Aberrant cerebral blood flow responses during cognition: implications for the understanding of cognitive deficits in fibromyalgia

Abstract

Objective: There is ample evidence for the occurrence of cognitive deficits in fibromyalgia syndrome (FMS). The present study investigated cerebral blood flow responses during arithmetic processing in FMS and their relationship with performance. Furthermore, the influence of clinical factors on performance and blood flow responses were also analyzed. **Method:** 46 FMS patients and 32 matched healthy controls completed a mental arithmetic task while cerebral blood flow velocities in the middle (MCA) and anterior (ACA) cerebral arteries were measured bilaterally using functional transcranial Doppler sonography (fTCD). **Results:** The patients´ performance was reduced in terms of slower cognitive processing. In contrast to patients, healthy controls showed a pronounced early blood flow response (seconds 4-6 after the warning signal) in all assessed arteries. MCA blood flow modulation during this time frame was associated with task performance. This early blood flow response component was strongly reduced in FMS patients in both MCAs. Furthermore, the patients displayed an aberrant pattern of lateralization, with a right hemispheric dominance especially in the ACA. Severity of clinical pain in FMS patients was associated with cognitive performance and cerebral blood flow responses. **Conclusions:** Cognitive impairment in FMS is associated with alterations in cerebral blood flow responses during cognitive processing. These results suggest a potential physiological pathway via which psychosocial and clinical factors can affect cognition.

Key words: fibromyalgia syndrome, cognitive performance, functional transcranial Doppler sonography (fTCD)

Introduction

Fibromyalgia syndrome (FMS) is a highly prevalent chronic pain disorder (Wolfe et al. 1990). Among its most frequently-presenting symptoms is reduced mental performance. Self-reported cognitive deficits include forgetfulness, concentration difficulties, loss of vocabulary and mental slowness (Glass, 2006; Glass, 2008; Glass, Park, Minear, & Crofford, 2005). Patients often state that these deficits significantly affect their everyday life and are therefore among the most serious complaints made about the disease (Glass et al., 2005). These cognitive problems are perceived as problematic particularly in the context of working life; patients frequently feel that their professional competence is compromised (Glass et al., 2005). Clinical and laboratory evidence, including that gathered via standardized neuropsychological assessment, confirms the reality of these deficits. FMS patients show substantial impairments in working, episodic, semantic and implicit memory, selective attention, speed of cognitive processing and executive control (Dick, Verrier, Harper, & Rashiq, 2008; Duschek, Werner, Winkelmann, & Wankner, 2013; Glass, 2006; Glass, 2008; Munguía-Izquierdo, Legaz-Arrese, Moliner-Urdiales, & Reverter-Masía, 2008; Pericot-Nierga et al., 2009; Reyes del Paso, Pulgar, Duschek, & Garrido, 2012; Verdejo-García, López-Torrecillas, Calandre, Delgado-Rodríguez, & Bechara, 2009).

Current evidence regarding the origin of these cognitive deficits suggests that one of the most important factors relates to the interfering, intrusive effect of pain, where significant associations between pain intensity and cognitive impairment have been obtained (Duschek et al., 2013; Glass, 2006; Glass, 2008; Grace, Nielson, Hopkins, & Berg, 1999; Karp et al., 2006; Munguía-Izquierdo et al., 2008; Park, Glass, Minear, & Crofford, 2001; Reyes del Paso et al., 2012; Verdejo-García et al., 2009). Pain is an attention-demanding condition that activates brain areas associated with cognitive processing such as the cingulate and the prefrontal cortex (Apkarian, Bushnell, Treede,

& Zubieta, 2005). It is possible that central nociceptive processing detracts from cognition because it requires enhanced neural resources to be employed in the respective brain areas (Baliki et al., 2006; Dick et al., 2008; Glass, 2008; Park et al., 2001; Munguía-Izquierdo et al., 2008). With regard to other factors such as depression, anxiety and fatigue, the majority of studies find that these play a secondary role in cognitive function in FMS (i.e. Glass, 2006; Glass, 2008; Munguía-Izquierdo et al., 2008; Park et al., 2001; Reyes del Paso et al., 2012; Verdejo-García et al., 2009).

One factor which has previously been related to cognitive performance is the ability to increase cerebral blood flow in response to cognitive demands (Duschek, Schuepbach, & Schandry, 2008a; Duschek, Heiss, Schmidt, Werner, & Schuepbach, 2010). For more than a century it has been known that there is a coupling between neuronal activity and cerebral blood flow. Cognitively induced changes in cerebral perfusion result from the tight coupling which exists between neural activity and brain metabolism (Logothetis, Pauls, Trinath, & Oeltermann, 2001). Mediated by a variety of biochemical factors, such as K+, H+, NO and adenosine, neural activation leads to the dilation of cerebral arterioles and capillaries, followed by an increase in cerebral blood flow (Iadecola, 2004; Paulson, 2002).

Functional transcranial Doppler sonography (fTCD) is used to measure cerebral blood flow and perfusion. This method allows for the continuous noninvasive registration of blood flow velocity changes in the basal cerebral arteries associated with neural activation. Unlike the diameters of the small vessels, those of the basal cerebral arteries, which are insonated by fTCD, remain virtually unchanged under varying conditions of stimulation (Giller, Bowman, Dyer, Mootz, & Krippner, 1993; Kontos, 1989). Therefore, blood flow changes in these arteries do not result from their own vasomotor activity, but rather reflect changing metabolic rates in their perfusion territories. In their pioneering studies with fTCD, Aaslid, Markwalder, & Nornes (1982)

found increases in cerebral blood flow velocities in response to visual stimulation. Subsequent studies found similar results during attentional (Knecht, Deppe, Backer, Ringelstein, & Henningsen, 1997), memory (Cupini et al., 1996), and other cognitive tasks (see Stroobant & Vingerhoets, 2000). The excellent temporal resolution provided by this technique allows for the assessment of the dynamic component of cerebral perfusion. A large number of studies provide evidence that fTCD constitutes an excellent tool for the quantification of the rapid changes in cerebral blood flow which accompany cognitive activity and other psychological processes (for an overview, see Duschek & Schandry, 2003).

