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Structural and functional hallmarks of amyotrophic lateral sclerosis progression in motor- and memory-related brain regions

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ABSTRACT

Previous studies have shown that in amyotrophic lateral sclerosis (ALS) multiple motor and extra-motor regions display structural and functional alterations. However, their temporal dynamics during disease-progression are unknown. To address this question we employed a longitudinal design assessing motor- and novelty-related brain activity in two fMRI sessions separated by a 3-month interval. In each session, patients and controls executed a Go/NoGo-task, in which additional presentation of novel stimuli served to elicit hippocampal activity. We observed a decline in the patients' movement-related activity during the 3-month interval. Importantly, in comparison to controls, the patients' motor activations were higher during the initial measurement. Thus, the relative decrease seems to reflect a breakdown of compensatory mechanisms due to progressive neural loss within the motor-system. In contrast, the patients' novelty-evoked hippocampal activity increased across 3 months, most likely reflecting the build-up of compensatory processes typically observed at the beginning of lesions. Consistent with a stage-dependent emergence of hippocampal and motor-system lesions, we observed a positive correlation between the ALSFRS-R or MRC-Megascores and the decline in motor activity, but a negative one with the hippocampal activation-increase. Finally, to determine whether the observed functional changes co-occur with structural alterations, we performed voxel-based volumetric analyses on magnetization transfer images in a separate patient cohort studied cross-sectionally at another scanning site. Therein, we observed a close overlap between the structural changes in this cohort, and the functional alterations in the other. Thus, our results provide important insights into the temporal dynamics of functional alterations during disease-progression, and provide support for an anatomical relationship between functional and structural cerebral changes in ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive muscular weakness and atrophy. Although the degeneration of upper and lower motor neurons is the pathological hallmark of the disease, several studies indicated that ALS is a multisystem disorder that also affects cognitive domains (Agosta et al., 2010; Raaphorst et al., 2010; Tsermentseli et al., 2012). Concordantly, neurodegenerative changes beyond the motor-system have been reported (Anderson et al., 1995; Grosskreutz et al., 2006; Kato et al., 1997; Neumann et al., 2006; Takeda et al., 2009; Wightman et al., 1992).

Besides such structural changes, functional alterations related to ALS have also been observed across multiple motor and extra-motor regions using a variety of different tasks (for recent review see Tsermentseli et al., 2012). Most studies observed increased activations of sensorimotor areas and/or recruitment of additional regions, which was interpreted as functional compensation or reorganization within the motor-system (Kew et al., 1993; Kollewe et al., 2011; Konrad et al., 2002; Mohammadi et al., 2011; Schoenfeld et al., 2005). However, some studies also found an activation decrease of sensorimotor and premotor areas (Mohammadi et al.,

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2011; Tessitore et al., 2006). One major reason for these controversial findings refers to the heterogeneity of the patient populations especially with regard to their particular disease stage during the time of study. Bearing this in mind, it is important to note that neurodegenerative alterations and therewith—interrelated functional loss or compensatory processes are certainly subject to change during progression of the disease. Thus, to identify patterns of functional alterations and their putative modifications during ALS disease-progression, it is indispensable to perform longitudinal within-subject investigations. The present study was designed to directly address such progression-related functional changes in motor and cognitive functions. To this end, brain activity in fourteen ALS patients and fourteen healthy controls was studied in two fMRI sessions separated by a 3-month interval, employing a simple Go/NoGo-task, in which the additional presentation of task-irrelevant novel stimuli allowed for assessment of novelty-related hippocampal activity.

In addition, to assess the relationship between functional and structural changes emerging during ALS disease-progression, we performed cross-sectional voxel-based morphometric (VBM) analyses on structural volumes acquired with magnetization transfer imaging in an independent, but socio-demographically comparable sample of 26 ALS patients and 28 controls. The magnetization transfer ratio of tissues depends on the surface chemistry and biophysical dynamics of macromolecules, as well as their tissue concentration (Cosottini et al., 2011; Eckert et al., 2004; Kato et al., 1997; Muller-Vahl et al., 2009; Wolff and Balaban, 1994). As such it has been shown to be strongly associated with tissue integrity (Grossman et al., 1994) and reduced magnetization transfer ratios have therefore repeatedly been suggested to mirror microstructural alterations like gliosis and changes in axonal density possibly related to early-stage neurodegenerative phenomena (Eckert et al., 2004; Kiefer et al., 2009; Perez-Torres et al., 2014; Ridha et al., 2007).

