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Neuroimaging correlates of domain-specific cognitive deficits in amyotrophic lateral sclerosis

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with frequent extra-motor involvement. In the present study, we investigated whether specific cognitive and behavioral deficits in ALS correlate with distinct extra-motor neurodegeneration patterns on brain MRI.

Methods: We performed multimodal brain MRI and Edinburgh cognitive and behavioral ALS screen (ECAS) in 293 patients and 237 controls. Follow-up data were acquired from 171 patients with a median duration of 7.9 months. Domain-level cognitive scores from the ECAS were compared with grey and white matter MRI parameters. Interaction analyses between patients and controls were performed to explore whether correlates were specific to ALS, rather than related to normal aging. Follow-up data were used to assess changes of domain-associated brain structures over time.

Results: Language impairment was significantly associated with (left predominant) frontal, temporal, parietal and subcortical grey matter neurodegeneration. Letter fluency with widespread cortical and subcortical grey matter involvement. Memory dysfunction with hippocampal and medial-temporal atrophy. Executive impairment was exclusively correlated with widespread white matter impairment. Visuospatial scores did not correlate with MRI parameters. Interaction analyses between patients and controls showed that most ECAS-MRI correlations were stronger in ALS than in controls (75.7% significant in grey matter, 52.7% in white matter). Longitudinal analyses showed that all grey matter structures associated with cognitive domains worsened over time while, for this study population, ECAS domain scores did not decline significantly.

Conclusions: MRI can capture the heterogeneity of cognitive and behavioral involvement in ALS and provides a useful longitudinal biomarker for progression of extra-motor neurodegeneration.

1. Introduction

Cognitive and behavioral deficits are a significant element of amyotrophic lateral sclerosis (ALS), in addition to progression of – eventually fatal – motor symptoms (van Es et al., 2017; Westeneng et al., 2018). Up to 50 % of patients show cognitive (ALS-ci) and/or behavioral impairment (ALS-bi) and 15 % meet criteria for fronto-temporal dementia (ALS-FTD) (Ringholz et al., 2005). Screening for cognitive and behavioral abnormalities in patients with ALS has, therefore, become standard practice.

The Edinburgh cognitive and behavioral ALS screen (ECAS) was developed specifically to assess cognitive and behavioral changes in patients with ALS, independent of motor disability. The ECAS assesses five cognitive and five behavioral domains (Niven et al., 2015). Prior cross-sectional studies suggest a parallel decline of motor function and cognition (Chiò et al., 2019; Crockford et al., 2018), yet, most longitudinal studies do not support this. A recent review found that 12 of 13 longitudinal ALS cognition studies show minor or no decline over time

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(Finsel et al., 2023).

Neuroimaging studies in ALS have shown, however, that extra-motor brain degeneration occurs throughout the course of the disease (Menke et al., 2014; van der Burgh et al., 2020) revealing reduced cortical thickness (Basaia et al., 2020; Elamin et al., 2013; Menke et al., 2014; Nitert et al., 2022; van der Burgh et al., 2020) and white matter disintegration of both motor- and extra-motor regions (Müller et al., 2016; Steinbach et al., 2021; van der Burgh et al., 2020). Nonetheless, the neuroanatomical basis of cognitive and behavioral deficits in ALS remains unclear. It is uncertain if they result from white or grey matter degeneration, or both, and whether they involve brain regions and networks known to be affected by ALS.

Improved understanding of how cognitive and behavioral symptoms evolve over time alongside extra-motor neurodegeneration could enhance our comprehension of ALS-ci, ALS-bi, and ALS-FTD. It could also direct our search for extra-motor neurodegeneration biomarkers. Thus, our study explored the longitudinal link between cognitive and behavioral deficits, assessed via ECAS, and brain MRI metrics like cortical thickness, subcortical volumes, and white matter connectivity.

2. Materials and methods

Between June 2014 and January 2020, we included 293 ALS patients and 237 controls. Participants were recruited from a population-based cohort as previously described (Huisman et al., 2011). Participants with contra-indications for an MRI-scan or structural brain abnormalities were excluded. In addition, 337 follow-up visits were conducted in 171 patients at 3 to 6-month intervals, with a maximum of five. Cross-sectional data of controls were used as reference. All participants were 18 years or older and gave written informed consent. This study was approved by the medical ethics committee of the University Medical Centre Utrecht (NL38994.041.11).

2.1. Data acquisition

Patients' clinical characteristics were collected. Patients were tested for the *C9orf72* hexanucleotide repeat expansion (van Rheenen et al., 2012). Participants' education levels were registered. At each study visit, we acquired a brain MRI scan and administered the ECAS to each participant. In four instances, due to logistical issues, the ECAS was not administered on the same day, but within 7 days of the scan. The Dutch version of the ECAS was applied, using normative data from previous studies (Bakker et al., 2019). The ECAS comprises 15 items across five cognitive domains: language, executive function, and letter fluency combine to an ALS-specific score, while memory and visuospatial functioning combine to an ALS non-specific score. If a patient's proxy was available, the ECAS behavioral questionnaire was administered, consisting of a structured interview based on five behavioral domains: behavioral disinhibition; loss of sympathy/empathy; apathy or inertia; perseverative, stereotyped, or compulsive/ritualistic behaviors; hyperorality and dietary changes. The ECAS scores were used to assess criteria for ALS with cognitive impairment (ALS-ci), ALS with behavioral impairment (ALS-bi), and ALS-FTD according to (Strong et al., 2017). To reduce learning effects, an alternative version of the Dutch ECAS was used alternatingly for follow-ups from 2017. The effect of alternating the ECAS in a longitudinal analysis was analyzed separately in a sensitivity analysis. The revised ALS functional rating scale (ALSFRS-R) was administered during each visit.

At each visit we acquired a high-resolution T1- and a diffusion-weighted image of the brain of all participants using a 3 T Philips Achieva Medical scanner (Philips Medical Systems, Best, the Netherlands). The T1-weighted images had the following parameters: three-dimensional fast field echo using parallel imaging; repetition time/echo time = 10/4.6 ms; flip angle 8°; sagittal slice orientation; voxel size = 0.75 × 0.75 × 0.8 mm; field of view = 160 × 240 × 240 mm; with a reconstruction matrix = 200 × 320 × 320 covering the whole brain. We used an 8 channel head coil. The diffusion-weighted images had the following parameters: DWI using parallel imaging SENSE p-reduction 3; high angular gradient set of 30 different weighted directions; TR/TE = 7035/68 ms; 2 × 2 × 2 mm voxel size; 75 slices; b = 1000 s/mm^2; second set with reversed k-space read-out to correct for susceptibility-induced distortions.

