Shape Analysis of the Subcortical Nuclei in Amyotrophic Lateral Sclerosis without Cognitive Impairment

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Background and Purpose Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that mainly affects the pyramidal motor system. However, recent studies have suggested that degeneration of the extramotor system plays a role in the disability experienced by patients with ALS. We investigated the local shape changes and mean volumes of the subcortical nuclei in sporadic ALS patients with preserved cognition.

Methods The participants comprised 32 patients with ALS and 43 age- and sex-matched healthy controls. Three-dimensional T1-weighted structural images were acquired. Surface-based vertex analysis was performed with fully automated segmentation of both amygdalae, hippocampi, caudate nuclei, nuclei accumbens, putamina, pallida, and thalami, and the brainstem. The scalar distances from the mean surfaces of the individual subcortical nuclei were compared between groups, and correlations of the local shape distances with initial Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALS-FRS-R) scores and the delta FRS-R and with the disease duration were analyzed.

Results ALS patients showed regional shape contractions on the lateral surfaces of both pallida, the lateroposterior surface of the right putamen, and the anterior basal surface of the right accumbens. Delta FRS-R scores were negatively correlated with local shape distances in the right hippocampus and the putamina. However, the initial ALS-FRS-R score and disease duration were not correlated with local shape distances.

Conclusions Subcortical gray-matter structures are involved in the neurodegenerative process of ALS before cognitive impairment becomes evident.

Key Words amyotrophic lateral sclerosis, magnetic resonance imaging, extrapyramidal tracts, basal ganglia, thalamus, hippocampus.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons.[1] The evidence that has accumulated over recent decades of widespread involvement of the extramotor system has changed the conventional concept of ALS to a multisystem degenerative disease.[2-5] Up to 60% of patients with ALS exhibit some form of measurable cognitive impairment, and patients with ALS combined with frontotemporal dementia (FTD) are frequently encountered.[6] Moreover, the coexistence of extrapyramidal motor symptoms such as rigidity, bradykinesia, and postural instability is not uncommon in ALS.[7,8]

Postmortem pathological studies and imaging studies using diffusion-tensor imaging and magnetic resonance spectroscopy have shown that deep gray-matter structures are extensively involved in ALS.[4,9-11] In addition, reduced nigrostriatal dopaminergic function in ALS was demonstrated by studies using positron-emission tomography and single-pho-

ton-emission computed tomography.[12,13] These studies revealed the need for further studies of structural changes in the subcortical nuclei to help improve our understanding of the overall pathogenesis of ALS.

Several cross-sectional studies[14-16] have performed detailed morphometric analyses of the subcortical nuclei using the surface-based vertex analysis (SVA) technique. However, those studies included patients with late-stage ALS, making it unclear whether the structural changes observed in the subcortical nuclei developed from the primary pathogenesis of ALS or were simply secondary atrophic changes due to the loss of synaptic transmitted signals. Another previous study performed shape analysis of the subcortical nuclei along the ALS-FTD continuum, but it did not find local atrophic changes except in the amygdala in ALS patients without cognitive impairment.[17]

We have therefore investigated the local shape changes and mean volumes of the subcortical nuclei in nonfamilial ALS patients without overt neuropsychological impairment and in healthy controls (HCs) using high-resolution structural magnetic resonance imaging (MRI) data, and correlated the findings with their clinical characteristics.

METHODS

Study population

We retrospectively enrolled patients who were diagnosed with ALS and subsequently underwent three-dimensional (3D) T1-weighted MRI and comprehensive neuropsychological assessment at a neurology clinic in Korea University Anam Hospital between January 2008 and January 2017. We included patients with definite or probable ALS according to the revised El Escorial criteria for ALS.[18] We further categorized the cognitive status of the patients using the Strong criteria.[19] Young-adult ALS patients who had experienced their first symptoms before the age of 40 years[20] and patients with a family history of ALS were excluded, as were patients with insufficient 3D T1-weighted MRI images or insufficient medical records. Age- and sex-matched HC volunteers with no neurological or psychological disorders were recruited from the community via advertisements as HCs.

