# Primary somesthetic cortex involvement in fibromyalgia: review of neuroimage studies

*Envolvimento do córtex somestésico primário na fibromialgia: revisão de estudos de neuroimagem*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** The mechanisms underlying nociplastic pain, such as fibromyalgia (FM), are not fully understood, however, it is believed that altered sensory processing and pain modulation play prominent roles in the maintenance of nociplastic pain. The hypothesis is that changes in the primary somesthetic cortex (S1) contribute to the generalized pain character of FM. The objective of this study was to evaluate the involvement of the primary somesthetic cortex in humans with fibromyalgia, as well as to investigate possible associations between S1 changes and clinical signs and symptoms of FM.

**CONTENTS**: For this integrative review, the following databases were used: Pubmed and Web of Science, including observational studies carried out in humans with FM. In total, 541 studies were identified and four were included. The majority of studies are case-control studies, published between 2016 and 2022. In total, data from 161 individuals were included in this review. It was identified that there are morphological changes, hyperactivation and increased functional connectivity between S1 and periaqueductal gray matter and between S1 and anterior cingulate cortex.

**CONCLUSION**: Patients with FM present morphological changes and hyperactivation in S1, as well as increased functional connectivity between S1 and periaqueductal gray matter and S1 and limbic system. Furthermore, different bilateral somatotropic subregions (legs, chest, fingers, hands, face and back) showed reduced functional connectivity in patients with FM. These regions are often presented as "tender points" in FM.

**Keywords**: Brain, General symptoms, Musculoskeletal pain.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: Os mecanismos subjacentes à dor nociplástica, como a fibromialgia (FM), não são totalmente compreendidos, contudo acredita-se que o processamento sensorial e a modulação da dor alterados desempenham papéis proeminentes para a manutenção da dor nociplástica. Com a hipótese de que alterações no córtex somestésico primário (S1) contribuam para o caráter de dor generalizada da FM, o objetivo deste estudo foi avaliar o envolvimento do córtex somestésico primário em humanos com FM, bem como investigar possíveis associações entre alterações de S1 com sinais e sintomas clínicos da FM.

**CONTEÚDO**: Para esta revisão integrativa, foram utilizadas as seguintes bases de dados: Pubmed e *Web of Science,* incluindo estudos observacionais realizados em humanos com FM. No total, 541 estudos foram identificados e quatro foram incluídos. A maioria dos estudos são do tipo caso-controle, publicados entre 2016 e 2022. Ao todo, dados de 161 indivíduos foram incluídos. Foi identificado que há alterações morfológicas, hiperativação e aumento da conectividade funcional entre S1 e substância cinzenta periaquedutal e entre S1 e córtex cingulado anterior.

**CONCLUSÃO**: Pacientes com FM apresentam alterações morfológicas e hiperativação em S1, bem como aumento da conectividade funcional entre S1 e substância cinzenta periaquedutal e S1 e sistema límbico. Ademais, diferentes sub-regiões somatotrópicas bilaterais (pernas, tórax, dedos, mãos, face e costas) apresentaram redução da conectividade funcional em pacientes com FM. Essas regiões são frequentemente apresentadas como "tender points" na FM.

**Descritores**: Dor musculoesquelética, Encéfalo, Sintomas gerais.

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**HIGHLIGHTS**

- Fibromyalgia is associated with morphological and functional brain alterations, such as changes in activity in the primary somesthetic cortex;
- Given that the somesthetic cortex has the function of somatosensory identification of the body, such as identifying the location and intensity of pain, the study proposes the hypothesis that alterations in S1 may contribute to the perception of generalized pain, allodynia and hyperalgesia in patients with fibromyalgia;
- Understanding encephalic alterations in fibromyalgia patients could help us understand signs and symptoms in order to adapt and develop interventions and treatments for the syndrome.