Duschek and colleages (Duschek, Hadjamu, & Schandry, 2007; Duschek & Schandry, 2004, 2006; Duschek et al., 2008a; Schuepbach, Boeker, Duschek, & Hell, 2007), have repeatedly found positive associations between the amplitude of the cerebral blood flow response and cognitive performance. These studies clearly suggest that for the correct activation of cerebral areas involved in the resolution of a task it is necessary to increase cerebral blood flow to these areas (Duschek & Schandry, 2003). Deficiencies in task-induced blood flow responses are associated with reduced cognitive performance (Duschek & Schandry, 2004). Until now no study has investigated the evocation of cerebral blood flow responses consequent on the performance of cognitive tasks in FMS. In this context, one relevant question to ask is whether the performance deficits found in FMS are associated with deficiencies in task-induced cerebral blood flow responses.

The present study evaluates cerebral blood flow in response to a serial mental arithmetic task, both in patients with FMS and in healthy controls. Additionally, associations between the amplitude of blood flow responses and cognitive performance are assessed. Cerebral perfusion is measured by fTCD bilaterally in both the middle (MCA) and anterior (ACA) cerebral arteries. A previous study using a paper-

pencil serial arithmetic task consisting of the addition of pairs of one digit numbers showed a reduced number of operations completed in FMS patients but no differences in success / error rate (Reyes del Paso et al., 2012). Based on this finding we hypothesize reduced performance in FMS in terms of lower speed in arithmetic processing. We also expect alterations in task-evoked increases in cerebral blood flow in FMS and that blood flow responses is associated to performance indices. Given that mental arithmetic is mainly associated with activation of the left gyrus angularis (Dehaene, 2000) in the inferior parietal cortex, and the left insular/orbitofrontal cortex (Menon, Rivera, White, Glover, & Reiss, 2000) (perfusion territories of the MCA), we predict that performance during the task will be specifically associated with increases in cerebral blood flow in the left MCA. Additionally, co-morbid emotional disorders, medication use, clinical pain, anxiety, depression, fatigue and sleep problems are measured and their influence on cognitive performance and blood flow responses analyzed. Based in our previous study using a similar task (Reyes del Paso et al., 2012) we do not predict cognitive differences as a function of emotional co-morbidity or medication use, but expect that severity of clinical pain is negatively associated to cognitive performance. Finally, taking into account that pain as an attention-demanding condition that may interfere with performance, negative associations between clinical pain severity and amplitude of the blood flow responses to task are expected.

Method

Participants

Forty-five women with FMS, recruited via the Fibromyalgia Association of Jaén, participated in the study. All patients had been examined by a rheumatologist and met the American College of Rheumatology criteria for FMS (Wolfe et al., 1990). Exclusionary criteria comprised cardiovascular diseases of any kind, metabolic abnormalities, inflammatory causes of pain, neurological disorders, and severe somatic

(e.g., cancer) or psychiatric (e.g. psychotic or bipolar) diseases. The control group included 32 healthy women recruited from women's associations. They were matched to the patients according 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 as were the patients. Table 1 displays demographic and clinical data of both groups. Most FMS patients were under combined pharmacological therapy: Nineteen patients (out of 45, 42.2%) were taking both antidepressants and anxiolytics, and 10 patients (22.2%) were taking a combination of antidepressants, anxiolytics, analgesics and opiates. Seven patients (15.5%) were using only non-opiate analgesics and 5 patients (11.1%) were without any medication. Ten participants of the control group (out of 31, 31.2%) used anxiolytics, mainly for sleep difficulties, and 5 participants (15.6%) used analgesic for relieve sporadic pain (e.g. headache).

* Table 1*

Mental arithmetic task

A small black cross was displayed on the screen (white background), acting as the fixation point. The disappearance of this cross served as a warning stimulus (S1) for the appearance, 5 s afterward, of two one-digit numbers (S2). Participants were instructed to add these two numbers together and then give their response by typing the last digit of the resulting sum with the computer keyboard. Performance was assessed in terms of response time (RT) and rate of correct responses. Participants were instructed to work as quickly and as accurately as possible. The task consisted of 15 trials with an inter-trial interval of 30 s. The task was preceded by three practice trials and was presented on a computer screen using the software ePrime (Psychology Software Tools, Inc., Sharpsburg, PA, USA).

Recording and analysis of Cerebral Blood Flow

Blood flow velocities were assessed by fTCD employing a digital Multi-Dop L2 DWI (Elektronische System eGmbh). Recordings were conducted bilaterally in both MCA and ACA arteries. Recordings were obtained through the temporal bone windows, using two 2-MHz transducer probes. Following vessel identification, the probes were fixed to the head via a head harness. The MCA were 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 a rate of 100 samples per second. The mean flow velocity index was applied as a measure of cerebral blood flow; this index is the least vulnerable to artifacts and has the highest correlation with blood volume flowing through an artery per unit of time (Duschek & Schandry, 2003). This parameter was obtained from the digital 100 Hz mean flow velocity output of the Multi-Dop L2 DWI.

In an initial data reduction step, the 100 Hz mean flow velocity recording was reduced by averaging to 4 Hz (one sample every 250 ms). Mean flow velocity during the 5 s prior to the warning signal (S1) served as the baseline; the 25 s after S1 were taken to be the task period (100 post-S1 values). Time-locked to the S1, responses were expressed as relative (percent) changes in flow velocity during task (dFV) with respect to baseline (FVbas) according to the formula dFV = (FV[t] - FVbas) *100/FVbas, where FV(t) is the flow velocity over the time-course of task.