Demographic and clinical data were collected, including sex, age at onset, age at surveillance, disease duration, and disease onset region (bulbar, upper limb, and lower limb). Functional status was assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALS-FRS-R)[21] at the first visit. The rate of disease progression at the time of enrollment in the study was evaluated using the delta FRS-R score, which was calculated as [(48−ALS-FRS-R score)/(disease duration from onset in months)]. This study was ap-

proved by the Institutional Review Board of the Korea University Anam Hospital (IRB number: 2015AN0334).

Neuropsychological assessment

The inclusion criterion was having ALS without documented neuropsychological impairment. The results for the Seoul Neuropsychological Screening Battery (SNSB)[22] and Caregiver-Administered Neuropsychiatric Inventory (CGA-NPI)[23] were used to exclude patients who fulfilled the diagnostic criteria for behavioral variant frontotemporal or other types of dementia.[24] Patients with neuropsychological impairment who were allocated to ALS with cognitive impairment and/or ALS with behavioral impairment based on the Strong criteria[19] were also excluded.

Magnetic resonance imaging

MRI images were acquired using a 3-T scanner (Achieva TX, Philips Healthcare, Best, the Netherlands) with a 32-channel sensitivity encoding (SENSE) head coil, and both head and neck paddles. Coronal 3D T1-weighted turbo field echo MRI scans of the whole brain were acquired with the following scanning parameters: TR=9.87 ms, TE=4.59 ms, number of excitations=1, flip angle=8°, slice thickness=1.0 mm (without gaps), matrix=224×224×190, field of view=224×224 mm^2, and voxel size=1.0×1.0×1.0 mm^3. Coronal MRI slices were acquired perpendicular to the long axis of the anterior and posterior commissures in the midsagittal plane. To increase the signal-to-noise ratio, the SENSE acceleration factor was not applied.

Surface-based vertex analysis of the subcortical nuclei

Volumetric analysis identifies the overall atrophy of brain substructures as a mass, and so it cannot reveal the local atrophy or hypertrophy of the subcortical nuclei. To compensate for this limitation of volumetric analysis, SVA was performed in addition to volumetric analysis.

Fully automated segmentations of 15 subcortical structures (both amygdalae, hippocampi, caudate nuclei, nuclei accumbens, putamina, pallida, and thalami, and the brainstem) were processed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; version 5.10).[25] The subcortical nuclei were automatically segmented using the FMRIB integrated registration and segmentation tool (FIRST) algorithm. The FIRST algorithm spatially registers the T1-weighted MRI images of individuals to the MNI 152 template, and these images of the subcortical nuclei in each individual were registered to an MNI 152 subcortical mask. To remove the effect of an individual's brain size on the volumes of the subcortical nuclei, the total intracranial cavity

volume (TICV) was automatically calculated using the Computational Anatomy Toolbox 12 (http://dbm.neuro.uni-jena.de/cat).

The SVA was performed using the FIRST of the FSL. SVA involves performing permutation-based nonparametric tests on a per-vertex basis using a multivariate general linear model. The surface meshes of the subcortical nuclei indicate the volumetric information of each nucleus and comprise parameterized deformable surfaces. The SVA pipeline was processed in native space, and the vertex locations of the subcortical nuclei were projected onto the surfaces of the averaged template shape generated using the data for all of the subjects.

The absolute distances from the mean surfaces of the 15 subcortical nuclei were calculated using the 'randomize' command in FSL, which performs univariate permutations at each vertex point.[26] Positive distance values indicate positions outside the averaged surface (hypertrophy), while negative values indicate positions inside the averaged surface (atrophy). Design matrices were generated by applying the 'general linear model' command in FSL to the exploratory variables of group (HC and ALS) and covariates (age, sex, and TICV), with all continuous variables being de-meaned.

