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Neural Correlates of Chronic Low Back Pain Measured by Arterial Spin Labeling

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Abstract

Background—The varying nature of chronic pain (CP) is difficult to correlate to neural activity using typical functional magnetic resonance imaging methods. Arterial spin labeling is a perfusion-based imaging technique allowing the absolute quantification of regional cerebral blood flow, which is a surrogate measure of neuronal activity.

Methods—Subjects with chronic low back and radicular pain and matched healthy normals, undergoing identical procedures, participated in three sessions—a characterization and training session and two arterial spin labeling sessions. In the first imaging session CP (if any) was exacerbated using clinical maneuvers and in the second session noxious heat was applied to the affected leg dermatome, the intensity of which was matched to the pain intensity level of the CP exacerbations for each back pain subject.

Results—The clinically significant worsening of ongoing CP (≥30%, n=16) was associated with significant regional blood flow increases (6–10 mm/100gr of tissue/min, $p<0.01$) within brain regions known to activate with experimental pain (somatosensory, prefrontal, and insular cortices) and in other structures observed less frequently in experimental pain studies, such as the superior parietal lobule (part of the dorsal attention network). This effect is specific to changes in ongoing CP as it is observed during worsening CP, but it is not observed after thermal pain application, or in matched, pain-free healthy controls.

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Conclusions—Our findings demonstrate the use of arterial spin labeling to investigate the neural processing of CP, and they are a step forward in the quest for objective biomarkers of the chronic pain experience.

Introduction

Neuroimaging modalities, such as functional magnetic resonance imaging (fMRI) or positron emission tomography, have contributed valuable insights into the processing of pain in the brain.[1, 2] The majority of these studies have been in healthy volunteers utilizing the application of experimental noxious stimuli, such as thermal pain.[3] This work has identified a complicated brain network associated with pain stimuli (although not necessarily specific only to pain),[4] often termed, the "pain matrix". The "pain matrix" includes the primary and secondary somatosensory (S1 and S2), anterior cingulate, insular and prefrontal cortices, and the thalamus.[5]

However, significant limitations have hindered the application of neuroimaging to the study of a patient's own clinical pain.[6] Foremost is the nearly constant and varying nature of the chronic pain experience (including the ongoing process of evaluating salient meaning) that is difficult to correlate to neural activity using typical fMRI methods, such as blood oxygen level dependent imaging (BOLD). The strength of BOLD imaging is the ability to correlate fMRI signal changes to stimulus changes that occur over a period of a few seconds. Unlike experimental pain, chronic clinical pain often cannot be switched on and (especially) off at will; for instance, the ongoing levels of pain in patients with chronic low back pain (CLBP) frequently linger above their baseline levels well after the end of a straight leg raising maneuver.[7] Given this decoupling between stimulation and pain sensation, CLBP (as well as other pain disorders) eludes 'two-state subtraction' design studies with BOLD imaging, as this technique requires multiple ON and OFF alternations to have sufficient statistical power.

Arterial spin labeling (ASL) is a perfusion-based fMRI technique which uses water in arterial blood as a freely diffusible tracer to measure perfusion noninvasively. This allows for the absolute quantification of regional cerebral blood flow (rCBF), which is a surrogate measure of neuronal activity,[8] and it may be superior to BOLD as a proxy measure of regional glucose utilization.[9] Owing to its better estimation of brain activity for low frequency experimental designs, and its ability to quantify in absolute units rCBF, ASL appears better suited to study some aspects of the chronic pain experience, although few studies have done so to date.[6] An important experimental pain study applied pulsed ASL (pASL) to healthy volunteers undergoing tonic, experimental muscle pain stimulation.[10] More recently, pASL has been applied in a patient during and after an acute migraine headache.[11]

In this study we use pASL to investigate the neural correlates of changes in baseline levels of ongoing CLBP and radicular pain. We hypothesized that the experimentally induced worsening of CLBP and/or radicular pain, but not the control conditions, would be associated with increased rCBF in a widespread network of brain regions, including (but not exclusively) those of the experimental 'pain matrix'.

Materials and Methods

Study Design and Population

This was an institutional review board-approved (Partners Healthcare, Boston, MA, USA), cohort study of 16, right-handed patients with CLBP and radicular pain and a control group of 16 healthy, right-handed subjects, with no pain, matched for age and gender. The

experimental design included within subject and between subject controls. Subjects participated in three sessions-- a characterization and training session, and then two fMRI sessions. One fMRI session ("clinical maneuvers session") included 10 second periods of temporary exacerbation of back and leg pain through clinical maneuvers, such as straight leg raising or pelvic tilt. The other session ("heat pain session") included periods of heat pain applied to the affected leg dermatome, the intensity of which was matched to the pain intensity level of the clinical pain exacerbation periods (Figure 1). Subjects with CLBP were included if they were: 1) between the ages of 21–65, 2) had ongoing chronic pain that averaged at least 3 on a 0–10 scale of pain intensity, 3) had no back surgery within the past year, 4) were not having pain management procedures during the study period, 5) were not taking opioids or benzodiazepines, 6) had low back pain with radicular pain of at least six months duration, 7) did not have sensory or motor deficits that precluded participation in the pain procedures, 8) were right handed, and 9) had a significant discogenic component to their pain syndrome, confirmed by lumbar magnetic resonance imaging study (MRI). Eligibility was determined by investigator ADW at the first visit through a review of a history and physical examination, and MRI findings confirming disc disease. Patients were included if this evaluation found that a source of pain was at least one degenerated, herniated, or torn lumbar disc with either a minimum Grade III disc degeneration,[12] abnormal morphology,[13] or a hyperintense zone.[14] These criteria, used by the authors in previous studies,[15, 16] exclude those with pain due purely to nonspecific or myofacial causes and include those with the commonly presenting mixed syndrome of low back pain with underlying disc pathology, and possibly spinal stenosis or facet disease.

