Published in final edited form as:

Eur J Neurol. 2017 January ; 24(1): 122–129. doi:10.1111/ene.13163.

Structural explanation of poor prognosis of amyotrophic lateral sclerosis in the non-demented state

H.-J. Kim^{a,*}, S.-I. Oh^{b,*}, M. de Leon^c, X. Wang^d, K.-W. Oh^a, J.-S. Park^a, A. Deshpande^c, M. Buj^c, and S. H. Kim^a

^aDepartment of Neurology, College of Medicine, Hanyang University, Seoul, Korea

^bDepartment of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

^cDepartment of Psychiatry, Center for Brain Health, NYU School of Medicine, New York, NY, USA

^dDepartment of Neurology, NYU School of Medicine, New York, NY, USA

Abstract

Background and purpose—Amyotrophic lateral sclerosis (ALS), a motor neuron disease, is associated with various cortical symptoms including mild cognitive decline with behavior changes, suggesting the involvement of extra-motor areas in ALS. Our aim was to investigate the specific patterns of brain atrophy in sporadic, impaired ALS patients without commonly known genetic mutations using voxel-based morphometry.

Materials and methods—Forty-seven patients with sporadic ALS and 28 age-matched healthy controls were recruited. ALS participants were divided into three groups according to comprehensive neuropsychological testing: pure (ALS-pure), cognitive impairment (ALSci) and behavioral impairment (ALSbi). Quantitative comparison of brain atrophy patterns was performed amongst these three groups using voxel-based analysis. All analyses were adjusted for total intracranial volume, age, sex, disease duration and functional disability score.

Results—The ALSci group exhibited decreased volume in the left cerebellum, fusiform gyrus, optic radiations and corticospinal tracts compared to healthy controls. ALSci patient imaging showed decreased brain volume in the bilateral cerebellum, right putamen gray matter and bilateral superior longitudinal fasciculi white matter compared to pure ALS patients ($P < 0.001$)

Correspondence: S. H. Kim, College of Medicine, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, 133-791, Seoul, South Korea (tel.: 82 2 2220 8371; fax: 82 2 2220 8371; kimsh1@hanyang.ac.kr).

*These authors contributed equally to this work.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest. This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea (HI12C0135).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Participant selection: A total of 120 ALS patients were enrolled. Forty-seven patients received neuroimaging for VBM. Twenty-eight age-matched controls were enrolled to compare the neuroimaging findings. ALS, amyotrophic lateral sclerosis; HC, healthy controls; ALSci, ALS with cognitive impairment; ALSbi, ALS with behavioral impairment; bvFTD, behavior variant frontotemporal dementia; SD, semantic dementia; PNFA, progressive nonfluent aphasia; AD, Alzheimer's disease; VBM, voxel-based morphometry.

Table S1. Relative cortical and subcortical volume decreases in ALSci patients.

uncorrected, corrected for the entire volume). Compared to healthy controls, ALS-pure and ALSbi groups did not show any significant volume changes in gray and white matter.

Conclusions—These findings also support the hypothesis that ALS pathogenesis has a dual focality of onset (cortex and anterior horn) with contiguous spread outwards. Additionally, neuropsychological features may be an important predictor of progression and survival rates in ALS.

Keywords

amyotrophic lateral sclerosis; atrophy; cognitive impairment; voxel-based morphometry

Background

Amyotrophic lateral sclerosis (ALS) predominantly affects the corticospinal tracts and is characterized by upper and lower motor neuron degeneration, leading to progressive muscle weakness of the bulbar, limb and thoracic regions [1]. ALS is a well-known disorder of unknown etiology that manifests primarily as degeneration of motor neurons; however, many discrepancies remain as to whether atrophy is involved in the motor or extra-motor areas of the brain. Recent pathological, neuropsychological and imaging studies have challenged the view that ALS is a disorder confined to the motor system. Many studies have demonstrated cognitive impairment and behavioral changes in a substantial proportion of patients with ALS. The occurrence of cognitive impairment has been reported in 36%–51% of patients with ALS and may serve as a prognostic factor [2,3].

