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14. ABSTRACT This project is aimed at evaluating the contribution of brain glia to the pathophysiology of Gulf War Illness, as well as fibromyalgia (a functional pain disorder characterized by similar symptoms). So far we have completed administrative and regulatory review, made substantial progress on subject enrollment, and completed some preliminary analyses. Over 400 participants have been pre-screened for the study. Of those, forty participants have completed the study, while an additional twenty-two participants were enrolled and found to be ineligible at the time of screening. Throughout the recruitment process, we have actively modified our inclusion criteria to address concerns of ambiguity as they have arisen. Recruitment was slower than anticipated initially, but has rapidly picked up over the past year and the study is now approaching completion.					
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1. INTRODUCTION:

In this project, we are using simultaneous magnetic resonance imaging (MR) and positron emission tomography (PET) with [¹¹C]PBR28 – a recently developed PET ligand which binds to activated microglia with unprecedented specific-to-nonspecific binding ratio – to test the hypothesis that patients with Fibromyalgia (FM) or Gulf War Illness (GWI) demonstrate over-activation of brain microglia. Microglia are a subpopulation of macrophages known to mediate the inflammatory response of the central nervous system. While under normal conditions these cells are involved in adaptive homeostatic defense responses, such as the destruction of invading microorganisms, animal models have also provided evidence for a role of microglial activation in the development of chronic pain. Recognizing the role of these chronically active microglial cells in FM and GWI might lead to the development of new and potentially more effective treatment approaches for both conditions. Furthermore, if disease-specific patterns of microglial activation can be identified, it would improve our ability to correctly diagnose the two conditions and treat them with specificity not possible to date.

2. KEYWORDS:

Fibromyalgia; Gulf War Illness; Chronic Pain; Microglia; Neuroinflammation; Positron Emission Tomography; Magnetic Resonance Imaging

3. ACCOMPLISHMENTS:

What were the major goals of the project?

As stated in approved Statement of Work, we anticipated the following accomplishments during Year 2 of the project:

- Task 2: Subject Recruitment (months 4-24)
- Task 3: Study Visits (Behavioral and Imaging; months 5-32)
- Task 4: Data Analysis (Data Preprocessing; months 5-32)
- Task 5: Publication of Results (month 28-36)

Based on our approved quarterly enrollment targets, we anticipated enrolling and scanning 15 participants in Year 3.

What was accomplished under these goals?

During year 3, we stated that we would continue to accomplish Tasks 2-5.

Since recruitment was slower than anticipated in the beginning of this project, we began Year 3 with a focus on recruitment (**Task 2**). We explored alternative strategies for the recruitment of Gulf War Veterans including reaching out to veteran's groups and utilizing social media. With the travel compensation that was added in Year 2, we were able to drastically increase the sample of both healthy and ill veterans who have been enrolled. So far, 32 veterans with Gulf War Illness and 30 healthy veterans were successfully contacted and completed the phone screening process. Of those who have been phone screened, 18 veterans with Gulf War Illness and 11 healthy veterans were identified as being potentially eligible. In this coming year, we aim to identify 8 more healthy veterans and 1 additional Gulf War Ill Veteran who can complete the study.

In year 3, Fibromyalgia recruitment and enrollment was completed for this study. Over 100 Fibromyalgia subjects were successfully contacted and completed the phone screening process. Of those subjects who were phone screened, 28 were found to be eligible to enroll in the study. Common reasons subjects were excluded from participation in the study include co-occurring major medical and psychiatric illness, as well as the use of disqualifying medications such as steroids or diazepam.

While not paid for by this award, 176 civilian healthy controls have also been prescreened as part of this study. Of those 176, 18 subjects have been enrolled in the study.

