Patterns of Cerebral Blood Flow Modulation During Painful Stimulation in Fibromyalgia: A Transcranial Doppler Sonography Study

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Abstract

Objective. This study analyzed the temporal dynamics of cerebral blood flow (CBF) modulations, during painful stimulation in fibromyalgia syndrome (FMS), using functional transcranial Doppler sonography.

Method. Blood flow velocities were recorded bilaterally in the anterior (ACA) and middle (MCA) cerebral arteries of 24 FMS patients and 20 healthy individuals during exposure to painful pressure stimulation. Participants were presented with two stimulation blocks: a) fixed pressure (2.4 kg) and b) stimulation pressure, individually calibrated to produce equal subjective and moderate pain intensity in all participants.

Results. A complex pattern of CBF modulations arose, comprising four main components: an anticipatory increase before stimulation onset, an early increase, a transient decrease to baseline or below, and a final increase. Group differences were observed in all components. The anticipatory component only arose in FMS patients, specifically in the ACA. Patients exhibited a greater early CBF increase under the fixed pressure condition, predominantly in the right ACA. A stronger CBF decrease after the early component was observed in patients during the equal pain condition, in the ACA and MCA. Significant associations were found between clinical pain severity and CBF responses in the MCA.

Conclusions. The results demonstrate that acute pain processing is associated with a complex pattern of CBF modulation, where FMS patients exhibited alterations in all phases of the response. The aberrances may be ascribed to psychophysiological phenomena, including central nervous nociceptive sensitization and protective-defensive reflex mechanisms. The anticipatory CBF response in patients may relate to various cognitive, emotional, and behavioral mechanisms involved in pain chronification.

Key Words. Fibromyalgia Syndrome; Pain Anticipation; Defensive Reflex; Clinical Pain; Cerebral Blow Flood; Functional Transcranial Doppler Sonography (fTCD)

Introduction

Fibromyalgia syndrome (FMS) is a chronic disease characterized by generalized diffuse musculoskeletal pain [1]. The etiology and pathophysiology of FMS remain to be confirmed, although the general consensus is that central nervous sensitization and deficient pain-inhibiting mechanisms may be involved [2,3]. This notion is supported by decreased pain thresholds and tolerance [4], the occurrence of allodynia [5], observations of temporal (windup) and spatial summation [6,7], and exaggerated activity of the central nervous pain neuromatrix [8–10]. Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have been used to analyze...
cerebral blood flow (CBF) responses to painful stimulation in FMS. During moderate pain stimulation, FMS patients exhibited activation of prefrontal and supplementary motor cortices and the insula, anterior cingulate, sensory-motor cortex, right thalamus, and basal ganglia. In healthy controls, the response was predominantly restricted to the somatosensory cortex [8–11]. This anatomical dissociation suggests activation of cerebral areas specifically related to the emotional and cognitive elaboration of pain in FMS patients, in contrast to predominantly sensory pain processing in healthy individuals [11].

One important factor in pain chronification is the anticipation of pain, characterized by future-oriented cognitions, negative emotions, and autonomic arousal. In patients with chronic pain, including those with FMS, pain anticipation has been related to exaggerated pain experience, fear of pain, pain-related behaviors, and functional disability [12–17], which may in turn exacerbate patients' suffering [18]. Pain anticipation is furthermore associated with the activation of nociceptive structures such as the medial frontal, insular, and dorsolateral cortices [11,15,18,19], which are assumed to be involved in the development of hyperalgesia and central nociceptive sensitization.

The above-mentioned brain mapping studies provide evidence concerning the spatial distribution of CBF responses during painful stimulation in FMS. In contrast, evidence concerning the temporal dynamics of these responses remains sparse. The investigation of CBF dynamics provides complementary information to that revealed by classic brain imaging paradigms [20,21]. Functional transcranial Doppler sonography (fTCD) allows for continuous, noninvasive measurement of CBF velocities in the basal cerebral arteries with excellent time resolution [20]. Changes in the flow velocity of these arteries reflect changes in blood demand in their perfusion territories as a result of neural activity [20]. Several studies have proven the validity of fTCD for the analysis of CBF responses during psychological processes, including the experience of acute pain [21–24]. The CBF response observed during pain stimulation consists of two basic components: an early response peaking after approximately 5 s, and a late response peaking around 15 s after stimulus onset [21,22]. Both components exhibited a degree of lateralization toward the right hemisphere [21]. The pain-related CBF response is relatively slow (latencies of 2–3 s) in comparison to cognitive activity (latencies < 1 s) [21]. Previous fTCD studies indicate that interindividual differences in hemodynamic responses, and associations between CBF responses and pain indicators, are time-dependent and usually restricted to specific time frames [21,22]. Similarly, associations between CBF responses and clinical parameters (e.g., clinical pain severity, anxiety, or depression) are highly dynamic, with correlations typically arising during limited response intervals [23,24].

