



Age at symptom onset influences cortical thinning distribution and survival in amyotrophic lateral sclerosis

Pilar M. Ferraro¹ · Corrado Cabona² · Giuseppe Meo³ · Claudia Rolla-Bigliani¹ · Lucio Castellani¹ · Matteo Pardini^{3,4} · Matilde Inglese^{3,4} · Claudia Caponnetto³ · Luca Roccatagliata^{1,5}

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Abstract

Purpose The lifetime risk of developing amyotrophic lateral sclerosis (ALS) increases in the elderly, and greater age at symptom onset has been identified as a negative prognostic factor in the disease. However, the underlying neurobiological mechanisms are still poorly investigated. We hypothesized that older age at symptom onset would have been associated with greater extra-motor cortical damage contributing to worse prognosis, so we explored the relationship between age at symptom onset, cortical thinning (CT) distribution, and clinical markers of disease progression.

Methods We included 26 ALS patients and 29 healthy controls with T1-weighted magnetic resonance imaging (MRI). FreeSurfer 6.0 was used to identify regions of cortical atrophy (CA) in ALS, and to relate age at symptom onset to CT distribution. Linear regression analyses were then used to investigate whether MRI metrics of age-related damage were predictive of clinical progression. MRI results were corrected using the Monte Carlo simulation method, and regression analyses were further corrected for disease duration.

Results ALS patients exhibited significant CA mainly encompassing motor regions, but also involving the cuneus bilaterally and the right superior parietal cortex ($p < 0.05$). Older age at symptom onset was selectively associated with greater extra-motor (frontotemporal) CT, including pars opercularis bilaterally, left middle temporal, and parahippocampal cortices ($p < 0.05$), and CT of these regions was predictive of shorter survival ($p = 0.004$, $p = 0.03$).

Conclusion More severe frontotemporal CT contributes to shorter survival in older ALS patients. These findings have the potential to unravel the neurobiological mechanisms linking older age at symptom onset to worse prognosis in ALS.

Keywords Amyotrophic lateral sclerosis · Age at onset · Prognosis · Cortical thinning · Structural magnetic resonance imaging

✉ Pilar M. Ferraro
PilarMaria.Ferraro@ext.unige.it

¹ Department of Neuroradiology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

² Department of Neurophysiology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

³ Department of Neurology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

⁴ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI), University of Genoa, Genoa, Italy

⁵ Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons in the cerebral cortex, brainstem, and spinal cord.

The mean or median age at symptom onset is highly variable, typically ranging from 51 to 66 years [1, 2]. This variability is also influenced by genetic factors, with younger age of onset reported in familial forms of ALS, and older age of onset observed in patients with sporadic forms of the disease [1], who represent the vast majority of cases [3].

ALS is an age-related neurodegenerative disease. As such, the lifetime risk of developing the disease increases in the elderly, even if it has been suggested that above the age of 75 years there may be a decline in incidence [2].

Notably, recent studies further suggest that age at symptom onset might influence a wide range of clinical features. Older ALS patients more frequently develop frontotemporal dementia (FTD) [4–6], exhibit a generalized onset, and manifest faster disease progression and shorter survival compared to younger cases [7, 8].

Despite these considerations, the neurobiological mechanisms contributing to worse prognosis in ALS patients with older age at symptom onset are still largely unknown.

Cross-sectional structural magnetic resonance imaging (MRI) studies have shown that ALS is a multisystem disorder, with cortical atrophy encompassing motor and extra-motor regions [9, 10]. However, recent longitudinal investigations suggest that, over the course of the disease, motor cortical atrophy does not further advance [11], while extra-motor brain regions further degenerate [12, 13].

It is therefore plausible to hypothesize that what contributes to the faster disease course observed in older ALS patients might be a more severe age-related involvement of extra-motor brain regions from the onset of the disease.

In this work, we therefore aimed at using structural MRI to test the hypothesis that older age at symptom onset would have been associated with greater extra-motor cortical degeneration leading to worse prognosis in ALS.

Methods

Subjects

As part of a larger study established in 2009 and still in operation, all patients diagnosed with ALS at our Center, who agree to participate, undergo a thorough baseline clinical evaluation (all the details are provided below) and are followed longitudinally with clinical evaluations at regular intervals (2–4 months). A standard form is used for collecting clinical information at each follow-up visit, including therapeutic interventions, and all the evaluations are performed by a team of experienced neurologists (C.C., C.C., and G.M.) operating at the Center.

