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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, have begun subject enrollment, and completed some preliminary analyses. Over 200 participants have been pre-screened for the study. Of those, eighteen participants have completed the study, while an additional twelve 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 few months.					
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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)

Based on our approved quarterly enrollment targets, we anticipated enrolling and scanning 20 participants in Year 2.

What was accomplished under these goals?

During year 2, we stated that we would continue to accomplish Tasks 2-4.

Subject Recruitment (**Task 2**) was initially slow to begin year 2, as referrals from the Gulf War Illness Consortium continued to be slower than anticipated through the beginning of this year. We began to explore alternative strategies for the recruitment of Gulf War Veterans including reaching out to veterans groups and utilizing social media. We also attempted to expand the pool of veterans we could recruit from by compensating for travel expenses. Since we began employing these methods, recruitment has rapidly increased and we have now enrolled 5 healthy Gulf War Veterans and 2 veterans with Gulf War Illness. So far, 17 veterans with Gulf War Illness and 6 healthy veterans were successfully contacted and completed the phone screening process. Of those who have been phone screened, 9 veterans with Gulf War Illness and 5 healthy veterans were identified as being potentially eligible. 8 of the veterans with Gulf War Illness will be participating from out of state, so they are being enrolled as they become available to travel to Boston. The remaining local veteran with Gulf War Illness is scheduled for study enrollment in early November. We expect that study recruitment will continue to steadily increase and we should be able to meet our recruitment targets of 15 veterans with Gulf War Illness and 15 healthy veterans within the expected timeframe.

While veteran recruitment was initially slow, Fibromyalgia recruitment was steady in year 2. We have been using several different methodologies to recruit Fibromyalgia patients for this study, including direct referrals

by study staff from rheumatology clinics at Brigham and Women's and Massachusetts General Hospital. In addition we have been taking advantage of existing Fibromyalgia patients from our other fMRI studies and making use of subject recruitment resources such as the Partners Research Patient Data Registry (RPDR) and RSVP. So far, 87 Fibromyalgia subjects have been successfully contacted and have completed the phone screening process. Of those subjects who were phone screened, 23 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, 64 civilian healthy controls have also been prescreened as part of this study. Of those 64, 9 subjects have been enrolled in the study.

In terms of Study Visits (**Task 3**), so far 21 participants with fibromyalgia, 9 civilian healthy controls, 2 veterans with Gulf War illness, and 5 healthy Gulf War veterans have completed the behavioral visit process. 9 Fibromyalgia subjects, 4 civilian healthy controls, 3 healthy Gulf War Veterans, and 1 veteran with Gulf War Illness have successfully completed all study procedures. To date 13 participants, all belonging to the fibromyalgia and civilian healthy control groups, were withdrawn from the study due to significant history of psychological illness (2), major medical illness (1), comorbid autoimmune disorder (2), peripheral neuropathy (2), low affinity binding (3), claustrophobia (1) as well as the use exclusionary medications (3). An additional 5 participants were found eligible, and are expected to complete study procedures within the next reporting period.

Data analyses (**Task 4**) performed thus far have primarily focused on data collected from our fibromyalgia subjects. Preliminary analyses suggest that whole brain uptake of [^{11}C]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 [^{11}C]PBR28, and this was especially significant in those subjects who were found to be high affinity TSPO binders.