Executive dysfunction and language impairments in ALS have been associated in part with structural abnormalities in the prefrontal cortex [4]. The view of ALS as a motor-neuron-specific disease has changed to that of a heterogeneous disease presenting with various neurological symptoms and involvement of non-motor areas of the brain. Neuroimaging studies, both structural and functional, also support this hypothesis of brain involvement beyond the motor areas as well as the idea of ALS as a multisystem disorder. Previous magnetic resonance imaging (MRI) studies, particularly fluid-attenuated inversion recovery images, in ALS have shown abnormalities along the pyramidal tract, such as the presence of hyperintense signals in subcortical white matter and hypointense signals in the precentral gyrus [5]. Whilst definite abnormalities along the pyramidal tract could be observed using various imaging methods, conflicting results have been obtained regarding cortical involvement in ALS based upon the imaging method used.

Clinical characteristics that have been associated with survival rate in ALS include the onset type and age of onset [6,7]. Previously, it was found that approximately half of ALS patients without known genetic variations have cognitive or behavioral impairments, and ALS patients with cognitive abnormalities have a poorer prognosis than those without cognitive impairment [8]. Non-demented cognitive and behavioral impairments in ALS are overlapping features of both cognitively intact ALS patients and ALS patients with frontotemporal dementia (FTD) [9]. Therefore, it was hypothesized that the atrophic gray and white matter patterns in non-demented ALS patients vary according to the neuropsychological features of ALS based on complete neuropsychological assessment. To

test this hypothesis, the differences in brain volume were analyzed using voxel-based morphometry (VBM) in ALS patients without any genetic variations, which affect cortical involvement in ALS [10]. All participants were divided into three groups according to their neuropsychological features, and their brain structural differences were analyzed.

Methods

Subjects

Amyotrophic lateral sclerosis patients were recruited from the Motor Neuron Disease Clinic in the Neurology Department at Hanyang University Hospital, Seoul, Korea, between January 2009 and October 2012. All patients had a diagnosis of clinically definite, probable or laboratory-supported ALS according to the revised El Escorial criteria [11]. A hundred and twenty patients were recruited after neuroimaging for VBM and underwent comprehensive neuropsychological and genetic testing. Sixty-seven patients were excluded based on comorbidities (medical disease and psychiatric disease), incompleteness of neuropsychological tests or VBM, and specific previously described genetic mutations (SOD1, C9ORF72, FUS, TARDBP, ANG and OPTN) [12,13]. Six ALS patients with dementia were also excluded. Finally, 47 patients were recruited after neuroimaging for VBM (Fig. S1) [11]. Twenty-eight sex- and age-matched healthy subjects [15 men and 13 women, mean age 47.9 years (range 28–60 years)] served as controls. Sex (M:F, 30:17 and 15:13, $P=0.380$) and age (49.8 ± 7.6 and 47.9 ± 8.6 , $P=0.958$) did not differ between the ALS and healthy groups, respectively. The clinical stage of ALS was determined using the Korean version of the ALS Functional Rating Scale Revised (K-ALSFRS-R) [14]. The progression rate of the disease from symptom onset to the time of examination was calculated as follows: $(48 - \text{K-ALSFRS-R score at time of examination}) / [\text{duration between symptom onset and time of examination (months)}]$. This study was approved by the Institutional Review Board of Hanyang University Hospital (HYU 2010-04-011). Confidentiality and anonymity of the participants were assured.

Neuropsychological testing

Neuropsychological assessment was performed using the following standardized instruments: (i) executive functions [contrasting program go, no-go test, category verbal fluency test (animal item), phonemic fluency test, Stroop test color reading and backward digit span test] [15]; (ii) attention (forward digit span test) [15]; (iii) language [Korean version of the Boston Naming Test (K-BNT)] [16]; auditory comprehension test (Korean version of the Western Aphasia Battery, yes or no question) [17]; (iv) calculation (three items each of addition, subtraction, multiplication and division) [15]; (v) visuospatial function [the Rey Complex Figure Test (RCFT)] [18]; and (vi) memory, including verbal memory [immediate, delayed recall and recognition tasks of the Seoul Verbal Learning Test (SVLT), Korean version of the Hopkins Verbal Learning Test] [19] and visual memory (immediate, delayed recall and recognition tasks of the RCFT) [20]. All participants were tested with the Mini-Mental State Examination (K-MMSE) [21] and Clinical Dementia Rating (CDR) scale [22] to examine their general neuropsychological function. Changes in behavior were assessed using the Caregiver-Administered Neuropsychiatric Inventory [23]. A comprehensive neuropsychological assessment was performed only for ALS patients,

using a previously published protocol [8]. Then, ALS patients were classified into the following four groups: (i) no cognitive impairment (ALS-pure); (ii) cognitive impairment (ALSci); (iii) behavioral impairment (ALSbi); and (iv) comorbid FTD (ALS-FTD). Twenty-one patients were ALS-pure, 20 patients were cognitively impaired (ALSci) without dementia and six were behaviorally impaired (ALSbi). Patients with dementia were excluded for evaluating cortical and subcortical involvement sites in the non-demented ALS patients (one with FTD, two semantic dementia, two progressive nonfluent aphasia and one Alzheimer's dementia).

