

ORIGINAL ARTICLE

Emotional empathy in amyotrophic lateral sclerosis: a behavioural and voxel-based morphometry study

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Abstract

Amyotrophic lateral sclerosis (ALS) is a multisystem condition, in which executive and/or behavioural symptoms can occur. Deficits of social cognition, including defective cognitive and emotional empathy, have been recently reported in ALS subjects. The neurostructural correlates of these disorders in ALS are still unknown. The aims of this study were to evaluate two components of empathy in non-demented ALS subjects, and to associate performance with regional grey-matter density using voxel-based morphometry (VBM). Twenty non-demented sporadic probable or definite ALS patients and 56 matched healthy controls (HC) participated in a non-verbal task requiring the attribution of emotional versus cognitive states to identify the correct ending of comic strips, compared with a control condition requiring identifying causal relationships devoid of social components. A subgroup of 14 ALS and 20 HC joined the VBM study. Results demonstrated that, compared with controls, ALS patients showed defective emotional empathy attribution, related with reduced grey-matter density in the anterior cingulate cortex and right inferior frontal gyrus. Our study provided evidence of a specific impairment of emotional empathy in ALS patients, reflecting neural damage in a limbic prefrontal network involved in emotional processing. Social cognition disorders may represent a marker of cognitive dysfunction in ALS.

Key words: *Imaging, biomarker, dementia, empathy, anterior cingulate cortex, social cognition*

Introduction

The classical view of amyotrophic lateral sclerosis (ALS) as a motor system disorder was drastically modified in the last few years by reports of behavioural and cognitive impairments in a high proportion of ALS patients (1,2). These findings suggest that ALS is a multisystem disorder, in which the involvement of extramotor cortical areas may result in a wide spectrum of accompanying symptoms, including sensory and autonomic disorders, as well as cognitive and behavioural impairments.

Cognitive impairment has been reported in up to 50% of sporadic ALS patients (2,3). Executive functions, free verbal recall and naming are the most affected cognitive functions (2,4), while reduced motivation and apathy are the predominant behavioural changes (1,3). Along with recent reports of

impaired social cognition and emotional processing (see (5) for a review), these observations highlight striking similarities between the cognitive and behavioural impairment in ALS and the behavioural variant of frontotemporal dementia (bvFTD) (6,7).

The 'continuum' hypothesis resulting from these observations has been supported by neuroimaging studies reporting the involvement of non-motor cortical regions, i.e. dorsolateral prefrontal, temporal and anterior cingulate cortex (7,8) in non-demented ALS patients. Moreover, these studies highlighted a significant relationship between the extent of right hemispheric damage and the severity of negative behavioural disorders (e.g. indifferent reactions and emotional blunting) (3). The latter observation is particularly relevant in the light of the phenotypic continuum between ALS and frontotemporal

dementia (FTD), particularly in view of the most recent genetic and neuropathological acquisitions (9,10). Impaired emotional and social processing, reflecting fronto-limbic damage with a right-hemispheric prevalence, are considered key elements for the early diagnosis of bvFTD (6). It is thus noteworthy that several studies highlighted defective emotional processing in non-demented ALS patients (11–14). Other facets of social cognition, and particularly Theory of Mind (ToM), i.e. the ability to understand and predict other people's behaviour by attributing to them mental or emotional states, have also been investigated in ALS. Gibbons et al. (15) described ToM performances ranging from normal to severely impaired and highly correlated with executive dysfunction in ALS patients, particularly in those with bulbar onset. Importantly, ALS patients' errors were similar to those commonly observed in FTD patients (16). Similar findings were found using other ToM tasks, such as the Reading-the-Mind-in-the-Eyes (17) and 'faux pas' (18) tests.

The observation of deficits affecting both the emotional processing and mentalizing about others' cognitive states in ALS suggests new venues for the phenotypic characterization of cognitive disorders in ALS. According to theoretical models (19), and neurological evidence (20,21), empathic abilities cover several phenomena, ranging from automatic affect sharing (i.e. emotional contagion) to the attribution of mental states, including emotional states or intentions (19). While a general mentalizing ability involves a broad network of areas including the medial prefrontal cortex (mPFC), temporo-parietal junction (TPJ), temporal poles and medial precuneus (22,23), lesion and imaging studies (20,24) specifically associate the attribution of intentions with the medial prefrontal cortex (20), and the attribution of emotional states with fronto-insular cortex (20) and limbic regions (25).

Given the complexity and heterogeneity, of the construct of empathy, evaluating the relative impairment of its specific facets requires a single task, in which both emotional and cognitive dimensions can be assessed within the same design and type of stimuli. For this purpose we studied for the first time a

sample of non-demented sporadic ALS patients, compared with age-, gender- and education-matched healthy controls, using a non-verbal task exploring both cognitive and emotional empathy, alongside a control condition requiring inferring physical relationship devoid of social components. Additionally, we investigated the relationship between neuropsychological test performance and grey-matter density using voxel-based morphometry (VBM).

