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Microstructural white matter correlates of emotion recognition impairment in Amyotrophic Lateral Sclerosis

Chiara Crespi [a,b], Chiara Cerami [a,b], Alessandra Dodich [a,b], Nicola Canessa [a,b], Marta Arpone [a], Sandro Iannaccone [b], Massimo Corbo [c,1], Christian Lunetta [c], Elisa Scola [a,b], Andrea Falini [a,b] and Stefano F. Cappa [a,b,*]

[a] Università Vita Salute San Raffaele, Milan, Italy
[b] San Raffaele Scientific Institute, Milan, Italy
[c] NEuroMuscolar Omnicentre (NEMO), Niguarda Cà Granda Hospital – Piazza Ospedale Maggiore 3, Milan, Italy

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is associated in about half of the cases with behavioral and cognitive disorders, including impairments in socio-emotional processing, considered as key-features for the diagnosis of the behavioral variant of frontotemporal dementia (bv-FTD). The neurostructural bases of emotional deficits in ALS, however, still remain largely unexplored. Here we aim to assess emotion recognition in non-demented sporadic ALS patients compared with healthy controls, and to explore for the first time its microstructural white-matter correlates. Twenty-two subjects with either probable or definite diagnosis of ALS and 55 age-, gender-, and education-matched healthy controls were recruited in the study. All participants performed the Ekman 60-Faces Test, assessing the recognition of six basic emotions (i.e., anger, disgust, fear, sadness, surprise and happiness). A subgroup of subjects, comprising 19 patients and 20 healthy controls, also underwent a Diffusion Tensor Imaging scanning. Behavioral analysis highlighted a significant decline of emotion recognition skills in patients compared to controls, particularly affecting the identification of negative emotions. Moreover, the Diffusion Tensor Imaging analyses revealed a correlation between this impairment and the alteration of white-matter integrity along the right inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. Our findings indicate the presence of an early emotion recognition deficit in non-demented sporadic ALS patients, associated with microstructural changes in ventral associative bundles connecting occipital, temporo-limbic and orbitofrontal regions in the right hemisphere. These changes may represent a frontotemporal-limbic microstructural marker of socio-emotional impairment in ALS.

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* *Corresponding author*. via Olgettina, 60 – 20132, Milan, Italy.
E-mail addresses: crespi.chiara@hsr.it (C. Crespi), cerami.chiara@hsr.it (C. Cerami), dodich.alessandra@hsr.it (A. Dodich), canessa.nicola@hsr.it (N. Canessa), m.arpone@studenti.unisr.it (M. Arpone), iannaccone.sandro@hsr.it (S. Iannaccone), massimo.corbo@centrocliniconemo.it, m.corbo@ccppdezza.it (M. Corbo), christian.lunetta@centrocliniconemo.it (C. Lunetta), scola.elisa@hsr.it (E. Scola), falini.andrea@hsr.it (A. Falini), cappa.stefano@hsr.it (S.F. Cappa).
[1] Present address: Department of Neurorehabilitation Sciences, Casa Cura Policlinico, via Dezza 48, 20144 Milan, Italy.
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1. Introduction

The traditional view of Amyotrophic Lateral Sclerosis (ALS) as a pure motor neuron disease underwent a dramatic revision over the last decades. It is now widely recognized that ALS represents a heterogeneous neurodegenerative condition, which can variously affect multiple brain networks other than the motor system (Chen & Ma, 2010; Ellis et al., 2001), resulting in a number of non-motor dysfunctions (Abrahams, Goldstein, Lloyd, Brooks, & Leigh, 1995; Abrahams, Goldstein, Suckling, Ng, Simmons, & Chitnis, 2005). Indeed, the progressive failure of both upper and lower motor neurons characterizing the ALS pathophysiology is accompanied in about half of the cases by cognitive and/or behavioral symptoms, mirroring the pattern of deficits typically observed in Frontotemporal Dementia (FTD) (Consonni et al., 2013; Lillo, Garcin, Hornberger, Bak, & Hodges, 2010; Lillo, Mioshi, Zoing, Kiernan, & Hodges, 2011; Phukan et al., 2012). This evidence, along with clinical, pathological, genetic and neuroimaging findings (Boeve et al., 2012; Lillo et al., 2012; Phukan, Pender, & Hardiman, 2007; Tsermentseli, Leigh, & Goldstein, 2012), provides support to the FTD-ALS continuum hypothesis, which considers FTD and ALS as extremes of a unique disease spectrum. In particular, similar to patients with diagnosis of behavioral variant of frontotemporal dementia (bv-FTD), a proportion of ALS subjects also display changes in the processing socio-emotional stimuli (Cavallo et al., 2011; Cerami et al., 2013; Elamin, Pender, Hardiman, & Abrahams, 2012; Girardi, Macpherson, & Abrahams, 2011; Lulé et al., 2005; Palmieri et al., 2010; Papps, Abrahams, Wicks, Leigh, & Goldstein, 2005), including the ability to recognize basic (negative) emotions from facial expressions (Zimmerman, Eslinger, Simmons, & Barrett, 2007). In contrast to these findings, preserved emotion processing has been reported in ALS patients without dementia (Savage et al., 2013).