Image acquisition

Magnetic resonance imaging scans were obtained on a 3.0-T Achieva system (Phillips) equipped with a standard quadrature head coil. Structural MRI sequences included a volumetric three-dimensional spoiled fast gradient echo MRI (repetition time 7.3; echo time 2.7 ms; slice thickness 1.0 mm; flip angle 13°; field of view 256 × 256 mm); the volume consisted of 200 contiguous coronal sections covering the whole brain.

Voxel-based morphometry analysis

Voxel-based morphometry is a fully automated, whole-brain technique for the detection of regional brain atrophy by voxel-wise comparison of gray and white matter volumes between groups of subjects. The technique comprises an image spatial preprocessing step followed by statistical analysis. Both stages are implemented in the Statistical Parametric Mapping 12 software package (SPM12, Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, UK; <http://www.fil.ion.ucl.ac.uk/spm>). Because the template and prior images provided by SPM are derived from young healthy brains, *ad hoc* age-matched *a priori* and template images were created. Patient and control images were normalized to the common template to allow inter-subject comparisons and were then segmented into gray, white and cerebrospinal fluid compartments using the VBM 8 technique. Gray and white matter volume was smoothed with a 12-mm full width half-maximum Gaussian filter.

Statistical analyses

The demographic and clinical characteristics of the ALS patients were analyzed using the mean and differences between groups assessed with Student's *t* test. Comparisons were made using an ANOVA for continuous variables and chi-squared tests for categorical variables. Bonferroni's correction method was applied to adjust the value in the case of *post hoc* analysis and where multiple comparisons were applied.

Specific statistical analyses were performed to investigate the regions of common atrophy in ALS groups compared to controls and to investigate the differences amongst the ALS-pure, ALSci and ALSbi groups. The gray and white matter volumes of patients with ALS were contrasted with controls using a two-sample *t* test to identify the anatomical distribution of significant atrophic regions. Group comparisons were performed in SPM12 using a two-sample *t* test. Age, sex, total intracranial volume, disease duration and K-ALSFRS-R were corrected as confounding variables in an analysis of covariance (ANCOVA). Specifically, the contrasts were performed in the different categories of ALS. A statistical threshold of $P <$

0.001 uncorrected, a family-wise error (FWE) of $P < 0.05$, and a cluster consisting of >100 adjacent, significantly corrected voxels were accepted.

Results

Clinical findings

The mean age of ALS patients was 49.8 years (SD 7.6), and 63.8% ($n = 30$) were men (Table 1). Six patients (12.8%) had bulbar onset of ALS, whilst the others had limb onset of ALS. Disease duration from symptom onset to assessment was 17.2 months (SD 11.2), and the K-ALSFRS-R score was 40.5 (SD 4.7). Age, education, K-MMSE and K-ALSFRS-R scores differed amongst the three groups; however, sex, CDR, region of onset, disease duration, respiratory function using forced vital capacity (%) and progression rate did not differ between the three groups.

Neuropsychological findings

The comprehensive neuropsychological results of the three groups were compared based on their cognitive profiles (Table 2). The frontotemporal domains in the ALSci group were impaired compared with the ALS-pure group. The executive domain, including the backward digit span, category verbal fluency, phonemic verbal fluency and Stroop tests, in addition to the attention domain, were significantly impaired in the ALSci group. The attention domain, examined by the forward digit span and calculation tasks, scored similarly amongst the ALS-pure, ALSci and ALSbi groups. In language function using the K-BNT, the ALSci group was significantly impaired compared to the ALS-pure group but not the ALSbi group. With memory function, the delayed recall and recognition scores of the SVLT in the ALSci group were impaired compared with the ALS-pure group.

