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Quantitative proton magnetic resonance spectroscopy detects abnormalities in dorsolateral prefrontal cortex and motor cortex of patients with frontotemporal lobar degeneration

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Abstract

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease of the frontal and temporal neocortex. The single most common pathology underlying FTLD is neuronal degeneration with ubiquitin-positive but tau-negative inclusions consisting of Tar DNA binding proteins (TDP-43). Inclusions containing TDP-43 in neurons are also the most common pathology underlying motor neuron disease (MND). The present study tested the hypothesis that abnormal metabolite patterns within the dorsolateral prefrontal cortex (DLPFC) as well as the motor cortex (MC) may be observed in FTLD patients without motor disorders, using proton magnetic resonance spectroscopy (^{1}H MRS). Twenty-six FTLD patients with cognitive damage and ten controls underwent multivoxel ^{1}H MRS. Absolute concentrations of *N*-acetyl aspartate (NAA),

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creatine (Cr), choline (Cho) and myo-inositol (mI) were measured from the DLPFC, the MC and the parietal cortex (PC, an internal control). Statistical analyses were performed for group differences between FTLD patients and controls. Comparisons were also made across brain regions (PC and DLPFC; PC and MC) within FTLD patients. Significant reductions in NAA and Cr along with increased Cho and mI were observed in the DLPFC of FTLD patients compared to controls. Significantly lower NAA and higher Cho were also observed in the MCs of patients as compared to controls. Within the FTLD patients, both the MC and the DLPFC exhibited significantly decreased NAA and elevated Cho compared to the PC. However, only the DLPFC had significantly lower Cr and higher mI. Abnormal metabolite pattern from the MC supports the hypothesis that FTLD and MND may be closely linked.

Keywords

Frontotemporal lobar degeneration; Motor neuron disease; Proton magnetic resonance spectroscopy; Dorsolateral prefrontal cortex; Motor cortex

Introduction

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative syndrome characterized by tau or ubiquitin positive spherical cortical inclusions, microvacuolar degeneration, and gliosis, affecting predominantly the frontal and anterior temporal lobes [12,17,25,35]. Patients usually present with a progressive decline in cognitive, social, behavioral, and/or language functions. The three major phenotypes of FTLD are categorized as frontal variant FTLD (fvFTLD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD) [17,21,36].

Evidence supporting the involvement of the dorsolateral prefrontal cortex (DLPFC) in FTLD is emerging and some investigators have observed reduced glucose metabolism [41] and blood flow [26] in the DLPFC. Voxel based morphometry analyses using high-resolution structural magnetic resonance imaging (MRI) have also demonstrated involvement of the DLPFC region in FTLD patients [18,39]. These neuroimaging findings are concordant with postmortem histopathological studies on human brain specimens demonstrating neuropathological features of FTLD in the DLPFC [1,12].

Proton magnetic resonance spectroscopy (^{1}H MRS) enables assessment of metabolic processes, which may lead to a better understanding of underlying pathophysiological events in neurodegenerative diseases [15,16]. Few ^{1}H MRS studies on FTLD patients have demonstrated multiple brain metabolite alterations, such as a decrease in *N*-acetyl aspartate (NAA) along with an increase in choline (Cho) and myo-inositol (mI), using creatine (Cr) as an internal reference. The abnormal metabolic features have been observed from different regions of the brain, such as anterior cingulate cortex (ACC) [8], posterior cingulate cortex (PCC) [29], medial frontal cortex (MFC) [11] and temporal cortex (TC) [8,11]. However, metabolite abnormalities from the DLPFC region have not been reported. The motor cortex (MC) is another region that remains unexplored on ^{1}H MRS of FTLD patients. There is increasing evidence of a clinical and pathological overlap between FTLD and motor neuron disease (MND). Recent discovery of Tar DNA binding protein-43 (TDP-43) as a disease protein, common to both FTLD and MND conditions [38], has helped to conceptualize the occurrence of FTLD syndromes in patients with clinical evidence of MND [22,38]. Some FTLD patients with clinically normal motor examinations have manifested abnormal needle electromyography (EMG) of the tongue and extremity muscles [34]. EMG nonspecifically demonstrates abnormalities of the lower motor neuron; evidence of an abnormality in the

upper motor neuron segment in FTLD patients without clinical evidence of MND would be valuable.

