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ORIGINAL RESEARCH

Cerebral Blood Flow Alterations in Pain-Processing Regions of Patients with Fibromyalgia Using Perfusion MR Imaging

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BACKGROUND AND PURPOSE: Widespread pain sensitivity in patients with FM suggests a CNS processing problem. The purpose of this study was to assess alterations in perfusion as measured by DSC in a number of brain regions implicated in pain processing between patients with FM and healthy controls.

MATERIALS AND METHODS: Twenty-one patients with FM and 27 healthy controls underwent conventional MR imaging and DSC. For DSC, 12 regions of interest were placed in brain regions previously implicated in pain processing. rCBF values were calculated for each region of interest. Subjects answered mood/pain coping questionnaires and underwent clinical/experimental pain assessment.

RESULTS: There were significant correlations between the thalamic rCBF values and the pain-control beliefs of FM subjects. The strength of the relationship between clinical pain measures and thalamic rCBF values increased after adjusting for pain-control beliefs. There was a significantly different distribution pattern of rCBF values across various brain regions between the FM group and the healthy controls. There was a lower degree of correlation in the FM group between the thalamic rCBF values and the other brain regions relative to the healthy controls.

CONCLUSIONS: Significant correlations were found between thalamic rCBF values and pain belief values. These data suggest that there are baseline alterations of brain perfusion in patients with FM. rCBF values of the thalami exhibited lower correlations with respect to other brain regions thought to be involved in pain processing compared with those in healthy controls.

ABBREVIATIONS: ANOVA = analysis of variance; BPCQ-INT = Beliefs about Pain Control Questionnaire-International; CBF = cerebral blood flow; CES-D = Center for Epidemiological Studies Depression Scale; CNS = central nervous system; CSQ-CAT = Catastrophizing Component of the Coping Strategies Questionnaire; DSC = dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging; EPI = echo-planar imaging; FM = fibromyalgia; fMRI = functional MR imaging; PET = positron-emission tomography; rCBF = relative cerebral blood flow; SE = spin-echo; SPECT = single-photon emission tomography; STPI = Spielberger's Trait Personality Inventory; VAS = visual analog scale

FM is the second most common rheumatologic disease, affecting 2%–4% of the population in industrialized countries.[1] Patients with FM exhibit hyperalgesia/allodynia[2-4] with increased sensitivity to painful stimuli, including heat, noise, and electricity.[5,6] These prior studies in conjunction with the finding that increased sensitivity to pain is not limited to a particular body region suggest a CNS process. However, the underlying pathophysiology of FM is still unknown.

Functional neuroimaging techniques are providing an invaluable tool for investigating the potential mechanisms of CNS pain processing. Functional imaging technique studies consistently identify the same brain structures, including the thalami and caudate nuclei, that are stimulated during painful conditions. PET and fMRI have demonstrated increased regional brain activation resulting from painful thermal, electrical, chemical, and pressure stimulations in structures involved in the processing of sensation, movement, cognition, and emotion.[7-9] In an fMRI investigation by Gracely et al,[10] both patients with FM and healthy controls were challenged with the same painful stimulus, resulting in a significant relative increased activation in multiple brain regions implicated in pain processing, including the primary and secondary somatosensory cortex, the insula, and the anterior cingulate in the FM group compared to healthy controls. Additional studies have also confirmed these findings of augmented central pain processing in chronic pain syndromes.[11,12]

There have also been several studies examining CBF differences in patients with FM by using SPECT. Kwiatek et al[13] showed decreased rCBF in the inferior dorsal pons and the right thalamus in patients with FM versus healthy controls. A study by Mountz et al[14] demonstrated decreased baseline rCBF in the bilateral thalami and caudate nuclei in patients with FM compared with healthy controls by using SPECT. SPECT imaging has demonstrated increases in rCBF in the bilateral thalami and basal ganglia of 14 subjects with FM following treatment with amitriptyline, suggesting that reductions in rCBF in FM normalize with clinical improvement.[15]

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To our knowledge, there are, however, no published studies using perfusion MR imaging in patients with FM. Perfusion MR imaging is a relatively new noninvasive technique that can also measure cerebral perfusion and is becoming increasingly important in the diagnosis and management of neurologic diseases, including stroke and brain tumors.[16] This technique avoids exposure to radiation and offers improved spatial resolution compared with SPECT.[17] Perfusion MR imaging is, therefore, potentially useful for the characterization of CBF differences within brain regions, some of which can be quite small, making precise localization possible. The purpose of the study was 2-fold: 1) to investigate whether there are rCBF differences detected by perfusion MR imaging in a number of brain regions implicated in pain processing between patients with FM and healthy age-matched controls, and 2) to explore correlations between rCBF differences in these areas and levels of both clinical and evoked pain.