Relative decrease in the cortical and subcortical regions of each ALS subgroup

This analysis was completed to identify regions of gray and white matter atrophy in each ALS subgroup compared to controls. Only the ALSci group showed scattered patterns of atrophic changes in the left cerebellum and fusiform gyrus after gray matter analysis (Fig. 1a, Table S1). Analysis of white matter showed atrophied regions in the optic radiations and corticospinal tracts (Fig. 1b, c, Table S1). All results were significant at $P < 0.001$ and uncorrected with an extended threshold of 100 voxels. There were no survival voxels under the FWE corrected to $P < 0.05$. There were no significant voxels in the ALS-pure and ALSbi groups compared to controls.

Relative decrease in the cortical and subcortical regions of ALS correlating to cognitive and behavioral impairments

Compared to the ALS-pure group, the ALSci group presented with degenerative changes in the bilateral cerebellum and right putamen in gray matter areas (uncorrected $P < 0.001$, extended threshold to 100 voxels; Fig. 1d, Table S1). A decreased volume of white matter was observed in the bilateral superior longitudinal fasciculi (Fig. 1e, f, Table S1). There were no survival voxels when the more atrophic areas in the ALSbi group were evaluated compared to the ALS-pure group.

Discussion

In this study, the different atrophic patterns of neuropsychological features before onset of overt dementia in ALS were analyzed, excluding (i) ALS patients with overt dementia [24] and (ii) ALS patients with known genetic mutations linked to cognitive impairment (SOD1, C9ORF72, FUS, TARDBP, ANG and OPTN) [12,25].

First, it was shown that ALS patients with cognitive impairment have specific areas of atrophy in the gray and white matter of the extra-motor regions as well as the left cerebellum, fusiform gyrus, optic radiations and corticospinal tracts compared to healthy controls. Secondly, the ALS-pure and ALSbi groups did not show any significant brain atrophy compared with healthy controls. The ALSbi patients did not present any significant survival voxels compared with the ALS-pure and ALSci patients. Thirdly, the ALSci patients showed specific atrophic changes in the brain regions associated with cognition and behavior such as the cerebellum, putamen and superior longitudinal fasciculus compared to the ALS-pure patients.

Our findings differ from those of previous studies. (i) By VBM, no structural differences in the ALS-pure patients without any cognitive or behavioral dysfunction could be found compared to healthy controls. Although different results have been found by varying analysis methods and categorization of participant groups [26], gray matter atrophy in ALS has been previously reported mainly in the motor areas [27] and the frontal and temporal lobes compared to other motor areas [28]. White matter analysis on diffusion tensor imaging showed hypointense signals primarily in the corpus callosum and corticospinal tracts [29,30]. These results suggest that subjects in the previous studies had both neuropsychological and corresponding imaging abnormalities. The other possible explanation is that ALS-pure patients without any neuropsychological features presented initially with lower motor system symptoms that progress more than ALS patients with cognitive impairment. In contrast, the ALSci patients presented with both upper and lower motor neuron symptoms and pathology. The ALSbi patients showed no significant voxels compared to healthy controls, ALS-pure patients and ALSci patients. (ii) Our results have shown that the ALSci patients had more atrophied regions in the left cerebellum, fusiform gyrus, optic radiations and corticospinal tracts than the healthy controls and in the bilateral cerebellum, right putamen and bilateral superior longitudinal fasciculi than the ALS-pure group. Cerebellar atrophy in ALS has been reported previously in ALS-FTD patients, mainly associated with motor and psychological symptoms [31,32]. Additionally, ubiquitin-positive inclusions were found in the granular layer of the cerebellum [33]. In our study, the major atrophied brain regions in ALSci patients were the cerebellum, putamen, fusiform gyrus and bilateral superior longitudinal fasciculi. The cerebellum, putamen and superior longitudinal fasciculus have roles in both cognitive and neuropsychiatric dysfunction in ALS [32]. The putamen is known to have a role in verbal fluency, working memory and speech production [34]. The white matter pathways of the brain mediate the long-range transmission of information across distributed brain networks and support the synchronization and integration of operations carried out by individual brain areas [35]. The most prominent tracts bridging the frontal, temporal and parietal regions are the superior longitudinal fasciculus, inferior longitudinal fasciculus, occipito-frontal fasciculus and the

uncinate fasciculus, which have important roles in attention, working memory and response selection [35,36]. Therefore, based upon these results, the neuropsychological features of ALS could be due to faulty brain pathways.

