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Interhemispheric connectivity in amyotrophic lateral sclerosis: A near-infrared spectroscopy and diffusion tensor imaging study

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ABSTRACT

Purpose: Aim of the present study was to investigate potential impairment of non-motor areas in amyotrophic lateral sclerosis (ALS) using near-infrared spectroscopy (NIRS) and diffusion tensor imaging (DTI). In particular, we evaluated whether homotopic resting-state functional connectivity (rs-FC) of non-motor associated cortical areas correlates with clinical parameters and disease-specific degeneration of the corpus callosum (CC) in ALS.
Material and methods: Interhemispheric homotopic rs-FC was assessed in 31 patients and 30 healthy controls (HCs) for 8 cortical sites, from prefrontal to occipital cortex, using NIRS. DTI was performed in a subgroup of 21 patients. All patients were evaluated for cognitive dysfunction in the executive, memory, and visuospatial domains.
Results: ALS patients displayed an altered spatial pattern of correlation between homotopic rs-FC values when compared to HCs ($p = 0.000013$). In patients without executive dysfunction a strong correlation existed between the rate of motor decline and homotopic rs-FC of the anterior temporal lobes (ATLs) ($\rho = -0.85$, $p = 0.0004$). Furthermore, antero-temporal homotopic rs-FC correlated with fractional anisotropy in the central corpus callosum (CC), corticospinal tracts (CSTs), and forceps minor as determined by DTI ($p < 0.05$).
Conclusions: The present study further supports involvement of non-motor areas in ALS. Our results render homotopic rs-FC as assessed by NIRS a potential clinical marker for disease progression rate in ALS patients without executive dysfunction and a potential anatomical marker for ALS-specific degeneration of the CC and CSTs.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease leading to paralysis of almost all voluntary muscles and eventually to death from respiratory failure. No curative treatment is currently available for this disease, with neither etiology nor pathogenesis being fully understood. There are, however, pathological, genetic, and clinical features that ALS shares with frontotemporal lobar degeneration (Irwin et al., 2015; Ng et al., 2015), which have led to the notion of ALS as a system failure of interconnected motor and extramotor neural networks. Disease related changes in functional and structural connectivity within the cerebral network have been investigated using different imaging modalities. Besides partial degeneration of the corticospinal tracts (CSTs) and the corpus callosum (CC), consistently reported by different groups employing diffusion tensor imaging (DTI) (Cardenas-Blanco et al., 2014; Chapman et al., 2014; Filippini et al., 2010), structural degeneration has also been observed in frontotemporal areas associated with cognition or behavior (Kasper et al., 2014). Indeed, in a recent neuropsychological study clinically overt cognitive dysfunction was observed in as many as 40% of ALS patients having no evidence of comorbid frontotemporal dementia (FTD) (Phukan et al., 2012). Moreover, cognitive dysfunction in the executive

Abbreviations: AC, anterior commissure; ALS, amyotrophic lateral sclerosis; ALS-EX, ALS with executive impairment; ALSFRS-R, revised ALS functional rating scale; ALS-NECI, ALS with non-executive cognitive impairment; ATL, anterior temporal lobe; CC, corpus callosum; CST, corticospinal tract; DD, disease duration; DPR, disease progression rate; DTI, diffusion tensor imaging; FA, fractional anisotropy; FTD, frontotemporal dementia; fMRI, functional magnetic resonance imaging; Hb, hemoglobin; HC, healthy control; NIRS, near-infrared spectroscopy; pALS, pure ALS no cognitive impairment; rs-FC, resting-state functional connectivity; rs-fNIRS, resting-state functional NIRS; TBSS, tract based spatial statistics; WM, white matter.

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domain was found to be associated with shorter survival (Elamin et al., 2011). However, these studies have not yet resulted in clinically established disease markers, even though they have further corroborated extramotor involvement in what was initially considered a pure motor-neuron disease.

Degeneration of the CC is a consistent feature in ALS and may be involved in the early pathogenesis of the disease (Filippini et al., 2010). As the CC predominantly interconnects homologous cortical areas, we sought to establish whether there are ALS-related changes in homotopic functional connectivity. In particular, we investigated whether homotopic resting-state connectivity of extramotor cortical areas as assessed by near-infrared spectroscopy (NIRS) correlates with clinical parameters and CC degeneration, as reflected by reduced fractional anisotropy (FA) in DTI. NIRS is an established and easily applicable investigation. It is particularly suitable for clinical application as the lack of contraindications and task demand allows for application even in severely impaired patients and patients for whom magnetic resonance imaging is contraindicated. NIRS allows assessing the cortical concentrations of oxygenated and des-oxygenated hemoglobin and here may represent an alternative for technically challenging functional magnetic resonance imaging (fMRI) investigations, although at a significant lower spatial resolution.

2. Materials and methods

2.1. Subjects

Thirty-one patients with clinically definite or probable ALS according to the revised El-Escorial criteria (Brooks et al., 2000) were enrolled in this study. Diagnosis and clinical characteristics including site of onset, disease duration (DD), revised ALS Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999), and disease progression rate (DPR = (48-ALSFRS-R)/(DD in months)) (Kimura et al., 2006) were ascertained by an experienced neurologist specialized in ALS. Patients fulfilling the criteria for frontotemporal dementia were excluded (Rascovsky et al., 2011). The local ethics committee approved the study and written informed consent from all subjects was obtained prior to enrollment.