In terms of Study Visits (**Task 3**), so far 28 participants with fibromyalgia, 18 civilian healthy controls, 15 veterans with Gulf War illness, and 10 healthy Gulf War veterans have completed the behavioral visit process. 15 Fibromyalgia subjects, 6 civilian healthy controls, 7 healthy Gulf War Veterans, and 12 veterans with Gulf War Illness have successfully completed all study procedures. To date 22 participants were withdrawn from the study due to significant history of psychological illness (4), major medical illness (4), comorbid autoimmune disorder (2), peripheral neuropathy (2), low affinity binding genotype (6), claustrophobia (2) as well as the use exclusionary medications (3). Another 2 subjects were lost to follow up, and 1 subject withdrew from the study since she was moving out of the area. An additional 3 participants were found eligible, and are expected to complete study procedures within the next reporting period.

Initial data analysis (**Task 4**) has been performed comparing fibromyalgia subjects to healthy civilians and veterans with Gulf War Illness to healthy veterans.

Preliminary analyses suggest that whole brain uptake of [¹¹C]PBR28 is increased in subjects with fibromyalgia when compared to pain-free civilian healthy controls. Mean whole-brain SUV demonstrated a trend-level effect of group ($p = 0.053$), while there was a significant main effect of genotype ($p=0.013$) as well as a significant group X genotype ($p=0.024$) interaction. To briefly summarize, fibromyalgia subjects demonstrated increased whole brain uptake of [¹¹C]PBR28, and this was especially significant in those subjects who were found to be high affinity TSPO binders.

