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Microstructural correlates of Edinburgh Cognitive and Behavioural ALS Screen (ECAS) changes in amyotrophic lateral sclerosis

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ABSTRACT

Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was designed for testing patients with amyotrophic lateral sclerosis (ALS), a multi-system neurodegenerative disease characterized by progressive physical disability. In this study, we aim to explore the potential brain microstructural substrates associated with performance on ECAS in the early stages of ALS, using a whole-brain tract-based spatial statistics diffusion tensor imaging approach. Thirty-six non-demented ALS patients, assessed using ECAS, and 35 age-, sex- and education-matched healthy controls underwent magnetic resonance imaging at 3 Tesla. The ALS patients showed decreased fractional anisotropy (FA) in the cortico-spinal tracts and corpus callosum (CC) and significant association between verbal fluency score, among ALS-specific ECAS scores, and FA measures in several long association fiber tracts in the frontal, temporal and parietal lobes. Furthermore, the ALS non-specific total score was inversely related to axial diffusivity (AD) in the mediodorsal nucleus of the thalamus, with more extended areas of correlation in the CC, when considering only the memory subscore. Our results point towards microstructural degeneration across motor and extra-motor areas in ALS, underlining that alterations in verbal fluency performances may be related to impairment of frontotemporal connectivity, while alterations of memory may be associated with damage of thalamocortical circuits.

1. Introduction

Widespread microstructural pathology of motor and non-motor neuraxis has been increasingly recognized over different stages of neurodegeneration in amyotrophic lateral sclerosis (ALS) (Braak et al., 2013; Eisen et al., 2017). This neurodegenerative disorder primarily involves motor neurons, leading to atrophy and weakness of bulbar, limb, and respiratory muscles (Burrell et al., 2016). However, the disease process may progressively spread towards extra-motor areas in ALS (Braak et al., 2013; Eisen et al., 2017). Clinical evidence, together with the widely described genetic (Chia et al., 2017), neuropathological (Braak et al., 2013; Eisen et al., 2017) and neuroimaging (Agosta et al., 2016) overlaps identified between ALS and frontotemporal lobar degeneration (FTLD), has supported the existence of a disease continuum between the two neurological syndromes (Burrell et al., 2016; Turner et al., 2015) within the umbrella of frontotemporal spectrum disorder (ALS-FTSD). In this regard, specific criteria for the diagnosis of frontotemporal dysfunction in ALS have been formulated (Strong et al., 2009; 2017). In particular, the recently revised Strong Criteria (Strong et al., 2017) further supported that behaviour and/or cognitive dysfunctions, not sufficient to diagnose frontotemporal dementia (FTD) (Neary et al., 1998; Rascovsky et al., 2011), could coexist with ALS (i.e., ALS with behavioural impairment [ALSbi], with cognitive impairment [ALSci] and with both [ALSbci]). In order to more appropriately characterize the extent and severity of frontotemporal dysfunction associated with ALS, the recently revised Strong Criteria accounted for the existence of executive and language impairments and behavioural and neuropsychiatric symptoms (Strong et al., 2017). Conversely, memory dysfunction, although extensively studied and revealed in several cohorts of ALS patients (Mantovan et al., 2003; Machts et al., 2014; Christidi et al., 2017), when isolated, does not meet the criteria for diagnosis of ALSci.

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Despite the increasing evidence of cognitive and behavioural impairment associated with ALS, concerning not only frontal-executive abilities, but also language and social cognition (Abrahams, 2013; Taylor et al., 2013; van der Hulst et al., 2015; Girardi et al., 2011), the cognitive status of most ALS patients may not be assessed by neuropsychological tests that are time consuming and inappropriate for patients with severe difficulties in speaking, writing or drawing. On the basis of these considerations, the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) has recently been developed to identify cognitive and behavioural changes in ALS patients (Abrahams et al., 2014; Niven et al., 2015). In particular, ECAS is a timely screening test (15–20 min), which can be carried out within the clinic premises or during home visits even by non-neuropsychology health professionals. ECAS includes ALS-specific tasks, assessing executive functions with verbal fluency, social cognition and language, and ALS non-specific tasks to explore memory and visuospatial abilities. Furthermore, assessment of behaviour changes and psychotic symptoms, also associated with ALS, may also be evaluated through a brief caregiver interview included in ECAS, which provides a checklist of symptoms from diagnostic criteria. Over the last few years the neuropsychological screening of cohorts of ALS patients by means of ECAS has been widely implemented in both clinical and research settings, since ECAS has been translated into several languages and validated in many countries (Niven et al., 2015; Lulé et al., 2015; Poletti et al., 2016; Siciliano et al., 2017). Lastly, from the psychometric point of view, total, ALS-specific and non-specific ECAS scores were found to be highly correlated with composite scores of a more extensive neuropsychological battery (Pinto-Grau et al., 2017). Therefore, ECAS is a practical and valid means to screen for cognitive impairment in ALS.

Although widely explored, microstructural correlates of cognitive and behavioural changes in ALS have been only partially clarified *in vivo* by advanced neuroimaging studies. In this regard, recent diffusion tensor imaging (DTI) studies revealed reduced white matter (WM) integrity, in terms of decreased fractional anisotropy (FA) and increased mean (MD), axial (AD) and radial diffusivity (RD) in the frontal, temporal, and parietal lobes of ALS patients with or without cognitive symptoms (Agosta et al., 2016; Christidi et al., 2017; Kasper et al., 2014; Branco et al., 2018). However, the correlations existing between regional distribution of WM damage and dysfunction of cognitive domains "specifically altered" (i.e., executive, language and social cognition domains) and "non-specifically altered" (i.e., memory and visuospatial abilities) in ALS, are still to be clarified. In particular, while scores on executive tasks were found associated with FA decrease in regions throughout the brain, with high predilection for the frontal lobes (Sarro et al., 2011; Agosta et al., 2016; Dimond et al., 2017), performances on verbal and non-verbal episodic memory tests were found associated with AD and RD increase in perforant pathway zone and uncinate fasciculus in cohorts of non-demented ALS patients (Christidi et al., 2014, 2017).

The objective of the present cross-sectional study was to investigate DTI patterns of FA decrease, and MD, AD and RD increase associated with ECAS performances in a cohort of 36 non-demented ALS patients in non-advanced stages of disease. Our hypothesis was to depict a structural pattern of extent of the neurodegenerative process consistent with the cognitive profile assessed by means of ECAS and to identify, for the first time, potential associations between microstructural damage in several WM tracts connecting the frontal lobes to other temporo-parietal areas and ECAS total, ALS-specific and non-specific scores in ALS patients. Although widely used in clinical practice as an ALS-specific cognitive assessment tool, microstructural brain correlates of ECAS abnormalities have yet to be investigated.

2. Methods

2.1. Case selection

Thirty-six right-handed patients (24 males; mean age 57.28 years ± 10.2), 18 with definite ALS, 18 with clinically probable or probable laboratory-supported ALS, according to the revised El-Escorial criteria (Brooks et al., 2000), were consecutively recruited at the First Division of Neurology of the University of Campania "Luigi Vanvitelli" (Naples, Italy) from June 2016 to June 2017.

With regard to clinical phenotypes, as previously identified by Chiò et al. (2011), 14 patients exhibited a "classic" phenotype; 2 a "bulbar" phenotype; and 10 "flail arm" and 10 "flail leg" fast progressors (van den Berg-Vos et al., 2003; Müller et al., 2018) phenotypes. We excluded patients with lower motor neuron disease phenotypes with slower disease progression (van den Berg-Vos et al., 2003; Müller et al., 2018) and "upper motor neuron (UMN) dominant" and "pure" upper motor neuron (i.e., PUMN) phenotypes, which have been shown to be far from the "classic" ALS phenotype in terms of disease course (Chiò et al., 2011) and characterized by significant differences in several clinical features with respect to other ALS variants (Sorarù et al., 2010; Sabatelli et al., 2011). None of the patients recruited had additional neurological disease or previous mental illness.

