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Evidence of neuroinflammation in fibromyalgia syndrome: a [^{18}F]DPA-714 positron emission tomography study

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Abstract

This observational study aimed to determine whether individuals with fibromyalgia (FM) exhibit higher levels of neuroinflammation than healthy controls (HCs), as measured with positron emission tomography using [^{18}F]DPA-714, a second-generation radioligand for the translocator protein (TSPO). Fifteen women with FM and 10 HCs underwent neuroimaging. Distribution volume (V_T) was calculated for in 28 regions of interest (ROIs) using Logan graphical analysis and compared between groups using multiple linear regressions. Group (FM vs HC) was the main predictor of interest and TSPO binding status (high- vs mixed-affinity) was added as a covariate. The FM group had higher V_T in the right postcentral gyrus ($b = 0.477$, $P = 0.033$), right occipital gray matter (GM; $b = 0.438$, $P = 0.039$), and the right temporal GM ($b = 0.466$, $P = 0.042$). The FM group also had lower V_T than HCs in the left isthmus of the cingulate gyrus ($b = -0.553$, $P = 0.014$). In the subgroup of high-affinity binders, the FM group had higher V_T in the bilateral precuneus, postcentral gyrus, parietal GM, occipital GM, and supramarginal gyrus. Group differences in the right parietal GM were associated with decreased quality of life, higher pain severity and interference, and cognitive problems. In support of our hypothesis, we found increased radioligand binding (V_T) in the FM group compared with HCs in several brain regions regardless of participants' TSPO binding status. The ROIs overlapped with prior reports of increased TSPO binding in FM. Overall, increasing evidence supports the hypothesis that FM involves microglia-mediated neuroinflammation in the brain.

Keywords: DPA-714, Translocator protein, Fibromyalgia, Neuroinflammation, Positron emission tomography

1. Introduction

Fibromyalgia (FM) is a chronic disease characterized by widespread musculoskeletal pain of unknown origin with associated symptoms of unresolving fatigue, unrefreshing sleep, depressed mood, cognitive deficits, and somatic symptoms such as headaches and abdominal pain.[54] Recent studies have implicated neuroinflammation as a contributing factor in FM development. During neuroinflammation, the brain's resident immune cells (microglia) change from a quiescent to an activated state and release proinflammatory cytokines. Chronic exposure to cytokines can produce behavioral symptoms that overlap with FM, including muscle pain, fatigue, depression, and cognitive problems.[11,12] Several studies have reported increased proinflammatory cytokines and chemokines in serum[5,16,18,20,25,33,46,47,50,51,61] and cerebrospinal fluid[5,25] of FM patients, as well as defective anti-inflammatory signaling.[21,48] Furthermore, experimental studies have demonstrated that the inhibition of microglial activation and proinflammatory cytokines alleviates FM symptoms in rodent models[10,57,58] and in humans.[59,60] Although these findings provide initial support for the neuroinflammatory hypothesis of FM, studies are still needed that directly visualize neuroinflammation in the brains of FM patients.

Positron emission tomography (PET) with radiolabeled ligands for the 18 kDa translocator protein (TSPO) is the most common way to measure neuroinflammation. Translocator protein receptors are preferentially upregulated on the mitochondrial membrane of activated microglia, so that imaging with TSPO-targeted radiopharmaceuticals can be used to infer microglial activation throughout the brain.[19] It is also believed to reflect microglial density, another putative marker of neuroinflammation.[49,56] Although many PET studies have been conducted in FM, only 2 have specifically investigated neuroinflammation. Albrecht et al.[1] used PET with the TSPO ligand [^{11}C]PBR28 to demonstrate increased microglial activation in widespread brain regions of FM patients compared with healthy controls (HCs), including the superior parietal lobe, primary somatosensory cortex, motor cortex, supramarginal gyrus, dorsolateral and dorsomedial prefrontal cortices, supplementary motor area, posterior cingulate, and precuneus. [^{11}C]PBR28 uptake in the cingulate cortex was associated with fatigue severity. Similarly, a recently published

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study using the first-generation TSPO ligand (*R*)-[^{11}C]PK11195 found increased neuroinflammation in FM patients compared with healthy individuals and patients with complex regional pain syndrome.[40]

[^{18}F]DPA-714 is a second-generation TSPO ligand that has not been evaluated in FM. Compared with the 20-minute physical half-life of ^{11}C-labeled compounds, the 110-minute half-life of the ^{18}F label allows for delayed imaging and simpler imaging logistics, as well as batch production of the PET tracer. In addition, direct comparisons of [^{11}C]PK11195 and [^{18}F]DPA-714 have revealed significantly higher specific binding and signal-to-noise ratio for [^{18}F]DPA-714.[7,8] The longer half-life also supports remote distribution and translation into clinical settings. [^{18}F]DPA-714 has also demonstrated favorable in vivo stability and biodistribution for the purposes of measuring neuroinflammation, so this novel radioligand warrants exploration in FM.[2]

The aim of the current study was to test whether individuals with FM exhibit higher levels of neuroinflammation than HCs, as measured with [^{18}F]DPA-714 PET. Our hypothesis was that the FM group would show higher TSPO binding in the brain compared with HCs.