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## INTRODUCTION

Fibromyalgia (FM) is a complex syndrome of chronic nociplastic pain and hyperalgesia, drastically reducing the patient's quality of life and increasing absence from their activities, generating economic losses for the members and their families, as well as for the nation[1,2]. In Brazil, around 2% of the population has FM (e.g. approximately 5,000,000 people), and the most commonly reported complaints are chronic and nociplastic pain[3-5]. Chronic pain is considered a public health problem and is associated with brain neuroplasticity. In view of this, chronic musculoskeletal pain conditions, such as FM, have attracted the interest of scientists in order to solve or alleviate this global problem.

Pain is defined as "an unpleasant sensory and emotional experience associated with, or similar to, actual or potential tissue injury", and is a dynamic and multidimensional experience. The multidimensions of pain processing are defined by three independent but closely related components: 1) sensory-discriminative (somesthetic cortex), 2) affective-emotional and 3) cognitive-motivational[6,7]. However, there is no specific cortex for the perception and processing of pain. Instead, there is a complex network of cerebral cortical areas involved in processing the perception of pain experience. This complex network is the target of scientists aiming to understand the brain mechanisms for pain and also its association/correlation with patients' clinical signs and symptoms[8].

With the evolution of functional magnetic resonance imaging (fMRI) studies and studies in experimental models, it has been identified that various musculoskeletal pain conditions are associated with morphological and functional brain alterations, influencing the behavior of some brain structures and regions[9]. In addition, some of these studies report the association of such alterations with signs and symptoms observed in chronic musculoskeletal conditions[10-13]. The mechanisms underlying nociplastic pain, such as FM, are not fully understood, but the belief is that increased pain in the central nervous system, altered sensory processing and pain modulation play prominent roles in maintaining nociplastic pain[1].

The somesthetic cortices (primary - S1 and secondary - S2) are cortical brain regions involved in the sensory-discriminative component of pain, providing recognition of the location and intensity of pain. This raises the hypothesis that alterations in the primary somesthetic cortex (S1) contribute to the "indiscriminate localization of pain". In other words, pain without a specific sensory location, such as generalized pain, a common condition in patients with FM.

Given this context, the aim of this study was to evaluate the involvement of the primary somesthetic cortex in humans with fibromyalgia, as well as to investigate possible associations between S1 alterations and clinical signs and symptoms of FM. The results of this study will provide information on the behavior of the S1 cortex in FM patients and its possible contributions to widespread pain.

## CONTENTS

An integrative review of observational neuroimaging studies was carried out[14,15]. Integrative reviews are research methods that provide the synthesis of knowledge and the incorporation of the applicability of significant study results into practice.

**Research question**

The PECO's[14] recommended items for formulating the question of review studies with observational studies were followed. The following research question was posed: in humans with FM (P, E), how does the primary somesthetic cortex (S1) (O) behave when compared to individuals without FM (control subjects)?

The searches were carried out by two reviewers and conducted on two meta-search engines: Pubmed and Web of Science, both of which have a wide range of studies on the topic[15]. The reference lists of each included study were also searched manually, looking for studies not found in the online database as a search strategy. The search strategies were carried out between March and April 2023.

**Selection of studies**

The search results were imported into the Rayyan systematic review website (https://www.rayyan.ai/) to exclude duplicate articles and identify studies that did not meet the eligibility criteria. After reading the full text, two independent reviewers made the final selection[16,17].

All articles were examined according to the following inclusion criteria: conducted on humans, observational studies (case-control, cross-sectional or cohort studies), English language and studies that reported alterations in functional or morphological S1 connectivity in FM patients without confounding variables (covariates) for brain alterations (e.g. severe psychiatric illness or neurological disease). An article was included in this review only when it met all the inclusion criteria.

**Data collection process**

The main data regarding functional and/or morphological brain alterations related to FM were extracted from the included studies. The data was obtained by the first author and a second reviewer verified the extracted data. In addition, other important information from each study was extracted: authors and year of publication, type of study, sample size and main results.

## RESULTS

In total, 541 studies were identified. Of these, four were included (Figure 1)[9-12]. Most of the studies were case-control studies published between 2016 and 2022. In total, data from 161 individuals were included in this review (Table 1).