The present study was designed to test the hypothesis that FTLD patients will exhibit abnormal ^{1}H MRS metabolite patterns within the DLPFC and MC regions. To test this hypothesis, we performed multivoxel proton magnetic resonance spectroscopic imaging (^{1}H MRSI) in the DLPFC and MC regions of patients with FTLD who presented with no clinical signs of motor system abnormality.

Materials and methods

Subjects

The primary inclusion criterion for this study was a diagnosis of FTLD with any of the three phenotypes (fvFTLD, PNFA and SD). All subjects were evaluated by an experienced neurologist (MG) with expertise in dementia illnesses using a semi-structured medical history, a complete neurological examination, and a detailed mental status evaluation, including administration of the Philadelphia Brief Assessment of Cognition [31]. All recruited patients met international consensus diagnostic criteria for FTLD [36]. Cognitive tests such as mini-mental state examination (MMSE), verbal fluency with phonemic and semantic cues tests, verbal short-term memory test (Digit Span), and executive function tests (Trail-Making Test B) were performed on all patients. Behavioral and psychiatric disturbances were evaluated with the Neuropsychiatric Inventory [9] and Frontal Behavioral Inventory [28]. The mean (±SD) MMSE score was 23.63 ± 5.82.

Exclusion criteria were: (1) presence of intracranial mass lesions or subdural hematomas on T1 and T2 weighted images as determined by a neuroradiologist (SW); (2) clinical evidence of stroke, although some patients demonstrated occasional white matter changes on conventional T1 and T2 weighted images; (3) history of traumatic brain injury or presence of other neurological disease; (4) major depressive disorder, bipolar disorder, schizophrenia, substance use, or mental retardation; (5) significant medical problems such as poorly controlled diabetes mellitus, or hypertension or cancer within the past 10 years.

Based upon the inclusion and exclusion criteria, twenty-six FTLD patients (mean age = 64.35 ± 6.66 years, 16M/10F) were recruited for this study. The study was approved by the Institutional Review Board and informed consent was obtained from all participants. Two independent examiners established consensus diagnosis for FTLD patients using a modification of published criteria [37], with a subsequent designation of one of the three major clinical subtypes: fvFTLD, PNFA, and SD [37]. Participants included 19 patients with fvFTLD, 5 patients with PNFA and 2 with SD phenotypes. None of the patients demonstrated clinical evidence of weakness, loss of muscle bulk, fasciculations or spasticity suggestive of MND. In addition, 10 normal healthy age-matched volunteers (mean age, 59.0 ± 8.79 years, 6M/4F) acted as controls. There was no statistical difference in the mean age between the patient group and healthy subjects ($p > 0.05$).

Data acquisition

Magnetic resonance imaging (MRI) and multivoxel magnetic resonance spectroscopic imaging (^{1}H MRSI) were performed on a 3 Tesla Tim Trio whole body MR system (Siemens Medical Systems, Erlangen, Germany) equipped with a standard quadrature head coil provided by the manufacturer. The imaging protocol included three-plane scout localizer, 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) [Repetition time (TR)/echo time (TE)/inversion time (TI)/flip angle (FA) = 1,620/3.9/950

ms/15°, 192 × 256 matrix size, 1 mm slice thickness] and axial T2 weighted images (TR/TE = 2,660/91 ms, 3 mm slice thickness).