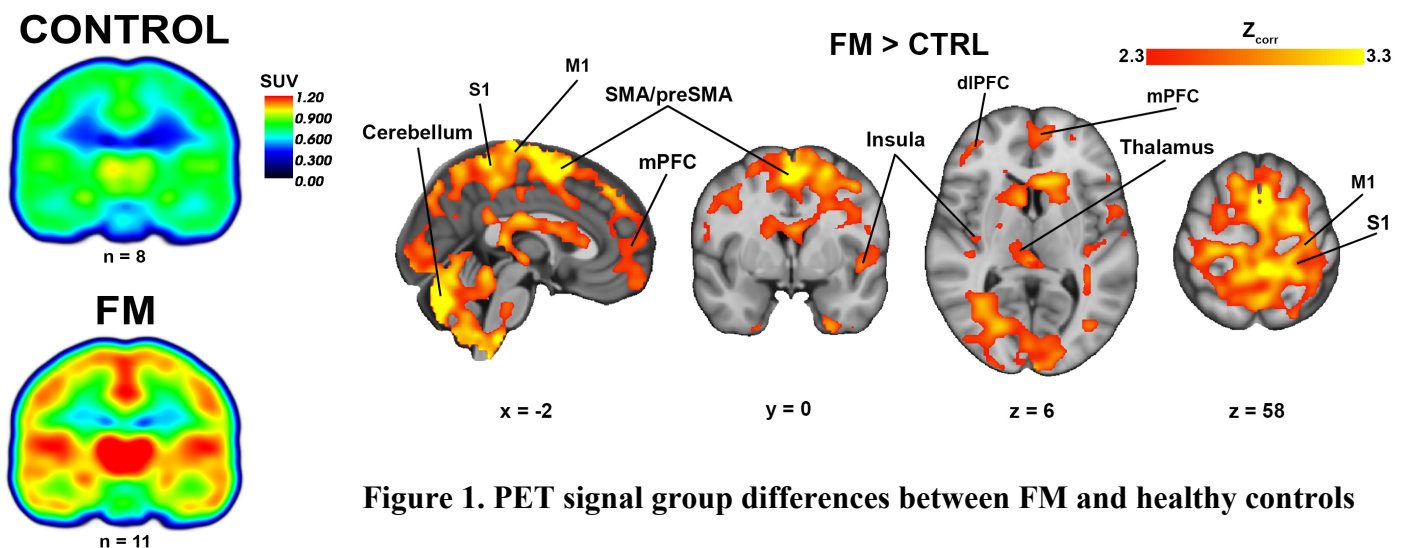


Figure 1. PET signal group differences between FM and healthy controls

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 [^{11}C]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.

When comparing the [^{11}C]PBR28 SUV data across the veterans, an elevation in the thalamic PET signal appears evident in the veteran with GWI (Figure 2). While it is certainly too early to draw any conclusion from this small sample of veterans, the elevations seen in the veteran with GWI appear substantial.

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

The project has supported travels at several international meetings, in which the FM results have already been presented.

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.

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

Within the next reporting period we aim to complete recruitment, study visits, and data analyses for this study,

as outlined in the SOW. Given the rapid increase in subject recruitment and enrollment since our implementation of travel reimbursement, we believe this it is still a reasonable goal to meet our enrollment target by the end of this reporting year. In addition to completing Tasks 2-4, we hope to begin to undertake the task of publishing our findings prior to the end of the reporting year. Given the significance of the findings thus far, we believe it is reasonable to expect manuscript submission by the end of the 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 symptoms. If these results continue to hold true, this may point to novel therapeutic targets for treating fibromyalgia and it may also help to improve diagnostic accuracy for this debilitating disorder.

What was the impact on other disciplines?

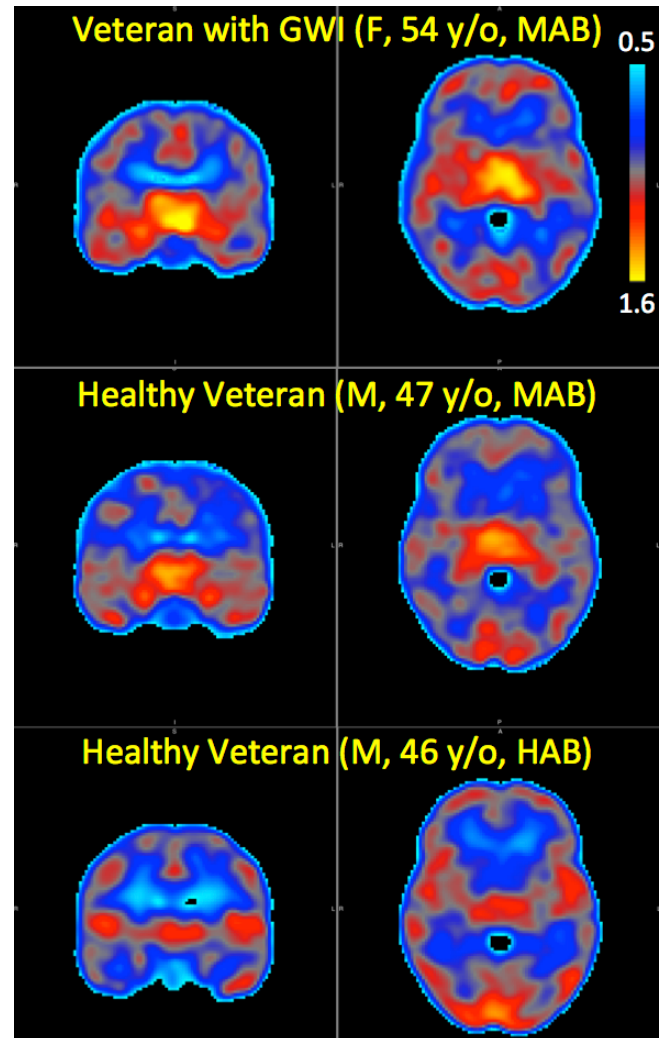


Figure 2. Single-subject PET data from veterans with (top) or without (middle, bottom) Gulf War Illness

Nothing to report.

What was the impact on technology transfer?