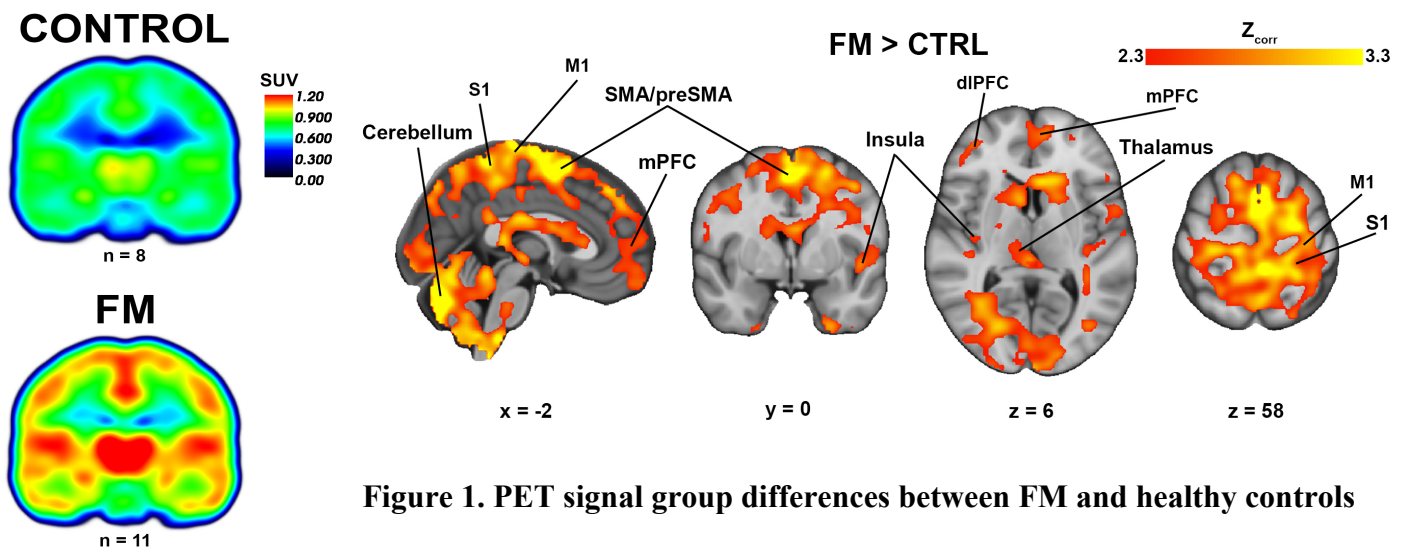


Figure 1. PET signal group differences between FM and healthy controls

A voxel-wise analysis revealed that high affinity binder fibromyalgia patients exhibited significantly elevated SUV in numerous sensory, motor, and higher-order cognitive regions compared to high affinity binding controls. There were no regions where control SUV was higher than fibromyalgia. When the mixed affinity binding subjects were included in the analysis, SUV were elevated in several of the same regions (e.g. S1, M1, cerebellum, preSMA), but at a lower statistical threshold ($p < 0.01$, uncorrected). FIQR was not significantly correlated with SUV in any region. The patterns of [¹¹C]PBR28 elevations in fibromyalgia support our hypothesis that microglial activation may play a role in the pathophysiology of fibromyalgia, however these findings were quite distinct from those observed in our previous chronic low back pain study. In accordance with the complex symptomatology of fibromyalgia, PET signal increases were widespread and encompassed a variety of sensory, motor and higher-order cognitive regions.

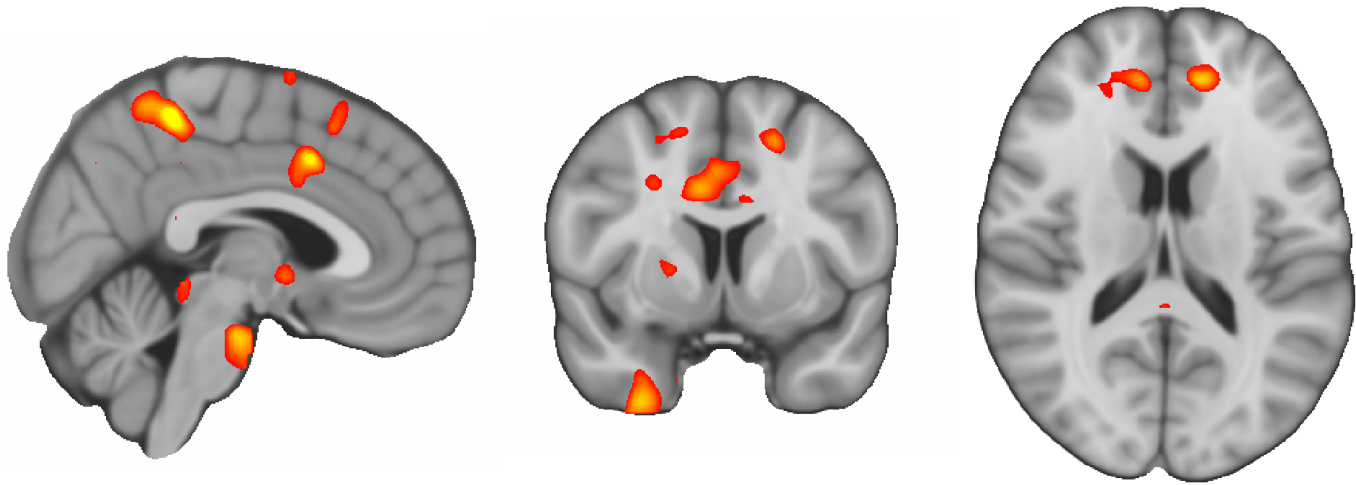


Figure 2. Regions where SUVR is elevated in GWI subjects

When comparing the [¹¹C]PBR28 SUV data across the veterans, an elevation in the PET signal appears evident in the veterans with GWI (Figure 2). Voxelwise analyses of 7 GWI veterans compared to 18 healthy controls, show significant increases in SUVR in the cingulate cortices, S1, brainstem, superior parietal lobule, and frontal cortex.

What opportunities for training and professional development has the project provided?

The project has supported travels at several international meetings, in which the results of our study have already been presented. In keeping with the award requirements, on November 11 2017 the data will be presented at the Society for Neuroscience meeting in Washington, DC.

How were the results disseminated to communities of interest?

