Neurobiological substrates of chronic low back pain (CLBP): A brain [99mTc]Tc-ECD SPECT/CT study

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Research Article

Keywords: Chronic low back pain, Brain SPECT, Neurobiological Substrate, Numeric Rating Scale, Douleur Neuropathique 4 Questions

Posted Date: June 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1708791/v1

Abstract

Recent neuroimaging studies have demonstrated pathological mechanisms related to cerebral neuroplasticity in chronic low back pain (CLBP). Few studies have compared cerebral changes between patients with and without pain in the absence of an experimentally induced stimulus. We investigated the neurobiological substrates associated with chronic low back pain using [^{99m}Tc]Tc-ECD brain SPECT and correlated rCBF findings with the numeric rating scale (NRS) of pain and douleur neuropathique en 4 questions (DN4). Ten healthy control volunteers and fourteen patients with neuropathic CLBP due to lumbar disc herniation underwent cerebral SPECT scans. A quantitative comparison of rCBF findings between patients and controls was made using the Statistical Parametric Mapping (SPM), revealing clusters of voxels with a significant increase or decrease of rCBF. The intensity of CLBP was assessed by NRS and by DN4. The results demonstrated rCBF increase in clusters A (occipital and posterior cingulate cortex) and B (right frontal) and decrease in cluster C (superior parietal lobe and middle cingulate cortex). NRS scores were inversely and moderately correlated with the intensity of rCBF increase in cluster B, but not to rCBF changes in clusters A and C. DN4 scores did not correlate with rCBF changes in all three clusters. ***Perspective:*** This study will be important for future therapeutic studies that aims to validate the association of rCBF findings with the pharmacokinetic and pharmacodynamic profiles of therapeutic challenges in pain.

Introduction

Chronic low back pain (CLBP) is a common neurological disorder in the lumbosacral segment and persists over 12 weeks after its onset. CLBP affects about 10–20% of patients who do not present pain resolution (Deyo and Weinstein 2001). The etiology of CLBP is variable; the discal hernia and the lumbar spinal canal stenosis are the most common causes (Tanaka et al. 2018).

Recent neuroimaging studies have demonstrated that pathophysiologic mechanisms of cerebral neuroplasticity are involved in CLBP (Nakamura et al. 2014a). These mechanisms are related to structural and functional changes, and they can be reversible after appropriate pain treatment (Seminowicz et al. 2011). CLBP patients presented several alterations, such as decreased gray substance in the prefrontal cortex, functional connectivity alterations of periaqueductal gray substance (PAG) (Yu et al. 2014), increased activation of the insula area, thalamus, amygdala, and the medial cingulate cortex (Rodriguez-Raecke et al. 2014).

Identifying specific regions involved in chronic pain and those related to each other, even if nonspecific, as well as the study of the development of pain and comorbidities associated with functional neuroimaging techniques, can allow the development of future target therapies (Martucci, Ng, and Mackey 2014).

However, few studies have compared cerebral changes between patients with and without pain in the absence of an experimentally induced stimulus (Schmidt-Wilcke 2015a). Additionally, the minority of

these studies have utilized the Cerebral Single Photon Emission Computed Tomography (SPECT), which allows the analysis of the tridimensional regional cerebral blood flow (rCBF) mapping (Catafau 2001). Functional magnetic resonance (fMRI) is the most commonly used method (Schmidt-Wilcke 2015b).

This study aimed to investigate the neurobiological substrates associated with chronic low back pain using [^{99m}Tc]Tc-ECD brain SPECT and correlate rCBF findings with the numeric rating scale (NRS) and *douleur neuropathique en 4 questions* (DN4).

