# Abnormal resting state functional connectivity of the periaqueductal grey in patients with fibromyalgia

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## ABSTRACT

**Objective.** *Emerging evidence associates chronic pain syndrome, such as fibromyalgia, with endogenous pain modulatory system dysfunction, leading to an impaired descending pain inhibition. In this study, using resting-state functional magnetic resonance imaging (fMRI), we aimed at seeking possible functional connectivity changes of the periaqueductal gray (PAG), a brainstem area that belongs to the endogenous pain modulatory system, in patients with fibromyalgia.*

**Methods.** *In 20 patients with fibromyalgia and 15 healthy subjects, we investigated PAG functional connectivity using resting-state fMRI. We also analysed the correlation between clinical variables, such as pain severity, disease duration, and depressive personality traits with PAG functional connectivity.*

**Results.** *Compared with control subjects, we identified that patients with fibromyalgia had an increased PAG connectivity with insula, anterior cingulate cortex, and anterior prefrontal cortex. The functional connectivity between PAG and the rostral ventral medulla, however, was not concordantly increased. PAG functional connectivity correlated with pain severity, disease duration, and the depressive personality trait rating.*

**Conclusion.** *Our fMRI study showing abnormal resting state functional connectivity of the PAG suggests that patients with fibromyalgia have an endogenous pain modulatory system dysfunction, possibly causing an impaired descending pain inhibition. This abnormal PAG functioning might underlay the chronic pain these patients suffer from.*

## Introduction

The pathophysiology of fibromyalgia (FM) is still unclear (1, 2). Many studies showing that as well as causing widespread pain and fatigue FM causes sleep disturbances, mood disorders, and neurocognitive impairment, led some to postulate a central nervous system dysfunction including pain matrix hyperexcitability and endogenous pain modulatory system abnormalities, leading to an impaired descending pain inhibition (3-9).

In a recent neurophysiological study, we have showed that patients with FM have signs of pain matrices hyperexcitability (9), probably contributing to the different symptoms patients with this condition experience. However, in this study we did not provide any information on how FM pathophysiology involves descending modulatory system structures, such as the periaqueductal gray (PAG). The PAG receives projections from the anterior cingulate cortex and modulates pain perception through brain stem structures, such as the Rostral Ventral Medulla (RVM), which directly sends inhibitory projections to the nociceptive dorsal horn neurons of the spinal cord (10). Given that PAG modulates pain perception, an abnormal PAG activity might underlie pain in patients with FM (11, 12). Having more information on the descending modulatory system function might be relevant to the pharmacological treatment of pain in this disease, lending a rational support to the use of antidepressants.

Continuing our research activity into the mechanisms underlying FM (9) and the endogenous pain modulatory system (11) in this clinical and neuroimaging study we sought possible PAG abnormalities in patients with FM. To do so, using functional magnetic resonance imaging (fMRI), we have investigated the resting state functional connectivity of PAG in 20 patients with FM and in 15 healthy controls.

## Methods

*Patients*

We prospectively enrolled 20 consecutive patients (19 F, 1 M; aged 28-67 years) referred to the Fibromyalgia Clinic at the Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, and 15 healthy, matched subjects (F 13, 2 M; aged 26-65 years). Inclusion criteria for patients were: patients aged >18 years; a medically confirmed diagnosis of FM according both 1990 and 2010 American College of Rheumatology criteria (13-15) and willingness to participate in the experimental procedures. Exclusion criteria included all autoimmune and rheumatic diseases, other and additional pain sources (including pain due to osteoarthritis) and neurological and psychiatric diseases, including major depression. None of the participants was taking pain medication potentially affecting the PAG connectivity, such as antidepressants, opioids or antiepileptics. Pregnancy was also an exclusion criterion for both patients and controls. The local Institutional Review Board approved the study and all patients and healthy volunteers gave informed consent.

All patients underwent clinical examination at the Rheumatology Unit. The Manual Tender Point Survey was used to rate the severity of pain elicited by palpating the 18 tender points defined by the American College of Rheumatology (16). We also collected the Zung Self-Rating Depression (ZSDS) and Anxiety Scales (ZSAS) (17, 18). We used a visual analogue scale (VAS) for assessing pain severity, at the time of examination.

After the rheumatologic examination, all the patients underwent MRI acquisition at the Department of Neurology and Psychiatry. They were asked to avoid occasional (rescue) analgesic drugs 72 hours prior to fMRI.