Whether there was any correlation between the MRI parameters and the results of the neuropsychological tests was determined using single regression analysis between the MRI parameters. However, no positive result was obtained in the ALSci and ALSbi groups. This might be because neuropsychological values of ALSci and ALSbi groups were below the sixteenth percentile compared to age-matched controls; however, minimal cognitive changes were observed although these do not clearly affect the relevant brain structure in this state.

Previous brain structural analysis studies in ALS have not shown consistent findings [37]. The differences may be due to diverse factors including covariates [38], matching, severity sampling, sample size [39], normalization template [40], threshold masking [41], imaging protocol [42], statistical modeling [43] and design of participant selection [44,45].

The contemporary concept of ALS is that it is a neurodegenerative disorder with frontotemporal dysfunction that can include FTD, behavioral or cognitive impairments, deficits in social cognition or language impairment [46]. A recent report using fluorodeoxyglucose positron emission tomography demonstrated frontal lobe metabolic impairment in a large cohort of patients ranging from patients with pure ALS to patients with intermediate cognitive deficits or ALS-FTD [47]. Patients with intermediate cognitive impairment display a characteristic metabolic pattern [47].

In this study, it was found that the ALSci subtype showed widespread volume reduction in comparison with all other groups. Previously, it had been found that the ALSci group including ALS-FTD patients had shorter survival times than the ALS-pure and ALSbi groups [8]. Our results support the possibility that ALS is a widespread multisystem degenerative disease that involves the extra-motor system as well as the motor system.

It was found that the ALSci patients had brain atrophy mainly in the symptom-specific regions. These results suggest that more atrophied connective regions of the brain may be responsible for the rapid progression and survival duration in the ALSci group. These findings also support the hypothesis that ALS pathogenesis has a dual focality of disease onset (cortex and anterior horn) with contiguous spread outwards [48]. It is very difficult to assess the neuropsychological features in ALS patients due to motor weakness, rapid progression and short survival time.

Sporadic ALS has to be classified according to the involvement of neocortical structures in cognition or behavior. Each involved region presented with different clinical symptoms and prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med*. 2001; 344:1688–1700. [PubMed: 11386269]
2. Neary D, Snowden JS, Mann DM. Cognitive change in motor neurone disease/amyotrophic lateral sclerosis (MND/ALS). *J Neurol Sci*. 2000; 180:15–20. [PubMed: 11090859]
3. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology*. 2005; 65:586–590. [PubMed: 16116120]
4. Lomen-Hoerth C. Clinical phenomenology and neuroimaging correlates in ALS-FTD. *J Mol Neurosci*. 2011; 45:656–662. [PubMed: 21971978]
5. Zhang L, Ulug AM, Zimmerman RD, Lin MT, Rubin M, Beal MF. The diagnostic utility of FLAIR imaging in clinically verified amyotrophic lateral sclerosis. *J Magn Reson Imaging*. 2003; 17:521–527. [PubMed: 12720261]
6. Ganesalingam J, Stahl D, Wijesekera L, et al. Latent cluster analysis of ALS phenotypes identifies prognostically differing groups. *PLoS One*. 2009; 4:e7107. [PubMed: 19771164]
7. Mandrioli J, Faglioni P, Nichelli P, Sola P. Amyotrophic lateral sclerosis: prognostic indicators of survival. *Amyotroph Lateral Scler*. 2006; 7:211–220. [PubMed: 17127559]
8. Oh SI, Park A, Kim HJ, et al. Spectrum of cognitive impairment in Korean ALS patients without known genetic mutations. *PLoS One*. 2014; 9:e87163. [PubMed: 24498297]
9. Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2009; 10:131–146. [PubMed: 19462523]
10. Lattante S, Ciura S, Rouleau GA, Kabashi E. Defining the genetic connection linking amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD). *Trends Genet*. 2015; 31:263–273. [PubMed: 25869998]
11. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial ‘Clinical limits of amyotrophic lateral sclerosis’ workshop contributors. *J Neurol Sci*. 1994; 124(Suppl):96–107. [PubMed: 7807156]
12. Jang JH, Kwon MJ, Choi WJ, et al. Analysis of the C9orf72 hexanucleotide repeat expansion in Korean patients with familial and sporadic amyotrophic lateral sclerosis. *Neurobiol Aging*. 2013; 34:1311.e1311–1311.e1319.
13. Kim EJ, Kwon JC, Park KH, et al. Clinical and genetic analysis of MAPT, GRN, and C9orf72 genes in Korean patients with frontotemporal dementia. *Neurobiol Aging*. 2014; 35:1213.e1213–1213.e1217.
14. Kim HY, Park KH, Koh SH, et al. Korean version of amyotrophic lateral sclerosis functional rating scale-revised: a pilot study on the reliability and validity. *J Korean Neurol Assoc*. 2007; 25:149–154.
15. Benton, A., Hamsher, K., Varney, N., Spreen, O. Contributions to Neuropsychological Assessment: A Clinical Manual. New York: Oxford University Press; 1983.
16. Kim H, Na DL. Normative data on the Korean version of the Boston Naming Test. *J Clin Exp Neuropsychol*. 1999; 21:127–133. [PubMed: 10421007]
17. Kim H, Na DL. Normative data on the Korean version of the Western Aphasia Battery. *J Clin Exp Neuropsychol*. 2004; 26:1011–1020. [PubMed: 15590457]
18. Shin MS, Park SY, Park SR, Seol SH, Kwon JS. Clinical and empirical applications of the Rey–Osterrieth Complex Figure Test. *Nat Protoc*. 2006; 1:892–899. [PubMed: 17406322]
19. Brandt, J., Benedict, R. Hopkins Verbal Learning Test – revised: Professional Manual. Lutz, FL: Psychological Assessment Resources Inc; 2001.
20. Meyers JE, Bayless JD, Meyers KR. Rey complex figure: memory error patterns and functional abilities. *Appl Neuropsychol*. 1996; 3:89–92. [PubMed: 16318537]

