RESEARCH ARTICLE

Involvement of the caudate nucleus head and its networks in sporadic amyotrophic lateral sclerosis-frontotemporal dementia continuum

Michihito Masuda, Joe Senda, Hirohisa Watanabe, Bagarinao Epifanio, Yasuhiro Tanaka, Kazunori Imai, Yuchi Riku, Yuanzhe Li, Ryoichi Nakamura, Mizuki Ito, Shinuke Ishigaki, Naoki Atsuta, Haruki Koike, Masahisa Katsuno, Nobutaka Hattori, Shinsuke Ishigaki, Naoki Atsuta, Haruki Koike, Masahisa Katsuno, Nobutaka Hattori, Shinji Naganawa, and Gen Sobue

1Department of Neurology and 2Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan, 3Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan, and 4Brain and Mind Research Center, Nagoya University, Nagoya

Abstract

We investigated common structural and network changes across the sporadic amyotrophic lateral sclerosis (ALS)-frontotemporal dementia (FTD) continuum. Based on cluster analysis using the frontotemporal assessment battery, 51 patients with sporadic ALS were subdivided into three groups: 25 patients with ALS with cognitive deficiency (ALS-CD); seven patients who satisfied FTD criteria (ALS-FTD), and 19 patients with ALS with normal cognitive function (ALS-NC). Compared with the controls, gray matter images from patients with ALS-FTD showed atrophic changes in the following order of severity: caudate head, medial frontal gyrus, thalamus, amygdala, putamen, and cingulate gyrus (peak level, uncorrected \( p < 0.001 \)). The caudate head was significant at the cluster level using FWE correction (\( p < 0.05 \)).

Diffusion tensor imaging with tract-based spatial statistics revealed white matter changes in the areas surrounding the caudate head, the internal capsule, and the anterior horn of the lateral ventricle in the ALS-CD and ALS-FTD. Probabilistic diffusion tractography showed a significant decrease in structural connectivity between the caudate head and the dorsomedial frontal cortex and the lateral orbitofrontal cortex, even in the ALS-NC. Our results indicated that the caudate head and its networks were the most vulnerable to lesion in sporadic ALS-FTD-spectrum patients associated with cognitive decline with FTD features.

Key words: Voxel-based morphometry (VBM), tract-based spatial statistics (TBSS), probabilistic diffusion tractography, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD)

Introduction

Amyotrophic lateral sclerosis (ALS) has traditionally been considered a progressive neurodegenerative disorder in which the motor system is selectively targeted. However, approximately 10–15% of patients with ALS also present with the characteristic clinical findings of frontotemporal dementia (FTD); these patients with ALS satisfy the clinical criteria for both ALS and FTD, and are therefore classified as patients with ALS-FTD. Moreover, 35–40% of ALS patients exhibit mild cognitive impairment (ALS with cognitive deficiency or ALS-CD) and/or behavioral features (1).

TAR DNA binding protein of 43 kDa (TDP-43), a major component of ubiquitinated inclusions, is a critically important pathogenic protein found in both sporadic ALS and sporadic frontotemporal lobar degeneration (FTLD) (2,3). A clinicopathological continuum between sporadic FTLD and sporadic ALS with TDP-43 pathology has been documented (4–6). We further demonstrated subclinical TDP-43 pathological involvement of the upper and lower motor neurons in patients with TDP-43 pathology who exclusively displayed FTD features without ALS symptoms (7). These findings suggest that the TDP-43 proteinopathy involved in FTLD and ALS is highly cross-linked.
However, there are many issues that remain to be solved regarding the pathological continuity and the clinical diagnosis of sporadic ALS and FTD. First, is there a unique brain structure commonly involved in both ALS and FTD? This question is relevant to the search for clinical diagnostic biomarkers for sporadic ALS and FTD. Secondly, what is the most vulnerable and thus possible early initial pathology of sporadic FTD? The unique and early pathological involvement of lesions in sporadic ALS assessed by brain imaging may provide an early diagnostic marker for sporadic ALS as well as sporadic FTD.

In this study we performed magnetic resonance imaging (MRI) of patients with sporadic ALS without cognitive features (ALS with normal cognition (ALS-NC)), ALS with cognitive decline (ALS-CD), and ALS with FTD (ALS-FTD) to: (1) assess both the specific and common features of cortical and subcortical gray matter and white matter involvement; and (2) to identify the most vulnerable structural network connectivity associated with cognitive decline with FTD features.