Materials and methods

Subjects

The experimental sample included 20 non-demented patients with probable or definite ALS diagnosis according to the revised El Escorial criteria (26) (14 males, six females; mean age 59.1 years, standard deviation (SD) 9.83, range 36–75 years) and 56 age-, gender- and education-matched healthy controls (33 males, 23 females; mean age 61.9 years, SD 7.92, range 43–79 years) (see Table I for details).

The patients group included sporadic ALS cases consecutively recruited from the Department of Clinical Neurosciences (Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy) and the NEuroMuscular Omnicentre (NEMO, Niguarda Ca' Granda Hospital, Milan, Italy), and evaluated by a team of experienced behavioural neurologists and neuropsychologists. All patients underwent a screening including a structured clinical interview, a full neurological examination and an instrumental evaluation including neurophysiological (i.e. EMG-ENG) and neuroimaging (i.e. brain MRI/CT) assessments, to exclude alternative diagnoses. None of patients carried *C9orf72* or *GRN* genes mutation. Exclusion criteria were severe dysarthria and communication difficulties potentially invalidating the interpretation of their performance at neuropsychological testing, mild respiratory disorders (forced vital capacity > 70% of predicted capacity), or moderate-to-severe depression and anxiety disorders. No patients presented evidence of hypoxia/hypercapnia at the arterial blood gas analysis, and all had an Epworth Sleepiness Scale

Table I. Demographic and clinical data are reported. From left to right, mean (standard deviation within parentheses), *t*-test statistics and the corresponding *p*-value for group comparison.

| | ALS (<i>n</i> = 20) | HC (<i>n</i> = 56) | <i>t</i> statistics | <i>p</i> -value |
|-------------------------------|----------------------|---------------------|---------------------|-----------------|
| Age in years | 59.1 (9.83) | 61.9 (7.92) | 0.63 | 0.53 |
| Education in years | 10.01 (3.88) | 11.05 (3.98) | 1.44 | 0.15 |
| Months from diagnosis | 7.53 (5.96) | – | – | – |
| Months from clinical onset | 23.90 (20.71) | – | – | – |
| Frontal Behavioural Inventory | 4.63 (7.99) | – | – | – |
| Neuropsychiatric Inventory | 11.74 (9.64) | – | – | – |
| ALSFRS-R global score | 36.84 (5.52) | – | – | – |
| ALSFRS-R bulbar score | 18.35 (5.51) | – | – | – |
| ALSFRS-R spinal score | 18.94 (7.1) | – | – | – |

ALS: amyotrophic lateral sclerosis; HC: healthy controls; ALSFRS-R: ALS Functional Rating Scale – revised.

score (27) ≥ 9 . No patients met consensus criteria for bvFTD (6) or other dementias. Motor neuron functional impairment was assessed using the revised ALS Functional Rating Scale (ALSFRS-R; mean 36.84, SD 5.52) (28). Patients were classified according to the disease-onset type (spinal or bulbar onset). Four patients had bulbar-onset disease (i.e. dysarthria and dysphagia). Mild bulbar signs (dysarthria/dysphagia) were also present in seven patients at the time of the examination (ALSFRS-R bulbar mean score 10.25, SD 2.03).

Healthy controls were recruited at local senior community centres. Exclusion criteria included any neuropsychiatric disorder, a positive neurologic examination, a Clinical Dementia Rating scale (CDR) global score > 0 , a MMSE raw score $\leq 28/30$, and verbal and visuospatial delayed memory performance ≤ 25 th percentile. None of the controls was taking any medication interfering with neurobehavioural functioning. A next of kin (i.e. the spouse) of each control subject was interviewed to corroborate his/her normal daily functioning. There was no significant difference between patients and healthy controls for gender ($\chi^2(1) = 0.77$, $p = 0.38$), age ($t(75) = 0.63$, $p = 0.53$) and educational level ($t(75) = 1.44$, $p = 0.15$).

All subjects, or their informants/caregivers, gave informed consent to the experimental procedure, which was in accordance with the Helsinki Declaration of 1975 and had been approved by the local ethics committee.

Standard neuropsychological assessment

ALS subjects underwent a battery of standard neuropsychological tests to provide background information about their cognitive and behavioural profile. The battery included tests of language (picture naming and single word comprehension), memory (Digit Span Forward; Rey Auditory Verbal Learning test) and executive functions (Raven Coloured Progressive Matrices; Digit Span backward; letter (P-F-L) and category (animals-fruits-car brands) fluency tests; Cognitive Estimation Task; Stroop Interference Test and either Wisconsin Card Sorting Test or Weigl's Sorting Test) (29). In order to control for individual differences in motor speed, the mean fluency indexes were calculated (30) and the reading time-difference between colour and word-coloured-interference conditions of the Stroop test was considered. If necessary, patients with arm weakness were assisted by the examiner to move the cards during the tasks.