Procedure

The study was conducted across two sessions which took place on different days. In the first session a clinical psychologist recorded the patients' clinical history, medication use, and socio-demographic data, and also confirmed that there were no violations of the exclusionary criteria. To assess possible mental disorders, the Structured Clinical

Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (First, Spitzer, Gibbon, Williams, 1999) was used. Clinical pain was evaluated trough the McGill Pain Questionnaire (Melzack, 1975; Lázaro et al., 1994), a widely used instrument that provides reliable measures of the sensory, affective and evaluative characteristics of pain. Four parameters were obtained from this instrument: (1) the number of 'pain points' marked on a picture of the human body; (2) the present pain index as an indicator of current pain intensity; (3) the number of words selected from a list of 66 features to describe pain; and (4) the total pain index, given by the sum of the sensory, affective and evaluative pain descriptors. Depression was evaluated by means of the Beck Depression Inventory (Sanz et al., 2003). Current and habitual anxiety were assessed using the State-Trait Anxiety Inventory (Spielberger et al., 1986). Fatigue was quantified via a Spanish adaptation of the Fatigue Severity Scale (Krupp et al., 1989; Bulbena et al., 2000). Sleep quality was assessed by means of the Oviedo Quality of Sleep Questionnaire (Bobes et al., 2000) from which the insomnia and hypersomnia indices were taken.

Some studies suggested poor cognitive effort leading to reduced validity of neuropsychological testing in a subset of FMS patients (e. g. Johnson-Greene et al., 2013). In order to control for this possibility, the present participants completed the 15-item Rey Memory Test (as indicator of possible simulated memory problems) and an N-back -1 and -2 task (as an indicator of cognitive effort-engagement through working memory abilities). The 15-item Rey Memory Test (Rey, 1964) assesses immediate visual memory. Its use for simulation detection is based on the premise that malingerers drastically overestimate the difficulties experienced by those with mild memory impairment and thus exaggerate their deficits to the extent that they score less than individuals with genuine memory impairment (Lezak, 1995). Many studies have reported that both probable malingerers (Greiffenstein, Baker, & Gola, 1996) and individuals simulating memory impairment (Arnett, Hammeke, & Schwartz, 1995)

perform significantly worse on the test than those with actual brain damage, whilst control subjects score higher than all of them (Bernard & Fowler, 1990). A score below 6 is commonly used as simulation criteria in this task. None of the present participants met this criterion. N-back tasks are used as a measure of working memory. Subjects are presented with a continuous stream of items (letters) and are instructed to press a key when they detect a repetition at a specified delay (we used delays of 1 and 2).

In the second session the actual experiment was carried out, by a second experimenter, in a sound-attenuated room set at a constant temperature of 22°C. Because it is not possible to reliably measure both MCA and ACA simultaneously, the entire procedure was repeated twice, once for each pair of arteries. The artery starting order (MCA vs. ACA) was counterbalanced across participants. The distance between the participant and the task´s monitor was fixed at 0.75 m; participants were also asked to avoid making movements and to fixate upon the cross during the tasks. Participants had been previously 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 which affect the cardiovascular system, beginning 24 hours before the study. Two FMS patients were removed due to outliers, RT longer than 9 s.

Individual differences in temporal bone thickness affect the possibility of insonation of the cerebral arteries. Furthermore, the insonation of the ACA is more difficult than that of the MCA (which is longer and has more thickness and flow; Duschek & Schandry, 2003). Given this fact, the number of participants with available data is different for each artery. Analyses were performed on the total number of participants in which data from each artery was available. The sample sizes were as follows: left MCA: 41 patients, 32 controls; right MCA: 40 patients, 32 controls; left ACA: 32 patients, 26 controls; and right ACA: 34 patients, 25 controls (complete data on the four arteries are available for 29 patients and 22 controls). The results of the comparison between FMS

patients and controls did not differ when the total data set or only participants with data for all four arteries were used. Given that the use of all participants with available data increased statistical power (especially in correlational analysis), we performed the analyses with all participants with data available for each artery as described above. All participants gave their informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Statistical analysis

Visual inspection of the pattern of blood flow velocity modulations revealed three response components: (1) an early increase component associated with the end of the warning period and presentation of the numbers, (2) a late component about 5 s after presentation of the numbers, and (3) a progressive final blood flow decrease (in some cases below baseline level). Peak amplitudes of the three components were computed in the time windows 5-6 s, 10-11 s and 21-22 s, respectively. Statistical analysis of the response pattern was based on a four (one for each artery and hemisphere) 2x(4) repeated measures ANOVAs, with one between-subject factor (group: FMS vs. controls) and one repeated-measure factor (the three peak amplitude values joint with the baseline starting point, which in relative percent variables is made equal to 0). Results are presented in terms of the F values and multivariate Wilks' lambda statistics.

Group differences in cognitive performance, clinical parameters and amplitudes of the three blood flow components were analyzed via Student's *t*-test for independent samples. In the FMS group, potential differences related to medication use and co-morbid emotional disorders were analyzed using Student's *t*-tests comparing patients using and not using each medication (separately for antidepressants, anxiolytics, analgesics and opiates) and for patients suffering or not suffering from depression and anxiety disorders. Relationships between cognitive performance, blood flow responses

and clinical variables were quantified by means of Pearson correlations. The correlations were computed in the whole sample and in each group separately. Correlation coefficients involving clinical parameters were only computed separately for each group to avoid spurious results due to the expected large group differences. In order to optimize the reliability of the analysis concerning cognitive performance, parameters of the arithmetic task were aggregated for the two completions of the test.

Results

1. Performance measures and their relationships to clinical variables.

FMS patients took longer to resolve the arithmetic addition problems, where this difference in performance was present on both of the occasions upon which the task was performed (*ps*<.01, see Table 2). No group differences were observed in the percentage of correct responses. In FMS patients no performance differences were observed as a function of antidepressant, anxiolytic, analgesic or opiate use (all *t*s< .5, all *p*s > .5). The same holds true for effects of co-morbid depression (all ts<1.50, all ps>.125) and anxiety disorders (all ts<1.7, all *ps*>.1). In the FMS sample present pain intensity (*r*=.342, *p*=.024) and state anxiety (*r*=.343, *p*=.023) were associated with longer RT and hypersomnia level was associated with a lower rate of correct responses (*r*= -.344, *p*=.023). In the control group trait anxiety was associated with longer RT (*r*= .517, *p*=.004). No overall group difference was found in performance on the N-back task, only a difference in the -1 false alarm was observed (see Table 2).

