1-312-503-0404; fax: +1-312-503-5101.
E-mail address: a-apkarian@northwestern.edu (A.V. Apkarian).

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undergone at least 8 weekly sympathetic blocks resulting in temporary pain relief) and 29 normal volunteers participated in the functional magnetic resonance imaging (fMRI) studies (21–46 years old, 15 females and 14 males). Patients with significant depression were excluded.

fMRI signals were collected on a 1.5 Tesla scanner using echo planar imaging gradient echo acquisition sequence (TR = 3500 ms; TE = 60 ms; FA = 90°) with a voxel size of $1.56 \times 1.56 \times 6.50$ mm when using a surface coil and scanning a third of the brain (eight slices), or a voxel size of $3.75 \times 3.75 \times 5.0$ mm when using a head coil and scanning the whole brain (23 slices). Anatomic spin echo images of the entire brain were also collected. In separate scans, the contralateral middle or frontal third of the brain, or the whole brain were studied. For the frontal studies 8 slices covered the region from 0 to 52 mm anterior to the anterior commissure. In the studies of the middle third of the brain (parietal area) the region extended from 6 to 58 mm posterior to the anterior commissure.

The details of the fMRI data analysis are presented in [1,5,9]. Briefly, a shifted boxcar model was used to identify fMRI activity changes between stimulus and control states. Significant activation was determined using a *t*-value cutoff ($P < 0.05$) in combination with a cluster cutoff ($P < 0.05$), resulting in an overall multiple comparison corrected $P < 0.03$. In the group analysis *t*-maps were filtered with a Gaussian FWHM of $5 \times 5 \times 5$ mm, converted to Fisher's *Z*-maps, transformed into standard brain atlas space, and averaged across subjects. *Z*-maps were thresholded with appropriate clustering (35 voxels for a *Z*-threshold of 2.5) resulting in a repeat measure corrected $P < 0.05$.

Thermal stimuli were delivered through two aluminum disks connected to two separate water baths. The painful task consisted of subjects alternating (on a verbal cue) the glabrous hand between two heated surfaces: one warm (37–39°C for 35 s); the other painful (1°C above pain threshold applied for 35 s), repeated six times during fMRI scans. At the end of scans, subjects rated the overall stimulus pain; patients also rated their chronic SMP pain, on a scale from 0 to 10, 0 = no pain and 10 = maximum imaginable pain.

Subjects were catheterized to access the axillary space of the appropriate arm. After the termination of the first set of functional scans, a local anesthetic (Bupivacaine 0.2% in 20 cc saline) was administered through the catheter. Fifteen minutes later functional scans were resumed. In the 15-min period post-injection subjects continuously described the sensations experienced. Subjects' tactile and thermal thresholds were tested pre- and post-sympathetic blocks to insure that the local anesthetic did not influence sensory afferents, using ascending and descending methods of limits. Skin temperature was also measured before and after blocks.

The SMP patients selected for this study all had spontaneous chronic pain limited to one hand. Seven SMP patients were studied in 45 fMRI scans. In SMP patients and normal volunteers, touch thresholds were not changed with the sympathetic blocks. Thermal thresholds were unchanged in the SMP patients, but increased in two of six normal volunteers after sympathetic blockade. The mean painful stimulus used in SMP patients was 46.0 ± 1.5°C, while in normal volunteers it was 47.5 ± 1.0°C, the difference in applied temperature reflecting the thermal hyperalgesia that the patients exhibit. Fig. 1 shows frontal cortical responses to thermal painful stimulation before and after a block in one patient, in the frontal cortex. There is large prefrontal (PF) cortical activity when the painful thermal stimulus is presented on the chronically painful hand. This activity dramatically decreases when the same stimulus is applied minutes after the sympathetic block that also leads to pain relief.