Materials and methods

Participants

Seventy-five participants were included in this study: controls (n = 24) and sporadic ALS patients (n = 51) who were referred to the Department of Neurology at Nagoya University from April 2009 to December 2013. Participants had no medical history of stroke or traumatic brain injury. Based on the Fazekas hyperintensity rating system, no focal deep white matter abnormalities characterized by hyperintensities more severe than grade 2 were observed in T2-weighted MR images acquired from the participants (8). We also excluded patients who had a family history of ALS or FTD. We analyzed 48 of 51 patients who provided consent, but C9orf72 gene mutations were not detected, in accordance with a recent report referring to the much lower frequency of the C9orf72 repeat expansion among Japanese patients than in Western populations (9,10). Among 563 Japanese patients with ALS (552 sporadic and 11 familial), C9orf72 repeat expansion was found in two patients with sporadic ALS (2/552 = 0.4%) and no patients with familial ALS (0/11 = 0%) (10). All patients with ALS-FTD met the criteria for bvFTD.

Clinical diagnoses of ALS were established using the El Escorial criteria (11). All ALS patients satisfied the criteria for probable laboratory-supported, probable, or definite ALS. Patients diagnosed with ALS-FTD fulfilled both the El Escorial criteria and FTD criteria (12). The study protocol was approved by the ethics committee of the Nagoya University Graduate School of Medicine.

Cognitive assessments

To assess the general cognitive function of each participant, we conducted a thorough medical interview concerning FTD. We further conducted an assessment using the Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Raven's Coloured Progressive Matrices (RCPM), Alzheimer's Disease Assessment Scale-cognitive component-Japanese version (ADAS-J cog), Stroop test, and digit span (both forward and backward) and word fluency (both letter and semantic) tests.

Classification of ALS patients into ALS-NC, ALS-CD, and ALS-FTD groups according to the cognitive function assessments

Although several diagnostic criteria of frontotemporal cognitive and behavioural syndromes in ALS have been proposed (13,14), others were also proposed and definitive criteria remain to be established. We thus first performed cluster analysis on 44 sporadic ALS patients who were not diagnosed as having ALS-FTD. We applied the principal factor method and varimax rotation to the scores obtained from the ADAS-J cog, digit span, word fluency, and FAB to classify the characteristics of the cognitive profiles in our patients. Consequently, two factors were extracted from this analysis: (1) executive function (digit span, letter and semantic fluency, and FAB); and (2) ADAS-J cog word recognition items as the amnesic factor. Cluster analysis based on factor scores classified the 44 patients into two clusters.

Some patients in Cluster 1 showed very mild impairment on one executive test (i.e. 10.5% of patients scored below the 5th percentile). However, no patients fulfilled the previously determined diagnostic criteria for frontotemporal cognitive or behavioral syndromes in ALS (14). Thus, we classified this cluster as patients with ALS-NC.

In Cluster 2, 12% of patients showed impairment on two tests of executive dysfunction, which fulfilled the previously determined diagnostic criteria (14). Moreover, there was a subgroup that had greater impairment in the ADAS-J cog word recognition in the Cluster 2 patients compared with the Cluster 1 patients. Therefore, we labelled Cluster 2 as patients with ALS-CD.

Finally, we examined the differences in MRI findings of the three groups: ALS-NC, ALS-CD, and ALS-FTD.

Brain image acquisition and processing

MRI protocol. Three-dimensional (3-D) T1-weighted images, conventional MRI (T2-weighted and fluid-attenuated inversion recovery [FLAIR] images), and diffusion tensor imaging data were acquired on a 3.0 Tesla scanner (Trio Siemens,
Germany). Structural T1 and T2/FLAIR images acquired from patients were reviewed to exclude patients with potential abnormalities. The parameters of T1-weighted images and diffusion-weighted images may be found in the Supplementary material.

Voxel-based morphometric data analysis of gray matter. The 3-D T1-weighted images were analysed using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neurosciences, London, UK; http://www.fil.ion.ucl.ac.uk/spm) (15) and VBM12 (Department of Psychiatry, University of Jena, Germany) running on MATLAB® (MathWorks, Natick, MA) with Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) (16). To facilitate an unbiased comparison among the regions of interest (ROIs) in different patients, gray matter images were finally smoothed by convolving the images with an 8-mm isotropic Gaussian kernel.