Identifying others' emotions represents a crucial skill within the realm of social cognition, requiring the integrity of both the occipital face-processing system and of fronto-temporal cortices (Gschwind, Pourtois, Schwartz, Van De Ville, & Vuilleumier, 2012), particularly in the right hemisphere when negative emotions are involved (Gur, Skolnick, & Gur, 1994). The conjoint role of these brain regions in the processing emotional facial expressions is supported by evidence of emotion recognition deficits following selective damage of the right Inferior Longitudinal Fasciculus (ILF) and/or Inferior Fronto-Occipital Fasciculus (IFOF) (Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009), ventral associative bundles linking occipital cortices (i.e., visual areas) to temporo-limbic (i.e., amygdala and hippocampal complex) and orbitofrontal regions, respectively (Catani & Thiebaut de Schotten, 2008).

Although a number of emotional alterations has been reported in ALS, even in the early stages of the disease (Lulé et al., 2005), its neurostructural bases still remain unexplored. The present study aims to investigate for the first time white-matter substrates underlying the ability to recognize emotions from facial expression in sporadic ALS patients. In particular, we tested the hypothesis that this deficit reflects the progressive degeneration of bundles, like the ILF and/or the IFOF, mediating the anatomical connectivity among occipital and fronto-temporal regions. Diffusion Tensor Imaging (DTI) techniques appear particularly suitable to achieve this study's goal, since the investigation of the microstructural properties of white-matter tracts can highlight subtle, but potentially relevant, changes related to the neuropathology of ALS.

2. Materials and methods

2.1. Participants

Twenty-two non-demented sporadic ALS subjects with either probable or definite ALS diagnosis (Brooks, Miller, Swash, & Munsat, 2000) and 55 age-, gender- and education-matched healthy controls (HC) participated in the study. All patients underwent a structured clinical interview, a full neurological examination, and a conventional Magnetic Resonance Imaging (MRI) investigation including T1, T2 and FLAIR (Fluid Attenuated Inversion Recovery) sequences, collected for diagnostic purposes. None of patients carried *C9ORF72* or *GRN* genes mutation. Exclusion criteria were left-handedness, the evidence of a positive history for other neuropsychiatric disorders, and the presence of other pathological findings on MRI scans. We also excluded patients with mild respiratory disorders (forced vital capacity $<$70% of predicted capacity), severe dysarthria and communication difficulties potentially invalidating the interpretation of neuropsychological performances.

We used the revised ALS-Functional Rating Scale (ALS-FRSr) to evaluate motor neuron impairment. Patients were classified according to disease-onset type (i.e., spinal or bulbar). Four patients had bulbar onset disease (i.e., dysarthria and dysphagia). Additionally, all patients completed a standard neuropsychological evaluation to assess the presence of cognitive impairments and/or behavioral disorders (Cerami et al., 2013). In particular, we administered a battery of tests evaluating language (picture naming and single word comprehension), memory (short-term verbal memory: digit span forward; long-term memory: Rey Auditory Verbal Learning test), and executive functions (Raven Colored Progressive Matrices; digit span backward; letter and category fluency tests; Cognitive Estimation Task; Stroop interference test and either Wisconsin Card Sorting Test or Weigl's Sorting Test), as well as inventories (Frontal Behavioral Inventory and Neuropsychiatric Inventory) assessing the presence of behavioral dysfunctions. HC were recruited from local senior community centers. Their inclusion criteria were the absence of neuropsychiatric disorders, a negative neurologic examination, global Clinical Dementia Rating score = 0, Mini-Mental State Examination score $\geq$28/30, verbal and visuo-spatial delayed memory performance (Rey Auditory Verbal Learning test and Rey Figure Recall task) $\geq$25th percentile. None of the HC was taking any medication potentially interfering with neurobehavioral functioning. A next of kin (e.g., spouse) of each control subject was interviewed to corroborate his/her normal daily functioning. All subjects or relative informants gave their written informed consent to the experimental procedure, which was approved by the local Ethics Committee.