To determine regions of the brain that are modulated with the sympathetic block, we subtracted the resultant 'post-block thermal pain responses' from the 'pre-block thermal pain responses' for successful and unsuccessful sympathetic blocks, in the studies where the whole brain was imaged and averaged across scans and patients (patient group II). In three patients (16 functional scans), results of subtracting post-block ($n = 4$ scans, ongoing pain = 0.9 ± 0.8, stimulus pain = 4.6 ± 4.3) from pre-block responses ($n = 8$ scans, ongoing pain = 7.9 ± 1.9, stimulus pain = 8.6 ± 2.6) when the sympathetic blocks significantly decreased the chronic pain are shown in Fig. 2a. Only two brain regions survived this subtraction, PF and the anterior cingulate (AC). These then are regions modulated with changes in the chronic pain-state. The portion of AC related with the chronic state is localized to where pain unpleasantness has been reported to be encoded in normal subjects [11]. Since sympathetic blocks decrease the unpleasantness and the intensity of the pain, our results partially correspond to this study and imply

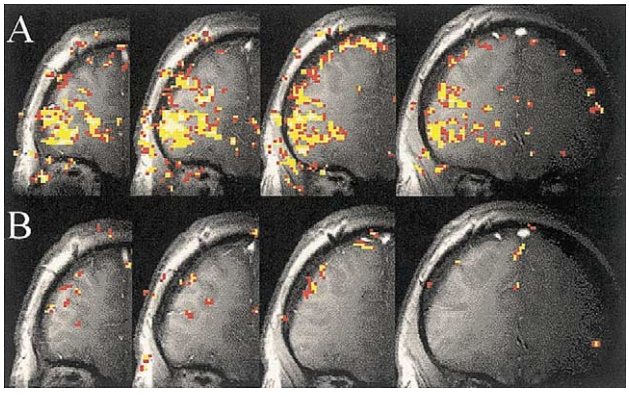

Fig. 1. Modulating chronic pain decreases frontal cortical activity to thermal painful stimuli. Activity is shown in the frontal cortex contralateral to the stimulated hand in a chronic SMP patient, before (A) and after (B) a sympathetic block that decreased the chronic pain. The thermal painful stimulus was 45.9°C; ongoing chronic pain was rated as 7 and 2; and stimulus pain as 11 and 6 (0–10 pain scale), in (A) and (B). The slices span 26 to 45.5 mm anterior from the anterior commissure. Colored voxels are activation intensities: red is $P < 0.05$, orange < 0.01, yellow < 0.001, and white < 0.0001; uncorrected and unclustered probabilities.

