18 F-FDG-PET correlates of cognitive impairment in ALS

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Abstract

Objective. To identify the metabolic signature of the various levels of cognitive deficits in ALS using ^{18}F-FDG-PET.

Methods. A total of 170 ALS cases consecutively enrolled at the ALS Center of Turin underwent brain ^{18}F-FDG-PET and were classified as displaying normal cognition (ALS-Cn=94), full-blown FTD (ALS-FTD=20), executive or non-executive cognitive impairment not fulfilling FTD criteria (ALS-Ci=37), prevalent behavioral changes (ALS-Bi=9) or non-classifiable impairment (ALS-Nc=10) according to neuropsychological testing. Group comparisons of ^{18}F-FDG-PET pattern were carried out among the cognitive subgroups.

Results. We found a significantly reduced frontal and prefrontal metabolism in ALS-FTD as compared to ALS-Cn, while ALS-Ci showed an intermediate metabolic behavior in frontal cortex, being hypometabolic as compared to ALS-Cn, and relatively hypermetabolic as compared to ALS-FTD. Hypometabolism in frontal regions was associated in all comparisons to hypermetabolism in cerebellum, midbrain and corticospinal tracts: the more severe the cognitive decline, the larger the size of the cluster and the statistical significance of ^{18}F-FDG uptake differences.

Conclusions. This is the first study demonstrating in a large ALS cohort a *continuum* of frontal lobe metabolic impairment reflecting the clinical and anatomic *continuum* ranging from pure ALS, through ALS with intermediate cognitive deficits, to ALS-FTD, and showing that patients with intermediate cognitive impairment display a characteristic metabolic pattern. Since ^{18}F-FDG-PET allows to estimate the cerebral lesion load *in vivo* in neurodegenerative diseases, it might be helpful to investigate in ALS its association with neuropsychological testing along the disease course to disclose the early metabolic signature of a possible cognitive impairment.

Keywords: Amyotrophic Lateral Sclerosis; Frontotemporal Dementia; 18F-FDG PET; Cognition

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of the adult life affecting upper and lower motor neurons involving bulbar and spinal regions, characterized by progressive muscle weakness and wasting and limb spasticity. Besides motor impairment, extramotor abnormalities in ALS may include cognitive and behavioral changes falling within the frontotemporal lobar degeneration (FTLD) spectrum. Overall, ~15% of ALS patients display a full-blown frontotemporal dementia (FTD), while ~35% have more subtle cognitive alterations involving executive and non-executive domains.[1,2]

^{18}F-2-fluoro-2-deoxy-D-glucose PET (^{18}F-FDG-PET) studies have shown hypometabolic clusters in frontal and temporal cortex as neurobiological correlates of ALS with comorbid FTD.[3] Moreover, two recent studies have shown that ^{18}F-FDG-PET can discriminate ALS patients from healthy controls with accuracy close to 94%.[4,5]

Some studies reported a gradient of increasing brain atrophy assessed through structural MRI along the ALS-FTD continuum, ranging from pure ALS, through ALS with cognitive and/or behavioral deficits, to ALS with frank FTD.[6,7] However, it is still unclear whether the clinical entities of such disease spectrum have distinct metabolic correlates reflecting the different degrees of cognitive impairment.

The aim of this study was to identify the metabolic signature of the various levels of cognitive deficits in ALS using ^{18}F-FDG-PET.

Methods

Patients

A total of 170 ALS patients who agreed to undergo both neuropsychological assessment and ^{18}F-FDG-PET were consecutively enrolled at the Turin ALS Center, Italy. All patients fulfilled the El Escorial Revised Diagnostic Criteria for definite, probable or probable laboratory-supported ALS.[8] Patients were recruited at the time of diagnosis or during the first follow up visit (2 months later). Neuropsychological evaluation and ^{18}F-FDG-PET were always performed within one month of each other and within 12 months from ALS diagnosis. Respiratory function was assessed for every subject within 4 weeks before or after neuropsychological evaluation and ^{18}F-FDG-PET. At the time of assessments none of the patients showed oxygen saturation <92% at pulse oximetry. Patients with a history of neurological disorders affecting cognition (major stroke, severe head injuries, mental retardation), alcohol- and drug-dependence, severe mental illness and use of high-dose psychoactive medications were not enrolled in the study as well as patients who were not of Italian mother tongue.