^{1}H MRSI

Single slice two-dimensional (2D) multivoxel ^{1}H MRSI was performed using a spin echo (point resolved spectroscopy) sequence with water suppression by means of a chemical shift selective saturation (CHESS) pulse. Sequence parameters included: TR/TE/FA = 17,00/30 ms/90°, number of excitations (NEX) = 3, field of view = 16 × 15 cm^2, slice thickness = 20 mm resulting in a voxel size of 10 × 9.4 × 20 mm^3, bandwidth = 1,200 Hz, matrix size = 16 × 16, vector size = 1,024. The volume of interest (VOI) was selected so as to include the DLPFC, MC and PC regions bilaterally avoiding the scalp, skull base or sinuses. The VOI was centered on the central sulcus, carefully chosen to ensure the same locations in each subject, based on anatomical landmarks. Eight outer volume saturation slabs (30 mm thick) were placed outside the VOI to suppress lipid signals from the scalp. The data set was acquired using elliptical k-space sampling with weighted phase encoding to reduce the acquisition time. Total acquisition time for ^{1}H MRSI sequence was 6 min and 53 s. Manual shimming was performed to achieve an optimal full width half maximum of <20 Hz (magnitude spectrum) of the water signal. A water unsuppressed ^{1}H MRSI spectrum was also acquired to use the water signal for computing metabolite concentrations.

Data analysis

^{1}H MRSI data were analyzed from voxels encompassing at least 50% of the DLPFC, MC and PC regions as shown in Fig. 1. The PC has been reported to be relatively spared from atrophy and metabolic abnormalities in FTLD patients [18,52], and was thus used as an internal control in this study. Absolute concentrations of metabolites were measured using a user-independent spectral fit program [Linear Combination (LC) Model] [44,45]. The region between 0.2 and 4.0 ppm of the spectrum was analyzed and the following metabolites were evaluated: NAA, 2.02 ppm; Cr, 3.02 ppm; Cho, 3.22 ppm; mI, 3.56 ppm. The average metabolite concentration from each region (DLPFC, MC and PC) was computed by calculating the mean concentration from all voxels within the specific region as shown in Fig. 1. The error in the spectral fitting routine (LC Model) was used to assess the spectral quality for a particular voxel; metabolite concentrations from only those voxels were used which had standard deviations (SD) of less than 20% for all the metabolites.

Statistical analysis

Concentrations of NAA, Cr, Cho, and mI were compared between FTLD and control groups from the DLPFC, MC and PC regions using a two-tailed Student t-test. A probability (p) value of less than 0.05 was considered significant. Comparisons were also made across brain regions (between PC and DLPFC, between PC and MC) within the FTLD group by one-way analysis of variance (ANOVA). If an ANOVA test was found to be significant ($p < 0.05$), a post-hoc test (Bonferroni test) was performed. All data analysis was performed using a statistical tool (SPSS for Windows, version 15.0; SPSS Inc., Chicago, III, USA).

Results

Representative spectra from the DLPFC, MC and PC regions of an FTLD patient are shown in Fig. 2. These spectra demonstrate lower NAA and Cr along with higher Cho and mI in the DLPFC and MC regions in comparison to the PC region. No significant difference in metabolite concentrations between the PC regions of patients and controls was observed ($p > 0.05$), confirming that the PC in FTLD patients is metabolically preserved.

A comparison of metabolite concentrations from different cortical regions of normal controls and FTLD patients is shown in Fig. 3. The DLPFC region in FTLD patients exhibited significant reductions in NAA and Cr along with increased Cho and mI in comparison to healthy controls ($p < 0.05$). Similarly, significantly lower NAA and higher Cho levels were observed from the MCs of FTLD patients as compared to normal controls ($p < 0.05$). A non-significant ($p = 0.06$), but higher mI was also observed from the MCs of FTLD patients in comparison to healthy controls.

Regional variations in metabolite concentrations were observed from FTLD patients in that both MC and DLPFC regions had significantly lower NAA [*F* ratio (variance between samples/variance within samples) = 76.38], and higher Cho (*F* ratio = 7.20) compared to PC ($p < 0.05$, one-way ANOVA). A significantly lower Cr (*F* ratio = 17.51) and elevated mI levels (*F* ratio = 16.74) were also observed from only the DLPFC region as compared to the PC region ($p < 0.05$; Fig. 4).