Poster presentations of these findings have been given at two conferences thus far: the 11th International Symposium on Functional NeuroReceptor Mapping, Boston, MA, 2016, and the 16th World Congress on Pain, the International Association for the Study of Pain (2016), Yokohama, Japan. As mentioned, the GWI findings will also be presented in November at Neuroscience 2017 in Washington, D.C.

What do you plan to do during the next reporting period to accomplish the goals?

Within the next reporting period we aim to complete all recruitment, study visits, data analyses and begin publishing our findings for this study. Given the number of subjects we were able to enroll in the last reporting period, this task is attainable in the next reporting year.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The results of this study thus far suggest that glial activation may play a significant role in the neurobiological mechanisms underlying fibromyalgia and Gulf War Illness symptoms. If these results continue to hold true, this may point to novel therapeutic targets for treating GWI and fibromyalgia and it may also help to improve diagnostic accuracy for these debilitating disorders.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

If glial activation does play a significant role in fibromyalgia and Gulf War Illness, then this could potentially

impact drug discovery efforts for these conditions.

What was the impact on society beyond science and technology?

People with chronic pain conditions such as fibromyalgia and Gulf War Illness often experience a significant amount of stigma surrounding their diagnosis, since these conditions lack objective diagnostic tests. Many professionals still believe these disorders are more psychological than physiological in nature. It is our hope that by beginning to identify the underlying pathophysiology of fibromyalgia and Gulf War Illness, stigma surrounding these disorders will be reduced.

5. CHANGES/PROBLEMS:

All of the significant changes described below were reported to the DoD HRPO at the time of their approval by the Partners IRB. All changes have also been reported in our continuing review documents.

Changes in approach and reasons for change

1. **Modifications to inclusion/exclusion criteria:** Minor modifications to the inclusion and exclusion criteria were made in order to reduce ambiguity in the subject selection process. The need for these changes became apparent as subjects were screened and patterns in subjects' medical histories were identified that suggested the need for the modification of certain exclusion criteria without threatening the scientific integrity of the protocol. These changes include allowing for the use of marijuana and commonly used steroid medications in subjects with Gulf War illness, excluding for sciatica in subjects with fibromyalgia and modifying the exclusion criteria for hypertension to only exclude for extreme, uncontrolled hypertension in all subjects.
2. **Modifications to study procedures:** To improve data quality, modifications were made to study procedures. Most notably, arterial blood sampling during the MR/PET scan was added back into the protocol, which also changed the study compensation. In addition, we added a mock scan to the screening visit for subjects who are uncertain of their ability to tolerate the scanning environment and we began measuring subjects' body temperature on the day of the scan to ensure that they don't have an elevated body temperature that could cause confounding inflammation.
3. **Modification of recruitment methods:** To increase our subject pool, Recruitment methods were modified to include: social media advertising, ResearchMatch, and the use of new Partners Healthcare databases such as patients who elected for researchers to contact them directly, and advertising on the new Partners Clinical Trials website.

Actual or anticipated problems or delays and actions or plans to resolve them

To date, the only major delays faced were issues presented by subject recruitment. Referrals coming from the Gulf War Consortium Study were initially slower than anticipated, affecting our ability to recruit both healthy and Gulf War ill veterans. After identifying alternative recruitment methods, we were able to substantially increase enrollment in the study. In addition, by covering the cost of travel for veterans participating in the study from out of state, we were able to increase the subject pool that we are able to recruit from.

Changes that had a significant impact on expenditures

The addition of arterial line placement and blood analysis, needed to improve quantification of the PET signal, increased the cost of each scan where this data is acquired by about \$750.00.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations

Albrecht DS, Protsenko E, Mawla I, Bergan C, Kim M, Lee Y, Edwards R, Catana C, Oluwaseun A, Cohen G, Hooker JM, Napadow V, Loggia ML. Does brain glial activation have a role in fibromyalgia? A [¹¹C]PBR28 PET study. Poster presented at: IASP. 16th World Congress on Pain; 2016 September 26-30; Yokohama, Japan.