Neuropsychological assessment

The selection of the neuropsychological tests, evaluating executive function, memory, visuospatial function and language, was based on the Clinical Diagnostic Criteria for Frontotemporal Lobar Degeneration[9], and the ALS-FTD Consensus Criteria.[10] Non-FTD dementias were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV-TR[11] and those of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.[12] The neuropsychological battery included: Mini Mental State Examination; Wisconsin Card Sorting Test; Trail Making Test A and B; Stroop Color-Word Interference Test; letter and category fluency test; Wechsler Memory Scale II - revised (Form 2); Rey-Osterrieth Complex Figure Test; Token Test; Wechsler Adult Intelligence Scale revised; Raven's Progressive Colored Matrices; Frontal Assessment Battery. Neurobehavioral dysfunction was assessed through the direct observation and the patient's history, and with the Frontal Systems Behavior Scale, using the Family-form compiled by a close relative.

The evaluation of anxiety and depression was based on the Hospital Anxiety and Depression Scale. Further details about the neuropsychological battery and the testing procedure have been reported elsewhere.[2]

Cognitive classification

Clinical diagnosis and cognitive classification were obtained by neurologists and neuropsychologists expert in ALS and FTD. Patients were subdivided in five cognitive groups:

1. ALS with normal cognition (ALS-Cn);
2. ALS cases fulfilling the diagnostic criteria for FTD (ALS-FTD);
3. ALS subjects with cognitive impairment not meeting the criteria for FTD, but presenting impairment in two tests for executive functions or in two tests for non-executive abilities (ALS-Ci);
4. ALS cases not meeting the criteria for FTD, with prevalent behavioral impairment and presenting deficit in none or only one executive test and no impairment in non-executive domains (ALS-Bi);
5. ALS with non-classifiable cognitive impairment (ALS-Nc), including patients displaying deficits in one executive and/or one non-executive test, sometimes associated with smooth behavioral changes.

ALS-Nc cases were excluded from subsequent analyses because the classification of this group as a distinct entity remains unclear.

^{18}F-FDG-PET

^{18}F-FDG-PET was performed according to previously published Guidelines.[13] PET/CT images were acquired by a Discovery ST-E System (General Electric). CT scan of the brain (thickness of 3.75 millimetres, 140kVolt, 60-80 mA/sec) was followed by PET brain scan (1 FOV of 30

transaxial centimetres). Data were collected in 128×128 matrices, the reconstructed voxel was 2.34 x 2.34 x 2.00 mm.

Group comparison

Clinical characteristics of patients belonging to different categories were compared using chi-square (discrete variables) or Student's t-test/ANOVA (continuous variables). Data were analysed using SPSS 21.0 statistical package. Detailed methods of group comparison of ^{18}F-FDG-PET data are provided elsewhere.[14] Preprocessing and statistical analyses were performed by SPM8 implemented in Matlab, 7.10.0. Scans were normalized by a ^{18}F-FDG-PET customized brain template, created at the same center and set up equally to the SPM8 default one. Group comparisons were carried out among ALS-Cn (n=94), ALS-FTD (n=20), ALS-Ci (n=37), and ALS-Bi (n=9) by the "two-sample t-test" model of SPM8, considering gender, type of onset and age at PET as 'nuisance' variables. The $p<0.001$ threshold, was used to create SPM t-maps at peak and cluster level and the threshold of $p<0.05$ corrected for multiple comparisons by False Discovery Rate was considered to be significant. If significant clusters where not found, the more liberal threshold at $p<0.001$ uncorrected for multiple comparisons was considered. The coordinates of SPM isocenters were corrected by the subroutine implemented by Matthew Brett (http://brainmap.org/index.html) to match the Talairach coordinates. Brodmann areas (BAs), were limited at a range of 0-3 mm, and identified by Talairach client (http://www.talairach.org/index.html).

Standard Protocol Approvals, Registrations and Patient Consents

The study was approved by the Institutional Ethical Committee of the Turin ALS Centre. All patients provided a written informed consent before the enrollment. Data were kept according to the Italian law for the protection of privacy.