Materials and Methods

Subjects

The subjects in this study were 21 patients (17 women, 4 men; 20–57 years of age; mean age, 41.0 years) who met the 1990 American College of Rheumatology criteria for FM[18] and 27 healthy controls (21 women, 6 men; 22–59 years of age; mean age, 43.9 years). The control subjects were considered healthy after we obtained a clinical history and an evaluation of self-report questionnaires. Informed consent was obtained for all participants, and the study was approved by the local institutional review board. Exclusion criteria included the following: pregnancy, left-handedness, the presence of comorbid conditions capable of causing worsening of physical functional status independent of the diagnosis of FM, a psychiatric disorder involving a history of psychosis, current suicide risk or attempt within the past 2 years, or substance abuse within the past 2 years. The study protocol and consent forms were approved by the institutional review board at the University of Michigan.

Overall Study Design

Subjects participated in a single-day study protocol that included obtaining a clinical history and administration of self-report questionnaires related to depression, anxiety, and coping strategies. Subjects then underwent experimental pressure pain testing followed by standard pre- and post-contrast-enhanced MR imaging, which included a perfusion MR imaging sequence (DSC).

Questionnaires

Four self-report questionnaires were administered, all of which have been validated in the appropriate population. The CES-D questionnaire, a 20-item self-report assessing symptoms of depression in nonpsychiatric adults[19]; the STPI anxiety questionnaire[20]; the BPCQ-INT[21]; and the CSQ-CAT[22] were administered to all subjects.

Pain Assessment

Experimental Pain. The patient's pressure pain threshold was assessed before perfusion MR imaging by using methods previously described.[23] A stimulation device was used to apply discrete pressure stimuli to the subject's left thumbnail, a design that eliminated any direct examiner/subject interaction. Pain-intensity ratings were recorded on the Gracely Box Scale questionnaire.[24] A random staircase testing design was used, and the stimulus pressures were determined interactively: A computer program continuously adjusted the stimulus pressures in the 3 staircases (faint pain, mild pain, and slightly intense pain) to produce the same response distribution in each subject.[25] The results of the 3 staircases were used to assess evoked pressure-pain sensitivity.

Clinical Pain. A 10-cm VAS was used to assess clinical pain immediately before the perfusion MR imaging. This scale was a 10-cm line anchored by the words "no pain" and "worst possible pain" on the left and right ends of the scale, respectively.

MR Imaging and Perfusion MR Imaging

All subjects were imaged on a 1.5T SignaLX MR imaging unit (GE Healthcare, Milwaukee, Wisconsin). The subjects underwent a standard adult-protocol brain MR imaging examination before and after the administration of IV contrast, gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Montville, New Jersey), which included the following sequences: axial and sagittal T1-weighted (SE; TR/TE, 470–550 ms/min full); axial T2-weighted (fast SE; TR/TE, 3000–5000/102 ms); axial fluid-attenuated inversion recovery MR imaging (T2-weighted; TR/TE, 10 000/95 ms); and axial, coronal, and sagittal postcontrast T1 SE.

Perfusion MR imaging (DSC) was performed as the last sequence of the study, with the following parameters: gradient-echo EPI sequence—dynamic T2* series; axial: FOV = 230 × 230 mm, matrix = 128 × 128, section thickness = 4 mm skip 1 mm, number of sections = 24; and single-shot field-echo EPI: TR/TE = 1500/50 ms, flip-angle = 40°, EPI factor = 43, number signal averages = 1, sensitivity encoding factor = 3, dynamic phases = 40, acquisition time = 1 minute 9 seconds. Contrast agent injection consisted of a 0.10-mmol/L/kg gadolinium dose, administered with an injector delay of 5 seconds, at 2-mL/s rate followed by a 15-mL saline flush.