From this large dataset, the present retrospective study selected all the ALS cases who were meeting the following inclusion criteria: (1) a diagnosis of possible, probable, or definite ALS according to revised El Escorial criteria [14]; (2) complete clinical characterization including time of symptom onset, age at symptom onset, and site of symptom onset (bulbar or spinal); (3) MRI examination with 3D T1-weighted sequences; (4) full baseline clinical evaluation performed either on the same date of the MRI examination, or within a maximum of 30 days from the MRI scan, including the ALS functional rating scale revised (ALSFRS-r) [15], the Medical Research Council (MRC) scale, and the clinical progression rate estimation (calculated with the formula $(48 - \text{ALFRS} -$

r score at the time of the evaluation)/disease duration); and (5) absence of overt FTD or clinical evidence of cognitive/behavioral impairment (including negative informant report of behavioral and/or social deficits).

An additional sample of demographically matched healthy controls (HC) was selected from our HC dataset which includes all subjects recruited among spouses of patients and by word of mouth fulfilling the following inclusion criteria: (1) absence of any psychiatric and/or neurological disorder (as ascertained from clinical interview, neurological assessment, and absence of any impairment in daily life activities), (2) absence of any history of cerebrovascular events, (3) MRI examination with 3D T1-weighted sequences, and (4) no territorial infarcts nor significant small vessel disease at routine MRI (Fazekas score > 1) [16].

These selection procedures resulted in the final sample of the present study: 26 ALS patients (11 females, 15 males; mean age 61.26 years) and 29 healthy controls (HC) (10 females, 19 males; mean age 59.55 years).

Written informed consent was obtained from each participant according to the institution's procedures and the Declaration of Helsinki. Retrospective analysis of the data was approved by the Hospital Review Board.

MRI acquisition

All subjects underwent a routine MRI protocol, including a standardized T1-weighted brain volumetric scan acquired with a 1.5-T system (SIGNA; General Electric Healthcare, Milwaukee, WI, USA) using an eight-channel high-resolution brain array coil. All the clinical scans were reviewed by an experienced neuroradiologist to exclude the presence of pathological findings independent from ALS.

The T1 volumetric sequence obtained was a sagittal three-dimensional spoiled gradient recalled (3D SPGR) sequence with the following parameters: TR 28 ms, TE 6 ms, flip angle 30°, FOV 256 × 256 mm, in-plane matrix 256 × 256, slice thickness 1.3 mm.

MRI analysis

Cortical reconstruction and estimation of cortical thickness were performed on the 3D SPGR images using the FreeSurfer image analysis suite, version 6.0 (<http://surfer.nmr.mgh.harvard.edu/>) [17]. After registration to Talairach space and intensity normalization, the process involved automatic skull stripping, which removes extracerebral structures, cerebellum, and brainstem, by using a hybrid method combining watershed algorithms and deformable surface models. Images were then carefully checked for skull stripping errors. After this step, images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF); cerebral hemispheres were separated; and subcortical

structures divided from cortical components. The WM/GM boundary was tessellated, and the surface was deformed following intensity gradients to optimally place WM/GM and GM/CSF borders, thus obtaining the WM and pial surfaces [18].

The results of this segmentation procedure were inspected visually, and, afterward, surface inflation and registration to a spherical atlas were performed [18]. Finally, cortical thickness was estimated as the average shortest distance between the WM boundary and the pial surface.

Statistical analysis

All data were analyzed using CRAN R Version 3.4.1. Normal distribution assumption was checked by means of Shapiro-Wilk test. *T* tests and Chi-square tests were applied, as appropriate, to compare demographic features between ALS patients and HC.

Using general linear models in FreeSurfer, a vertex-by-vertex analysis was used to assess differences of cortical thickness between ALS patients and HC, and to perform univariate regression analyses relating age at symptom onset to cortical thinning in the ALS group.

Mean cortical thickness values from regions showing cortical thinning related to older age at onset were then entered in linear regression models to test their role as significant predictors of clinical markers of poor prognosis (clinical progression rate and survival (calculated as the time in months from symptom onset to death)).

All the MRI results were corrected for multiple comparisons using the Monte Carlo simulation method implemented in FreeSurfer ($p < 0.05$) and regression analyses were further corrected for disease duration at the time of the MRI exam.