All patients were classified according to the King's clinical staging system (Balendra et al., 2015): 10 were in stage 1 (i.e., functional involvement of one region: symptom onset), 17 were in stage 2 (i.e., functional involvement of two regions) and 9 were in stage 3 (i.e., functional involvement of three regions). No patients had percutaneous endoscopic gastrostomy (PEG) or were in non-invasive ventilation (NIV) (stage 4). Moreover, as clinical parameters, we measured the ALS functional rating scale-revised (ALSFRS-R) score, index of disability status (Cedarbaum et al., 1999), and the UMN score, measure of pyramidal dysfunction through the evaluation of the number of pathologic reflexes elicited from 15 body sites (i.e., glabellum, masseter, and orbicularis oris, biceps, triceps, finger jerks, knee, ankle, and Babinski responses bilaterally) (Turner et al., 2004). Respiratory function, measured by forced vital capacity (FVC), was above 70% in all ALS patients and there was no evidence of nocturnal hypoventilation. All patients were treated by riluzole (100 mg/day). Thirty-one patients also carried out physical therapy.

Genetic analysis was performed in all patients, exploring *C9orf72* expansion and mutations of *SOD1, TARDBP* and *FUS/TLS*, revealing no ALS-related mutation.

All patients included in the study underwent the Italian version of ECAS (Poletti et al., 2016; Siciliano et al., 2017). It contains 15 tasks exploring the following ALS-specific (1–3) and non-specific (4–5) cognitive domains: (1) executive functions and social cognition (score range 0–48), assessed by means of reverse digit span task (max score: 12 points), alternation task (12 points), sentence completion task (12 points), and social cognition task (12 points); (2) verbal fluency (score range 0–24), assessed by verbal fluency task for words beginning with the letter "S" (12 points) and verbal fluency task for 4-letter words starting with the letter "C" (12 points); (3) language (score range 0–28), assessed by means of naming (8 points), comprehension (8 points) and spelling tasks (12 points); (4) memory (score range 0–24), assessed by means of immediate recall (10 points), delayed recall (10 points) and delayed recognition tasks (4 points); (5) visuospatial abilities (score range 0–12), assessed by Dot counting (4 points), cube counting (4 points) and number location tasks (4 points). In addition, mood and anxiety, that may potentially affect cognitive performances, were assessed in all patients through two self-rated questionnaires (i.e., the Beck Depression Inventory -BDI-II- and the State-Trait Anxiety Inventory-Y -STAI-Y, for both state -STAI-Y1- and trait -STAI-Y2- anxiety components assessment), previously used in ALS (Wicks et al., 2007; Carelli et al., 2018). The BDI-II standard cut-off ranges are as follows: 0–9 indicates minimal depression, 10–18 indicates mild depression,

19–29 indicates moderate depression, 30–63 indicates severe depression. The 40-item STAI-Y scores range from 20 to 80. Scores higher than 65 indicate a clinically relevant anxiety.

As a control group (healthy controls, HCs) for the imaging study, 35 right-handed neurologically and cognitively normal subjects (23 males; mean age: 54.06 years ± 10.09) were enrolled among staff, employees of the University, friends of patients and by word of mouth.

ALS patients and HCs underwent the same MRI examination protocol.

The research was conducted according to the principles expressed in the Declaration of Helsinki. Ethics approval was obtained from the Ethics Committee of the University of Campania "Luigi Vanvitelli". Patient or family written consent was obtained from each participant.

2.2. Imaging acquisition

Magnetic-resonance images were acquired on a 3T scanner equipped with an 8-channel parallel head coil (General Electric Healthcare, Milwaukee, Wisconsin). The imaging protocol included: whole-brain DTI, performed using a GRE EPI sequence (repetition time = 10,000 ms, echo time = 88 ms, field of view = 320 mm, isotropic resolution = 2.5 mm, b value = 1000 s/mm^2, 32 isotropically distributed gradients, frequency encoding RL); T2-fluid attenuation inversion recovery to exclude severe cerebrovascular disease according to standard clinical neuroradiological criteria on visual inspection by three experienced radiologists. The DTI scan time was 8 min and 40 s; T2-fluid attenuation inversion recovery scan time was 6 min.

2.3. Diffusion tensor imaging (DTI) analysis

A voxel-based TBSS approach was used for group analysis of DTI data (Smith et al., 2006), as also performed for previous DTI analyses on other cohorts of ALS patients (Kasper et al., 2014; Trojsi et al., 2015; Christidi et al., 2018; Geraldo et al., 2018). DTI data sets were processed with the Functional MRI of the Brain (FMRIB) Software Library (FSL) software package (www.fmrib.ox.ac.uk/fsl). Preprocessing included eddy current and motion correction and brain-tissue extraction. After preprocessing, DTI images were averaged and concatenated into 33 (1 $B = 0$ + 32 $B = 1000$) volumes and a diffusion tensor model was fitted to each voxel, generating FA, MD, AD and eigenvalue (λ1, λ2, λ3) maps. The average of the second and third eigenvalues of the diffusion tensor was used for the RD definition. Images were warped to the Montreal Neurological Institute (MNI) 152 template, available as standard T1 data set in the FSL software package. TBSS was run with FA maps to create the "skeleton", which represents the center of all fiber bundles in common to all subjects, and which was used for all other maps. To this purpose, FA images of all subjects ($n = 71$) were aligned to a common target (1 × 1 × 1 mm MNI152 FMRIB58_FA standard space) using nonlinear registration. A mean FA skeleton was then created with threshold of FA > 0.2. Age, gender and education were considered as covariates. Moreover, the TBSS results were linked to standard anatomic data derived from the International Consortium of Brain Mapping DTI-81 WM (ICBM-DTI-81-WM) labels atlas (Johns Hopkins University, Baltimore, MD) (Wakana et al., 2007; Hua et al., 2008).

In addition to the TBSS analysis, a volume of interest (VOI) analysis was also performed, according to previous studies (Cirillo et al., 2012; Kasper et al., 2014; Trojsi et al., 2015). We defined 12 WM tracts typically used in studies on ALS *a priori*, based on the ICBM-DTI-81-WM labels atlas (Wakana et al., 2007; Hua et al., 2008): corpus callosum (CC); superior (to primary motor cortex to cerebral peduncle) and inferior part (from cerebral peduncle to bulb) of the corticospinal tracts (CST-Left/Right); inferior longitudinal fasciculus (ILF-Left/Right); inferior fronto-occipital fasciculus (IFOF-Left/Right); superior longitudinal fasciculus (SLF-Left/Right); fornix and uncinate fasciculus (UF-Left/Right). Mean FA, MD, AD, and RD values within these tract labels in MNI space were extracted from the spatially normalized and skeletonized FA, MD, AD, and RD maps of each individual. The DTI parameters of the VOIs were compared between the two groups of subjects using Mann-Whitney U test ($p < 0.05$, Bonferroni corrected).

Individual skeleton images were submitted to a General Linear Model (GLM) analysis with appropriate design matrices and linear contrasts defined for the group comparisons and the correlations between all diffusivity parameters (FA, RD, AD, MD) and ECAS total scores and subscores, evaluated only in ALS patients, related to ALS-specific (i.e., executive functions, verbal fluency and language) and ALS non-specific (i.e., memory and visuo-spatial abilities) tasks. The resulting statistical maps were thresholded at $p < 0.05$ (family-wise error [FWE] corrected) using the threshold-free cluster enhancement (TFCE) method (Smith et al., 2006). Moreover, a minimum cluster size was calculated that protected against false-positive clusters at 5% after 5000 Montecarlo simulations (Tijssen et al., 2009).

2.4. Statistical analysis

Shapiro-Wilk tests were used to assess normality and, according to distribution of the data, t-test, Mann-Whitney U test, and Chi-square test (all Bonferroni corrected) were used to compare demographics, clinical and neuropsychological scores and subscores between ALS patients and HCs. Correlational analysis of DTI measures with ECAS total score, ALS-specific and non-specific subscores within the ALS group was performed using a three covariate (i.e., age, gender and education) regression analysis in the general linear model, applied throughout the whole WM FA skeleton ($p < 0.05$, FWE corrected).

3. Results

3.1. Demographics

No significant differences between patient groups and the control cohort were found on demographic variables (Table 1). According to the Revised Strong Criteria for cognitive impairment in ALS (Strong et al., 2017), four patients exhibited cognitive impairment (i.e., 4 ALSci, with executive dysfunction) and seven patients had behavioural impairment (i.e., 6 ALSbi and 1 ALSbci). With regard to psychological assessment, among the 30 patients who completed the BDI-II, twenty-eight (94%) ranged from minimum-to-mild depression levels and two had moderate depression (6%) (Table 1). Among the 30 patients who completed the STAI-Y, no patients showed clinically significant state anxiety or trait anxiety levels (Table 1).