2. Blood flow responses to cognitive task

The response patterns are characterized by two increases in blood flow velocity: an early component associated with the end of the warning period and presentation of the numbers, and a late component about 5 s after presentation of the numbers. The late

component is of much greater amplitude than is the early one. From the peak of the late component a progressive decrease and recovery of blood flow velocity is observable (see figures 1-4).

Figure 1

Figure 2

Figure 3

Figure 4

For all four arteries the factor Response Pattern (analyzed through component amplitudes) was significant (all *Fs* > 39, all *ps* <.0001, all η^2s >.630). The same holds true for the interaction Group x Response Pattern (all *Fs* > 3.05, all *ps*<.04, all η^2s >.115). For the left MCA the factor Group was significant ($F(1, 72)= 5.53$, $p=.021$, $\eta^{2=}.071$). Post-hoc comparisons showed group differences for the first increase component and the decrease component, in both cases the FMS group displayed lower blood flow velocity (see Table 3). For the right MCA the factor Group was also significant ($F(1, 71)= 7.22$, $p=.009$, $\eta^{2=}.092$). As in the left MCA, the groups differed in the first increase component and in the decrease component, where the FMS group displayed lower blood flow velocity. For the left ACA differences were restricted to the decrease component, where the FMS group showed lower blood flow velocity. Finally, for the right ACA, group comparisons revealed differences for the late increase component, where the FMS group showed higher blood flow velocity (see Table 3).

The response in the MCA for the late component is lateralized to the left hemisphere for the control group ($t=2.41$, $p=.022$) but not for the FMS group ($t=1.52$, $p=.137$). Lateralization in the ACA to the left hemisphere remained marginally significant in the control group ($t=1.85$, $p=.079$) and were absent in the FMS group ($t=-.88$, $p=.385$). In the early component no lateralization was seen in the control group, but in the FMS the response was lateralized to the right in the ACA ($t=-2.13$, $p=.043$).

3. Associations between blood flow responses and performance

In the whole sample RT, was associated with the amplitude of the first component in the MCA, both in the left (r=-.320, p=.006) and right (r= -.271, p=.021) hemispheres and with the amplitude of decrease component in the right MCA (r= -.293, p=.012). In the whole sample, RT was also associated with the amplitude of the decrease component in the right ACA (r=-.288 p=.029), and marginally with the amplitude of the first component in the left ACA (r=-.251, p=.057). In the FMS group, RT was associated with the amplitude of the first component in the right MCA (r= -.339, p=.032) and the second component in the left MCA (r= -.354, p=.023). In the control group, the amplitude of the second component in the right ACA was associated with longer RT (r=.444, p=.034) and a lower rate of correct responses (r= -.450, p=.031).

4. Associations between blood flow responses and clinical parameters

In the FMS group, current pain intensity, the total score of the McGill Pain Questionnaire and hypersomnia level were negatively associated with blood flow velocities in the left MCA (see Table 4). Furthermore, current pain intensity was associated with the amplitude of the second component in the right MCA (r= -.328, p=.039) and the decrease component in the ACA of right (r= -.404, p=.018) and left (r= -.368, p=.038) hemispheres. Also in the FMS group, state anxiety was associated with lower blood flow during the recuperation component in the right MCA (r= -.340, p=.032; r= -.308, p=.053 for trait anxiety) and insomnia was associated with a reduced amplitude of the first component in the right ACA (r= -.358, p=.038). In the control group, state anxiety was negatively associated with the amplitude of the first component in the MCA of the left (r= -.404, p=.030) and the right (r= -.403, p=.030)

hemispheres. Finally, in the control group, fatigue was related to lower amplitude of the first component in the left MCA (r= -.386, p=.039).

Discussion

Despite the simplicity of the task employed, FMS patients exhibited reduced cognitive performance in terms of longer time required to complete mental additions. This result points to a reduction in the speed of cognitive processing, or mental slowness, under arithmetic processing. These results corroborate previous evidence regarding cognitive deficiencies in FMS and specifically confirm a slowness in cognitive processing, as reported previously (Cherry et al., 2012; Reyes del Paso et al., 2012; Veldhuijzen, Sondaal, & Oosterman, 2012). As expected and corroborating previous evidence (e.g. Reyes del Paso et al., 2012), presence of co-morbid emotional disorders or medication use does not affect cognitive performance in the FMS group.

Clinical pain severity, as expected, was associated with cognitive slowness, supporting previous evidence on the interfering effect of pain on cognition (Grace et al., 1999; Park et al., 2001; Dick et al., 2008; Glass, 2008, 2009, Munguía-Izquierdo et al., 2008; Reyes del Paso et al., 2012; Verdejo-García et al., 2009). Anxiety was associated with longer RT both in FMS patients and healthy controls, showing an interference of emotional state with performance. Similarly, Munguía-Izquierdo et al. (2008) found a negative association between anxiety and cognitive performance in FMS patients and Reyes del Paso et al. (2012) obtained this same relation in a healthy group. Finally, hypersomnia level was associated with a lower rate of correct responses in the FMS group pointing towards a negative effect of the sleep problems which are common in the disorder.

No significant overall effect for performance on the n-back task was found (only in the parameter -1 false alarm) suggesting no group difference in cognitive effort. Together with the finding that none of the participants met the simulation criteria of the 15-item Rey Memory, this finding supports the validity the mental arithmetic task as a measure of cognitive performance.