Results

Demographic and clinical features

ALS patients and HC were matched in terms of age and gender (Table 1). The majority of patients ($N = 21$, 80.76%) had a spinal onset form of ALS, the mean age at symptom onset was 60.07 years ($SD = 9.56$), mean disease duration was 14.69 months ($SD = 12.22$), mean ALSFRS-r score was 39.95 ($SD = 5.35$), mean MRC score was 131.42 ($SD = 17.47$), and the mean clinical progression rate was 0.72 ($SD = 0.64$) (Table 1). Two patients were found to carry ALS-associated genetic mutations (C9orf72 expansion in one case, and TARDBP mutation in the other case).

MRI findings

Cortical thickness comparison between ALS patients and healthy controls Compared to HC, ALS patients showed

cortical atrophy mainly encompassing motor regions (precentral and paracentral cortices bilaterally) ($p < 0.05$) (Fig. 1).

Peaks of cortical atrophy were also observed in the cuneus bilaterally as well as in the right superior parietal cortex ($p < 0.05$) (Fig. 1). Results remained significant when we applied a more stringent threshold ($p < 0.01$). When we repeated the analysis excluding the genetic cases ($N = 2$), the results remained largely unchanged (Supplementary Figure 1).

Cortical thinning related to older age at symptom onset in ALS patients

Older age at symptom onset was selectively associated with a predominant frontotemporal pattern of cortical thinning, including pars opercularis bilaterally as well as left middle temporal and parahippocampal cortices ($p < 0.05$) (Fig. 2). When we repeated the analysis excluding the genetic cases ($N = 2$), the results remained largely unchanged (Supplementary Figure 2).

Prognostic role of age-related cortical thinning Mean cortical thickness values of the left parahippocampal and middle temporal cortices were significant predictors of shorter survival (respectively, $\text{coeff} = 0.03$, t value = 4.15, $p < 0.001$, and $\text{coeff} = 0.03$, t value = 3.43, $p = 0.002$) (Fig. 3). No significant associations were observed between age-related cortical thickness measures and the rate of clinical progression.

Discussion

To our knowledge, this is the first study investigating the cortical correlates of older age at symptom onset in ALS and exploring their prognostic role in the disease.

Our results confirmed the initial hypothesis of greater extra-motor cortical degeneration related to older age at symptom onset, and further revealed a focal frontotemporal distribution of disease burden. Moreover, in line with our expectation, the degree of extra-motor damage was predictive of worse prognosis.

Relative to HC, cortical atrophy in the ALS group mainly encompassed motor regions, with a widespread bilateral pattern, in accordance with classical MRI findings in the disease [19–21].

However, in line with the emerging literature of extra-motor cortical involvement in ALS [9, 10], we further found peaks of cortical atrophy in the parietal and occipital areas, confirming that cortical pathology in ALS also extends beyond the motor cortex.

Intriguingly, while widespread cortical involvement was observed compared to HC, the regression analysis with age at symptom onset revealed a focal, frontotemporal pattern of atrophy.

Table 1 Demographic and clinical features of healthy controls and patients with amyotrophic lateral sclerosis

	HC	ALS patients	<i>p</i> value
Number	29	26	-
Age (years)	59.55 ± 4.40	61.26 ± 9.71	0.42
Gender (f/m)	10/19	11/15	0.15
Site of onset (s/b)	-	21/5	-
Side of onset (r/l)	-	11/10	-
El Escorial category (definite/probable/probable-laboratory supported/ possible)	-	9/8/7/2	-
Age at symptom onset (years)	-	60.07 ± 9.56	-
Disease duration (months)	-	14.69 ± 12.22	-
ALSFRS-r (0–48)	-	39.95 ± 5.35	-
Clinical progression rate (ALSFRS-r rate of decline per month)	-	0.72 ± 0.64	-
MRC (0–150)	-	131.42 ± 17.47	-
Decease (yes/no)	-	22/4	-
Survival (months)	-	32.54 ± 14.38	-
Time from MRI and clinical evaluation to death (months)	-	17.27 ± 12.35	-

Values are means ± standard deviations. *p* values refer to Chi-square or *T* test