3.2. TBSS DTI analysis

3.2.1. Differences between ALS patients and controls

When compared to HCs, ALS patients exhibited decreased FA ($p < 0.05$, FWE corrected) in the body of CC, in the right and left CSTs underneath precentral gyri (Fig. 1), as also confirmed by VOI-based analysis (Table 2). Between-group comparisons revealed no significant differences in RD, AD and MD skeleton values.

3.2.2. Voxel-wise correlation analysis

We did not detect significant correlations between ECAS total scores and DTI parameters. On the contrary, among ALS-specific ECAS scores, verbal fluency score was positively related to FA in the left ILF, IFOF, SLF and uncinate fasciculus ($p < 0.05$, FWE corrected) (Fig. 2).

Among ALS non-specific scores, the total ALS non-specific score was inversely related to AD ($p < 0.05$, FWE corrected) in the left mediodorsal nucleus of the thalamus (Fig. 3A). Moreover, negative correlations ($p < 0.05$, FWE corrected) were also reported between the isoleted memory subscore and MD/RD measures in the left mediodorsal nucleus of the thalamus and in the genu, anterior body and splenium of the CC (Fig. 3B, C).

Table 1
Detailed patients and controls characteristics.

Parameters	ALS patients mean (SD) (n = 36)	Controls mean (SD) (n = 35)	t-test/χ^2	p-value
Demographic and clinical measures				
Age (years)	57.28 (10.19)	54.06 (10.09)	1.33	0.19
Education	10.19 (4.68)	11.57 (3.55)	−1.39	0.17
Male/Female	24/12	23/12	0.00	0.93
Disease duration (months from disease onset to MRI)	27.42 (18.64)	–	–	–
King's stage (1/2/3)	10/17/9	–	–	–
ALSFRS-R total score	38.78 (6.69)	–	–	–
ALSFRS-R subscore:				
Bulbar	11.00 (1.59)	–	–	–
Fine motor	8.22 (3.22)	–	–	–
Gross motor	8.11 (3.22)	–	–	–
Respiratory	11.5 (1.30)	–	–	–
UMN score	7.22 (4.68)			
Neuropsychological parameteres				
ALS Specific Functions	68.11 (18.18)	73.39 (10.03)	−1.55	0.12
Executive functions	29.97 (9.50)	33.39 (6.34)	−1.83	0.07
Language functions	21.50 (5.08)	22.31 (2.92)	−0.85	0.39
Fluency	16.63 (6.50)	17.65 (4.16)	−0.80	0.42
ALS Non-specific Functions	24.72 (5.26)	26.31 (3.21)	−1.58	0.12
Memory functions	14.19 (4.22)	15.68 (3.02)	−1.75	0.08
Visuospatial functions	11.05 (1.56)	10.63 (1.47)	1.19	0.23
ECAS total score	92.83 (22.83)	99.81 (11.19)	−1.72	0.90
BDI-II	7.8 (6.79)	–	–	–
State anxiety – Y1 (T-score)*	35.87 (11.30)	–	–	–
Trait anxiety – Y2 (T-score)*	37.93 (11.76)	–	–	–

BDI-II = Beck Depression Inventory; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ECAS = Edinburgh Cognitive and Behavioural ALS Screen; State-Trait Anxiety Inventory-Y = STAI-Y; UMN = Upper Motor Neuron; χ^2 = Chi-square test; SD = Standard Deviation.
* these scores were available in 30 subjects.

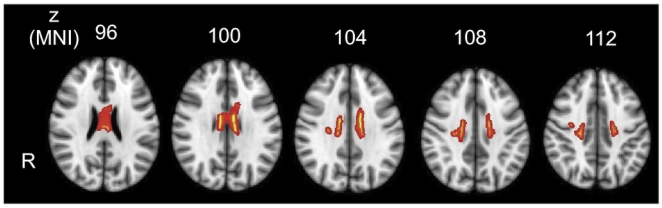

Fig. 1.. Comparison between FA statistic parametric maps of ALS patients versus HCs. FA decrease in the body of CC and in the right and left CSTs, underneath primary motor areas (coloured clusters are overlaid on the MNI standard brain, showing regions with significant changes at $p < 0.05$, FWE corrected). R = right.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

This cross-sectional study presents the first evidence of a widespread correlation between ALS-specific and non-specific ECAS scores and whole-brain DTI parameters. In our population of non-demented ALS patients, although characterized by a small subgroup of patients with cognitive (16%) and behavioural impairment (19%), the comparisons between ALS and HCs groups revealed mostly WM pathology in the motor areas of the ALS group. Moreover, the present study revealed significant correlations between verbal fluency score, among ALS-specific ECAS scores, and FA in several extra-motor WM tracts in the left hemisphere. As concerns ALS non-specific scores, both the subtotal and isolated memory scores were significantly related, respectively, to AD and RD/MD in the left thalamus and in the CC.

We designed our study starting from previous *in vivo* evidence about microstructural correlates of cognitive and behavioural dysfunctions revealed in the frontal, temporal, and parietal lobes of non-demented ALS patients (Cirillo et al., 2012; Agosta et al., 2016; Christidi et al., 2014, 2017, 2018; Kasper et al., 2014; Sarro et al., 2011; Dimond et al., 2017; Branco et al., 2018). However, with respect to these studies, we emphasized the previous evidence of significant correlations between the verbal fluency score (included in the ALS-specific cognitive domain) and FA measures in long association WM tracts (Christidi et al., 2014; Sarro et al., 2011; Dimond et al., 2017). Firstly, we reported the potential association between several DTI metrics (i.e., AD, MD and RD) in the left mediodorsal nucleus of the thalamus and the ECAS subscores, assessing the ALS non-specific cognitive domains (i.e., memory, visuo-spatial abilities), and these findings are in line with previous evidence revealing early extra-motor WM abnormalities in ALS patients without cognitive impairment (Christidi et al., 2018). Moreover, FA decrease in the body of CC and in the right and left CSTs underneath precentral gyri, also revealed in other cohorts of patients through the between-group analysis (Cirillo et al., 2012; Agosta et al., 2016), has been previously demonstrated to be significantly related to clinical indices of motor disability (Cirillo et al., 2012) and the best predictor of verbal fluency deficits and behavioural symptoms (Agosta et al., 2016). In the light of these findings, structural abnormalities in motor and extra-motor WM tracts have been suggested as potential radiological markers of both motor and cognitive deficits in ALS.

Despite the lack of correlations between ECAS total score and FA, RD and MD metrics, the significant association between the verbal fluency score and FA measures in the left ILF, IFOF, SLF and uncinate fasciculus may mark the potential involvement of long association WM tracts, especially those underlying “clustering” and “switching” strategies (Troyer et al., 1998; Turner, 1999), in regulating fronto-temporal networks in ALS patients (Christidi et al., 2014; Kasper et al., 2014; Sarro et al., 2011; Dimond et al., 2017; Branco et al., 2018). In particular, letter-guided fluency, as assessed by ECAS verbal fluency task, has been shown to require more executive resources than semantic-guided fluency (Libon et al., 2009). FA decrease in motor and extra-motor fiber tracts in both pure motor-ALS syndromes and ALS with cognitive and/or behavioural impairment has been more consistently revealed by other DTI-based analyses (Cirillo et al., 2012; Agosta et al., 2016; Geraldo et al., 2018; Christidi et al., 2018). However, other DT MRI metrics, such as MD measures in the CC, the left SLF, cingulum and CST, have been revealed as the best predictors of fluency deficits in ALS (Agosta et al., 2016). Our finding concerning a significant positive correlation between FA and verbal fluency score in long association tracts may be explained on the basis of a myelin sheath disintegration, related to chronic injury, in these tracts involved in fluency tasks. This correlation recalls what was previously revealed in cohorts of patients with Parkinson's disease (Theilmann et al., 2013) or focal frontal lesions (Robinson et al., 2012), supporting the hypothesis that fluency tasks are sensitive to frontal damage (Robinson et al., 2012) and confirming the specific involvement of the anterior-dorsal network in fluency, as also revealed in the nonfluent/agrammatic variant of primary progressive aphasia (Mandelli et al., 2014).