Albrecht DS, Protsenko E, Lee Y, Edwards R, Catana C, Oluwaseun A, Cohen G, Hooker JM, Napadow V, Loggia ML. Brain glial activation in fibromyalgia: a [¹¹C]PBR28 pilot study. Poster presented at: NRM2016. 11th International Symposium on Functional NeuroReceptor Mapping of the Living Brain; 2016 July 13-16; Boston, MA.

Website(s) or other Internet site(s)

scholar.harvard.edu/loggia

This is the lab's official website, hosted within the Harvard University network. The website provides an introduction to the lab's research, recent news, and a complete list of publications.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Personnel who have devoted at least 1 calendar month to the project are listed below:

Name:	Marco Loggia, PhD
Project Role:	Principal Investigator
Researcher Identifier (ORCID ID):	0000-0002-8026-5265
Nearest Person Month Worked:	3
Contribution to Project:	Directed the project, hired and supervised personnel, collected data
Funding Support:	

Name:	Courtney Bergan
Project Role:	Research Assistant
Researcher Identifier (ORCID ID):	N/A
Nearest Person Month Worked:	3
Contribution to Project:	Recruited and screened participants, collected data
Funding Support:	

Name:	Ciprian Catana
Project Role:	Co-investigator
Researcher Identifier (ORCID ID):	0000-0002-3249-5971
Nearest Person Month Worked:	1
Contribution to Project:	Provided advice on data processing
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The only investigator devoting at least 1 cal. mo. was the PI, Marco Loggia. Below are the changes in other support occurring after the beginning of the project.

New sources of support

1R61AT009306-01 (Napadow), *Optimization of brain-based mechanism supporting psychosocial aspects of acupuncture therapy – a hyperscanning fMRI study*, 0.36 cal.

R01AG053582-01 (Johnson-Akeju), *Pathophysiology of Postoperative Delirium and the Use of Biomimetic Sleep as a Treatment Strategy in the CSICU*, 0.6 cal.

5R01AR064367-04 (Edwards/Napadow), *Brain Mechanisms Underlying CBT-Related Reductions in Fibromyalgia*, 0.42 cal.

Reduced effort

1R01NS094306-01A1 (Loggia), *The role of brain glial activation in knee osteoarthritis*, from 4.56 cal. to 4.14 cal.

1R01NS095937-01A1 (Loggia), In-vivo imaging of spinal and brain glial activation in low back pain patients, from 3.24 cal to 2.76.

Terminated

Football Players Healthy Study at Harvard University, (S/C PI: Loggia), Imaging pain-related glial activation in retired professional football players

1R21NS087472 (PI: Loggia), The Role of Neuroimmune Activation in Chronic Pain and Negative Affect

NCMIC Foundation grant (PI: Loggia), Neural Correlates of Spinal Manipulative Therapy

R01 AT007550 (PI: Harris/Napadow) Neuroimaging Approaches to Deconstructing Acupuncture for Chronic Pain.

1R21NS082548-01A1 (PI: Zhang/Hooker), PET/MRI Imaging of Neuroaxial Inflammation in Sciatica Patients

What other organizations were involved as partners?

Organization Name:	Brigham and Women's Hospital
Location of Organization:	Boston, MA
Partner's Contribution to the Project: Financial Support In-kind Support Facilities Collaboration Personnel Exchange Other	Dr. Lee has been working with project staff on the project.