A previous study, that used fTCD to quantify CBF responses during painful heat stimulation in FMS [21], revealed stronger blood flow increases in FMS patients vs. healthy individuals in the anterior cerebral arteries (ACA), which supply medial-anterior cerebral regions. Two response components were identified: only the early one correlated with clinical pain. The exaggerated CBF response in the ACA has been interpreted in terms of hyperactivity of the medial part of the pain neuromatrix, which comprises structures specifically mediating the emotional and cognitive components of pain such as the medial prefrontal cortex and anterior cingulate [21,25]. In contrast, no group difference arose in CBF responses in the middle cerebral arteries (MCA), which supply lateral brain areas associated with the sensory pain component including the fraction of the primary somatosensory cortex representing the forearm, the inferior parietal lobe and lateral prefrontal cortex [11] (c.f. Figure 1 for the perfusion territories of the MCA and ACA).

Transient changes in CBF have been traditionally discussed in the context of orienting (OR) and defense (DR) reflexes and non-associative learning mechanisms—that is, habituation and sensitization [26–28]. These basic reflex mechanisms are implicated in the modulation of sensory input, where they exert opposing effects on sensory processing. During the OR—elicited by novel stimuli of low intensity—receptor and CNS sensitivity is increased, while the DR—elicited by intense, aversive stimulation—is associated with elevated sensory threshold and diminished CNS sensitivity [27]. One of the mechanisms thought to be involved in the modulation of receptor and CNS sensitivity is adjustment of CBF. Increased CBF has been related to the OR and low sensory thresholds, and reduced CBF to the DR and elevated thresholds [27]. Further research on the physiological differentiation of the OR and DR revealed a more-complex picture [26,28]. The CBF response associated with the DR (measured via photoplethysmography at the forehead or temporal sites) consists of an
increase component during the first few seconds after aversive stimulus onset, and a decrease component starting 15 s and peaking below baseline level approximately 25 s post-stimulus. For stimuli eliciting the OR, the first CBF increase component is smaller and the decrease below baseline does not occur [28].

The present fTCD study analyzed the temporal dynamics of CBF responses to painful pressure stimulation in FMS patients and healthy individuals. Blood flow velocities were recorded bilaterally in the ACA and MCA while participants were exposed to painful pressure stimulation. We adapted the protocol designed for the fMRI study of Gracely et al. [8] Participants were presented with two stimulation blocks: a) fixed pressure of 2.4 kg and b) stimulation pressure individually calibrated to produce equal subjective pain intensity in all participants (corresponding to a value of 6 on a 10-point VAS). Associations between clinical pain severity and CBF responses were also investigated. Considering the central nervous nociceptive sensitization involved in FMS, we expected that the fixed pressure condition (2.4 kg) would produce greater CBF responses in the FMS group vs. healthy controls. Based on previous studies [21,22], we furthermore hypothesized that group differences would predominantly arise in the ACA, particularly in the right hemisphere. Assuming greater pain expectancy and catastrophizing in FMS patients [12,15], we expected a stronger CBF response during pain anticipation in FMS patients. According to neuropsychological theories that ascribe particular roles to the anterior cingulate and ventromedial prefrontal cortices during anticipatory processing [19,29–31], the anticipatory CBF component may be particularly pronounced in the ACA. Regarding time dynamics, we predicted a response pattern consisting of a CBF increase before stimulus onset, related to pain anticipation, as well as early- and late-increase component related to nociception. Based on previous observations in FMS [21,22], we hypothesized that group differences would be restricted to the anticipatory and early response components. Similarly, we expected that associations between CBF responses and clinical pain would mainly arise for these components. Taking into account the hyperalgesia and central nervous nociceptive sensitization associated with FMS, we predicted that painful stimulation would elicit a stronger DR in patients. We finally hypothesized that the DR would be evidenced by a decrease in CBF after the early increase component, and further that this decrease would be of a greater magnitude in FMS patients vs. healthy individuals [28].

**Method**

**Participants**

Forty-four women, 24 with FMS and 20 healthy controls, participated in the study. Patients were recruited via the Fibromyalgia Association of Jaén and met the American College of Rheumatology criteria for FMS [32]. The presence of cardiovascular diseases, metabolic abnormalities, neurological disorders, drug abuse, or severe somatic (e.g., cancer) or psychiatric (e.g., psychotic) diseases were used as exclusionary criteria. The control group was recruited from women’s associations and was matched to the patient group with respect to age, body mass index and educational level. In addition to having any kind of pain disorder, the control group was subject to the same exclusionary criteria applied to patients. All participants were right handed. Table 1 displays the demographic and clinical data of both groups.

