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Elevated Insular Glutamate in Fibromyalgia Is Associated With Experimental Pain

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Objective. **Central pain augmentation resulting from enhanced excitatory and/or decreased inhibitory neurotransmission is a proposed mechanism underlying the pathophysiology of functional pain syndromes such as fibromyalgia (FM). Multiple functional magnetic resonance imaging studies implicate the insula as a region of heightened neuronal activity in this condition. Since glutamate (Glu) is a major cortical excitatory neurotransmitter that functions in pain neurotransmission, we undertook this study to test our hypothesis that increased levels of insular Glu would be present in FM patients and that the concentration of this molecule would be correlated with pain report.**

Methods. **Nineteen FM patients and 14 age- and sex-matched pain-free controls underwent pressure pain testing and a proton magnetic resonance spectroscopy session in which the right anterior insula and right posterior insula were examined at rest.**

Results. **Compared with healthy controls, FM patients had significantly higher levels of Glu (mean ± SD 8.09 ± 0.72 arbitrary institutional units versus 6.86 ± 1.29 arbitrary institutional units; $P = 0.009$) and combined glutamine and Glu (i.e., Glx) (mean ± SD 12.38 ± 0.94 arbitrary institutional units versus 10.59 ± 1.48 arbitrary institutional units; $P = 0.001$) within the right posterior insula. No significant differences between groups were detected in any of the other major metabolites within this region ($P > 0.05$ for all comparisons), and no group differences were detected for any metabolite within the right anterior insula ($P > 0.11$ for all comparisons). Within the right posterior insula, higher levels of Glu and Glx were associated with lower pressure pain thresholds across both groups for medium pain (for Glu, $r = -0.43$, $P = 0.012$; for Glx, $r = -0.50$, $P = 0.003$).**

Conclusion. **Enhanced glutamatergic neurotransmission resulting from higher concentrations of Glu within the posterior insula may play a role in the pathophysiology of FM and other central pain augmentation syndromes.**

Although acute pain can function beneficially to alert an organism to immediate or imminent tissue damage, chronic pain can often occur in the absence of tissue damage or inflammation. Functional chronic pain syndromes are a subset of pain disorders in which patients paradoxically report frequent pain symptoms in the absence of anatomic injury or objective pathologic findings (1,2). As such, these disorders are particularly troublesome for patients and clinicians alike. Although new treatment options exist (3–5), significant disability and dysfunction are prevalent.

Fibromyalgia (FM) is the prototypical functional

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chronic pain condition, and it affects ~2–4% of individuals (6–8). Although the etiology of this disorder remains largely unknown, emerging data suggest that FM arises through augmentation of central pain processing pathways. This hypothesis is based largely upon findings of previous functional neuroimaging studies showing that FM patients display augmented neuronal responses to both innocuous and painful stimuli (9,10), corroborating the allodynia and hyperalgesia seen in this condition (11).

A growing body of literature suggests that glutamate (Glu), an excitatory neurotransmitter, within the central nervous system may play a role in FM pathology. A study by Peres et al found that cerebrospinal fluid (CSF) levels of Glu were elevated in FM patients, possibly having consequences for glutamatergic neurotransmission (12). In a separate line of inquiry, the concentration of glutamine (Gln; a precursor in Glu biosynthesis) in the CSF of FM patients was positively correlated with a number of evoked pain measures—greater Gln levels were associated with greater pain (13). Moreover, administration of ketamine, a Glu channel blocker, has been found to reduce experimental (14) and clinical (15) pain in FM. While these studies are informative, they do not identify a specific brain region(s) that is either the origin or the target of Glu in FM.

We recently demonstrated that long-term treatment of FM patients with acupuncture and/or sham acupuncture led to changes in Glu levels within the posterior insula that were correlated with changes in experimental and clinical pain (16). Patients displaying greater reductions in Glu also had greater decreases in both experimental and clinical pain.