Methods

Participants

Our institution's Human Research Ethics Committee approved the present study, and all participants signed the informed consent. This case-control study compares the regional cerebral blood flow (rCBF) mapping between patients with CLBP and healthy volunteers. Participants were identified only by number, not name or initials. The study size was set based on previous similar studies. The study group consisted of 14 patients, aged 25–62 years old, with neuropathic CLBP due to lumbar disc herniation verified by structural magnetic resonance imaging (MRI), in follow up at Neuropathic Pain Ambulatory from January to December 2016. The inclusion criteria were CLBP lasting longer than three months, with pain intensity equal to or greater than 3 in the numeric rating scale (NRS). The control group consisted of non-age matched healthy volunteers, aged 22 to 39 years old, and enrolled in the study after meeting the following criteria: 1) age above 18; 2) no complaints of acute or chronic pain at the time of evaluation; 3) absence of clinical, neurological, psychiatry, or cognitive disorders; and 4) no chronic use of medications. This study excluded patients with diabetes mellitus, arterial hypertension, anemia, severe cardiomyopathy, nephropathy, morbid obesity (BMI > 40), or any neurologic disease that presents neuropathic pain, besides chronic alcoholics and smokers. We also excluded participants with functional and anatomical alterations on brain SPECT. The study investigated the complete blood count, biochemical exams (total bilirubin and fractions, serum creatinine, glycemia, aspartate transaminase, gamma-glutamyl-transferase), and electrocardiogram of patients.

Pain measurement

The Numerical Rating Scale (NRS) measured the intensity of CLBP from 0 (no pain) to 10 (worst pain). Douleur Neuropathique en 4 Questions (DN4), which combines seven items regarding symptoms and three findings on clinical examination, was also used for assessing CLBP. A recent study showed the good performance of DN4 in screening for various neuropathic pain syndromes. However, sensitivity varied by the syndrome. A positive DN4 was associated with greater pain catastrophizing, disability, and anxiety/depression, which may be explained by the severity of the disease (VanDenKerkhof et al. 2018).

SPECT Protocol

All patients underwent cerebral SPECT scans, and the tracer [^{99m}Tc]Tc-ECD (ethyl cysteinate dimer) was injected at a maximum dose of 1,295 MBq (35 mCi). SPECT was performed during resting state, with eyes open, in a quiet and darkroom, refrained from talking and listening.

SPECT scans were acquired in a double-headed rotating gamma camera (SPECT/CT BrightView XCT, Philips Medical Systems Inc., Cleveland, OH, USA), equipped with a low-energy high-resolution collimator (LEHR), symmetrical acceptance energy window of 20%, and photopeak centered on 140 keV, using a 128 x 128 matrix, zoom factor of 1.0, and pixel size 2.13 mm. Data were collected in step-and-shoot mode over 360 degrees, in 128 projections (64 per head), with a total acquisition time of 30 min and about 100,000 counts/projection/head.

Tomographic images were processed in the workstation EBW (Extended Brilliance TM Workspace, Philips Medical Systems Inc., Cleveland, OH, USA), reconstructed in transaxial slices parallel to the orbitomeatal line, using Ordered Subset Expectation Maximization (OSEM) algorithm and a Butterworth filter order two and cut-off frequency 0.3. Chang's method was applied over transaxial slices for the attenuation correction of photon effects ($\mu = 0.12$ cm-1).

SPM Processing

The Statistical Parametric Mapping 8 (SPM8) software package (Wellcome Trust Center for Neuroimaging, University College of London, London, UK) converted brain SPECT images from DICOM to NIfTI format. The SPM software processed differences in rCBF between CLBP patients and healthy volunteers. The images were reoriented by setting the crosshairs to the anterior commissure, aligned and spatially normalized to the Montreal Neurological Institute (MNI) standard space using a 12-parameter affine transformation, followed by nonlinear transformations and trilinear interpolation. Normalized images were written with a bounding box equal to the image perfusion standard template, with 2 x 2 x 2 mm voxel dimensions. A binary mask was applied over the normalized images to remove all signals outside the brain structure and then convoluted with an isotropic kernel Gaussian function of 12 x 12 x 12 mm full-width at half maximum (FWHM) to smooth images before starting statistical analyses. Also, to remove the confounding effects of global brain counts between CLBP and healthy controls scans (two-sample t-test), the images were globally normalized for signal activity using proportional scaling with a threshold of 0.8 of the global mean. Thus, a voxel-by-voxel analysis compared each CLBP subject with the DN4 mean image (two-sample t-test). SPM-T maps were shown through a glass brain with threshold p-values = 0.001, uncorrected for multiple comparisons, at peak and cluster levels, with the cluster size being k = 125 voxels. Only clusters that overcame the correction for multiple comparisons with $p < 0.05$ were considered significant. The results displayed perfusion maps on the three-dimensional planes of a standard T1-MRI template.