*MRI acquisition and statistical analysis*

All subjects underwent anatomical and functional scanning on a 3 Tesla Siemens-Verio scanner in a single session equipped with a 12 channel head-coil. rs-fMRI data of fibromyalgia patients were compared to those of 15 aged matched healthy controls. During the resting-state, subjects were instructed to keep their eyes closed and to remain motionless and to not think of anything in particular. To minimise motion artefacts, subjects lay supine with pillows under the head, foam wedges at the sides and a retaining strap. For each subject images were obtained using a interleaved double-echoTurbo Spin Echo sequence proton density and T2-weighted images (repetition time: 3320 ms, echo time: 10/103 ms, matrix: 384 × 384, field of view: 220 mm, slice thickness: 4 mm, gap: 1.2 mm, 50 axial slices) and 3D T1-weighted MPRAGE (repetition time: 2300 ms, echo time: 2.98 ms, inversion time: 900 ms, flip angle: 9°, field of view: 256 mm, 208 slices in the sagittal plane, 1 mm isometric voxel). rs-fMRI study was performed with single-shot EPI images (repetition time: 3000 ms, echo time: 30 ms, flip angle: 90°, field of view: 240 mm, 46 axial slices, thickness: 3 mm, 140 volumes).

A seed analysis approach was performed to identify those voxels showing functional signal time-courses correlated with the PAG. Seeds were manually selected in standard space based on the anatomy; the right and left PAG were selected as regions of interest (peak MNI coordinates: left PAG= -2; -28; -6; right PAG= 4; -28; -6, with 3 mm radius).

Functional data were processed using FSL as described previously (19), including motion correction, spatial smoothing with 5mm full width half maximal Gaussian kernel, and a temporal high-pass filter. MELODIC Independent Component Analysis (ICA) was performed in order to identify and remove noisy components due to scanner-related and physiological artefacts from the 4D fMRI data. Nonlinear registration using FMRIB's Nonlinear Image Registration Tool (FNIRT) was applied between the subject's structural and the standard space (the Montreal Neurological Institute 2mm brain) (20). Average time courses were extracted from seeds using FSL's feat query function. The pre-processed time series were then fitted with a linear model consisting of a regressor representing the extracted time courses. The spatially normalised effect size and standard error volumes served as input to a mixed effects group analysis in FSL FEAT. The modeled group effect size and standard error were then divided to produce a volume whose voxels were t scores, subsequently transformed to Z scores. Within and between groups comparisons of correlation effect size were performed using one sample t-test in each group and unpaired t-test in patients versus controls. Images and were thresholded using clusters determined by Z>3 (within group) and Z>2 (between group) and a corrected cluster significance threshold of $p<0.05$, including at least 20 contiguous voxels. We did not detect laterality differences between the two seed used.

## Results

In both healthy subjects and patients, PAG showed positive functional connectivity with brain structures related to the endogenous pain modulatory system and the pain matrices, such as prefrontal cortex, insula, anterior cingulate cortex (ACC) and RVM (Fig. 1; Table I, II). Compared to the healthy subjects, patients with FM had a PAG increased connectivity with the ACC, amygdala and insula but not with RVM (Fig. 2; Table III).

Clinical-MRI correlation showed that the disease duration correlated with the connectivity between PAG and insula and bilateral temporal poles (Z> 2.3, corrected clusters $p<0.05$). The severity of pain elicited by pressing the tender points correlated with the connectivity between PAG and inferior frontal gyrus, precuneus, insula and opercular cortex (Z> 2.3, corrected clusters $p<0.05$). More specifically, the longer the duration and the higher the pain scores, the higher the PAG functional connectivity.

Depression as assessed with the ZSDS correlated with the connectivity between PAG and opercular cortex, superior frontal gyrus and supramarginal gyrus (Z> 2.3, corrected clusters $p<0.05$). More specifically the higher the depression rating scores, the lower the PAG functional connectivity.