Characterization Methods

After signing written, informed consent, the following self-report questionnaires were administered at the start of each of the three sessions. The low back pain subjects completed all of the scales below, while the healthy subjects only completed the Pain Catastrophizing Scale and the Gracely Box Scales (GBS), since they had no chronic pain.

Brief Pain Inventory—This is a 15 item questionnaire assessing pain location, and 0–10 ratings of pain intensity, relief, quality, pain-related quality of life, and function. It has been validated in cancer and non-cancer pain conditions.[17, 18] The activity interference items measure separate domains of function, such as pain interference with activity, sleep, or work.[19]

Neuropathic Pain Questionnaire—This validated scale describes the presence or absence of neuropathic pain symptoms, using self-rated descriptive terms for neuropathic pain symptoms such as burning or numbness.[20] It has a predictive accuracy for neuropathic pain of 73%, and is used to classify the neuropathic components of a pain syndrome (Yes/No).

Oswestry Disability Index—This is an extensively used 10-item scale to describe the level of disability in patients with chronic low back pain.[21]

Pain Catastrophizing Scale—This 13-item survey assesses beliefs and thoughts about pain which have been shown to have an independent relationship to pain from other psychological constructs.[22] It can be administered to patients with chronic pain and healthy volunteers.

Gracely Box Scales (GBS)—These 20-point scales rate perception of the sensory and affective (unpleasantness) components of pain sensations.[23] They were administered at the beginning of each pASL scan and throughout both fMRI sessions to characterize the

subjects' level of baseline, ongoing chronic pain and the levels of pain during the acute pain exacerbation periods and thermal pain stimuli. The Gracely scales include descriptors anchored to values from 0–20, such as "0--no pain sensation" and "18--extremely intense". The GBS are exponential, ratio scales ranging from 10^0 to $10^{2.0}$, and they are structured to correct for the non-linearity of the 0–10 or 0–100 numerical or visual analogue pain scales. They are particularly suited and sensitive to determining the degree of change in pain within an experimental session.[24] The raw change scores can be converted into percent changes in pain. Throughout the imaging sessions, these scales were presented to the subjects in the scanner with EPRIME software(Psychology Software Tools, Sharpsburg, PA), using a mirror to project them onto a screen comfortably in their field of view. Subjects used an MRI compatible button box to rate pain levels. This method and these scales have been used extensively and validated by our group to assess pain during an fMRI scan session.[25]

Chronic Pain Exacerbation—For each CLBP subject, if the radicular pain was greater than the axial pain component, a bilateral, passive straight leg maneuver was performed, with the height and angle of elevation recorded. Using an fMRI compatible device custom-made for this study, the legs were raised to two levels that when held for 10 seconds would acutely worsen the pain to either a Moderate level (10–11 on the GBS sensory scale, "moderate pain condition") or a Strong level (14–15 on the GBS, "high pain condition"). To familiarize subjects with an actual fMRI session, they were placed in a mock scanner and underwent four stimulations (2 moderate and 2 high pain conditions in random order, spaced 110–120 seconds apart). Prior to each stimulation, they rated their baseline (current) pain using the GBS sensory scale and after each stimulation they rated pain intensity and unpleasantness experienced during the exacerbation periods using both the GBS sensory and affective scales, presented in random order.

For each subject it was confirmed that their pain returned to a lower level within 30 seconds after a 10 second exacerbation period, with the understanding that their baseline pain rating prior to each stimulus may or may not rise over time with repeated stimuli. Subjects could not go further in the study if the pain stimulation acutely worsened their ongoing, baseline pain beyond this time (which was communicated in discussions with potential subjects prior to enrollment). Thus, this method enables subjects to distinguish between and assess pain exacerbations and ongoing chronic pain.

Each healthy subject underwent identical passive straight leg raising maneuvers to the same angles of elevation matched to a CLBP patient for the moderate and high pain stimuli. They participated in an identical fMRI mock scanning session and performed the same rating procedures before and after each stimulus as the CLBP group.

For those CLBP subjects whose axial pain was greater than their radicular pain, to exacerbate their pain they performed either a pelvic tilt or lumbar extension maneuver[26] while supine (depending on whichever method most reliably worsened their pain and allowed it to return to a lower level within 30 seconds). We recorded the distance the hips were raised off of the MRI table or the degrees of extension using an inclinometer, for the moderate and high pain stimuli levels. They underwent identical calibrated pain stimuli and rating procedures as those who performed straight leg raising. The healthy normal subjects performed these exact procedures to the same distances or degrees as the CLBP patient to which they were matched.

Thermal Pain Stimuli—Noxious heat was applied to the affected lower leg dermatome in the CLBP patients and to the identical area in the matched healthy controls using a Medoc TSA-II device (Medoc, Ramat Yishai, Israel). The thermode size is 30 × 30 mm, with a rate of rise in temperature of 5 degrees Celsius/second. During the training session thermal

stimuli were applied to each subject by gradually escalating the temperature to find the level that produced a rating of Moderate (10–11, 'moderate pain') and Strong (14–15, 'high pain') on the GBS sensory scale when applied for 5 seconds (calibrated thermal pain stimuli). Subjects were then placed into the mock scanner and underwent a trial run of four random stimuli, 2 moderate and 2 high pain, spaced 90–110 seconds apart. The required temperatures were adjusted if needed. For each subject it was confirmed that there was no lingering thermal pain prior to the subsequent stimulus, and the probe was moved slightly after each stimulus to prevent tissue sensitization. The rating procedures were identical to the back and leg pain exacerbation methods.