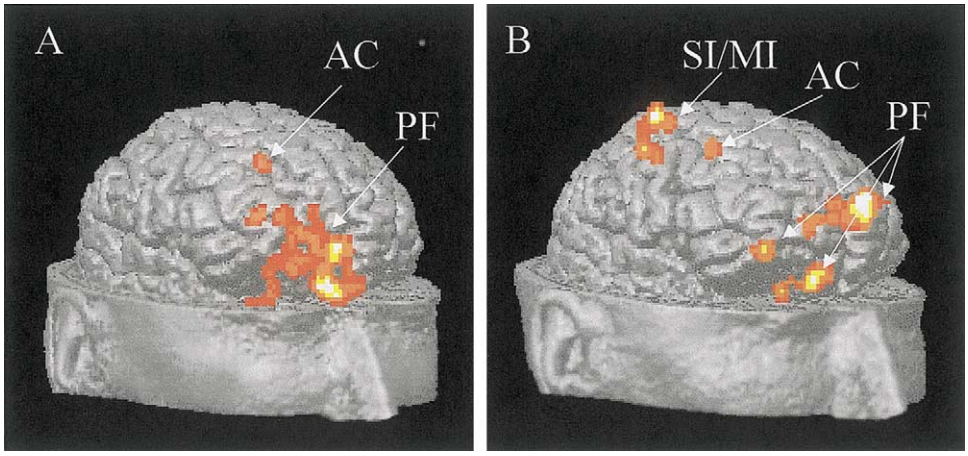

Fig. 2. Effects of modulating chronic pain on group-averaged cortical responses to painful thermal stimuli applied on the chronic SMP hand. (A) Difference in activity between responses prior to blocking (eight scans) to those after successful blocks (four scans). Two regions show significant activity: anterior cingulate (AC, activity covered 344 mm^3 volume, with a peak Z-value of 3.46), and the prefrontal cortex (PF) where multiple subdivisions are activated: mid-dorsolateral PF (region 9 with 432 mm^3 volume, peak Z 3.71), frontal pole (region 10 with 824 mm^3 volume, peak Z of 3.88) and cingulate at the level of the genu (areas 24 and 32 with a total volume of 1224 mm^3, peak Z 3.20). (B) Shows group-averaged responses (sum of 12 scans). Cortical activity is seen in the contralateral sensorimotor cortex (SI/MI, hand region with 2232 mm^3 volume, peak Z 3.73), as well as in AC (352 mm^3 volume, peak Z 3.14), and PF (area 10 with a volume of 4288 mm^3, peak Z 3.99; and area 11 with a volume of 408 mm^3, peak Z 3.39). Colored voxels are activation intensities: red is $P < 0.01$; orange < 0.001; yellow < 0.0001; and white < 0.00001, uncorrected clustered probabilities.

that the distinguishing feature between normal subjects and SMP patients is the activity in PF.

When the same subtraction was done for cases where the sympathetic blocks did not affect the chronic pain (the injections either missed the nerve bundle or were ineffective for unknown reasons, four failed block scans subtracted from eight pre-block scans), no cortical region passed threshold for significant activity. Fig. 2b illustrates the average response to thermal pain when all scans with sustained chronic pain were combined (eight pre-block and four failed post-block scans). The main cortical activity is still in PF, including multiple subdivisions. More posteriorly significant activity is seen in the contralateral primary sensorimotor cortex (SI/MI), and AC. Therefore, these three regions are the main areas involved in the perception of the thermal pain when the patients are experiencing their chronic SMP pain.

Brain imaging studies [4,7,8] have described decreased thalamic activity in chronic pain. We tested this hypothesis in the studies where the whole brain was imaged and averaged across scans and patients (patient group II). The boundaries of the thalamus were delineated on four slices and the mean Z-score calculated from group averaged Z-maps. Mean fMRI activity in the thalamus showed borderline significant asymmetry for the grouping where all scans with sustained chronic pain were combined (eight pre-block and four failed post-block scans). In this case, the thalamus contralateral to the SMP hand showed decreased fMRI activity ($Z = -0.47 + /-0.04$, vs. $Z = 0.12 + /-0.36$, for thalamus contralateral and ipsilateral to the SMP hand, $P < 0.1$). The same analysis was done for the grouping of the subtraction of post- from pre-block responses when the blocks significantly decreased the chronic pain (four successful post-block scans subtracted from the eight pre-block scans). In this condition a similar but larger asymmetry was observed between the two thalami ($Z = -0.9 + / -0.13$ vs. $Z = 0.83 + /-0.20$, for contralateral and ipsilateral thalami to the SMP hand, $P < 0.005$).

Three groups of normal right-handed volunteers were used as controls (29 volunteers, 94 fMRI scans). In control I middle-, and control II frontal-third of the brain was scanned during a thermal pain task. In control III scans were done for thermal painful tasks pre- and post-sympathetic blocks, mimicking the procedure implemented in SMP patients. Thermal painful stimulation in the control subjects showed an activation pattern similar to previous findings, see [13], described in detail in [1,5].