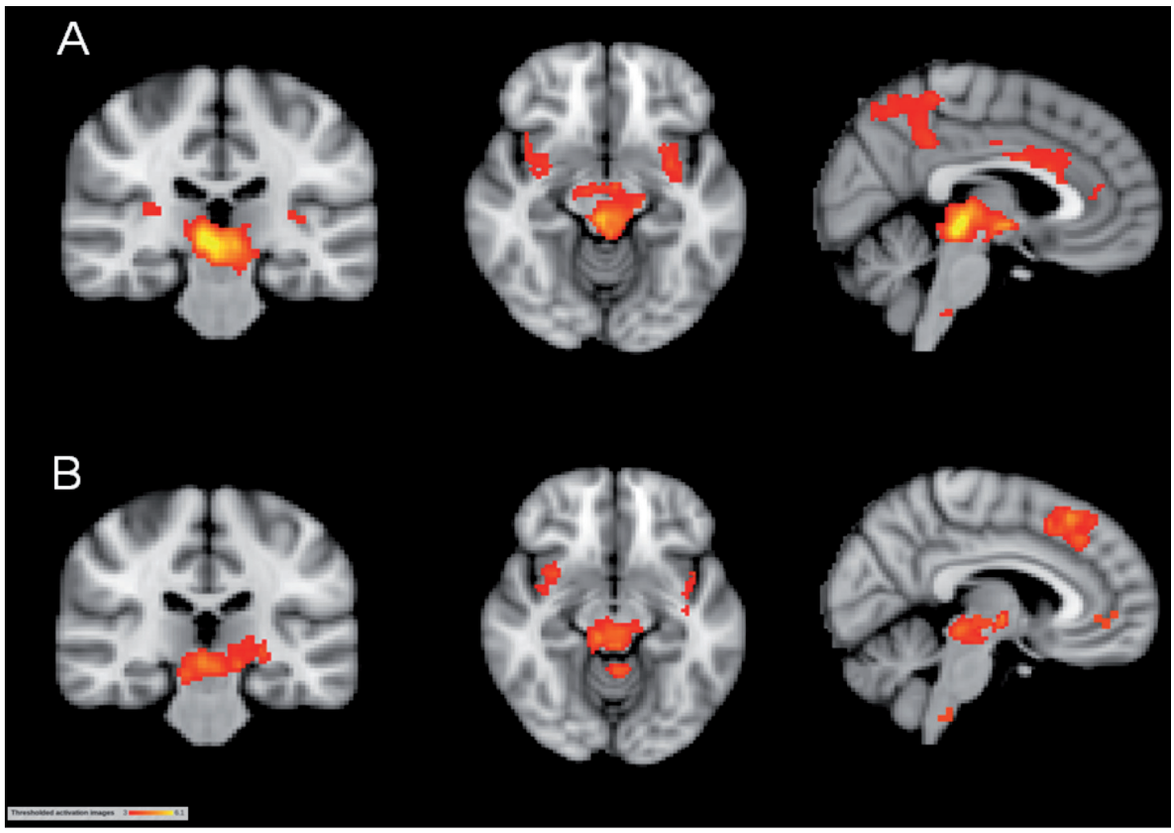


**Fig. 1.** Statistical maps of positive functional resting state connectivity with the PAG in (A) 20 fibromyalgia patients and in (B) 15 age and gender matched healthy controls. Statistical threshold corresponded to Z>3 and a correct cluster significance of p<0.05.

**Table I.** Functional connectivity of PAG during resting state in 15 control subjects demonstrating positive correlations between brain areas and PAG.

| | MNI coordinates | | | |
|---|---|---|---|---|
| | x | y | z | Z max |
| PAG and surrounding areas (midbrain, hypotalamus, striatum, globus palludum, thalamus) | 4 | -28 | -6 | 5.2 |
| Paracingulate BA 8 | 4 | 32 | 40 | 5 |
| R - Superior frontal gyrus BA 8 | 4 | 28 | 50 | 4.8 |
| L - Cerebellum | -10 | -70 | -28 | 4.8 |
| R - Insula | 36 | 20 | -4 | 4.7 |
| R - Cerebellum | 20 | -70 | -38 | 4 |
| L - Insula | -40 | 0 | -10 | 3.8 |
| ACC | 6 | 36 | 8 | 3.8 |
| RVM | 2 | -38 | -52 | 3.1 |

## Discussion

Our clinical and neuroimaging study in patients with FM showed an abnormal PAG resting state functional connectivity: while the PAG connectivity with ACC is enhanced, that with RVM is not concordantly increased. This unbalanced PAG functional connectivity might entail an impaired descending pain inhibition, possibly underlying pain in patients with FM.