FMRI Sessions—The scanning bed was modified to maximize comfort for the CLBP subjects, so that chronic pain was less likely to increase from simply lying in the scanner. In both sessions (Figure 1), two 6 minute pASL scans were collected using the "PICORE-Q2TIPS" MRI labeling method,[27] with a 3 T Siemens TIM Trio MRI System (Siemens Medical, Erlangen, Germany), equipped with a 32-channel head coil (TR/TE/TI1/TI2= 3000/13/700/1700ms, voxel size = 3.515*3.515*6.25 mm, number of slices = 16). 'Tag' images were acquired by labeling a thick inversion slab (110 mm), proximal to the imaging slices (gap=21.1 mm). 'Control' images were acquired interleaved with the tag images, by applying an off-resonance inversion pulse without any spatial encoding gradient. At the beginning of each pASL scan, an M_0 scan (i.e., the longitudinal magnetization of fully relaxed tissue) was acquired for rCBF quantification purposes (see next paragraph below). The resting state (eyes closed) pASL scans were acquired before and after 12 clinical maneuvers (session 1) or 12 heat pain stimuli (session 2, both sessions had 6 moderate pain and 6 high pain stimuli, randomized), delivered in three separate runs. At the start of the 'clinical maneuvers session' session, just before scanning, the CLBP subjects had the level of the clinical maneuver "recalibrated" to determine the levels of leg raising, pelvic tilt, or lumbar extension capable of eliciting ratings of moderate and high pain. Before and after each of the six minute pASL scans, subjects rated their level of baseline pain (if any) using the GBS sensory scale. The delivery of pain stimuli, the duration of each run, and the pain rating procedures were performed identically to the training session. The thermal pain fMRI session was conducted in exactly the same fashion: subjects were recalibrated to the appropriate heat pain levels, rated their pain (if any) just prior to the pASL scan, underwent three runs of four stimuli each, rated their pain just prior to a stimulus and after the third run, and then had a repeat pASL scan. A high resolution MPRAGE scan (TR/TE = 2300/3.39 ms, voxel size 1*1*1.33mm) was also acquired during one of the two sessions, for the purposes of cortical surface reconstruction.

Statistical Analyses

For the demographic history factors and baseline pain questionnaire responses, analysis of variance (ANOVA) and Chi square was used to describe the groups. The ratings of chronic pain obtained just before and after a pASL scan were averaged. Repeated measures ANOVA was used to characterize the serial ratings of ongoing pain during the fMRI session, to determine the percent change in pain over time, and to compare groups. Comparisons of each time point to baseline were made using Dunnett's test for multiple comparisons. All confidence intervals (CI) were reported at 95% and all testing was 2-tailed. ASL data analysis was performed using a combination of analysis packages including FSL♣ and Freesurfer◆ The 'tag', 'control' and M_0 scans were first motion-corrected using MCFLIRT.[28] Then, tag and control scans were surround subtracted (i.e., given each tag_X, $[(control_{X-1} + control_{X+1})/2 - tag_X]$) to achieve perfusion-weighted images. All the

♣FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl. Last accessed 2/2/2011
◆http://surfer.nmr.mgh.harvard.edu/. Last accessed 2/2/2011

perfusion-weighted maps were then averaged, and scaled by a factor proportional to the M_0 scan to obtain rCBF maps in absolute values (mm/100gr of tissue/min).[29] As accurate measurement of rCBF in white matter presents methodological challenges (particularly given the poor signal-to-noise ratio and longer arterial transit time),[30] further processing and analyses were carried out on the cortical surface level. RCBF maps were registered to the high resolution anatomical images using FreeSurfer's bbregister tool,[31] interpolated onto Freesurfer-reconstructed cortical surfaces,[32] and then smoothed at the surface level with a kernel of 7.03mm (=2*voxel size). Average global CBF was calculated for both ASL sessions and compared using two-way, repeated measures ANOVA. Raw changes in rCBF values (ΔrCBF, i.e., $rCBF_{ASL1}$-$rCBF_{ASL2}$) were computed for each subject, interpolated to a standard surface space (fsaverage), and then group-averaged. The clusters of change in CBF were extracted from the whole brain data. The same calculations were performed on normalized rCBF data. Montecarlo simulations were run on both the raw change and normalized rCBF change analyses to identify the clusters exhibiting a significant ΔrCBF,[33] using a vertex-level threshold of p=0.01 and a cluster-level threshold of 0.05. We compared within session and between session differences between groups for the ΔrCBF calculated for each session (i.e., $rCBF_{ASL1}$-$rCBF_{ASL2}$ for the same session). Montecarlo simulations control for multiple comparisons when reporting p values of the clusters. Cluster-size approaches (as opposed to single voxel level approaches) are based on the assumption that the probability is low that a given number of pixels exceeding threshold due to chance will be contiguous.[34] Montecarlo simulations allow for the estimation of the probability distribution of cluster size as a function of alpha level, and thus the identification of a cluster-size threshold, by creating high numbers (10000 in our case) of simulated null datasets.

Linear regression was used examine whether there were significant linear correlations between changes in pain and changes in rCBF activation patterns in either of the 2 sessions in the CLBP patients. This was performed on a whole brain and a cluster level of analysis.

