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Cortical thinning and its relation to cognition in amyotrophic lateral sclerosis

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ABSTRACT

Clinical, genetic, and pathological findings suggest a close relationship between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). We studied the patterns of cortical atrophy across the spectrum between ALS and ALS-FTD. A surface-based morphometry analysis based on an age- and sex-matched sample of 81 ALS patients and 62 healthy control subjects (HC) was conducted. In addition, we used an age-matched subsample of 57 ALS patients and 31 HC to compare cortical thickness between 3 groups of neuropsychologically characterized ALS patients: (1) cognitively unimpaired; (2) cognitively impaired; and (3) ALS-FTD patients. Compared with HC, the entire sample of patients demonstrated cortical thinning in the bilateral precentral gyrus, right precuneus, and right frontal and temporal lobes. ALS-FTD patients showed cortical thinning in regions including the frontal and temporal gyri and the posterior cingulate cortex. Cognitively impaired ALS patients showed cortical thinning in regions largely overlapping with those found in ALS-FTD, but changes were less widespread. In conclusion, the cognitive status of ALS subjects is associated with different patterns of cortical atrophy.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder resulting in progressive muscle weakness (Talbot, 2009). Motor symptoms might be accompanied by a spectrum of cognitive impairments ranging from mild impairment to severe frontotemporal dementia (FTD). Cognitive impairment is present on neuropsychological testing in approximately 50% of patients (Phukan et al., 2007; Ringholz et al., 2005).

This high prevalence of cognitive impairment in ALS is in accordance with neuropathological, genetic, and neuroimaging findings that suggest a continuum between ALS and FTD (Chang et al., 2005; DeJesus-Hernandez et al., 2011; Lillo et al., 2012; Neumann et al., 2006; Renton et al., 2011; Tsermentseli et al., 2011; Whitwell et al., 2006).

Structural magnetic resonance imaging (MRI) allows determination of morphological correlates of neurodegeneration in vivo. A sensitive measure of cortical atrophy is cortical thickness, expressed in a biologically meaningful metric (thickness in mm). Patients with FTD show a characteristic pattern of cortical thinning in the temporal and frontal lobes. The progression of cortical thinning is associated with disease severity and its pattern is consistent with the clinical deficits in FTD (Du et al., 2007; Rohrer et al., 2009). Most studies that examined cortical atrophy in ALS have used voxel-based morphometry (VBM) of gray matter density. Several found gray matter reduction in the motor cortex (for a summary see the supplementary data in Verstraete et al., 2012). Only a few studies have analyzed the cortical thickness in ALS patients using a surface-based approach, all of them revealing a significant thinning of the precentral gyrus (Agosta et al., 2012; Kwan et al., 2013; Roccatagliata et al., 2009; Verstraete et al., 2012). In addition, thinning of the temporal lobe (Verstraete et al., 2012) or the left sensorimotor cortex (Agosta et al., 2012) were associated with rapid disease progression. However, the association between morphological and cognitive changes in ALS has, to date, received little attention (Turner et al., 2012).

In the present study we investigated a large group of ALS patients and healthy age- and sex-matched control subjects to determine the association between cortical thinning and the degree of cognitive

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Table 1
Demographic and clinical features

	HC, $n = 62$	ALS, $n = 81$	HC, $n = 31$	ALSnci, $n = 25$	ALSci, $n = 24$	ALS-FTD, $n = 8$
Male sex, *n*	37	53	19	8	8	5
Age, y (mean/SD)	62.4/10.6	59.6/10.9	64.3/8.9	61.4/9.1	65.5/9.1	68.6/6.1
Handedness (right/left/ambidextrous)	57/2/3	77/4/0	29/1/1	24/1	22/2	8/0
Duration of disease, mo (mean/SD)		27.5/24.7		25.4/20.7	26.4/26.3	18.3/11
Type of onset, *n*						
Bulbar/spinal		27/54		5/20	9/15	5/3
El Escorial diagnostic category, *n*						
NA/possible/probable/definitive		13/13/42/13		4/3/14/4	3/6/12/3	2/1/3/2
Phenotype						
Classical/UMN/LMN		57/8/16		16/1/8	18/4/2	6/1/1
ALSFRS-R, mean ± SD		37.7 ± 6.5		35.5 ± 7.5	39.2 ± 5.5	38.6 ± 8.1
Bulbar subscore, mean ± SD		9.9 ± 2.5				
Progression rate, mean ± SD		0.55 ± 0.38		0.62 ± 0.33	0.56 ± 0.43	0.61 ± 0.48

The first HC group refers to the control group compared with the entire ALS cohort. The second HC group, a part of the previous HC group, was selected to match for the subgroup analysis.
Key: ALS, patients with amyotrophic lateral sclerosis; ALSci, amyotrophic lateral sclerosis patients with cognitive impairment; ALSFRS-R, ALS Functional Rating Scale-Revised; ALS-FTD, amyotrophic lateral sclerosis patients with additional diagnosis of frontotemporal dementia; ALSnci, amyotrophic lateral sclerosis patients with no cognitive impairment; HC, healthy control subjects; LMN, lower motor neuron variants; NA, not assigned; UMN, upper motor neuron variants.

impairment in ALS. We expected a more widespread pattern of cortical thinning in subgroups of ALS with cognitive impairment or FTD compared with cognitively unimpaired ALS patients.

