Functional transcranial Doppler ultrasonography in the study of central sensitization to pain in fibromyalgia

Fibromyalgia syndrome (FMS) is a chronic disease characterized by persistent and widespread musculoskeletal pain in addition to symptoms like depression, fatigue, sleep disturbance and impaired mental performance. 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. Brain mapping studies supports this hypothesis by providing evidence concerning the spatial distribution of CBF responses during painful stimulation in FMS. Specifically, an exaggerated activity of the central nervous pain neuromatrix is observed. In contrast, evidence concerning the temporal dynamics of these responses remains sparse. The investigation of CBF dynamics can provide complementary information to that revealed by classic brain imaging paradigms. In this regards, several studies have proven the validity of transcranial Doppler sonography (fTCD) for the analysis of CBF responses during psychological processes, including the experience of acute pain. fTCD allows for continuous, noninvasive measurement of CBF velocities in the basal cerebral arteries and provides excellent time resolution. Changes in the flow velocity of these arteries reflect changes in blood demand in their perfusion territories as a result of the close coupling between neural and vascular activity.

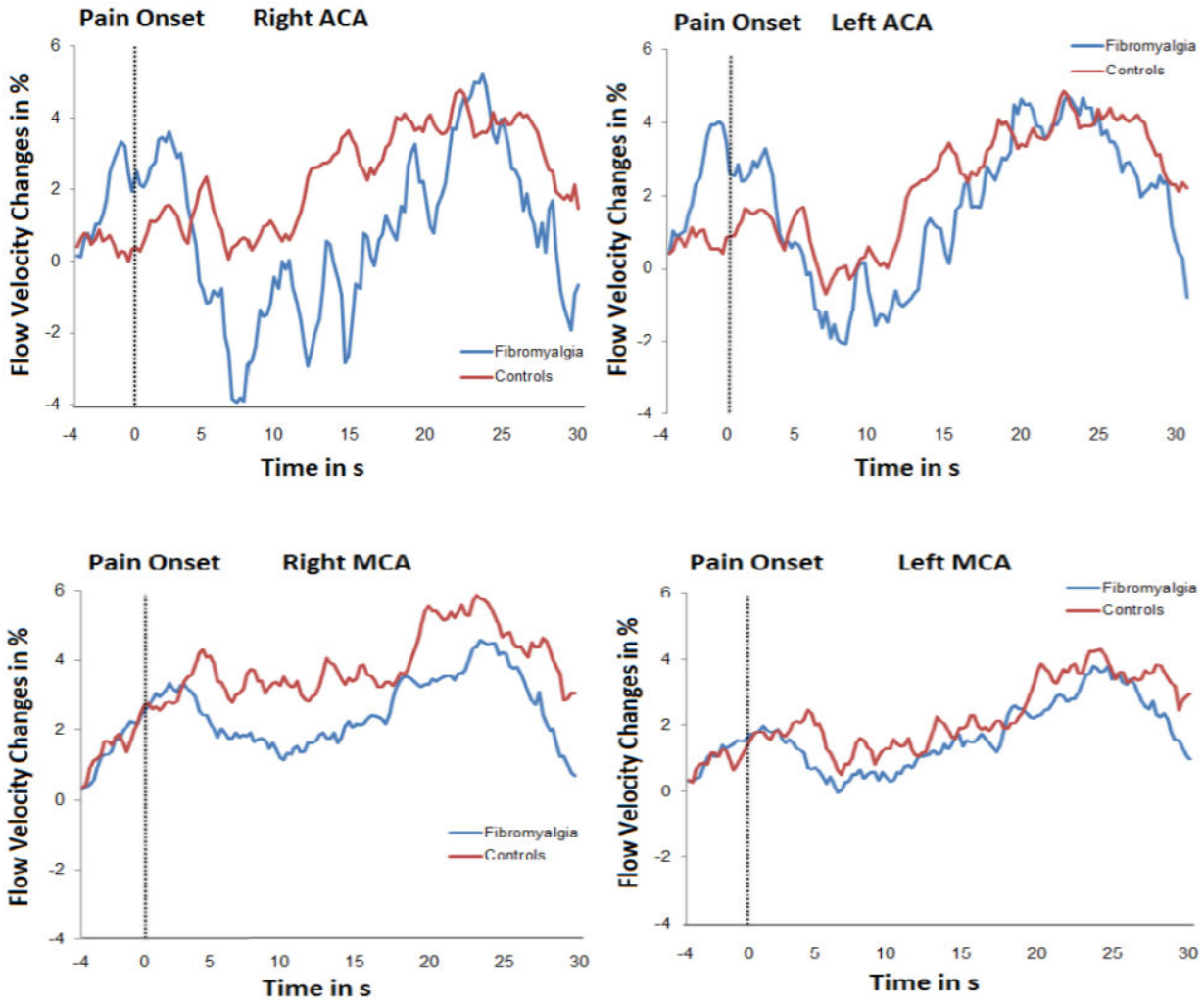

Fig. 1.

Our recent study published in *Pain Medicine* in 2016 analyzed the temporal dynamics of cerebral blood flow (CBF) modulations during painful pressure stimulation in FMS patients and healthy individuals, using functional transcranial Doppler sonography. 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 (average of 3.52 kg for FMS patients and 5.12 kg for healthy controls).