We also revealed that the ALS non-specific total score, evaluating both memory and visuo-spatial cognitive domains, was negatively related to AD increase, mainly associated with axonal damage, in the left thalamus. This result recalls previous evidence of microstructural abnormalities of thalamocortical circuits in ALS (Barbagallo et al., 2014; Menke et al., 2017; Zhang et al., 2017). Furthermore, the significant correlations described between several DTI metrics (i.e., AD, MD and RD) in the left mediodorsal nucleus of the thalamus and the ALS non-specific total score, as well as the isolated memory subscore, may be explained on the basis of the role recognized to this nucleus as a “higher order thalamic relay”, substantially contributing to interaction between association cortices via cortico-thalamo-cortical connections (Guillery, 1995). In the light of previous results of lesional and

Table 2
Confidence intervals of FA, MD, RD and AD in the volumes of interest (VOIs), derived from Johns Hopkins University (JHU, Baltimore, Maryland) white matter tractography Atlas of FSL (44, 45). T-values (t) and p value (p), derived from significant differences by comparing patients to healthy controls, are displayed in bold and brackets.

VOIs (MNI x,y,z)	FA HCs	FA ALS	MD HCs	MD ALS	RD HCs	RD ALS	AD HCs	AD ALS
CC 0;−9;28	0.6663 ± 0.02080	0.6385 ± 0.01653 **($t = 3.1$; $p = 0.037$)**	0.0009 ± 0.0000197	0.0009 ± 0.0000182	0.0005 ± 0.00002817	0.0005 ± 0.00002474	0.0016 ± 0.00001828	0.0016 ± 0.00001605
Right CST (superior) 22;−33;35	0.495 ± 0.010605	0.4604 ± 0.009048 **($t = 2.997$; $p = 0.041$)**	0.0007 ± 0.000007811	0.0008 ± 0.000007961	0.0006 ± 0.00001221	0.0006 ± 0.000009943	0.0011 ± 0.00001548	0.0011 ± 0.00001720
Left CST (superior) −22;−33;35	0.5233 ± 0.01335	0.4842 ± 0.01100 **($t = 3.115$; $p = 0.039$)**	0.0007 ± 0.000008525	0.0008 ± 0.00001227	0.0005 ± 0.00001146	0.0006 ± 0.00001342	0.0011 ± 0.00001835	0.0012 ± 0.00001774
Right CST (inferior) 7;−23;−29	0.654 ± 0.01257	0.6324 ± 0.01107	0.0007 ± 0.000009775	0.0007 ± 0.000009074	0.0004 ± 0.00001366	0.0004 ± 0.00001170	0.0014 ± 0.00001526	0.0014 ± 0.00001409
Left CST (inferior) −7;−23;−29	0.6599 ± 0.01310	0.6431 ± 0.01240	0.0007 ± 0.00001169	0.0007 ± 0.00001175	0.0004 ± 0.00001420	0.0004 ± 0.00001404	0.0014 ± 0.0000200	0.0013 ± 0.00001717
Right SLF 39;−14;30	0.4482 ± 0.01200	0.4414 ± 0.01010	0.0008 ± 0.000009234	0.0008 ± 0.000008805	0.0006 ± 0.00001241	0.0006 ± 0.00001141	0.0012 ± 0.00001238	0.0011 ± 0.00001084
Left SLF −39;−14;30	0.4565 ± 0.01200	0.4524 ± 0.01010	0.0007 ± 0.000008616	0.0007 ± 0.000009050	0.0005 ± 0.00001158	0.0006 ± 0.00001109	0.0011 ± 0.00001457	0.0011 ± 0.00001307
Right ILF 31;−69;−3	0.5346 ± 0.0140	0.5245 ± 0.01068	0.0008 ± 0.00001534	0.0008 ± 0.0000122	0.0006 ± 0.00001903	0.0006 ± 0.00001382	0.0014 ± 0.00001552	0.0014 ± 0.00001906
Left ILF −31;−69;−3	0.5322 ± 0.0147	0.5287 ± 0.01077	0.0009 ± 0.00001378	0.0009 ± 0.00001418	0.0006 ± 0.00001823	0.0006 ± 0.00001567	0.0014 ± 0.00001688	0.0014 ± 0.00002036
Right IFOF 29;38;3	0.4252 ± 0.01178	0.4169 ± 0.008775	0.0008 ± 0.00001298	0.0008 ± 0.00001011	0.0006 ± 0.00001575	0.0006 ± 0.00001237	0.0012 ± 0.00001252	0.0013 ± 0.00001153
Left IFOF −29;38;3	0.4175 ± 0.011693	0.411 ± 0.009772	0.0008 ± 0.00001175	0.0008 ± 0.00001159	0.0006 ± 0.00001472	0.0006 ± 0.00001453	0.0012 ± 0.00001351	0.0012 ± 0.00001316
Fornix −29;38;3	0.3817 ± 0.02481	0.3474 ± 0.02127	0.0018 ± 0.0001300	0.002 ± 0.0001112	0.0014 ± 0.000131	0.0016 ± 0.00011585	0.0026 ± 0.0001312	0.0027 ± 0.0001042
Right UF 27; 13;−7	0.3882 ± 0.01189	0.3854 ± 0.009718	0.0009 ± 0.00001341	0.0009 ± 0.00001216	0.0007 ± 0.00001570	0.0007 ± 0.00001377	0.0013 ± 0.00002736	0.0014 ± 0.00003096
Left UF −27; 13;−7	0.3808 ± 0.01223	0.3737 ± 0.010083	0.0008 ± 0.00001397	0.0009 ± 0.00001281	0.0007 ± 0.00001667	0.0007 ± 0.0000148	0.0013 ± 0.00002518	0.0013 ± 0.00002611

AD = axial diffusivity; ALS = amyotrophic lateral sclerosis; CC = corpus callosum; CST = corticospinal tract; FA = fractional anisotropy; HC = healthy control; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; MD = mean diffusivity; RD = radial diffusivity; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus; VOI = volume of interest.

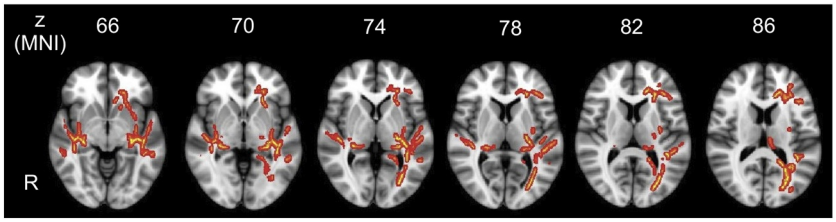

Fig. 2.. Voxel-wise correlation analysis between fluency subscores and FA measures in the studied ALS sample. Verbal fluency score was positively related to FA in the left ILF, IFOF, SLF and uncinate fasciculus (coloured clusters are overlaid on the MNI standard brain, showing regions with significant changes at $p < 0.05$, FWE corrected). R = right.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

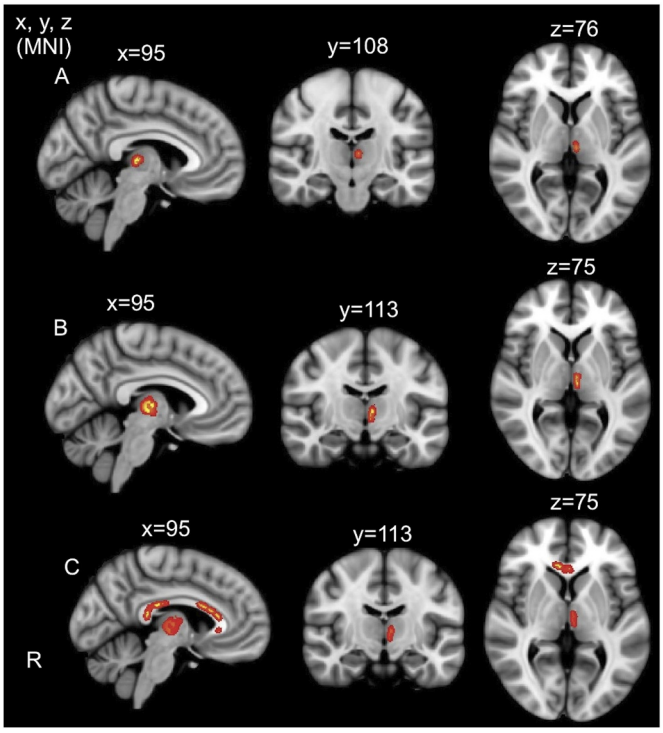

Fig. 3.. Voxel-wise correlation analysis between ALS non-specific ECAS score and AD/MD/RD metrics in the studied ALS sample. The total ALS non-specific (A) and the isolated memory (B, C) scores were inversely related to AD/MD/RD (respectively, A, B, C) in the mediodorsal nucleus of the thalamus and in the genu, anterior body and splenium of the CC (coloured clusters are overlaid on the MNI standard brain, showing regions with significant changes at $p < 0.05$, FWE corrected). R = right.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

