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# Limbic neurochemical changes in patients with functional motor symptoms

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*Neurology*® 2019;93:1-7. doi:10.1212/WNL.0000000000007717

## Abstract

### Objective

To assess by magnetic resonance spectroscopy (MRS) the *N*-acetylaspartate, myo-inositol, choline, sum of glutamate and glutamine (Glx), and creatine (Cr) content in the anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) and in the occipital cortex (OCC) (control region) in patients with functional motor symptoms (FMS) and healthy controls, and to determine whether neurochemical limbic changes as estimated by MRS correlate with FMS-related motor symptom severity, alexithymia, anxiety, depression, and quality of life.

### Methods

This case-control study enrolled 10 patients with FMS and 10 healthy controls. Participants underwent MRS and were tested with the Mini-Mental State Examination, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, 20-Item Toronto Alexithymia Scale, and EuroQol 5D.

### Results

In patients with FMS, MRS showed increased Glx/Cr in the ACC/mPFC but normal content in the control OCC. All the other metabolites tested were normal in both regions. The increased Glx/Cr content in the ACC/mPFC correlated with alexithymia, anxiety, and severity of symptoms.

### Conclusions

The abnormal limbic Glx increase could have a crucial pathophysiologic role in FMS, possibly by altering limbic-motor interactions, ultimately leading to abnormal movements.

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## Glossary

**ACC** = anterior cingulate cortex; **ANOVA** = analysis of variance; **Cho** = choline; **Cr** = creatine; **EQ-5D** = EuroQol 5D; **FMS** = functional motor symptoms; **Glx** = sum of glutamate and glutamine; **HAM-A** = Hamilton Rating Scale for Anxiety; **HAM-D** = Hamilton Rating Scale for Depression; **MI** = myo-inositol; **MMSE** = Mini-Mental State Examination; **mPFC** = medial prefrontal cortex; **MRS** = magnetic resonance spectroscopy; **NAA** = *N*-acetylaspartate; **OCC** = occipital cortex; **PMRDS** = Psychogenic Movement Disorders rating scale; **TAS-20** = 20-item Toronto Alexithymia Scale; **TE** = echo time; **TR** = repetition time.

The pathophysiology of functional motor symptoms (FMS) remains unknown.[1] Nor do we fully understand FMS-related neurochemical changes, or how abnormal mechanisms link to psychological or biological changes. Brain MRI studies describe increased cortical thickness and increased gray matter volume in the premotor cortices in patients with functional hemiparesis.[2] Others describe significantly smaller left thalamic volumes in patients with FMS[3]; a resting-state fMRI study in patients with FMS showed decreased functional connectivity between the right temporo-parietal junction and right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area, and right insula.[4] Although these MRI findings describe the functional and clinical neuroanatomy in FMS, they leave neurochemical mechanisms unclear. Having reliable information would help direct research to improve FMS management.

Because the limbic system is thought to be involved in FMS,[2–4] in this study, seeking information on limbic neurochemicals in patients with FMS, we used magnetic resonance spectroscopy (MRS) to quantify the brain metabolites *N*-acetylaspartate (NAA), a neural and axonal integrity marker; myo-inositol (MI), an inflammatory marker; choline (Cho), involved in cell membrane synthesis and degradation; the sum of glutamate—the major excitatory neurotransmitter—and glutamine (Glx); and creatine (Cr) in the anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) and in the occipital cortex (OCC) (control region) in patients with FMS and healthy controls. We also determined correlations between limbic metabolite content and FMS-related clinical features: motor symptom severity, alexithymia, anxiety, depression, and quality of life.

## Methods

### Participants

Ten patients with FMS were recruited and their data compared with those of 10 healthy controls, matched for age, sex, and Mini-Mental State Examination (MMSE). Healthy controls were visitors to the hospital and hospital staff. The MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment,[5] and commonly used in clinical practice to screen for dementia. We used the MMSE to screen for cognitive impairment because 3/10 patients and 3/10 healthy controls were older than 60 years.