T1 images were processed using Freesurfer v6.0 using the high resolution processing option with the recommended patches. The brain was parcellated into cortical regions (according to the Desikan-Killiany atlas), and subcortical regions, including the ventricles, cerebellum, and brain stem (Fischl et al., 2004). Mean cortical thickness and subcortical volumes were calculated for each region. Diffusion tensor imaging (DTI) was used to reconstruct a connectome, comprising the white matter connections between all cortical regions and 15 subcortical structures (excluding ventricles, including the brainstem). The method for connectome reconstruction is described in previous work (Schmidt et al., 2014). DTI tracts were included in our analysis when successfully reconstructed in at least 50 % of the control subjects (de Reus and van den Heuvel, 2013). Weighted fractional anisotropy was calculated for each tract.

2.2. Cognitive impairment in ALS and controls

We first assessed the cognitive profile of ALS patients by comparing their ECAS scores (sum scores, domain scores, and individual tasks) to those of controls. ECAS scores are composed of non-negative natural numbers whose distributions are inherently skewed (Supplementary Fig. 1). To overcome this, we performed negative binomial regression using inverted ECAS scores (i.e., subtracting the observed scores from the maximum possible score) as a response variable. For all analyses in this study, age, sex, and education level were included as covariables. Scores in the fluency domain are scored in increments of two and are inherently skewed (Supplementary Fig. 1), making it hard to fit any distribution to the data (Supplementary Fig. 2). To improve model fit, scores of 12 were adjusted to 10. Afterwards, all fluency scores were divided by 2. Scores of 12 are infrequent, both in controls and patients, and likely do not contain information of disease-related change, based on normative data (Bakker et al., 2019). Fluency scores were not altered when calculating sum scores.

2.3. Correlation between ECAS scores and MRI parameters

We analyzed the association between ECAS scores and MRI parameters in patients using the negative binomial model. The relationship between ECAS domain score and brain region was tested separately for each grey matter structure. Analyses with subcortical volumes were also corrected for total intracranial volume, together with covariables mentioned above. Results were corrected for multiple testing using Benjamini and Hochberg's false discovery rate (FDR), within each cognitive domain. Each white matter connection was separately analyzed in the same manner. Nominal significant connections ($p < 0.05$) were used for network-based statistic to identify significantly impaired components within the white matter network at 1000 permutations. For behavioral impairment, a complete case analysis was performed in patients for whom the ECAS behavioral screen had been administered. Logistic regression models were used to analyze correlation between MRI parameters and ECAS behavioral changes (five domains), ALS-ci, ALS-bi and ALS-FTD. With a sensitivity analysis we examined possible influences of *C9orf72* repeat length expansion on the results in threefold. First, we included the mutation status as a covariate to our models, second, we excluded *C9orf72* mutation carriers from the models and third, we modelled *C9orf72* mutation carriers separately.

2.4. Specificity of ECAS-MRI correlations to ALS

We performed an interaction analysis in patients and controls to

Table 1
Demographic and clinical characteristics.

	ALS	Controls
N	293	237
Sex, Male (%)	184 (62.8)	162 (68.4)
Age at first MRI, y	62.9 (54.7–68.8)	64.5 (58.3–70.8)
Education level, ISCED > 5 (%)	105 (35.8)	103 (43.5)
Number of MRI scans per subject, 1/2/3/4/5	122/82/38/25/26	237/0/0/0/0
Age at onset, y	60.8 (52.6–67.0)	
Diagnostic delay, m	10.3 (6.0–18.0)	
Disease duration, m	17.6 (11.8–27.2)	
Bulbar symptom onset (%)	66 (22.5)	
***C9orf72* repeat length expansion (%)**	25 (8.8)	
King's clinical stage at visit 1, 1/2/3/4/missing	81/95/107/8/2	
ECAS, abnormal total score[a] (%)	32 (11.5)	9 (3.9)
ECAS, abnormal ALS-specific score[a] (%)	34 (12.1)	10 (4.3)
ECAS, abnormal ALS-non-specific score[a] (%)	18 (6.3)	3 (1.3)
ALS-ci (Strong criteria)[b] (%)	74 (25.8)	
ALS-bi (Strong criteria)[b] (%)	45 (23.8)	
ALS-FTD (Strong criteria)[b] (%)	18 (9.6)	
ALSFRS-R score at visit 1	39 (35–42)	
ALSFRS-R slope	0.5 (0.3–0.8)	

Overview of demographics and clinical characteristics. Data are median (IQR) or count (%). Disease duration is time from first symptoms to first MRI. King's stages 4a and 4b were taken together. Abbreviations: ALS = amyotrophic lateral sclerosis; ISCED = International Standard Classification of Education (1997); ECAS = Edinburgh cognitive and behavioral ALS screen; ALS-ci = ALS with cognitive impairment; ALS-bi = ALS with behavioral impairment; ALS-FTD = ALS with frontotemporal dementia; ALSFRS-R = revised ALS functional rating scale.

[a]Cut-off is set at the 5th percentile of normative data after correction for age, sex and education levels, as previously reported (Fischletal., 2004).

[b]Classification according to the revised criteria by Strong et al. (2017). In 190 patients (64.8%), the ECAS behavioral screen could be administered.

explore whether ECAS-MRI correlations found within patients are driven by neurodegeneration and not by naturally occurring variation of cognition. We used a similar negative binomial model and additionally included an interaction term of brain region and patient/control status. These analyses were only performed within structures or connections that were significantly correlated to ECAS scores in ALS patients, without correction for multiple testing.

2.5. Longitudinal analysis of MRI parameters associated with ECAS domain scores

Using longitudinal data, we compared the progression of ECAS and MRI markers over the course of our follow-up. For the ECAS domain scores, we analyzed longitudinal changes since inclusion, using a linear mixed model with the same covariables, together with a random intercept and random slope (time since inclusion) for each patient. The longitudinal rates of ALS-bi were analyzed using mixed effects logistic regression. For MRI, the measurements associated with each ECAS domain and ALS-bi were normalized. Afterwards, the data were pooled in a linear mixed model, including a random intercept and slope for each patient and additionally a random intercept and slope for brain region.