To quantify differences in brain activity in the SMP patients between pain-states and in comparison to normal subjects a spatial and intensity integrated fMRI measure of activity was used: activation index (AI, see Ref. [1]; AI counts were summed over eight slices of either frontal or parietal cortex contralateral to the stimulated hand). Fig. 3 shows activity values averaged over all scans and subjects in the three control groups and in the SMP patients pre- and post-block (patient group I). In the frontal brain, activity is significantly higher in SMP patients prior to sympathetic blocks (AI $= 976 \pm 205$, mean $\pm$ SEM, $n = 7$ scans) than in normal subjects (AI $= 310 \pm 86$, $n = 6$ subjects prior to blocking; AI $= 496 \pm 217$ $n = 11$ unblocked subjects; $P < 0.008$ and $P < 0.009$ between the patients and each control group). The sympathetic block significantly decreases the frontal brain activity of SMP patients, as compared to their pre-block values (post-block AI $= 270 \pm 89$, $n = 5$; $P < 0.005$ pre- vs. post-block), making it similar to the responses

in the normal subjects. Brain activity counts in the control group who underwent sympathetic blocks are revealing since they show that the block does not affect frontal cortical activity (AI = 311 ± 86 pre-block, and 392 ± 145 post-block, $n = 6$), but decreases activity in the parietal brain although not statistically significantly.

The prefrontal hyperactivity to painful thermal stimuli observed in the chronic pain-state in SMP patients provides direct evidence for a brain pathophysiology for this state. The prefrontal hyperactivity is accompanied with decreased parietal cortical activity and decreased unilateral thalamic activity. This pattern reverses when the chronic pain is diminished or decreased with sympathetic blocks, to become more similar to the responses to painful stimuli seen in normal subjects. The latter implies that chronic pain and acute stimulus induced pain engage distinct cortical networks, suggesting central reorganization.

The cortical network described for pain-states have generally been interpreted as being mediated through the spinothalamic pathway, especially for experimentally induced painful stimuli [13]. The cortical pattern of activity that we observe in the normal subjects is consistent with this interpretation. In contrast, the chronic SMP state does not seem compatible with nociceptive transmission through the spinothalamic pathway. The decreased thalamic activity, contralateral to the SMP hand, accompanied with decreased parietal cortical activity is consistent with each other and implies decreased nociceptive transmission through the spinothalamic pathway. The only other direct spinal nociceptive pathway that can access frontal cortical regions is the spino-limbic/hypothalamic projection [6]. We, therefore, conclude that this pathway may be preferentially involved in at least SMP type chronic pain. Other indirect nociceptive pathways, e.g. spinal-brainstem-amygdala projections [2], may also be important in the SMP chronic pain.