Results

Twenty three CLBP patients were enrolled, and 7 could not complete the first session due to failure of their pain to return to a lower level with 30 seconds of a pain stimulation. Baseline data for the 16 CLBP subjects and 16 matched healthy controls who completed the study are displayed in Table 1. The majority of CLBP subjects were female, had a duration of pain greater than 5 years, did not have a clinically significant neuropathic component to their pain, were clinically and statistically more significantly disabled than their healthy counterparts, and had clinically and statistically greater levels of pain catastrophizing. Ten CLBP patients had predominantly right-sided low back and radicular pain and six had predominantly left-sided pain. Thirteen patients had the L5 dermatome most affected, two had S1 most affected, and one had L4 most affected.

Nine CLBP subjects did bilateral straight leg raising for their clinical pain exacerbations. For the moderate clinical pain condition the average degree of elevation was 17, and for the high pain condition the average was 22. Five subjects did pelvic tilt, raising their hips on average 10 cm for the moderate and 14 cm for the high pain conditions. Two subjects did low back arching, extending 14 and 18 degrees on average for the two conditions, respectively. For the thermal pain testing the average temperature across both groups for the moderate pain condition was 45 degrees Celsius and 47 degrees for the high pain condition.

Psychophysics

Figure 2 displays the means of the baseline pain ratings collected during the 'clinical maneuvers session' and 'heat pain session' using the GBS Sensory Scale for the CLBP

patients. For the clinical maneuvers session, the mean baseline level of CLBP at the start of the scanning session was 6.4/20 ('very mild') vs. 4.3/20 ('very weak') in the heat pain session (p=0.006). The CLBP subjects experienced an average 34.3% (CI,18.9,49.8) worsening of pain during the clinical maneuvers session and the healthy controls reported no pain (p=0.0001). During the heat pain fMRI session, the CLBP patients had an average 19.4% (CI, 2.1,36.7) increase in pain, and the healthy controls reported no ongoing pain (only transient heat pain due to the thermal stimuli, p=0.0001).

ASL data

Baseline whole-brain within subject and between subject comparisons contrasted pre-stimulation rCBF maps in both sessions (i.e., ASL_1, before clinical maneuvers or heat pain stimuli) and revealed no statistically or clinically significant differences between session or between group in global CBF values (mean=50.8 mm/100 gr. tissue/min session 1, CI=43.3, 63.3; and 51.7, CI=45.4, 62.4, for session 2). Table 2 lists the brain clusters demonstrating significant differences in rCBF changes between the first and second ASL scans for the two sessions. Of note, mean baseline rCBF values in each of these clusters were not significantly different statistically between session or group. Figure 3 displays these clusters on inflated cortical surfaces. For the clinical maneuvers session in the CLBP subjects, statistically significant activity increases (ASL_2 vs. ASL_1) were observed in the *bilateral* medial and dorso-lateral prefrontal cortices, the superior parietal lobules, S1/M1 (primary somatosensory and motor cortices), and S2 (secondary somatosensory cortex) after enhancement of endogenous CLBP by clinical maneuvers. The activations in S1/M1 corresponded to the homuncular areas for the low back and leg. Statistically significant *unilateral* increases were found in the right anterior insula, pre-supplementary motor area and supra-marginal gyrus. The bilateral occipital cortices serve as a control region, and they did not show any statistically significant changes in rCBF (Figure 4). Similarly, in the normalized analysis activations were found in the above listed areas as well as in the anterior cingulate cortex and insula bilaterally. In contrast, the healthy controls (HCs) did not exhibit any statistically significant changes in rCBF during their clinical maneuvers session in the raw change or normalized data analyses. A comparison between changes across groups in this session (the $CLBP_{(ASL2-ASL1)}$ minus $HC_{(ASL2-ASL1)}$ interaction) revealed statistically significant clusters consistent with left S1/M1 and superior parietal lobules (Figure 5).

During the heat pain session the CLBP subjects did not have any statistically significant clusters of change in rCBF in the raw change and normalized analyses. The HCs exhibited small clusters of rCBF change in the left posterior cingulate gyrus and in the right superior temporal gyrus (Table 2). However, no clusters were statistically significant when changes were compared across groups in the raw change and normalized analyses. In addition, for each of the clusters listed above there were no statistically significant within subject differences in the rCBF values in the baseline ASL scans at the start of each session in the each CLBP and healthy normal subject. Figure 5 illustrates the mean changes in rCBF across all sessions. During the clinical maneuvers session, these clusters in CLBP subjects exhibited an average increase in rCBF which ranged between 6 and 10 ml/100gr of tissue/min, corresponding to a 17–25% increase ($p<0.01$). These statistically significant increases in rCBF were not found in the aforementioned brain regions for the heat session in CLBP subjects, in either session in the healthy normal subjects, or in the occipital control regions.

A sensitivity analysis examining whether there were statistically significant linear correlations between changes in pain and changes in rCBF activation patterns in either of the 2 sessions in the CLBP patients indicated that there were no significant clusters that had a linear relationship to changes in chronic pain.

Discussion

In this study we were able to characterize on a behavioral level a patient's ongoing chronic back and leg pain following temporary periods of evoked, acute exacerbation. We were then able to associate the ongoing experience of chronic pain to neural correlates of brain activity using ASL. Using assessment methods particularly suited to detect these changes (the Gracely Box Scales), the CLBP subjects experienced a mean 34% increase in their chronic pain following clinical maneuvers vs. a mean 19% increase in chronic pain following heat pain application. Given that a minimum 30% increase in pain has been shown to be clinically relevant,[35] the clinical maneuvers session meaningfully worsened chronic pain while the heat session did not.