3. Results

Demographics and clinical characteristics of 293 ALS patients and 237 controls are shown in Table 1. The control group had a slightly older median age (62.9 years vs 64.5 years, $p = 0.020$) and higher education level, but this was not statistically significant (35.8 % vs 43.5 % with higher education, $p = 0.090$). These characteristics were used as covariables in our analysis.

3.1. Cognitive impairment in ALS and controls

ALS patients exhibited lower performance across total ECAS score ($p < 0.001$), the ALS-specific score ($p < 0.001$) and the ALS non-specific score ($p = 0.011$) compared to controls. At the level of cognitive domains, scores were lower in patients for language ($p < 0.001$), fluency ($p < 0.001$), executive ($p = 0.001$), and memory ($p = 0.009$), but not for

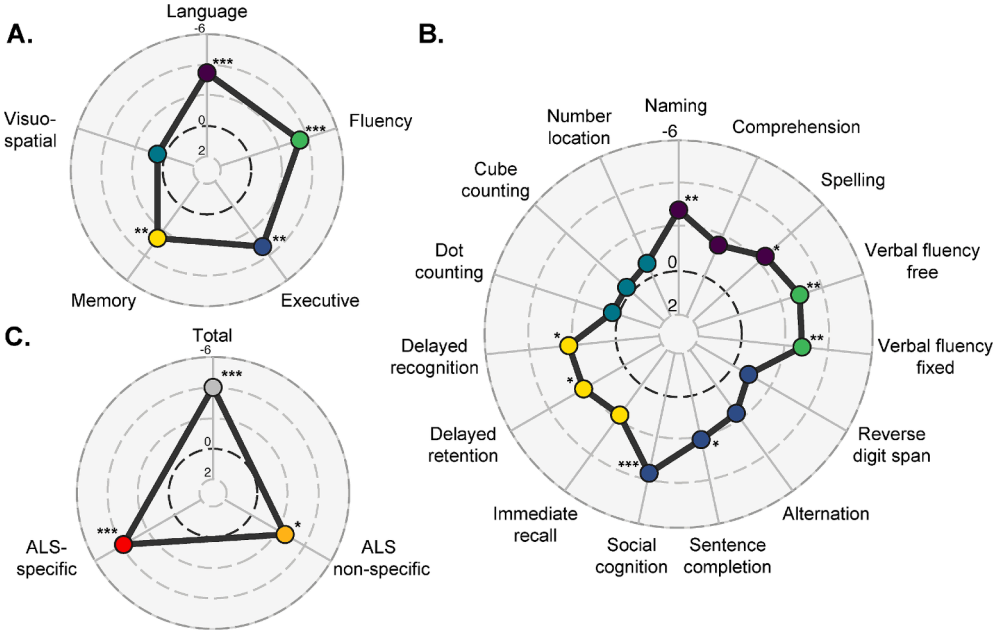

Fig. 1. Comparison of ECAS scores: ALS vs Controls. Radar chart showing ECAS performance in ALS, expressed in Z-scores based on a multivariable negative binomial model fitted on control subjects and adjusted for age, sex, and level of education. Colors represent different domains and sum scores. (A) ECAS domain scores. (B) ECAS task scores, colored by their corresponding domain. (C) ECAS sum scores. * p-value < 0.05. ** p-value < 0.01. *** p-value < 0.001.