electrophysiological studies in animals (Kim et al., 2011; Parnaudeau et al., 2013) and humans (Carlesimo et al., 2011; Pergola et al., 2013), microstructural damage of the mediodorsal nucleus of the thalamus has been shown to relate to impairment of executive function rather than learning and memory deficits per se (Carlesimo et al., 2011; Pergola and Suchan, 2013). In particular, using both complex neuropsychological testing and neuroimaging to identify the extent of the damage within the medial thalamus and the associated cognitive symptoms, some authors (Pergola and Suchan, 2013; Pergola et al., 2013) have shed light on the impact of more selective damage to the mediodorsal nucleus on some cognitive functions, such as recognition memory and semantic retrieval. Recently, emerging interest regards the investigation of thalamic changes in ALS, considering that the thalamus is a major neural hub. To note, we did not reveal significant atrophy of the thalamus comparing the ALS group to HCs, by applying a preliminary, whole-brain voxel-based morphometry (VBM) analysis (data not shown). However, two recent investigations of volumetric changes of sub-cortical structures in ALS patients by atlas-based volumetric (Schönecker et al., 2018) and shape-analysis (Menke et al., 2017) approaches showed, respectively, significant atrophy of the thalamus in a cohort of *C9orf72* mutation carriers compared to a group of sporadic ALS patients and a two-year progression of local atrophy of the thalamus in a group of sporadic ALS patients. Interestingly, the findings derived from the longitudinal VBM analysis by Menke et al. (2017) were in favour of the hypothesis that also MRI measures of gray matter atrophy may represent potential radiological markers of disease progression in ALS.

Besides the association revealed between increase of MD/RD values in the thalamus and decrease of the isolated memory score of ECAS, we also found that this score was negatively related to MD/RD increase in the genu, anterior body and splenium of the CC. In this regard, recent multi-domain neuropsychological investigations confirmed the evidence of a heterogeneous scenario of memory dysfunction in ALS (Mantovan et al., 2003; Burke et al., 2017; Christidi et al., 2017), although some reports revealed a further dimension of cognitive impairment in ALS, including a pure episodic memory dysfunction (Machts et al., 2014; Consonni et al., 2016). Remarkably, from the neuroanatomical point of view, recent evidence supported the potential role of regional WM integrity of the CC in influencing different cognitive performances in healthy subjects. Specifically, an antero-posterior gradient of age-related decline has been shown in the CC fibers (Voineskos et al., 2012) with significant associations identified between executive abilities (especially “task switching”) and WM integrity of the genu and splenium of the CC (Voineskos et al., 2012). In this regard, a major limitation of both our as well as other neuroimaging analyses (Bueno et al., 2018) was related to the low sensitivity of the memory subscore adopted. In particular, individual subtests of ECAS exploring ALS non-specific domains have been proven adequately specific, but with low to medium sensitivity to impairments of memory and/or visuo-spatial abilities (Pinto-Grau et al., 2017). In particular, ECAS has been acknowledged as a valid measure to screen for cognitive impairment in ALS, as also previously suggested by the developers of the test (Niven et al., 2015) and found in other cohorts of ALS patients (Lulé et al., 2015; Poletti et al., 2016; Siciliano et al., 2017). However, Pinto-Grau et al. (2017) revealed that ECAS is characterized by high sensitivity and specificity in detecting global cognitive impairment as well as dysfunction of both ALS-specific and ALS non-specific cognitive domains, by validating ECAS against standard (non ALS-specific) neuropsychological batteries. Of note, ALS-specific cognitive domains showed high sensitivity and specificity, while ALS non-specific domains and individual subtests showed medium to low sensitivity. Taken together, these results suggested that the total and subtotal scores, especially for ALS-specific cognitive domains, may be considered good indicators of cognitive function in ALS, although individual subtests should be interpreted with caution (Pinto-Grau et al., 2017).

Other major limitations of our study were related to the heterogeneity of the population investigated, which may reflect the phenotypic variability of ALS, probably with an underlying complex and heterogeneous disease process (Chiò et al., 2011; Hardiman et al., 2017). In this regard, an exploratory between-subgroup analysis revealed that the “classic ALS” subgroup of patients ($n = 14$) did not significantly differ from the “flail arm” and “flail leg” fast progressors subgroup ($n = 20$) in ECAS performances and DTI measures (i.e., AD, FA, MD, RD) in the studied VOIs ($p < 0.05$, Bonferroni corrected), suggesting a clinical and DTI similarity between the two subgroups, also according to previous evidence (Chiò et al., 2011; Müller et al., 2018). Moreover, other limitations were related to the DTI model per se

in comparison to more advanced diffusion models [i.e., high angular resolution diffusion imaging, HARDI; diffusion spectrum imaging (DSI) or neurite orientation dispersion and density imaging (NODDI)] (Abhinav et al., 2014a, 2014b) or graph-theoretic connectomics approaches (Zhou et al., 2016; Schmidt et al., 2016; Dimond et al., 2017; Caiazzo et al., 2018), shown to be more advantageous in the early detection of brain networks abnormalities predictive of cognitive impairment (Dimond et al., 2017) or disease progression (Abhinav et al., 2014a; Zhou et al., 2016; Schmidt et al., 2016) in ALS. Moreover, we did not design to perform a multi-modal neuroimaging analysis, also exploring gray matter structural changes, using VBM or surface-based morphometry (SBM) techniques. However, we have also applied a preliminary VBM analysis to the acquired T1-weighted anatomical sequence to detect brain volume changes, reporting no differences in gray matter volumes by comparing ALS patients to HCs ($p > 0.05$, FWE corrected; data not shown). This preliminary result, together with previous evidence, supports the concept that multi-modal algorithms may be more advantageous in the differentiation between pure motor-ALS syndromes and ALS with cognitive and/or behavioural impairment (Lillo et al., 2012; Rajagopalan and Pioro, 2014; Agosta et al., 2016; Consonni et al., 2018) or other motor neuron diseases (Ferraro et al., 2017) than each MRI technique per se.

In conclusion, our findings suggest that extra-motor brain microstructural alterations probably underlie the cognitive profile of ALS patients. Particularly, cognitive performances at both ALS-specific (i.e., verbal fluency) and non-specific (i.e., memory, visuo-spatial abilities) tasks of ECAS have been shown related, respectively, to degeneration of WM fronto-temporo-parietal and cortico-thalamo-cortical pathways. Moreover, the correlation between FA decrease in long association WM tracts and verbal fluency impairment may be translated into future research exploring more robust relationships between DTI abnormalities and different cognitive functioning, some of which could be prognostic of cognitive deterioration in ALS. Longitudinal and multimodal assessments, including both neuropsychological and structural and functional neuroimaging investigations, may be useful to early characterization of ALS patients in order to stratify the ALS populations by genetic mutations or clinical phenotypes. These future approaches may turn helpful in monitoring ALS, thereby positively impacting disease management.

Conflict of interest

The authors declare that there is no conflict of interest regarding this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Outside this work, Dr. Caiazzo perceived grants from Sanofi Genzyme, Dr. Siciliano from Merck Serono, and Prof. Tedeschi from Italian Ministry of Health (RF-2011-02,351,193).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.04.001.

References

Abhinav, K., Yeh, F.C., El-Dokla, A., Ferrando, L.M., Chang, Y.F., Lacomis, D., Friedlander, R.M., Fernandez-Miranda, J.C., 2014a. Use of diffusion spectrum imaging in preliminary longitudinal evaluation of amyotrophic lateral sclerosis: development of an imaging biomarker. Front. Hum. Neurosci. 8, 270. https://doi.org/10.3389/fnhum.2014.00270.

Abhinav, K., Yeh, F.C., Pathak, S., Suski, V., Lacomis, D., Friedlander, R.M., Fernandez-Miranda, J.C., 2014b. Advanced diffusion MRI fiber tracking in neurosurgical and neurodegenerative disorders and neuroanatomical studies: a review. Biochim. Biophys. Acta 1842, 2286–2297. https://doi.org/10.1016/j.bbadis.2014.08.002.