**Table 1.** Studies included

| Authors | Type of study | Sample | Results |
|---|---|---|---|
| Kim et al.[10] | Case-control | 35 patients and 14 controls | Altered S1 functional connectivity in different bilateral S1 somatotropic subregions (legs, back, chest, hand, finger, face) with fibromyalgia (FM), showing reduced connectivity at rest between several different S1 regions, patients also showed greater reduction of functional connectivity in S1 during sustained pain stimuli and outside the seed cortical presentation. |
| Lim et al.[11] | Case-control | 19 patients and 21 controls | Increased activity in S1 was observed in FM patients when compared to perception- and intensity-controlled activation in CH subjects. Intracortical inhibition in S1 is impaired in FM patients. Rostral anterior cingulate cortex activity is increased in FM patients after painful pressure stimulation. |
| Soldatelli et al.[12] | Cross-sectional study | 33 patients | Resting-state functional connectivity (rs-FC) between the left somatosensory cortex (S1) and the periaqueductal gray matter is significantly related to dysfunction of the descending pain modulator system. S1, rs-FC, and periaqueductal gray matter may be able to distinguish patients with descending pain modulator system failure according to groups of responders and non-responders to the conditioned pain modulation test. The S1, rs-FC and periaqueductal gray matter were negatively associated with a lower quality of life, poor sleep quality, and more intense pain in women with FM, and were positively associated with central sensitivity. Increased connectivity may indicate "pain sensitization" rather than "pain intensity". The S1, rs-FC and periaqueductal gray matter may be a marker to distinguish individuals with FM with greater dysfunction of the descending pain modulator system. |
| Lim et al.[13] | Case-control | 19 patients and 20 controls | S1 amplitudes were increased in patients compared to controls. |

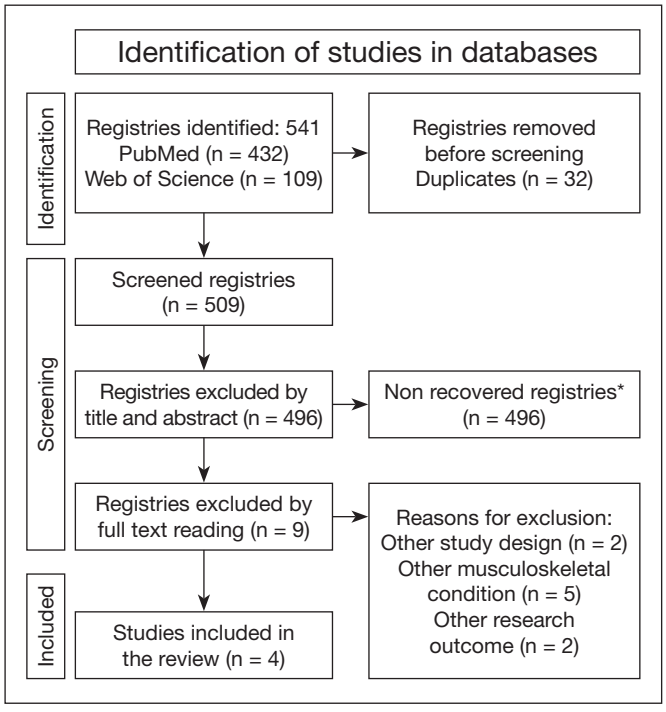


**Figure 1**. Flowchart of the study.

*Non-recovered articles are articles that have not been reconsidered after deletion.