Imaging Postprocessing and Analysis

Conventional MR images were interpreted by a neuroradiology attending physician and were specifically evaluated for brain volume loss, abnormal signal intensity, pathologic contrast enhancement, abnormal restricted diffusion, the presence of hemorrhage or mineralization, and any additional abnormalities. If a tumor or area of ischemia was present, the subject's data were excluded from the analysis. These and any other clinically relevant findings on structural MR imaging were reported to the patient's primary physician.

Postprocessing involved systematically placing multiple 94-mm^2 regions of interest in a number of gray and white matter regions that have been implicated in pain processing. A total of 12 regions of interest were placed in each study; the neuroradiologist (B.R.F.) was blinded to the disease status of the subjects. Regions of interest were placed in the thalami, putamen, caudate nuclei, anterior and posterior insulae, and the occipital white matter bilaterally (Fig 1). The locations of these regions of interest were chosen a priori because of their known involvement in pain transmission or because they had shown abnormalities in previous neuroimaging studies of pain.[13,14,23,26-28]

rCBF was obtained by using a quantitative analysis program, Penguin (Aarhus University, Aarhus, Denmark),[29-31] with an arterial input function chosen automatically at the level of the circle of Willis and single-value decomposition. The CBF maps were imported into ImageJ, Version 1.38 (National Institutes of Health, Bethesda, Maryland) for placement of the regions of interest. An rCBF value for each region of interest was then assigned by using the patient's bilateral occipital white matter CBF mean value as the denominator (ie, the

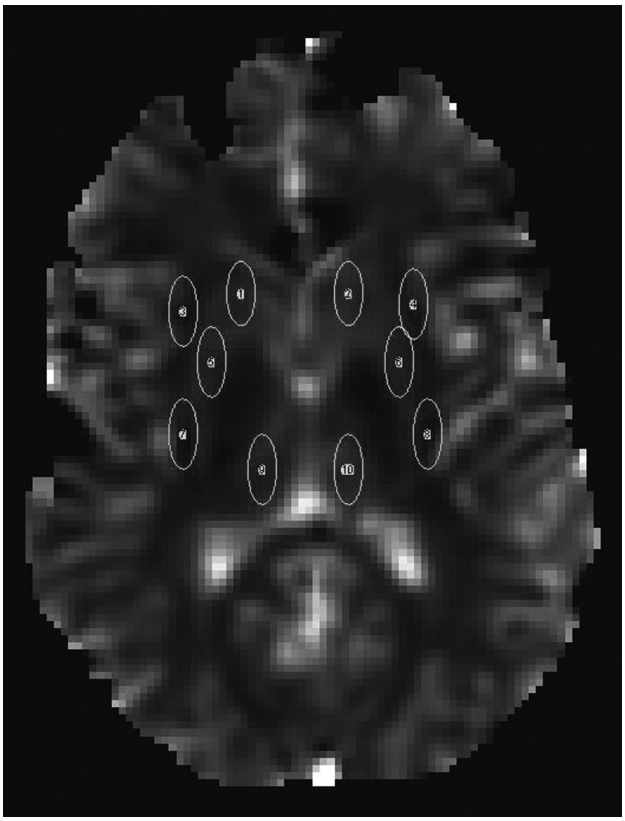

Fig 1. Image illustrates region-of-interest placement at the level of the basal ganglia, including the caudate nuclei, anterior insulae, putamen, posterior insulae, and thalami.

internal reference). To assess measurement reliability, we randomly selected 5 subjects with FM and 5 healthy controls. After blinding, the primary investigator (B.R.F.) repeated the region-of-interest measurements and a second investigator (M.P.) performed the region-of-interest measurements on the same 10 subjects.

Statistical Analysis

A repeated-measures ANOVA was used to assess the effect of brain location, group (FM versus healthy control), and group-location interaction on perfusion ratio values. Fixed effects of group, location, and group-location interaction were used as factors in the model. An unstructured variance-covariance pattern was assumed for the observations on the same subject, to account for the clustering effect. rCBF comparisons between groups for each location were adjusted for multiple comparisons by using a Bonferroni correction.

To analyze the rCBF variability for each location within each group, we calculated the absolute SDs of the observations from their respective means. These deviations were then analyzed under the framework of repeated-measures ANOVA as described in the previous paragraph.