To discern a possible mechanism which may mediate the group difference in cognitive performance, we analyzed task-elicited blood flow responses. In order to activate cerebral regions involved in the resolution of a task it is necessary to increase cerebral blood flow to these areas (Duschek & Schandry, 2003). In this way, one factor relevant in obtaining successful cognitive performance is the ability to increase cerebral blood flow in response to cognitive demands (Duschek & Schandry, 2006). fTCD has been applied to the investigation of cerebral hemodynamic modulation during arithmetical processing. Increased blood flow velocities in the anterior and medial cerebral arteries of both hemispheres have been documented during the execution of arithmetical additions, consisting of the obtained response in a biphasic blood flow increase (Duschek, Werner, Kapan, & Reyes del Paso, 2008b; Szirmai et al., 2005).

The performance of the mental arithmetic task was associated with a certain pattern of response in cerebral blood flow, consisting of two distinct periods of increase: an early increase associated with the processing of the warning signal and anticipation of the numbers to be added, and a late increase occurring approximately 5-6 s subsequent to the presentation of the numbers. This later increase component is characterized by a higher amplitude than is the early one. The early increase, which onsets before actual presentation of the numbers, can be accounted for in terms of anticipatory attention, whereas the late increase is associated with arithmetical processes (Bäcker et al., 1999).

It has been hypothesized that the connection between neural activity and cerebral blood flow modulation is closer during the initial period of the hemodynamic response than it is during its later components (Sheth, Nemoto, Guiou, Walker, & Toga, 2005) and further that the early response may be particularly useful for the investigation of brain-behavior relationships (Duschek et al., 2008a). In support of this suggestion, in the present study the amplitude of the early component (especially that of the MCA) was most strongly associated with cognitive performance in terms of negative correlations with RT. The association between blood flow responses and RT is in accordance with the studies of Duschek et al. (Duschek & Schandry, 2004, 2006; Duschek et al., 2007; Duschek et al., 2008a; Schuepbach et al., 2007), who repeatedly found positive associations between the amplitude of the early cerebral blood flow response and cognitive performance.

Taking into account the arithmetical nature of our task, and in accordance with previous evidence showing specific activation of the left gyrus angularis and the left insular/orbitofrontal cortexes during arithmetic calculations (Dehaene, 2000; Menon et al., 2000), we expected that the left MCA would show the greater association with cognitive performance. In line with our hypothesis, the amplitude of the early component in the left MCA was the period most closely associated with RT. This suggests a relevant role of anticipatory attention in modulating task performance. In the FMS group, the amplitude of the second increase component in the left MCA was also positively associated with performance. In contrast, the amplitude of the second increase component of the ACA, whose perfusion territories are not essential for completion of the task, was not associated with cognitive performance in the whole sample. Specifically, the amplitude of the right ACA late component in the control group was associated with an increased RT and lower rate of correct responses.

With regard to group differences in the blood flow response, the early component in both MCAs -which exhibits a stronger relationship with performance- was strongly reduced in the FMS group. This may indicate that the cerebral areas involved in the correct resolution of this kind of task are not fast-activated. Given the reduced activation of these areas during the critical time window in the FMS group, lower performance should be expected and was indeed observed. The amplitude of the late increase component for both MCAs did not show significant group differences. With regard to the ACAs, the most relevant finding concerns the right ACA. Specific to this artery, the late increase component shows greater amplitude in the FMS than in the control group. Activation of the cerebral areas irrigated by the right ACA are irrelevant for the resolution of the arithmetic task and, as shown in the control group, its activation is negatively associated with performance in healthy individuals. The cerebral territories of the ACA (such as the ventral-medial frontal cortex), especially with regard to the right hemisphere, are not required for the performance of the arithmetic task. Activation of these areas in the FMS group could interfere with task performance by reducing available resources in the appropriate areas irrigated by the MCA.

The left asymmetry expected in an arithmetic task (see Duschek & Schandry, 2006; Duschek et al., 2008b) was observed in the control group with reference to the late component (that related to arithmetic processing), especially for the MCA. However, this asymmetry is not observed in the FMS group. These results point to an aberrant pattern of lateralization in FMS under arithmetic processing, suggesting that patients with FMS activate the right hemisphere, specifically its anterior middle and ventral structures, even when performing tasks that do not require these cerebral centers. This may act as an interference mechanism, reducing resources needed in other areas in order to activate the appropriate cerebral areas for resolution of the task.

Another difference between the response patterns of the two groups related to the recuperation phase; that is, the decrements in blood flow after the late component. For all four arteries, this decrease component is greater for the FMS group, such that blood flow reaches levels lower than baseline. This might be explained as an exaggerated counter-response to the late increase component, which may indicate the existence of aberrant homeostatic regulatory mechanisms in FMS which maintain the constancy of cerebral blood flow. Interestingly, RT was associated with blood flow during this recuperation phase in the right arteries (i.e. greater response decrements were associated with longer RT), suggesting that homeostatic regulatory mechanisms might relate in some ways to cognitive performance. Regarding this, it may be a limitation of the study that the observed lower blood flow velocity during the final recuperation period in the FMS group may have persisted to some degree during the following baseline period, which may have affected the results. This is a relevant point for future studies using fTCD techniques, suggesting the need to use longer inter-stimulus intervals.

In the FMS sample, clinical pain severity was associated with blood flow velocity responses in the left MCA, i.e. stronger pain related to lower amplitudes of both the early (anticipatory attention) and late (arithmetic processing) increase components. Furthermore, pain severity was negatively associated with blood flow during the decrease component suggesting a possible role of pain in modulating regulatory homeostatic mechanisms. Similarly, greater hypersomnia levels were associated with lower blood flow during the second increase and recuperation components in the left MCA, while insomnia was inversely related to the amplitude of the first increase component in the right ACA. In the control, group both anxiety and fatigue were negatively associated with the amplitude of the first component in the MCA.