Discussion

In the present study, we observed an abnormal metabolite pattern in the DLPFC and MC regions in patients with FTLD reflecting metabolic deterioration in these regions. Previous ^{1}H MRS studies in FTLD patients have reported abnormal metabolite patterns from the anterior cingulate cortex, posterior cingulate cortex, medial frontal cortex and temporal cortex of the brain [8,11,29]. Abnormal glucose metabolism from other gray matter structures of the brain in FTLD patients has also been observed [24] suggesting that metabolic abnormality in FTLD is more diffuse and widespread than previously understood, extending beyond the previously reported regions.

The DLPFC and MC regions constitute major functional loci in the normal brain. The DLPFC, encompassing Brodmann's areas 9, 10 and 46 [42] regulates executive functions and organizes behavioral responses and strategies in learning new tasks [2]. It is one of the last regions to mature in the human brain, consistent with its integrative role in cognitive functions [14,49]. Damage to the DLPFC causes dorsolateral syndrome, which impairs decision making, working memory and planning [23]. In a recent study, patients with FTLD performed poorly on neuropsychological tests assessing prefrontal functioning in comparison to healthy subjects [31], implicating involvement of the DLPFC, and confirmed in patients with known FTLD pathology [19].

The MC region encompasses Broadman's areas 4 and 6 and is considered not only as an executive locus for simple voluntary movements but is also known to participate in motor functions [13]. Metabolite alterations have been observed from MC regions in MND patients without any evidence of FTLD [3,5,43,50]. We observed decreased NAA and elevated Cho within this region in our population of FTLD patients who did not have any overt motor impairment. It is now widely believed that FTLD and MND represent different manifestations of the same neurodegenerative disorder. As many as 50% of patients screened for MND meet the criteria for possible or probable FTLD [32]. In addition, about 30% of FTLD patients meet the criteria for possible or definite MND [33]. Increasing neuropathological evidence [1,20] supports the observations of clinical overlap between FTLD and MND [38]. Ubiquitination of TDP-43 protein that aggregates in the cytoplasm and/or nucleus of neurons is the key characteristic shared by these two neurodegenerative diseases [38].

Recently, a ^{1}H MRS study reported an abnormal metabolite pattern from the MC region in an FTLD patient who also had clinical MND [47]. Our observation of an abnormal metabolite pattern from the MC region in FTLD patients who were clinically asymptomatic

for motor impairments extends this finding and is in concordance with reports of subclinical MND in patients with FTLD [27]. While FTLD patients may not exhibit clinical features of MND, this body of work suggests that there is a continuum of pathological process from FTLD to FTLD/MND and to MND.

Our observation of reduced NAA in both the DLPFC and MC regions is consistent with other reports of reduced NAA in many pathological conditions [7,46,53]. Reduced NAA concentration reflects loss or dysfunction of neurons and axons. It is believed that nerve cell degeneration in FTLD is probably induced by accumulation of mutated and structurally misfolded and ubiquitinated proteins [38].

We observed a significant reduction in Cr in the DLPFC compared to the PC. Decreased Cr from the midfrontal cortex has also been reported in FTLD patients [11]. The reduction in Cr is indicative of an energy deficit that might result from a defect in oxidative metabolism in impaired cells. Such a hypothesis is concordant with a report of ultrastructural damage in neuronal mitochondria in a patient with FTLD [6].

We also observed higher mI in the DLPFC and MC regions of FTLD patients. ^{1}H MRS detectable mI is thought to be a marker of neuroglial cells and is an important organic osmolyte [4]. Increased mI might indicate elevated neuroglial concentration. In neuropathological studies of dementia including FTLD, gliosis has been associated with neuronal loss [48]. It is possible that in response to neuronal loss, neuroglial cells become diseased, resulting in disruption of osmotic balance. Myoinositol may accumulate within the neuroglial cells to regulate osmotic balance, thereby maintaining cell volume homeostasis. We believe that the combined effect of gliosis and osmotic stress may be responsible for increased mI concentration observed in the DLPFC and MC regions.