These clinically meaningful increases in endogenous pain ratings were positively associated with statistically significant increases in rCBF in a widespread network of cortical areas, including the bilateral medial and dorso-lateral prefrontal cortices, superior parietal lobules, S1, and S2, and unilaterally in the right insula. As noted in previous studies of experimental pain,[36] these areas encompass the sensory-discriminative and affective pain processing regions related to pain. While many of these regions are well-accepted as key areas of the 'pain matrix', the superior parietal lobules are important as a component of the dorsal attention network,[37] whose functional connectivity to pain matrix areas has also been associated with greater clinical pain in fibromyalgia patients.[38] While not specific to pain per se, increased activity within the superior parietal lobules may reflect increased vigilance to a salient stimulus.[4] Activation of these areas during the clinical maneuvers session but not the heat pain session in the CLBP patients is further evidence of the clinical salience of the worsening of CLBP in the clinical maneuvers session. One could argue that the differences in rCBF increases found for the CLBP group in the sessions may have been due to the different baseline levels of pain measured at the start of the first ASL scan in each session (Figure 2). However, mitigating this concern is that the mean rCBF values recorded in these clusters during the first (baseline) ASL scan in each session were not statistically significantly different from each other.

Overall, the measured changes in rCBF appear to have a specificity for meaningful changes in chronic pain, as statistically significant activations of pain matrix areas only occurred in the clinical maneuvers session in the CLBP subjects and not in their heat pain session or in the healthy normal group. Moreover, the positive interaction analysis for the comparison of statistically significant changes in rCBF between CLBP and healthy subjects in the clinical session also indicates that the rCBF increases in these areas are related to changes in clinical pain ratings, after controlling for any possible areas of significant rCBF changes in the healthy normals. Furthermore, the lack of a linear relationship between changes in pain and changes in rCBF in specific clusters can be expected because we did not see significant changes in rCBF when the change in pain was <30%. This threshold effect serves as a neural marker for clinically significant changes in pain, *i.e*, >30%.

As noted, brain areas deemed to be components of the pain matrix are largely derived from studies of acute experimental pain in healthy volunteers, and it is unclear to what extent these findings apply to a "clinical pain matrix," the network of brain areas underlying clinical pain processing in chronic pain patients. Our results indicate that previously defined pain matrix brain areas are also activated in worsening CLBP, and our findings provide neural correlates for the chronic pain experience. Recent studies have attempted to address this scientific gap between experimental pain and clinical pain. In one study, 13 patients with CLBP rated spontaneous, moment to moment fluctuations in their pain while undergoing BOLD fMRI imaging.[39] Baliki, Apkarian, and colleagues used an experimental model that isolated the neural correlates of a possible neuropathic component of

spontaneous pain (a specific component of the chronic pain experience), which was most highly associated with activity in the medial prefrontal cortex. Other neuroimaging approaches include fMRI studies of resting (intrinsic) brain connectivity in chronic pain conditions, in particular, fibromyalgia in which connectivity of insula cortex was linearly related to greater spontaneous clinical pain at the time of the scan.[38] We also found that significant activity in the medial prefrontal and insular cortices were associated with higher ratings of clinical pain in CLBP.

Another recent study by Kobayashi and colleagues[40] used the application of 30 seconds of pressure (with an air-filled syringe) to painful back areas of 6 CLBP subjects while undergoing BOLD imaging. While this study reported that the predominant areas of activation were in the right insula, prefrontal cortices, and posterior cingulate cortex, the experimental approach used in this study (evoked pain) suggests that these brain areas are likely related more to acute experimental pain processing in CLBP, than to chronic clinical pain. Our experimental model worsening chronic low back and leg pain to a clinically significant level, as would often occur throughout a patient's typical daily activities.

Several limitations of this study merit discussion. First, the order of the clinical maneuvers and heat pain sessions was not randomized and could be a confounder. However, the lack of differences in baseline rCBF values between sessions for each CLBP or HC subject, using a whole brain map or region of interest level of analyses, speaks against this notion. Secondly, on average the baseline level of CLBP at the start of each session was significantly different. This difference can be attributed to the recalibration of the painful stimuli required prior to ASL scanning in session 1, but not required for session 2, the heat pain session. As noted, it is unlikely that this is a significant confounder. Third, we did not find a linear relationship between pain ratings and rCBF changes, which argues against a specificity of this neural marker for chronic pain severity. And lastly, in conducting the thermal pain testing to find the temperatures eliciting a moderate and high pain response, we used the methods of ascending limits and adjustment, but not descending limit methods. Thus, even though these temperatures reliably reproduced the target pain within a fMRI session, they may not be accurate temperatures if used across several sessions.

Conclusions

As a highly subjective experience, development of objective, physiological correlates of patient reports of chronic pain can significantly improve the practice of pain medicine. Our results suggest that neural correlates of CLBP found during pASL scanning could be developed as biomarkers for detection of pain or as surrogate endpoints in clinical outcome studies. Much has been written on the potential for neuroimaging findings to become surrogate endpoints in drug development.[41, 42] One unique feature of our study is that we increased CLBP using a calibrated maneuver, which allowed us to consistently evoke chronic pain to a target level, transiently, and then to track a gradual increase in baseline pain ratings over time. Our study presents results pertinent for Phases 0 (assay development) and I (feasibility and clinical relevance) of biomarker development.[43] Of course, much work needs to be done to fulfill the promise of this potential biomarker, such as experiments in Phase II (validation and standardization for clinical utility), Phase III (independent confirmation of results), and Phase IV (impact assessment).[44]