To investigate mechanisms underlying FM, a challenging task, we concentrated on PAG, being a converging brain area for pain modulation and playing a key role in the endogenous pain modulatory system (21). Several observations suggest that the descending pain modulatory system dysfunction contributes to the development of chronic pain conditions such as headache and low back pain (10, 22). To seek information on PAG function in patients with FM we have used resting-state fMRI. This technique measures fluctuations in the blood oxygenation level in the brain, thought to be representative of neuronal activity. Functional connectivity measures the degree to which two brain regions have synchronous fluctuations in activity over time; regions with similar fluctuations are referred to as highly functionally connected. Hence, the resting state fMRI showing the PAG functional connectivity provides reliable information on the endogenous pain modulatory system and the brain areas functionally connected with the PAG.

We found that patients with FM have an increased PAG functional connectivity with several pain-related brain areas, such as the anterior cingulate cortex, insula, and amygdala. We hypothesise that the increased functional connectivity between PAG and these areas, including the ACC, presumably reflects the chronic pain these patients were suffering from. This hypothesis

**Table II.** Functional connectivity of PAG during resting state in 20 fibromyalgia patients demonstrating positive correlations between brain areas and PAG.

| | MNI coordinates | | | |
|---|---|---|---|---|
| | x | y | z | Z max |
| PAG and surrounding areas (midbrain, hypotalamus, striatum, globus palludum, thalamus) | -2 | -28 | -6 | 5.4 |
| Precuneous | -2 | 52 | 52 | 4.5 |
| L - Amygdala | -28 | 0 | -20 | 4.2 |
| PCC | 2 | -42 | 38 | 4.1 |
| R - Superior parietal lobule BA7 | 32 | -44 | 42 | 4 |
| ACC | 2 | 20 | 20 | 4 |
| R- Cerebellum | 30 | -52 | -39 | 4 |
| R - Frontal pole BA 10 | 36 | 46 | 24 | 4 |
| L - Insula | -38 | 6 | -2 | 3.9 |
| R - Insula | 40 | 0 | -8 | 3.9 |
| L - Amygdala | -20 | -2 | -20 | 3.9 |
| L -Central opercolar cortex | -62 | -20 | 10 | 3.9 |
| L - Cerebellum | -12 | -66 | -28 | 3.8 |
| L - Frontal pole BA 10 | -38 | 40 | 26 | 3.8 |
| L -Superior parietal lobule BA7 | -30 | -48 | 48 | 3.6 |
| RVM | 4 | -34 | -50 | 3.6 |

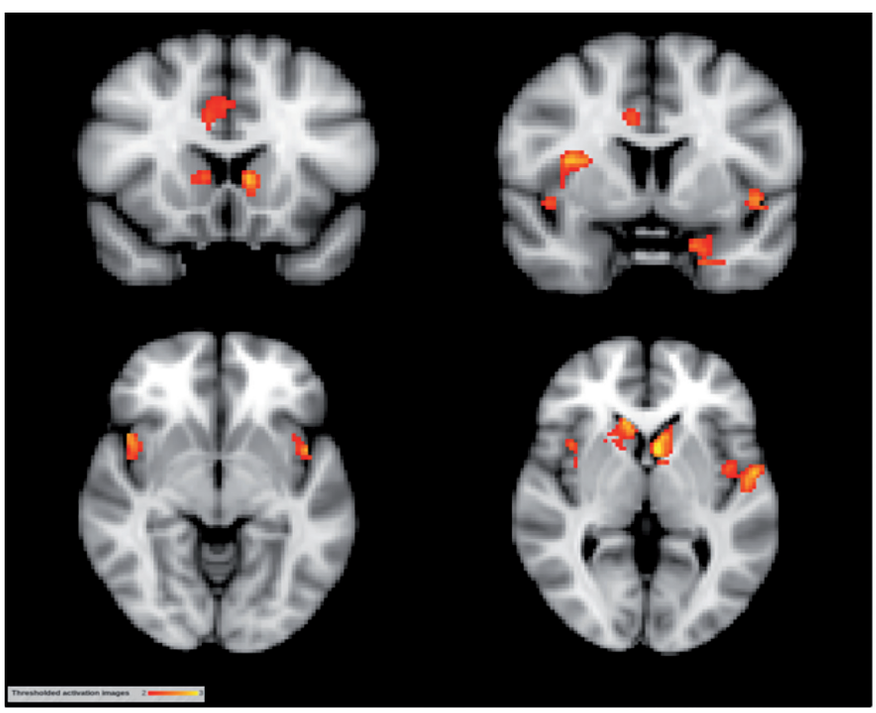

**Fig. 2.** Statistical maps of brain regions of increased functional resting state connectivity with the PAG in 20 fibromyalgia patients compared to 15 age and gender matched healthy controls. Statistical threshold corresponded to Z>2 and a correct cluster significance of $p<0.05$.