Results

Clinical data

The clinical features of patients included in the analysis are summarized in Table 1. We found no difference in gender, site of onset (bulbar/spinal), mean age at time of PET, mean time from diagnosis to PET scan, and ALSFRS-R total score among groups.

Group comparison of ^{18}F-FDG-PET data

ALS-Cn *vs* ALS-FTD

ALS-FTD patients showed a large cluster of relative hypometabolism at $p<0.05_{corrected}$ (Figure 1A, Table 2) including bilateral premotor, frontal and anterior prefrontal cortex with left predominance as well as left lateral prefrontal (Broca's area) and orbitofrontal cortex. Large regions with relative increased metabolism in ALS-FTD were found at the same threshold in cerebellum, midbrain, and corticospinal tracts, bilaterally (Figure 1B).

ALS-Cn *vs* ALS-Ci

In ALS-Ci at $p<0.001_{uncorrected}$ a relative hypometabolic cluster in right anterior cingulate, frontal and prefrontal cortex as well as in left prefrontal cortex (Figure 1C, Table 2) and a relative hypermetabolic cluster including midbrain and corticospinal tracts bilaterally were found (Figure 1D).

ALS-Ci *vs* ALS-FTD

Relative hypometabolism was found at $p<0.001_{uncorrected}$ in ALS-FTD in left orbitofrontal, prefrontal and lateral frontal (Broca's area) cortex (Figure 1E, Table 2). Also in this comparison the most cognitively impaired group (ALS-FTD) showed a relative hypermetabolism in cerebellum, midbrain and corticospinal tracts bilaterally at $p<0.001_{uncorrected}$ (Figure 1F).

No difference at the set statistical threshold was found between ALS-Bi and any other group.

Discussion

This is the first study exploring the metabolic correlates of the different degrees of cognitive impairment in ALS patients. We identified a decreasing gradient of frontal lobe metabolism going from ALS with normal cognition to ALS with full-blown FTD, through cases with intermediate cognitive deficits (ALS-Ci). According to these findings, ALS-Ci seems to represent a discrete category, showing less severe cognitive deficits and a distinct metabolic pattern as compared to ALS-FTD, being intermediate between pure ALS and ALS-FTD.

The groups with different degrees of cognitive impairment did not significantly differ for gender distribution, site of onset, mean age at PET examination, mean time from diagnosis to PET scan and total ALSFRS-R score. However, we included these variables as 'nuisance' in the ^{18}F-FDG-PET analyses and their contribution to data variability was kept under control.

We found a significantly reduced frontal and prefrontal metabolism in the ALS-FTD group as compared to patients with normal cognitive status. Furthermore, ALS-Ci showed in frontal cortex an intermediate metabolic behavior, being hypometabolic as compared to ALS-Cn, and demonstrating a cluster of higher relative metabolism as compared to ALS-FTD. Such cluster was included in the same left frontal regions found to be more severely hypometabolic in ALS-FTD as compared to ALS-Cn, suggesting a *continuum* between cognitive decline and metabolic activity in these areas. This finding is consistent with cognitive classification criteria and highlights the distinct metabolic pattern of ALS-Ci.

Our findings are in keeping with MRI studies comparing ALS patients with different levels of cognitive impairment. A structural MRI study on 39 ALS cases reported that ALS-FTD patients display significantly more atrophy of prefrontal and anterior temporal cortex as compared to ALS with cognitive and behavioral symptoms not fulfilling FTD criteria (ALS-plus) and that the ALS-

plus group shows significantly more atrophy than the pure ALS group in various areas including the superior frontal gyrus and the left planum temporale, supporting the hypothesis of a gradient of atrophy across groups.[6] Another MRI study showed that both ALS-FTD and ALS patients with cognitive impairment display cortical thinning of bilateral frontal and temporal cortex, with a more pronounced atrophy in the former group, suggesting the concept of a morphological *continuum* reflecting the clinical one.[7]