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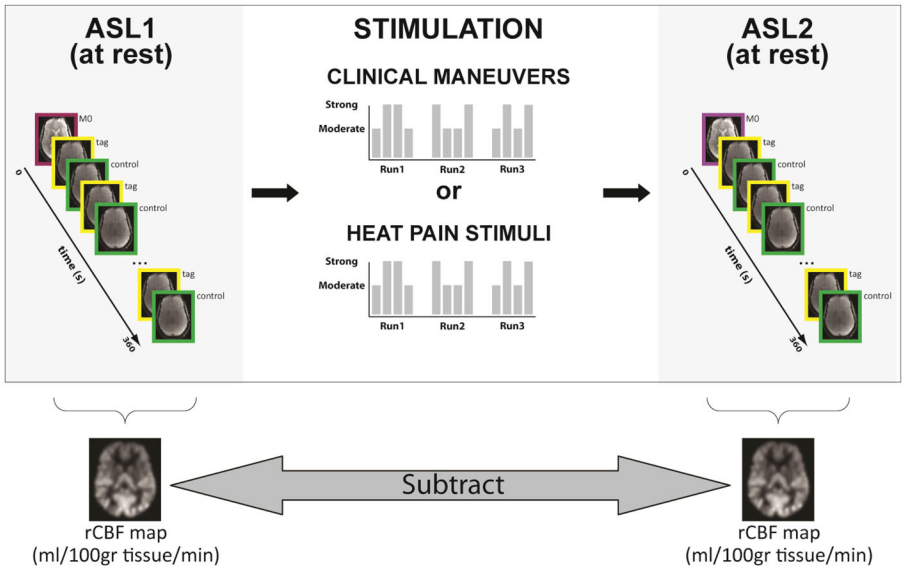

Figure 1.
Study Design
ASL=arterial spin labeling, gr=grams, min=minute, ml=milliliters, M0=the longitudinal magnetization of fully relaxed tissue scan, rCBF=regional cerebral blood flow, s=seconds,

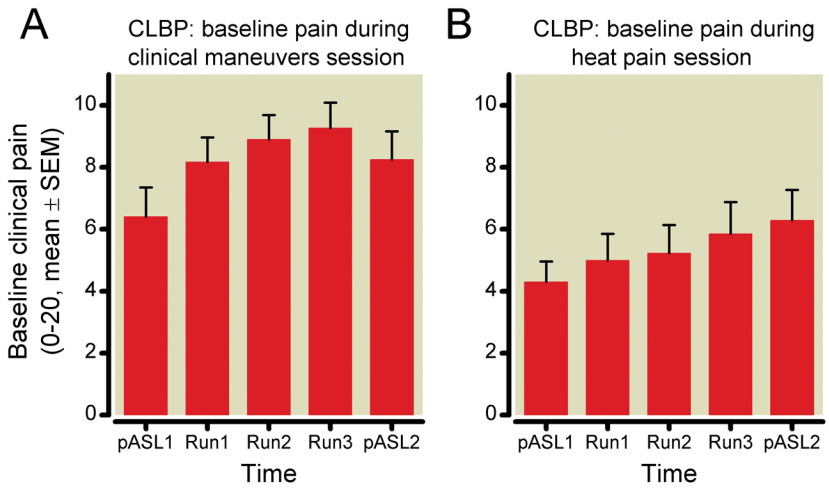

Figure 2.

Mean ratings of baseline clinical pain in chronic low back pain patients (0–20 Gracely Box Scale). Ratings were obtained in-between pain stimulations (~1min after the end of the preceding heat or clinical maneuver). Bars represent group averages (±SEM) of the following: pASL1,2= ratings before and after each pASL scan (2 ratings per timepoint); Run1–3= ratings within each run (4 ratings per timepoint).
pASL=pulsed arterial spin labeling, SEM=standard error of the mean

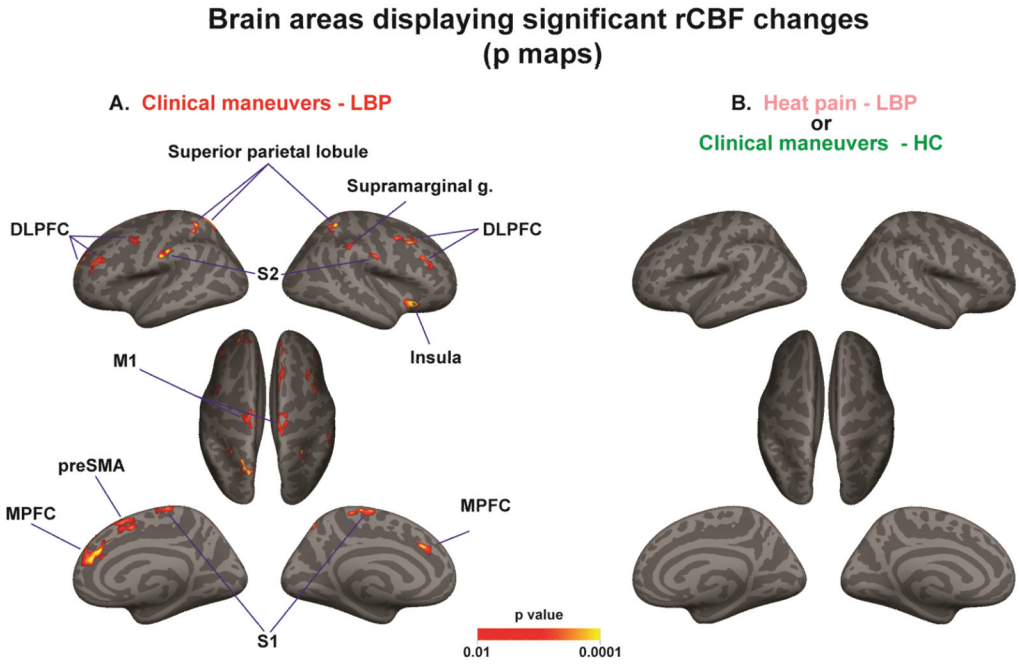

Figure 3.