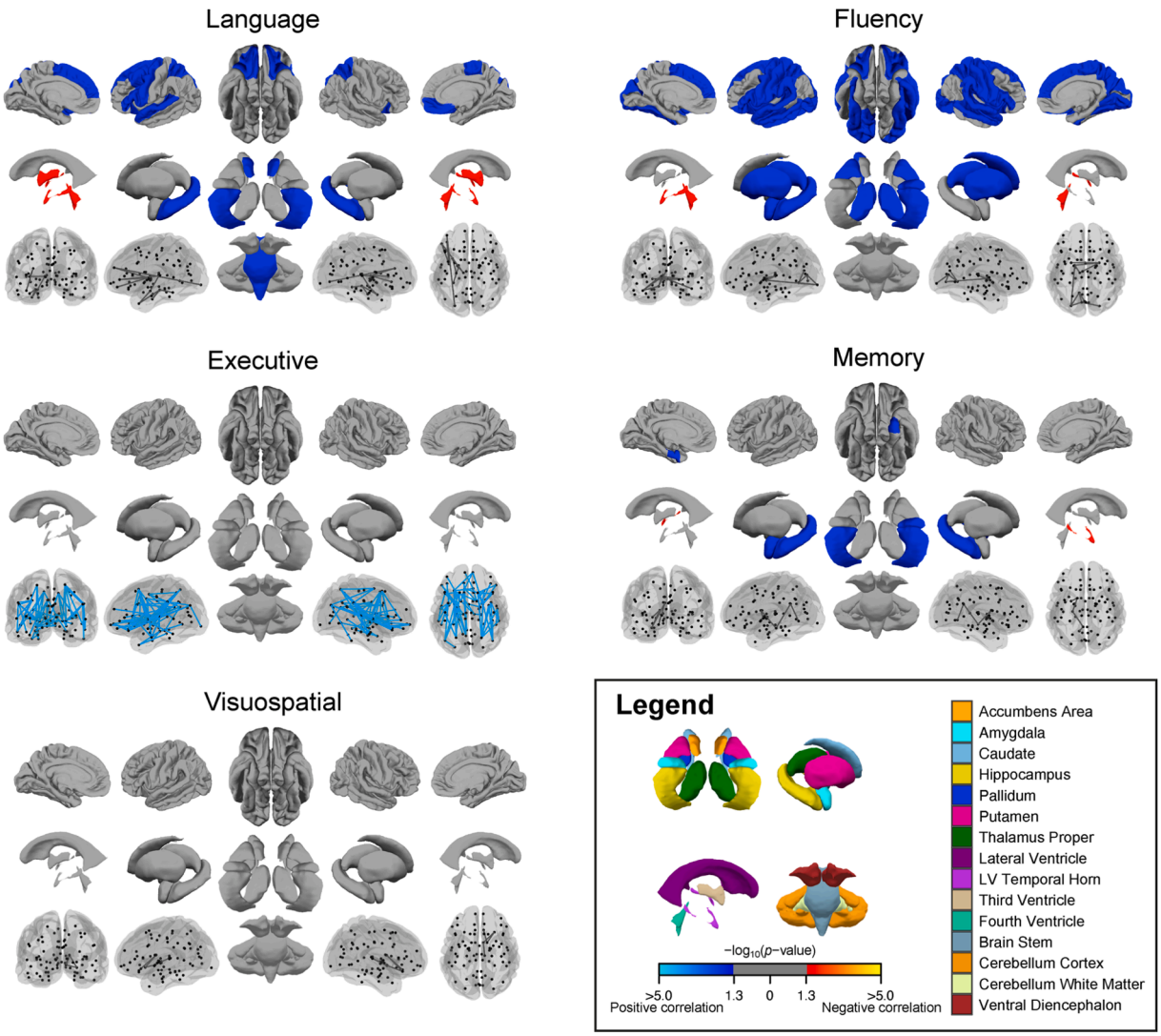

Fig. 2. Grey and white matter correlates of domain-specific ECAS scores. Overview of grey and white matter structures correlated to ECAS domain scores. Blue-cyan and red-yellow-colored regions represent significant findings corrected for multiple testing using FDR in grey matter structures and network-based statistics in white matter connections. In the case of absent significant network connections, dark grey connections show the largest connection. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

visuospatial domain ($p = 0.61$). Fig. 1 illustrates the differences in ECAS scores between patients and controls using Z-scores.

3.2. Correlation between ECAS scores and MRI parameters

ECAS correlations with MRI revealed distinct patterns for each of the five domains (Fig. 2). Language impairment correlated with cortical grey matter loss in frontal, temporal and parietal regions, with a more prominent involvement of the left frontal lobe, as well as volume loss from both hippocampi, nuclei accumbens and brainstem. Fluency deficits were associated with symmetrical widespread cortical and subcortical grey matter loss. Executive functioning exclusively correlated with large-scale white matter impairment throughout the entire brain, sparing occipital connections. Memory dysfunction was associated with hippocampal volume loss, left medial temporal cortical thinning and right lateral ventricle temporal horn enlargement. Visuospatial scores did not show significant correlations with grey or white matter parameters.

Correlates of ECAS sum scores are shown in Supplementary Fig. 3. Total ECAS and ALS-specific score were associated with extensive grey and white matter involvement.

Correlations between individual tasks and MRI are displayed in Fig. 3 and Supplementary Fig. 4. Intra-domain discrepancies were found for the executive domain (Fig. 3): the sentence completion task correlated with frontotemporal white matter impairment and focal subcortical grey matter loss, while the social cognition task was associated with widespread grey matter loss without significant white matter impairment. The reverse digit span and alternation tasks of the executive domain were not correlated with degeneration of brain structures. Individual tasks of the other domains are displayed in Supplementary Fig. 4. Within the language domain, naming and comprehension tasks were mainly associated with grey matter loss, while spelling was not. Within the fluency domain, the free verbal fluency task was associated with widespread grey matter loss and frontotemporal white matter network impairment (which was not seen in the fluency domain score). Individual memory tasks were not correlated with brain abnormalities. For visuospatial tasks, only cube counting was associated with thinning of the right lingual gyrus.

In a sensitivity analysis examining possible influences of *C9orf72* repeat length expansion we found no changes of patterns in grey and white matter correlates for ECAS domains when we included *C9orf72* mutation status to our models (Supplementary Fig. 7). When we

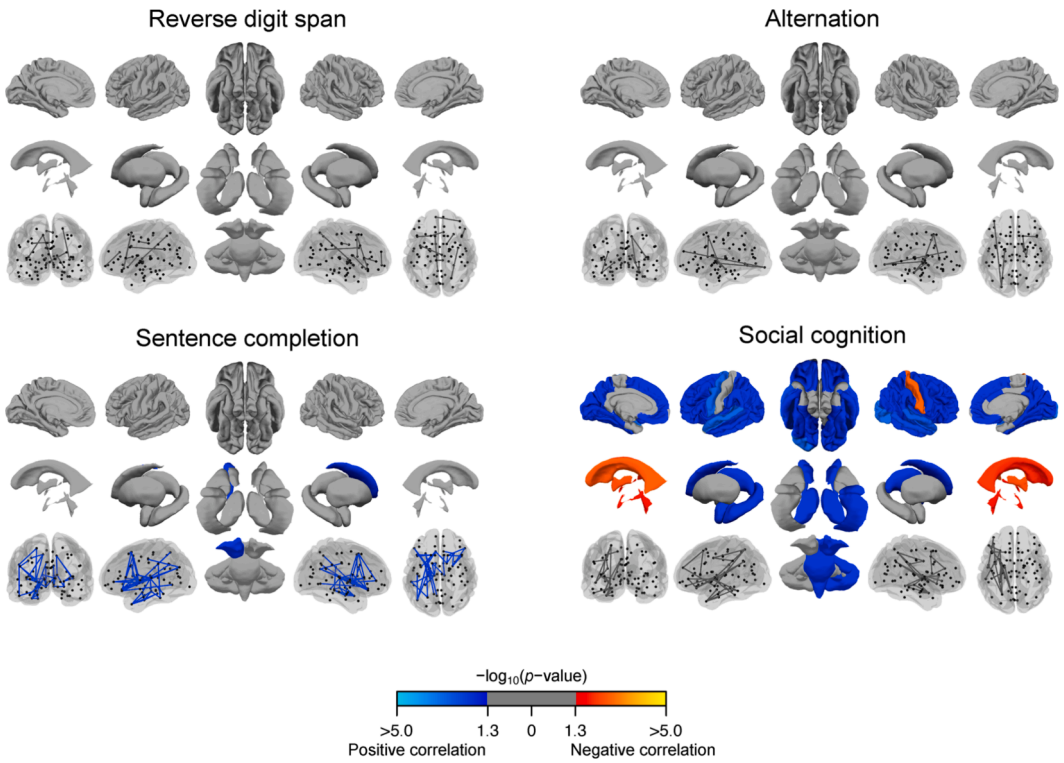

Fig. 3. Differences in grey and white matter correlates of individual tasks of the Executive domain. Overview of grey and white matter structures correlated to individual ECAS tasks of the Executive domain. Blue-cyan and red-yellow-colored regions represent significant findings corrected for multiple testing using FDR in grey matter structures and network-based statistics in white matter connections. Legend for subcortical structures can be found in Fig. 2. The social cognition task is significantly correlated to marked cortical thinning and subcortical volume loss, which shows a different pattern than the other subtasks of the Executive domain. For display purposes, the 11 individual tasks of other domains are displayed separately in Supplementary Fig. 4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