Abrahams, S., 2013. Executive dysfunction in ALS is not the whole story. J. Neurol. Neurosurg. Psychiatry 84, 474–475. https://doi.org/10.1136/jnnp-2012-303851.

Abrahams, S., Newton, J., Niven, E., Foley, J., Bak, T.H., 2014. Screening for cognition and behaviour changes in ALS. Amyotroph. Lateral Scler. Frontotemporal Degener. 15, 9–14. https://doi.org/10.3109/21678421.2013.805784.

Agosta, F., Ferraro, P.M., Riva, N., Spinelli, E.G., Chiò, A., Canu, E., Valsasina, P., Lunetta, C., Iannaccone, S., Copetti, M., Prudente, E., Comi, G., Falini, A., Filippi, M., 2016. Structural brain correlates of cognitive and behavioral impairment in MND. Hum. Brain Mapp. 37, 1614–1626. https://doi.org/10.1002/hbm.23124.

Balendra, R., Jones, A., Jivraj, N., Steen, I.N., Young, C.A., Shaw, P.J., Turner, M.R., Leigh, P.N., Al-Chalabi, A., UK-MND LiCALS Study Group, Mito Target ALS Study Group, 2015. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J. Neurol. Neurosurg. Psychiatry 86, 45–49. https://doi.org/10.1136/jnnp-2013-306865.

Barbagallo, G., Nicoletti, G., Cherubini, A., Trotta, M., Tallarico, T., Chiriaco, C., Nisticò, R., Salvino, D., Bono, F., Valentino, P., Quattrone, A., 2014. Diffusion tensor MRI changes in gray structures of the frontal-subcortical circuits in amyotrophic lateral sclerosis. Neurol. Sci. 35, 911–918. https://doi.org/10.1007/s10072-013-1626-z.

Braak, H., Brettschneider, J., Ludolph, A.C., Lee, V.M., Trojanowski, J.Q., Del Tredici, K., 2013. Amyotrophic lateral sclerosis - a model of corticofugal axonal spread. Nat. Rev. Neurol. 9, 708–714. https://doi.org/10.1038/nrneurol.2013.221.

Branco, L.M.T., de Rezende, T.J.R., Roversi, C.O., Zanao, T., Casseb, R.F., de Campos, B.M., França Jr, M.C., 2018. Brain signature of mild stages of cognitive and behavioral impairment in amyotrophic lateral sclerosis. Psychiatry Res. Neuroimaging 272, 58–64. https://doi.org/10.1016/j.pscychresns.2017.11.010.

Brooks, B.R., Miller, R.G., Swash, M., Munsat, T.L., World Federation of Neurology Research Group on Motor Neuron Diseases, 2000. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Other Motor Neuron Disord. 1, 293–299.

Bueno, A.P.A., Pinaya, W.H.L., Moura, L.M., Bertoux, M., Radakovic, R., Kiernan, M.C., Teixeira, A.L., de Souza, L.C., Hornberger, M., Sato, J.R., 2018. Structural and functional papez circuit integrity in amyotrophic lateral sclerosis. Brain Imaging Behav. https://doi.org/10.1007/s11682-018-9825-0.

Burke, T., Lonergan, K., Pinto-Grau, M., Elamin, M., Bede, P., Madden, C., Hardiman, O., Pender, N., 2017. Visual encoding, consolidation, and retrieval in amyotrophic lateral sclerosis: executive function as a mediator, and predictor of performance. Amyotroph. Lateral Scler. Frontotemporal Degener. 18, 193–201. https://doi.org/10.1080/21678421.2016.1272615.

Burrell, J.R., Halliday, G.M., Kril, J.J., Ittner, L.M., Götz, J., Kiernan, M.C., Hodges, J.R., 2016. The frontotemporal dementia-motor neuron disease continuum. Lancet 388, 919–931. https://doi.org/10.1016/S0140-6736(16)00737-6.

Caiazzo, G., Fratello, M., Di Nardo, F., Trojsi, F., Tedeschi, G., Esposito, F., 2018. Structural connectome with high angular resolution diffusion imaging MRI: assessing the impact of diffusion weighting and sampling on graph-theoretic measures. Neuroradiology 60, 497–504. https://doi.org/10.1007/s00234-018-2003-7.

Carelli, L., Solca, F., Faini, A., Madotto, F., Lafronza, A., Monti, A., Zago, S., Zago, S., Doretti, A., Ciammola, A., Ticozzi, N., Silani, V., Poletti, B., 2018. The complex interplay between depression/anxiety and executive functioning: insights from the ECAS in a large ALS population. Front. Psychol. 9, 450. https://doi.org/10.3389/fpsyg.2018.00450.

Carlesimo, G.A., Lombardi, M.G., Caltagirone, C., 2011. Vascular thalamic amnesia: a reappraisal. Neuropsychologia 49, 777–789. https://doi.org/10.1016/j.neuropsychologia.2011.01.026.

Cedarbaum, J.M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., Nakanishi, A., 1999. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J. Neurol. Sci. 169, 13–21.

Chia, R., Chiò, A., Traynor, B.J., 2017. Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. Lancet Neurol. 17, 94–102. http://dx.doi.org/10.1016/S1474-4422(17)30401-5.

Chiò, A., Calvo, A., Moglia, C., Mazzini, L., Mora, G., PARALS study group, 2011. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J. Neurol. Neurosurg. Psychiatry 82, 740–746. https://doi.org/10.1136/jnnp.2010.235952.

Christidi, F., Karavasilis, E., Riederer, F., Zalonis, I., Ferentinos, P., Velonakis, G., Xirou, S., Rentzos, M., Argiropoulos, G., Zouvelou, V., Zambelis, T., Athanasakos, A., Toulas, P., Vadikolias, K., Efstathopoulos, E., Kollias, S., Karandreas, N., Kelekis, N., Evdokimidis, I., 2018. Gray matter and white matter changes in non-demented amyotrophic lateral sclerosis patients with or without cognitive impairment: a combined voxel-based morphometry and tract-based spatial statistics whole-brain analysis. Brain Imaging Behav. 12, 547–563. https://doi.org/10.1007/s11682-017-9722-y.

Christidi, F., Karavasilis, E., Zalonis, I., Ferentinos, P., Giavri, Z., Wilde, E.A., Xirou, S., Rentzos, M., Zouvelou, V., Velonakis, G., Toulas, P., Efstathopoulos, E., Poulou, L., Argyropoulos, G., Athanasakos, A., Zambelis, T., Levin, H.S., Karandreas, N., Kelekis, N., Evdokimidis, I., 2017. Memory-related white matter tract integrity in amyotrophic lateral sclerosis: an advanced neuroimaging and neuropsychological study. Neurobiol. Aging 49, 69–78. https://doi.org/10.1016/j.neurobiolaging.2016.09.014.

Christidi, F., Zalonis, I., Kyriazi, S., Rentzos, M., Karavasilis, E., Wilde, E.A., Evdokimidis, I., 2014. Uncinate fasciculus microstructure and verbal episodic memory in amyotrophic lateral sclerosis: a diffusion tensor imaging and neuropsychological study.