In the present study, we extend these findings by investigating the relationship between insular Glu and combined Gln and Glu (i.e., Glx) in individuals with FM and in age- and sex-matched pain-free controls. We hypothesized that if insular hyperactivity is due to enhanced glutamatergic neurotransmission in FM, patients should display elevated levels of Glu as compared with controls. Furthermore, if these levels are indicative of augmented pain processing, Glu and Glx levels should be negatively correlated with evoked pressure pain thresholds.

PATIENTS AND METHODS

Participants. We studied 19 female FM patients (mean ± SD age 45.2 ± 15.0 years) and 14 age- and sex-matched healthy controls (mean ± SD age 45.9 ± 11.1 years) ($P = 0.89$). All participants gave written informed consent, and all study protocols were approved by the University of Michigan Institutional Review Board.

All participants with FM fulfilled the following conditions: 1) met the American College of Rheumatology (ACR) 1990 criteria for the classification of FM (17) for at least 1 year, 2) had continued presence of pain for >50% of days, 3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study, 4) were >18 years old and <75 years old, 5) were female, 6) were right-handed, and 7) were capable of giving written informed consent. FM participants were excluded if they 1) currently used or had a history of use of opioid or narcotic analgesics; 2) had a history of substance abuse; 3) had the presence of concurrent autoimmune or inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc., that causes pain; 4) were concurrently participating in other therapeutic trials; 5) were pregnant and/or nursing mothers; 6) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, substance abuse within the previous 2 years); or 7) had current major depression. A list of concomitant medications for FM participants is available at http://www.med.umich.edu/painresearch/about/Supplementary%20Table%201%20Concurrent%20Medications%20for%20FM%20Participants.pdf. Longitudinal proton magnetic resonance spectroscopy (H-MRS) data for 10 of the FM patients have been reported previously (16).

All healthy controls were >18 years old and <75 years old, female, capable of giving written informed consent, right-handed, and willing to complete all study procedures. Healthy controls were excluded if they had ever met the ACR 1990 criteria for the classification of FM, had any chronic medical illness including psychiatric disorders (psychosis, schizophrenia, delusional disorder, etc.), or were pregnant.

H-MRS. All subjects underwent conventional magnetic resonance imaging (MRI) of the brain on a 3.0T MR scanner (General Electric Medical Systems, Milwaukee, WI). Single-voxel spectroscopy was performed using the following parameters: point resolved spectroscopy, repetition time 3,000 msec, echo time 30 msec, flip angle 90°, number of excitations 8, field of view 16 cm, with a volume of interest (VOI) of $2 \times 2 \times 3$ cm. During each session, 2 separate single-voxel spectroscopy sequences were performed, once with the VOI placed in the right anterior insula and once in the right posterior insula (Figure 1A). The approximate Montreal Neurological Institute coordinates for the centers of the anterior and posterior voxels were 34,19,0 and 38,–17,8, respectively. These coordinates include regions shown previously to be activated during acute pain (18). Also, functional MRI trials in FM have shown augmented pain activity in these regions (9,10).

Given the time constraints for our H-MRS session, we examined the right insula, since it was contralateral to the location where pain stimuli were previously applied in our group's functional MRI trials of FM (9,16). Participants were at rest during the H-MRS session. The raw data from each single-voxel MR spectroscopy sequence underwent manual postprocessing using H-MRS software (LCModel; Stephen Provencher, Oakville, Ontario, Canada). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra (Figure 1B). Values for Glu, Gln, Glx, and other metabolites including