**Pressure Stimulation and Pain Quantification**

Pain was evoked using a wireless pressure algometer (Traker Freedom, JTECH Medical, Lawndale, USA) with a surface area of 1 cm². The algometer was connected to a computer that allowed for the control of pressure and rate of increase (kg/s), and was inserted in a

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics (mean ± SD) and medication use in the FMS and control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FMS patients</td>
</tr>
<tr>
<td>Age</td>
<td>48.96 ± 9.15</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>25.31 ± 3.37</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.64 ± 3.05</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Anxiety disorders (%)</td>
<td>13 (52)</td>
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<tr>
<td>Antidepressant use (%)</td>
<td>13 (52)</td>
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<tr>
<td>Anxiolytic use (%)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Analgesic use (%)</td>
<td>21 (84)</td>
</tr>
<tr>
<td>Opiate use (%)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>McGill: sensorial</td>
<td>38.56 ± 22.14</td>
</tr>
<tr>
<td>McGill: emotional</td>
<td>6.40 ± 5.75</td>
</tr>
</tbody>
</table>

Results of the group comparisons are also displayed (\( t \) or \( \chi^2 \)).
screw-piston specifically designed to fix and press the finger-nails, such that stimulation pressure could be reliably delivered. When stimulation commenced, the piston sent an electrical pulse to the fTCD system signaling the start of a trial. Pain pressure was delivered to the nail of the index finger of the left hand. For the measurement of pain threshold (the pressure at which the participant started to feel pain) and tolerance (the maximum pressure tolerated), pressure was continuously increased at a rate of 1 kg/s. Subjective pain intensity was evaluated using a 10-cm line visual analogue scale (VAS; “How strong was the pain?”) running from 0 (not at all) to 10 (extremely). The stimulation protocol allowed for the investigation of pain anticipation. Although participants did not receive explicit task instructions, they could see their nail in the screw-piston, as well as the investigator approaching the device approximately 4 s prior to stimulus onset, enabling them to quickly ascertain as to when the pain would be delivered. This knowledge was most likely acquired already during the familiarization phase of the protocol (see the “Procedure” section).

Recording of Cerebral Blood Flow

Blood flow velocity was assessed by fTCD employing a digital Multi-Dop L2 DWL (Elektronische Systeme, Inc., Sipplingen, Germany). Recordings were conducted bilaterally, in both the ACA and MCA, through the temporally bone windows using two 2-MHz transducer probes. Following vessel identification, the probes were fixed to the head via a head harness. The MCA was insonated at a depth of 48–55 mm, and the ACA at a depth of 60–70 mm. The spectral envelope curves of the Doppler signal were recorded at 100 Hz. The mean flow velocity index was applied as a measure of CBF. This index is the least vulnerable to artifacts and exhibits the highest correlation with blood volume flowing through an artery per unit of time [20].

The 100 Hz mean flow velocity recording was resampled at 4 Hz. The 30 s period after stimulus onset was defined as the stimulation period; the 4 s period before stimulus onset was the anticipatory period. Mean flow velocity during the 10 s prior to the anticipation period served as the baseline. Responses were expresses as relative (percent) changes in flow velocity (dFV) with respect to baseline (FVbas) according to the formula \( dFV = (FV(t) - FVbas) \times 100/FVbas \), where \( FV(t) \) is the flow velocity over time.

Procedure

The study was performed across two separate sessions that took place on different days. During the first session a clinical psychologist obtained the patients’ clinical history and socio-demographic data, checked the exclusionary criteria, conducted the Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders [33] and presented the McGill Pain Questionnaire [34]. Only the scores representing the sensorial and emotional pain dimensions obtained in this instrument were included in the analysis. During administration of the McGill Questionnaire to the control group, participants were asked to refer to possible sporadic pains, or the corporeal area in which they usually felt some discomfort. Through the second session the experimental procedure took place across two phases, which represented an adaptation of the method used by Gracely et al. [8] study. In the first phase, participants were familiarized with the stimulation protocol, while in the second phase the actual experiment was performed. During the first phase participants received instructions pertaining to the concepts of pain threshold and tolerance and the use of the VAS. Threshold and tolerance data were obtained thereafter. In order to reduce anxiety and familiarize participants with the procedure, seven pressure stimuli of 5 s duration were applied with 20 s inter-trial intervals (sequence: 1.35, 4.5, 0.9, 2.7, 0.45, 1.8, and 3.6 kg). Finally, a sequence of 5 s pressure stimuli was applied in ascending order, beginning at 0.45 kg/cm² and increasing in 0.45 kg/cm² intervals until the tolerance level was reached, or to a maximum of 9 kg/cm². With the subjective pain evaluation obtained using this sequence of increases, a psychophysics function relating physical pressure (in kg) to subjective pain ratings (VAS) was computed for each participant. From this regression function, the individual pressure (in kg) required to produce moderate pain (a value of 6 on the 10-point VAS) was individually calculated.