21. Kang Y. A normative study of the Korean-Mini Mental State Examination (K-MMSE) in the elderly. *Korean J Psychol Gen.* 2006; 25:1–12.
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993; 43:2412–2414.
23. Kang SJ, Choi SH, Lee BH, et al. Caregiver-administered Neuropsychiatric Inventory (CGA-NPI). *J Geriatr Psychiatry Neurol.* 2004; 17:32–35. [PubMed: 15018695]
24. Chang JL, Lomen-Hoerth C, Murphy J, et al. A voxel-based morphometry study of patterns of brain atrophy in ALS and ALS/FTLD. *Neurology.* 2005; 65:75–80. [PubMed: 16009889]
25. Kwon MJ, Baek W, Ki CS, et al. Screening of the SOD1, FUS, TARDBP, ANG, and OPTN mutations in Korean patients with familial and sporadic ALS. *Neurobiol Aging.* 2012; 33:1017.e17–23.
26. Rajagopalan V, Yue GH, Pioro EP. Do preprocessing algorithms and statistical models influence voxel-based morphometry (VBM) results in amyotrophic lateral sclerosis patients? A systematic comparison of popular VBM analytical methods. *J Magn Reson Imaging.* 2014; 40:662–667. [PubMed: 24470336]
27. Agosta F, Pagani E, Rocca M, et al. Voxel-based morphometry study of brain volumetry and diffusivity in amyotrophic lateral sclerosis patients with mild disability. *Hum Brain Mapp.* 2007; 28:1430–1438. [PubMed: 17370339]
28. Mezzapesa D, Ceccarelli A, Dicuonzo F, et al. Whole-brain and regional brain atrophy in amyotrophic lateral sclerosis. *AJNR Am J Neuroradiol.* 2007; 28:255–259. [PubMed: 17296989]
29. Turner MR, Agosta F, Bede P, Govind V, Lulé D, Verstraete E. Neuroimaging in amyotrophic lateral sclerosis. *Biomark Med.* 2012; 6:319–337. [PubMed: 22731907]
30. Foerster BR, Dwamena BA, Petrou M, Carlos RC, Callaghan BC, Pomper MG. Diagnostic accuracy using diffusion tensor imaging in the diagnosis of ALS: a metaanalysis. *Acad Radiol.* 2012; 19:1075–1086. [PubMed: 22749050]
31. Prell T, Grosskreutz J. The involvement of the cerebellum in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013; 14:507–515. [PubMed: 23889583]
32. Tan RH, Devenney E, Dobson-Stone C, et al. Cerebellar integrity in the amyotrophic lateral sclerosis–frontotemporal dementia continuum. *PLoS One.* 2014; 9:e105632. [PubMed: 25144223]
33. King A, Maekawa S, Bodi I, Troakes C, Al-Sarraj S. Ubiquitinated, p62 immunopositive cerebellar cortical neuronal inclusions are evident across the spectrum of TDP-43 proteinopathies but are only rarely additionally immunopositive for phosphorylation-dependent TDP-43. *Neuropathology.* 2011; 31:239–249. [PubMed: 21118398]
34. Sefcsik T, Nemeth D, Janacek K, et al. The role of the putamen in cognitive functions – a case study. *Learn Percept.* 2009; 1:215–227.
35. Mesulam M. Brain, mind, and the evolution of connectivity. *Brain Cogn.* 2000; 42:4–6. [PubMed: 10739582]
36. Turken U, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *NeuroImage.* 2008; 42:1032–1044. [PubMed: 18602840]
37. Turner MR, Verstraete E. What does imaging reveal about the pathology of amyotrophic lateral sclerosis? *Curr Neurol Neurosci Rep.* 2015; 15:45. [PubMed: 26008817]
38. Pell GS, Briellmann RS, Chan CH, Pardoe H, Abbott DF, Jackson GD. Selection of the control group for VBM analysis: influence of covariates, matching and sample size. *NeuroImage.* 2008; 41:1324–1335. [PubMed: 18467131]
39. Pereira JM, Nestor PJ, Williams GB. Impact of inconsistent resolution on VBM studies. *NeuroImage.* 2008; 40:1711–1717. [PubMed: 18342543]
40. Shen S, Szameitat AJ, Sterr A. VBM lesion detection depends on the normalization template: a study using simulated atrophy. *Magn Reson Imaging.* 2007; 25:1385–1396. [PubMed: 17467945]
41. Ridgway GR, Omar R, Ourselin S, Hill DL, Warren JD, Fox NC. Issues with threshold masking in voxel-based morphometry of atrophied brains. *NeuroImage.* 2009; 44:99–111. [PubMed: 18848632]
42. Tardif CL, Collins DL, Pike GB. Sensitivity of voxel-based morphometry analysis to choice of imaging protocol at 3 T. *NeuroImage.* 2009; 44:827–838. [PubMed: 18996205]