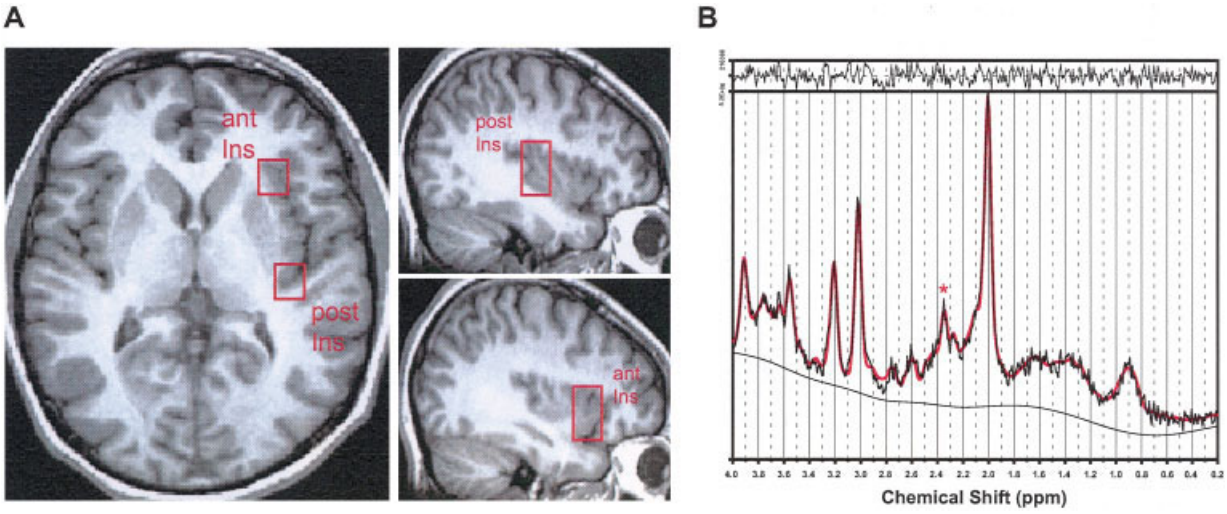

Figure 1. Insula voxel placement and resulting spectrum. **A,** Axial and sagittal T1-weighted images showing single-voxel placements for right anterior insula (ant Ins) and right posterior insula (post Ins). **B,** Representative proton magnetic resonance spectroscopy spectrum from the posterior insula fit with LCModel (red trace; ∗ = resonance from 2 glutamate [Glu] γ proton resonances at 2.35 parts per million [ppm]). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra. Absolute concentrations of Glu were calculated in arbitrary institutional units using water as an internal scaling factor.

N-acetylaspartate (NAA), choline compounds, creatine, and *myo*-inositol were calculated as absolute concentrations using the water signal for normalization (19). Resulting metabolite absolute concentrations were reported in arbitrary institutional units.

Since our voxels incorporated CSF, and the volume of CSF dilutes H-MRS–derived metabolite values, we corrected our metabolite levels for CSF volume for each participant. For this we used Voxel Based Morphometry, a toolbox that operates within the image analysis program Statistical Parametric Mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm/software). High-resolution T1-weighted images were segmented into gray matter, white matter, and CSF, and then regions of interest within the anterior and posterior insula were used to extract gray matter, white matter, and CSF volumes from these images using the SPM2 toolbox Marsbar (http://marsbar.sourceforge.net). Metabolite values were corrected by dividing the observed concentration in arbitrary institutional units by the percentage of volume of the entire voxel that was not occupied by CSF (i.e., the percentage of voxel volume occupied by gray matter plus white matter). Corrected metabolite concentrations were entered into SPSS version 16 (SPSS, Chicago, IL) for calculation of differences between FM and healthy control groups and for correlational analyses with pain outcomes.

Experimental pain. Pressure pain tenderness was assessed prior to the H-MRS session as described previously (20,21). Briefly, discrete pressure stimuli were applied to the subject's thumbnail using a stimulation device, which eliminates any direct examiner/subject interaction. Pain intensity ratings were recorded on the Gracely Box Scale (GBS) questionnaire using a random presentation paradigm (21). During the testing, stimulus pressures were determined interactively. A computer program continuously adjusted stimulus pressure levels (low = GBS 0.5, medium = GBS 7.5, high = GBS 13.5) to produce the same response distribution in each subject. Pressure pain thresholds were then correlated with H-MRS–derived metabolite levels using SPSS version 16.