Patients were included if they had clinically established and documented FMS according to Williams et al.[6] criteria. FMS was diagnosed by a neurologist and a psychiatrist from the patient's clinical presentation and diagnostic investigations. When examined, all the patients with FMS had symptoms. To have a more homogeneous group, we included only patients with nonremittent symptoms. The typical FMS symptoms were gait disorder (30%), tremor (20%), dystonia (20%), myoclonus (10%), and functional mixed disorder (20%). In the 2 patients with a functional mixed disorder, one had a functional gait disorder + functional tremor and the other a functional gait disorder + functional myoclonus. Two patients also had also a history of psychogenic nonepileptic seizures. Functional motor symptoms were assessed with the Psychogenic Movement Disorders rating scale (PMDRS).[7] The PMDRS rates 10 phenomena (rest tremor, action tremor, dystonia, chorea, bradykinesia, myoclonus, tics, athetosis, ballism, cerebellar incoordination), 2 functions (gait, speech), and 14 body regions. The Total Psychogenic Movement Disorder Score is the sum of the Total Phenomenology Score and the Total Function Score. All patients were also screened for psychiatric comorbidities by a structured psychiatric interview (Structured Clinical Interview for DSM-IV Axis I Disorders). Patients receiving psychotropic medications were asked to stop taking them 5 days before the MRS.[8]

### Exclusion criteria

Exclusion criteria were as follows: age less than 18 years; inability to communicate with the researcher or complete questionnaires due to language difficulties, severe learning disabilities, or dementia; any other neurologic disorders (including dementia) or medical diseases; the presence of an overlap between functional and other movement disorders; and contraindication to MRI.

### Experimental protocol

After the preliminary neurologic and psychiatric assessment, participants completed an experimental session lasting about 100 minutes, during which they underwent a psychological assessment and brain MRS.

### Psychological evaluation

All the patients and healthy controls underwent the following assessments:

- The 20-item Toronto Alexithymia Scale (TAS-20) is a multidimensional self-report scale of alexithymia. As well as comparing TAS-20 scores across the groups, we took the suggested TAS-20 criterion score of ≥61 as categorically denoting alexithymia.[9]

- The Hamilton Rating Scale for Depression (HAM-D) is the one of the most widely used clinician-administered depression assessment scales. Each item on the questionnaire is scored on a 3- or 5-point scale, depending on the item, and the total score is compared with the corresponding descriptor; it has been shown to yield reliable and internally consistent scores and to demonstrate criterion-related validity.[10]
- The Hamilton Rating Scale for Anxiety (HAM-A) is the first rating scale developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety and somatic anxiety. Several studies have shown that it is reliable, internally consistent, and valid.[11]
- EuroQol 5D (EQ-5D) assesses the generic quality of life. The EQ-5D questionnaire comprises 2 components: health state description and evaluation. In the description part, health status is measured for 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale. The scale has good validity and reliability.[12]

## Magnetic resonance spectroscopy

MRI scans were acquired on a magnetic resonance Achieva 1.5T scanner (Philips Healthcare, Best, the Netherlands), equipped with an 8-channel head coil. In addition to anatomical images (volumetric acquisition fast field echo T1 for positioning the voxel and turbo spin echo T2 to exclude brain diseases), short-TE spectra (repetition time [TR]/echo time [TE] = 1,700/8.8 ms) and medium-TE spectra (TR/TE = 2,000/144 ms) were acquired in each participant from two 8-mL volumes of interest: one in the ACC also containing portions of the mPFC, hence referred to as ACC/mPFC, and a second in the OCC. We selected the OCC as a control region because it lies outside the brain circuits thought to be involved in FMS (figure, A).[13] Another advantage is that technically, the voxel can be set on the median line as for the ACC. For each MRS scan, a reference spectrum was acquired without water suppression and used later for phase correction of the corresponding water-suppressed spectrum. We acquired short TE spectra to obtain information about all the neurochemicals and especially for fast T2 decay metabolites (such as Glx).[14] We scanned the medium TE spectra because they are widely used clinically as MRS scan to assess NAA, Cr, and Cho metabolite levels (which are altered in several neurologic disorders) and the presence of lactate (important also in several neurologic and oncologic diseases) with a significantly flatter baseline than that for short TE MRS scans.[15]

We report metabolite concentrations as ratios compared with the total creatine concentration (a commonly used denominator for in vivo spectroscopy). MRS data processing and quantification was fully automated and included zero order phase correction followed by a recursive least square fitting routine (SpectroView processing tool, Philips). MRS also included phase correction and least-squares spectral fitting followed by peak identification and area quantification for each single metabolite.

## Statistical analysis

Means and standard deviations were calculated. Values were normally distributed. Sociodemographic variables were compared by group using Fisher exact test or $t$ test for independent variables, depending on whether the variable was qualitative or quantitative ($p < 0.05$).