The behavioural assessment was performed through an interview with an adult family member or caregiver of each patient. The Frontal Behavioural Inventory and the Neuropsychiatric Inventory were used as formal measures of change in affect, personality and social behaviour functioning. Depression and anxiety were investigated with the Hamilton

Depression and Anxiety Rating Scale, in order to exclude those patients with interfering mood disorders. According to recent consensus criteria (31), all ALS patients were thus classified as behaviourally and/or cognitively impaired or unaffected.

The whole battery (including empathy assessment; see below) lasted approximately 80 min. Group differences were investigated using either parametric (two-sample *t*-test) or non-parametric (Mann-Whitney-*U*) statistics after testing for the normal distribution of data (Kolmogorov-Smirnov and Lilliefors tests).

Experimental empathy assessment

All subjects participated in a non-verbal task of attribution of mental states to other individuals, specifically requiring the recognition of their emotional states versus intentions, compared with inferring physical relationships devoid of social components. The task procedure and stimuli were developed ad hoc for this study, and derive from those previously employed by Sarfati et al. (32), Brunè et al. (33) and Völlm et al. (21). Compared with these studies, some stories were modified in their content and others were added de novo. All strips were redrawn by a professional graphic designer in order to improve the graphical style and clarity.

The whole task, lasting about 15–20 min, consists of two main experimental conditions, i.e. identifying emotional states (emotion attribution – EA) and intentions (intention attribution – IA), plus a control condition entailing the comprehension of causality reaction based on knowledge about the physical properties of objects or human bodies (causal inferences – CI). Each condition included six randomly presented trials. The task requires: 1) to describe the story, which is presented in a comic strip composed of three pictures in the upper half of the screen; 2) to formulate a possible story ending, and then; 3) to select the correct ending (from three possible endings of the story, i.e. plausible, implausible, and plausible but incorrect, in random positions across different trials), later presented in the lower half of the screen (see Figure 1 for examples of EA and IA conditions). Thus, a failure to correctly select the story ending entails a misjudgement on intentions and emotions of the main character on EA and IA sub-conditions or an erroneous comprehension of causality on CI sub-condition. Unlike Völlm et al. (21), we used the same general question across experimental conditions (i.e. “What is the correct ending of the story?”), in order to prevent the induction of specific strategies that may confound the interpretation of specific story-content effects.

Stimuli had been tested in a preliminary pilot study in two groups of 20 healthy young subjects each. Subjects from the first group were administered the same experimental procedure as described



Figure 1. Examples of a comic strip from the intention attribution – IA – condition (left), and from the emotion attribution – EA – condition (right), based on disgust. The three pictures at the top depict the story, while those at the bottom show its three possible endings.

above (EA task mean score 5.5 ± 0.83 ; IA task mean score 5.6 ± 0.60 ; CI task mean score 5.6 ± 0.59). Subjects from the second group, in contrast, underwent the procedure employed by Völlm et al. (20) (EA task mean score 5.75 ± 0.43 ; IA task mean score 5.9 ± 0.43 ; CI task mean score 5.65 ± 0.21). These subjects were asked to provide rating scores for overall clarity, for emotion understanding in EA task, and for intention understanding in IA task. Average scores of the finally included stories were 4.44 ± 0.45 , for emotion understanding 4.5 ± 0.3 , and for intention understanding 4.38 ± 0.47 , with no significant difference across conditions. No significant difference was found between the two pilot groups. Additionally, participants provided sensible descriptions of the story-line and used mentalistic and emotional terms to describe the intentions and emotions of the main character. Overall, the results of the pilot assessment in healthy young individuals indicated that the cartoons were easy to comprehend, and that they elicited the understanding of intentions and emotional states for the main story character.

Neuroimaging data

MRI data acquisition. A subset of 14 ALS and 20 matched HC underwent a magnetic resonance (MR) scanning session including T1-weighted images (220 slices, TR = 600 ms, TE = 20 ms, voxel size $0.9 \times 0.9 \times 0.8 \text{ mm}^3$). FLAIR and T2-weighted images were also collected for diagnostic purposes. All MR images were collected with a 3-Tesla Philips Achieva scanner (Philips Medical Systems, Best, NL) using an 8-channels Sense head coil.

Voxel-based morphometry (VBM) data pre-processing and statistical analysis. VBM pre-processing and statistical analyses were performed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) on Matlab v7.4 (Mathworks-Inc., Sherborn, MA), along with the VBM8 (<http://dbm.neuro.uni-jena.de>) and Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) toolboxes. VBM entailed four

main steps: 1) spatial normalization of all images to a standardized anatomical space by removing differences in overall size, position, and global shape; 2) extraction of grey matter (GM) and white matter (WM) from the normalized images; 3) smoothing (8 mm) of the normalized images; and 4) statistical analysis of local differences in GM density values across the whole brain.