Organization Name:	Boston University School of Public Health – Gulf War Illness Consortium
Location of Organization:	Boston, MA
Partner's Contribution to the Project: Financial Support In-kind Support Facilities Collaboration Personnel Exchange Other	Dr. Sullivan has been working with project staff on the project

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Nothing to report

QUAD CHARTS:

Nothing to report

9. APPENDICES:

A. Albrecht DS, Protsenko E, Mawla I, Bergan C, Kim M, Lee Y, Edwards R, Catana C, Oluwaseun A, Cohen G, Hooker JM, Napadow V, Loggia ML. Does brain glial activation have a role in fibromyalgia? A [¹¹C]PBR28 PET study. Poster presented at: International Association for the Study of Pain conference; September 2016; Yokohama, Japan.



Does brain glial activation have a role in fibromyalgia? A [¹¹C]PBR28 PET study

*D. S. Albrecht^{1,2}, Ekaterina Protsenko¹, Ishtiaq Mawla¹, Courtney Bergan¹, Minhae Kim¹, Yvonne Lee³, Robert R. Edwards⁴, Ciprian Catana¹, Oluwaseun Akeju⁴, George Cohen⁵, J. M. Hooker¹, Vitaly Napadow¹, M. L. Loggia¹

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INTRODUCTION

Fibromyalgia (FM) is characterized by widespread pain and fatigue, and other symptoms.

FM pathophysiology is poorly understood, but central mechanisms have been implicated^{1,2}. While some have postulated a role for **neuroinflammation / glial activation** in FM^{3,4}, no study has ever demonstrated its occurrence in FM.

We have recently shown that patients with chronic low back pain demonstrated elevated levels in the **18 kDa Translocator Protein (TSPO)**, a marker of glial activation⁵.

In this preliminary study, we evaluate the brain levels of TSPO in FM, using integrated positron emission tomography / magnetic resonance imaging and the radioligand [¹¹C]PBR28

METHODS

- 13 FM patients and 14 pain-free healthy controls received a [¹¹C]PBR28 PET/MR brain scan.
- All subjects were genotyped for the Ala147Thr TSPO polymorphism, which predicts [¹¹C]PBR28 binding affinity (i.e., Ala/Ala=High affinity binders, HAB; Ala/Thr=Mixed affinity binders, MAB; Thr/Thr=Low affinity binders, LAB)⁶.
- Integrated PET/MR scans conducted on a 3T Siemens PET/MRI scanner with [¹¹C]PBR28 for 90 minutes
- Static images were generated from 60-90 minute post-injection PET data, and divided by injected dose per body weight (Standardized Uptake Value, SUV). We adopted this approach, instead of performing kinetic modeling with an arterial input function, because of the difficulties inherent to accurate quantification of TSPO binding with these methods⁷.
- Mean whole-brain SUV was compared between groups by univariate GLM analysis, with group as a fixed factor and genotype as a covariate of no interest.
- SUV maps were compared across groups using voxelwise t-tests, with genotype, sex, and age included as covariates of no interest. The same analysis was repeated in HAB subjects only, with sex and age as covariates. Resulting statistical maps were cluster corrected for multiple comparisons using a cluster-forming voxel-wise threshold of $z > 2.3$, and a (corrected) cluster significance threshold of $p < 0.05$.
- The association between FM symptoms (i.e. Revised Fibromyalgia Impact Questionnaire [FIQR] total score) and SUV was assessed with regression analyses

Subject Characteristics

Variable	FM (n=13)	CTRL (n=14)
Age	51.6 ± 10	51.3 ± 11
Gender	12F; 1M	9F; 5M
TSPO Genotype	11 Ala/Ala (HAB) 2 Ala/Thr (MAB)	6 Ala/Ala (HAB) 6 Ala/Thr (MAB)
FIQR	49.3 ± 17	N/A

Data are mean ± s.d. FM – fibromyalgia; CTRL – control; HAB – high affinity binder; MAB – mixed affinity binder; FIQR – Revised Fibromyalgia Impact Questionnaire

REFERENCES

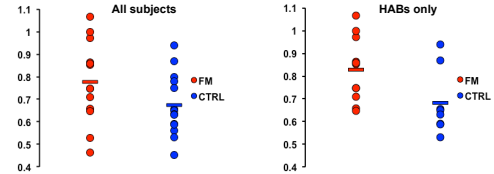
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- Zürcher, N. R. et al., *NeuroImage Clin* 7, 408-414 (2015).
- Albrecht, D. S. et al., *ACS Chem Neurosci* 7(4), 470-83.
- Lypo, H. L. et al. *J Nucl Med* 56, 701-706 (2015).