2.2. Emotion recognition assessment

Emotion recognition abilities were assessed with the Ekman 60-Faces Test (Ekman & Friesen, 1976), which includes 60

pictures depicting 10 actors' faces, each one expressing the six basic emotions (i.e., surprise, happiness, fear, disgust, anger and sadness). Pictures were serially presented on a computer screen and participants were asked to report verbally the emotion expressed in each of them selecting one out of the six available options (i.e., emotion words) displayed on the bottom of the screen. The scoring procedure resulted in a maximum score of 60 for global performance, and a maximum of 10 for single emotion sub-scores. Additionally, according to the standardization of the Italian version of the Ekman 60-Faces Test (Dodich et al., 2014), single emotion subscores were dichotomously classified as normal or impaired on the basis of a cutoff point, while the global performance was also adjusted for age, education and gender. We assessed group differences with either parametric or nonparametric tests, depending on data distribution.

2.3. *Diffusion Tensor Imaging study*

A subgroup of 19 ALS patients and 20 HC also underwent a DTI study, aiming to investigate group differences in white-matter integrity and to correlate microstructural measures with emotion recognition performance in patients. Three out of 21 ALS patients who participated in the behavioral session dropped out of the MRI examination due to claustrophobia, presence of pacemaker or refusal. All the other patients completed the whole MRI protocol. MRI scans were performed using a 3T Philips Achieva scanner (Philips Medical Systems, Best, NL) with an 8-channels head coil. Whole-brain DTI data were collected using a single-shot echo planar sequence (TR/TE = 8986/80 msec; FOV = 240 mm^2; 56 sections; 2.5 mm isotropic resolution) with parallel imaging (SENSE factor = 2.5) and diffusion gradients applied along 32 non-collinear directions (b-value = 1000 sec/mm^2). One non-diffusion weighted volume was also acquired. We performed DTI data pre-processing and analysis with the FMRIB Software Library tools (FSL: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Single-subject datasets were first corrected for eddy current distortions and motion artifacts, skull-stripped and finally, as a result of the fitting of the diffusion tensor model at each voxel, maps of diffusion scalar measures were generated. We then carried out whole-brain analyses on the diffusion parameters using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006). Briefly, the TBSS method includes a voxel-wise non-linear registration of all subjects' Fractional Anisotropy (FA) maps that, once aligned, are affine-transformed on a standard space ($1 \times 1 \times 1$ mm^3 MNI152). After co-registration, FA maps are averaged to create a mean FA image, and then used to generate a mean FA tract skeleton, representing all common tracts across subjects. In order to exclude from further analysis those parts of the skeleton that could not ensure a good correspondence across subjects, we applied a threshold of .20 to the mean FA skeleton image. Finally, to account for residual misalignments after the initial nonlinear registration, all subjects' FA data were projected onto the thresholded mean FA skeleton, creating a 4D dataset of all subjects' FA skeletonized data, which was fed into whole-brain voxel-wise statistical analysis. In addition, the non-FA TBSS script was ran on maps of mean diffusivity (MD) and mode of anisotropy (MO), a recently developed measure of anisotropy providing information about the shape of the tensor (Ennis & Kindlmann, 2006). Group comparisons were conducted with *randomise*, setting a number of 10,000 random permutations per contrast. We employed the Threshold-Free Cluster Enhancement option (Smith & Nichols, 2009) and set the significance threshold for group differences at $p < .05$. Finally, for graphic purposes, maps of corrected results were smoothed applying a Gaussian Kernel of 3 mm via the *tbss_fill* script. In order to test the *a priori* hypothesis that the right ILF and IFOF are involved in the processing of (negative) emotions (Philippi et al., 2009), we performed off-line correlation analyses between DTI metrics from these bundles and emotion recognition skills in ALS patients, in terms of both global score and negative emotions subscore. To this purpose, we binarized and thresholded (at 10%) probability maps of ILF and IFOF (JHU White-Matter Tractography Atlas, Hua et al., 2008) using *fslmaths* script. Then we employed *fslmeants* to mask the FA skeletonized 4D image with binary maps of ILF and IFOF and to extract mean FA values of both bundles for each subject. Finally, we ran correlational analyses with the Statistica software (http://www.statsoft.com/). The same procedure was applied to significant clusters found along ILF/IFOF in statistical maps outputted from *randomise*. Finally, correlation *p*-values were adjusted for multiple comparisons using the False Discovery Rate correction (FDR) (Benjamini & Hochberg, 1995).