During the second experimental phase, two blocks of 12 pressure stimuli were presented in a counterbalanced order: one block used a fixed pressure of 2.4 kg and the other used an individually calculated pressure in order to evoke a subjective pain intensity of 6 on the VAS. Previous studies showed that pressures of approximately 2.4 kg are associated with low pain ratings in healthy individuals, and with low-to-moderate pain in FMS patients [8,15]. In both sequences, stimulation was maintained for 10 s and inter-trial intervals were 60 s.

Given the impossibility of measuring blood flow velocity in the MCA and ACA simultaneously, the entire procedure was repeated for each pair of arteries. The artery starting order (MCA vs. ACA) was counterbalanced across participants. Participants were instructed to refrain from smoking, caffeine, alcohol, and vigorous exercise for 2 hours prior to the experiment. They were also asked not to consume analgesics or other drugs affecting the cardiovascular system beginning 24 hours before the study. All participants provided informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Data Reduction and Analysis

Based on previous fTCD studies conducted in the fields of pain processing [21,22], and on visual inspection of the CBF data, four delimitable response components were identified: 1) an anticipatory increase component...
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(approximately 2 s before stimulus onset), 2) an early increase component (s 1 to 3 after stimulus onset), 3) a decrease component (s 5 to 11), and 4) a late increase component (s 12 to 22). Peak amplitudes during these periods (maximum values for components 1, 2, and 4, and minimum values for component 3) were obtained for each participant. Statistical analysis of the CBF response was conducted using 2x4[repeated measures ANOVAs, with the between-subjects factor 'group' (i.e., FMS patients vs. control group) and the repeated-measure factor 'CBF component' (i.e., the four response amplitudes). Data were analyzed using the multivariate test statistic Wilks’ lambda. Group differences and post-hoc analysis of interactions were evaluated using Student's t-test. Group differences and post-hoc analysis of interactions were evaluated using Student's t-test for independent samples. Potential effects of medication on CBF responses were analyzed by comparing CBF components within the FMS group between patients using and not using antidepressants, anxiolytics, analgesics, and opiates (Student's t-test). Associations between pain parameters and CBF responses were quantified using Pearson correlations.

Results

Pain Parameters and CBF Responses

Pain threshold (1.61 ± 0.77 vs. 3.78 ± 2.73, for FMS and controls, respectively, t = 3.76, P = 0.001, η² = 0.247) and tolerance (4.00 ± 1.39 vs. 7.52 ± 3.23, for FMS and controls, respectively, t = 4.92, P < 0.0001, η² = 0.360), and the pressure required to evoke a VAS rating of 6 (3.52 ± 2.12 vs. 5.12 ± 2.15, for FMS and controls, respectively, t = 2.49, P = 0.017, η² = 0.13) were lower in FMS patients vs. controls.

For all cerebral arteries and pain conditions, the repeated-measures factor (response component) was significant (all Fs (3, 40) > 22, all Ps < 0.0001, all η²s > 0.62). The response pattern in CBF was characterized by early (peaking at s 2–3 from stimulus onset) and late (peaking at s 17–19 from stimulus onset) increase components. Between these peaks a decrease component (peaking at s 8–9 from stimulus onset) arose, where CBF fell to the baseline level or below. An anticipation component was present in the right ACA for the fixed pressure (2.4 kg) and equal pain (6 VAS) conditions, and in the left ACA for the equal pain condition, but only in the FMS group (c.f. Figures 2 and 3).

Group × response interactions were observed for the right ACA under the fixed pressure condition (F(3, 41) = 3.58, P = 0.022, η² = 0.21) and for the right (F(3, 41) = 4.65, P = 0.007, η² = 0.25), and left ACA under the equal pain condition (F(3, 41) = 3.56, P = 0.028, η² = 0.20). For the right ACA under the fixed pressure condition, the FMS group displayed greater CBF increases compared to the control group, during both the anticipation and early components. For the right ACA under the equal pain condition, patients exhibited greater CBF responses during anticipation and reduced CBF during the decrease component. For the left ACA under the equal pain condition, the FMS group displayed increased CBF during anticipation (see Table 2). Finally, for the MCA under the equal pain condition, the FMS group exhibited overall decreased CBF, the difference being significant for the right (F(1, 42) = 5.59, P = 0.023, η² = 0.12), and marginally for the left, hemisphere (F(1, 42) = 3.23, P = 0.079, η² = 0.071).