A possible advantage of ^{18}F-FDG-PET as compared to structural MRI is that abnormalities of cortical metabolism may precede grey matter atrophy and therefore may be identified earlier along the disease course. This concept is supported by a study comparing brain structural MRI and metabolic ^{18}F-FDG-PET changes in brain grey matter of patients with ALS-FTD, showing metabolic alterations in most of the brain regions displaying structural changes but also isolated ^{18}F-FDG uptake reduction in some other areas.[15]

In our study hypometabolism in frontal regions was associated in all comparisons to hypermetabolism in cerebellum, midbrain and corticospinal tracts: the more severe the cognitive decline, the larger the size of the cluster and the statistical significance of ^{18}F-FDG uptake differences (Figures 1B, 1D and 1F). This finding supports the hypothesis that astrocytosis, mainly in white matter, is associated with ALS neurodegeneration and possibly anticipates cortical changes.[14,16-18]

Overall, our results support the notion that ALS cases with cognitive impairment not fulfilling FTD criteria represent a distinct category with a peculiar metabolic pattern placed between the two extremities of the ALS-FTD spectrum. This point is of outstanding importance, since the commixture of pure ALS cases with ALS patients with cognitive deficits without frank FTD might produce inconsistent findings in the research on structural and functional correlates of cognitive impairment in ALS.[6]

A neuropathological staging system of the spreading of brain pathology in ALS has been proposed, based on the propagation of phosphorylated TDP-43 (pTDP-43) proteinopathy, since pTDP-43 aggregates seem to be strictly linked to neuron degeneration.[19] According to this model, pTDP-43 necessarily tends to spread with disease progression via axonal transport from the primary motor cortex to the prefrontal areas, suggesting that all ALS patients are susceptible to develop frontal cognitive impairment over time, according to disease duration and rate of progression. ^{18}F-FDG-PET is a measure of neuronal injury and degeneration *in vivo*,[20] allowing prospective studies, unlike neuropathology. Therefore, functional neuroimaging might enrich neuropsychological testing in the longitudinal evaluation of cognitive impairment in ALS, providing early information on the spreading of brain pathology along disease progression.

Possible limitations of this study should be considered. First, we have no longitudinal data on brain metabolism in ALS-Ci patients. The area of the course of cognitive impairment over time in ALS remains largely unexplored. A few longitudinal studies with small sample size showed a limited, if any, deterioration of cognitive performance over time.[21-25] A recent larger population-based longitudinal study reported that ALS patients displaying normal cognition at diagnosis tend to remain cognitively intact over time and that, in the absence of minimal alteration at baseline, executive dysfunction may arise in very late stages, if at all. Otherwise, patient with early executive or non-executive cognitive change may show a certain degree of spreading of cognitive impairment.[26] Second, we did not evaluate the possible role of cognitive reserve, a concept that has been proved to be valid for dementias other than frontotemporal syndromes related to ALS and that aims at explaining the possible mismatch between cerebral lesion load and clinical deficits we sometimes observe in clinical practice. Third, we could not characterize the metabolic pattern ALS-Bi and ALS-Nc patients, because of the small size of these cognitive subgroups in our sample. On the other hand, a notable strength of this work is the high sample size (n=170), making it the largest survey on ALS including both neuropsychological assessment and ^{18}F-FDG-PET performed so far.

This is the first study demonstrating in a large ALS cohort that frontal lobe metabolic impairment reflects the clinical and functional *continuum* ranging from ALS with normal cognition, through ALS with subtle, intermediate cognitive deficits, to ALS with comorbid FTD, and showing that patients with intermediate cognitive impairment display a characteristic metabolic pattern. ^{18}F-FDG-PET is considered a valuable tool to estimate the cerebral lesion load *in vivo* in neurodegenerative diseases. Our data indicate that it might be helpful to investigate the neurobiological basis of cognitive impairment in ALS along the disease course, since it can show the early regional spreading of brain metabolic alterations.