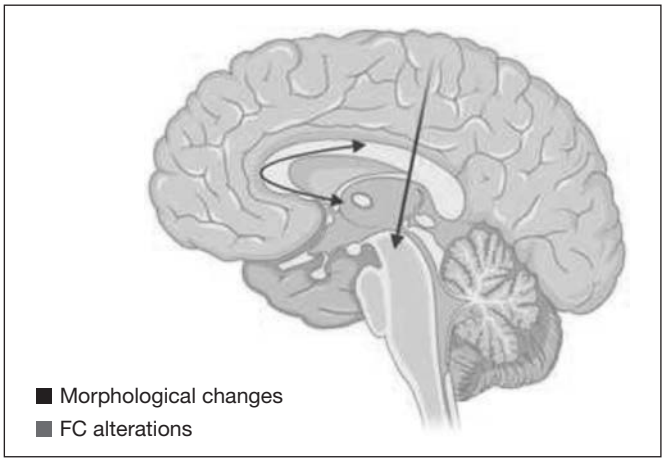


**Figure 2**. Morphological and functional changes in the primary somesthetic cortex in people with fibromyalgia.

FC = functional connectivity

## DISCUSSION

It was identified that FM is associated with morphological and functional brain alterations in the primary somesthetic cortex. Increased resting-state functional connectivity between the left somatosensory cortex and the periaqueductal gray matter is significantly related to dysfunction of the descending pain modulator system. Given that the somatosensory cortex has the function of somatosensory identification for the whole body, as well as identifying the location and intensity of pain, the hypothesis is that these S1 alterations may contribute to the perception of generalized pain in FM patients.

The authors Lim et al. observed increased activity in the somatosensory cortex in FM patients when compared to controls. In other words, the S1 cortex is more activated in FM, perceiving more somatosensory information than in control individuals (without FM). This may play an important role in allodynia (perception of pain in ineffective stimuli) and hyperalgesia (exacerbated perception of pain in stimuli that should be perceived as mild pain) in these patients.

According to the study[9], there was an alteration in the functional connectivity of S1 in different bilateral somatotropic sub-regions

(legs, chest, fingers, hands, face and back) in patients with FM, showing that there is a reduction in functional connectivity in the resting state in various areas of the somatosensory cortex. Interestingly, these regions are often presented as regions of pain, where the "tender points", common in FM and often used to diagnose FM, are located. It is therefore possible that increased activity in these somatotropic subregions is associated with allodynia and hyperalgesia in the tender points. In this same study, it was observed that patients also showed a greater reduction in connectivity during sustained pain stimuli. In addition, intracortical inhibition in S1 is also compromised in patients, which could potentiate pain in the described tender points.

**Strengths and limitations**

Understanding the possible alterations in the functional and structural connectivity of the somatosensory cortex in FM patients could lead the scientific community to understand the emergence of painful signs, such as generalized pain, allodynia, and hyperalgesia, as well as the emotional involvement of the individual as part of the patient's symptomatology, given that some altered cortical areas in FM patients may be linked to emotional processing. This study is of great importance, since FM is a chronic musculoskeletal disease prevalent not only in Brazil, but all over the world, generating suffering for the patient and continuous expenses for family members and the state. Therefore, comprehending the encephalic changes that occur in the brain of patients with FM allows for a better understanding of the signs and symptoms, enhancing future studies in the development of interventions that can reduce the impact of this disease on the individual and the nation. One of the limiting factors of this study was not assessing the risk of bias of the studies included, making it impossible to determine the quality of the data analyzed. In addition, only four studies were included, which may limit the findings. Nevertheless, it should be noted that this study identified the involvement of the S1 in FM and possible implications for understanding the signs and symptoms of the disease.

## CONCLUSION

Patients with FM have morphological alterations of S1 and functional connectivity between S1 and the periaqueductal gray matter and S1 and the limbic system, which may suggest an involvement between sensory information and the descending system modulating pain and emotion, highlighting that the emotional factor may play a fundamental role in modulating pain and sensory information perceived by the primary somesthetic cortex. In addition, different bilateral somatotropic sub-regions (legs, chest, fingers, hands, face and back) showed reduced functional connectivity in FM patients. These regions are often presented as "tender points" in FM. Finally, it should be noted that S1 alterations contribute to generalized perception and pain intensity.

## AUTHORS' CONTRIBUTIONS

**Maria Mônica da Silva Menezes**
Data Collection, Research, Writing - Preparation of the Original, Writing - Review and Editing
**Flavio José Neto Campos**
Data Collection, Conceptualization, Research, Writing - Preparation of the Original
**Marília Silveira Maia**
Data Collection, Conceptualization, Research
**Felipe Ribeiro Fernandes da Silva**
Data Collection, Conceptualization, Research, Writing - Preparation of the original
**Jeffeson Hildo Medeiros de Queiroz**
Statistical Analysis, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the Original, Supervision, Visualization

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