2. Materials and methods

2.1. Subjects

Two patient samples with sporadic ALS were recruited from the ALS outpatient clinics of the departments of Neurology at the Medical School Hannover and at the Medical School of the Otto-von-Guericke University Magdeburg. All patients met the criteria for probable or definitive ALS as defined by the El Escorial diagnostic criteria for ALS (Brooks et al., 2000) and had either a limb or bulbar onset. Exclusion criteria were other neurological conditions that could affect motor performance and cognition (e.g. stroke, traumatic brain injury). The first sample of fourteen patients took part in the fMRI experiment. The second sample of twenty-six patients participated in the VBM study. All participants underwent clinical examination on the day of study with active follow-up. Disease severity was assessed using the revised ALS Functional Rating Scale (ALSFRS-R; Cedarbaum et al., 1999). Disease duration was defined as time in months between symptom onset and the date of the experiment. From these measures the disease-progression rate was then calculated as (48 − ALSFRS-R)/disease duration (Ellis et al., 1999). In addition, the neuromuscular impairment was quantified by the five-point Medical Research Council (MRC) scale. 15 muscles were tested on the right and left for a maximum score of 150 (sternocleidomastoids, shoulder abductors and adductors, elbow flexors and extensors, wrist flexors and extensors, long finger flexors, thumb opponent, finger abductors and adductors, hip flexors, knee flexors and extensors, and ankle dorsiflexors). Good reliability and reproducibility for manual muscle testing in patients with ALS have previously been shown (Great lakes ALS Study Group, 2003; Andres et al., 1988). Furthermore, a detailed neuropsychological assessment lasting about 2 h was performed during the baseline visit in the first sample of fourteen patients who took part in the fMRI experiment.

Forty-two healthy individuals similar to the patients in age and gender were recruited as controls. Twenty-eight of the subjects were included in the VBM study and the remaining fourteen took part in the fMRI experiment. Ethical approval for all procedures was obtained prior to study (Vote number 11/06-75/11, Ethical committee of the Medical Faculty of the Otto-von-Guericke University, Magdeburg) and all participants gave written informed consent before participation. All experimental procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Subject demographics and all relevant clinical data are shown in Table 1.

2.2. Neuropsychological assessment

For neuropsychological assessment a range of standardized neuropsychological tests were employed (see Table 2). Verbal memory performance was tested using the VLMT, a German version of the Rey Auditory Verbal Learning Task (Lezak et al., 2004), and non-verbal memory using the Rey Complex Figure Test (Shin et al., 2006). Furthermore, we measured the Digit Span and the Visual Memory Span (Lezak et al., 2004). To address executive frontal functions, the Ruff Figural Fluency Test (Ruff et al., 1987), the Trail-making Test (Soukup et al., 1998), the Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000), and the copy subtest of the Rey Complex Figure Test were employed. Attention was assessed using the d2 attention test (Brickenkamp and Zillmer, 1998). Deficient verbal memory performance was defined as abnormal performance (<2 standard deviations compared to an age matched reference population) in ≥2 different memory tasks (Phukan et al., 2012). Executive dysfunction was defined as an abnormal performance in ≥2 different executive tests (Strong et al., 2009). Adjustments were made

Table 1
Participant demographics and clinical features.

	VBM study		fMRI experiment	
	ALS patients	Healthy controls	ALS patients	Healthy controls
Gender (M/F)	13/13	13/15	13/1	13/1
Age (years)	60.4 ± 2.2a,c (30-86)	60.1 ± 1.9a,d (33-78)	60.3 ± 3.1b,c (39-76)	59.7 ± 3.3b,d (42-79)
Disease duration (months)	23.8 ± 4.8(6–120)	NA	18.3 ± 3.1 (6-49)	NA
Site of onset (spinal/bulbar)	22/4	NA	11/3	NA
ALSFRS-R	36.2 ± 1.2(20-46)	NA	38.2 ± 1.3 (26-44)	NA
MRC-Megascore	NA	NA	130.9 ± 5.1 (79-150)	NA
Rate of disease-progression	0.74 ± 0.09 (0.13–2.0)	NA	0.66 ± 0.09 (0.22–1.5)	NA

Data for the subjects' age, disease duration, ALSFRS-R, MRC-Megascore, and the rate of disease-progression are presented as mean ± standard error of the mean. Abbreviations: ALSFRS-R, revised ALS Functional Rating Scale; MRC, Medical Research Council.
Two-sample t-tests
[a] $T(1,52) = 0.08$, $p > 0.9$;
[b] $T(1,26) = 1.45$, $p > 0.1$;
[c] $T(1,38) = 0.02$, $p > 0.9$;
[d] $T(1,40) = 1.79$, $p > 0.1$.