2. Methods

2.1. Participants

Women aged 18 to 65 who met 2016 American College of Rheumatology (ACR) case definition for FM[54] were recruited by online advertisements and flyers posted around the University of Alabama at Birmingham (UAB) campus. We also contacted women from an existing database maintained by our laboratory. Individuals with FM must have reported average daily pain levels of 6 or above on an 11-point scale (0-10) to qualify. Healthy women were recruited through the same channels and age-matched to the FM participants. Healthy women must have reported average daily pain levels of 1 or below on the same 0 to 10 scale. The following were exclusionary for all participants: (1) contraindications to magnetic resonance imaging (MRI), (2) pregnancy or lactation, (3) inability to undergo imaging due to the severity of the medical condition, (4) chronic infectious disease (eg, HIV and HCV), (5) viral or bacterial illness requiring systemic treatment within 1 month of participation, (6) diagnosis of cancer, (7) blood or blood clotting disorder, (8) autoimmune disorders, (9) diabetes, and (10) current enrollment in a clinical trial using experimental treatments. In addition, out of normal range values on the following blood tests were exclusionary: thyroid function (T3, T4, thyroid-stimulating hormone), complete blood count (CBC), erythrocyte sedimentation rate (>60 mm/hour), high-sensitivity C-reactive protein (>10 mg/L), fasting glucose (>100 mg/dL), positive rheumatoid factor (>13 IntUnits/mL), or positive antinuclear antibody test (>1:80).

2.2. Procedures

All study procedures were approved by the UAB Institutional Review Board (IRB), and the study was registered on clinicaltrials.gov (NCT03759522). Because this study was an observational study, there was no randomization to treatment groups. The study consisted of a phone screening to determine initial eligibility, followed by an in-person screening visit and a neuroimaging visit. For the screening visit, participants meeting initial criteria attended the UAB Advanced Imaging Facility (AIF) to provide written informed consent, complete questionnaires, undergo urine pregnancy testing, fasting blood draws, and a tender point examination.

2.2.1. Blood draws and genotyping

Thirty-six milliliters of whole blood were collected from the antecubital fossa using aseptic procedures. Blood was collected into EDTA-coated and SST blood collection tubes to run the screening tests. Some of the blood was transported to the UAB Specimen Processing and Biorepository Unit (SPAN) for serum separation and storage at −80°C, as well as DNA extraction and preparation for genotyping. A single nucleotide polymorphism (SNP) in the TSPO gene (rs6971) confers high, mixed, or low affinity for [^{18}F]DPA-714 binding to the TSPO protein. Participants were classified as either high-affinity binders (HABs; 2 copies of high affinity SNP), mixed affinity binders (MABs; one copy each of high and low affinity SNPs), or low-affinity binders (LABs; 2 copies of low affinity SNP). Based on prior literature demonstrating poor TSPO radioligand binding in LABs,[32] these individuals were excluded from participating.

2.2.2. Questionnaires and tender point exam

Fibromyalgia participants completed a demographics form, the Brief Pain Inventory (BPI),[9] Hospital Anxiety and Depression Scale (HADS),[43] Fibromyalgia Impact Questionnaire (FIQ),[6] Multiple Ability Self-Report Questionnaire (MASQ),[38] Multidimensional Fatigue Inventory (MFI),[42] and the 36-item short form (SF-36) [52,53] as a measure of general health status. Healthy controls completed the same questionnaires, except for the FIQ. Participants also underwent a tender point examination according to ACR criteria,[55] administered with a FPK20 manual algometer (1 cm diameter; Wagner Instruments, Greenwich, CT) and 4 kg pressure applied to each tender point. Fibromyalgia patients were excluded if demonstrating fewer than 11 of 18 tender points, and HCs were excluded if demonstrating 11 or more tender points. Participants meeting all study criteria were invited back to the AIF to complete the neuroimaging visit.

2.3. Neuroimaging acquisition

[^{18}F]DPA-714 was produced at the UAB Cyclotron PET Production Facility on the morning of each scheduled brain scan as per literature procedures.[17] Simultaneous PET/MRI was performed at the AIF on a General Electric Signa PET/MRI system (General Electric Company, Boston, MA) with 19-channel head and neck coil. Up to 185 MBq (5 mCi) of [^{18}F]DPA-714 in a total injected volume of ≤10 mL were administered through intravenous bolus injection over the course of 30 seconds. Dynamic list-mode PET of the head was acquired for 60 minutes after radioligand administration, with participants keeping their eyes closed to minimize distortions in blood flow related to visual stimulation.

General Electric's volumetric T1-weighted BRAVO sequence, an inversion recovery (IR)-prepped, fast spoiled gradient recalled (SPGR) sequence, was acquired simultaneously with the PET acquisition with the following parameters: TR = 8.08 milliseconds, TE = 3.02, flip angle = 12°, 184 slices, slice thickness = 1 mm, FoV = 228 × 228 mm, matrix = 512 × 512, and voxel resolution = 0.445 × 0.445 × 1 mm. The PET acquisition was performed as a 60-minute dynamic study for all subjects. DPA-714 was injected as a bolus at the beginning of the scan time. Dynamic frame reconstruction was set up as 12 10-second, 9 20-second, 5 60-second, and 10 5-minute frames. List mode data were acquired and later reconstructed with an ordered-subset expectation maximization (OSEM) algorithm (4 iterations, 16 subsets) with correction for radionuclide decay, random events, scatter, and dead time. Time-of-flight information and point spread functions were both used in the PET reconstruction. Attenuation correction was based on a

zero-echo-time MRI-derived attenuation map.[39] The matrix size was 256 × 256 × 89, with a voxel resolution of 1.17 × 1.17 × 2.78 mm.