ALS, amyotrophic lateral sclerosis; ALSFRS-r, ALS functional rating scale-revised; *b*, bulbar; *f*, females; HC, healthy controls; *l*, left; *m*, males; MRC, Medical Research Council; MRI, magnetic resonance imaging; *r*, right; *s*, spinal

ALS onset has been postulated to be driven by a progressive damage of specific central nervous system (CNS) regions. While this damage might remain subclinical for several decades, it makes those affected especially prone to the consequences of age-related neuronal attrition [2]. Neural degeneration is indeed a gradual process, and it is plausible that it must rely on a vulnerable substrate in order to propagate. In line with this observation, our finding of greater frontotemporal damage associated with older age at symptom onset suggests that previously reported age-related frontotemporal atrophy [22] might provide a vulnerable substrate for faster and more severe disease propagation in older

ALS patients. Accordingly, we further found that age-related frontotemporal thinning exerted a significant negative impact on survival, providing a neurobiological explanation for the worse prognosis frequently observed in older cases.

Furthermore, the anatomical distribution of cortical damage in our study well matches with other negative prognostic features previously reported in older ALS patients.

Firstly, patients with older age at symptom onset more frequently develop cognitive impairment or overt FTD over the course of the disease [4–6]. Accordingly, in older patients, we observed greater cortical thinning encompassing frontal

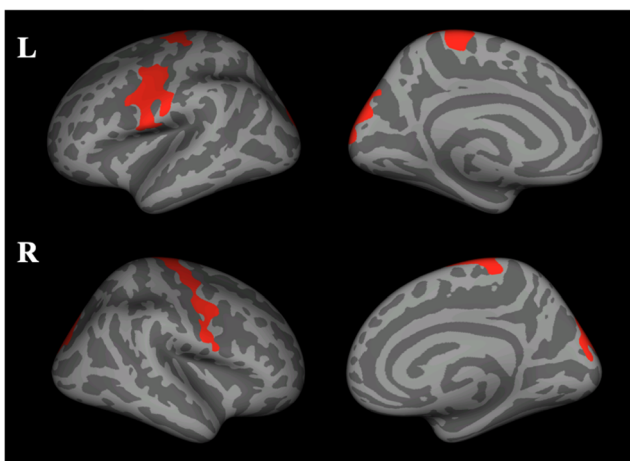


Fig. 1 Three-dimensional reconstructed MR imaging maps show regions of significant cortical atrophy on the inflated surface in the left (L) and right (R) hemispheres in ALS patients compared to healthy controls (Monte Carlo, $p < 0.05$)

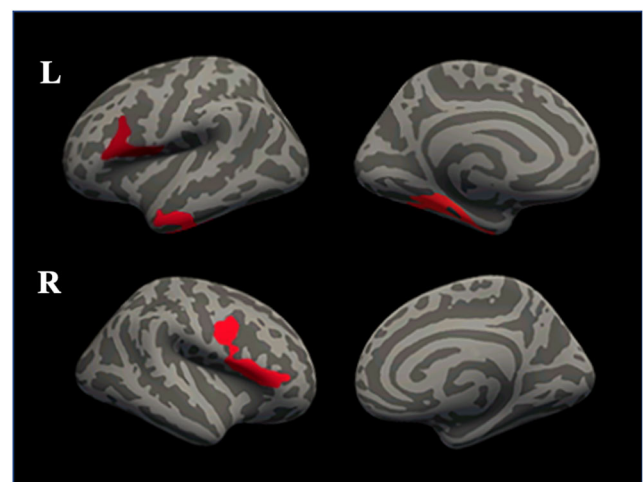


Fig. 2 Three-dimensional reconstructed MR imaging maps show regions of significant cortical thinning related to older age at symptoms onset on the inflated surface in the left (L) and right (R) hemispheres in ALS patients (Monte Carlo, $p < 0.05$)