Results

Mean rCBF Values in Different Brain Regions

Significant differences between rCBF values in various brain locations were observed in all subjects as expected ($P < .0001$). There were no significant differences in the rCBF values between subjects with FM and healthy controls for specific brain locations (ie, group-location interaction was not significant). There was a significant effect of group ($P = .048$). This was not due to a significant difference in the overall rCBF values (calculated by averaging the brain-location rCBF values of each subject) between FM and control subjects. The significant effect of group was due to a differential distribution pattern of rCBF values across brain locations for the FM and healthy control groups.

rCBF Values and Clinical Measures

Correlations between FM rCBF values and the questionnaire data as well as the pain testing measures were examined. Statistically significant negative correlations were detected between the BPCQ-INT scale and the right and left thalamic rCBF values ($r = -0.75$, $P = .003$, Fig 2*A*; $r = -0.58$, $P = .03$, Fig 2*B,* respectively). Furthermore, there was a correlation trend between the CSQ-CAT score and the left thalamic rCBF values ($r = 0.50$, $P = .08$).

Given the above findings, regression models between the thalamic rCBF values and the VAS pain testing results were performed before and after adjusting for the CES-D, STPI, BPCQ, and CSQ-CAT scores. The right and left thalamic rCBF values were considered separately and were dependent variables, and the clinical pain score on the VAS was the independent variable. In the regression model between the right thalamic rCBF and the VAS pain score, the strength of the relationship increased after correcting for the BPCQ-INT score ($b = 0.04$, $P = .28$ without including the BPCQ-INT score; $b = 0.07$, $P = .13$ after including the BPCQ-INT scores in the model). To a lesser extent, this was also the case in the regression model between left thalamic rCBF and the VAS pain score ($b = 0.05$, $P = .31$ without including the BPCQ-INT score; $b = 0.06$, $P = .25$ after including the BPCQ-INT scores in the model).

Variability and Correlation of rCBF Values across Brain Regions

In addition to the average rCBF values, we also examined the differences in variability of the data. There was a significant difference between rCBF value variabilities in various brain locations for both the subjects with FM and healthy controls ($P < .001$ for both). The effect of group was also significant ($P < .001$) when all locations were considered collectively, with the FM group demonstrating more overall variability than the healthy control group. Group-location interaction was not statistically significant (ie, there was no significant variability for each specific brain region between subjects with FM and healthy controls).

To examine the association of the rCBF values among the different brain regions, Pearson correlations were calculated within each group. We found that within the healthy control group, the rCBF values among the different brain regions were highly correlated. However, in the FM group, the overall strength of the correlations was less, and in particular, several of the correlations between the thalami relative to the other brain regions were not significant (Table).

For the healthy control group, rCBF values between both thalami and the other brain regions, including the right and left anterior insulae, the posterior insulae, and the putamen were highly correlated with r values ranging between 0.679 and 0.765 and P values ranging between $< .0001$ and .003. In contrast, in the FM group, all of the