2.4. Image processing

Images were processed according to an existing protocol.[34,35] T1-weighted structural images were processed with the FreeSurfer (v.7.1.1, Martinos Center, Boston, MA)[15] automated pipeline that includes registration to Montreal Neurological Institute (MNI) space, intensity normalization, skull removal, segmentation into a 3-compartment model (gray matter, GM; white matter, WM; and cerebrospinal fluid) and parcellation into cortical and subcortical regions of interest (ROIs) from the Desikan–Killiany atlas included with FreeSurfer.[13] For the current paper, we selected 28 ROIs for the analyses based on Seo et al.[40] Positron emission tomography images were reconstructed using an OSEM algorithm with correction for radionuclide decay, random events, scatter, and dead time. All images from the dynamic PET data were coregistered to the last frame. The T1-weighted MR images were also aligned to the last frame with in-house software to minimize involuntary patient motion during the study. The FreeSurfer parcellations were applied to the original dynamic PET. Positron emission tomography time-activity curves (TACs) for the target regions were extracted from the ROIs based on the FreeSurfer parcellations and then corrected for partial volume effects with the Geometric Transformation Matrix method in the PETPVC toolbox.[36,45] For each subject, distribution volume (V_T) was calculated for each target region using Logan graphical analysis.[30,31] The cerebellar cortex was selected as the reference region based on prior literature.[17,23]

2.5. Statistical analyses

Statistical analyses were performed in IBM SPSS Statistics for Macintosh, version 27 (IBM Corp., Armonk, NY). V_T from the 28 a priori defined ROIs was compared between the FM and HC groups using multiple linear regressions. Group (FM vs HC) was the main predictor of interest and binding status (HAB vs MAB) added as a covariate. Statistical significance was assumed at $P < 0.05$. Corrected P-values using a false discovery rate (FDR) of 0.05 were determined with Storey's adaptation of the Benjamini and Hochberg FDR approach[44] and used to correct for the number of regressions conducted (equivalent to uncorrected $P < 0.0127$). Because analyses were already restricted to certain brain regions based on a priori hypotheses, we report both the corrected and uncorrected results.

Between-group (FM vs HC) differences were also tested in the HAB individuals only. Simple linear regressions without the binding status variable were used for these analyses. To test whether abnormalities in [^{18}F]DPA-714 uptake are related to clinical outcomes, we obtained Pearson correlation coefficients between V_T and questionnaire scores in regions with significant between-group differences.

Secondary voxel-based analyses on the main FM vs HC data were conducted using SPM12.[3] Data were smoothed with a 3-mm Gaussian kernel. The model was built as a main effect for group, controlling for the nuisance covariate of binding status. A voxel-height threshold of $P < 0.001$ was used with a cluster size threshold of 5 contiguous voxels. Coordinates of significant clusters were described using the MNI coordinate system.

3. Results

3.1. Sample characteristics

Thirty-one women with FM and 18 HCs were recruited. Fourteen participants were excluded after screening due to out-of-range values on blood tests, 3 participants were excluded due to low-affinity binding status, 4 participants withdrew, and 2 participants were excluded due to incomplete scans. Data from one FM participant were excluded due to image acquisition errors, leaving data from 15 FM and 10 HC participants for the final analyses. Demographic information, questionnaire data, and TSPO binding status for included participants in each group are summarized in **Table 1**.

Groups did not differ in mean age ($t(23) = -1.325$, $P = 0.198$). As expected, FM participants had significantly higher scores on the BPI pain severity ($t(19.517) = -13.395$, $P < 0.001$) and pain interference ($t(8.728) = 14.229$, $P < 0.001$) scales; the HADS Depression ($t(16.569) = 5.143$, $P < 0.001$) and Anxiety ($t(23) = 3.703$, $P = 0.001$) subscales; the MASQ language ($t(22) = 3.285$, $P = 0.003$), visual perceptual ($t(22) = 2.706$, $P = 0.013$), verbal memory ($t(21.789) = 2.743$, $P = 0.012$) subscales; and the total MASQ score ($t(22) = 3.011$, $P = 0.006$), but not the visual memory subscale ($t(22) = 2.073$, $P = 0.05$). Fibromyalgia participants also had higher scores on the MFI general fatigue ($t(10.288) = 7.126$, $P < 0.001$), physical fatigue ($t(22) = 5.522$, $P < 0.001$), reduced activity ($t(22) = 5.265$, $P < 0.001$), reduced motivation ($t(22) = 5.151$, $P < 0.001$), and mental fatigue ($t(22) = 5.763$, $P < 0.001$) subscales and the total MFI score ($t(22) = 7.657$, $P < 0.001$), indicating greater pathology compared to HCs. The FM group scored lower on all 36-item short-form subscales, including energy ($t(23) = -10.540$, $P < 0.001$), bodily pain ($t(22.8) = -9.499$, $P < 0.001$), general health perceptions ($t(18.587) = -7.225$, $P < 0.001$), mental health ($t(23) = -3.474$, $P = 0.002$), physical functioning ($t(15.111) = -7.013$, $P < 0.001$), physical limitations ($t(14) = -11.602$, $P < 0.001$), emotional limitations ($t(23) = -2.765$, $P = 0.011$), and social functioning ($t(17.609) = -7.124$, $P < 0.001$), indicating lower quality of life in all domains. No adverse events attributed to the administration of [^{18}F]-DPA-714 occurred in any of the subjects.