Statistical analysis

All statistical analyses and graphs were performed using Statistical Product and Service Solutions (SPSS) software (V24.0; IBM SPSS Statistics, IBM, Armonk, NY, USA). Spearman's rank correlation coefficient (Spearman's rho) is a nonparametric measure of rank correlation used to assess the

relationship between NRS and DN4 scores. Kendall's tau nonparametric rank correlation measured the association between signal intensity within clusters with increased or decreased rCBF on SPM and the NRS and DN4 scores and produced scatterplots. The statistical significance was set at $\alpha = 0.05$.

Results

Participants

A total of 16 participants with CLBP participated in the study. Two patients were excluded by previous aneurysm clipping and meningioma. The final group consisted of 14 subjects (8 men and 6 women), with a mean age of 40.5 (± 9.4) years. The mean scores of NRS and DN4 were 5.7 (± 2.0) and 4.7 (± 2.6), respectively. Table 1 describes patients' characteristics.

The median NRS-observer and DN4 scores were 5.5 (IQR 4 to 7) and 5.0 (IQR 2 to 6.2), respectively. The NRS scores were 3 (n=1, 7.1%), 4 (n=4, 28.6%), 5 (n=2, 14.3%), 6 (n=3, 21.4%), 7 (n=2, 14.3%), 9 (n=1, 7.1%), and 10 (n=1, 7.1%). The DN4 scores for the same group were 0 (n=1, 7.1%), 2 (n=3, 21.4%), 4 (n=2, 14.3%), 5 (n=2, 14.3%), 6 (n=3, 21.4%), 7 (n=2, 14.3%), and 10 (n=1, 7.1%). The correlation between NRS and DN4 for patients with CLBP showed no significant association for all 14 patients (Spearman's rho 0.357, p=0.211). (See Figure 1)

rCBF findings in patients with CLBP

Table 2 describes, and Figure 2 shows the significant increase and decrease of rCBF changes in patients with CLBP. The right hemisphere presented the more significant increase of rCBF in occipital and posterior cingulate areas, frontal middle and inferior gyri, and the opercular frontal area. A cluster including bilateral regions of both parietal lobes and the right cingulate gyrus presented a significant decrease in rCBF.

The correlation between individual rCBF changes in the three clusters and NRS and DN4 scores are shown in Figure 2 (*a* to *f*). NRS scores were inversely and moderately correlated with the intensity of hyperperfusion in cluster B (Kendall's tau = -0.445, p = 0.033), but were not correlated to hyperperfusion in cluster A (Kendall's tau = -0.023, p = 0.911) or hypoperfusion in cluster C (Kendall's tau = -0.141, p = 0.502). DN4 scores were not correlated with any rCBF changes in clusters A (Kendall's tau = 0.000, p = 1.000), B (Kendall's tau = -0,185, p = 0.374), or C (Kendall's tau = -0.069, p = 0.739).

No patients presented abnormal findings on brain X-ray computed tomography (CT).

Discussion

We investigated the neurobiological substrates associated with chronic low back pain due to lumbar disc herniation using [^{99m}Tc]Tc-ECD brain SPECT in 14 patients with a mean age of 40 years compared with

ten healthy controls. The results revealed rCBF increase in the right frontal, occipital and posterior cingulate cortex, and rCBF decrease in the superior parietal lobe and middle cingulate cortex in patients with CLBP in patients with CLBP. Numeric rating scale of pain was inversely and moderately correlated with the intensity of rCBF increase in the right frontal lobe, and no correlation was observed between rCBF changes and douleur neuropathique en 4 questions.