3. Results

3.1. *Emotion recognition in non-demented sporadic ALS patients*

Demographic and clinical characteristics of patients are summarized in Table 1. ALS subjects were also classified according to Strong's consensus criteria (Strong et al., 2009) on the basis of the presence/absence of cognitive and/or behavioral impairments on a standard neuropsychological battery. In particular, 5 out of 22 patients (23%) obtained poor performances on tasks assessing executive functioning, and were thus classified as cognitively impaired (Amyotrophic Lateral Sclerosis with cognitive impairments – ALSci). Two

Table 1 – Subjects demographic and clinical characteristics.

	ALS	HC	*p*-value
Age (years)	60.40 ± 10.08	61.61 ± 7.46	.56[a]
Gender (males:females)	15:7	32:23	.41[b]
Education (years)	9.59 ± 4.58	10.80 ± 3.80	.27[c]
Disease duration:	23.09 ± 20.57	–	–
-months from symptoms onset	8.95 ± 10.60		
-months from diagnosis			
ALS-FRSr	39.86 ± 9.01	–	–

[a] Student's *t*-test.
[b] Chi-squared test.
[c] Mann–Whitney *U* test.

Table 2 – Patients' classification according to Strong's consensus criteria (Strong et al., 2009).

	Whole ALS sample ($n = 22$)	ALS subgroup enrolled in the DTI study ($n = 19$)
ALSci	23% (5/22)	16% (3/19)
ALSbi	9% (2/22)	10% (2/19)
ALSci/bi	4% (1/22)	0% (0/19)
Pure ALS	64% (14/22)	74% (14/19)

out of 22 ALS subjects (9%) presented behavioral symptoms reaching clinical significance (i.e., apathy, irritability and disinhibition), and leading to patients' classification as behaviorally impaired (Amyotrophic Lateral Sclerosis with behavioral impairments – ALSbi). Finally, only one patient presented both cognitive and behavioral deficits (ALSci/bi). All the other patients were both cognitively and behaviorally unimpaired (pure ALS) (Table 2).

Because of differences in data distributions, group comparisons on the global score of the Ekman 60-Faces Test (Liliefors test $p > .05$) were investigated using a parametric approach (Student *t*-test), while group differences in single emotions (Liliefors test $p < .01$) were estimated with nonparametric tests (Mann–Whitney *U* Test). These analyses revealed a global impairment of emotion recognition in ALS patients compared with HC ($t(75) = -3.29$, $p = .0015$, effect size $r = .35$). This effect was driven by a significant impairment in the recognition of negative emotions ($U = 395.5$, $p = .018$, Cliff's delta = .35), which specifically involved the misidentification of anger ($U = 381$, $p = .01$, Cliff's delta = .37) and disgust ($U = 429$, $p = .042$, Cliff's delta = .29). No group differences were observed for the other emotions, apart from a marginal trend for sadness ($U = 457$, $p = .089$, Cliff's delta = .24) and surprise ($U = 459$, $p = .09$, Cliff's delta = .24). These findings are further confirmed by complementary analyses based on cut-off points, showing a significant alteration in patients compared with HC at the global performance level (Pearson's Chi-square = 7.80, $p = .0052$). Once again, the identification of negative emotions is particularly compromised in patients, with 41% of ALS subjects performing below the cut-off point in at least one of the four negative emotions assessed. Specifically, a significantly higher proportion of patients obtained a poor performance, i.e., below the cut-off, in the recognition of anger (Pearson's Chi-square = 4.63, $p = .031$) and sadness (Pearson's Chi-square = 6.93, $p = .0085$).