excluded *C9orf72* mutation carriers of our analyses and corrected for multiple testing we found similar patterns for the Executive, Memory and Visuospatial domain, although there were differences in the Language and Fluency domains as in the latter no significant involvement were found (Supplementary Fig. 8). However, examining the results without correction for multiple testing, similar patterns were found for Language and Fluency domains (Supplementary Fig. 9). Separate analyses in C9orf72 mutation carriers revealed more extensive cortical grey matter loss associated with decreased language, fluency and memory performance. Diffuse white matter impairment was associated with decreased fluency, but not executive dysfunction (Supplementary Fig. 10).

3.3. Specificity of ECAS-MRI correlations to ALS

We performed interaction analyses to investigate whether neurodegeneration patterns associated with ECAS domain scores were specific to ALS or could be explained by naturally occurring variation in controls (Fig. 4). In total, 51/68 (75.0 %) of the grey matter regions associated with ECAS domain scores showed a significant interaction between thickness or volume and ALS/control status. These numbers varied between domains: for language, 11/20 (55.0 %) of the associated grey matter regions showed a significant interaction; for fluency (36/43, 83.7 %); for memory (4/5, 80.0 %). For the executive domain, there was a significant interaction between fractional anisotropy and ALS/control status in 39/74 (52.7 %) of the white matter connections. This pattern was similar in sum scores (Supplementary Fig. 5): the ALS-specific score showed significant interactions for 31/43 (72.1 %) of grey matter regions and 41/75 (54.7 %) of white matter connections; for the ALS non-specific score, this was 1/1 (100 %) of the grey matter regions; for the total score, this was 19/24 (79.1 %) of grey matter regions and 36/57 (63.2 %) of white matter connections.

3.4. Correlation of behavioral domains and ALS-ci, ALS-bi and ALS-FTD to MRI parameters

Behavioral screens were administered to proxies of 190 patients. For disinhibition, apathy, loss of sympathy/empathy and perseverative behavior, patterns of extensive white matter impairment were found (Fig. 5). Loss of sympathy/empathy was also associated with thinning of the right medial temporal cortex. Hyperorality did not show any correlation with brain structures. 74 out of 293 patients (25.3 %) fulfilled criteria for ALS-ci, 45/190 (23.7 %) for ALS-bi and 18/190 (9.5 %) for ALS-FTD and their MRI-correlates are presented in Supplementary Fig. 6.

3.5. Longitudinal analysis of MRI parameters associated with ECAS domain scores

We collected 337 longitudinal measurements (MRI and ECAS) from 171 patients, at a median total follow-up duration of 7.9 months. Together with the 293 baseline measurements this resulted in a total of 630 measurements. The normalized trajectories of brain structures associated with ECAS domain scores are displayed in Fig. 6. An overview of longitudinal data is shown in Supplementary Table 1.

Longitudinal analyses showed no decline of ECAS sum and domain scores. A sensitivity analysis was performed from which patients with same-version follow-up ECAS were excluded ($n = 215$, 432 scans); this did not alter the observations. The absence of decline in ECAS scores could not be explained by extreme scores in individuals. The differences in ECAS scores were similar between first and second visit compared to the differences between third and fifth visit, indicating that censoring of