Significant clusters on inflated brain maps showing significant mean changes in rCBF for the clinical maneuvers (Panel A, bilateral: prefrontal cortices, S1, S2, SPL, and right insula, $p<.01$) and heat pain sessions in the CLBP subjects, and the clinical maneuvers session in the healthy normal subjects (Panel B).

CLBP=chronic low back pain, DLPFC=dorsolateral prefrontal cortex, M1=primary motor cortex, MPFC=medial prefrontal cortex, preSMA=pre-supplementary motor area, rCBF=regional cerebral blood flow, S1=primary somatosensory cortex, S2=secondary somatosensory cortex

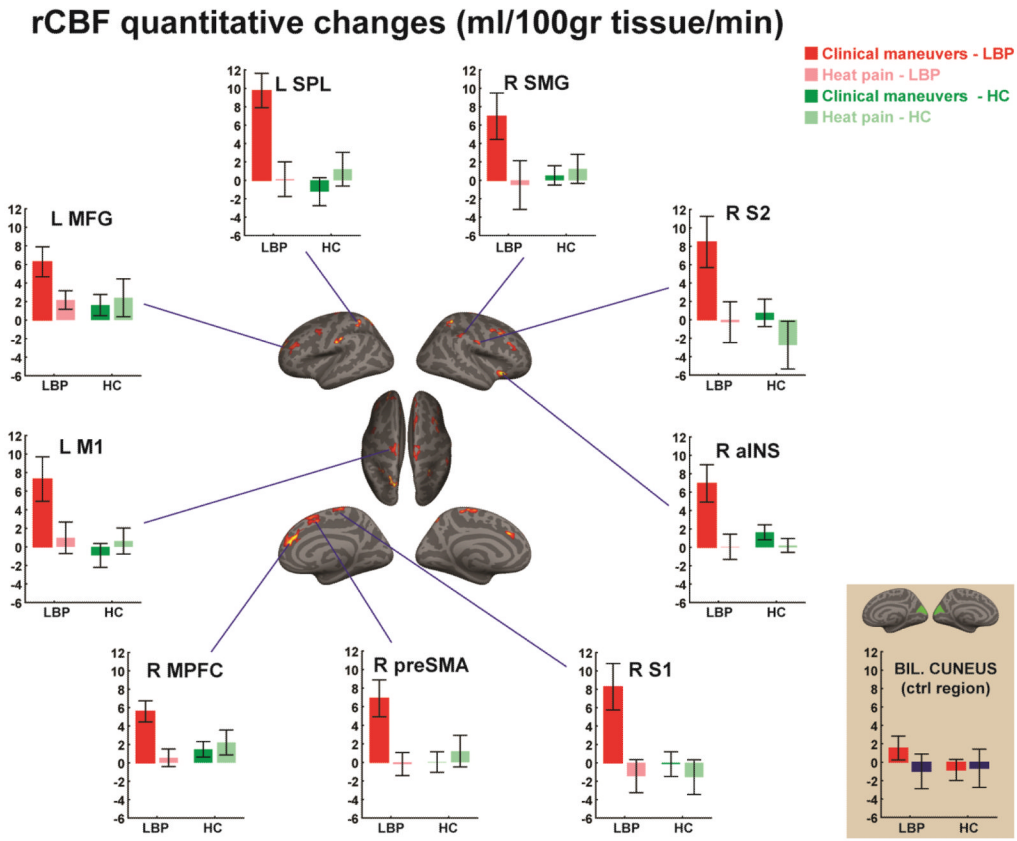

Figure 4.

Significant clusters of activation on inflated brain maps for the subtraction comparison of CLBP subjects vs. healthy controls for the clinical maneuvers session (Panel A vs. Panel B, left SPL, S1, M1).

ASL=arterial spin labeling, CLBP=chronic low back pain, HC=healthy controls, M1=primary motor cortex, S1=primary somatosensory cortex, SPL=superior parietal lobule