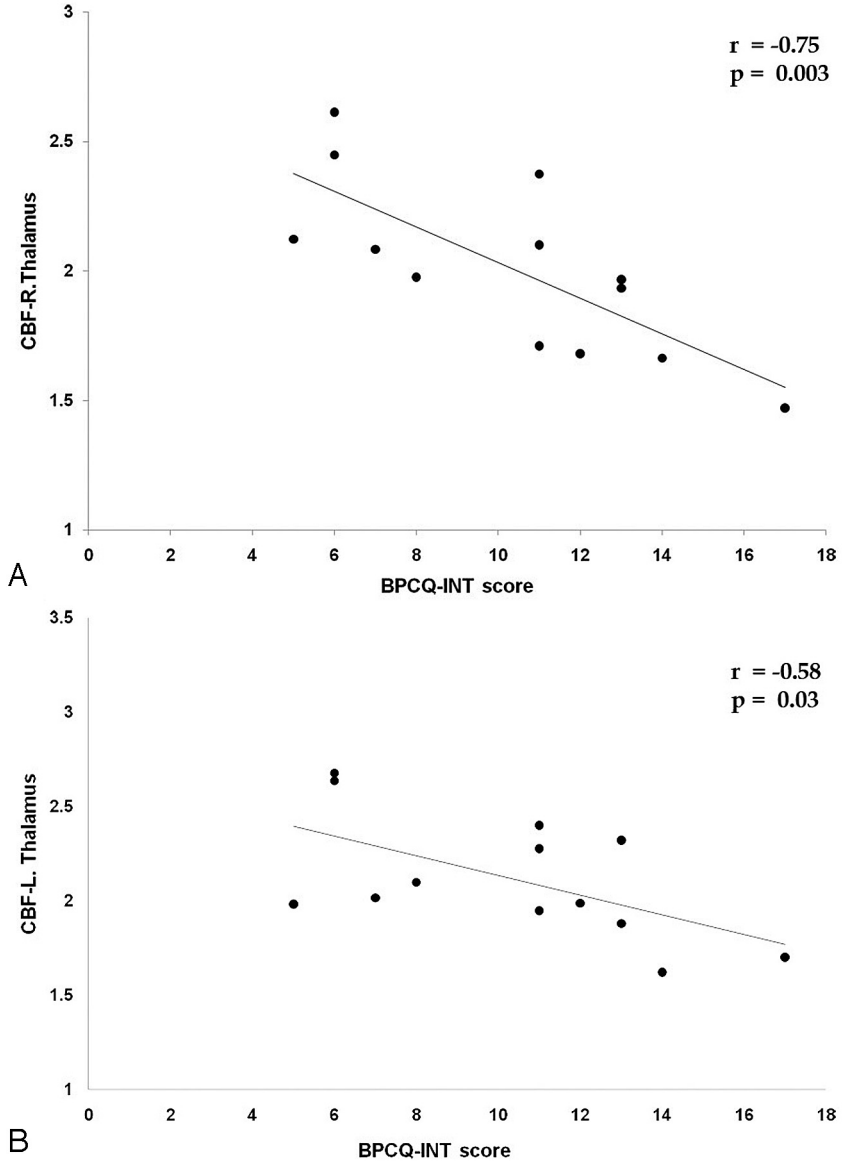

Fig 2. Significant correlations between BPCQ-INT testing and CBF values in the right thalamus (*A*) and the left thalamus (*B*).

Correlations between thalami and different brain regions

	Controls		FM	
	Right Thalamus	Left Thalamus	Right Thalamus	Left Thalamus
Right anterior insula	0.7132[a]	0.695[a]	0.390[b]	0.288[b]
Left anterior insula	0.760[a]	0.752[a]	0.509[d]	0.447[b]
Right posterior insula	0.663[c]	0.678[c]	0.236[b]	0.229[b]
Left posterior insula	0.723[a]	0.765[a]	0.269[b]	0.364[b]
Right putamen	0.706[a]	0.697[a]	0.573[d]	0.552[d]
Left putamen	0.671[c]	0.679[c]	0.550[d]	0.544[d]

[a] $P < .0001$.
[b] Not significant ($P > .05$).
[c] $0.0001 < P < .001$.
[d] $0.01 < P < .05$.

correlations of the rCBF values between each of the thalami and the right and the left anterior insulae, the posterior insulae, and the putamen had lower respective *r* values, ranging between 0.299 and 0.573. In addition, several of the correlations between the thalami and the brain regions in the FM group were nonsignificant ($P > .05$), including the right thalamus−right anterior insula, the right thalamus−right posterior insula, the right thalamus−left posterior insula, the left thalamus−right anterior insula, the left thalamus−left anterior insula, the left thalamus−right posterior insula, and the left thalamus−left posterior insula.

Assessment of Measurement Reliability

Ten examinations (5 subjects with FM and 5 healthy controls) were selected at random. After blinding, placement of regions of interest was repeated by the primary investigator as well as performed by a secondary investigator. The intraclass coefficient was 0.90–0.95 for the different brain regions, and the interclass coefficient was 0.85–0.91 for the different brain regions, indicating excellent agreement.

Conventional structural MR imaging findings were normal for all subjects included in the study with respect to evaluation of the brain parenchyma.

Discussion

Previous neuroimaging research studies, including fMRI, MR spectroscopy, diffusion tensor imaging, and SPECT studies, have identified and confirmed the presence of an anatomic circuit pathway characterizing a functional top-down influence on pain processing via brain stem structures.[10,12,32-35] Several studies have suggested that a CNS-based processing problem causes the widespread pain sensitivity in FM.[4-6] Functional neuroimaging modalities have been used to demonstrate changes in neuronal activity or blood flow in regions implicated in pain processing between patients with FM and controls.[7,10,11,13,14] MR spectroscopy studies have also described metabolic changes in patients with FM.[23,27] However, to our knowledge, no previous studies have used perfusion MR imaging techniques to investigate perfusion alterations in FM.