3.2. *DTI results: TBSS whole-brain comparison*

Whole-brain TBSS analyses highlighted significant microstructural white-matter changes within the motor pathway in ALS subjects compared with HC (Fig. 1). We found a significant decrease (about 10%) of FA in patients in a large cluster involving the bilateral corticospinal tract (right > left) and the body of corpus callosum ($p < .05$ FWE-corrected; cluster size: 2058 voxels; cluster maximum: $x = 20$, $y = -20$, $z = 49$). A co-localized, but more restricted pattern of alteration, encompassing the right CST, also emerged for MO ($p < .05$ FWE-corrected; cluster size: 738 voxels; cluster maximum: $x = 21$, $y = -20$, $z = 41$), which resulted significantly reduced (on average, about 42%) in ALS subjects. Finally, as previously reported (Filippini et al., 2010), no significant group differences were found in mean diffusivity. Furthermore, beside the alterations identified along the corticospinal tract, we also detected group differences (ALS < HC, $p < .005$ uncorrected) in

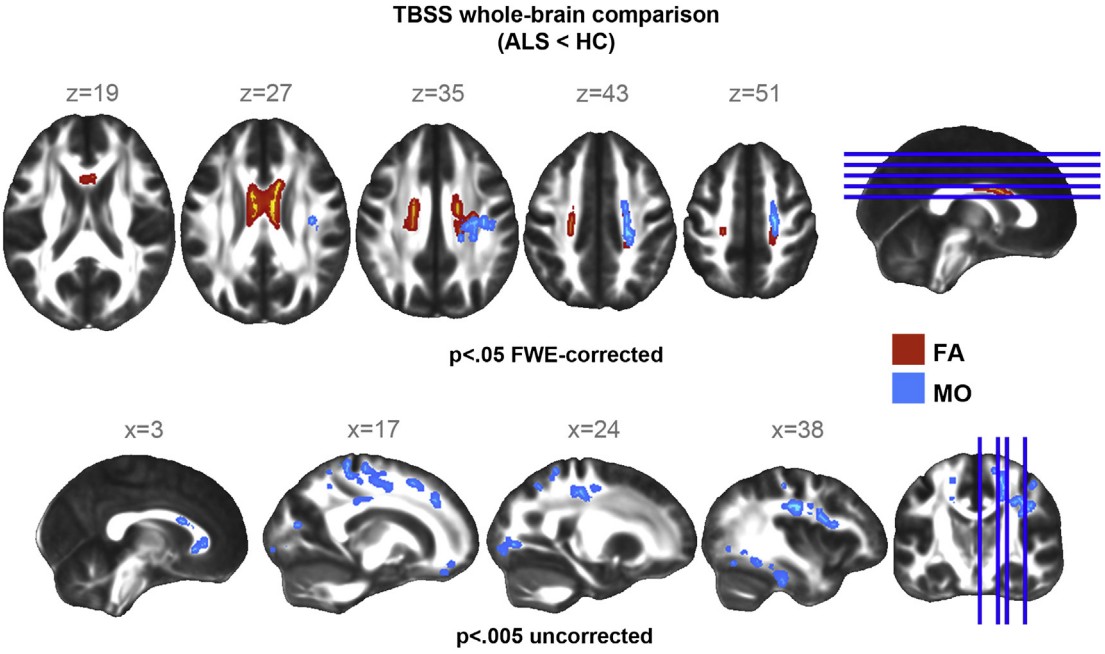

Fig. 1 – TBSS whole-brain comparison. Statistical maps of microstructural impairment in patients compared to HC are superimposed to the FMRIB standard-space FA template. On top, we report statistical maps illustrating both FA (red) and MO (light-blue) alterations ($p < .05$, FWE-corrected). On bottom, we show significant change in MO (light-blue) in extra-motor regions ($p < .005$, uncorrected).