Effects of Medication on CBF Responses in FMS Patients

Patients using antidepressants exhibited smaller CBF responses in the right MCA during the decrement component and fixed pressure condition than did patients not using this medication (−1.73 ± 1.23 vs. −3.34 ± 2.36 for patients taking and not taking antidepressants, respectively; t (23) = −2.15, P = 0.042, η² = 0.17). Patients using analgesics showed greater CBF responses under the equal pain condition during the MCA anticipatory component both for the left (3.32 ± 2.16 vs. 0.51 ± 1.19 for patients taking and not taking analgesics, respectively; t (23) = −3.69, P = 0.007, η² = 0.21) and right artery (3.96 ± 2.61 vs. 1.47 ± 0.85 for patients taking and not taking analgesics, respectively, t (23) = −3.48, P = 0.003, η² = 0.13) than did patients not using this medication.

Associations Between Clinical Pain and CBF Responses in FMS Patients

Correlations between the amplitudes of the CBF components and the sensorial and emotional pain ratings on the McGill Pain Questionnaire are listed in Table 3. No significant associations were found for the anticipatory period. For the early component assessed in the MCA, associations differed between pain stimulation conditions. Regarding the fixed pressure condition, significant positive associations were observed both for sensorial and emotional pain. In contrast, for the equal pain condition, associations were lower and negative and only reached significance for sensorial pain in the right MCA. No associations arose for the early ACA component. For the decrease component and the MCA, the associations followed the same trend. Under the fixed pressure condition, significant positive associations were observed for sensorial and emotional pain. With respect to the equal pain condition, both the left and right MCA responses were inversely associated with emotional pain. No significant associations were obtained for the ACA decrease component. Regarding the late CBF component and the equal pain condition, negative associations arose for the MCA and ACA. However, these associations only reached significance in the right MCA for emotional pain, while the correlation with sensorial pain was only marginally significant (r = −0.36, P = 0.058).

Associations of Pain Threshold and Tolerance with CBF Responses

In the FMS group pain threshold was negatively associated with MCA CBF responses during the
anticipatory period \((r = -0.51, P = 0.010\) for left MCA fixed pressure and \(r = -0.49, P = 0.013\) for right MCA fixed pressure), the early \((r = -0.41, P = 0.040\) for right MCA fixed pressure, and \(r = -0.35, P = 0.083\) for left MCA fixed pressure), and late components \((r = -0.54, P = 0.005\) for left MCA equal pain). Pain tolerance was inversely associated with the late CBF component under the equal pain condition \((r = -0.65, P < 0.001\) for left MCA, \(r = -0.50, P = 0.012\) for right MCA), but positively for the decrease component under the fixed pressure condition \((r = 0.43, P = 0.032\) for right ACA).

In the control group these correlations only reached significance for the ACA decrease component under the equal pain condition with regard to pain threshold \((r = 0.47, P = 0.039\) for the left, and \(r = 0.43, P = 0.049\) for the right ACA). For pain tolerance these associations did not reach significance \((r = 0.41\) for the left, and \(r = 0.38\) for the right ACA, n.s.).

**Discussion**

A complex pattern of CBF modulation during painful pressure stimulation was observed in FMS patients and healthy individuals, underlining the notion that time dynamics are an important aspect of hemodynamic adjustment during central nervous nociceptive processing. Although the CBF pattern differed as a function of group, artery, hemisphere, and stimulation condition, it was generally characterized by an increase component during stimulus anticipation, an early increase component after stimulus onset followed by transient CBF decrease to baseline level or below, and a final increase component.

The anticipatory component was observed only in FMS patients, specifically in the ACA. Under the fixed pressure condition \((2.4\) kg) this component was restricted to the right ACA, while under the equal pain condition \((6\) VAS), which was of higher average physical intensity
(M = 3.52 kg), it arose in both hemispheres. These results support our predictions and accord with neuropsychological theories postulating the involvement of anterior-medial structures, such as the anterior cingulate and ventromedial prefrontal cortices, in anticipatory processing [19,29–31]. Pain anticipation encompasses increased negative affect and modulation of attentional and cortical tone, processes that are well-known to be lateralized toward the right hemisphere [24,35,36]. This is consistent with the restriction of the response to the right ACA under the fixed pressure condition.

The results concerning the anticipatory CBF component in FMS cohere with the occurrence of a pain sensitization processes in FMS. Pain sensitization could include the presence and development of a cognitive bias, in both the interpretation of pain sensations and attention paid to them (hypervigilance to pain). This bias can lead to individuals ascribing greater relevance to pain in general life, in addition to fear of pain, catastrophizing, pain-related behaviors, emotional alterations, etc. [12–17,21,30,37], all of which can in turn reinforce the previous cognitive bias and, by means of a “vicious circle,” stimulate a pain chronification process.