3.2. Main neuroimaging results

V_T results are summarized in **Table 2** for the combined MAB and HAB sample, and in **Table 3** for HAB participants only. In the combined group of MABs and HABs, the FM group had higher V_T in the right postcentral gyrus (FM mean = 1.654, SD = 0.278; HC mean = 1.499, SD = 0.199; $b = 0.477$, $P = 0.033$), right occipital GM (FM mean = 1.449, SD = 0.143; HC mean = 1.400, SD = 0.111; $b = 0.438$, $P = 0.039$), and the right temporal GM (FM mean = 1.264, SD = 0.103; HC mean = 1.182, SD = 0.117; $b = 0.466$, $P = 0.042$). The FM group also had lower V_T than HCs in the left isthmus of the cingulate gyrus (FM mean = 1.127, SD = 0.094; HC mean = 1.225, SD = 0.108; $b = -0.553$, $P = 0.014$). None of the results remained significant after corrections for multiple comparisons.

In the subgroup of HABs, the linear regressions showed that the FM group had higher V_T in the left precuneus ($b = 0.551$, $P = 0.027$), right precuneus ($b = 0.580$, $P = 0.019$), left postcentral gyrus ($b = 0.547$, $P = 0.028$), right postcentral gyrus ($b = 0.576$, $P = 0.020$), left parietal GM ($b = 0.591$, $P = 0.016$), right parietal GM ($b = 0.615$, $P = 0.011$), left occipital GM ($b = 0.540$, $P = 0.031$) and right occipital GM ($b = 0.556$, $P = 0.025$), and the left supramarginal gyrus ($b = 0.508$, $P = 0.044$) and right supramarginal gyrus ($b = 0.555$, $P = 0.026$). The results for the right parietal GM remained significant after FDR corrections for multiple comparisons.

3.3. Secondary neuroimaging results

Fibromyalgia vs HC data were examined with voxel-based analyses. Three clusters showed greater signal in the FM group

Table 1

Participant characteristics.

	FM (N = 15)		HC (N = 10)		t	*P*
	Mean	SD	Mean	SD		
Age	47.80	13.39	40.40	14.11	1.325	0.198
Brief Pain Inventory (BPI)						
Pain severity	5.62	1.41	0.20	0.55	13.395†	<0.001***
Pain interference	5.61	2.45	0.07	0.18	8.728†	<0.001***
HADS						
Depression	7.87	4.94	1.00	1.25	4.277	<0.001***
Anxiety	9.60	3.81	4.10	3.35	3.703	0.001**
FIQ total score	62.03	18.92	—	—	—	—
MASQ						
Language	19.53	5.66	12.78	3.07	3.285	0.003**
Visual perceptual	15.53	5.67	9.89	3.33	2.706	0.013*
Verbal memory	21.40	7.47	15.00	3.94	2.743†	0.012*
Visual memory	17.27	6.08	12.56	3.91	2.073	0.050
Attention	22.13	6.42	15.78	3.67	2.701	0.013*
Total score	95.87	26.89	66.00	16.04	3.011	0.006**
MFI						
General fatigue	18.40	1.92	8.33	3.97	7.126†	<0.001***
Physical fatigue	15.33	4.45	6.22	2.73	5.522	<0.001***
Reduced activity	13.87	3.54	6.44	2.96	5.265	<0.001***
Reduced motivation	13.07	3.86	5.56	2.60	5.151	<0.001***
Mental fatigue	14.73	3.49	6.56	3.13	5.763	<0.001***
Total score	75.40	13.20	33.11	12.93	7.657	<0.001***
36-item short form‡						
Energy/vitality	14.67	11.41	72.00	15.85	−10.540	<0.001***
Bodily pain	35.33	17.14	92.75	10.17	−9.499	<0.001***
General health perceptions	41.00	23.92	89.50	8.32	−7.225†	<0.001***
Mental health/emotional wellbeing	60.27	22.55	87.60	12.57	−3.474	0.002**
Physical functioning	45.00	28.97	98.50	4.74	−7.013†	<0.001***
Physical limitations	16.67	27.82	100.00	0.00	−11.602†	<0.001***
Emotional limitations	46.67	39.44	86.67	28.11	−2.765	0.011*
Social functioning	41.67	27.82	96.25	8.44	−7.124†	<0.001***
TSPO binding affinity	HAB: N=7 MAB: N=8		HAB: N=9 MAB: N=1		—	—

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

† df adjusted for unequal variances.

‡ Higher scores reflect better functioning.

FIQ, Fibromyalgia Impact Questionnaire; HADS, Hospital Anxiety and Depression Scale; MASQ, Multiple Abilities Self-Report Questionnaire; MFI, Multidimensional Fatigue Inventory.

than the HC group. The clusters included the right precuneus (4, −60, 62; F = 16.8, $P < 0.001$), right inferior temporal GM (48, −46, −16; F = 16.7, $P < 0.001$), and right inferior occipital GM (38, −84, −22; F = 17.9 $P < 0.001$). **Figure 1** shows FM > HC results. No clusters showed significantly greater signal in the HC group than the FM group.

3.4. Associations between elevated [^{18}F]DPA-714 uptake and fibromyalgia symptoms

We next assessed associations between [^{18}F]DPA-714 uptake and behavioral (questionnaire) outcomes. We assessed correlations with V_T in the right parietal GM in HAB participants, as this was the only result that remained significant after corrections for multiple comparisons. Higher V_T in the right parietal GM was associated with decreased quality of life in SF-36 physical functioning ($r = -0.580$, $P = 0.019$), energy ($r = -0.544$, $P = 0.030$), and pain domains ($r = -0.535$, $P = 0.033$). Higher V_T in this region was also associated with higher BPI pain severity ($r = 0.590$, $P = 0.016$) and pain interference ($r = 0.515$, $P = 0.041$), and with anxiety ($r = 0.565$, $P = 0.023$). Furthermore, higher V_T was associated with more severe cognitive problems on the MASQ in the visual perceptual ($r = 0.551$, $P = 0.033$) and visual memory domains ($r = 0.536$, $P = 0.039$). **Figure 2** shows significant correlations with behavioral outcomes.