For group comparisons, the pre-processed data were analyzed using an analysis of covariance (ANCOVA) model, with age, gender, and total volume (i.e., total brain volume added from the gray and white matter volumetric analyses) added as nuisance variables. The statistical threshold for the resulting maps was set at $p < 0.05$, familywise error corrected at the cluster level for multiple comparison (FWE) with a cluster forming threshold set at $p = 0.001$.

Diffusion tensor imaging analysis. Diffusion tensor imaging datasets were analyzed using FMRIB Software Library (FSL) (17). For group analyses, images were warped to the Montreal Neurological Institute (MNI) 152 standard space. Tract based spatial statistics (TBSS) (18) were run with fractional anisotropy (FA) maps to create ‘skeletonized’ FA data, which represented the center of all fibre bundles common to all subjects. For this purpose, FA images from all participants were non-linearly registered to a $1 \times 1 \times 1$ mm standard space using a common target (FMRIB 58_FA standard space) image. All standardized FA images were then merged into a single 4-D image file and the mean FA image was calculated. This mean FA image was then fed into a skeletonization program, a part of the FSL, to obtain the mean FA skeleton. A binary skeleton mask, which defined the set of voxels used in the group analysis, was generated by applying a threshold set to 0.2 to the mean FA skeleton. All standardized FA images were then projected onto the skeleton mask to obtain the skeletonized FA data. We used Randomise, another program from the FSL software package, with the skeletonized FA data to compute group differences. After threshold-free cluster enhancement (TFCE), significant voxels were found by applying a familywise error (FWE) corrected threshold corresponding to $p < 0.01$. TBSS analysis was repeated for mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps. Results were overlaid on the mean FA image.

Probabilistic diffusion tractography was performed using a single-mask (seed ROI) approach in FSL’s FMRIB’s Diffusion Toolbox (FDT 3.0). Under this approach, fiber tracts were initiated from all voxels within the specified mask. We set the probtrackx to generate 5000 streamline samples for each voxel within the seed ROI using a step length of 0.5 mm and curvature threshold equal to 0.2. This generated a probability map where the value of each voxel represented the number of streamlines passing through the voxel. To obtain a group average, we divided this number by the total number of streamlines generated for the seed ROI. This map was then thresholded by a value equal to 40% of the 95th percentile of the distribution of all voxel values. The tract maps reconstructed from each subject were then averaged to identify the tract distribution for each group. The caudate head ROI used as the seed region for the tractography was generated using the Automated Anatomical Labeling (AAL) template included in the Talairach Daemon (TD) database (19,20). This seed ROI was transformed into the native diffusion space of each participant using a non-linear transformation field estimated by FSL’s FNIRT toolbox.

Statistical analyses

Clinical backgrounds were compared using a two-way analysis of variance (ANOVA) followed by post hoc tests (Tukey or Games–Howell) or non-parametric Kruskal–Wallis tests followed by post hoc tests (Mann–Whitney). Exploratory factor analysis (generalized least-squares method) was performed on the cognitive profile variables of patients with ALS to extract factors, followed by varimax rotation. Fits of the data for the final factor solution were examined using the Kaiser–Meyer–Olkin measure of sampling adequacy and Bartlett’s test of sphericity. Components with eigenvalues $>1$ were selected. Subsequently, cluster analysis (Ward’s method) on the basis of the factor scores classified patients with ALS into clusters according to the similarity of predominant cognitive profiles in each patient. $p$-values $<0.05$ were considered to be statistically significant.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL).

Results

Demographic and cognitive features of the ALS-NC, ALS-CD, and ALS-FTD groups

Participant characteristics are summarized in Table I and Supplementary Table 1. The ALS-NC group was significantly younger on examination compared
Table I. Participant characteristics.