The combined Cho resonance visible on ^{1}H MRS is thought to be due to cytosolic Cho, phosphocholine (precursor for membrane phosphatidylcholine biosynthesis) and glycerophosphocholine (breakdown product of membrane phosphatidylcholine) [30]. A possible explanation for the elevation of Cho in FTLD patients is an increase in membrane turnover, secondary to dying back of the neurophil (degeneration of axons and dendritic processes following disruption of axonal/dendritic transport and/or nerve cell death). Thus a significant increase in Cho concentration from both DLPFC and MC regions in the present study is suggestive of a higher membrane turnover occurring in these regions.

Previous ^{1}H MRS studies on FTLD patients have reported their results as metabolic ratios with respect to Cr. However, as demonstrated in the present study, a reduction in Cr concentration is observed in FTLD patients, which may lead to an over-estimation in metabolic abnormality in NAA and Cho. Variations in Cr level have also been observed in patients with dementia [51]. Thus, we believe that measurement of absolute metabolite concentrations as performed in the present study provides a more reliable and sensitive indicator of metabolic abnormality in FTLD patients.

Although the ^{1}H MRSI technique offers the ability to acquire spectra from multiple contiguous voxels simultaneously, the current study is limited by the fact that ^{1}H MRSI was performed from a single slice, which covered only the frontal and parietal regions of the brain. The temporal lobe is another important region that is known to be affected in FTLD, and was not covered in the FOV of the present single slice study. In order to cover a larger segment of the brain, it is necessary to perform 3D ^{1}H MRSI studies. However, 3D ^{1}HMRSI techniques are limited by increased acquisition times that could be prohibitive in clinical settings. A strategy to overcome this shortcoming may be the use of parallel ^{1}H MRS [40] or echo-planar spectroscopic imaging [10] techniques.

Conclusion

The present study demonstrates ^{1}H MRS abnormalities in the DLFPC and MC regions of FTLD patients and provides further evidence that FTLD and MND present a pathophysiological continuum of neurodegeneration.

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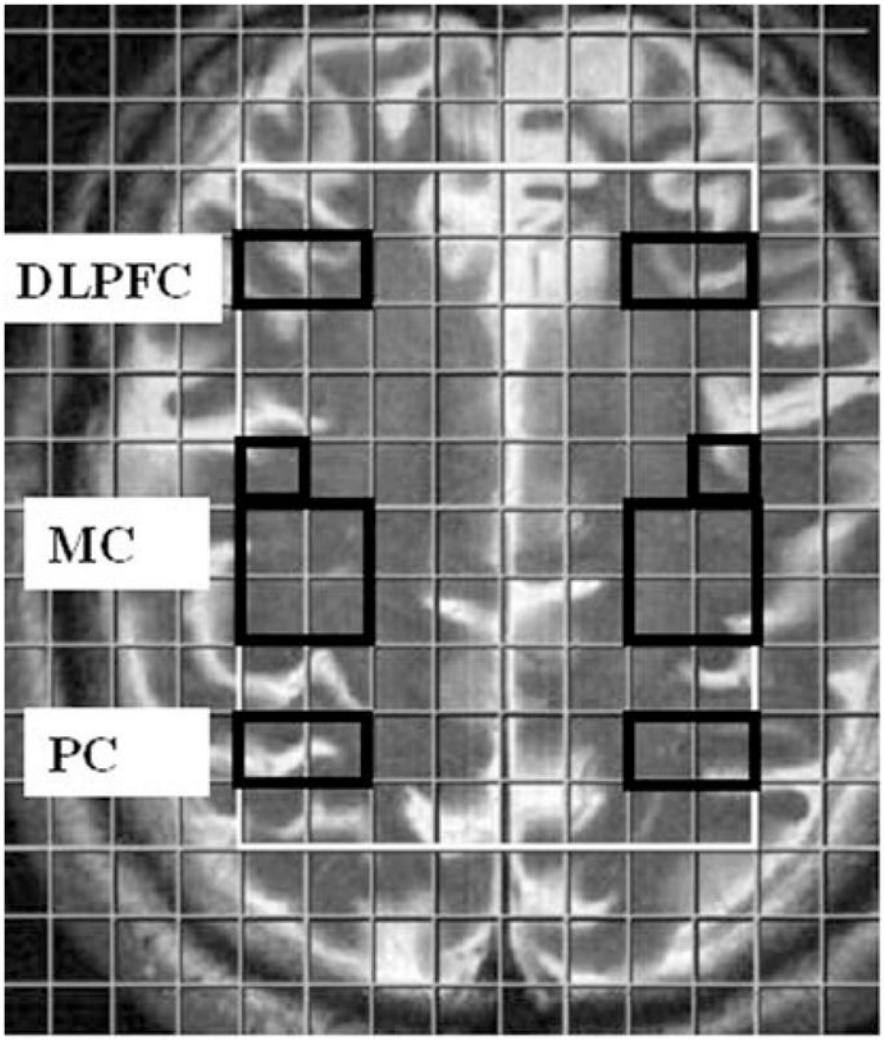