Brain Imaging Behav. 8, 497–505. https://doi.org/10.1007/s11682-013-9271-y.
Cirillo, M., Esposito, F., Tedeschi, G., Caiazzo, G., Sagnelli, A., Piccirillo, G., Conforti, R., Tortora, F., Monsurrò, M.R., Cirillo, S., Trojsi, F., 2012. Widespread microstructural white matter involvement in amyotrophic lateral sclerosis: a whole-brain DTI study. Am. J. Neuroradiol. 33, 1102–1108. https://doi.org/10.3174/ajnr.A2918.
Consonni, M., Catricalà, E., Dalla Bella, E., Gessa, V.C., Lauria, G., Cappa, S.F., 2016. Beyond the consensus criteria: multiple cognitive profiles in amyotrophic lateral sclerosis? Cortex 81, 162–167. https://doi.org/10.1016/j.cortex.2016.04.014.
Consonni, M., Contarino, V.E., Catricalà, E., Dalla Bella, E., Pensato, V., Gellera, C., Lauria, G., Cappa, S.F., 2018. Cortical markers of cognitive syndromes in amyotrophic lateral sclerosis. Neuroimage Clin. 19, 675–682. https://doi.org/10.1016/j.nicl.2018.05.020.
Dimond, D., Ishaque, A., Chenji, S., Mah, D., Chen, Z., Seres, P., Beaulieu, C., Kalra, S., 2017. White matter structural network abnormalities underlie executive dysfunction in amyotrophic lateral sclerosis. Hum. Brain Mapp. 38, 1249–1268. https://doi.org/10.1002/hbm.23452.
Ferraro, P.M., Agosta, F., Riva, N., Copetti, M., Spinelli, E.G., Falzone, Y., Sorarù, G., Comi, G., Chiò, A., Filippi, M., 2017. Multimodal structural MRI in the diagnosis of motor neuron diseases. Neuroimage Clin. 16, 240–247. https://doi.org/10.1016/j.nicl.2017.08.002.
Geraldo, A.F., Pereira, J., Nunes, P., Reimão, S., Sousa, R., Castelo-Branco, M., Pinto, S., Campos, J.G., de Carvalho, M., 2018. Beyond fractional anisotropy in amyotrophic lateral sclerosis: the value of mean, axial, and radial diffusivity and its correlation with electrophysiological conductivity changes. Neuroradiology 60, 505–515. https://doi.org/10.1007/s00234-018-2012-6.
Girardi, A., Macpherson, S.E., Abrahams, S., 2011. Deficits in emotional and social cognition in amyotrophic lateral sclerosis. Neuropsychology 25, 53–65. https://doi.org/10.1037/a0020357.
Guillery, R.W., 1995. Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review. J. Anat. 187, 583–592.
Hardiman, O., Al-Chalabi, A., Chiò, A., Corr, E.M., Logroscino, G., Robberecht, W., Shaw, P.J., Simmons, Z., van den Berg, L.H., 2017. Amyotrophic lateral sclerosis. Nat. Rev. Dis. Primers 3, 17085. https://doi.org/10.1038/nrdp.2017.85.
Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D.S., Calabresi, P.A., Pekar, J.J., van Zijl, P.C., Mori, S., 2008. Tract probability maps in stereotaxic spaces: analysis of white matter anatomy and tract-specific quantification. Neuroimage 39, 336–347. https://doi.org/10.1016/j.neuroimage.2007.07.053.
Kasper, E., Schuster, C., Machts, J., Kaufmann, J., Bittner, D., Vielhaber, S., Benecke, R., Teipel, S., Prudlo, J., 2014. Microstructural white matter changes underlying cognitive and behavioural impairment in ALS–an in vivo study using DTI. PLoS One 9, e114543. https://doi.org/10.1371/journal.pone.0114543.
Kim, J., Woo, J., Park, Y.G., Chae, S., Jo, S., Choi, J.W., Jun, H.Y., Yeom, Y.I., Park, S.H., Kim, K.H., Shin, H.S., Kim, D., 2011. Thalamic T-type Ca(2)+channels mediate frontal lobe dysfunctions caused by a hypoxia-like damage in the prefrontal cortex. J. Neurosci. 31, 4063–4073. https://doi.org/10.1523/JNEUROSCI.4493-10.2011.
Libon, D.J., McMillan, C., Gunawardena, D., Powers, C., Massimo, L., Khan, A., Morgan, B., Farag, C., Richmond, L., Weinstein, J., Moore, P., Coslett, H.B., Chatterjee, A., Aguirre, G., Grossman, M., 2009. Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. Neurology 73, 535–542. https://doi.org/10.1212/WNL.0b013e3181b2a4f5.
Lillo, P., Mioshi, E., Burrell, J.R., Kiernan, M.C., Hodges, J.R., Hornberger, M., 2012. Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PLoS One 7, e43993. https://doi.org/10.1371/journal.pone.0043993.
Lulé, D., Burkhardt, C., Abdulla, S., Bohm, S., Kollewe, K., Uttner, I., Abrahams, S., Bak, T.H., Petri, S., Weber, M., Ludolph, A.C., 2015. The Edinburgh Cognitive and Behavioural Swiss population. Amyotroph. Lateral Scler. Frontotemporal Degener. 16, 16–23. https://doi.org/10.3109/21678421.2014.959451.
Machts, J., Bittner, V., Kasper, E., Schuster, C., Prudlo, J., Abdulla, S., Kollewe, K., Petri, S., Dengler, R., Heinze, H.J., Vielhaber, S., Schoenfeld, M.A., Bittner, D.M., 2014. Memory deficits in amyotrophic lateral sclerosis are not exclusively caused by executive dysfunction: a comparative neuropsychological study of amnestic mild cognitive impairment. BMC Neurosci. 15, 83. https://doi.org/10.1186/1471-2202-15-83.
Mandelli, M.L., Caverzasi, E., Binney, R.J., Henry, M.L., Lobach, I., Block, N., Amirbekian, B., Dronkers, N., Miller, B.L., Henry, R.G, Gorno-Tempini, M.L., 2014. Frontal white matter tracts sustaining speech production in primary progressive aphasia. J. Neurosci. 34, 9754–9767. https://doi.org/10.1523/JNEUROSCI.3464-13.2014.
Mantovan, M.C., Baggio, L., Dalla Barba, G., Smith, P., Pegoraro, E., Sorarù, G., Bonometto, P., Angelini, C., 2003. Memory deficits and retrieval processes in ALS. Eur. J. Neurol. 10, 221–227.
Menke, R.A.L., Proudfoot, M., Talbot, K., Turner, M.R., 2017. The two-year progression of structural and functional cerebral MRI in amyotrophic lateral sclerosis. Neuroimage Clin. 17, 953–961. https://doi.org/10.1016/j.nicl.2017.12.025.
Müller, H.-P., Agosta, F., Riva, N., Spinelli, E.G., Comi, G., Ludolph, A.C., Filippi, M., Kassubek, J., 2018. Fast progressive lower motor neuron disease is an ALS variant: a two-centre tract of interest-based MRI data analysis. Neuroimage Clin. 17, 145–152. https://doi.org/10.1016/j.nicl.2017.10.008.
Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F., 1998. Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. Neurology 51, 1546–1554.
Niven, E., Newton, J., Foley, J., Colville, S., Swingler, R., Chandran, S., Bak, T.H., Abrahams, S., 2015. Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): a cognitive tool for motor disorders. Amyotroph. Lateral Scler. Frontotemporal Degener. 16, 172–179. https://doi.org/10.3109/21678421.2015.1030430.
Parnaudeau, S., O'Neill, P.K., Bolkan, S.S., Ward, R.D., Abbas, A.I., Roth, B.L., Balsam, P.D., Gordon, J.A., Kellendonk, C., 2013. Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. Neuron 77, 1151–1162. https://doi.org/10.1016/j.neuron.2013.01.038.
Pergola, G., Ranft, A., Mathias, K., Suchan, B., 2013. The role of the thalamic nuclei in recognition memory accompanied by recall during encoding and retrieval: an fMRI study. Neuroimage 74, 195–208. https://doi.org/10.1016/j.neuroimage.2013.02.017.
Pergola, G., Suchan, B., 2013. Associative learning beyond the medial temporal lobe: many actors on the memory stage. Front. Behav. Neurosci. 7, 162. https://doi.org/10.3389/fnbeh.2013.00162.
Pinto-Grau, M., Burke, T., Lonergan, K., McHugh, C., Mays, I., Madden, C., Vajda, A., Heverin, M., Elamin, M., Hardiman, O., Pender, N., 2017. Screening for cognitive dysfunction in ALS: validation of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) using age and education adjusted normative data. Amyotroph. Lateral Scler. Frontotemporal Degener. 18, 99–106. https://doi.org/10.1080/21678421.2016.1249887.
Poletti, B., Solca, F., Carelli, L., Madotto, F., Lafronza, A., Faini, A., Monti, A., Zago, S., Calini, D., Tiloca, C., Doretti, A., Verde, F., Ratti, A., Ticozzi, N., Abrahams, S., Silani, V., 2016. The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS). Amyotroph. Lateral Scler. Frontotemporal Degener. 17, 489–498. https://doi.org/10.1080/21678421.2016.1183679.
Rajagopalan, V., Pioro, E.P., 2014. Distinct patterns of cortical atrophy in ALS patients with or without dementia: an MRI VBM study. Amyotroph. Lateral Scler. Frontotemporal Degener. 15, 216–225. https://doi.org/10.3109/21678421.2014.880179.
Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., Van Swieten, J.C., Seelaar, H., Dopper, E.G.P., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134, 2456–2477. https://doi.org/10.1093/brain/awr179.
Robinson, G., Shallice, T., Bozzali, M., Cipolotti, L., 2012. The differing roles of the frontal cortex in fluency tests. Brain 135, 2202–2214. https://doi.org/10.1093/brain/aws142.
Sabatelli, M., Zollino, M., Luigetti, M., Grande, A.D., Lattante, S., Marangi, G., Monaco, M.L., Madia, F., Meleo, E., Bisogni, G., Conte, A., 2011. Uncovering amyotrophic lateral sclerosis phenotypes: clinical features and long-term follow-up of upper motor neuron-dominant ALS. Amyotroph. Lateral Scler. 12, 278–282. https://doi.org/10.3109/17482968.2011.580849.
Sarro, L., Agosta, F., Canu, E., Riva, N., Prelle, A., Copetti, M., Riccitelli, G., Comi, G., Filippi, M., 2011. Cognitive functions and white matter tract damage in amyotrophic lateral sclerosis: a diffusion tensor tractography study. Am. J. Neuroradiol. 32, 1866–1872. https://doi.org/10.3174/ajnr.A2658.
Schmidt, R., de Reus, M.A., Scholtens, L.H., van den Berg, L.H., van den Heuvel, M.P., 2016. Simulating disease propagation across white matter connectome reveals anatomical substrate for neuropathology staging in amyotrophic lateral sclerosis. Neuroimage 124, 762–769. https://doi.org/10.1016/j.neuroimage.2015.04.005.
Schönecker, S., Neuhofer, C., Otto, M., Ludolph, A., Kassubek, J., Landwehrmeyer, B., Anderl-Straub, S., Semler, E., Diehl-Schmid, J., Prix, C., Vollmar, C., Fortea, J., FTLD-Konsortium, Deutsches, Huppertz, H.J., Arzberger, T., Edbauer, D., Feddersen, B., Dieterich, M., Schroeter, M.L., Volk, A.E., Fließbach, K., Schneider, A., Kornhuber, J., Maler, M., Prudlo, J., Jahn, H., Boeckh-Behrens, T., Danek, A., Klopstock, T., Levin, J., 2018. Atrophy in the thalamus but not cerebellum is specific for C9orf72 FTD and ALS patients - an atlas-based volumetric MRI study. Front. Aging Neurosci. 10, 45. https://doi.org/10.3389/fnagi.2018.00045.
Siciliano, M., Trojano, L., Trojsi, F., Greco, R., Santoro, M., Basile, G., Piscopo, F., D'Iorio, A., Patrone, M., Femiano, C., Monsurrò, M., Tedeschi, G., Santangelo, G., 2017. Edinburgh Cognitive and Behavioural ALS Screen (ECAS)-Italian version: regression based norms and equivalent scores. Neurol. Sci. 38, 1059–1068. https://doi.org/10.1007/s10072-017-2919-4.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024.
Sorarù, G., Ermani, M., Logroscino, G., Palmieri, A., D' Ascenzo, C., Orsetti, V., Volpe, M., Cima, V., Zara, G., Pegoraro, E., Angelini, C., 2010. Natural history of upper motor neuron-dominant ALS. Amyotroph. Lateral Scler. 11, 424–429. https://doi.org/10.3109/17482960903300867.
Strong, M.J., Abrahams, S., Goldstein, L.H., Woolley, S., Mclaughlin, P., Snowden, J., Mioshi, E., Roberts-South, A., Benatar, M., HortobáGyi, T., Rosenfeld, J., Silani, V., Ince, P.G., Turner, M.R., 2017. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria. Amyotroph. Lateral Scler. Frontotemporal Degener. 18, 153–174. https://doi.org/10.1080/21678421.2016.1267768.
Strong, M.J., Grace, G.M., Freedman, M., Lomen-Hoerth, C., Woolley, S., Goldstein, L.H., Murphy, J., Shoesmith, C., Rosenfeld, J., Leigh, P.N., Bruijn, L., Ince, P., Figlewicz, D., 2009. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. 10, 131–146.
Taylor, L.J., Brown, R.G., Tsermentseli, S., Al-Chalabi, A., Shaw, C.E., Ellis, C.M., Leigh,