RESULTS

FM patients display higher mean whole-brain [¹¹C]PBR28 SUVs

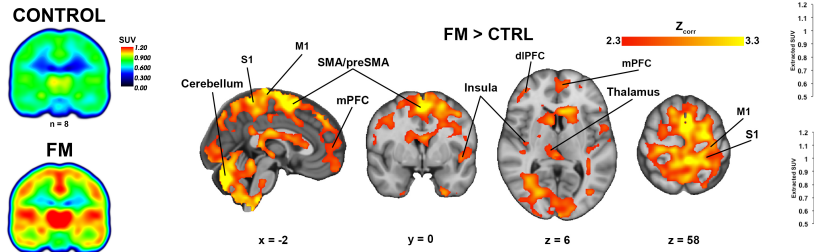
Mean whole-brain SUV demonstrated a trend-level effect of group ($p = 0.053$), a significant main effect of genotype ($p = 0.013$), and a significant group x genotype interaction ($p = 0.024$).

Post-hoc tests revealed that the group effect was driven by HAB subjects, as group differences in whole-brain SUV were significant only in HABs ($p = 0.04$).



Voxelwise comparison identifies widespread regions of increased [¹¹C]PBR28 signal in FM

A voxel-wise analysis revealed that HAB FM patients exhibit significantly elevated SUV in numerous sensory, motor, and higher-order cognitive regions compared to HAB controls. There were no regions where control SUV was higher than FM. When the MABs subjects were included in the analysis, SUV were elevated in several of the same regions (e.g. S1, M1, cerebellum, preSMA), but at a lower statistical threshold ($p < 0.01$, uncorrected). FIQR was not significantly correlated with SUV in any region.



Supported by DoD W81XWH-14-1-0543 (M.L.L.), IASP Early Career Award (M.L.L.), Martinos Center Pilot Grant for Postdoctoral Fellows (D.S.A.), Harvard Catalyst Advance Imaging Pilot Grant (J.M.H.) and P41RR14075

DISCUSSION AND CONCLUSIONS

- Fibromyalgia patients exhibited higher [¹¹C]PBR28 SUV across the entire brain, compared to controls.
- The patterns of [¹¹C]PBR28 elevations in FM were quite distinct from those observed in our previous chronic low back pain study⁸. In accordance with the complex symptomatology of FM, PET signal increases were widespread and encompassed a variety of sensory, motor and higher-order cognitive regions.
- In TSPO PET imaging, the large interindividual variability in the global signal makes the utilization of intensity normalizing strategies (e.g., whole brain normalization^{9,10}) desirable, in order to identify effects that may be obscured by large within-group variance⁹. The fact that we were able to observe significant increases even in non-normalized SUVs, indicates that the group differences in TSPO expression may be substantial enough to overcome the large within-group variance in [¹¹C]PBR28 data.
- Nonetheless, future investigations will need to validate alternative quantification methods, such as the use of a suitable pseudo-reference region¹⁰, in order to improve the characterization of the [¹¹C]PBR28 signal in FM. The presence of significant differences in whole-brain SUV across groups indicates that the use of whole brain uptake to intensity-normalize [¹¹C]PBR28 data, previously adopted for the study of different pathologies^{5,8}, may not be appropriate in FM.
- In sum, these data provide preliminary evidence of increased global TSPO expression in FM, suggesting the occurrence of widespread glial activation. If validated in a larger dataset, these observations would support the exploration of glia-based therapeutic approaches for FM³.