Images were bias corrected for field-intensity inhomogeneities, registered using linear (12-parameter affine) and non-linear (warping) transformations, and tissue-classified in GM, WM and cerebrospinal fluid components. The segmented tissue maps were then registered to the stereotactic space of the Montreal Neurological Institute (MNI) using the iterative high-dimensional normalization approach provided by DARTEL toolbox. Finally, the normalized GM segments were written with an isotropic voxel resolution of 1.5 mm^3 , smoothed with an 8-mm Full-Width-Half-Maximum (FWHM) Gaussian kernel and entered into whole brain and brain behaviour correlation analyses.

Whole brain and correlation analyses. In whole brain analyses, regional GM density differences between ALS patients and healthy controls were investigated using a two-sample *t*-test. We excluded all voxels with a GM value < 0.2 (maximum, 1) to avoid edge effects at the border between GM and WM. The statistical threshold was set at $p < 0.05$ Family-wise-Error (FWE) corrected for multiple comparisons at the cluster level (34). Correlation analyses were then performed in the ALS sample among single-task condition scores and GM density in the brain regions that resulted significantly impaired in ALS compared with controls. For this purpose we first used the SPM toolbox Marsbar (<http://marsbar.sourceforge.net/>) to manually create spherical ROIs (radius 2 mm) centred on the peak voxels of the clusters highlighted by VBM. From these ROIs we extracted average GM density values, which were then separately correlated with EA, IA and CI condition scores. In order to confirm the actual impairment of the regions

showing a significant correlation with performance in ALS patients, GM density values in these regions were compared across patients and controls.

Cerebral regions showing significant effects were localized using the SPM Anatomy toolbox v1.8.

Results

Standard neuropsychological assessment

ALS patients were first classified according to the recent consensus criteria (31). Four out of 20 ALS patients (20%) displayed executive dysfunctions, leading to their classification as cognitively impaired (ALSci). Only one of them presented with bulbar onset. Mild short-term memory deficits and action naming difficulties were also found in these subjects. Apathy, irritability and disinhibition reached clinical relevance in two ALS patients (10%), both with spinal onset, who were thus classified as behaviourally impaired (ALSbi). None of the ALS subjects presented both cognitive and behavioural disorders. Therefore, according to Strong et al. (31), 14 out of 20 ALS patients were classified as cognitively and behaviourally unimpaired. Overall, the proportion of patients with either cognitive or behavioural impairments in our sample is 30% (six out of 20). No evidence of depression or anxiety symptoms were detected in ALS patients, whose Hamilton Depression and Anxiety Rating Scale scores were within normal range.

Empathy assessment

Mean global task performance was significantly lower in ALS compared with healthy controls ($U = 388$; $p = 0.042$). In particular, the analysis of single conditions revealed significantly reduced performance in patients, compared with controls, for emotion attribution ($U = 379$; $p = 0.032$). Non-significant differences were found both for intention attribution ($U = 412$; $p = 0.081$) and causal inferences ($U = 549$; $p = 0.90$) scores (see Table II and Figure 2A for details).

When focusing on the single subjects' scores, we observed impaired global task performance (at or below the 5th percentile compared with healthy controls) in one subject (an ALSbi patient), while

emotion attribution score was impaired in two subjects (10%) of the whole ALS sample. One of these two patients did not display any executive or behavioural impairment at the standard neuropsychological assessment.

Significant correlations were observed between the ALSFRS-R bulbar sub-scale score and both global ($r = 0.692$; $p = 0.007$) and CI condition ($r = 0.722$; $p = 0.0003$) scores. No significant correlations were found between experimental empathy task conditions and measures of executive functions.

VBM results

Whole brain VBM analyses highlighted a specific pattern of GM density reduction in ALS patients compared with healthy controls. This pattern included three main clusters, encompassing the fronto-insular cortex bilaterally as well as the anterior cingulate and ventromedial prefrontal cortex (see Figure 3, Table III). Among these clusters, in ALS patients emotion attribution scores were significantly and positively correlated with GM density in the right fronto-insular cortex ($r = 0.65$) and anterior cingulate cortex ($r = 0.62$) ($p < 0.05$) (see Figure 2B and 3 for details). In contrast, no significant correlation was found between both IA or CI scores and GM density in any of the clusters resulting from the main VBM analysis.

Discussion

We aimed to evaluate emotion and intention attribution, i.e. two critical facets of empathic ability, in ALS patients, by using a single non-verbal cartoon task. Compared with healthy controls, ALS patients displayed significantly reduced performance in the emotion attribution condition, i.e. in the ability to recognize others' emotional states. We then tested whether possible neural markers of this specific behavioural impairment in ALS may be found in the underlying pattern of GM atrophy. In agreement with other studies (7), despite the limited sample size and the application of a ROIs approach, our VBM results documented GM density reduction in non-motor cortical regions, previously associated with the empathic ability, namely in ventromedial

Table II. Behavioural results at the different subscales of the experimental task. From left to right, median (range within parentheses), Mann-Whitney U statistics and the corresponding p -value and effect size for group comparison are reported.

| | ALS ($n = 20$) | HC ($n = 56$) | U statistics | p -value | Cliff's delta |
|--------------------------|------------------|-----------------|----------------|------------|---------------|
| Emotion attribution-EA | 4 (2–6) | 5 (1–6) | 379 | 0.032 | 0.33 |
| Intention Attribution-IA | 5 (3–6) | 6 (4–6) | 412 | 0.081 | 0.26 |
| Causal inference-CI | 5 (3–6) | 5 (1–6) | 549 | 0.90 | 0.02 |
| Global score | 15 (9–17) | 16 (8–18) | 388 | 0.042 | 0.30 |

ALS: amyotrophic lateral sclerosis; HC: healthy controls.