P.N., Goldstein, L.H., 2013. Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? J. Neurol. Neurosurg. Psychiatry 84, 494–498. https://doi.org/10.1136/jnnp-2012-303526.

Theilmann, R.J., Reed, J.D., Song, D.D., Huang, M.X., Lee, R.R., Litvan, I., Harrington, D.L., 2013. White-matter changes correlate with cognitive functioning in Parkinson's disease. Front. Neurol. 4, 37. https://doi.org/10.3389/fneur.2013.00037.

Tijssen, R.H., Jansen, J.F, Backes, W.H., 2009. Assessing and minimizing the effects of noise and motion in clinical DTI at 3 T. Hum. Brain Mapp. 30, 2641–2655. https://doi.org/10.1002/hbm.20695.

Trojsi, F., Caiazzo, G., Corbo, D., Piccirillo, G., Cristillo, V., Femiano, C., Ferrantino, T., Cirillo, M., Monsurrò, M.R., Esposito, F., Tedeschi, G., 2015. Microstructural changes across different clinical milestones of disease in amyotrophic lateral sclerosis. PLoS One 10, e0119045. https://doi.org/10.1371/journal.pone.0119045.

Troyer, A.K., Moscovitch, M., Winocur, G., Alexander, M.P., Stuss, D., 1998. Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. Neuropsychologia 36, 499–504.

Turner, M.A., 1999. Generating novel ideas: fluency performance in high functioning and learning disabled individuals with autism. J. Child Psychol. Psychiatry 40, 189–201.

Turner, M.R., Cagnin, A., Turkheimer, F.E., Miller, C.C., Shaw, C.E., Brooks, D.J., Leigh, P.N., Banati, R.B., 2004. Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [(11)C](R)-PK11195 positron emission tomography study. Neurobiol. Dis. 15, 601–609. https://doi.org/10.1016/j.nbd.2003.12.012.

Turner, M.R., Swash, M., 2015. The expanding syndrome of amyotrophic lateral sclerosis: a clinical and molecular odyssey. J. Neurol. Neurosurg. Psychiatry 86, 667–673. https://doi.org/10.1136/jnnp-2014-308946.

van den Berg-Vos, R.M., Visser, J., Franssen, H., de Visser, M., de Jong, J.M., Kalmijn, S., Wokke, J.H., van den Berg, L.H., 2003. Sporadic lower motor neuron disease with adult onset: classification of subtypes. Brain 126, 1036–1047.

van der Hulst, E.J., Bak, T.H., Abrahams, S., 2015. Impaired affective and cognitive theory of mind and behavioural change in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 86, 1208–1215. https://doi.org/10.1136/jnnp-2014-309290.

Voineskos, A.N., Rajji, T.K., Lobaugh, N.J., Miranda, D., Shenton, M.E., Kennedy, J.L., Pollock, B.G., Mulsant, B.H., 2012. Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. Neurobiol. Aging 33, 21–34. https://doi.org/10.1016/j.neurobiolaging.2010.02.009.

Wakana, S., Caprihan, A., Panzenboeck, M.M., Fallon, J.H., Perry, M., Gollub, R.L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., Mori, S., 2007. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 36, 630–644. https://doi.org/10.1016/j.neuroimage.2007.02.049.

Wicks, P., Abrahams, S., Masi, D., Hejda-Forde, S., Leigh, P.N., Goldstein, L.H., 2007. Prevalence of depression in a 12-month consecutive sample of patients with ALS. Eur. J. Neurol. 14, 993–1001. https://doi.org/10.1111/j.1468-1331.2007.01843.x.

Zhang, J.Q., Ji, B., Zhou, C.Y., Li, L.C., Li, Z.H., Hu, X.P., 2017. Differential impairment of thalamocortical structural connectivity in Amyotrophic Lateral Sclerosis. CNS Neurosci. Ther. 23, 155–161. https://doi.org/10.1111/cns.12658.

Zhou, C., Hu, X., Hu, J., Liang, M., Yin, X., Chen, L., Zhang, J., Wang, J., 2016. Altered brain network in amyotrophic lateral sclerosis: a resting graph theory-based network study at voxel-wise level. Front. Neurosci. 10, 204. https://doi.org/10.3389/fnins.2016.00204.