Beliefs about internal or personal control of pain as measured by the BPCQ-INT scale are highly correlated with rCBF values in the bilateral thalami. Furthermore, after adjusting for the BPCQ-INT score, the strength of the relationship between the thalamic rCBF scores and the VAS clinical pain scores grew; this change strengthens the likelihood that thalamic perfusion alterations may have pathophysiologic significance in FM. It is possible that internal or personal control of pain may serve as a mediator of the affective dimension of pain as processed by the thalami.[36]

Many studies have suggested that the widespread pain sensitivity of FM is caused by a CNS-based problem in pain processing. The current study results also indicate that there may be alterations of brain perfusion in patients, with the distribution pattern of rCBF values in the different brain regions significantly different between the FM group and the healthy control group. There was also higher variability in the overall rCBF values in the FM group compared with the healthy control group, also suggesting that perfusion may not be as tightly regulated in chronic pain conditions. Furthermore, the rCBF values of the thalami in the FM group demonstrated less correlation with respect to other brain regions compared with the correlations found in the healthy controls. The thalamus is considered a key component of the "pain matrix" because it serves as a conduit for all nociceptive input before being processed by the cortex.[32,37] The deep structures of the "pain matrix" appeared to be affected by this "perfusion uncoupling," perhaps reflecting changes in pain-processing pathways; it has been previously suggested that blood flow and neural activity may be uncoupled during chronic pain.[38] Each of the brain regions studied is thought to be involved with pain processing. For example, it is thought that the anterior insula may be more involved with emotional regulation and the affective dimension of pain, whereas the posterior insula is proposed to be involved more with sensory perception of pain.[39,40]

Two additional studies have identified changes in cerebral perfusion in patients with FM. Mountz et al[14] demonstrated significantly reduced rCBF in the bilateral thalami and caudate nuclei in 10 patients with FM, whereas Kwiatek et al[13] only found reduced rBCF in the right thalamus in 17 subjects with FM. Although we did find slightly lower rCBF values in the bilateral thalami and bilateral caudate nuclei in subjects with FM compared with healthy controls, these differences were not significant. This could perhaps be explained by the use of different imaging techniques. In addition, Kwiatek et al were able to manually draw regions of interest around the entire cerebral gray matter structure of interest; we used a smaller region of interest, only measuring a portion of the structure of interest, given the limitations of the postprocessing software. These differences could be resolved by studying the same set of subjects with perfusion MR imaging and SPECT studies.

As with any other abnormalities detected with advanced neuroimaging techniques, the precise cause for these perfusion abnormalities is unclear. Previous SPECT, PET, and fMRI studies have shown that pain stimuli increase synaptic activity in the sensory dimension (somatosensory and inferior parietal cortices) and in the affective-attention dimension of pain (insula, hippocampus, amygdala, cerebellum, and prefrontal and cingulate cortices).[41-43] It has been speculated that perfusion changes seen in patients with FM are due to abnormalities in neuronal functional levels.[13,14]

Although the number of subjects included in the study was limited, it is comparable with or larger than those in other studies investigating FM with functional neuroimaging techniques. However, this sample size may still be inadequate when subtle differences between groups are being sought. This small sample size may explain our inability to identify significant differences of rCBF values for individual locations between the 2 groups. Another limitation of perfusion imaging is the lack of absolute perfusion values; the bilateral occipital white matter was chosen as a reference because it was judged to be the least involved structure relative to pain processing.[44] The size of the regions of interest is also a limitation, particularly when measuring small inherent structures such as the insular cortex, as well as the inherent low resolution of perfusion maps. However, given the importance of the anterior and posterior insulae in central pain processing as evidenced by other neuroimaging techniques, the authors chose to include the data from the insular region.

Conclusions

No baseline differences in mean rCBF values obtained in a number of predefined brain regions thought to be involved in pain processing were detected between patients with FM and healthy controls. There were significant correlations between thalamic rCBF values and internal or personal control belief values. In addition, the rCBF values of the thalami demonstrated less correlation with respect other brain regions in the FM group than in the healthy control group.

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