4. Discussion

The aim of the current study was to determine whether individuals with FM exhibit neuroinflammation, as measured with [^{18}F]DPA-714. In support of our hypothesis, we found increased V_T in the FM group compared with HCs in the right postcentral gyrus, right occipital GM, and the right temporal GM, regardless of participants' TSPO binding affinity (MAB or HAB). High-affinity binders in the FM group additionally demonstrated increased V_T in the bilateral precuneus, the left in addition to the right postcentral gyrus, the bilateral parietal GM, the left in addition to the right occipital GM, and the bilateral supramarginal gyri, when compared with HC HABs.

The results are largely consistent with Seo et al.[40] and Albrecht et al.,[1] who also reported increased TSPO binding in FM in the precentral and postcentral gyri, supramarginal gyrus, and parietal

Table 2

Mean distribution volume and standard deviations in the fibromyalgia and healthy control group for combined sample of participants with mixed affinity and high-affinity binding status.

ROI	FM (N = 15)		HC (N = 10)		Estimate (*b*)	*P*
	Mean	SD	Mean	SD		
L anterior cingulate	1.549	0.130	1.551	0.154		
Group					0.125	0.590
Binding status					0.300	0.204
R anterior cingulate	1.538	0.174	1.587	0.160		
Group					−0.049	0.834
Binding status					0.222	0.345
L precuneus	1.394	0.156	1.393	0.070		
Group					0.278	0.173
Binding status					0.620	0.005**
R precuneus	1.400	0.164	1.328	0.124		
Group					0.427	0.056
Binding status					0.429	0.055
L precentral gyrus	1.514	0.260	1.549	0.147		
Group					0.181	0.379
Binding status					0.588	0.008**
R precentral gyrus	1.556	0.236	1.519	0.137		
Group					0.302	0.173
Binding status					0.474	0.037*
L postcentral gyrus	1.567	0.293	1.506	0.154		
Group					0.368	0.085
Binding status					0.552	0.013*
R postcentral gyrus	1.654	0.278	1.499	0.199		
Group					0.477	0.033*
Binding status					0.396	0.073
L pre and postcentral gyrus	1.536	0.269	1.529	0.142		
Group					0.275	0.187
Binding status					0.588	0.008**
R pre and postcentral gyrus	1.595	0.248	1.510	0.161		
Group					0.391	0.080
Binding status					0.442	0.050
L thalamus	1.183	0.094	1.147	0.087		
Group					0.346	0.133
Binding status					0.338	0.141
R thalamus	1.196	0.107	1.179	0.083		
Group					0.223	0.338
Binding status					0.314	0.181
L hippocampus	1.010	0.040	0.978	0.064		
Group					0.326	0.164
Binding status					0.051	0.823
R hippocampus	0.999	0.069	0.987	0.069		
Group					0.232	0.315
Binding status					0.330	0.159
L parietal GM	1.426	0.210	1.389	0.107		
Group					0.356	0.094
Binding status					0.567	0.011*
R parietal GM	1.461	0.210	1.369	0.144		
Group					0.425	0.059
Binding status					0.414	0.065
L frontal GM	1.419	0.210	1.439	0.185		
Group					0.146	0.510
Binding status					0.445	0.053
R frontal GM	1.507	0.242	1.517	0.138		
Group					0.152	0.502
Binding status					0.398	0.086

(*continued on next page*)

Table 2 (*continued*)

ROI	FM (N = 15)		HC (N = 10)		Estimate (*b*)	*P*
	Mean	SD	Mean	SD		
L occipital GM	1.468	0.178	1.435	0.065		
Group					0.383	0.065
Binding status					0.608	0.005**
R occipital GM	1.449	0.143	1.400	0.111		
Group					0.438	0.039*
Binding status					0.572	0.009**
L temporal GM	1.203	0.107	1.166	0.110		
Group					0.342	0.134
Binding status					0.377	0.101
R temporal GM	1.264	0.103	1.182	0.117		
Group					0.466	0.042*
Binding status					0.246	0.266
L cerebellum	0.965	0.027	0.960	0.011		
Group					0.013	0.956
Binding status					−0.232	0.326
R cerebellum	0.981	0.023	0.977	0.027		
Group					−0.034	0.885
Binding status					−0.240	0.311
L white matter	0.638	0.083	0.571	0.075		
Group					0.042	0.767
Binding status					−0.792	<0.001***
R white matter	0.629	0.082	0.570	0.084		
Group					0.014	0.931
Binding status					0.738	<0.001***
L Inferior parietal GM	1.384	0.215	1.320	0.106		
Group					0.404	0.064
Binding status					0.508	0.023*
R Inferior parietal GM	1.407	0.222	1.318	0.154		
Group					0.395	0.082
Binding status					0.386	0.088
L superior parietal GM	1.525	0.228	1.481	0.132		
Group					0.346	0.111
Binding status					0.524	0.019*
R superior parietal GM	1.473	0.220	1.404	0.140		
Group					0.392	0.076
Binding status					0.479	0.033*
L supramarginal gyrus	1.328	0.239	1.287	0.157		
Group					0.346	0.105
Binding status					0.560	0.012*
R supramarginal gyrus	1.479	0.236	1.353	0.183		
Group					0.428	0.062
Binding status					0.322	0.152
L Isthmus of cingulate gyrus	1.127	0.094	1.225	0.108		
Group					−0.553	0.014*
Binding status					−0.236	0.266
R Isthmus of cingulate gyrus	1.157	0.123	1.231	0.109		
Group					−0.246	0.285
Binding status					0.134	0.557