Underlining the notion that time dynamics are an important aspect of hemodynamic adjustment during central nervous nociceptive processing, this study revealed a complex pattern of CBF modulations in FMS patients and healthy individuals. This pattern was generally characterized by

four main components: an anticipatory increase before pain 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, supporting the occurrence of a pain sensitization process in FMS and accord with neuropsychological theories postulating the involvement of anterior-medial structures, such as the anterior cingulate and ventromedial prefrontal cortices, in anticipatory processing. In line with the view of specific hyperactivity of the medial pain matrix, which represents emotional and cognitive pain components, patients exhibited a greater early CBF increase under the fixed pressure condition, predominantly in the right ACA. Furthermore, a stronger CBF decrease after the early component was observed in patients during the equal pain condition, in the ACA and MCA (Fig. 1 and 2), suggesting the occurrence of a defense reflex in FMS. As a protective mechanism that limits stimulus processing and prevents overstimulation, defense reflex became also apparent in a CBF reduction during the entire MCA response. Finally, significant associations were found between clinical pain severity and CBF responses in the MCA.

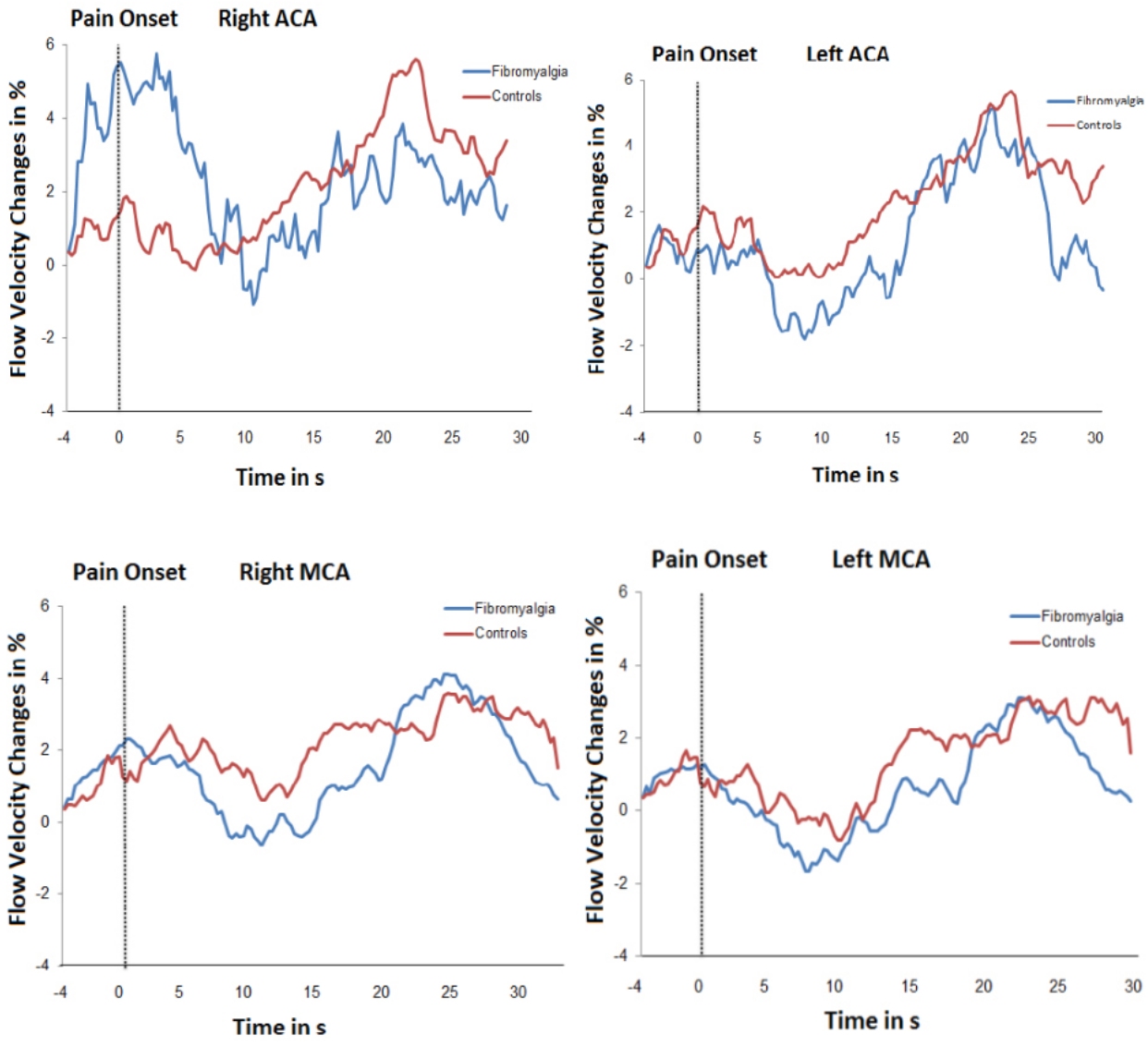

Fig. 2.

In summation, 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 (defense reflex). The anticipatory CBF response in patients may relate to various cognitive, emotional and behavioral mechanisms involved in pain chronification.

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Publication

Patterns of Cerebral Blood Flow Modulation During Painful Stimulation in Fibromyalgia: A Transcranial Doppler Sonography Study.
Montoro CI, Duschek S, de Guevara CM, Reyes Del Paso GA
Pain Med. 2016 May 31