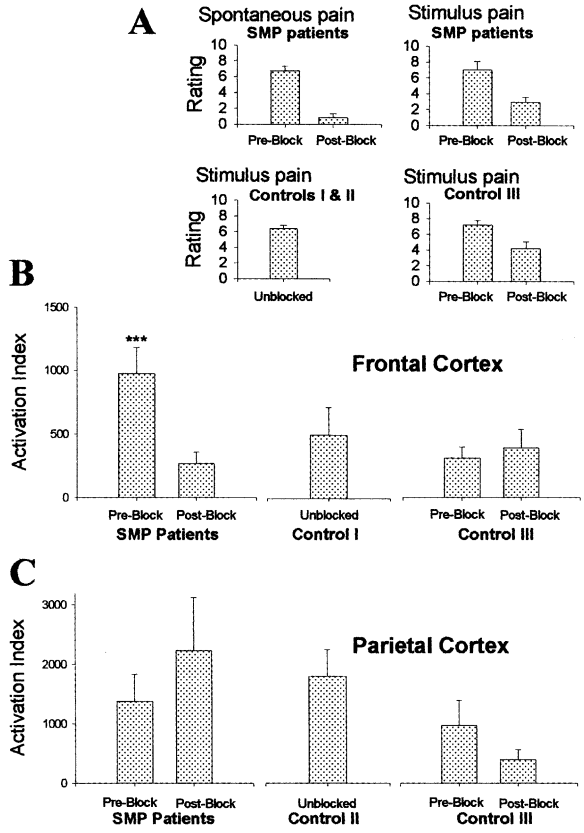

Fig. 3. Frontal cortical responses reflect post-block changes in chronic pain. (A)-top. SMP patients, spontaneous and thermal stimulus evoked pain ratings, pre- and post-sympathetic block. (A)-bottom. Stimulus ratings in normal volunteers who were not blocked (Controls I and II) and in volunteers (Control III) before and after sympathetic blocks. Quantitative measures of cortical activity (total activation index, AI, in the cortex contralateral to the stimulated hand) in the frontal (B) and parietal cortex (C) are shown for the subject groupings in (A). Frontal cortex activity in SMP patients is high pre-block, compared to control groups and to post-block activity. Its post-block activity reflects the decreased chronic pain and stimulus pain ratings. In contrast, parietal activity changes in the SMP patients are not related to the pain rating changes. Bars are means ± SEM.

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[1] Apkarian, A.V., Darbar, A., Krauss, B.R., Gelnar, P.A. and Szeverenyi, N.M., Differentiating cortical areas related to pain perception from stimulus identification: temporal analysis of fMRI activity, J. Neurophysiol., 81 (1999) 2956–2963.
[2] Bernard, J.F., Bester, H. and Besson, J.M., Involvement of the spino-parabrachio-amygdaloid and -hypothalamic pathways in the autonomic and affective emotional aspects of pain, Prog. Brain Res., 7 (1996) 243–255.
[3] Bonica, J.J., General Considerations of Chronic Pain. The Management of Pain, Leo & Fibinger, Malvern, PA, 1990, pp. 180–196.
[4] Di Piero, V., Jones, A.K.P., Iannotti, F., Powell, M., Perani, D., Lenzi, G.L. and Frackowiak, R.S.J., Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy, Pain, 46 (1991) 9–12.
[5] Gelnar, P.A., Krauss, B.R., Sheehe, P.R., Szeverenyi, N.M. and Apkarian, A.V., A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks, Neuroimage, 10 (1999) 460–482.
[6] Giesler Jr, G.J., Katter, J.T. and Dado, R.J., Direct spinal pathways to the limbic system for nociceptive information, Trends Neurosci., 17 (6) (1994) 244–250.
[7] Hsieh, J.C., Belfrage, M., Stone-Elander, S., Hansson, P. and Ingvar, M., Central representation of chronic ongoing neuropathic pain studied by positron emission tomography, Pain, 63 (1995) 225–236.
[8] Iadarola, M.J., Max, M.B., Berman, K.F., Byas-Smith, M.G., Coghill, R.C., Gracely, R.H. and Bennett, G.J., Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain, Pain, 63 (1995) 55–64.
[9] Krauss, B. and Apkarian, A.V., Group average activation maps of functional MRI: methodology of identifying group brain areas activated during painful thermal stimuli,

motor and vibrotactile tasks in humans, Riv. Neuroradiol., 11(Suppl. 2) (1998) 135–138.
[10] Ochoa, J.L., Verdugo, R.J. and Campero, M., Pathophysiological spectrum of organic and psychogenic disorders in neuropathic pain patients fitting the description of causalgia or reflex sympathetic dystrophy, In G.F. Gebhart, D.L. Hammond and T.S. Jensen (Eds.), Proceedings of the 7th World Congress on Pain, IASP Press, Seattle, 1994, pp. 483–494.
[11] Rainville, P., Duncan, G.H., Price, D.D., Carrier, B. and Bushnell, M.C., Pain affect encoded in human anterior cingulated but not somatosensory cortex, Science, 277 (1997) 968–971.
[12] Schwartzman, R.J. and McLellan, T.L., Reflex sympathetic dystrophy: a review, Arch. Neurol., 44 (1987) 555–561.
[13] Treede, R.D., Kenshalo, D.R., Gracely, R.H. and Jones, A.K., The cortical representation of pain, Pain, 79 (1999) 105–111.