|                      | Controls (n = 24) | ALS-NC (n = 19) | ALS-CD (n = 25) | ALS-FTD (n = 7) | p-value |
|----------------------|------------------|-----------------|-----------------|----------------|---------|
| Gender (M:F)         | 12:12            | 9:10            | 17:8            | 6:1            | 0.313   |
| Age at examination (years) | 62.3 ± 6.1       | 57.2 ± 8.3     | 63.9 ± 11.9    | 67.3 ± 6.8     | 0.004   |
| Education (years)    | 14.4 ± 1.7       | 14.6 ± 2.3      | 13.3 ± 1.9      | 13.7 ± 2.1      | 0.119   |
| Duration (years)     | NA               | 1.5 ± 1.2       | 1.7 ± 1.7       | 3.0 ± 2.0       | 0.066   |
| ALSFRS-R             | NA               | 40.9 ± 5.5      | 39.3 ± 4.2      | 41.9 ± 5.7      | 0.282   |
| Onset form           | NA               | 6/7/5/1         | 12/3/9/1       | 2/0/4/1        | 0.373   |

Data are shown as mean ± standard deviation (SD). Mann–Whitney U-tests with Bonferroni post-hoc comparison correction revealed significant differences (\(p < 0.05\)). Disease duration did not significantly differ according to the ALSFRS-R scores or onset form among the ALS-NC, ALS-CD, and ALS-FTD groups. The ALS-NC group was significantly younger upon examination compared with the ALS-CD and ALS-FTD groups.

ALS-NC: amyotrophic lateral sclerosis-normal cognitive; AS-CD: ALS-cognitive deficiency; ALS-FTD: ALS-frontotemporal dementia; duration: time between symptom onset and testing date; ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; UL: upper limb; LL: lower limb; NA: not applicable.

Table II. Cognitive function in patients with ALS-NC, ALS-CD, and ALS-FTD.

|                      | Controls (n = 34) | ALS-NC (n = 19) | ALS-CD (n = 25) | ALS-FTD (n = 7) | p-value |
|----------------------|------------------|-----------------|-----------------|----------------|---------|
| MMSE                 | 29.3 ± 1.0       | 29.1 ± 1.1      | 28.2 ± 2.7      | 23.6 ± 5.1*    | 0.003   |
| FAB                  | 15.9 ± 1.6*      | 16.3 ± 1.7*     | 15.0 ± 1.5*     | 8.6 ± 5.4**    | <0.001  |
| RCPM                 | 31.9 ± 2.8       | 32.2 ± 2.5      | 31.7 ± 3.7      | 27.4 ± 1.7*    | 0.029   |
| Stroop test part 2   | 25.7 ± 6.8       | 25.9 ± 6.7      | 33.0 ± 10.3*    | 41.2 ± 8.9**   | <0.001  |
| Digit span forward   | 8.4 ± 2.6*       | 11.1 ± 1.8      | 9.2 ± 2.2*      | 7.3 ± 1.6*     | <0.001  |
| Digit span backward  | 6.5 ± 1.9*       | 7.7 ± 2.5       | 5.6 ± 1.8*      | 3.9 ± 2.1*     | <0.001  |
| Letter fluency       | 10.3 ± 3.0       | 13.5 ± 2.5      | 7.9 ± 1.7**     | 4.1 ± 4.3**    | 0.001   |
| Semantic fluency     | 17.3 ± 4.1       | 20.5 ± 4.2      | 13.9 ± 3.9**    | 8.1 ± 6.1**    | <0.001  |
| ADAS word recognition| 0.34 ± 0.25*     | 0.25 ± 0.27     | 0.6 ± 0.67      | 1.8 ± 1.6      | n.s.    |

Data are shown as mean ± SD. All mean scores of the cognitive function tests showed deterioration in the following order: FTD-ALS > ALS-CD > ALS-NC. \(\hat{p} < 0.05\), 

with the other groups \(p < 0.005\). No significant differences were detected in disease duration, ALS Functional Rating Scale-Revised (ALSFRS-R) scores, or disease phenotype among the ALS-NC, ALS-CD, and ALS-FTD groups.

The results of the cognitive and language function tests performed on patients in the ALS-NC, ALS-CD, and ALS-FTD groups are shown in Table II and Supplementary Table 1. All mean scores of the cognitive function tests showed deterioration in the following order: ALS-FTD > ALS-CD > ALS-NC. The ALS-FTD group had greater deficits in all cognitive tests compared with the ALS-NC group, with the exception of the ADAS word recognition test.