As expected, FMS patients exhibited a greater CBF response than did healthy participants under the fixed pressure condition, specifically for the early right component in the ACA. This is congruent with previous evidence of an increased ACA blood flow response during painful heat stimulation in FMS patients [21]. Application of mild pressure (2.4 kg) in FMS patients resulted in a stronger CBF response compared to the control group even during the equal pain condition, where an average of 5.12 kg was delivered. This clearly supports theories postulating exaggerated central nervous pain processing in FMS [8–11] and also accords with previous fMRI evidence of activation of larger brain areas in FMS patients during fixed pressure stimulation of 2.4 kg [8]. The restriction of the group difference in early CBF modulation to the (right) ACA supports the view of specific hyperactivity of the medial pain matrix, which represents

![Figure 3](https://academic.oup.com/painmedicine/article-abstract/17/12/2256/2741175/Patterns-of-Cerebral-Blood-Flow-Modulation-During)
emotional and cognitive pain components \[11,22\] and is also in line with prefrontal anterior asymmetry theories that postulate right hemispherical dominance of negative emotional and motivational states \[35\]. Previous studies on CBF responses during cognition indicate stronger right hemispherical lateralization of ACA responses in FMS vs. healthy individuals \[23,24\] even in an arithmetic task for which one would expect left hemispherical dominance. There may be a general tendency toward right hemispherical ACA blood flow increases, possibly due to alterations in arousal regulation or a negatively biased cognitive or emotional style \[35,36,38\].

During the decrease component, CBF was lower in the FMS vs. control group under the equal pain condition. A marginally significant group difference in the same direction also arose for the left ACA. The CBF decrease, after the early component under the (stronger) equal pain condition, is consistent with traditional reflex theory \[26,28\] and suggests the occurrence of a DR in FMS patients. The CBF reduction below baseline level is in line with previously observed decreases in cephalic (forehead and temporal) blood flow elicited by aversive acoustic stimulation \[28\]. It is commonly assumed that the DR represents a reduction of central nervous and sensorial receptor sensitivity during conditions of intense aversive stimulation \[26–28\]. It has been related to Pavlov’s concept of protective, or transmarginal, inhibition, which is regarded as a protective mechanism against overstimulation \[39\]. Cephalic and peripheral vasoconstriction (and muscle vasodilatation) is assumed to occur during the DR to facilitate engagement in protective behaviors and diminish the processing of aversive stimulation \[27\].

Results of the group comparisons are also displayed \((P, \eta^2)\) (only arteries with significant group x response pattern interactions are displayed).

### Table 2

Mean values \((± SD)\) of relative (%) blood flow velocity changes in the anterior cerebral arteries (ACA) of the right and left hemispheres, under the fixed pressure and equal pain conditions for the anticipatory (1), early increase (2), decrease (3), and late increase components (4).

<table>
<thead>
<tr>
<th></th>
<th>FMS patients</th>
<th>Control group</th>
<th>(t(43))</th>
<th>(P)</th>
<th>(\eta^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right, fixed pressure, 1</td>
<td>4.85 (1.34)</td>
<td>0.78 (0.53)</td>
<td>2.70</td>
<td>0.01</td>
<td>0.13</td>
</tr>
<tr>
<td>Right, fixed pressure, 2</td>
<td>5.35 (1.53)</td>
<td>0.01 (0.77)</td>
<td>2.76</td>
<td>0.009</td>
<td>0.14</td>
</tr>
<tr>
<td>Right, fixed pressure, 3</td>
<td>−3.72 (1.45)</td>
<td>−3.06 (1.37)</td>
<td>0.41</td>
<td>0.68</td>
<td>0.006</td>
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<tr>
<td>Right, fixed pressure, 4</td>
<td>8.75 (1.96)</td>
<td>6.82 (1.05)</td>
<td>0.83</td>
<td>0.41</td>
<td>0.115</td>
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<tr>
<td>Right, equal pain, 1</td>
<td>5.14 (0.94)</td>
<td>1.78 (0.57)</td>
<td>2.73</td>
<td>0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Right, equal pain, 2</td>
<td>4.76 (1.46)</td>
<td>3.61 (0.84)</td>
<td>0.68</td>
<td>0.50</td>
<td>0.028</td>
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<tr>
<td>Right, equal pain, 3</td>
<td>−6.46 (1.42)</td>
<td>−2.80 (1.01)</td>
<td>2.19</td>
<td>0.035</td>
<td>0.097</td>
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<tr>
<td>Right, equal pain, 4</td>
<td>6.03 (0.92)</td>
<td>7.23 (0.84)</td>
<td>0.95</td>
<td>0.35</td>
<td>0.009</td>
</tr>
<tr>
<td>Left, equal pain, 1</td>
<td>3.99 (1.45)</td>
<td>0.060 (0.71)</td>
<td>2.52</td>
<td>0.016</td>
<td>0.12</td>
</tr>
<tr>
<td>Left, equal pain, 2</td>
<td>5.92 (1.98)</td>
<td>3.35 (0.79)</td>
<td>1.25</td>
<td>0.22</td>
<td>0.036</td>
</tr>
<tr>
<td>Left, equal pain, 3</td>
<td>−5.88 (1.06)</td>
<td>−3.69 (0.59)</td>
<td>1.79</td>
<td>0.08</td>
<td>0.067</td>
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<tr>
<td>Left, equal pain, 4</td>
<td>7.01 (1.6)</td>
<td>7.33 (0.89)</td>
<td>0.17</td>
<td>0.89</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3