Statistical analysis. Metabolite levels and pain ratings were entered into SPSS version 16. We performed two-way analysis of variance to determine differences in metabolite levels, with group (FM group or healthy control group) and age strata as fixed factors. Since there was evidence of differences in the variability of Glu and Glx levels between the healthy control and FM groups, we performed an additional analysis using weighted least squares, with weights equaling the inverse of the corresponding estimated group variances. We next correlated pressure pain thresholds with Glu and Glx levels from the posterior insula, since these levels were found to be elevated in the FM participants. Pearson's correlations were calculated on the combined group of FM and healthy control participants. Separate multiple linear regression models were constructed with Glu or Glx levels as dependent variables and with group (FM group or healthy control group) medium pressure threshold and age strata as independent variables. *P* values less than 0.05 were considered significant.

RESULTS

FM patients have elevated Glu and Glx levels in the posterior insula. As shown in Table 1 and Figure 2A, compared with healthy controls, individuals with FM displayed elevated levels of both Glu ($P = 0.009$) and Glx ($P = 0.001$) within the posterior insula. Glu and Glx levels remained significantly elevated in similar analyses

Table 1. Comparison of posterior and anterior insula corrected metabolite levels (in arbitrary institutional units) between FM patients and healthy controls*

Location, metabolite	FM patients	Healthy controls	*P*
Posterior insula			
Glu	8.09 ± 0.72	6.86 ± 1.29	0.009
Glx	12.38 ± 0.94	10.59 ± 1.48	0.001
Gln	4.30 ± 0.86	3.73 ± 1.13	0.13
NAA	10.47 ± 0.64	9.46 ± 1.58	0.06
Creatine	7.15 ± 0.78	6.52 ± 1.15	0.10
Myo-inositol	4.94 ± 0.60	4.86 ± 0.98	0.98
Cho	1.81 ± 0.27	1.63 ± 0.37	0.15
Anterior insula			
Glu	9.91 ± 1.47	9.29 ± 1.11	0.52
Glx	14.30 ± 2.48	13.78 ± 1.93	0.85
Gln	4.40 ± 1.82	4.49 ± 1.77	0.82
NAA	12.49 ± 1.77	11.38 ± 1.02	0.12
Creatine	8.29 ± 1.41	7.92 ± 0.88	0.60
Myo-inositol	5.66 ± 1.16	5.74 ± 0.53	0.45
Cho	2.32 ± 0.43	2.21 ± 0.32	0.49

* Values are the mean ± SD. FM = fibromyalgia; Glu = glutamate; Glx = Glu plus glutamine (Gln); NAA = *N*-acetylaspartate; Cho = choline compounds.

that used weighted least squares ($P = 0.008$ for Glu, $P = 0.001$ for Glx). Eighteen of the 19 FM patients had mean Glu levels that were higher than the mean level in healthy controls, whereas all FM patients had higher Glx levels than the mean level in healthy controls. FM patients also had a trend toward higher NAA levels in the posterior insula ($P = 0.06$); however, this did not reach statistical significance. There were no differences between FM and healthy control groups in levels of the other major metabolites (Gln, *myo*-inositol, creatine, and choline compounds) within the posterior insula ($P \geq 0.10$ for all comparisons). These data suggest a relatively specific elevation of Glu and Glx levels in the right posterior insula for the FM group.

As shown in Table 1 and Figure 2B, there were no significant group differences in the levels of Glu and Glx or other metabolites within the anterior insula ($P > 0.11$ for all comparisons). These data suggest that the elevated levels of Glu are specific for the posterior insula and do not extend into the anterior regions.