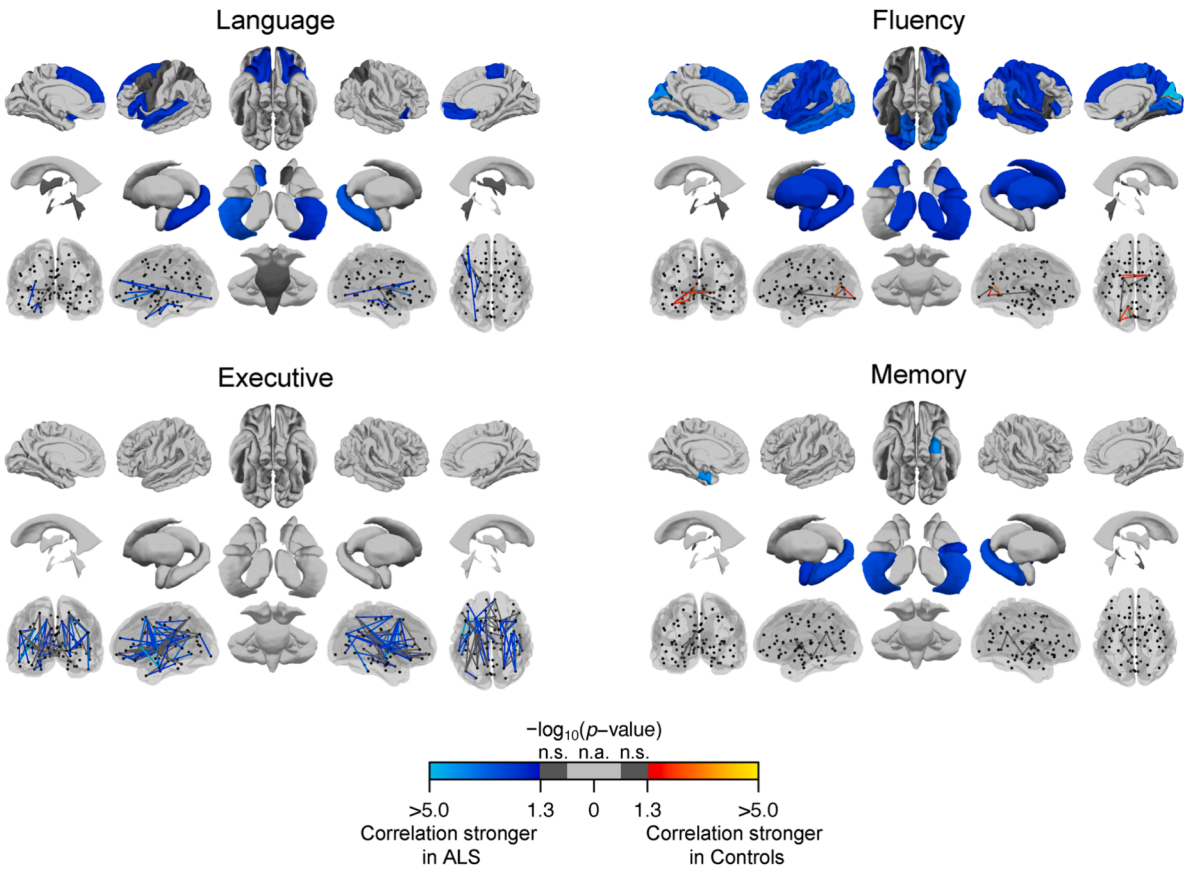

Fig. 4. ALS-Control interactions of domain score-correlated brain regions. Interaction analysis to compare correlations between ALS patients and controls. Only brain regions associated with ECAS scores (Fig. 2) were considered in this analysis (dark grey and colored regions). Since there were no significant correlations of brain regions and visuospatial domain scores, no interaction analyses were performed. Light grey structures were not included in the analysis. In most ECAS-MRI correlations, the correlation is stronger in ALS patients, indicating that the correlations with ECAS scores are specific to ALS. n.s. = not significant. n.a. = not analyzed (since this structure was not correlated with a domain score).

patients during the study was not causing this effect.

Our imaging analyses revealed a significant deterioration over time for sum scores: grey matter regions declined significantly over time (total score: cortex $p < 0.001$ and subcortical $p = 0.016$; ALS-specific: cortex $p < 0.001$ and subcortical $p = 0.015$; ALS non-specific: subcortical $p = 0.003$), as well as white matter for the ALS-specific score (ALS-specific: $p = 0.042$; total score: $p = 0.053$). Cortical and subcortical structures associated with language, fluency and memory showed a significant decrease over time (cortex: $p < 0.001$ for language and fluency, $p = 0.034$ for memory; subcortical: $p = 0.033$ for language, $p = 0.016$ for fluency, $p = 0.002$ for memory). For the executive score, white matter did not deteriorate significantly over time ($p = 0.060$). Longitudinal presence of ALS-bi was negatively correlated with time since inclusion ($p = 0.038$). Associated white matter tracts did show a decline over time which was not significant ($p = 0.062$).

4. Discussion

We demonstrated that domain- and task-specific cognitive scores directly correlate with distinct patterns of grey and white matter degeneration. These findings suggest that the various cognitive phenotypes observed in ALS result from involvement of corresponding extra-motor brain regions. Interaction analyses demonstrated that the observed degeneration patterns are specific to ALS, rather than normal aging. This includes hippocampal volume loss correlating with memory domain impairment, currently considered as ALS non-specific in the ECAS. Behavioral impairment predominantly correlates with white matter impairment. Our longitudinal analyses revealed that domain-associated grey matter brain regions each showed disease progression, while cognitive scores did not during the same median follow-up duration of 7.9 months. Together, these findings provide a neuroanatomical explanation for cognitive and behavioral deficits in ALS and show that brain MRI could serve as a biomarker for extra-motor disease progression within eight months, an interval which is also feasible for clinical trials.

Previous smaller studies compared neuroimaging patterns of patients with impairment of language, fluency and executive domains to controls (Chenji et al., 2021; Illán-Gala et al., 2020). They described frontal, temporal and parietal neurodegeneration patterns using T1 and DTI metrics. However, since these analyses were conducted in comparison to cognitively unimpaired controls, they might not capture the true association between cognitive impairment and cerebral change. When comparing these groups with cognitively normal patients, the associations were weak (Chenji et al., 2021). For behavioral impairment, two studies found localized neurodegenerative features in frontotemporal and left parietal cortex (Caga et al., 2021; Consonni et al., 2019). Other studies have stratified on general cognitive impairment criteria (*i.e.*, ALS-bi/ci or ALS-FTD) and detected frontal, temporal and parietal involvement (Agosta et al., 2016; Cividini et al., 2022). Utilizing our large multi-modal neuroimaging dataset, we demonstrate that most regional extra-motor atrophy, seen in analyses of ALS patients versus controls, can be directly linked to cognitive function (50/80 structures, 62.5 %) (Supplementary methods and Supplementary Fig. 11). This is an increase compared to previous studies combined (22/80 structures, 27.5 %) (Supplementary Fig. 11).