An American epidemiological study showed a higher prevalence of CLBP among adults in the 5th and 6th decades of life (Shmagel, Foley, and Ibrahim 2016). Other studies have shown a higher incidence of CLBP in the third decade of life, with prevalence increasing until the age of 65 when it falls again (Loney and Stratford 1999), (Waxman, Tennant, and Helliwell 2000), (Hoy et al. 2010). A population study involving more than 10,000 volunteers in Portugal showed that CLBP prevalence increases significantly with age. Whereas the age group 36–45 years old had an estimated prevalence of CLBP in 7.2%, this proportion increased to 29.7% in the group above 86 years old (Gouveia et al. 2016a).

This study found a mean of 5.7 points on the NRS scale, close to the 6.0 points of a similar study that showed higher scores in women (6.2 ± 2.53) than men (5.7 ± 2.29) (Gouveia et al. 2016b). Nakamura et al. (2014) evaluated patients with acute and chronic low back pain and found a mean NRS of 6.3 (Nakamura et al. 2014b). Interestingly, Hiyama et al. (2015) found that CLBP patients with neuropathic disease reported NRS of 7.4 (± 1.9) points, while patients with nociceptive disease reported NRS of 5.1 (± 2.0). They also found that cases with either nociceptive or neuropathic CLBP present greater severity of pain than acute and subacute cases (Hiyama et al. 2015).

The pain was also assessed by the *Douleur Neuropathique en 4 Questions* (DN4), which was validated for Portuguese by Santos et al. (2010). DN4 seems, in this study, to help identify a neuropathic pain component in a consecutive population of patients with chronic pain in a moderate way (median DN4 scores 5.0; IQR 2 to 6.2) (Timmerman et al. 2017a).

The validity of DN4-signs is equal to the DN4 outcome, and, more importantly, both are more valid than the DN4-symptoms alone. It seems that the patients' symptoms and signs don't reliably reflect the underlying mechanisms, indicating that there is a need for a more objective way to assess patients' pain to facilitate improvement in the treatment of patients with CLBP. The physicians' assessment cannot be replaced by a screening tool as the DN4, but it gives the physician a slight hint towards the (non-)existence of the neuropathic pain component (Timmerman et al. 2017b).

Considering the brain SPECT findings of patients with CLBP, there was a significant rCBF increase in the right hemisphere, involving the right occipital and posterior cingulate areas, right middle and inferior frontal gyri, besides the right opercular frontal area. Nakamura et al. (2014) found increased blood flow in the bilateral posterior lobe of the cerebellum in patients with CLBP, whose pain had continued for more than six months despite conventional medical treatment and with indigent structural abnormalities (Nakamura et al. 2014c). Recent fMRI studies with CLBP patients during rest have demonstrated increased activation in the medial prefrontal cortex, cingulate cortex, amygdala, insula, and sensory-motor integration regions, together with a disrupted default mode network (DMN) (Kregel et al. 2015). In

another fMRI study, older disabled CLBP patients presented activation of the right mesial prefrontal cortex at rest, whereas the non-disabled demonstrated activation of the left lateral prefrontal cortex (Buckalew et al. 2010).

The posterior cingulate cortex is a region traditionally linked to visuospatial orientation (Vogt, Derbyshire, and Jones 1996), episodic memory and pleasant stimuli (Maddock 1999), major depression (Ho et al. 1996), and anxiety (Reiman n.d.). Hsieh et al. (1995) found an rCBF increase in the posterior cingulate cortex of patients with chronic neuropathic pain and the right anterior cingulate cortex, suggesting its participation in the affective-motivational aspect of pain. They described a possible tendency to lateralization to the right hemisphere of the affective processes involved in chronic neuropathic pain (Hsieh et al. 1995). Other studies have also demonstrated the right lateralization of affective processes involved in chronic neuropathic pain (Hari et al. 1997) (Neri and Agazzani 1984).