The constructed matrices were utilized as a statistical model for permutation-based nonparametric tests. The multiple-comparison issue was corrected at the cluster level using threshold-free cluster enhancement (TFCE)[27] for a family-wise error (FWE) rate of $p<0.05$. The group comparisons were independently tested using analysis of covariance (ANCOVA), with age, sex, and TICV as confounders for both hippocampi, amygdalae, caudate nuclei, putamina, nuclei accumbens, thalami, and pallida, and the brainstem. All nonparametric tests for the SVA were performed using 5,000 permutations. The statistical group differences and correlations were visualized using significance masks (TFCE FWE-corrected, $p<0.05$), which were overlaid on each 3D template. To enhance the interpretability, the statistical results following SVA and the mean 3D surfaces of the 15 subcortical nuclei were converted into 3D mesh models using the Visualization Toolkit format (www.vtk.org).

Volumetric analysis of the subcortical nuclei

The volume of each subcortical nucleus was calculated using the 'fslstats' command with the labels of the subcortical nuclei that were automatically segmented by the FIRST during the SVA process. The clinical demographics of the ALS patients and HCs were compared using the chi-square test for the sex distribution, and independent two-sample t-tests for age and TICV. The volumetric differences in the subcortical nuclei were statistically tested using ANCOVA with the subcortical volumes as dependent variables, the groups as independent variables, and the effects of age, sex, and TICV regressed out

as covariates. Assumptions of normal distributions, linearity, and the homogeneity of variances were tested and verified. The statistical tests of volumetric analysis and demographic variables were performed using SPSS (IBM SPSS Statistics for Windows, version 24.0 released 2016, IBM Corp., Armonk, NY, USA).

The correlations between the volumes of the subcortical nuclei and the delta FRS-R scores, initial ALS-FRS-R scores, and disease durations were tested using a two-tailed partial correlation analysis with age, sex, and TICV as confounders. Multiple comparisons were corrected for using the false discovery rate[28] in all of the statistical analyses.

RESULTS

Clinical characteristics of the subjects

This study included 32 patients with ALS and 43 HCs whose demographic and clinical data are summarized in Table 1. The mean age at the time of enrollment in the study and the proportion of males did not differ significantly between the ALS and HC groups. The mean age at disease onset was 51.6 years, and the mean disease duration at the time of enrollment in the study was 13.0 months. The mean ALS-FRS-R score at the first visit was 39.7.

Volumetric analysis of the subcortical nuclei

The volumes of the 15 subcortical nuclei and TICV did not differ significantly between the ALS patients and the HC

**Table 1.** Demographic and clinical information of the study population

Variable	ALS patients	Healthy controls	p
Number of patients	32	43	
Sex, male	20 (62.5)	24 (55.8)	0.561
Age at study entry, years	53.13±8.44	55.63±8.43	0.208
Age at onset, years	51.59±8.48	–	
Disease duration at study entry, months	12.99±6.12	–	
El Escorial criteria		–	
Definite	6 (18.8)		
Probable	26 (81.3)		
Onset region		–	
Bulbar	6 (18.8)		
Upper limb	14 (43.8)		
Lower limb	12 (37.5)		
Initial ALS-FRS-R score	39.72±3.98	–	
ΔFRS-R*	0.75±0.55	–	

Data are n (%) or mean±standard-deviation values.
*ΔFRS-R was calculated as [(48–ALS-FRS-R)/(disease duration from onset in months)].
ALS: amyotrophic lateral sclerosis, ALS-FRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised.