These results indicate that the disrupting effect of pain and other clinical variables on cognitive performance in FMS might partly be meditated by aberrant cerebral blood flow regulation during task performance. Specifically, our results suggest that pain intensity and insomnia interfered the with blood flow response related to anticipatory attention (i.e. first increase component) and pain intensity and hypersomnia interfered with the blood flow response during arithmetic processing (i.e. second left MCA increase component).

We have previously found that parameters of systemic hemodynamics (i.e. blood pressure and heart rate) can to some extent modulate cerebral blood flow supply (Duschek et al., 2008b; Duschek et al., 2010), and further that FMS patients show aberrant autonomic cardiovascular regulation, including in their responses to mental and physical stress (Reyes del Paso et al., 2010, 2011). Thus we cannot rule out that some of the group differences in the blood flow response might be explained to some degree by these related autonomic cardiovascular deficits.

In conclusion the results of the present study show that selective cognitive deficit in FMS could be associated with deficiencies in task-evoked increases in cerebral blood flow. Specifically, the great reduction of an early component of increase in blood flow that is associated with the processing of the warning signal and anticipatory attention to the presentation of task material in both MCAs. Furthermore, results point to aberrances in the blood flow response in FMS: activation of cerebral areas (especially of the right hemisphere) irrelevant for the appropriate resolution of the task may cause an interference effect in the activation of the crucial cerebral structures needed for completion of the task. Moreover, some characteristic clinical features in FMS (like pain and sleep problems) might modulate these abnormalities in cerebral blood flow. Altogether, our study suggests a potential physiological pathway by which psychosocial

factors can affect cognition, that is cerebral blood flow modulation during cognitive processing.

Future research should be focused on the resolution of some of the questions which arose in this initial study of the application of fTCD to the understanding of cognitive deficits in FMS. These questions include the replication and explanation for the great reduction of the early component in the MCAs in the FMS; the source or origin of the greater activation of the right ACA in FMS; the observation and replication of the aberrant asymmetry we found for the arithmetic task in FMS, via study of the lateralization of other psychological functions in the disorder (such as language, emotions, etc.); and the study and explanation of the exaggerated decrement in blood flow after the late component observed in FMS patients, via replication of this effect with other kind of tasks and using of longer inter-stimulus intervals.

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Table 1. Demographic and clinical characteristics (mean ± SD) and medications use (number of participants and percentage in brackets) in the FMS and control groups. Results of group comparisons were also reported (Student's *t*-test or χ^2).

	Fibromyalgia	Control group	*t or* χ^2	*p*
Age	49.48±8.23	47.03±9.26	1.504	.224
Body Mass Index	26.53±3.61	25.35±4.44	1.196	.200
Years of education	12.04±3.16	12.87±3.50	1.679	.278
Depression (%)	22(48.8)	4(12.9)	10.56	.001
Anxiety disorders (%)	23(51.1)	4(12.9)	11.70	.001
Antidepressant use (%)	23 (51.1)	1 (3.1)	20.07	<.0001
Anxiolytic use (%)	26 (57.7)	10 (31.2)	5.29	.021
Analgesic use (%)	37 (82.2)	5 (15.6)	33.45	<.0001
Opiate use (%)	17 (37.7)	0 (0)	15.51	<.0001
State anxiety (STAI)	31.82±10.18	21.34±9.71	4.39	<.0001
Trait anxiety (STAI)	35.37±8.92	19.93±10.71	6.171	<.0001
Depression (BDI)	21.17±12.12	7.32±7.75	5.61	<.0001
Fatigue (FSS)	49.37±11.96	21.00±8.83	10.97	<.0001
Insomnia (OQSQ)	30.51±3.72	18.09±7.77	7.42	<.0001
Hypersomnia (OQSQ)	8.18±3.74	4.67±1.92	4.78	<.0001
Nº pain points	30.62±16.06	4.54±4.82	8.75	<.0001
Pain intensity index	3.62±.80	1.09±1.32	10.82	<.0001
Nº pain words	24.51±10.60	8.83±5.06	7.54	<.0001
Total McGill	53.42±31.98	18.06±11.93	5.87	<.0001

STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; FSS, Fatigue Severity Scale; OQSQ, Oviedo Quality of Sleep Questionnaire.

Table 2. Cognitive performance data (mean ± SD). For the mental arithmetic task, response time (RT) and the rate of correct responses (% successes) are displayed. Regarding the n-back task, the numbers of correct responses (successes) and false alarms are displayed for the -1 and -2 version of the task. Results of group comparisons are also denoted (Student's *t*-test). Note: The mental arithmetic task was performed twice, once for the recording of the anterior cerebral artery (ACA) and once for the recording of the middle cerebral artery (MCA).

	Fibromyalgia	Control group	*t*	*p*
RT (in s) (ACA)	3.64±1.28	2.70±1.25	2.88	.005
RT (in s) (MCA)	3.84±1.48	2.93±1.00	3.19	.002
% successes (ACA)	96.96±5.79	95.80±6.4	.738	.463
% successes (MCA)	95.21±5.09	96.25±6.76	.702	.485
Nback_1 success	26.66±4.55	28.04±2.86	-1.40	.165
Nback_1 false alarms	2.09±2.71	.81±1.11	2.32	.023
Nback_2 success	21.35±5.22	21.22±8.09	.085	.932
Nback_2 false alarms	8.20±5.37	8.00±6.60	.151	.991

Table 3. Peak amplitudes (mean±SD) of the three identified blood flow velocity components (1 = early increase, 2 = late increase, 3 = recovery) as a function of artery (A=anterior cerebral artery, M=medial cerebral artery) and group (FMS patients vs. control group), and results of the group comparison (*t* and *p*).