Functional neuroimaging techniques, like SPECT and arterial spin labeling (ASL), assess regional cerebral flow and can be used to obtain task-free information according to the ongoing brain activity that may reflect natural pain characteristics of chronic pain (Davis and Moayedi 2013a). Previous studies described activated brain areas in response to pain. These constitute the “pain matrix”: the primary and secondary somatosensory cortices (S1, S2), the insular cortex (IC), the anterior cingulate cortex (ACC), the thalamus, and the prefrontal cortex (PFC) (Davis and Moayedi 2013b).

The present study showed decreased rCBF in a cluster including both parietal lobes and the right cingulate gyrus. Previous studies have shown that both the posterior parietal region and dorsolateral prefrontal cortex are involved in the cognitive-discriminative aspect of pain (Peyron et al. 1999), with an asymmetric predominance of involvement in the right hemisphere (Derbyshire et al. 1994) (Derbyshire and Jones 1998). CBLP patients exhibited reduced rCBF on the bilateral prefrontal cortex and increased rCBF in posterior lobes of the cerebellum (Nakamura et al. 2014d). Furthermore, reduction in resting DMN connectivity to the medial prefrontal cortex, including pregenual anterior cingulate cortex (pgACC), was described after physical maneuvers that exacerbate clinical back pain in CLBP patients. The pgACC is a region involved in pain inhibition due to its descending projections to periaqueductal gray matter (Loggia et al. 2013).

Neuroimaging studies involving the evaluation of neuropathic pain show heterogeneous patterns of brain activation. These probably reflect patients’ heterogeneity in etiology of pain, lesion topography, symptoms, and stimulation procedures for activation neuroimaging studies (Moisset and Bouhassira 2007). Also, the interpretation of results should consider the history of pain, anatomical distribution, genetic constitution, and personality, which may alter the cerebral circuits involved in chronic pain processes (Kupers and Kehlet 2006).

Strengths And Limitations

The present study's findings contribute to the investigation of the neurobiological substrates of chronic lumbar back pain. Knowing the brain systems involved in CLBP and the functional activation and deactivation of these structures during the pain may represent the background for future pharmacokinetics and pharmacodynamic modeling studies. A limitation is the small sample of patients and healthy controls undergoing the study. However, the quantitative SPM technique offered sophisticated analysis tools that dispensed large samples, avoiding unnecessary exposure of patients to radiation. The group of participants with CLBP had a slightly older mean age than the control group.

Declarations

DISCLOSURE

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

No applicable.

FUNDING

The authors gratefully acknowledge financial support from: (a) Grant #049/2013 (AUXPE No. 2880/2013) from CAPES / NUFFIC, Brazil Netherlands International Cooperation; (b) Grant #2015/50089-3 and Grant #2021/12671-3, São Paulo Research Foundation (FAPESP).

CONFLICT OF INTEREST/DISCLOSURE

The authors report no conflicts of interest.

AVAILABILITY OF DATA AND MATERIALS

The data sets generated and/or analyzed during the current study are not publicly available due to patient confidentiality reasons but are available from the corresponding author on reasonable request and pending approval from the Ethics Committee of our University Clinical Hospital.

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Contributions

ENL, LWA and ODP contributed to the study conception and design. ACT, LELS and LAS contributed to the data processing. ENL, PCP, FD, EBC, VLL and LWA contributed to the data presentation and writing of the manuscript. ENL, JHS and LWA contributed to the figures. All authors read and approved the final manuscript.

ETHICS DECLARATIONS

Ethics approval and consent to participate

Informed consent was obtained from all individual participants included in the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of our University Clinical Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 - Patients’ characteristics