group (p>0.05, ANCOVA with age, sex, and TICV as confounders) (Supplementary Table 1 in the online-only Data Supplement). There were no correlations between the vol-
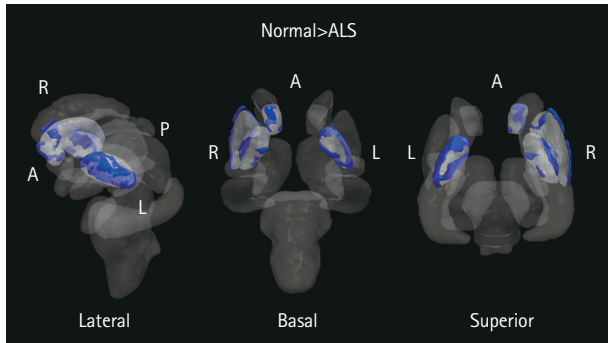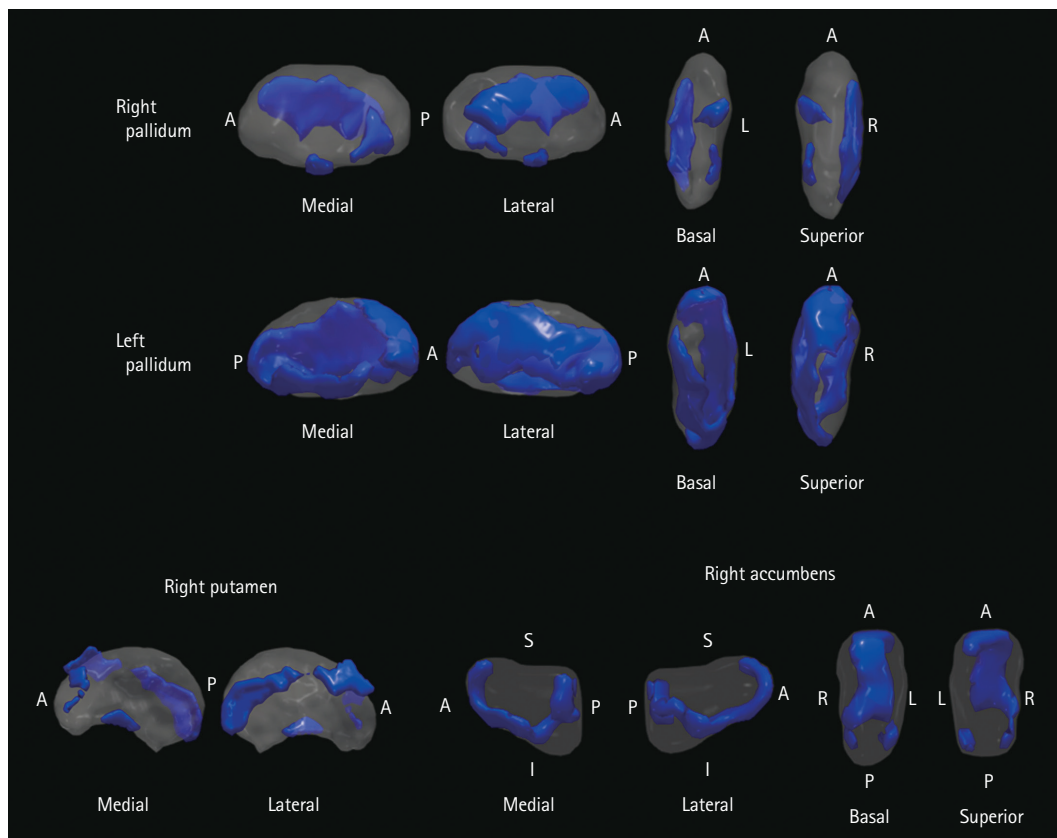

Fig. 1. Three-dimensional views of contracted shape deformations in all subcortical nuclei of ALS patients. Compared to healthy controls, ALS patients showed regional shape contractions in both pallida, the right putamen, and the right nucleus accumbens [analysis of covariance with age, sex, and the total intracranial cavity volume as confounders; threshold-free cluster enhancement for a family-wise error-corrected, p<0.05]. Other subcortical nuclei did not show significant regional shape changes. A: anterior, ALS: amyotrophic lateral sclerosis, L: left, P: posterior, R: right.

ume of each subcortical nucleus and the initial ALS-FRS-R scores, delta FRS-R scores, or disease duration in the patient group (p>0.05, partial correlation with age, sex, and TICV as confounders).