**VBM studies**

Compared with the controls, the gray matter images from patients with ALS-FTD showed atrophic changes in the following order of severity: the caudate head, medial frontal gyrus, thalamus, amygdala, putamen, and cingulate gyrus (peak level, uncorrected \(p < 0.001\)). Gray matter volume reduction in the caudate head was significant at the cluster level using FWE correction \(p < 0.05\) (Figure 1, Supplementary Table 2). Gray matter images showed atrophic changes in the caudate nucleus head, insula, and dorsomedial frontal cortex in patients with ALS-CD compared with the controls if we set the statistical thresholds as uncorrected at \(p < 0.001\). However, this trend was not statistically significant after correction (FWEc at \(p < 0.05\)). No obvious atrophic changes were observed in the ALS-NC group.

**Diffusion tensor imaging of TBSS**

TBSS analysis revealed a widespread decrease in FA in the white matter, specifically in anterior lesions of the corona radiata, anterior limb of the internal capsule, the superior thalamic radiation,
surrounding the caudate nucleus, the corticospinal and corticobulbar tracts, and the stria terminalis in patients with ALS-CD or ALS-FTD compared with the controls \((p < 0.01, \text{corrected for multiple comparisons after TFCE})\) (Figure 2). A similar tendency was observed in patients with ALS-NC compared with the controls; however, this tendency was not statically significant after correction (corrected for multiple comparisons after TFCE). MD, RD, and AD did not show any significant changes in ALS-NC compared to controls. ALS-CD showed increased RD, and decreased AD limited to part of decreased FA areas but did not show any changes in MD. ALS-FTD showed increased RD, decreased AD, and increased MD corresponding to decreased FA areas (Supplementary Figures 1–3). The surrounding subcortical areas of head of the caudate nucleus were observed in both ALS-CD and ALS-FTD groups with TBSS, but there were significant FA changes surrounding the amygdala in ALS-FTD but not in ALS-CD (Supplementary Figure 4).

**Probabilistic diffusion tractography of the head of the caudate nucleus**

We found the greatest atrophic changes in the caudate nucleus head at the voxel level; the VBM analysis showed that this finding was also significant at the cluster level (FWE corrected). Further, the TBSS revealed that there was severely decreased FA around the head of the caudate nucleus in both the ALS-CD and ALS-FTD groups. Therefore, we focused on the caudate nucleus and investigated the changes to its structural connectivity using probabilistic diffusion tractography. Probabilistic diffusion tractography demonstrated that the networks between the caudate nucleus head and the dorsomedial frontal lobe, including the cingulate gyrus or orbitofrontal cortex of the lateral inferior frontal lobe, were markedly retracted, even in patients with ALS-NC, compared with the controls (Figure 3). This finding indicated that the connections among the caudate head and frontal lobe cortex are involved even in ALS patients without frontotemporal cognitive dysfunction, suggesting that these connections are affected prior to cognitive symptom manifestation. Patients with ALS-FTD showed widespread and severe disruption of the connectivity from the head of the caudate nucleus and the medial orbitofrontal cortex as well as the dorsolateral prefrontal cortex.

**Discussion**

In this study, we used VBM and diffusion tensor imaging with TBSS to reveal common cortical and subcortical gray matter and white matter lesions in patients with ALS. In patients with ALS-FTD, gray matter images revealed significant atrophic changes in the caudate head, medial frontal gyrus, thalamus, amygdala, putamen, and cingulate gyrus. In particular, the most severe gray matter volume reduction was found in the head of the caudate nucleus at the peak level; this was significant at the cluster level using FWE correction. Decreased FA with TBSS analyses revealed that anterior lesions of the corona radiata, anterior limb of the internal capsule, the superior thalamic radiation, areas surrounding the caudate nucleus, the corticospinal and corticobulbar tracts, and the stria terminalis were widely observed; however, the surrounding subcortical white matter of the caudate head was severely affected in the
ALS-CD and ALS-FTD groups. Thus, we focused on caudate head-based connectivity. Using probabilistic diffusion tractography, even the patients with ALS-NC had significantly impaired connectivity between the caudate head and the dorsomedial frontal cortex, including the anterior cingulate cortex or the lateral orbitofrontal cortex. Therefore, in sporadic ALS patients, caudate head and related connectivity may be early structural lesions in addition to those found in the motor neuron system.