Previous neuroimaging studies found more widespread and

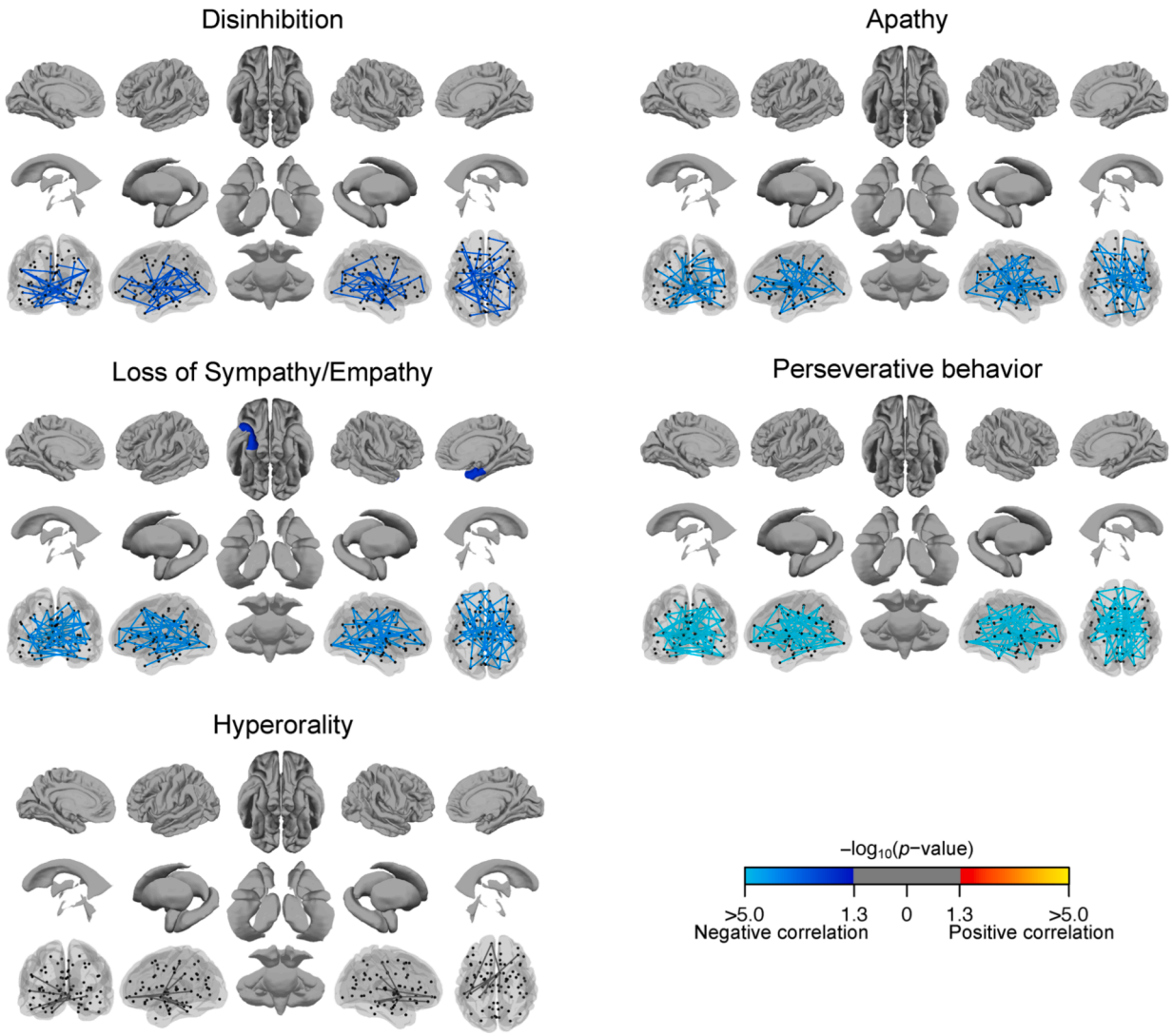

Fig. 5. Grey and white matter correlates with behavioral changes. Overview of grey and white matter structures associated with behavioral changes. 13 Patients showed signs of disinhibition, 33 displayed apathy, 27 loss of sympathy/empathy, 18 perseverative behavior and 21 displayed hyperorality. Blue-cyan and red-yellow-colored regions represent significant findings corrected for multiple testing using FDR in grey matter structures and network-based statistics in white matter connections. Legend for subcortical structures can be found in Fig. 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

extensive neurodegeneration in *C9orf72* mutation carriers compared to sporadic ALS patients (Li Hi Shing et al., 2021; van der Burgh et al., 2020). In our analysis within C9orf72 carriers, we found that language, fluency and memory dysfunction are associated with more extensive cortical degeneration and relatively less subcortical volume loss. Considering the difference in sample size, the associations are still evidently more pronounced in C9orf72 carriers. However, when trying to infer the localization of cognitive defects in ALS, the extensiveness of involvement is likely overexaggerated, since there are high degrees of collinearity between different brain regions in the widespread involvement within the C9orf72 carrier phenotype. Direct comparison between patterns of involvement found in our study should be interpreted with reservations.

Our longitudinal MRI data indicate progressive extra-motor degeneration in ALS. Therefore, multimodal brain MRI could serve as an objective biomarker for cognitive or behavioral decline. The progressive nature of cognitive and behavioral deficits in ALS has been debated, with previous studies showing conflicting evidence (Agostaetal., 2016; Consonnietal., 2021;Kasperetal., 2016;Robinsonetal., 2006). Although our cross-sectional results showed that ECAS performs well in detecting the presence of extra-motor involvement, no decline of ECAS scores could be detected, even when alternating versions were used. This is consistent with 12/13 earlier studies (Finseletal., 2023).

Longitudinal decline in our cohort might be more obscured due to increased attrition from MRI safety-related exclusion criteria. However, these criteria are commonly applied in ALS clinical trials (van Eijk et al., 2019). Therefore, it might be preferable to include neuroimaging parameters in clinical trials; even with identical attrition rates, they are able to detect decline.

In contrast to prevailing views suggesting that memory deficits in ALS originate in prefrontal cortical impairment or in executive dysfunction (Consonnietal., 2017;Phukanetal., 2007;Raaphorstetal., 2011), our study reveals that memory deficits are specifically correlated with hippocampal and medial-temporal neurodegeneration. These findings align with neuroimaging studies that found volume loss in the temporal and hippocampal regions (Abdulla et al., 2014; Christidi et al., 2019; Bede et al., 2013; Westeneng et al., 2016; Ishaque et al., 2022) and temporal and hippocampal hypermetabolism (Cistaroetal., 2014; DeVochtetal., 2023;Paganietal., 2014) in ALS patients. Furthermore, neuropathological studies showed hippocampal localization of ALS-