	FMS	Control group	*t*	*p*
M left (1)	1.14 ± 2.80	3.05 ± 3.25	-2.65	.010
M left (2)	5.55 ± 4.39	6.30 ± 4.88	-.68	.495
M left (3)	-2.31 ± 4.03	-.07 ± 3.62	-2.51	.014
M right (1)	1.38 ± 2.95	3.28 ± 3.65	-2.46	.016
M right (2)	4.60 ± 4.31	5.10± 4.98	-.63	.645
M right (3)	-2.58± 4.37	.58 ± 2.93	-3.52	.001
A left (1)	1.79 ± 3.84	3.18 ± 3.49	-1.45	.153
A left (2)	4.50 ± 3.60	5.08 ± 4.75	-.53	.596
A left (3)	-2.40 ± 4.37	-.07 ± 3.76	-2.17	.034
A right (1)	2.18 ± 4.01	2.78 ± 2.59	-.64	.522
A right (2)	4.93 ± 4.35	2.86 ± 2.83	2.20	.032
A right (3)	-2.20 ± 4.14	-.71 ± 2.65	-1.68	.097

Table 4. Correlations between amplitudes of the three left MCA components and scores in the current pain intensity index and total score of from the McGill Pain Questionnaire), and hypersomnia levels from the Oviedo Quality of Sleep Questionnaire.

Components	Pain Intensity Index (McGill Pain Questionnaire)	Total (McGill Pain Questionnaire)	Hypersomnia
1er	-.384*	-.320*	-207
2nd	-.355*	-.396**	-.382*
3re	-.188	-.317*	-.366*

*p<.05, **p<.01

Figure legends:

Figure 1. Blood flow velocity response for the left MCA (continuous line represent the fibromyalgia group and doted points the control group).

Figure 2. Blood flow velocity response for the right MCA (continuous line represent the fibromyalgia group and doted points the control group).

Figure 3. Blood flow velocity response for the left ACA (continuous line represent the fibromyalgia group and doted points the control group).

Figure 4. Blood flow velocity response for the right ACA (continuous line represent the fibromyalgia group and doted points the control group).