Estimates and *P* values refer to standardized coefficients from multiple linear regressions testing group (FM vs HC) and binding status (HAB vs MAB) as predictors of regional V_T. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
FM, fibromyalgia; GM, gray matter; HAB, high affinity binders; HC, healthy control; L, left; MAB, mixed affinity binders; R, right; ROI, region of interest; V_T, distribution volume.

lobes, but here, we identified several additional regions in FM patients with HAB status. Overall, increasing evidence supports the hypothesis that FM involves microglia-mediated neuroinflammation in several brain regions.

One potential pathway connecting neuroinflammation with FM symptoms is central sensitization, which is an abnormal increase in central nervous system signaling due to increases in membrane excitability, synaptic efficiency, and reduced inhibition.[41] This leads to activation of nociceptive pathways in the brain under conditions that do not normally involve these pathways, causing allodynia (experience of pain in response to nonpainful stimuli) and hyperalgesia (excessive pain to an already painful stimulus).[28] Under inflammatory conditions, activated microglia release proinflammatory cytokines, such as interleukin (IL)-1β,[29] IL-6,[29] and tumor

Table 3

Mean distribution volume and standard deviations in high-affinity binders in the fibromyalgia and healthy control group.

ROI	FM (N = 7)		HC (N = 9)		Estimate (*b*)	*P*
	Mean	SD	Mean	SD		
L anterior cingulate	1.578	0.128	1.572	0.147	0.023	0.933
R anterior cingulate	1.566	0.195	1.605	0.160	−0.117	0.666
L precuneus	1.503	0.107	1.391	0.073	0.551	0.027*
R precuneus	1.494	0.123	1.323	0.130	0.580	0.019*
L precentral gyrus	1.663	0.155	1.569	0.141	0.321	0.226
R precentral gyrus	1.661	0.134	1.536	0.133	0.446	0.084
L postcentral gyrus	1.731	0.190	1.520	0.157	0.547	0.028*
R postcentral gyrus	1.777	0.192	1.510	0.207	0.576	0.020*
L pre and postcentral gyrus	1.691	0.157	1.546	0.139	0.464	0.071
R pre and postcentral gyrus	1.706	0.148	1.525	0.163	0.522	0.038*
L thalamus	1.226	0.096	1.146	0.092	0.410	0.115
R thalamus	1.243	0.096	1.174	0.086	0.373	0.155
L hippocampus	1.015	0.034	0.978	0.068	0.332	0.210
R hippocampus	1.025	0.070	0.990	0.072	0.249	0.352
L parietal GM	1.550	0.113	1.396	0.111	0.591	0.016*
R parietal GM	1.566	0.103	1.369	0.153	0.615	0.011*
L frontal GM	1.517	0.177	1.454	0.189	0.178	0.509
R frontal GM	1.607	0.228	1.525	0.144	0.230	0.391
L occipital GM	1.568	0.139	1.448	0.054	0.540	0.031*
R occipital GM	1.537	0.080	1.411	0.113	0.556	0.025*
L temporal GM	1.244	0.056	1.176	0.111	0.368	0.161
R temporal GM	1.295	0.079	1.187	0.123	0.475	0.063
L cerebellum	0.961	0.033	0.957	0.008	0.105	0.700
R cerebellum	0.976	0.013	0.975	0.028	0.031	0.910
L white matter	0.569	0.048	0.554	0.055	0.152	0.574
R white matter	0.566	0.065	0.552	0.066	0.108	0.690
L inferior parietal GM	1.493	0.126	1.330	0.107	0.600	0.014*
R inferior parietal GM	1.518	0.075	1.313	0.162	0.636	0.008**
L superior parietal GM	1.662	0.103	1.481	0.140	0.607	0.013*
R superior parietal GM	1.597	0.100	1.403	0.149	0.622	0.010*
L supramarginal gyrus	1.465	0.128	1.302	0.159	0.508	0.044*
R supramarginal gyrus	1.571	0.132	1.357	0.194	0.555	0.026*
L isthmus of cingulate gyrus	1.122	0.076	1.201	0.084	−0.463	0.071
R isthmus of cingulate gyrus	1.194	0.109	1.219	0.109	−0.122	0.652

Estimates and *P*-values refer to standardized coefficients from simple linear regressions testing group (FM vs HC) as a predictor of regional V_T. *$P < 0.05$, **$P < 0.01$.
FM, fibromyalgia; GM, gray matter; HC, healthy control; L, left; R, right; ROI, region of interest; V_T, distribution volume.

necrosis factor (TNF)-α,[29] which have been shown to enhance afferent spinal cord signals by increasing excitatory transmission and decreasing inhibitory transmission.[26] In the brain, proinflammatory cytokines, reactive oxygen species, and reactive nitrogen species released from microglia can cause neuronal damage, further leading to hyperexcitability and spontaneous firing. Depending on the brain areas affected, this can lead to various symptoms experienced by FM patients and other neuroinflammatory conditions, including cognitive problems, pain, and fatigue. In support of this hypothesis, we found correlations between increased [^{18}F] DPA-714 uptake in the right parietal GM and reduced quality of life, increased pain, and cognitive problems in the current study. The parietal lobes are involved in sensory processing (including pain), spatial awareness, attention, and perception, among other functions. It is very plausible that neuroinflammation and neuronal damage in this region could negatively affect cognitive abilities (particularly visual perceptual and visual memory abilities) and worsen pain severity and interference with everyday functioning. Longitudinal studies measuring neuroinflammation after FM treatment and symptom remission would be needed to conclusively determine whether neuroinflammation is causing or exacerbating these symptoms in FM.