Correlations between amplitudes of the cerebral blood flow responses and the sensory and emotional pain ratings on the McGill Pain Questionnaire (only arteries and components with significant correlations are displayed)

<table>
<thead>
<tr>
<th></th>
<th>Fixed pressure</th>
<th></th>
<th></th>
<th>Equal pressure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensory pain</td>
<td>Emotional pain</td>
<td>Sensory pain</td>
<td>Emotional pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early component</td>
<td>Left MCA</td>
<td>0.46*</td>
<td>0.49*</td>
<td>−0.26</td>
<td>−0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right MCA</td>
<td>0.44*</td>
<td>0.49*</td>
<td>−0.40*</td>
<td>−0.24</td>
<td></td>
</tr>
<tr>
<td>Decrement component</td>
<td>Left MCA</td>
<td>0.46*</td>
<td>0.48*</td>
<td>−0.07</td>
<td>−0.54*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right MCA</td>
<td>0.40*</td>
<td>0.40*</td>
<td>−0.12</td>
<td>−0.55*</td>
<td></td>
</tr>
<tr>
<td>Late component</td>
<td>Right MCA</td>
<td>−0.06</td>
<td>−0.08</td>
<td>−0.38</td>
<td>−0.44*</td>
<td></td>
</tr>
</tbody>
</table>

\(^* P < 0.05.\)

ACA = anterior cerebral artery; MCA = middle cerebral artery.
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Central nervous nociceptive sensitization in FMS, it may be hypothesized that the DR helps to limit neural activation during acute painful stimulation, where the reduction of CBF is regarded as one of the mechanisms involved in restricting stimulus processing [26–28].

Concerning the MCA, the patients’ DR may have become apparent in the CBF reduction during the entire response (especially in the right hemisphere). The MCA supply the somatosensory cortex, where the sensory pain component is processed. This is again in accordance with a proposed protective inhibition that serves to limit stimulus processing and prevent overstimulation [27,28,39]. Noceptive information is predominantly processed contralateral to the stimulated side, which is illustrated by the presently observed overall stronger right hemispherical CBF response. The fact that group differences during the equal pain condition were more pronounced in the right vs. left ACA and MCA supports the occurrence of a DR, functioning to limit central noceptive activation. During the more intense equal pain condition, only emotional pain correlated with amplitudes of the decrement components in both MCAs; stronger emotional pain was associated with stronger CBF decreases (i.e., a more pronounced DR). This is in accordance with neuroimaging studies on the DR, in which higher anxiety levels, indexed by subjective and peripheral autonomic measures, were related to lower cortical perfusion [40].

The DR is characterized by different components occurring within different time frames after stimulation depending of the physiological variable under consideration. For example, the heart rate increase component related to the motivational feature of the DR starts approximately 20 s after aversive stimulation and reaches its maximal amplitude within 30–35 s [41,42]; the increase in stroke volume is initiated 10 s after stimulus onset [43]; the increase component in blood pressure reaches its maximum between 9 and 14 s after stimulus onset [43]; and the decrease in cerebral blood flow (forehead) peaks approximately 25 s after stimulus onset [28]. On account of the temporal dissociations among the different parameters and the lack of previous studies assessing CBF velocities during the OR and DR, the interpretation of the CBF decrease in terms of the DR must remain somewhat speculative and further research is certainly required. However, these results accord with functional neuroimaging studies on the DR, in which exposure to phobic stimulus in phobic and obsessive-compulsive patients results in decreases in regional CBF in several sub- and cortical regions such as the hippocampus, orbitofrontal, prefrontal, temporopolar, and posterior cingulate cortex [40,44].

The use of antidepressants was associated with a lower magnitude of the right ACA decrement component under the fixed pressure condition, which may possibly be explained by the analgesic properties of antidepressants. However, patients using analgesics showed stronger CBF responses in the MCA anticipatory components during the equal pain condition. In addition to overall greater symptom severity in patients taking analgesics, this may have been due to withdrawal or rebound effects following the discontinuation of analgesics (24 hours before experiment).