Patient	Age (y)	Gender	LDH	Duration of Pain	Medications in Use
1 EMVB	38	F	L4-L5, Early fractured L2	1y	Amitriptyline, Sertraline, Clonazepam
2 VC	44	M	L4-L5	2y	-
3 LDC	31	M	L4-L5-S1	3y	Acetaminophen
4 JAT	62	M	L4-L5	10y	Cytidine, Uridine, Hydroxocobalamin
5 EAS	48	M	L2-L3-L4	6y	-
6 ACAVS	33	F	L4-L5-S1	3m	-
7 PHM	41	M	L4-L5	4y	Anthraquinone, Prednisone, Thiamine
8 TCCM	35	F	L5-TV	1y 8m	-
9 IRR	48	F	L3-L4	3y	Paroxetine, Bupropion, Clonazepam
10 IR	50	M	L4-L5	1y 6m	Dexamethasone, Betamethasone dipropionate, Ketoprofen, Celecoxibe, Cyclobenzaprine
11 KDBBS	25	F	L4-L5	1y	-
12 MECO	34	F	L4-L5	1y 6m	Nimesulide, Dipyrone
13 CHFCF	37	F	L4-L5	12y	-

14 JBC	41	F	L4-L5-TV	10y	-

Abbreviations: y, years; m, months; M, Male; F, Female; LDH, location of the Lumbar Disc Herniation; TV, Transitional Vertebra.

Table 2 - Brain regions of significant rCBF changes in CLBP patients

Brain Regions	*p**	Cluster volume (*k*)	Talairach coordinates x, y, z	Maximum voxel *Z* score
Increased rCBF				
Cluster A - R Occipital Lobe (Calcarine, Cuneus, Lingual, Middle Occipital Gyri), R Posterior Cingulate Gyrus	0.023	733	20, -70, 4	4.35
Cluster B - R Frontal Lobe (Middle and Inferior Frontal Gyri), R anterior (BA 10), and dorsolateral (BA 46) prefrontal cortex	0.032	660	36, 44, 18	4.14
Decreased rCBF				
Cluster C - L Parietal Lobe (Precuneus, Paracentral Lobe), R Parietal Lobe (Postcentral Gyrus, Paracentral Lobe) (BA 5 and 7) and R middle Cingulate Gyrus	0.000	2,774	0, -52, 68	1.84

Abbreviations: *p value of cluster significance; R, right; L, left; BA, Brodmann Area.

Table 3 - Correlation between individual rCBF changes and NRS and DN4 pain scales.

Patient	Cluster 1	Cluster 2	Cluster 3	NRS Score	DN4 Score
1	3193,57	2955,77	2835,19	6	10
2	2937,39	2968,07	2747,25	7	5
3	3189,93	2978,79	2796,52	5	7
4	3054,53	3124,16	2826,39	6	4
5	3203,44	2937,76	2804,74	7	2
6	3288,88	2976,96	2817,65	5	5
7	3144,52	3097,09	2778,34	3	2
8	3096,13	3050,18	2773,34	4	0
9	3152,95	3050,84	2757,04	4	2
10	3220,76	3023,11	2727,28	4	4
11	3355,50	3020,13	2632,55	10	6
12	3036,08	3075,75	2755,31	4	7
13	3069,31	3112,38	2705,10	6	6
14	2855,60	2835,26	2537,44	9	6
Mean (SD)	3128,47 132,95	3014,73 79,02	2749,58 81,22		

Abbreviations: NRS, Numeric Rating Scale; DN4, Douleur Neuropathique en 4 Questions (Fishbain et al. 2014).