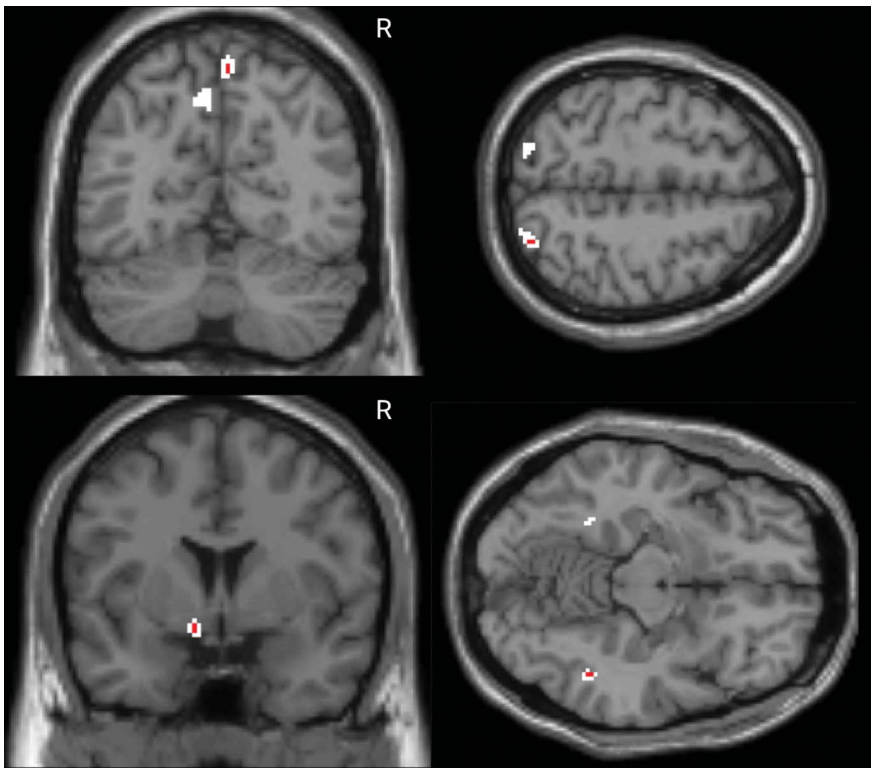

Figure 1. Voxel-based analyses of fibromyalgia (FM) vs healthy controls (HC; all subjects included). All clusters are FM > HC. Clusters were thresholded at voxel height $P < 0.005$ and cluster size of 5 voxels (red). Voxels in white were thresholded at voxel height $P < 0.001$ and are provided to identify the regions most likely driving the ROI-based results. ROI, regions of interest.

The finding of decreased [^{18}F]DPA-714 uptake in the left cingulate gyrus was unexpected. This region was selected a priori because of its involvement in emotional aspects of pain processing and pain perception, and we expected to observe increased inflammation in this area. Because the result did not remain significant after corrections for multiple comparisons, we caution against over-interpreting this finding. However, previous studies have also yielded inconsistent results regarding the role of the cingulate gyrus in FM, reporting both increased and decreased activation.[37] We suggest that future studies measuring neuroinflammation in FM retain the cingulate gyrus as a region of interest for further clarification of its role in FM.

As expected, TSPO binding affinity (HAB vs MAB) significantly influenced [^{18}F]DPA-714 uptake, with HABs exhibiting higher V_T than MABs in several regions. Some research has suggested that TSPO binding affinity may be involved in FM symptomatology. Kosek et al.[27] demonstrated that FM patients with HAB status report more severe FM symptoms and higher pain intensity in response to nociceptive stimulation than FM patients with LAB or MAB status. In the same study, TSPO binding affinity also affected functional connectivity in the right frontoparietal network in response to painful stimulation, indicating altered activity in the affective–motivational components of pain perception. Although the mechanism by which TSPO binding affects FM symptomatology is unclear, the authors speculated that due to TSPO's effects on neurosteroid synthesis, it could exert analgesic effects during early or localized disease, with opposite effects during more severe or widespread disease. Similarly, Fanton et al.[14] showed that individuals with FM with HAB status show deficits in pain inhibition and expectancy-induced reduction of pain compared with FM patients with MAB status, lending further support to the idea that genetic polymorphisms related to glial activation impact FM symptomatology. An assessment of the relationship between binding status and FM symptoms was outside the scope of the current study but should be considered in future studies.

