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Multimodal structural MRI in the diagnosis of motor neuron diseases

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ABSTRACT

This prospective study developed an MRI-based method for identification of individual motor neuron disease (MND) patients and test its accuracy at the individual patient level in an independent sample compared with mimic disorders. 123 patients with amyotrophic lateral sclerosis (ALS), 44 patients with predominantly upper motor neuron disease (PUMN), 20 patients with ALS-mimic disorders, and 78 healthy controls were studied. The diagnostic accuracy of precentral cortical thickness and diffusion tensor (DT) MRI metrics of corticospinal and motor callosal tracts were assessed in a training cohort and externally proved in a validation cohort using a random forest analysis. In the training set, precentral cortical thickness showed 0.86 and 0.89 accuracy in differentiating ALS and PUMN patients from controls, while DT MRI distinguished the two groups from controls with 0.78 and 0.92 accuracy. In ALS *vs* controls, the combination of cortical thickness and DT MRI metrics (combined model) improved the classification pattern (0.91 accuracy). In the validation cohort, the best accuracy was reached by DT MRI (0.87 and 0.95 accuracy in ALS and PUMN *vs* mimic disorders). The combined model distinguished ALS and PUMN patients from mimic syndromes with 0.87 and 0.94 accuracy. A multimodal MRI approach that incorporates motor cortical and white matter alterations yields statistically significant improvement in accuracy over using each modality separately in the individual MND patient classification. DT MRI represents the most powerful tool to distinguish MND from mimic disorders.

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset neurodegenerative disorder of the motor system characterized by upper (UMN) and lower motor neuron (LMN) degeneration, leading to progressive muscular paralysis and death (Kiernan et al., 2011). The El Escorial criteria for the diagnosis of ALS, which were established 20 years ago, are essentially clinical and rely on the detection of motor neuron signs in multiple body segments (Brooks et al., 2000). Although these guidelines have been repeatedly shown to be useful inclusion criteria for clinical trials, concerns have been raised regarding their use in clinical practice (Agosta et al., 2015; Belsh, 2000). The false-positive rate has been estimated to be as high as eight to 10%, while the false-negative rate approaches 45% (Davenport et al., 1996; Traynor et al., 2000). Furthermore, the average delay from the symptom onset to diagnosis is 12 months (Mitchell et al., 2010).

The use of magnetic resonance imaging (MRI) in patients suspected of having ALS is yet restricted to exclude other causes of signs and symptoms of motor neuron pathology (Filippi et al., 2010). However, the recent growing recognition of ALS as a diffuse central nervous system pathology has been a major driver of the application of advanced neuroimaging techniques to the study of the disease (Filippi et al., 2015). Structural MRI detects *in vivo* both grey matter (GM) and white matter (WM) alterations associated with ALS, providing potential reliable diagnostic markers of the disease (Chiò et al., 2014; Menke et al., 2017). A pathological hallmark of ALS is the atrophy of the primary motor cortex, and numerous studies have detected bilateral precentral gyrus thinning in ALS patients (Agosta et al., 2012; Schuster et al., 2013; Verstraete et al., 2011). Degeneration of the corticospinal tracts (CST) and body of the corpus callosum (CC) represents another

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disease-defining signature (Agosta et al., 2014; Agosta et al., 2010; van der Graaff et al., 2011), particularly in patients with a predominant UMN (PUMN) variant (Agosta et al., 2014; Iwata et al., 2011; Unrath et al., 2010).

Increasing attempts have been made to test the diagnostic accuracy of structural MRI measures in ALS. Precentral gyrus thickness showed a good accuracy in distinguishing ALS from healthy controls (Agosta et al., 2012; Verstraete et al., 2011; Walhout et al., 2015). Diffusion Tensor (DT) MRI measures in small subject cohorts provided good discrimination between ALS and controls (Agosta et al., 2014; Graham et al., 2004; Nelles et al., 2008). However, these studies reported results at a group level, raising the question of the applicability of such measures in clinical settings. An individual patient data meta-analysis of CST fractional anisotropy (FA) revealed its diagnostic power to be modest relative to healthy controls (Foerster et al., 2013). This disappointing finding may result from the heterogeneity of both the methodology and patient populations but it may also suggest that a single MR technique lacks sufficient diagnostic power. A multimodal neuroimaging approach may be a strategy to improve accuracy (Douaud et al., 2011; Foerster et al., 2014; Schuster et al., 2016). A model incorporating the cortical thickness of the precentral gyrus and DT MRI measures of the CST and CC was able to discriminate ALS and healthy controls with good sensitivity (85.7%) and accuracy (78.4%) (Schuster et al., 2016). However, almost all previous MRI studies have recruited healthy controls as reference group to identify ALS-specific abnormalities, while a comparison with ALS-mimic disorders is mandatory to test the specificity of these markers.

The aims of this study were: to develop a method for individual identification of motor neuron disease (MND) patients using multimodal structural MRI data of ALS-specific anatomical regions (*i.e.*, precentral cortical thickness and DT MRI metrics of motor WM tracts), and to test the validity of such an approach in an independent patient cohort relative to subjects with ALS-mimic disorders.