Figures

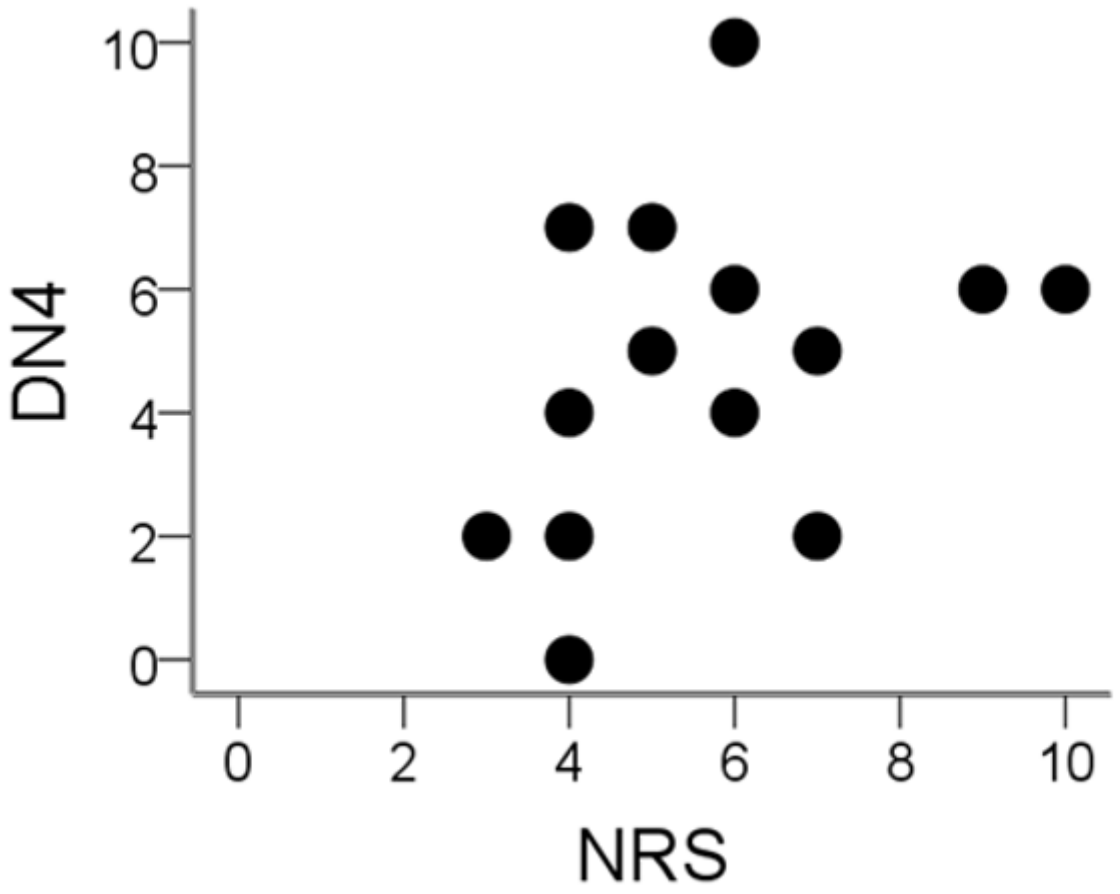

Figure 1

Scatter plot showing no correlation between DN4 and NRS scales for 14 patients (Spearman's Kendall's rho 0.357, p=0.211). DN4, Douleur Neuropathique en 4 Questions; NRS, Numeric Rating Scale.