Fig. 1.
^{1}H MRSI grid overlaid over axial T2 weighted image demonstrating the location of voxels from DLPFC, MC and PC regions of the brain

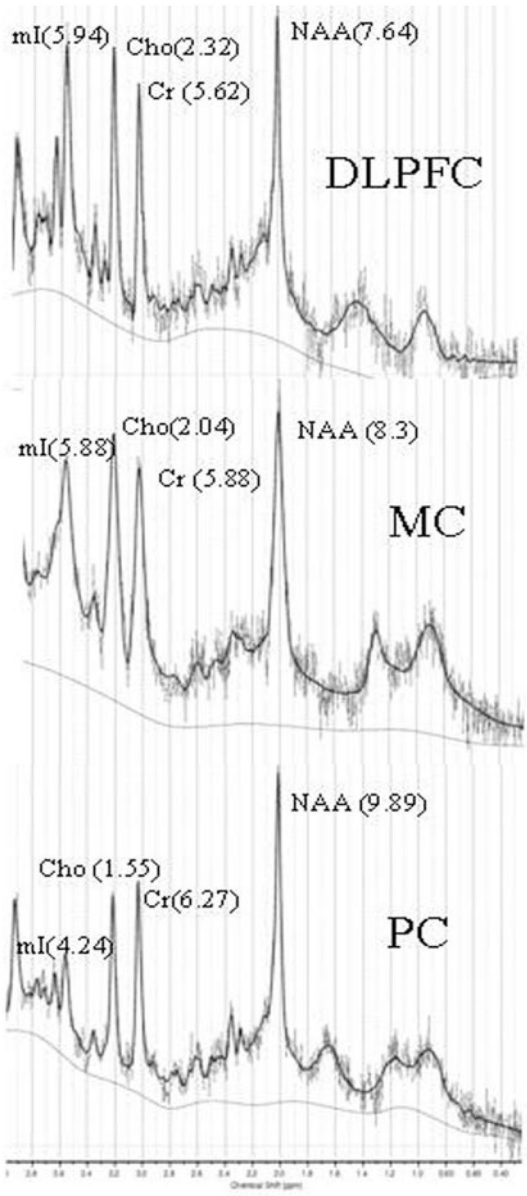

Fig. 2.