Glu and Glx levels are negatively correlated with pressure pain thresholds. Significant negative correlations between pressure pain thresholds and posterior insula Glu and Glx levels were observed when both groups were combined (Table 2). A scatterplot of posterior insula Glx values versus medium pressure pain thresholds is illustrated in Figure 3. These data suggest that, regardless of whether an individual is an FM patient or a healthy control, individuals with higher levels of Glu and/or Glx also have enhanced sensitivity to experimentally induced pressure pain.

Since group status (FM group or healthy control group) and pressure pain thresholds were both related to Glu and Glx levels in the posterior insula, we constructed separate linear regression models with either Glu or Glx levels as dependent variables and group (FM group or healthy control group) and medium pressure

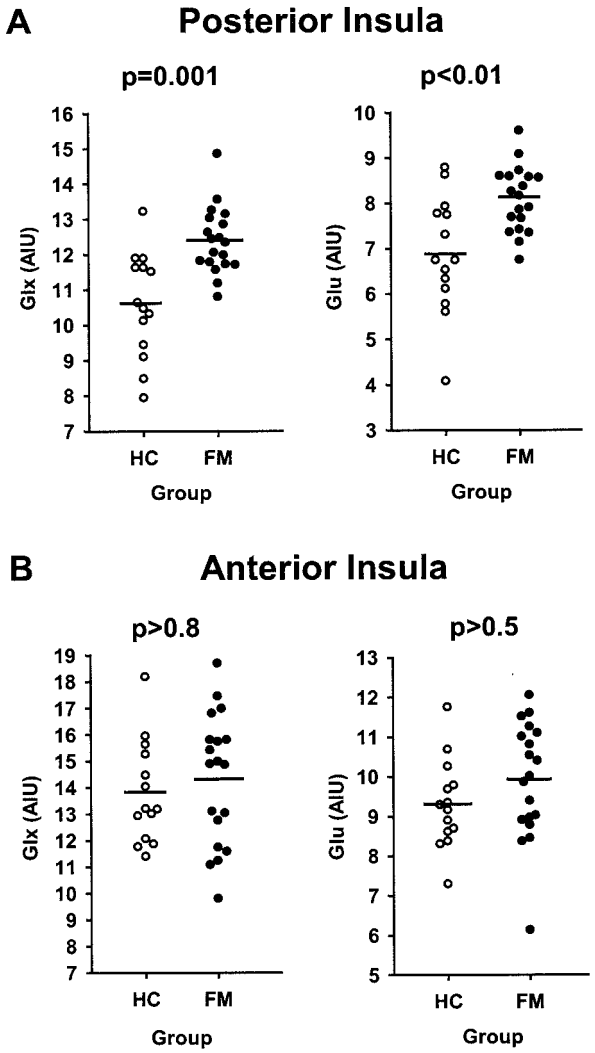

Figure 2. Elevated levels of glutamate (Glu) and combined glutamine and Glu (Glx) within the posterior insula of patients with fibromyalgia (FM). Circles represent corrected Glx and Glu levels in the posterior insula **(A)** and in the anterior insula **(B)** for individual FM patients and healthy controls (HC). Horizontal bars indicate the mean. FM patients have elevated concentrations of Glu and Glx in the posterior insula, while there is no difference between FM patients and healthy controls in Glu and Glx levels in the anterior insula. AIU = arbitrary institutional units.

Table 2. Correlation of posterior insula Glu and Glx levels with pressure pain thresholds in the combined groups of FM patients and healthy controls*

Pressure threshold	Glu		Glx	
	r	*P*	r	*P*
Low pain	−0.53	0.002	−0.55	0.001
Medium pain	−0.43	0.012	−0.50	0.003
High pain	−0.38	0.03	−0.54	0.001

* See Table 1 for definitions.

pain threshold as independent variables. Since the FM patients and healthy controls were matched by age, we further used age as a stratum variable (factor) in the regression model. This is akin to the stratified analysis traditionally carried out in case–control designs.