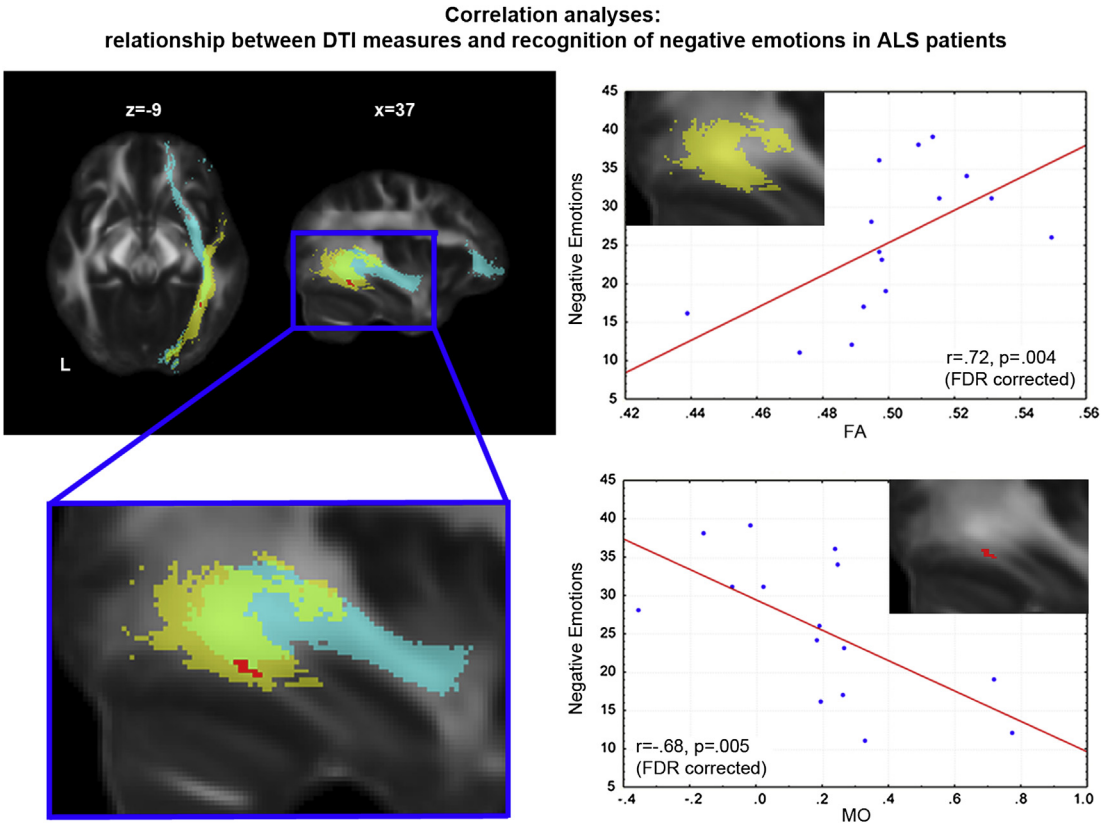

Fig. 2 – Significant correlations between microstructural white-matter integrity and the recognition of negative emotions in ALS patients. On the left, probabilistic maps employed to extract FA from the right ILF (yellow) and IFOF (light-blue) are superimposed to the FMRIB standard-space FA template. In the same panel, we report one cluster (red) in which we found a significant reduction in the type of anisotropy (MO) in ALS patients versus HC. On the right, the scatter-plots illustrate significant relationships between patients' ability to recognize negative emotions and: on top, mean FA index along the right ILF; on bottom, mean MO index in a cluster along the right ILF/IFOF.

MO in a number of clusters along extra-motor bundles including association tracts, namely the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, as well as commissural fibers, i.e., the genu of the corpus callosum and the forceps minor.

3.3. *Relationship between DTI metrics and emotion recognition skills in patients*