If glial activation does play a significant role in fibromyalgia, and other chronic pain disorders, then this could potentially impact drug discovery efforts for these conditions.

What was the impact on society beyond science and technology?

People with fibromyalgia often experience a significant amount of stigma surrounding their diagnosis, since many professionals still believe symptoms of fibromyalgia are more psychological than physiological in nature. It is our hope, that by beginning to identify the underlying pathophysiology of fibromyalgia, stigma surrounding the disorder will be reduced.

5. CHANGES/PROBLEMS:

All of the changes described below were reported to the DoD HRPO at the time of their approval by the Partners IRB. None of the changes listed required full meeting review by either the Partners IRB or the DoD HRPO. All changes have also been reported in the quarterly technical progress reports.

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 reducing the eligibility age for subjects with fibromyalgia and allowing for the use of certain benzodiazepines, when there is evidence to suggest that there is no effect of the medication on [11C]PBR28 binding. These changes were further outlined in the technical reports.
2. **Increasing the number of subjects enrolled in this study:** After completing numerous behavioral visits it became readily apparent that nearly half the subjects enrolled in the fibromyalgia group did not meet eligibility criteria due to reasons previously detailed. For this reason we decided to increase the number of subjects to be consented for the study. In addition we increased the number of subjects that can complete the study to 21 subjects per group since a number of fibromyalgia subjects were scanned under other awards and we did not want to exceed maximum number we were able to scan under this protocol.
3. **Addition of travel reimbursement:** After valid attempts were made at subject recruitment within the Boston area, it became readily apparent that travel reimbursement was needed in order to complete enrollment of the veteran populations for this study. Numerous veterans from outside of the Boston area contacted us and expressed interest in participating in our study if we could help to defray the cost of travel. We are now covering up to \$600.00 in travel expenditures (to include the cost of transportation and hotel accommodations) for the purposes of study participation.

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. However, recently, we have identified alternative avenues for recruiting veterans including reaching out to veterans groups and other researchers in the field. While we are still primarily relying on the consortium study for veteran referrals, these additional avenues have allowed us to supplement our recruitment efforts and 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 are increasing the subject pool that we are able to recruit from.

Changes that had a significant impact on expenditures

Given that we have begun to reimburse for travel costs, \$10,000 in scanning funds were reallocated to cover the costs associated with travelling from out of state. Both the DOD and the Partners IRB approved this change.

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 [^{11}C]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 [^{11}C]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:	4
Contribution to Project:	Directed the project, hired and supervised personnel, collected data
Funding Support:	

Name:	Ekaterina Protsenko
Project Role:	Research Assistant
Researcher Identifier (ORCID ID):	N/A
Nearest Person Month Worked:	2
Contribution to Project:	Recruited and screened participants, collected data
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

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

1R01NS095937-01A1 (PI: Loggia), *In-vivo imaging of spinal and brain glial activation in low back pain patients* (3.24 cal)

Football Players Healthy Study at Harvard University, (S/C PI: Loggia), *Imaging pain-related glial activation in retired professional football players* (0.6 cal)

Reduced effort

1R21NS087472 (PI: Loggia), *The Role of Neuroimmune Activation in Chronic Pain and Negative Affect* (from 2.76 cal to 0.24)

NCMIC Foundation grant (PI: Loggia), *Neural Correlates of Spinal Manipulative Therapy* (from 1.92 cal to 0.12 cal)

Terminated

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

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 [^{11}C]PBR28 PET study. Poster presented at: International Association for the Study of Pain conference; September 2016; Yokohama, Japan.

B. 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 [^{11}C]PBR28 pilot study. Poster presented at: 11th International Symposium on Functional NeuroReceptor Mapping of the Living Brain; July 2016; Boston, MA.

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1. Napadow and Harris. *Arthritis Res Ther* **16**(5), 425 (2014).
2. Loggia et al., *Arthritis Rheumatol* **66**(1), 203-212 (2014).
3. Younger et al., *Clin Rheumatol* **33**(4), 451-9 (2014).
4. Littlejohn et al., *Nat Rev Rheumatol* **11**(11), 639-48 (2015).
5. Loggia et al., *Brain* **138**(pt 3), 604-615 (2015).
6. Owen, D. R. et al. *Clin and Transl Imaging*, 1-6 (2015).
7. Turkheimer et al., *Biochem Soc Trans* **43**(4), 586-592 (2015).
8. Zurcher, N. R. et al. *NeuroImage Clin* **7**, 409-414 (2015).
9. Albrecht, D. S. et al. *ACS Chem Neurosci* **7**(4), 470-83.
10. Lyoo, H. L. et al. *J Nucl Med* **56**, 701-706 (2015).