As shown in Table 3, both group and pressure pain threshold were significant predictors of Glx levels, and these factors showed a trend toward significance for Glu levels. For both Glu and Glx, FM patients exhibited higher values than the controls. For example, the FM patients had on average 1.16 units higher Glx values compared with the healthy controls, for a fixed pressure pain level and age stratum. Further, medium pressure pain threshold was negatively associated with each of the outcomes. No significant group–pressure pain interaction term was detected for either model (both $P > 0.25$), and for this reason, the interaction term was not included in the final models. Similar results were obtained in analyses using weighted least squares (for Glx, group $\beta = 1.28$, $P = 0.009$; medium pressure $\beta = -0.47$, $P = 0.007$ and for Glu, group $\beta = 0.78$, $P = 0.07$; medium pressure $\beta = -0.41$, $P = 0.007$). Similar effects were also obtained when using general linear models with the high pressure threshold (for Glx, group $\beta = 1.23$, $P = 0.01$; high pressure $\beta = -0.37$, $P = 0.008$ and for Glu, group $\beta = 0.89$, $P = 0.05$; high pressure $\beta = -0.18$, $P = 0.17$).

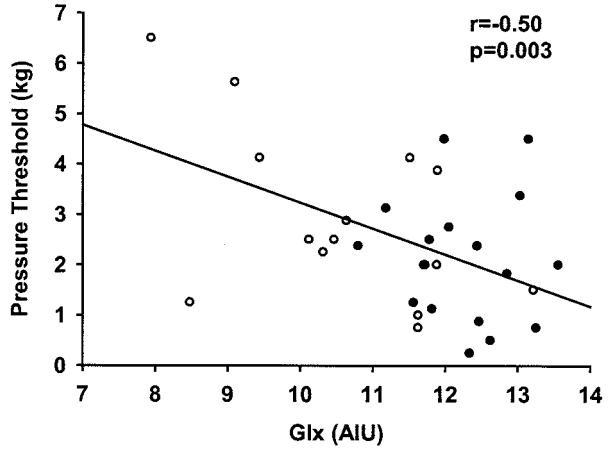

Figure 3. Glx levels within the posterior insula are negatively correlated with pressure pain thresholds. Shown is a scatterplot of Glx concentrations versus medium pressure pain thresholds for FM patients (solid circles) and healthy controls (open circles). Also shown is the regression line across groups. See Figure 2 for definitions.

Table 3. Regression results of association of posterior insular Glx and Glu levels with group and pressure threshold*

Dependent variable, predictor	β (95% CI)	Standard error	*P*
Glx level			
Group†	1.16 (0.30 to 2.03)	0.42	0.01
Pressure pain (medium)	−0.54 (−0.87 to −0.22)	0.16	0.002
Glu level			
Group†	0.75 (−0.09 to 1.59)	0.41	0.08
Pressure pain (medium)	−0.36 (−0.68 to −0.05)	0.15	0.03

* 95% CI = 95% confidence interval (see Table 1 for other definitions).
† The healthy controls group is the reference group.

Overall, these data indicate that FM patients have elevated Glu and Glx levels within the posterior insula and that these levels are associated with pressure pain thresholds. Since there was no significant group–pressure pain interaction term, the relationship between Glu and Glx levels and pain threshold was similar across groups. Although the relationship was similar, it was shifted toward higher metabolite levels for the patient group.

DISCUSSION

These findings point toward a potential role of insular Glu in the pathophysiology of FM. The levels of Glu in the posterior insula were higher for individuals with FM than for controls, and the levels of Glu were negatively correlated with pressure pain thresholds. This suggests that the "leftward shift" in the stimulus response function seen in both experimental pain testing and functional imaging in FM (i.e., hyperalgesia) is associated with higher levels of Glu in certain brain regions involved in pain processing, such as the posterior insula (9,11). The posterior insula is known to play a prominent role in pain and interoceptive sensory processing (22,23), whereas the anterior insula is involved in the affective processing of pain and other subjective feelings (22,24). Since the levels of Glu in the anterior insula did not differ between the groups, this could suggest that a component of this disorder involves an amplification in sensory, but not affective, processing.