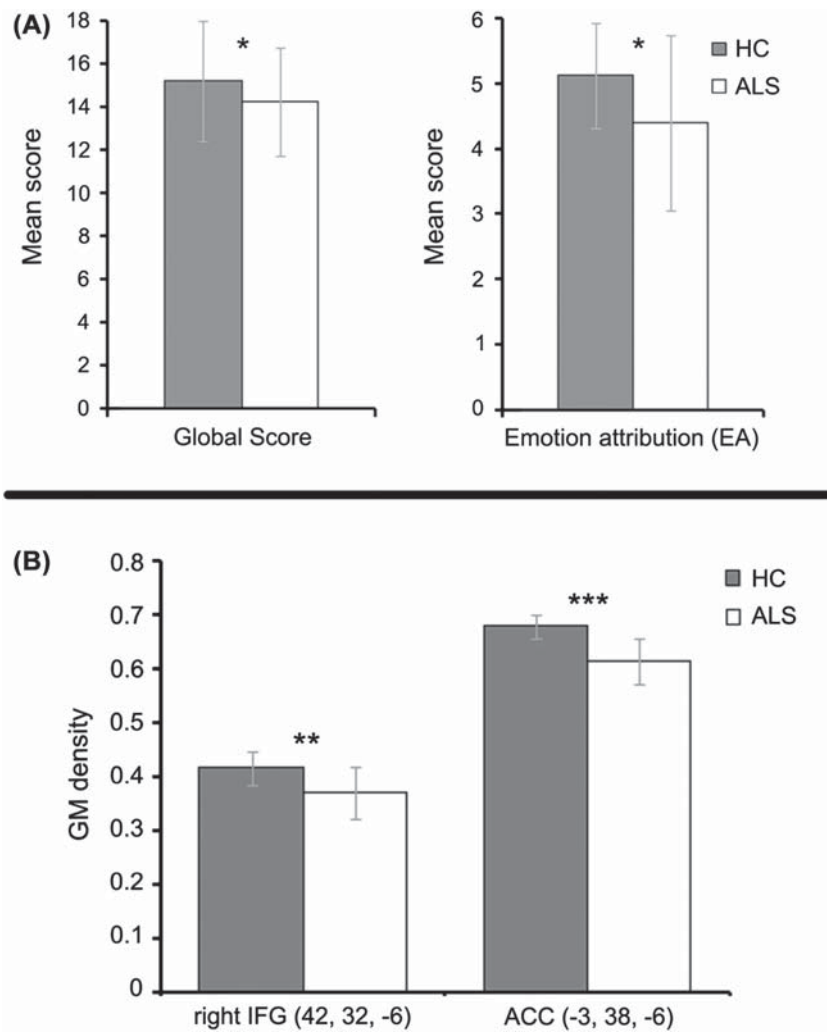


Figure 2. A. Empathy assessment: the global and the emotion attribution – EA – condition performances are depicted, separately for healthy controls and amyotrophic lateral sclerosis patients. B. Correlation between EA score and GM density within the significantly impaired clusters: average GM density in the regions showing a significant correlation with emotional empathy scores, separately for healthy controls and amyotrophic lateral sclerosis patients. ALS: amyotrophic lateral sclerosis; HC: healthy controls; GM: grey matter; IFG: right inferior frontal cortex; ACC: anterior cingulate cortex. p -values: * $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$. Vertical bars represent standard deviations.

prefrontal cortex (20) and anterior cingulate cortex, and fronto-insular cortex bilaterally (34–36). The significant correlation between emotional empathy performance and GM density in the anterior cingulate cortex and right fronto-insular cortex in ALS supported our hypothesis.

Unexpectedly, we did not find grey matter density reduction in premotor and/or motor cortices, as previously reported (35,37). This result could be explained by the less severe motor neuron impairment and disease duration of our sample compared to other studies. We cannot exclude, however, that this negative finding may be attributed to the small sample size.

Besides confirming the role of specific fronto-limbic regions in the ability to recognize others' emotional states, our results highlight their damage as the neural marker of empathy impairment in ALS. Noteworthy, in line with previous studies (38), this impairment can occur either alone or in association with other cognitive/behavioural disorders. Our

findings further confirm that cognitive impairments in non-demented ALS subjects are relatively subtle, and cannot be merely ascribed to executive dysfunction. An in-depth neuropsychological evaluation, specifically including the assessment of social cognition abilities, may thus be necessary to detect mild and subclinical dysfunctions in ALS. Overall, the variable vulnerability to cognitive changes observed in ALS indicates that larger longitudinal studies are needed to estimate the prevalence of social cognition and executive disorders in non-demented ALS patients, and to evaluate the putative presence of different cognitive subtypes in ALS.