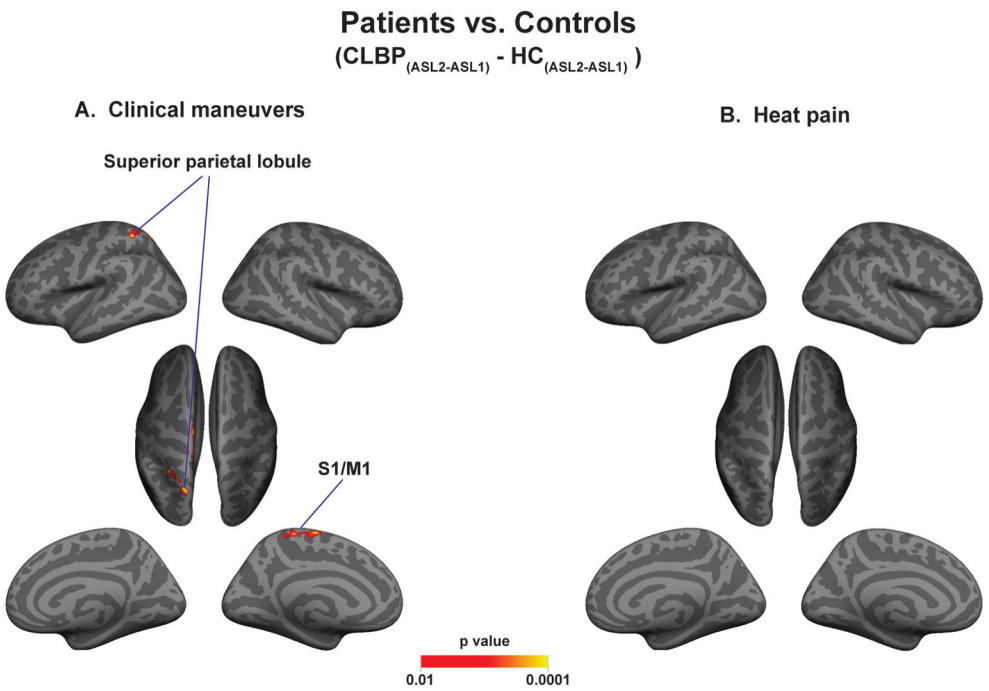

Figure 5.

The mean changes in rCBF in the activation clusters across all sessions. For the clinical maneuvers session in the CLBP subjects, these areas had a 17–25% increase in rCBF. For all comparisons to the clinical maneuvers session, p<.01.

aINS=anterior insula, ASL=arterial spin labeling, BIL=bilateral, CLBP=chronic low back pain, CTRL=control, gr=grams, HC=healthy controls, L=left side, M1=primary motor cortex, MFG=medial frontal gyrus, min=minute, ml=milliliters, MPFC=medial prefrontal cortex, preSMA=pre-supplementary motor area, R=right side, rCBF=regional cerebral blood flow, S1=primary somatosensory cortex, S2=secondary somatosensory cortex, SMG=superior marginal gyrus, SPL=superior parietal lobule

Table 1

Baseline demographic and pain history information

Variable	CLBP Patients (N=16)	Healthy Controls (N=16)
Age (yrs., CI)**	47.4 (40.0,54.8)	46.7(40.1,53.2)
Gender (%female)	69	69
Avg. duration of pain (yrs., CI)	6.24 (3.9,11.8)	--
Avg. pain (0–10, CI)	4.8 (3.8,5.9)	--
Neuropathic Pain (NPQ, %yes)	44	--
Disability Level (ODI,%, CI)	35.8 (30.0,41.6)	0* (0,0)
Pain Catastrophizing (PCS, mean, CI)	36 (27.8,42.1)	14.2* (12.2,16.2)

* p=0.0001

** all confidence intervals (CI's) are 95%

Abbreviations: Avg=average, CLBP=chronic low back pain, NPQ=Neuropathic Pain Questionnaire, ODI=Oswestry Disability Index, PCS=Pain Catastrophizing Scale, Yrs=years

Table 2

Significant Vertex-Level Clusters

Anatomical Label	Size(mm^2)	Cluster p-value ASL2-ASL1	x_{MAX}	y_{MAX}	z_{MAX}	ASL1 rCBF*	ASL2 rCBF*
PATIENTS – clinical maneuvers session							
L superior parietal lobule	507.55	0.0001	−10.4	−69.4	52.1	40.2	50.0
L secondary somatosensory cx	186.54	0.0104	−58.1	−17.1	27.4	41.4	49.0
L superior frontal gyrus	142.65	0.0481	−11.6	25.5	32.9	43.7	49.5
L rostral middle frontal gyrus	496.51	0.0001	−21.2	56.3	16.2	42.4	48.7
L superior parietal lobule	179.31	0.0135	−35.6	−49.4	59.2	41.9	48.2
L paracentral gyrus	231.62	0.0017	−6.4	−25.4	66.0	37.1	44.2
L rostral middle frontal gyrus	344.29	0.0001	−38.9	40.2	24.2	51.1	57.3
L precentral gyrus	226.56	0.0022	−12.4	−18.8	69.5	33.1	40.4
L caudal middle frontal gyrus	221.09	0.0034	−37.9	6.2	43.0	52.3	58.3
R insula	214.31	0.0018	28.9	18.6	−5.4	51.3	58.3
R superior frontal gyrus	647.65	0.0001	13.3	40.9	20.8	37.9	43.4
R superior parietal lobule	227.75	0.0012	34.7	−46.0	60.0	37.7	46.2
R caudal middle frontal gyrus	445.01	0.0001	40.8	19.2	43.2	47.0	53.2
R superior frontal gyrus	475.42	0.0001	8.8	4.7	49.7	38.6	45.5
R paracentral gyrus	400.65	0.0001	4.8	−26.5	68.3	31.7	40.0
R rostral middle frontal gyrus	237.04	0.0006	45.8	23.9	30.4	45.6	51.8
R postcentral gyrus	139.06	0.0385	60.6	−10.7	31.1	41.5	50.0
R supramarginal gyrus	182.88	0.0066	52.8	−35.2	46.0	46.4	53.4
PATIENTS – heat pain session							
No significant clusters							
CONTROLS – clinical maneuvers session							
No significant clusters							
CONTROLS – heat pain session							
L isthmus cingulate gyrus	88.8	0.0033	−5.6	−36.4	32.3	61.2	69.0
R superior temporal gyrus	*115.6*	*0.0001*	*49.9*	*−14.4*	*−4.4*	*54.9*	*48.8*

*mm/100gr. tissue/min; *Italic* indicates ASL2<ASL1

Abbreviations: ASL=arterial spin labeling, L=left, R=right, rCBF=regional cerebral blood flow.