43. Kawasaki Y, Suzuki M, Kherif F, et al. Multivariate voxel-based morphometry successfully differentiates schizophrenia patients from healthy controls. *NeuroImage*. 2007; 34:235–242. [PubMed: 17045492]
44. Grieve SM, Menon P, Korgaonkar MS, et al. Potential structural and functional biomarkers of upper motor neuron dysfunction in ALS. *Amyotroph Lateral Scler Frontotemporal Degener*. 2015; 17:85–92. [PubMed: 26458122]
45. Walhout R, Westeneng HJ, Verstraete E, et al. Cortical thickness in ALS: towards a marker for upper motor neuron involvement. *J Neurol Neurosurg Psychiatry*. 2015; 86:288–294. [PubMed: 25121571]
46. Strong MJ, Grace GM, Orange JB, Leeper HA. Cognition, language, and speech in amyotrophic lateral sclerosis: a review. *J Clin Exp Neuropsychol*. 1996; 18:291–303. [PubMed: 8780963]
47. Canosa A, Pagani M, Cistaro A, et al. 18F-FDG-PET correlates of cognitive impairment in ALS. *Neurology*. 2016; 86:44–49. [PubMed: 26590270]
48. Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology*. 2009; 73:805–811. [PubMed: 19738176]

Figure 1.

Regional atrophic patterns in the gray and white matter in each ALS subtype. The ALSci group showed scattered patterns of atrophic change in the left cerebellum and fusiform gyrus in the cortex (a) and in the optic radiation and corticospinal tracts in the subcortical areas (b, c) (displayed at $P < 0.001$, uncorrected, extended threshold 100 voxels). ALSci patient imaging showed decreased volumes in the bilateral cerebellum and right putamen in the gray matter (d) and the bilateral superior longitudinal fasciculi of the white matter (e, f) (displayed at $P < 0.001$, uncorrected, extended threshold 100 voxels). The color bar

represents the *T*score. ALS, amyotrophic lateral sclerosis; HC, healthy controls; ALSci, ALS with cognitive impairment. [Colour figure can be viewed at wileyonlinelibrary.com].