The identification of deficits that specifically reflect a damage of fronto-limbic structures such as ventromedial prefrontal, anterior cingulate and fronto-insular cortices is in line with the hypothesis of a neuropsychological continuum between ALS cognitive dysfunctions and those of bvFTD patients. While comorbidity between ALS and FTD is not so frequent (13.8% of cases of the large series reported

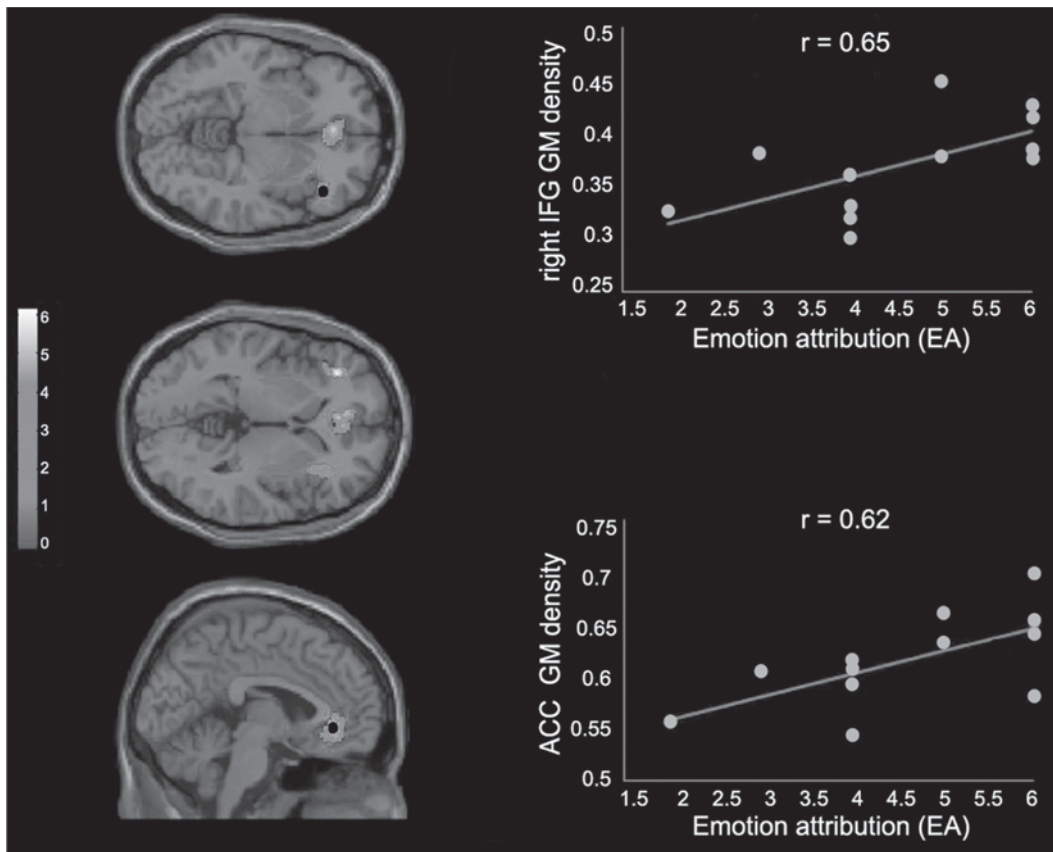


Figure 3. Pattern of regional GM density reduction in non-demented amyotrophic lateral sclerosis patients, compared with healthy controls, is depicted on an axial ($z = -6$, $z = 0$) and sagittal slice ($x = -3$) of a standard template brain. Scatter plots represent the correlation between emotion attribution – EA – score and GM density within the two significantly impaired clusters (green dots) in the ALS group. ALS: amyotrophic lateral sclerosis; GM: grey matter; IFG: right inferior frontal cortex; ACC: anterior cingulate cortex.

by Phukan et al. (20)), mild dysexecutive and behavioural syndromes have been reported in a larger number of ALS patients (2,39). The link between ALS and FTD is also supported by a wealth of evidence at the genetic, pathological and clinical levels (9,10,40–43). In particular, pathological observations documented neuronal loss, spongiosis and ubiquitinated intraneuronal inclusions in extramotor

brain regions of ALS patients (44). Importantly, both the subtype and locations of these changes overlap with those reported in frontotemporal lobar degeneration (FTLD). TDP-43 proteinopathy, widely distributed in multiple brain areas including the neocortical and allocortical areas in many FTD cases, has also been found in ALS cases without dementia (44). Moreover, the recently recognized

Table III. The local maxima of the brain regions showing a significant GM density reduction in amyotrophic lateral sclerosis patients, compared with healthy controls, are reported.