All patients underwent neuropsychological classification and resting-state functional NIRS (rs-fNIRS). DTI was performed in 21 patients, while 8 patients met the exclusion criteria for this imaging modality (i.e. metal implants, pacemaker or tinnitus). Two patients could not undergo DTI because of difficulties in swallowing and breathing, respectively. Thirty healthy age- and gender-matched participants were recruited as healthy controls (HCs) for NIRS. Clinical and demographic characteristics of the study population are summarized in Table 1.

2.2. Neuropsychological assessment

In the patient group, a comprehensive neuropsychological test battery was applied to evaluate disease-related impairment in different cognitive domains (Machts et al., 2014). Executive dysfunction was assessed with the Trail Making Test, the Regensburg Word Fluency Test, and the Backward Digit Span Test; memory dysfunction with the Digit Span Test and the Verbal Learning and Memory Test (German equivalent of the Rey auditory verbal learning test) or the short version of the California Verbal Learning Test; and visuospatial dysfunction with the Rey-Osterrieth Complex Figure Test. Impairment in the domains of memory and executive function was assumed if scores in at least 2 of the respectively associated tests were below the 5th percentile of a healthy reference population. Dysfunction in the visuospatial domain was established solely based on the Rey-Osterrieth Complex Figure Test. Adapting the classification scheme suggested by Phukan et al. (2012) each patient was assigned to one of three mutually exclusive groups (Table 1, for individual neuropsychological scores see Supplementary Table 1): pALS (pure ALS, no cognitive impairment), ALS-EX (executive impairment), and ALS-NECI (non-executive cognitive impairment, i.e. memory or visuospatial impairment).

2.3. Near-infrared spectroscopy

rs-fNIRS was performed using a multi-channel continuous wave device (ETG-4000; Hitachi Medical Corporation, Tokyo, Japan) employing near-infrared light at 2 wavelengths (695 and 830 nm). Two rows of 8 measurement sites, arranged mirror-symmetrically about the mid-sagittal plane at the level of the temporal lobes, were used to allow for evaluation of 8 homotopic connections (Sasai et al., 2011). Spontaneous changes in concentration of oxy- and deoxy-hemoglobin (Hb) were recorded over a period of 20 min (sampling rate 10 Hz) with participants in supine position with eyes closed. Measurement sites, each defined by a light emitter/detector pair, were located relative to 5 anatomical landmarks (nasion, inion, right and left pre-auricular point, and Cz) using an electro-magnetic digitizer system (Polhemus ISOTRAK II, Inition, London), then probabilistically mapped into MNI152 space (Montreal Neurological Institute, McGill University, Canada) for visualization (Fig. 1) (Singh et al., 2005).

2.4. Diffusion tensor imaging

Twenty-one patients (9 pALS, 7 ALS-EX, 5 ALS-NECI) underwent DTI on a Siemens Magnetom Verio 3T system with a standard 32-channel phased array imaging head coil (Siemens Medical Systems, Erlangen, Germany). Scans were acquired by single-shot, spin-echo, echo-planar imaging with a twice-refocused echo-sequence (FOV = 256 × 256 mm^2, 128 × 128 acquisition matrix, slice thickness = 2 mm, TR = 12,700 ms, TE = 81 ms, receiver bandwidth = 1628 Hz/pixel, echo spacing = 0.72 ms, 1 non diffusion-weighted scan, 30 diffusion gradient directions, b = 1000 s/mm^2, 2 averages).

2.5. Data pre-processing

2.5.1. Homotopic rs-fNIRS connectivity

For each homotopic connection functional resting state connectivity (rs-FC) was determined by means of squared coherence between the

Table 1
Demographic and clinical data[c].

	Patients				Controls	*p*
	all	pALS	ALS-EX	ALS-NECI		
n	31	14	11	6	30	
Mean age (years)	61.4 ± 12.1	59.8 ± 11.8	63.0 ± 15.2	62.3 ± 6.8	62.6 ± 9.9	0.85[a]
Gender (male:female)	16:15	7:7	6:5	3:3	14:16	0.97[b]
ALSFRS-R	36.5 ± 5.4	38.1 ± 5.5	35.6 ± 4.0	34.5 ± 7.0	N/A	N/A
DPR	0.5 ± 0.37	0.32 ± 0.22	0.69 ± 0.42	0.58 ± 0.38	N/A	N/A
Site of onset (bulbar: limb:both:unknown)	9:19:2:1	4:10:0:0	2:6:2:1	3:3:0:0	N/A	N/A

[a] and [b] denote the *p*-values for the ANOVA and Pearson's Chi-square test, respectively.
[c] ALSFRS-R denotes revised amyotrophic lateral sclerosis functional rating scale, DPR disease progression rate, pALS ALS without cognitive impairment, ALS-EX ALS with executive impairment, ALS-NECI ALS with non-executive cognitive impairment.