Figure 1

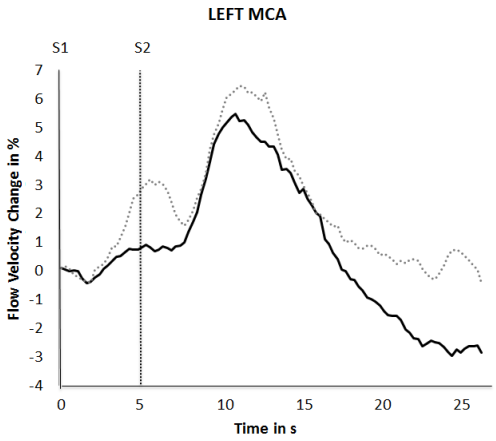

Figure 2

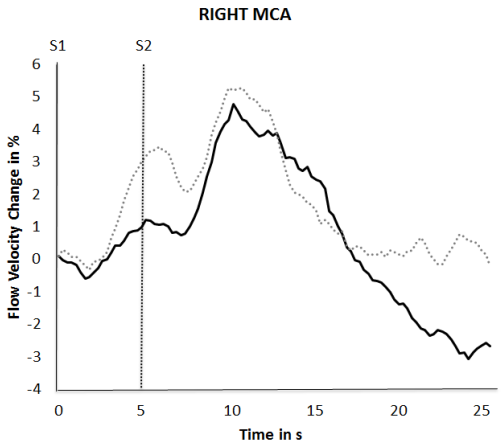

Figure 3

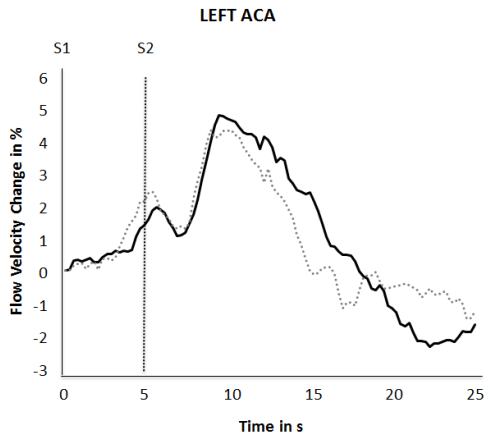

Figure 4

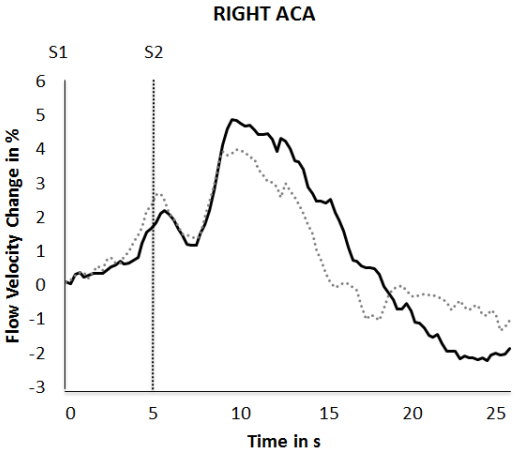

Figure 1

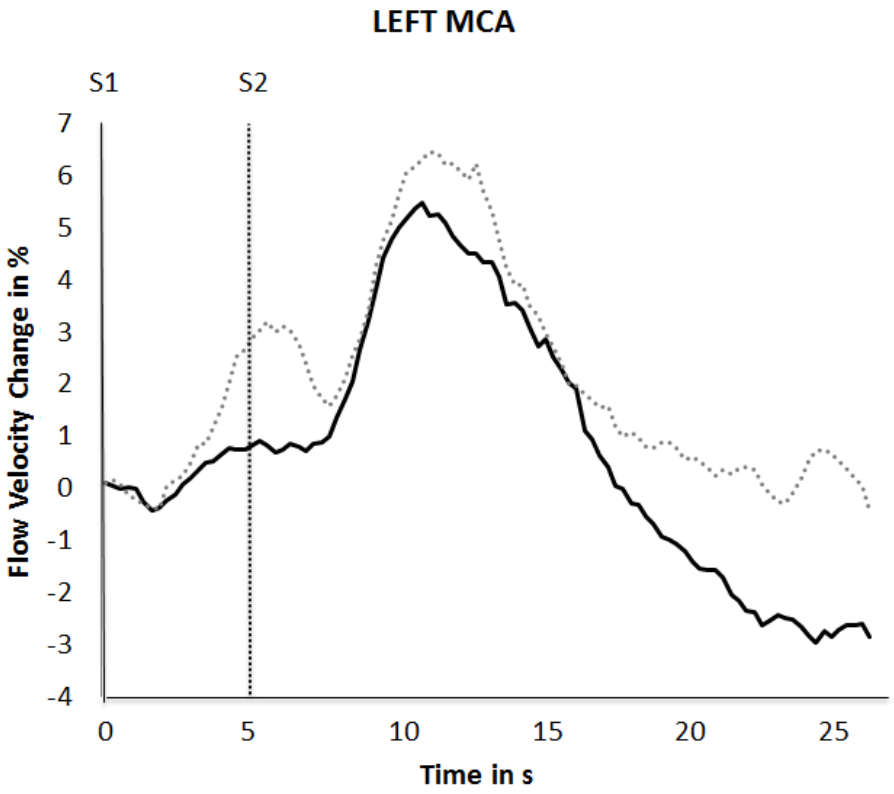

Figure 2

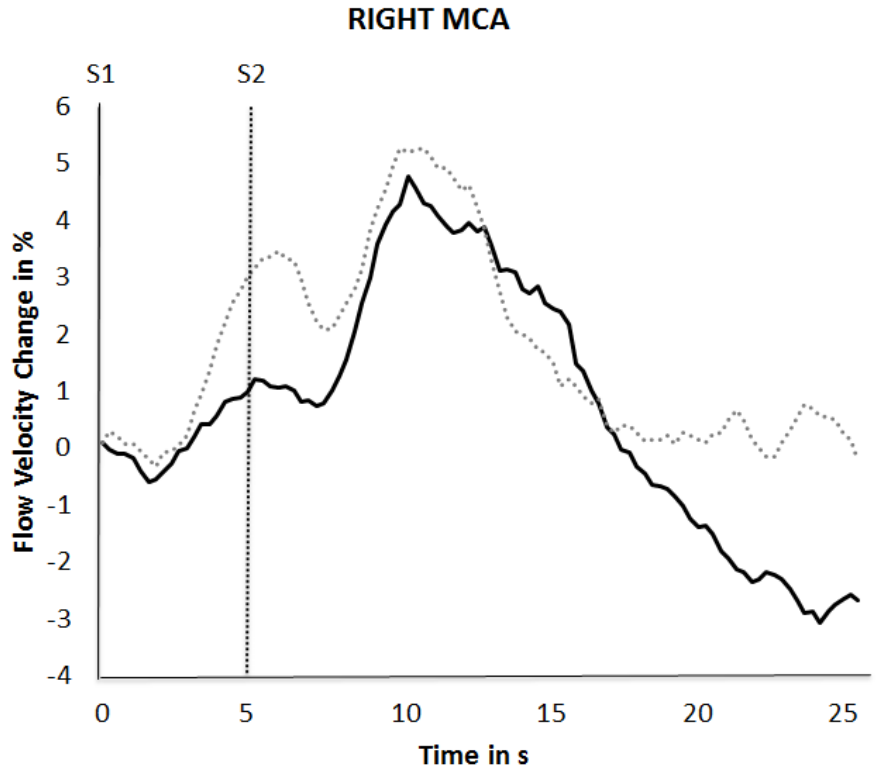

Figure 3

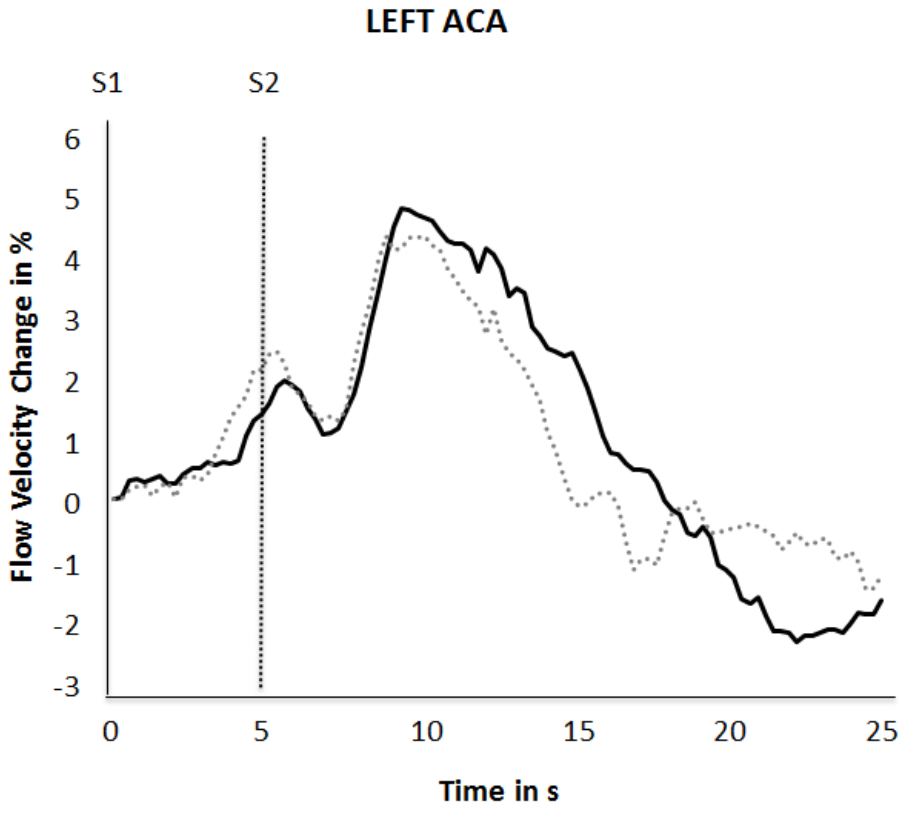

Figure 4