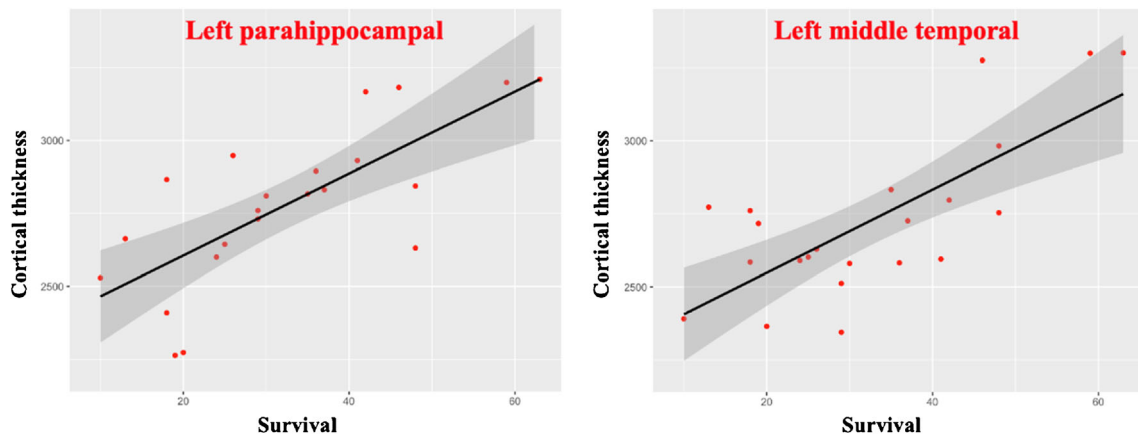


Fig. 3 Relationship between the mean cortical thickness values of the left parahippocampal cortex (left panel) and of the left middle temporal cortex (right panel) and survival

regions bilaterally and left temporal cortices, in line with the previously reported patterns of cortical atrophy in overt FTD [23] and ALS-FTD cases [24]. Moreover, the same pattern of atrophy has been recently found to be associated with the development of cognitive and behavioral deficits in ALS [25].

Secondly, older age at symptom onset has been consistently identified as a predictor of worse outcome in ALS [7, 8].

Our observation of greater age-related pars opercularis thinning is therefore in agreement with previous evidences of a significant association between more extensive atrophy in extra-motor gray matter regions, pars opercularis in particular [26], and a faster rate of disease progression in ALS.

The greater extra-motor cortical thinning we observed and its relation to shorter survival might also suggest a more advanced disease state in patients with older age at onset, in agreement with recent longitudinal studies reporting a progressive involvement of frontotemporal regions related to disease progression in ALS [12, 13].

Notably, by embedding disease duration as a covariate in the statistical model, we were able to rule out a possible effect of longer symptom duration on the observed extra-motor pattern of atrophy. Our results, indeed, point toward the hypothesis of a greater burden of subclinical cortical damage in patients with older age at disease onset.

Intriguingly, the triggering factors of this subclinical damage are still unknown, even if an interindividual heterogeneity in susceptibility to ageing might contribute to the explanation, with recent evidences suggesting that certain individuals age better and others worse than expected, termed “delta aging” [27, 28].

This exploratory study is not without limitations. The first shortcoming deals with the relatively small ALS sample size. Patients were indeed selected based on the availability of homogeneous T1-weighted sequences and complete clinical characterization, as well as full clinical evaluation within a maximum of 30 days from the date of the

MRI exam. As a result, the intrinsic variability of the ALS sample in terms of age at MRI could not be mitigated by further selecting more homogeneous cases. The second limitation is the absence of a standardized cognitive evaluation to better characterize the cognitive status of the included patients. While all patients had no clinical evidence of overt FTD or cognitive impairment, it is not possible to rule out the presence of subtle neuropsychological deficits in some of the cases. Yet, the mild degree of eventual cognitive alterations in a subset of patients would not be expected to significantly influence the obtained MRI findings. Despite these limitations, our work provides a preliminary contribution to unravel the neurobiological mechanisms linking older age at symptom onset to worse prognosis in ALS.

Conclusions

In conclusion, our study demonstrated the presence of significant age-related brain structural changes in ALS, and further proved that these alterations are predictive of reduced survival in this devastating disease. Future studies in larger, ideally more homogeneous, and deeply phenotyped samples are warranted to further prove our findings, and to investigate genetic and environmental factors triggering the onset of the clinical manifestations of the disease.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00234-021-02681-3>.

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Code availability Not applicable.

Data Availability Raw data are available upon appropriate request.

Declarations

Ethic approval Retrospective analysis of the data was approved by the IRCCS Ospedale Policlinico San Martino Review Board.

Consent to participate Written informed consent was obtained from each participant according to the institution's procedures and the Declaration of Helsinki.

Consent for publication Not applicable.

Conflict of interest We declare that we have no conflict of interest.

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