Brain metabolites were considered as independent variables, and therefore analyzed separately. To assess the differences in each brain metabolite level between patients with FMS and healthy controls, we performed a 2-way analysis of variance (ANOVA) with factors "group" (between-factor, 2 levels "patient" and "healthy control") and "brain site" (within-factor, 2 levels "ACC/mPFC" and "OCC"). Single factors and their interaction were considered significant for $p < 0.05$. Tukey honest post hoc test was then applied ($p < 0.05$), which already considers the effects of multiple comparisons.[16] To further verify the consistency of our analysis, and exclude the effects of other variables, we then entered HAM-D, HAM-A, and TAS-20 scores as covariates in the same model.

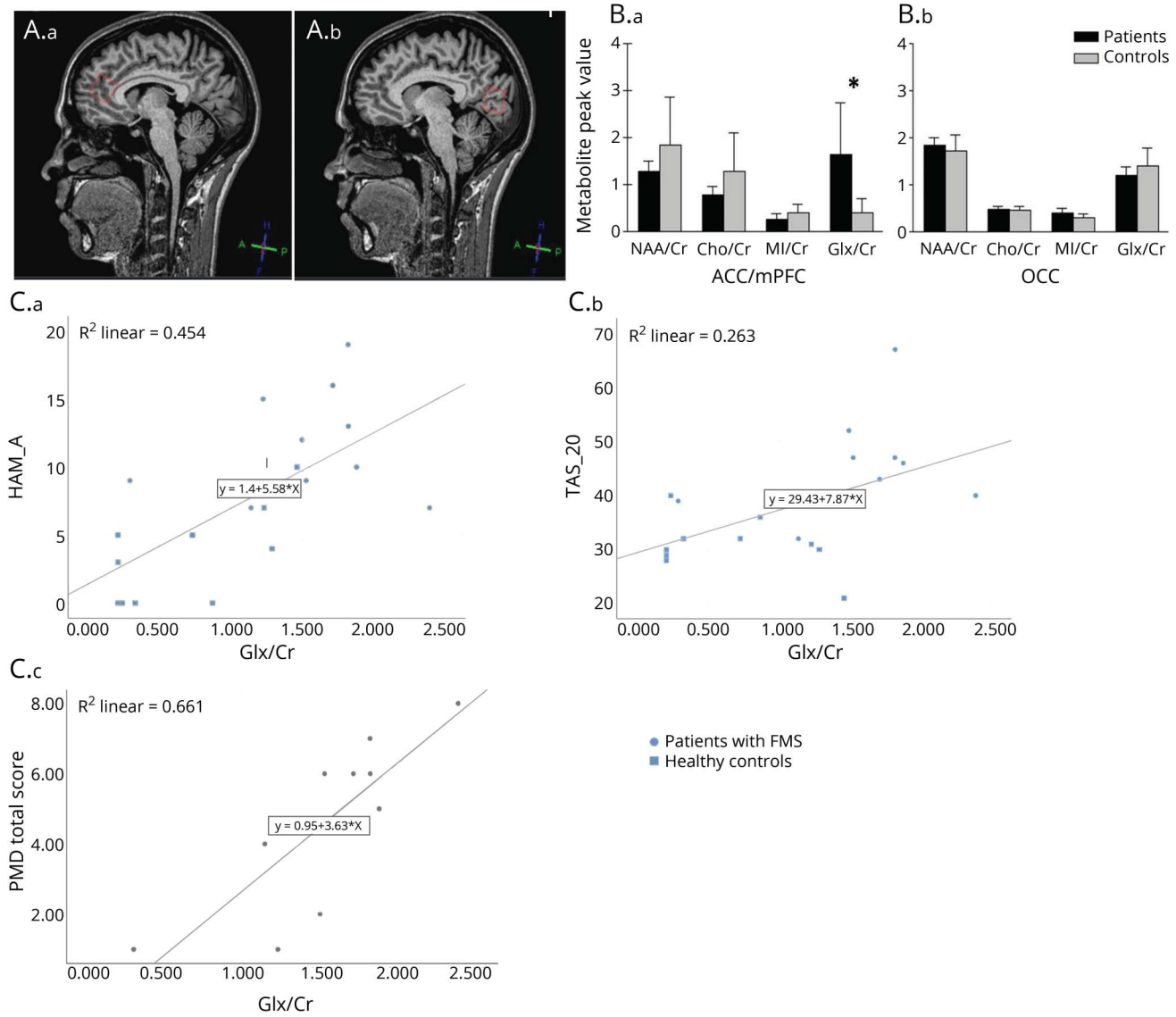
To verify whether there was a relationship between brain metabolites and psychological variables that have been known to be involved in the disease[17] and have been previously found to correlate with Glx/Cr[18] (namely, alexithymia and anxiety), we conducted a univariate correlation analysis (Pearson correlation coefficient) between the brain metabolites that were shown as significantly different between patients and healthy controls and psychological tests (TAS-20, HAM-A) in the overall population (n = 20). To account for the multiple correlations (2 correlation analyses for each metabolite), we corrected the type I error value according to Bonferroni, and considered $p < 0.025$ as significant, instead of $p < 0.05$. In addition, in the patient group, we assessed the relationship between characterizing metabolites (i.e., those showing significant differences between patients and healthy controls) and the symptoms severity (PMDRS).