Based on previous fTCD findings in FMS [21], we expected significant associations between CBF modulation and clinical pain severity, especially for the early response component. Such associations may represent the increased pain-related CBF responses due to hyperalgesia that characterize FMS. In our study correlations were higher for the MCA vs. ACA and varied in accordance with stimulation condition. Under the fixed pressure condition correlations were similar for the two hemispheres, while under the equal pain condition, where overall stronger pressures were applied, correlations only reached significance for the right hemisphere. In FMS patients, early MCA blood flow increases under the fixed pressure condition were positively associated with sensory and emotional pain. In contrast, the magnitude of the early MCA response under the equal pain condition correlated weakly and negatively with clinical pain. The same pattern of correlations was observed for the decrease component. For the late MCA response negative correlations with clinical pain arose under the equal pain condition. Greater clinical pain was associated with higher CBF responses in both MCA under the fixed pressure condition, but with lower right MCA responses under the equal pain condition. The dissociation in these patterns of associations (i.e., positive relationships during less intense and inverse relationships during more intense stimulation) is consistent with the notion of a DR in FMS patients under the equal pain condition. During intense stimulation, protective inhibition may occur in patients to prevent overstimulation, where the threshold and magnitude of inhibition depend on inter-individual differences in hyperalgesia as represented by clinical pain indices. The results support the view that clinical pain level modulates the magnitude of the DR, in the sense that more severe pain is associated with a stronger reduction of MCA perfusion. No significant associations were observed for the ACA, which may suggest that the influence of clinical pain on CBF modulation is widely restricted to sensory pain processing in the somatosensory cortex. The fact that negative associations between CBF responses and clinical pain, under the equal pain condition, were only observed for the right hemisphere again suggests the elicitation of a DR that functioned to restrict sensorial processing of aversive stimuli.

The observed CBF response patterns are only partly in accordance with previous fTCD studies of FMS patients and healthy individuals. At first, the present group differences between patients and healthy individuals mainly arose in the ACA, especially the right hemisphere. This is consistent with our hypotheses and previous fTCD studies investigating pain-related CBF modulations in FMS [22]. However, despite the group differences in ACA blood flow, associations between clinical pain and...
CBF responses were restricted to the MCA. This is inconsistent with the previously reported positive association between clinical pain severity and early ACA blood flow modulation during thermal pain stimulation of 45° in FMS [22], suggesting that clinical pain specifically modulated the activity of the medial neuromatrix representing the emotional/cognitive pain elaboration component. In healthy individuals, interindividual differences in subjective pain intensity during 45° thermal stimulation were associated with differences in relatively late CBF responses in both the ACA and MCA [21]. In explaining the divergent results, methodological differences among the studies have to be considered. In addition to differences in the populations investigated, and the fact that only the present paradigm allowed investigation of pain anticipation, results may vary according to the pain stimulation technique (20 s of thermal stimulation in [21] and [22] vs. 10 s of pressure stimulation in the present study). Furthermore, stimulus intensities can hardly be compared between induction methods (e.g., 45° vs. 2.4 kg). In interpreting differences between ACA and MCA responses, the generally low spatial resolution of fTCD should be acknowledged [20]. This is particularly important when assigning the ACA to the medial (emotional/cognitive), and the MCA to the lateral (sensory), pain neuromatrix. In addition to areas involved in sensory pain processing, the MCA supply structures such as the lateral prefrontal cortex, amygdala, insula and basal ganglia, which play a role in emotional/cognitive interoceptive processing, for example by ascribing emotional significance to sensory stimulation, pain-related learning and memory, and cognitive processing of aversive information or uncertain expectations [45,46]. Therefore, the assignment of both vessels to specific pain components must, to a certain extent, remain simplistic.

Patients’ pain thresholds were inversely associated with CBF responses, in both MCA under the fixed pressure condition for the anticipatory and early components, and under the equal pain condition for the late component. No correlations reached significance for the ACA, once again suggesting that interindividual differences in pressure pain sensitivity specifically modulate sensory pain processing in the somatosensory cortex. The close association found for the anticipatory component suggests that the degree of anticipation of painful stimulation varies subject to the extent of hyperalgesia and central nervous sensitization.

In summation, the present study demonstrated that acute pain processing is associated with a complex pattern of CBF modulation, where in FMS patients alterations in each of the specific components was apparent. The aberrances are likely due to psychophysiological phenomena, particularly central nervous sensitization, and protective defensive mechanisms. Furthermore, the anticipatory CBF response, which only arose in patients, may relate to various emotional, cognitive, and behavioral mechanisms contributing to pain chronification. From a methodological point of view, the study supports the utility of analyzing rapid hemodynamic modulation to complement the analysis of local CBF distribution patterns using neuroimaging.

References


12 Edwards RR, Bingham CO III, Batson J, Haythornthwaite JA. Catastrophizing and pain in


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