| H | Region | T-score | Coordinates | | | p-value |
|---|--|---------|-------------|----|-----|---------|
| | | | x | y | z | |
| L | Inferior frontal gyrus (pars triangularis) | 6.13 | -36 | 36 | 1 | 0.020 |
| L | Anterior cingulate cortex | 5.09 | -3 | 38 | -6 | <0.0001 |
| L | Middle orbital gyrus | 4.74 | -8 | 44 | 0 | |
| R | Middle orbital gyrus | 4.58 | 3 | 42 | 1 | |
| L | Rectus gyrus | 4.54 | 0 | 32 | -12 | |
| R | Anterior cingulate cortex | 4.28 | 8 | 32 | -12 | |
| L | Superior medial gyrus | 3.64 | -10 | 44 | 9 | |
| R | Inferior frontal gyrus | 4.51 | 42 | 32 | -6 | 0.006 |
| R | Insula lobe | 3.86 | 28 | 21 | -3 | |
| R | Insula lobe | 3.79 | 42 | 12 | 6 | |
| R | Insula lobe | 3.72 | 33 | 20 | 0 | |

H: hemisphere; L: left; R: right.

C9orf72 mutation represents not only a major cause of familial ALS cases, but also of sporadic ones (9,10), with a variety of phenotypic presentation even in the same family pedigree (i.e. FTD subtypes, ALS, or a combination of both). In particular, according to recent neuropathological evidence in ALS subjects carrying a *C9orf72* gene mutation (45), an extramotor cortical involvement consistent with FTLD-TDP type B (46) can be present in subjects with a clinical diagnosis of pure ALS. Overall, these data strongly support that the two neurodegenerative disorders share common neuropathological mechanisms, and actually represent distinct phenotypes within a clinico-pathological continuum ranging from ALS through ALS/FTLD to FTLD.

Besides their theoretical interest, deficits in social behaviour and empathic abilities, and in social behaviour in general, may entail practical implications for the management of patients and should be appropriately taken into account in the evaluation of therapeutic approaches and critical life choices.

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Declaration of interest: The authors alone are responsible for the content and writing of the paper.

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References

- Strong MJ. The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2008;9:323–8.
- Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry*. 2012;83:102–8.
- Murphy J, Henry R, Lomen-Hoerth C. Establishing subtypes of the continuum of frontal lobe impairment in amyotrophic lateral sclerosis. *Arch Neurol*. 2007;64:330–4.
- Taylor LJ, Brown RG, Tsermentseli S, Al-Chalabi A, Shaw CE, Ellis CM, et al. Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? *J Neurol Neurosurg Psychiatry*. 2012 Oct 2. (Epub ahead of print).
- Elamin M, Pender N, Hardiman O, Abrahams S. Social cognition in neurodegenerative disorders: a systematic review. *J Neurol Neurosurg Psychiatry*. 2012;83:1071–9.
- Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456–77.
- Tsermentseli S, Leigh PN, Goldstein LH. The anatomy of cognitive impairment in amyotrophic lateral sclerosis: more than frontal lobe dysfunction. *Cortex*. 2012;48:166–82.
- Mezzapesa DM, Ceccarelli A, Dicuonzo F, Carella A, de Caro MF, Lopez M, et al. Whole brain and regional brain atrophy in amyotrophic lateral sclerosis. *AJNR Am J Neuro-radiol*. 2007;28:255–9.
- Chiò A, Borghero G, Restagno G, Mora G, Drepper C, Traynor BJ, et al. Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of *C9orf72*. *Brain*. 2012;135:784–93.
- Sabatelli M, Conforti FL, Zollino M, Mora G, Monsurrò MR, Volanti P, et al. *C9orf72* hexanucleotide repeat expansions in the Italian sporadic ALS population. *Neurobiol Aging*. 2012;33:15–20.
- Zimmerman EK, Eslinger PJ, Simmons Z, Barrett AM. Emotional perception deficits in amyotrophic lateral sclerosis. *Cogn Behav Neurol*. 2007;20:79–82.
- Palmieri A, Naccarato M, Abrahams S, Bonato M, D’Ascenzo C, Balestreri S, et al. Right hemisphere dysfunction and emotional processing in ALS: an fMRI study. *J Neurol*. 2010;257:1970–8.
- Papps B, Abrahams S, Wicks P, Leigh PN, Goldstein LH. Changes in memory for emotional material in amyotrophic lateral sclerosis (ALS). *Neuropsychologia*. 2005;43:1107–14.
- Schmolck H, Mosnik D, Schulz P. Rating the approachability of faces in ALS. *Neurology*. 2007;69:2232–5.
- Gibbons ZC, Snowden JS, Thompson JC, Happé F, Richardson A, Neary D. Inferring thought and action in motor neuron disease. *Neuropsychologia*. 2007;45:1196–207.
- Snowden JS, Gibbons ZC, Blackshaw A, Doubleday E, Thompson J, Craufurd D, et al. Social cognition in fronto-temporal dementia and Huntington’s disease. *Neuropsychologia*. 2003;41:688–701.
- Cavallo M, Adenzato M, Macpherson SE, Karwig G, Enrici I, Abrahams S. Evidence of social understanding impairment in patients with amyotrophic lateral sclerosis. *PLoS One*. 2011;6:e25948.
- Meier SL, Charleston AJ, Tippett LJ. Cognitive and behavioural deficits associated with the orbitomedial prefrontal cortex in amyotrophic lateral sclerosis. *Brain*. 2010;133:3444–57.
- de Vignemont F, Singer T. The empathic brain: how, when and why? *Trends Cogn Sci*. 2006;10:435–41.
- Shamay-Tsoory SG. The neural bases for empathy. *Neuroscientist*. 2011;17:18–24.
- Völlm BA, Taylor AN, Richardson P, Corcoran R, Stirling J, McKie S, et al. Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a non-verbal task. *Neuroimage*. 2006;29:90–8.
- Frith U, Frith CD. Development and neurophysiology of mentalizing. *Philos Trans R Soc Lond B Biol Sci*. 2003;358:459–73.
- van Overwalle F, Baetens K. Understanding others’ actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage*. 2009;48:564–84.
- Gallese V, Keysers C, Rizzolatti G. A unifying view of the basis of social cognition. *Trends Cogn Sci*. 2004;8:396–403.
- Singer T, Seymour B, O’Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science*. 2004;303:1157–62.
- Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000;1:293–9.
- Vignatelli L, Plazzi G, Barbato A, Ferini-Strambi L, Manni R, Pompei F, et al. Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci*. 2003;23:295–300.
- Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments

- function. BDNF ALS Study Group (Phase III). *J Neurol Sci.* 1999;169:13–21.
29. Lezak M. *Neuropsychological assessment.* 1995. Oxford University Press, USA 3rd edn.
 30. Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Gris  D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). *Neuropsychologia.* 2000;38:734–47.
 31. Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2009;10:131–46.
 32. Sarfati Y, Hardy-Bayl  MC, Besche C, Widl cher D. Attribution of intentions to others in people with schizophrenia: a non-verbal exploration with comic strips. *Schizophr Res.* 1997;25:199–209.
 33. Brunet E, Sarfati Y, Hardy-Bayl  MC, Decety J. A PET investigation of the attribution of intentions with a non-verbal task. *Neuroimage.* 2000;11:157–66.
 34. Hayasaka S, Nichols TE. Combining voxel intensity and cluster extent with permutation test framework. *Neuroimage.* 2004;23:54–63.
 35. Thivard L, Pradat PF, Leh ricy S, Lacomblez L, Dormont D, Chiras J, et al. Diffusion tensor imaging and voxel based morphometry study in amyotrophic lateral sclerosis: relationships with motor disability. *J Neurol Neurosurg Psychiatry.* 2007;78:889–92.
 36. Bernhardt BC, Singer T. The neural basis of empathy. *Annu Rev Neurosci.* 2012;35:1–23.
 37. Lillo P, Mioshi E, Burrell JR, Kiernan MC, Hodges JR, Hornberger M. Grey and white matter changes across the amyotrophic lateral sclerosis/frontotemporal dementia continuum. *PLoS One* 2012;7:e43993.
 38. Girardi A, Macpherson SE, Abrahams S. Deficits in emotional and social cognition in amyotrophic lateral sclerosis. *Neuropsychology.* 2011;25:53–65.
 39. Consonni M, Iannaccone S, Cerami C, Frasson P, Lacerenza M, Lunetta C, et al. The cognitive and behavioural profile of amyotrophic lateral sclerosis: application of the consensus criteria. *Behav Neurol.* 2012 Sep 21. (Epub ahead of print).
 40. Cerami C, Scarpini E, Cappa SF, Galimberti D. Frontotemporal lobar degeneration: current knowledge and future challenges. *J Neurol.* 2012;259:2278–86.
 41. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol.* 2012;8:423–34.
 42. Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor neuron dysfunction in frontotemporal dementia. *Brain.* 2011;134:2582–94.
 43. Lillo P, Savage S, Mioshi E, Kiernan MC, Hodges JR. Amyotrophic lateral sclerosis and frontotemporal dementia: a behavioural and cognitive continuum. *Amyotroph Lateral Scler.* 2012;13:102–9.
 44. Mackenzie IR, Feldman H. The relationship between extramotor ubiquitin-immunoreactive neuronal inclusions and dementia in motor neuron disease. *Acta Neuropathol.* 2003;105:98–102.
 45. Stewart H, Rutherford NJ, Briemberg H, Krieger C, Cashman N, Fabros M, et al. Clinical and pathological features of amyotrophic lateral sclerosis caused by mutation in the C9orf72 gene on chromosome 9p. *Acta Neuropathol.* 2012;123:409–17.
 46. Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, et al. A harmonized classification system for FTLT-DTP pathology. *Acta Neuropathol.* 2011;122:111–3.