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Baseline demographics of ALS patients and healthy controls

	ALS-pure ^b (n = 21)	ALSci (n = 20)	ALSbi (n = 6)	Total (n = 47)	P value
Age, years	46.0 ± 7.8	52.4 ± 6.5 *	54.0 ± 4.4	49.8 ± 7.6	0.007
Male (%)	13 (61.9)	11 (55.0)	6 (100)	30 (63.8)	0.128 ^a
Education, years	9.3 ± 1.3	6.8 ± 2.4 *	8.7 ± 1.6	8.1 ± 2.2	<0.001
K-MMSE	28.7 ± 1.0	26.0 ± 2.7 *	26.5 ± 3.8	27.3 ± 2.6	0.001
CDR	0.02 ± 0.11	0.15 ± 0.24	0.08 ± 0.20	0.09 ± 0.19	0.103
Bulbar onset (%)	4 (19.0)	2 (10.0)	0 (0)	6 (12.8)	0.415 ^a
ALSFRS-R score	41.0 ± 3.8	41.5 ± 4.0	35.5 ± 6.9	40.5 ± 4.7	0.016
Disease duration, months	16.2 ± 9.2	17.9 ± 12.9	18.5 ± 12.9	17.2 ± 11.2	0.851
FVC (%)	83.0 ± 16.2	85.3 ± 12.1	70.2 ± 23.9	82.3 ± 16.1	0.128
Progression rate	0.62 ± 0.69	0.49 ± 0.31	0.87 ± 0.61	0.60 ± 0.55	0.326

ALS, amyotrophic lateral sclerosis; ALSbi, ALS with behavioral impairment; ALSci, ALS with cognitive impairment; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; CDR, Clinical Dementia Rating; FVC, forced vital capacity; K-MMSE, Korean version of the Mini Mental State Examination. Disease duration is the time from symptom onset to diagnosis; progression rate is estimated from the decline in ALSFRS-R score subsequent to symptom onset (48 - ALSFRS-R/disease duration). Data are means/percent ± SD. *Post hoc* tests were performed using Bonferroni's method.

^a Chi-squared tests were performed;

^b reference group;

* $P < 0.05$ compared with the reference group.

Table 2

Cognitive domain scores in ALS patients

	ALS-pure ^a (n = 21)	ALSci (n = 20)	ALSbi (n = 6)	Total (n = 47)	P value
Backward digit span	5.0 ± 1.5	3.8 ± 1.0 *	4.7 ± 0.8	4.4 ± 1.3	0.006
Category word fluency	18.9 ± 3.4	14.2 ± 3.5 *	16.7 ± 2.6	16.5 ± 4.0	<0.001
Phonemic verbal fluency	33.5 ± 9.7	22.3 ± 8.2 *	26.7 ± 5.5	27.8 ± 10.0	0.001
Stroop test color reading	106.3 ± 8.5	93.1 ± 17.1 *	102.8 ± 13.7	100.3 ± 14.5	0.014
Forward digit span	6.8 ± 1.5	6.2 ± 1.3	6.7 ± 1.5	6.5 ± 1.4	0.337
K-BNT	52.6 ± 4.7	47.6 ± 6.2 *	52.3 ± 5.1	50.3 ± 5.9	0.020
Calculation	11.9 ± 0.3	10.5 ± 2.9	11.8 ± 0.4	11.3 ± 2.0	0.047
RCFT	35.1 ± 0.3	33.9 ± 2.7	34.8 ± 0.8	34.6 ± 2.1	0.245
SVLT immediate recall	22.2 ± 4.0	19.8 ± 5.3	19.3 ± 5.4	20.8 ± 4.8	0.208
SVLT delayed recall	7.3 ± 2.4	4.9 ± 3.3 *	4.8 ± 2.6	5.9 ± 3.0	0.022
SVLT recognition score	11.2 ± 1.0	10.4 ± 1.0 *	10.0 ± 1.3	10.7 ± 1.1	0.010
RCFT immediate recall	21.3 ± 7.1	17.8 ± 6.3	20.0 ± 5.8	19.7 ± 6.7	0.275
RCFT delayed recall	21.3 ± 6.0	17.4 ± 6.5	18.5 ± 7.2	19.3 ± 6.5	0.182
RCFT recognition score	20.7 ± 1.8	20.4 ± 1.5	19.4 ± 1.7	20.4 ± 1.7	0.315

ALS, amyotrophic lateral sclerosis; ALSbi, ALS with behavioral impairment; ALSci, ALS with cognitive impairment; K-BNT, Korean version of the Boston Naming Test; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test. Data are means ± SE; *post hoc* tests were performed using Bonferroni's method (<0.05).

^aReference group;

* $P < 0.05$ compared with cognitively and behaviorally intact ALS patients as a reference group.