A previous report demonstrated that extensive cortical and subcortical-frontotemporal involvement was identified in the ALS patients associated with the C9orf72 mutation, compared to the relatively limited extramotor pathology in patients with C9orf72-negative ALS. In this study, we also showed that even patients without C9orf72 phenotype also showed cortical and subcortical frontotemporal involvement particularly in the caudate head in association with severity of cognitive decline. Further studies will be needed to clarify the similarity and difference of cortical and subcortical structural changes in ALS patients with the C9orf72 mutation and those without (21).

The connections between the caudate head and the dorsomedial frontal cortex play an important role in learning the value of actions (22), and the lateral orbitofrontal cortex is associated with disadvantageous or risky decision making (23,24) and reversal errors (25). The integrity of the frontostriatal region was reportedly important for probabilistic learning (26). Meier et al. also reported that a subpopulation of patients with ALS without obvious cognitive decline displayed altered social awareness and subtle changes in behavior, emotional processing, and decision-making, in association with changes in the orbitomedial prefrontal cortex (27). Machts et al. demonstrated correlations between basal ganglia measures and neuropsychological performance in C9orf72-negative ALS (28). Our observation suggests that disruption of the caudate head and its network connections to the medial prefrontal cortex or lateral orbitofrontal cortex,
which were most severely affected in the ALS-FTD group, play an important role in social and emotional changes in sporadic ALS.

Recent imaging studies using diffusion tensor imaging and VBM showed that the basal ganglia were involved in sporadic ALS (28–32). However, many of these studies did not investigate the relationship between cognitive status and subcortical involvements. Our probabilistic diffusion tractography results further demonstrated that the observed connectivity impairments between the caudate head and the dorsomedial medial prefrontal cortex and the ventrolateral orbitofrontal cortex were present even in patients with ALS that did not present with cognitive impairment.

Probabilistic diffusion tractography is a novel analysis method to overcome uncertainty issues in fiber tracking (33). Many current algorithms are deterministic and will always produce the same unique streamline when seeded from the same point. Probabilistic diffusion tractography estimates the range of connections to which the seed point might possibly be connected, given various sources of uncertainty, and offers significant advantages in sensitivity when tracking non-dominant fiber populations. In this study, even patients with ALS-NC showed significant involvement of networks from the caudate head with probabilistic diffusion tractography, suggesting that probabilistic diffusion tractography is a highly sensitive tool for detecting connectivity deficiency due to early CNS lesions in ALS as well as in other neurodegenerative diseases.

With respect to MD, RD, and AD, ALS-FTD showed FA, MD, RD, and AD abnormalities supporting the view that there was chronic white matter degeneration with a loss of both axons and myelin. ALS-CD showed decreased FA, increased RD and decreased AD without any changes of MD. According to a previous study (34), these characteristics (i.e. a decrease in FA with a simultaneous subtle or significant increase in RD, a decrease in AD, and non-significant difference in MD) suggest mild microstructural alterations or secondary Wallerian degeneration, because the abnormalities were observed in the same area detected by TBSS analysis based in FA. Thus, these different diffusivity parameters suggest the pathological background of white matter microstructural changes in ALS in accordance with cognitive impairment.

In this study, we focused on patients with sporadic ALS and ALS-FTD, in order to detect the most vulnerable and thus possible early CNS
changes. A clinicopathological continuum between sporadic FTLD and sporadic ALS with TDP-43 pathology has been documented (4–6). Therefore, established brain connectivity lesions and volumetric cortical lesions detected in sporadic ALS patients without clinically diagnosed FTD features could also presumably act as a clinical marker of early presymptomatic sporadic FTLD-TDP. Appropriate connectivity study methods (e.g. probabilistic diffusion tensor imaging) have great potential as detection tools for vulnerable and thus possible early lesions, as demonstrated in this study and previous studies of genetic FTD cases.

Conclusion
We observed disrupted networks between the caudate head and the medial prefrontal cortex or lateral orbitofrontal cortex in patients with sporadic ALS. Our imaging findings indicate that if we can develop further specific methodology to evaluate very mild cognitive and behavioral changes in association with these anatomical involvements, we may be able to assess preclinical or early and subtle socioemotional alterations in ALS. Although there are currently no adequate methods for identifying the preclinical stage of sporadic FTLD-TDP, these clinicoradiological approaches applied to patients with ALS will provide a technique for detecting preclinical or very subtle impairments in subjects who will subsequently develop FTLD-TDP. Further prospective studies will be necessary to clarify these issues.

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Declaration of interest
The authors declare no conflicts of interest.

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