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

- The patterns of [¹¹C]PBR28 elevations in FM were quite distinct from those observed in our previous chronic low back pain study⁶. 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^{5,9}) desirable, in order to identify effects that may be obscured by large within-group variance⁸. 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.



Brain glial activation in fibromyalgia: a [¹¹C]PBR28 pilot study

*D. S. Albrecht^{1,2}, Ekaterina Protchenko¹, 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 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 activation².

In this preliminary study, we evaluate the brain levels of TSPO in FM, using the radioligand [¹¹C]PBR28.

METHODS

- 10 FM patients received a [¹¹C]PBR28 brain scan. 10 controls, scanned as part of a previous study², were included in these analyses
- All subjects were genotyped for *TSPO* genotype, 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)⁵
- Integrated PET/MR scans conducted on a 3T Siemens PET/MRI scanner and [¹¹C]PBR28 for 90 minutes
- Static images generated from 60-90 minute post-injection PET data, and divided by injected dose per body weight (Standardized Uptake Value, SUV)
- In order to account for interindividual differences in PET signal variability, SUV images were normalized by whole brain uptake to create SUVR parametric maps, as reported previously^{2,6}
- SUVR maps were compared across groups using voxelwise t-tests. 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 SUVR was assessed with exploratory regression analyses

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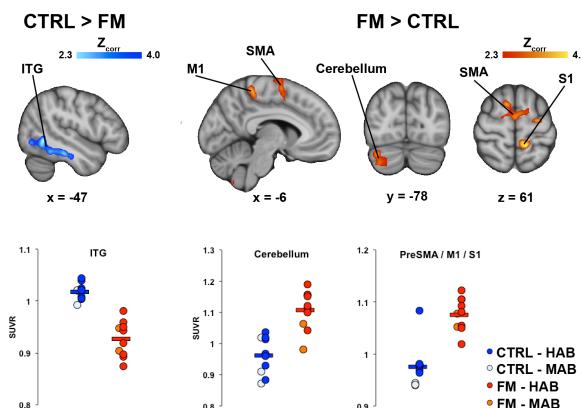
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Subject Characteristics

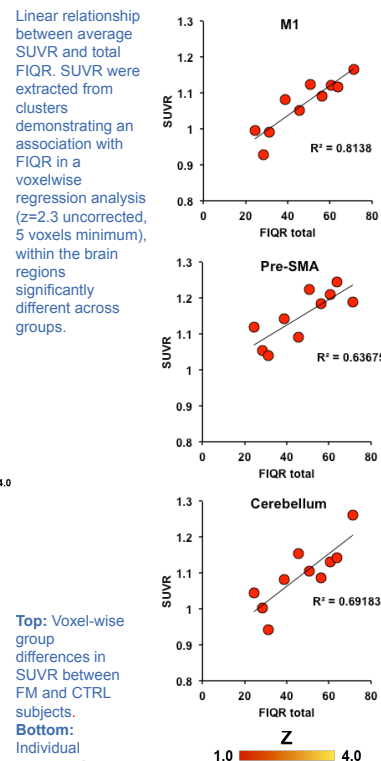
Variable	FM (n=10)	CTRL (n=10)
Age	51.2 ± 9.2	52.3 ± 12
Gender	9F; 1M	6F; 4M
<i>TSPO</i> Genotype	8 Ala/Ala (HAB) 2 Ala/Thr (MAB)	7 Ala/Ala (HAB) 3 Ala/Thr (MAB)
FIQR	47.1 ± 16	N/A

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

[¹¹C]PBR28 signal is significantly different between patients with fibromyalgia and controls



Enhanced [¹¹C]PBR28 SUVR is associated with fibromyalgia symptoms



Top: Voxel-wise group differences in SUVR between FM and CTRL subjects.
Bottom: Individual subjects' SUVRs for significant clusters in top panel.

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

CONCLUSIONS

- Fibromyalgia patients exhibited higher [¹¹C]PBR28 signal in several motor regions (M1, preSMA, Cerebellum), as well as in the primary somatosensory cortex.
- SUVR was significantly positively correlated with fibromyalgia symptoms, indicating a potential relationship between enhanced glial activation and FM pathophysiology.
- Disruption in motor regions in FM have been demonstrated⁷⁻⁹, and M1 has been targeted by tDCS for relief of FM symptoms¹⁰.
- Surprisingly, FM patients exhibited *lower* [¹¹C]PBR28 signal in left inferior temporal gyrus.
- These data provides preliminary evidence of dysregulation in TSPO expression in FM: increases in motor and somatosensory regions suggest the occurrence of glial activation. In addition, as TSPO is a mitochondrial protein, reductions in TSPO levels might be related to mitochondrial dysfunction in FM patients¹¹. These observations will need to be validated in a larger dataset.