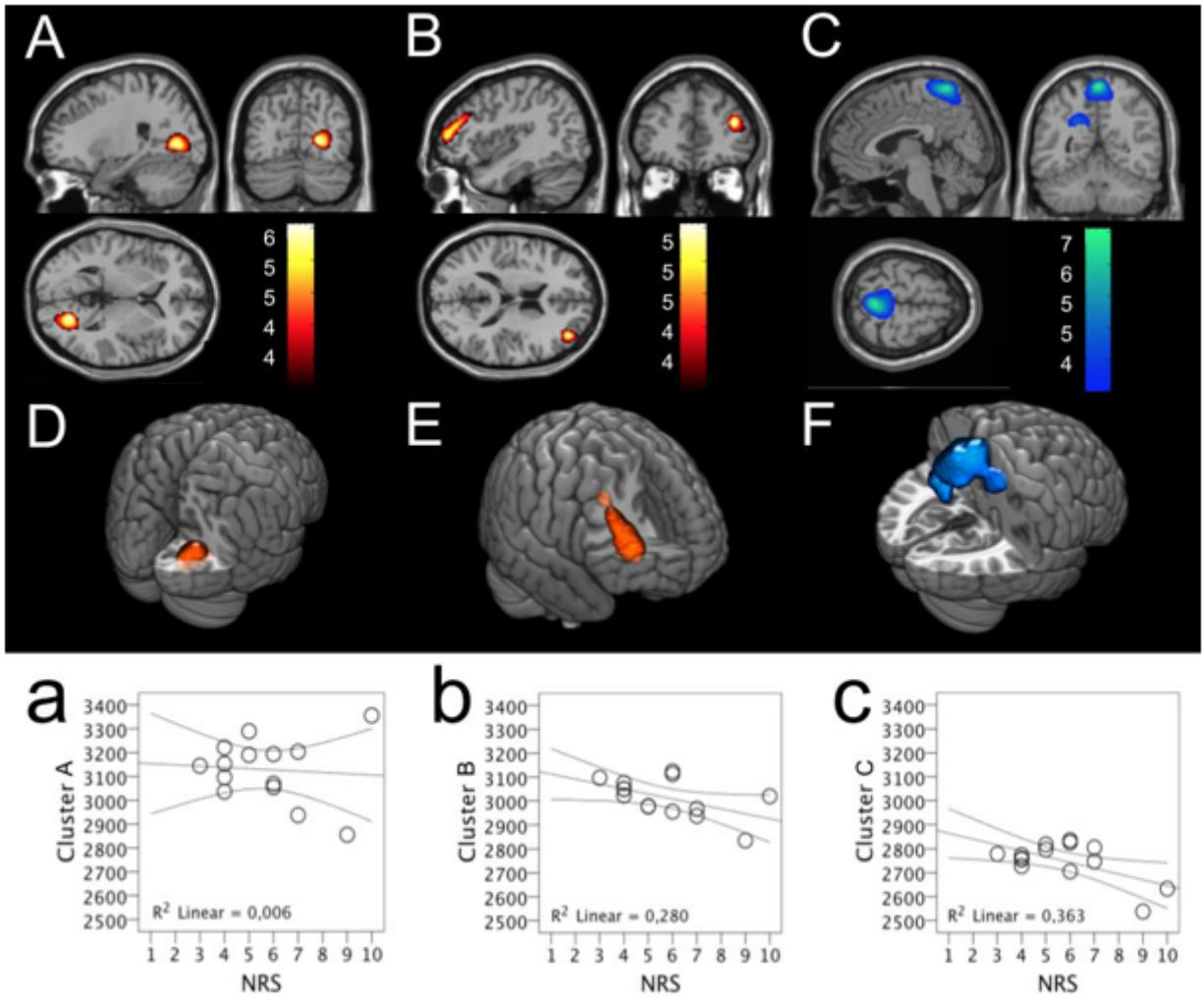

Figure 2

Results of the statistical parametric mapping (SPM) analysis showing brain regions with significant rCBF changes in 14 patients with CLBP, compared to ten healthy controls. The figure shows the overlay of clusters upon T1-weighted magnetic resonance imaging from the SPM template. Images show areas with a significant increase (A, B, D, and E) and decrease (C and F) of the regional cerebral blood flow (rCBF). The significant increase of rCBF was found in clusters A (3D view in D; R occipital lobe and R posterior cingulate gyrus) and B (3D view in E; R anterior prefrontal and dorsolateral frontal lobe). Cluster C presented a decrease of rCBF (3D view in F; bilateral parasagittal and postcentral parietal lobe and R middle cingulate cortex). Table 2 describes the Talairach coordinates. Results are shown in P value less than 0.05, corrected for multiple comparisons. A correlation coefficient with 95% CI according to Kendall's tau non-parametric rank correlation was used to assess the relationship between the rCBF increase (a, b, d, and e) and decrease (c and f) and the results of the NRS (a, b and c) and DN4 (d, e and f) scores. The curved lines show the 95% CI around the regression line. In b, higher NRS scores were inversely and moderately correlated with the intensity of rCBF increase in cluster B (Kendall's tau = -0.445, p = 0.033). In

a, c, d, e, and *f*, there was no significant correlation between rCBF changes and NRS or DN4 scores. NRS, Numeric Rating Scale; DN4, Douleur Neuropathique en 4 Questions.