## Surface-based vertex analysis of the subcortical nuclei

Compared to HCs, ALS patients showed regional shape contractions that suggested local atrophy in both pallida, the right putamen, and the right nucleus accumbens (ANCOVA with age, sex, and TICV as confounders; TFCE FWE-corrected, p<0.05) (Fig. 1). Specifically, the lateral surfaces of both pallida were dominantly contracted, and the lateroposterior surface of the right putamen and the anterior/basal surface of the right accumbens were contracted (Fig. 2). None of the other subcortical nuclei showed significant regional shape changes.

The analyses of the correlations between delta FRS-R scores and local shape distances from the mean surface of each subcortical nuclei revealed that the delta FRS-R scores were negatively correlated with the local shape distances in the sub-

Fig. 2. Detailed three-dimensional view of contracted shape deformations. The lateral surfaces of both pallida were dominantly contracted. The lateroposterior surface of the right putamen and the anterior/basal surface of the right accumbens were also contracted (analysis of covariance with age, sex, and total intracranial cavity volume as confounders; threshold-free cluster enhancement for a family-wise error-corrected, p<0.05). A: anterior, I: inferior, L: left, P: posterior, R: right, S: superior.
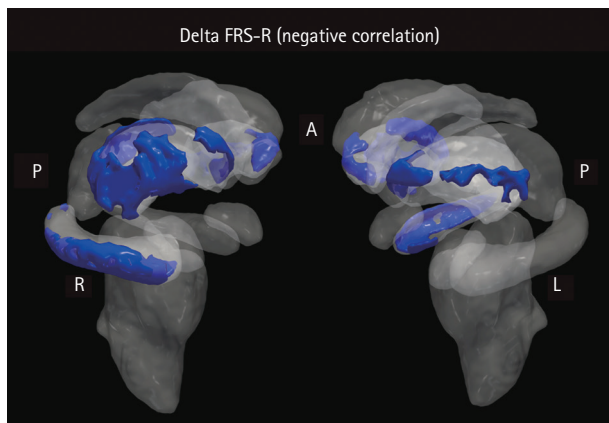
Fig. 3. Partial analysis of the correlations between delta FRS-R scores and local shape distances from the mean surface of each subcortical nucleus. Negative correlations between delta FRS-R scores and local shape distances were found in the right hippocampus and both putamina (threshold-free cluster enhancement for a family-wise error-corrected, *p*<0.05; the effects of age, sex, and total intracranial cavity volume were regressed out). However, the initial ALS-FRS-R score was not correlated with the shape deformation of the subcortical nuclei. A: anterior, ALS-FRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised, L: left, P: posterior, R: right.

regions of the right hippocampus (entorhinal cortex, cornu ammonis 1, and cornu ammonis 2) and both putamina (TFCE FWE-corrected, *p*<0.05, with age, sex, and TICV as confounders) (Fig. 3). However, the initial ALS-FRS-R scores and disease duration were not correlated with the shape deformation of any of the subcortical nuclei.