4.1. Limitations

The current study has limitations to consider when interpreting the results. First, quantification of [^{18}F]DPA-714 V_T in the current study was based on a reference region because arterial blood sampling and arterial input functions were not available. The cerebellar cortex was chosen as the reference region based on prior literature demonstrating the suitability of this region for [^{18}F]DPA-714 quantification.[17,40] Of note, however, is that a reference region should ideally have similar radioligand binding between groups, and this cannot be guaranteed in the case of FM. To date, only 2 PET studies have assessed neuroinflammation in FM, one of which did not report TSPO binding in the cerebellum,[1] and one of which used the cerebellum as the reference region for V_T quantification.[40]

Second, the small sample size in the current study makes it difficult to minimize false positives while maintaining an acceptable level of statistical sensitivity for detecting group differences. We mitigated the potential for false positives by assessing a small number of predefined brain regions which have shown abnormalities in previous neuroimaging studies with FM populations and by applying additional corrections for multiple comparisons. Although we report both corrected and uncorrected results, we caution against over-interpreting results that did not remain

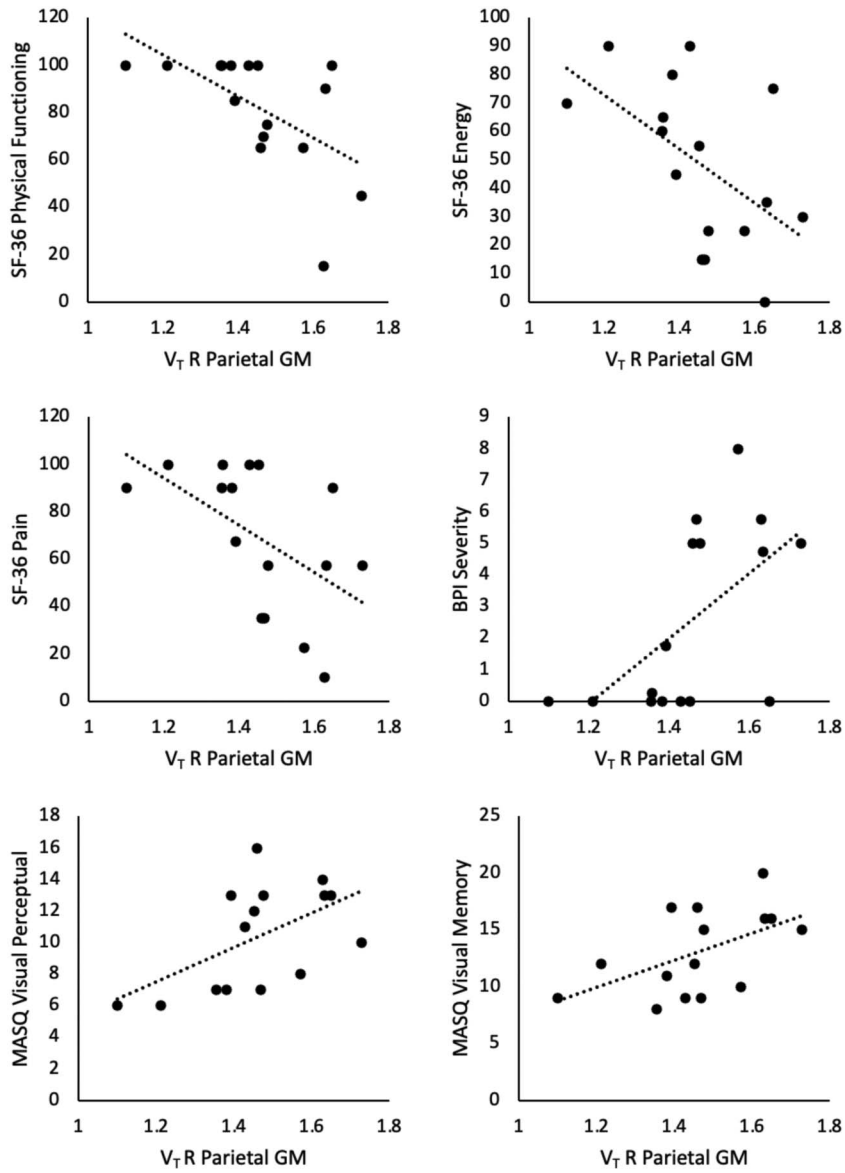

Figure 2. Significant correlations between distribution volume (V_T) in the right parietal gray matter and behavioral outcomes in high-affinity binders. Dotted lines are linear trend lines. For SF-36 subscales, lower values indicate lower quality of life. BPI, Brief Pain Inventory; GM, gray matter; MASQ, Multiple Ability Self-Report Questionnaire; R, right; SF-6, 36-item short form; V_T, distribution volume.

significant after the additional thresholds until the results are confirmed in larger samples.

Third, there was an unequal number of participants with MAB status in the FM (n = 8) and HC (n = 1) groups, which could have affected the findings. We added TSPO binding status as a covariate in the statistical analyses to reduce the effect of this variable, but future studies could recruit a larger sample of HCs with MAB status to confirm the generalizability of the current findings to this group. A related limitation is that most TSPO radioligands cannot be used in low-affinity binders, so the results of the current study are likely not applicable to FM patients with LAB status.

Finally, the utility of [^{18}F]DPA-714 imaging in FM will be limited by the nonspecific nature of TSPO as a disease marker. Increased TSPO binding on [^{18}F]DPA-714 PET is not specific to FM but has been shown in a number of neurological conditions, including multiple sclerosis,[22] Alzheimer disease,[24] and stroke.[4] Like other TSPO radioligands, [^{18}F]DPA-714 is unlikely to become a diagnostic marker for FM on its own, but it could be used to confirm the involvement of the central nervous system and neuroinflammation in certain cases. Nevertheless, it should be considered an important research tool in the quest to disentangle FM pathophysiology.

5. Conclusion

The current study is the first to use a novel TSPO radioligand, [^{18}F]DPA-714, to demonstrate the presence of neuroinflammation in FM. We showed increased neuroinflammation in the bilateral precuneus, bilateral postcentral gyri, bilateral parietal and occipital GM, bilateral supramarginal gyri, right temporal GM, and the left isthmus of the cingulate gyrus in FM compared with HCs.

Conflict of interest statement

The authors have no conflict of interest to declare.

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