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Table 1. Clinical characteristics of patients according to cognitive category

	ALS-Cn (n=94)	ALS-FTD (n=20)	ALS-Ci (n=37)	ALS-Bi (n=9)	Total (n=160)	p-value
Gender (Male/Female)	61/33	13/7	19/18	4/5	97/63	0.38
Onset (Bulbar/Spinal)	31/63	12/8	13/24	4/5	60/100	0.21
Mean age at PET (years) (SD)	62.1 (11.5)	64.4 (12)	68.4 (8.4)	66.3 (9.8)	63.9 (10.9)	0.07
Mean time diagnosis-PET (months) (SD)	6.4 (3.2)	7.1 (4.3)	6.1 (4.9)	5.5 (3.2)	6.3 (4.1)	0.65
Mean ALSFRS–R total score (SD)	39.8 (6.2)	37.2 (5.5)	39.6 (4.3)	35.7 (7.4)	39.31 (6.1)	0.24

ALS-Cn, ALS cognitively normal; ALS-FTD, ALS with frontotemporal dementia; ALS-Ci, ALS with cognitive impairment; ALS-Bi, ALS with behavioral impairment

Table 2. Results of ^{18}F-FDG brain PET group comparison: ALS-Cn vs ALS-FTD; ALS-Cn vs ALS-Ci; ALS-Ci vs ALS-FTD.

	Cluster extent	p FDRcorr	Talairach Coordinates			Region	Cortical Region	BA
ALS-Cn vs ALS-FTD	7689	0.000	-26.0	16.0	54.0	Frontal Lobe	Middle Frontal Gyrus	6
			-53.0	33.0	-2.0	Frontal Lobe	Inferior Frontal Gyrus	47
			32.0	29.0	45.0	Frontal Lobe	Middle Frontal Gyrus	8
			-24.0	26.0	48.0	Frontal Lobe	Superior Frontal Gyrus	8
			26.0	41.0	37.0	Frontal Lobe	Middle Frontal Gyrus	9
			-42.0	4.0	31.0	Frontal Lobe	Inferior Frontal Gyrus	9

			20.0	24.0	52.0	Frontal Lobe	Superior Frontal Gyrus	6
			-16.0	47.0	38.0	Frontal Lobe	Superior Frontal Gyrus	8
			-40.0	44.0	-14.0	Frontal Lobe	Middle Frontal Gyrus	11
			-50.0	28.0	17.0	Frontal Lobe	Inferior Frontal Gyrus	46
			-34.0	48.0	22.0	Frontal Lobe	Superior Frontal Gyrus	10
ALS-Cn vs ALS-Ci	780	0.006	2.0	25.0	28.0	Limbic Lobe	Cingulate Gyrus	32
			12.0	52.0	31.0	Frontal Lobe	Superior Frontal Gyrus	9
			22.0	30.0	46.0	Frontal Lobe	Superior Frontal Gyrus	8

			6.0	44.0	29.0	Frontal Lobe	Medial Frontal Gyrus	9
			6.0	43.0	13.0	Limbic Lobe	Anterior Cingulate	32
ALS-Ci vs ALS-FTD	1735	0.002	-53.0	33.0	-2.0	Frontal Lobe	Inferior Frontal Gyrus	47
			-38.0	41.0	5.0	Frontal Lobe	Middle Frontal Gyrus	46
			-42.0	25.0	32.0	Frontal Lobe	Middle Frontal Gyrus	9
			-50.0	28.0	12.0	Frontal Lobe	Inferior Frontal Gyrus	46
			-22.0	42.0	-16.0	Frontal Lobe	Superior Frontal Gyrus	11
			-	52.0	-1.0	Frontal Lobe	Superior Frontal Gyrus	10

			30.0					
			-40.0	40.0	-14.0	Frontal Lobe	Middle Frontal Gyrus	11
			-51.0	26.0	17.0	Frontal Lobe	Inferior Frontal Gyrus	45
			-38.0	48.0	-7.0	Frontal Lobe	Middle Frontal Gyrus	11

ALS-Cn, ALS cognitively normal; ALS-FTD, ALS with frontotemporal dementia; ALS-Ci, ALS with cognitive impairment; ALS-Bi, ALS with behavioral impairment; BA, Broadman's area;

Figure legend

Figure 1. ^{18}F-FDG-PET data: group comparison. **A-B**: ALS-Cn *vs* ALS-FTD. **C-D**: ALS-Cn *vs* ALS-Ci. **E-F**: ALS-Ci *vs* ALS-FTD. **A-C-E**: clusters of relative hypometabolism. **B-D-F**: clusters of relative hypermetabolism.

Figure 1