A univariate independent-measures ANOVA with factor "group" (between-factor, levels "patients" and "healthy controls") was run to assess differences in psychological tests between patients and healthy controls. Statistical data were analyzed using SPSS version 24 (SPSS Inc., Chicago, IL). Values throughout the text are means ± SD.

## Standard protocol approvals, registrations, and patient consents

The study was approved and registered by the local ethics committee. Participants gave their informed written consent.

**Figure** Magnetic resonance spectroscopy neurochemical findings in patients with functional motor symptoms (FMS) and healthy controls




(A) Magnetic resonance spectroscopic (MRS) voxel (red square) in the anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) (A.a) and occipital cortex (OCC) (A.b) in a representative patient with FMS. Anatomical imaging was acquired in all 3 orthogonal planes for positioning the MRS voxels. (B) Relative metabolite concentration values in patients with FMS (n = 10) and healthy controls (HC, n = 10) in the ACC/mPFC (B.a) and in the OCC (B.b), obtained by short echo time (TE) spectra; error bars are SDs; Cho = choline, Cr = creatine, Glx = glutamate + glutamine, MI = myo-inositol, NAA = *N*-acetylaspartate; * $p < 0.05$. Glx/Cr levels in the ACC/mPFC were approximately 4 times higher in patients than in healthy controls. (C) Correlations of Glx/Cr in the ACC/mPFC obtained by short TE spectrum with Hamilton Rating Scale for Anxiety (HAM-A) (C.a) (ρ = 0.732, $p = 0.003$), 20-item Toronto Alexithymia Scale (TAS-20) score (C.b) (ρ = 0.432, $p = 0.023$), and Psychogenic Movement Disorders rating scale (PMDRS) score (C.c) (ρ = 0.765, $p = 0.002$). The limbic Glx content correlated with the FMS symptoms anxiety, alexithymia, and severity of motor disturbances.

## Data availability

Anonymized data will be shared by request from any qualified investigator.

# Results

## Sociodemographic variables, psychological and clinical evaluation

No differences were found between patients and healthy controls for sex, age, marital status, educational level, or MMSE score. Whereas the control group had normal rating scores for psychopathology, patients had abnormal scales. Psychiatric comorbidities were as follows: major depressive disorders in 2 patients and panic disorder for 1 patient. When examined, 3 patients were taking selective serotonin reuptake inhibitors and 4 were taking benzodiazepines but they stopped any drugs 5 days before the MRS.[8] None of the patients was on antipsychotic drugs. None of the healthy controls was taking psychotropic medications. Patients had high scores in depression assessed with the HAM-D and anxiety assessed with the HAM-A, high scores on the TAS-20, and low quality of life as measured by the EQ-5D (see table).

**Table** Demographic variables and psychometric assessment

| | Patients with FMS (n = 10) | HC (n = 10) | Significance |
|---|---|---|---|
| **Sex, female, n (%)** | 9 (90) | 9 (90) | $p = 1$ |
| **Age, y, mean (SD)** | 47.10 (17.00) | 44.3 (12.85) | $t = 0.415$, $p = 0.683$ |
| **Educational level, y, mean (SD)** | 13.50 (3.68) | 15.40 (2.36) | $t = -1.371$, $p = 0.187$ |
| **Marital status, n (%)** | | | $p = 1$ |
| **Single** | 2 (20) | 1 (10) | |
| **Married** | 8 (80) | 9 (90) | |
| **MMSE mean score (SD)** | 29.60 (0.96) | 29.90 (0.31) | $t = -9.33$, $p = 0.363$ |
| **TAS-20 mean score (SD)** | 44.60 (9.54) | 33.30 (4.05) | $t = 3.44$, $p = 0.003$ |
| **HAM-D mean score (SD)** | 9.00 (5.32) | 1.4 (3.27) | $t = 3.852$, $p = 0.001$ |
| **HAM-A mean score (SD)** | 9.9 (4.53) | 5.10 (4.28) | $t = 2.435$, $p = 0.026$ |
| **EQ-5D mean score (SD)** | 92.5 (18.5) | 61. (9.2) | $t = -4.731$, $p = 0.000$ |
| **PMDRS mean score (SD), range** | 5.6 (3.4), 5.2–7.4 | — | — |
| **Disease duration, y, mean (SD)** | 6.2 (1.2) | — | — |