We performed correlation analyses (Spearman's Rank Coefficient) between the microstructural properties of our target bundles (i.e., right ILF and IFOF; see Introduction) and ALS patients' performance in the Ekman 60-Faces Test. The results highlighted a significant positive correlation between global performance and the mean FA index extracted from the right ILF ($r = .54$, $p = .04$). Additionally, the cumulative score of the sub-scales assessing the recognition of negative emotions (i.e., fear, disgust, anger and sadness) showed a positive correlation with FA values of both the right ILF ($r = .72$, $p = .004$) and IFOF ($r = .59$, $p = .02$) (Fig. 2). Moreover, FA values along these bundles were positively associated with the ability to recognize *specific* negative emotions. In particular, mean FA values along the right ILF were associated with the identification of fear ($r = .58$, $p = .03$), disgust ($r = .68$, $p = .01$), and sadness ($r = .69$, $p = .008$), while FA along the IFOF was significantly correlated with fear ($r = .71$, $p = .008$), anger ($r = .52$, $p = .05$) and sadness ($r = .63$, $p = .02$). We found no significant correlation between the emotion recognition abilities and mean MO along tracts of interest. Therefore, we performed additional analyses to assess possible relationship between mean MO values from significant clusters resulted from whole-brain TBSS group comparisons (statistic maps were thresholded at $p < .005$ uncorrected) and the recognition of negative emotions in ALS patients. In particular, we selected a set of significant clusters localized along the right ILF and/or the right IFOF. These analyses revealed a significant negative correlation between MO from one cluster close to the fusiform cortex (cluster size: 20 voxels; cluster maximum: 37, −47, −11) and the identification of faces expressing negative emotions at both global (i.e., cumulative score obtained from the sum of negative emotions sub-scores; $r = -.68$, $p = .005$; Fig. 2) and specific levels (i.e., single emotion sub-scores; fear: $r = -.61$ $p = .04$; disgust: $r = -.51$, $p = .05$; anger: $r = -.50$, $p = .05$; sadness: $r = -.72$, $p = .008$).

Finally, in order to exclude the possibility that the correlation between microstructural properties along the right ILF/IFOF and the recognition of negative emotions observed in ALS patients was a simple reflection of a wider cognitive

impairment, we computed supplementary analyses on a smaller subgroup ($n = 14$), including only those patients who were both cognitively and behaviorally unimpaired (namely, the *pure* ALS subjects; see Paragraph 3.1 and Table 2). Overall, these analyses confirmed the main findings we highlighted in the main ALS subgroup ($n = 19$), by showing a significant association between the recognition of negative emotions and microstructural properties along the right ILF/IFOF. Indeed, in pure ALS patients the cumulative score of single negative emotions resulted positively correlated with mean FA values along both the right ILF ($r = .62$, $p = .05$) and IFOF ($r = .66$, $p = .03$), and negatively correlated to mean MO values extracted from the cluster we previously found associated with negative emotion recognition in the main ALS subgroup ($r = -.85$, $p = .002$).