is in line with human studies showing that the PAG activity increases during pain (23), and this activation correlates with the severity of pain (11). Our findings on an increased PAG functional connectivity clash with two previous fMRI resting state studies (8, 24) that showed an overall reduction of resting state functional connectivity, and more specifically a hypo-connectivity between PAG and insula and amygdala. The contrasting results probably reflect the different sample sizes and methodological approaches. One study included only nine subjects and both investigated the functional resting state connectivity of multiple brain regions. Conversely, in our study we included twenty patients and selected *a priori* the PAG as the region of interest in the functional resting state analysis. Most important our patients were not taking any pain medication such as antidepressant, drug potentially affecting the PAG connectivity.

Unexpectedly, the increased functional connectivity between PAG and ACC was not paralleled by a similar increase of functional connectivity between PAG and RVM. In normal conditions the increased functional connectivity between PAG and ACC is followed by a coherent increased connectivity with RVM, according to a top-down modulation mechanism (25). This unbalanced PAG functional connectivity might imply a descending modulatory system deficit. This deficit prevents the activation of inhibitory projections to the nociceptive dorsal horn neurons of the spinal cord.

When we analysed the clinical-fMRI correlations we found that the resting state functional connectivity between PAG and the pain-related brain areas, such as the insula, correlated with the duration of disease and the pain severity. This finding agrees with previous observations (26) and supports the hypothesis that FM-related pain is directly associated with altered brain function, more specifically the more severe the disease in terms of duration and pain severity, the more the resting state abnormalities. We also found that the functional connectivity between PAG and opercular cortex, superior frontal gyrus and supramarginal gyrus inversely correlated with depression, as assessed with the ZSDS. This finding is in line with a previous study (24) and might indicate that in patients with FM the depressive trait directly affects pain related brain areas. This hypothesis supports the common knowledge that pain and psychiatric disturbances are closely related (24-26).

Our study has some limitations. Admittedly, the abnormalities of PAG functional connectivity might merely represent the consequence, rather than the cause, of the chronic nociceptive input. We consider this interpretation unlikely, however, given that we found a peculiar abnormality such as an unbalanced PAG functional connectivity, namely a relative reduction of functional connectivity between the PAG and the RVM. Hence, we hypothesise that the PAG functional connectivity we describe in

**Table III.** Brain areas with increased connectivity with the PAG during resting state in 20 fibromyalgia patients compared to 15 control subjects.

| | MNI coordinates | | | |
|---|---|---|---|---|
| | x | y | z | Z max |
| Caudate | -4 | 12 | 2 | 2.6 |
| R - Insula | 44 | 10 | -4 | 2.5 |
| L - Insula | -42 | 4 | -4 | 2.5 |
| R - Frontal pole BA 10 | 36 | 48 | 28 | 2.4 |
| L - Amygdala | -24 | 0 | -26 | 2.3 |
| L - Central opercolar cortex | -54 | -12 | 10 | 2.3 |
| ACC | 2 | 10 | 32 | 2.2 |
| L - Frontal pole BA 10 | -36 | 48 | 24 | 2.2 |
| R - Amygdala | 16 | -2 | -18 | 2.2 |

patients with fibromyalgia probably plays a direct pathophysiological role in this disease. Another limitation is that insofar as our study focuses only on PAG functional connectivity, we cannot provide information whether fibromyalgia also involves peripheral nociceptive nerve fibres. A recent study using pain-related evoked potentials and skin biopsy demonstrated distally distributed peripheral nervous system damage, selectively involving nociceptive Aδ- and C-fibres (30). Although the peripheral nerve damage in patients with fibromyalgia still deserves confirmatory studies, we hypothesise that fibromyalgia might be associated with multiple abnormalities involving both the central and peripheral nervous system (31). Further studies investigating both peripheral and central nervous systems should therefore verify whether distally distributed peripheral nervous system damage and central nervous system abnormalities coexist in the same patient.

Our study showing an abnormally unbalanced PAG functional connectivity might indicate that in patients with FM pain is provoked by an impaired descending pain inhibition. The abnormal PAG functional connectivity correlates with clinical variables, including the depressive trait. These findings lend strong support to the use of antidepressants in patients with FM, given that antidepressants balance descending modulatory system and improve depression.

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