Abbreviations: EQ-5D = EuroQol 5D; FMS = functional motor symptoms; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; HC = healthy controls; MMSE = Mini-Mental State Examination; PMDRS = Psychogenic Movement Disorders rating scale; TAS-20 = 20-item Toronto Alexithymia Scale.

## Magnetic resonance spectroscopy

### Short TE spectra

MRS showed that Glx/Cr is higher in patients with FMS than in healthy controls in ACC/mPFC, but not in OCC. More specifically, the 2-way ANOVA showed a significant interaction between the factors "brain site" and "group" ($p = 0.001$) and the post hoc analysis showed increased Glx/Cr in the ACC/mPFC in patients compared to healthy controls (patients vs healthy controls, mean ± SD: 1.52 ± 0.56 vs 0.677 ± 0.050, $p = 0.0005$). Significant differences in the Glx/Cr level remained when HAM-D, HAM-A, and TAS-20 scores were entered as a covariate in the same model. No differences were found for NAA/Cr, Cho/Cr, or MI/Cr between patients and healthy controls, either in the ACC/mPFC or OCC (figure, B).

To better understand the nature of the Glx/Cr difference between patients and healthy controls in the ACC/mPFC, we ran a correlation analysis between this metabolite and psychological scales and found that, in the overall population, the Glx/Cr in ACC/mPFC correlated with anxiety (HAM-A, $\rho = 0.732$, $p = 0.003$) and alexithymia (TAS-20, $\rho = 0.432$, $p = 0.02$). In patients, Glx/Cr content in the ACC/mPFC correlated also with the severity of functional motor symptoms (PMDRS) (figure, C).

### Medium TE (144 ms) spectra

No differences between patients with FMS and healthy controls were found for the brain metabolites assessed by medium-TE spectra ($F_{1,11} = 0.121$, $p = 0.734$ for NAA/Cr, $F_{1,11} = 1.081$, $p = 0.312$ for Cho/Cr).

# Discussion

In this brain MRS study, designed to provide information on limbic neurochemical content and pathophysiologic mechanisms in FMS, the main finding is that patients have abnormally increased Glx/Cr in the ACC/mPFC. These brain metabolite changes correlate with FMS psychopathologic features (TAS-20, HAM-A) and severity of motor symptoms (PMDRS). Because MRS showed no differences in Glx/Cr content in the occipital cortex between patients with FMS and healthy controls, the finding is specific for the limbic cortex. This datum remains significant after covarying for the typical FMS symptoms anxiety, depression, and alexithymia. Because MI, Cho, and NAA are altered in a number of neurologic and psychiatric conditions,[19] we also assessed these brain metabolites, although they yielded normal findings. Despite the small study sample (though comparable to other spectroscopic studies in neuropsychiatric conditions),[8,14,15] several specific methodologic approaches we used strengthen our results. First, when investigated, patients were psychotropic drug-free; second, although some patients had various FMS manifestations, we included only those with nonremittent symptoms; third, disease duration was similar within patients, defining a homogenous pathologic population for symptom chronicity.

The increase we report in limbic glutamate adds to current knowledge yet raises several issues related to brain metabolites in limbic sites containing circuits involved in FMS. Glutamate is ubiquitary in the CNS, ionotropic and