4. Discussion

Non-motor alterations have been widely documented in non-demented ALS patients, since early stages of the disease (Abrahams et al., 1995, 2005). The refined characterization of the neuropsychological profile of ALS patients highlights a constellation of dysfunctions at both cognitive and behavioral levels (Consonni et al., 2013; Lillo et al., 2010; 2011; Phukan et al., 2012). These deficits, consistently observed in about 50% of ALS patients, generally mirror the typical bv-FTD syndrome (Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). Such findings provide further support to the large body of evidence indicating ALS and FTD as extremes of a disease continuum, ranging from conditions primarily involving the motor pathway to disorders in which cognitive and/or behavioral changes are predominant, and neurally associated with functional and structural frontotemporal damage. The neuropsychological overlap between ALS and bv-FTD also concerns impairments of the socio-emotional processing, like modifications of emotion perception and memory, emotional judgment and decision-making (Elamin et al., 2012; Girardi et al., 2011; Lulé et al., 2005; Palmieri et al., 2010; Papps et al., 2005), as well as alterations in the recognition of (negative) emotions from facial expression (Zimmerman et al., 2007). The ability to identify emotions in others is crucial for social understanding, and represents a prerequisite for the accurate attribution of emotional states in others, a skill that appear significantly compromised in a proportion of non demented ALS patients (Cerami et al., 2013). Our finding of a significant dysfunction in the overall ability to recognize emotions – and particularly the negative ones – from facial expressions stands in contrast to the results of Savage and coworkers (Savage et al., 2013), which reported preserved emotion processing in non-demented ALS patients. This inconsistency may be due to a difference in test material. The Ekman Caricature task used by Savage and colleagues is less demanding than the Ekman 60-Faces Test from a cognitive standpoint, as the amplification of the intensity of emotion expressions in the former reduces the amount of both attentional and perceptual resources needed to perform the latter (Kumfor, Irish, Hodges, & Piguet, 2013). It is thus possible that subtle deficits affecting socio-emotional processing in non-demented subjects may not be detected using the Caricature task. Additional factors which can account for diverging results are the variable vulnerability to cognitive changes characterizing ALS, associated with the limited size of the patient samples. It must be underlined that, as previously reported by our group (Cerami et al., 2013), social cognition impairments can occur independently of other cognitive deficits (in particular executive dysfunctions) in some ALS patients. This evidence is further complemented by volumetric brain imaging demonstrating specific grey matter reduction in fronto-limbic structures in non-demented ALS patients. Most importantly, we report for the first time the potential microstructural white-matter correlates underlying this impairment, which involve the right hemispheric ventral associative bundles, i.e., the ILF and the IFOF. From a functional standpoint, the ILF, linking occipital cortex with temporo-limbic regions, has been associated with several skills including, among others, face recognition (Catani & Thiebaut de Schotten, 2008). Moreover, the microstructural impairment of this bundle was reported as a common feature to conditions laying on the ALS-FTD continuum (Lillo et al., 2012). In addition, some suggestions have been advanced about the involvement of the IFOF in conscious vision. Briefly, this bundle would subserve a top-down modulation mechanism on the processing of visual information (Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012), facilitating detection and retrieval of the emotional value of percepts (Philippi et al., 2009). Our results show that the degree of orientation coherence of the diffusion along these bundles, measured as the global mean FA index, appears directly related to the accuracy in recognizing negative emotions in ALS patients. This means that low degrees of orientation coherence (i.e., low FA values in either the ILF or the IFOF) correspond to more severe impairments (i.e., low scores at the Ekman 60-Faces Task). In addition, beside the expected decrease in microstructural integrity in the bilateral cortico-spinal tract and corpus callosum in ALS patients compared to HC (Filippini et al., 2010), the change in the type of anisotropy observed along the ILF/IFOF, which is significantly correlated with the recognition of all negative emotions in patients, provides plausible evidence to support our *a priori* hypothesis. Additionally, in line with previous reports on brain-lesioned patients (Philippi et al., 2009), this neurostructural impairment mainly involves the right hemisphere. This evidence is also supported by a recent fMRI study (Palmieri et al., 2010), revealing altered functional asymmetry in ALS patients compared with controls. Namely, ALS subjects showed lateralized left-hemispheric activations in tasks entailing the processing of negative emotions, likely reflecting a compensatory mechanism. Finally, the supplementary correlation analysis performed on pure ALS patients further underlines the association between negative emotions and microstructural properties along the right ventral circuitry. Noteworthy, this evidence suggests that a decrease in the ability to recognize (negative) emotions from facial expressions can be independent from the presence/absence of cognitive and/or behavioral impairments. Taken together our findings suggest that the abnormal functioning of the right ILF and IFOF may be linked to the deficit displayed by ALS patients in recognizing negative emotions at both global and specific levels. Poor behavioral performance in (negative) emotion recognition in

ALS may thus reflect an incipient decrease of structural connectivity between right occipital face-responsive regions and fronto-limbic areas (amygdala, insula and orbitofrontal cortex), due to a damage affecting the integrity of the ventral circuitry. Importantly, the predominant deficit in the recognition of negative emotions exhibited even by ALS patients without dementia shows striking similarities with the profile traditionally reported in bv-FTD (Omar, Rohrer, Hailstone, & Warren, 2011), corroborating the continuum hypothesis. At the clinical level, the consistent evidence of social cognition impairments in ALS may have important implications for patients' management and caregivers' training during the whole course of the disease.

5. Conclusion

Despite a relatively small sample size, the present study confirms the early loss of white-matter integrity along the motor pathway in ALS and, most importantly, describes a possible neural correlate of emotion recognition impairment in non-demented sporadic ALS patients. This deficit appears independent from the presence of cognitive and/or behavioral impairments, and involves microstructural changes along the ventral associative bundles connecting occipital, temporo-limbic, and orbitofrontal regions in the right hemisphere, associated with the processing of facial expressions displaying negative emotions. Therefore, although further confirmations are required, such an emotion attribution deficit, correlated with subtle white-matter alterations within the fronto-limbic circuitry, may represent an early marker of social cognition impairment in non-demented ALS patients.

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