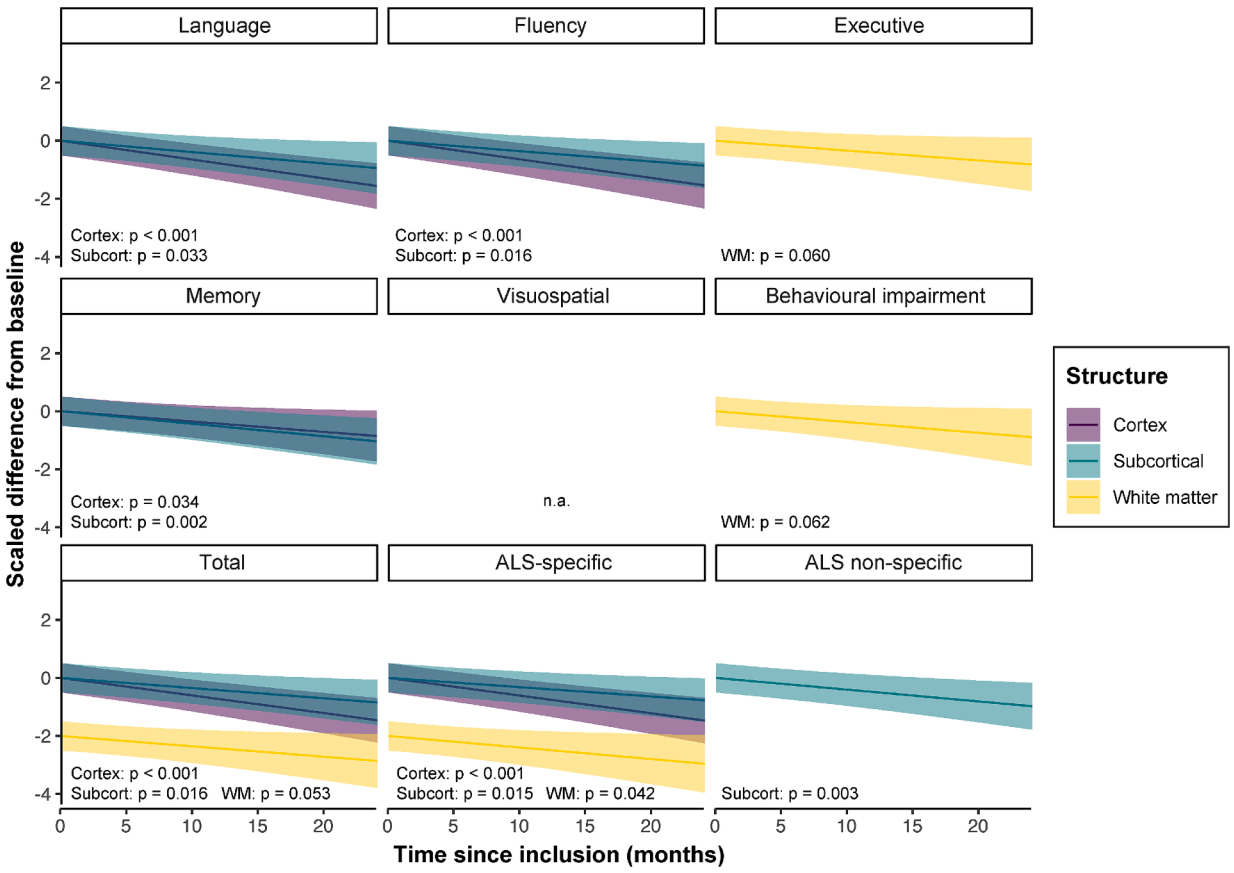

Fig. 6. Longitudinal trajectories of ECAS domain-associated MRI-parameters from time since inclusion. Overview of longitudinal courses of brain MRI parameters associated with ECAS scores, over the time since inclusion, of ALS patients. Lines represent normalized estimated marginal means and 95 % confidence intervals of MRI parameters, as modelled by linear mixed models, adjusted for age, sex and level of education. *p*-values for time since inclusion are displayed. For Total and ALS-specific scores, white matter trajectories were shifted 2 units down for display purposes. n.a. = not analyzed (since the visuospatial domain was not associated with any structure). subcort = subcortical. WM = white matter.

related TAR DNA-binding protein 43 inclusions (Brettschneideretal., 2013;Yangetal., 2018), with the presence of apolipoprotein ε2 haplotype increasing the risk of FTD (Chiòetal., 2016) and the presence of apolipoprotein ε4 haplotype increasing risk for hippocampal sclerosis (Yang et al. 2018). At the clinical level, a meta-analysis reviewing neuropsychological studies reports marked delayed verbal memory deficits in ALS, corresponding to medial-temporal lobe dysfunction (Beeldmanetal., 2016). Currently, synthesis of cognitive and neuroimaging data in sufficiently large cohorts of ALS patients is lacking (Christidietal., 2018), although reviewing the aggregated data suggests the hippocampi and its connections are involved in ALS (Mohammadietal., 2024). In our study we demonstrate that memory score is not associated with other brain regions than hippocampal and medial-temporal regions, and in our interaction analysis with controls we show that these findings are attributable to ALS. Together, this underscores the specificity of hippocampus-related memory deficits in ALS.

Currently, the ECAS classifies the social cognition task within the executive domain. However, our analysis revealed that social cognition impairment is associated with widespread cortical thinning and subcortical volume loss. This contrasts with executive tasks which show exclusive white matter network impairment. Our finding offers a neuroanatomical basis for findings from a prior meta-analysis indicating that social cognition may constitute its own distinct domain (Beeldmanetal., 2016).

Our study has its limitations. Because of MRI safety procedures, we could not include patients with severe bulbar or respiratory impairment. To mitigate this bias, we included patients relatively early in the disease (median disease duration 17.6 months; earlier than other neuroimaging cohorts) (Agostaetal., 2016;Basaiaetal., 2020;Chenjietal., 2021), but this still resulted in a relatively low percentage of patients with bulbar symptom onset (22.5 % vs 35.3 %) (Visseretal., 2018). However, relevant clinical characteristics are similar to those in a meta-analysis of 38 clinical trials (van Eijk et al., 2019).

ECAS is designed as a screen and is purposely less comprehensive than an extensive neuropsychological examination (Nivenetal., 2015). Future studies using detailed neuropsychological assessments might reveal associations with different patterns of neurodegeneration, although extensive examination might increase study burden.

To conclude, distinct patterns of extra-motor neurodegeneration in ALS elucidate the correlation between extra-motor degeneration and cognition and behavior. Our findings may motivate a revision of ALS-specific domains and show that brain MRI is a more sensitive longitudinal cognitive biomarker than the ECAS in a population similar to that included in clinical trials.

5. Declaration of generative AI in scientific writing

During the preparation of this work the authors used ChatGPT-4o of OpenAI in order to provide suggestions for sentence construction. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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CRediT authorship contribution statement

Harold H.G. Tan: Writing – original draft, Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **Abram D. Nitert:** Writing – original draft, Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **Kevin van Veenhuijzen:** Writing – review & editing, Visualization. **Stefan Dukic:** Writing – review & editing, Visualization. **Martine J.E. van Zandvoort:** Writing – review & editing, Data curation. **Jeroen Hendrikse:** Writing – review & editing, Data curation. **Michael A. van Es:** Writing – review & editing, Conceptualization. **Jan H. Veldink:** Writing – review & editing, Conceptualization. **Henk-Jan Westeneng:** Writing – review & editing, Methodology, Conceptualization, Funding acquisition, Supervision. **Leonard H. van den Berg:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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Disclosure statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103749.

Data availability

Data will be made available on request.

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