Our findings are entirely consistent with the broader literature and knowledge regarding FM and related syndromes, which suggests that individuals with these conditions are at the far right end of the bell-shaped curve of pain and sensory processing in the population (25). Our data suggest that Glu is playing a role in this augmented pain processing in those individuals who have elevated Glu levels. Since higher Glu levels were associated with lower pain thresholds, this suggests that Glu in the posterior insula is related to pain processing. The elevated levels of Glu in the FM group could raise the set point of baseline neural activity in this region, which could result in augmented responses to painful stimuli. In a related line of inquiry, cold pain has been shown to increase Glu levels within the cingulate of pain-free controls (26).

FM patients may have more Glu within their synaptic vesicles, higher numbers or densities of glutamatergic synapses, or even less uptake of Glu from the synaptic cleft. Any of these changes would be consistent with the hypothesis that there is augmentation of pain and sensory processing in FM. If true, this aspect of the pathophysiology of FM may be more similar to conditions such as epilepsy or neurodegenerative diseases than to the rheumatic syndromes with which it has historically been associated. For example, in epilepsy, cortical and subcortical neurons appear to be hyperexcitable as a result of elevated concentrations of Glu (27). These clusters of excited neurons are thought to form a locus of heightened activity, which can then initiate a spreading wave of action potentials that propagate to other connected brain regions. FM may simply represent a condition in which glutamatergic "hyperactivity" occurs within brain regions devoted to processing and modulating pain. This could arise from local increases in Glu levels or enhanced ascending activity to this area. This hypothesis is consistent with the fact that one of the Food and Drug Administration–approved medications for FM is pregabalin, a drug whose action is thought to involve inhibition of presynaptic Glu release (28). Interestingly, this drug is also used in the treatment of epilepsy (29).

As with any trial, our study has limitations. The voxels used during H-MRS include multiple cell types. Our metabolite estimates of Glu and Glx reflect an ensemble average of all cell types (i.e., neurons, astrocytes, and glia) within the tissue samples. As such, our findings must be interpreted with the knowledge that the cellular and subcellular location of the elevated Glu is unknown. That said, our methods have been empirically validated by other reported single-voxel spectroscopy studies (30,31), indicating that this approach is "state of the art" for noninvasive assessment of molecular concentrations within the brain.

We also recognize that our findings pertain only to the insula. Future studies that detect Glu levels in other pain processing structures, such as the secondary somatosensory cortex, amygdala, cingulate, etc., are needed to determine the spatial extent of elevated Glu levels. Of note, a recent H-MRS study has shown decreased NAA levels within the hippocampus of individuals with FM (32), whereas we observed increased NAA levels in the posterior insula, although this was only a trend. In addition, our patient population excluded individuals with current major depression. It is possible that Glu levels within the anterior insula of depressed FM patients might be elevated, since it is known that the anterior insula is more involved in emotional processing of sensory information. Thus, our lack of group differences in anterior insula Glu levels may be due to the absence of depressed individuals in our sample.

Finally, although our results are significant, they originate from a relatively small number of participants. Validation of these findings in other studies could be made with larger study populations.

Overall, we find that Glu within the posterior insula is a potential pathologic factor in FM. The previously observed allodynia and hyperalgesia seen in these patients may be due to elevated excitatory glutamatergic neurotransmission within the posterior insula. Future studies are needed to determine whether these findings are observed in other functional pain syndromes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Harris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Harris, Clauw.

Acquisition of data. Harris, Kirshenbaum, Clauw.

Analysis and interpretation of data. Harris, Sundgren, Craig, Sen, Napadow, Clauw.

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