metabotropic glutamate receptors being distributed throughout the brain. Limbic and paralimbic regions (hippocampus, amygdala, orbitofrontal cortex, anterior cingulate cortex, medial prefrontal cortex, and insula), which have been extensively linked to stress response and anxiety-related disorders, are innervated by glutamatergic pyramidal cells.[20] Here we studied the association between alexithymia, anxiety, and glutamate level in patients with FMS. Failure to identify and describe emotions in oneself and a difficulty in distinguishing and appreciating the emotions of others is called alexithymia, a term coined by Sifneos[21] to describe certain clinical characteristics observed among patients with psychosomatic disorders who had difficulty engaging in insight-oriented psychotherapy. We have previously reported that patients with FMS have more severe alexithymia than patients with organic movement disorders and healthy controls, speculating that their inability to describe and identify feelings prevents them from recognizing their emotional states of anxiety, leading them to misinterpret anxiety as a symptom of physical illness (attributing sensations to organic rather than psychological causes).[17] Our findings in this MRS study confirm that patients with FMS have higher scores for the comorbidities alexithymia and anxiety than healthy controls. They also underline that alexithymia and anxiety correlate with limbic glutamate levels. Our findings in the group overall are consistent with those in healthy controls in whom others report a correlation between alexithymia and limbic glutamate.[18] At this point, some might argue that, regardless of whether patients have FMS, the abnormal limbic Glx level correlates with alexithymia and anxiety, because rather than being an FMS marker, this neurochemical reflects patients' comorbidities. But, against this possible explanation, MRS studies on patients with anxiety disorders reported a pattern of neurochemical changes that differs from our findings, characterized by decreased GABA in the ACC/mPFC[14]; and the increased glutamate observed in high-anxiety behavior animals involves another brain region, the hippocampus.[22] Also, in our MRS study, the Glx/Cr content in the ACC/mPFC correlated with the severity of FMS symptoms (PMDRS), supporting our hypothesis that neurochemical changes correlate with the motor symptoms in FMS. Some might also argue that alexithymia could be a symptom-related disability, suggesting a theoretically possible reverse causality. Conversely, others have excluded alexithymia related to functional symptoms by traditionally defining it as a personality trait rather than a state condition. In this view, we conjecture that a preexisting alexithymic state and abnormal limbic Glx might act as a fertile substrate for the development of FMS.

Finally, but equally important, our findings should prompt research to test novel pharmacologic approaches with drugs acting on NMDA receptors in FMS. Several drugs modulate glutamatergic activity and research in recent years has assessed their effects on various psychiatric conditions but not in FMS: to date, the most studied drugs are ketamine and memantine,[23] but small clinical trials have addressed other small molecules (such as D-cycloserine and riluzole).[24,25] Among NMDA receptor antagonists, memantine is a promising drug for several psychiatric disorders other than the dementias as an add-on in resistant depression and severe psychosis.[23] Small trials have also addressed patients with anxiety disorders, drug and alcohol abuse, and eating disorders.[26] Ketamine, traditionally used as an anesthetic drug, has also been used to manage widely ranging conditions, including major depressive disorders, bipolar disorder, and posttraumatic stress disorder.[27] Among other NMDA receptor agonists, D-cycloserine improves stereotypic symptoms in autistic patients and might also reduce the motor symptoms in FMS.[28] It also seems to enhance the effects of behavioral therapy for anxiety disorders.[29] Although our results prevent us from formulating a specific hypothesis, because they cannot answer the question whether the increased Glx peak reflects primary glutamatergic hyperactivity, or an increased glutamate concentration compensatory to an NMDA receptor desensitization, we suggest designing clinical trials with NMDA antagonists and agonists. Because the abnormal Glx increase in the limbic system might have a crucial pathophysiologic role in FMS possibly by altering limbic–motor interactions, ultimately leading to abnormal movements, drugs modulating glutamatergic activity, such as D-cycloserine, memantine, or ketamine, could be therefore offer an additional strategy in managing these disabling disorders.

Our study has several limitations: first, though comparable to other MRS studies in psychiatry,[8,14,15] the small sample size might make it harder to interpret our results; second, although cognitive impairment is not considered a specific feature in patients with FMS,[1] a complete neuropsychological assessment is lacking.

Despite its limitations, our MRS study in patients with FMS discloses an abnormal limbic glutamate increase that may be of pathogenetic interest and suggests a target for future therapeutic approaches.

## Acknowledgment

The authors thank the hospital staff and patients who took part in the study.

## Study funding

The study was partly supported by the "Aldo Ravelli" Research Center on Neurotechnology and Experimental Brain Therapeutics at the Department of Health Sciences, University of Milan, Italy.

## Disclosure

B. Demartini has been funded by "Dottorato in Medicina Molecolare e Traslazionale" and by the "Aldo Ravelli" Center for Neurotechnology and Experimental Brain Therapeutics, Università degli Studi di Milano, Italy. O. Gambini, C. Uggetti, and M. Cariati report no disclosures relevant to the manuscript. M. Cadioli is employed by Philips Spa. D. Goeta, S. Marceglia, R. Ferrucci, and A. Priori report no disclosures

relevant to the manuscript. Go to Neurology.org/N for full disclosures.

## Publication history

Received by *Neurology* July 12, 2018. Accepted in final form February 11, 2019.

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