2. Methods

2.1. Subjects

All patients were consecutively recruited at three tertiary referral MND Clinics in Northern Italy and underwent a comprehensive evaluation including neurological history, neurophysiological assessment, genetic analysis, and MRI. The main sample consisted of 167 right-handed patients with MND (123 patients with ALS and 44 patients with PUMN), including 17 ALS cases carrying a genetic mutation (11 with hexanucleotide repeat expansions in chromosome 9 open reading frame 72, two with a TARDBP mutation, three with a SOD1 mutation, and one with a FUS mutation) (Table 1). Diagnosis of classic ALS was made according to the revised Escorial criteria (Brooks et al., 2000). Patients with a clinical PUMN phenotype did not have any LMN sign on clinical assessment or any evidence of active denervation on repeated electromyographical examinations (Chio et al., 2011). In the PUMN sample, 33 cases had a disease duration ≥ 3 years and were therefore diagnosed with primary lateral sclerosis (PLS) (Pringle et al., 1992). An additional sample of 20 patients with ALS-mimic disorders (Traynor et al., 2000) was enrolled (Table 1). This group included 13 patients with spinobulbar muscular atrophy (Kennedy's Disease), two patients with multifocal motor neuropathy with conduction blocks, two patients with chronic sensorimotor polyneuropathy, two patients with lumbar radiculopathy, and one case with distal spinal muscular atrophy. Prior to diagnosing a mimic disorder, these patients had been referred to our centers because of a clinical suspicion of ALS. Experienced neurologists blinded to the MRI results performed the clinical assessment. Site of disease onset and disease duration were recorded. Disease severity was assessed using the ALS Functional Rating Scale-revised (ALSFRS-r). The rate of disease progression was calculated as follows: (48–ALSFRS-r score)/time from symptom onset. 72 ALS, 35 PUMN and 14 ALS-mimic patients underwent cognitive and behavioral evaluations following published recommendations (Montuschi et al., 2015; Phukan et al., 2012), as previously described (Agosta et al., 2016).

In addition, data were acquired in 78 right-handed, age-matched healthy controls who were recruited among spouses of patients and by word of mouth (Table 1). Healthy controls were included if the neurological assessment was normal and the Mini-Mental State Examination was ≥ 28. Patients and controls were excluded if they had: significant medical illnesses or substance abuse that could interfere with cognitive functioning; any (other) major systemic, psychiatric, or neurological illnesses; and (other) causes of focal or diffuse brain damage, including lacunae, and extensive cerebrovascular disorders at routine MRI. Approval was obtained from the local ethical standards committee on human experimentation and written informed consent from all subjects (or their legal guardians) before enrolment.

2.2. MRI study

2.2.1. MRI protocol

Using a 3.0 Tesla Philips Intera scanner, the following brain MRI sequences were acquired: *T2*-weighted spin echo; fluid-attenuated inversion recovery; 3D T1-weighted fast field echo (FFE); and pulsed-gradient spin echo, echo planar with sensitivity encoding and diffusion gradients applied in 32 noncollinear directions (Agosta et al., 2014).

2.2.2. Cortical thickness measurement

Cortical reconstruction and estimation of cortical thickness were performed on the 3D T1-weighted FFE images using the FreeSurfer image analysis suite, version 5.3 (http://surfer.nmr.mgh.harvard.edu/). After registration to Talairach space and intensity normalization, the

Table 1
Demographic and clinical findings of healthy control subjects, and ALS, PUMN and mimic disorder patients.

	Healthy controls	ALS patients	PUMN patients	ALS-mimic patients	p ALS *vs* HC	p PUMN *vs* HC	p ALS *vs* PUMN	p ALS *vs* ALS-mimic	p PUMN *vs* ALS-mimic
Number	78	123	44	20	–	–	–	–	
Age (years)	63.23 ± 8.90	63.49 ± 10.07	62.99 ± 8.22	55.85 ± 10.31	0.85	0.88	0.77	0.002	0.004
Sex (W/M)	45/33	64/59	23/21	2/18	0.43	0.56	0.98	< 0.001	0.001
Site of onset (bulbar / limb / bulbar + limb)	–	40/81/2	6/38/0	0/20/0	–	–	0.02	0.002	0.16
Disease duration (months)	–	19.28 ± 16.94	80.16 ± 56.81	118.24 ± 64.54	–	–	< 0.001	< 0.001	< 0.001
ALSFRS-r	–	38.14 ± 6.88	36.67 ± 6.49	42.17 ± 1.34	–	–	0.23	0.046	0.01
Rate of disease progression	–	0.75 ± 0.70	0.29 ± 0.48	0.05 ± 0.02	–	–	< 0.001	< 0.001	0.10
No CI or BI/CI or BI/MND-FTD	–	37/30/5	17/18/0	7/7/0	–	–	–	–	–

Values are means ± standard deviations or number. *p* values refer to Fisher exact test or ANOVA models, followed by *post hoc* pairwise comparisons. Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-r = ALS functional rating scale-revised; BI = behavioral impairment; CI = cognitive impairment; HC = healthy controls; M = men; MND = motor neuron disease; W = women.