DISCUSSION

The SVA applied in this study revealed local contractions on the lateral surface of both pallida, the lateroposterior surface of the right putamen, and the anterior basal surface of the right accumbens in the ALS group compared to the HC group. Local shape distances in the right hippocampus and both putamina were negatively correlated with the delta FRS-R scores. Based on the anatomy, the regions that exhibited local contractions were part of the following three parallel, segregated circuits that connect the frontal lobe and subcortical structures: motor, associative, and limbic circuits. This suggests that dysfunction in diffuse frontal-subcortical circuits probably occurs in ALS.[29]

Regional shape changes of the putamen and pallidum would provide radiological evidence of the presence of a compromised extrapyramidal motor system in ALS. From the clinical viewpoint, the coexistence of extrapyramidal and pyramidal features in ALS has long been recognized. The pervasiveness of extrapyramidal motor deficits in patients with ALS has been investigated in many population-based cross-sectional and cohort studies.[30,31] Also, overlap syndromes of motor neuron disease and parkinsonism have frequently been reported as case series.[32-34] Recent studies have attempted to further characterize extrapyramidal motor symptoms and their impact on the disability. One characterization of the types of stiffness in a series of ALS patients without noticeable leg weakness reported that these extrapyramidal features are common in classical ALS patients, and are correlated with the severity of balance problems.[7] Another study used computational gait analyses to document extrapyramidal deficits contributing to the gait disturbances in a group of ALS patient with impaired postural reflex.[35] Our study showed the degree of regional atrophy in the putamen—which is a part of the extrapyramidal motor network—was also correlated with the delta FRS-R scores, which represents the progression of traditional pyramidal symptoms in ALS.

The atrophic change that we observed in the nucleus accumbens is consistent with the findings of previous postmortem and volumetric studies.[10,14] Since the nucleus accumbens controls impulsivity and aggression, pathological changes in this structure may be related to the behavioral changes in ALS patients.[17] Several previous studies[14,15,36] have found reduced hippocampal volumes, whereas we found no significant differences in the volume of the hippocampus. This discrepancy might be related to our study only enrolling patients with relatively early-stage ALS who did not have obvious cognitive impairment. The correlation analysis revealed an association between the hippocampus and the delta FRS-R scores, which also suggests that a diffuse degenerative process is in progress in the brain, including in the hippocampus.

The present study showed that structural changes in the subcortical nuclei had already taken place even in patients without overt neuropsychiatric symptoms. This also implies that subtle cognitive and behavioral deficits—which do not satisfy the standard criteria—are pervasive, and may be present early during the disease course. A previous large cohort study demonstrated that the neuropsychiatric symptoms even precede the classic motor features of ALS.[37] Basal ganglia structures are part of frontal-subcortical circuits that not only regulate voluntary movement, but are also associated with higher-order cognitive aspects of motor control.[38] Pyramidal and extrapyramidal motor deficits, coupled with dysfunction in motor planning and action execution, contribute to the heterogeneity of motor disability in ALS patients.

This study had some limitations. To establish a clinical correlation with dysfunction of deep gray-matter structures, it would have been helpful to collect information on the extent of extrapyramidal symptoms in the ALS group. However, this clinical information was not available due to the retrospective design of the study. Documenting the relationship between

the degree of atrophic changes of basal ganglia structures and the motor disability in ALS is particularly challenging because extrapyramidal symptoms tend to be masked by pyramidal symptoms as the disease progresses. Thus, the extrapyramidal features have greater clinical significance in patients in a relatively early stage of the disease than in those in a late stage. We expect that our findings suggesting basal ganglia involvement in ALS will prompt future studies assessing extrapyramidal profiles in early-stage ALS. The correlations between the extrapyramidal symptoms and imaging parameters and their roles in the disability of patients would then be elucidated.

Another limitation is the relatively small number of patients. We only enrolled patients with relatively early-stage ALS, which might not involve diffuse brain over the pyramidal motor system. We excluded patients with early-onset ALS and those with a familial history of ALS in order to decrease the likelihood of enrolling patients with different pathogeneses. Future studies with prospective designs and larger numbers of patients are therefore needed.

In conclusion, the present study used SVA to show that the subcortical nuclei might be involved in the primary pathogenesis of ALS. Future studies need to investigate the role of the dysfunctional network of the subcortical nuclei in the worsening of the disabilities and in the deterioration of the quality of life in ALS patients.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.4.592.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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