2. Methods

2.1. Subjects

The sample consisted of 81 ALS patients recruited from the university hospitals in Rostock and Magdeburg. An age- and sex-matched healthy control group (HC) of 62 participants was recruited though public advertisement in both cities. Exclusion criteria were a history of brain injury, epilepsy, or a psychiatric illness. Additionally, healthy control subjects with a score lower than 26 of 30 in the Montreal Cognitive Assessment (Nasreddine et al., 2005) were excluded. All MRI scans were visually inspected by a radiologist to rule out major neuropathologies such as tumor, stroke, or advanced white matter disease. All patients were diagnosed according to the revised El Escorial criteria (Brooks et al., 2000), characterized using the ALS Functional Rating Scale (ALSFRS-R; Cedarbaum et al., 1999) and the disease progression rate since symptom onset to the time of testing was calculated (48 − ALSFRS-R/disease duration in months; Ellis et al., 1999).

The classification of ALS-FTD patients was done according to Rascovsky et al. (2011) and Gorno-Tempini et al. (2011), resulting in 3 patients with a possible behavioral variant FTD (bvFTD), 2 patients with a probable bvFTD, 2 patients with a definite bvFTD, and 1 patient with a nonfluent/agrammatic variant primary progressive aphasia.

The demographic data and clinical characteristics are reported in Table 1. The first part of the table refers to the overall analysis of patients versus healthy control subjects; the second, to the subgroup comparison for which groups were again age and sex-matched, resulting in the exclusion of some participants (for more information see 3.1.).

All participants gave written informed consent. The study was approved by the local medical ethics committees and conducted according to the Declaration of Helsinki.

2.2. Data acquisition

2.2.1. Neuropsychological assessment

Patients and healthy control subjects underwent a comprehensive neuropsychological test battery administered by 2 psychologists from both sites. All examiners tested healthy control subjects and patients. The test battery assessed executive functioning, memory, language, and visuospatial abilities, lasted approximately 90 minutes, and was adapted to speech and motor incapabilities by implementing tempo-independent (e.g., ratios) or tempo-adjusted parameters (e.g., the fluency index; Abrahams et al., 2000; see Table 2 for a complete list of administered tests).

Categorization of ALS patients was made according to Strong et al. (2009) and Phukan et al. (2012). Cognitive impairment was defined as follows. Patients who scored less than 2 standard deviations compared with age- and education-matched control subjects on at least 2 distinct subfunctions from 1 cognitive domain were considered impaired in this domain. For the language domain and for the visuospatial skills, only 2 tests were conducted. Therefore, patients were categorized as impaired if their performance in both tests was classified as impaired (Phukan et al., 2012). Patients with a frontotemporal syndrome who did not fulfill the criteria for frank FTD were classified as ALSci.

2.2.2. MRI

All data were acquired with two 3T Siemens Magnetom Verio Scanners (Siemens, Erlangen, Germany; software, syngo MR B17) in Rostock and Magdeburg using a 32-channel head coil. T1-weighted, high-resolution structural MRI volumes of the brain were scanned using a 3-D magnetization-prepared rapid gradient-echo sequence (echo time (TE) = 4.82 ms, repetition time (TR) = 2500 ms, inversion time (TI) = 1100 ms, flip angle = 7°, bandwidth = 140 Hz per pixel, matrix = 256 × 256 × 192, isometric voxel size = 1.0 mm^3).

2.3. Data analysis

2.3.1. Neuropsychological assessment

Based on the neuropsychological testing, 45 patients showed no cognitive impairment (ALSnci), 28 patients were cognitively impaired in at least 1 cognitive domain (ALSci), and 8 patients were diagnosed as ALS-FTD. The ALSnci group was significantly younger. A previous study of healthy participants showed a specific anatomical pattern of age-associated cortical thinning consisting of prominent atrophy of the frontal cortex near the primary motor and premotor areas in addition to relative sparing of the temporal cortex and the parahippocampal gyrus (Salat et al., 2004). An association between age and cortical thinning has been found to be even stronger in ALS patients (Agosta et al., 2012). Therefore, to rule

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