Representative spectra from different cortical regions of an FTLD patient demonstrating various metabolites. *Numbers in parenthesis* indicate the metabolite concentrations in mM

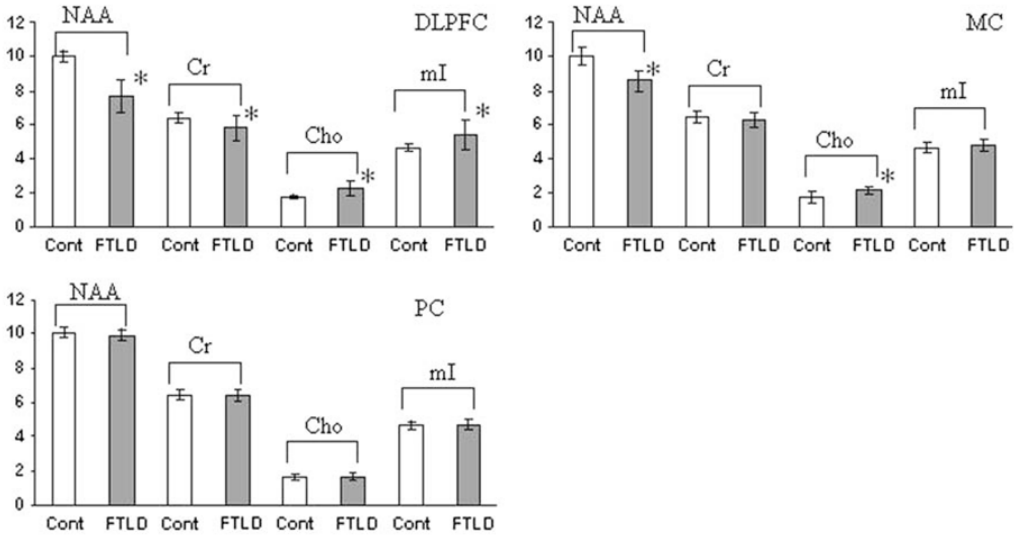

Fig. 3.

Bar diagrams demonstrating comparison of mean metabolite concentration (mM units) between normal controls (Cont) and FTLD patients (FTLD) from DLPFC, MC and PC regions. *Error bars* indicate ± 1SD. *indicates statistical significance ($p < 0.05$)

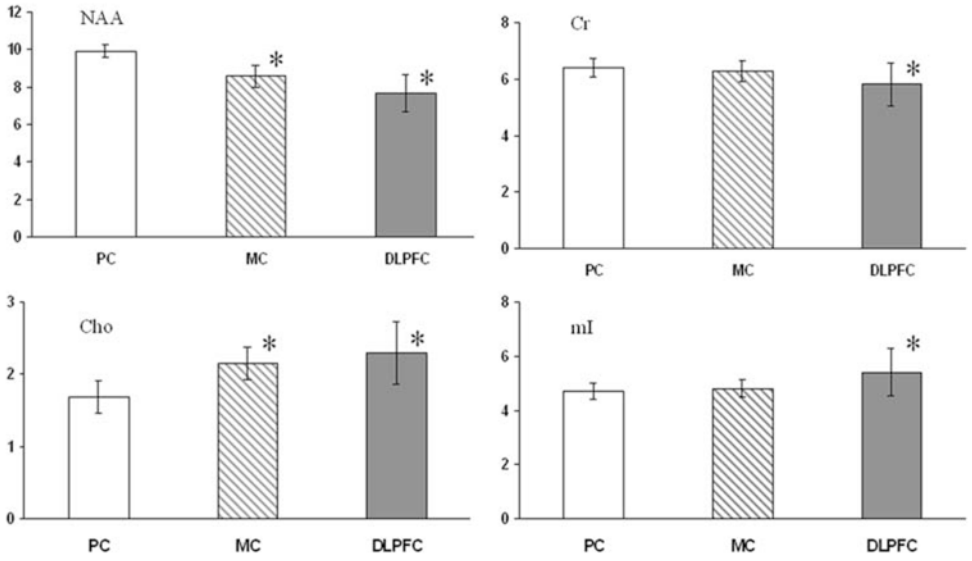

Fig. 4.

Bar diagrams showing variations in mean concentration (mM units) of metabolites from different cortical regions within FTLD patients. *Error bars* indicate ± 1SD. * indicates that results from ANOVA test are significant (p <0.05)