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**Neuroimaging of multimodal sensory stimulation in
Amyotrophic Lateral Sclerosis (ALS)**

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ABSTRACT

Aim: Structural and functional imaging techniques were combined to investigate sensory system function in amyotrophic lateral sclerosis (ALS).

Methods: Functional magnetic resonance imaging (fMRI) was used to investigate cortical activity during visual, auditory, and somato-sensory stimulation in fourteen ALS patients and eighteen control subjects. Changes in amplitude, latency and duration of the BOLD response were modelled. Furthermore, diffusion tensor imaging was used to investigate changes in white matter networks.

Results: During visual stimulation, fMRI demonstrated a decreased response in secondary visual areas in ALS possibly related to demyelination of sensory nerve fibres. Increasing brain activity in associative cortices was linked to decrease in physical functioning and might represent a compensatory process. Additionally, reduced white matter functioning became evident for fibres projecting to extra-striate visual cortex.

For auditory stimulation, a delayed response in secondary auditory areas probably linked to prolonged nerve conductance time and an altered cortical pattern in areas involved in target processing/detection became evident in ALS patients. Structural white matter changes in the primary and secondary auditory cortices were observed.

For somato-sensory stimulation a prolonged/reduced response in sensory integration areas of the parietal lobe was observed perhaps linked to the reduced visceral inflow due to immobility.

Conclusion: Multiparametric MRI suggests a progressive functional deficit in secondary/higher order sensory processing areas in ALS, probably associated with reduction of re-afferent information flow due to progressive immobility. The changes described might as well represent an expression of the disease process itself. Evidence for compensatory processes in multimodal associative cortices was found.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disease of the upper and lower motor neurons. There is ample evidence for degeneration not restricted to the motor system.[1] In different groups of ALS patients, alterations in non-motor areas were observed by volumetric/morphometric studies [2, 3] and in histopathological studies. [4, 5] Electrophysiological evidence for functional alterations of the sensory system such as slower nerve fibre conductance was provided [5, 6], probably associated with demyelination. A reduced and delayed response to auditory and visual stimuli was observed in early sensory cortical processing areas in ALS patients. [7, 8] Clinically, a subgroup of patients reports sensory symptoms (22% with numbness and neuropathic pain) and abnormalities on sensory examination (20% with diminished vibration sense). [5] The electrophysiologic and pathologic findings indicate a pattern of demyelination and axonal loss in the sensory systems which may occur independently of motor system degeneration.

Evidence for non-neuronal cell involvement in ALS such as in astrocytes increased over the last years.[9] Decreased glutamate uptake by astrocytes results in motor-neuron overload and finally in terminal retraction of the neuron from the effector i.e. the muscle.[10] Similar mechanisms can be expected for other glutamatergic neurons e.g. in the sensory systems.

The pathological findings in the sensory system may as well be a result of reduced external information flow due to progressive immobility in ALS (less movement causes less information about body part positions to be processed in the brain) following the concept of the 'somatic marker hypothesis'. [11]

In order to further investigate functional and structural changes in the sensory pathway in ALS, functional magnetic resonance imaging (fMRI) in the present study measured activity patterns of the brain during multimodal sensory stimulation (visual, auditory and tactile stimuli) in ALS patients and controls. Diffusion tensor imaging (DTI) was used to analyse alterations of fibre tracks projecting into sensory processing areas.

The understanding of how the sensory brain changes in association with ALS may help us with some behavioural problems and perceptual deficits on the one hand, i.e. why patients without voluntary motor control have not been able to control

brain computer interfaces (BCIs).[12] On the other hand, progressive sensory deprivation may mark some of the motor-social deteriorations. A life less driven by external stimuli may contribute to the surprisingly high quality of life even in end-stage patients.[13]

MATERIAL AND METHODS

Participants

Fourteen ALS patients participated in the study (6 women and 8 men; mean age 54.7 ± 13 years, 39-67 range). Probable (N=7) or definite ALS (N=7) was diagnosed according to the revised El Escorial criteria (Brooks 1998). All cases were sporadic forms with spinal onset, none of the patients exhibited major bulbar symptoms.

Mean duration of the disease was 28.0 ± 26.8 months (range 4-96 months), as determined by the onset of motor symptoms. Mean clinical severity of ALS was 33.4 ± 8.2 (range 18-44) as measured by the ALS functional ratings scale (revised form, ALSFRS-R);[14] all patients were still able to walk; two patients were intermittently treated by non-invasive positive pressure ventilation.

Neuropsychological tests were conducted to control for clinically relevant depression or major cognitive deficits, both of which were exclusion criteria (mini mental state examination cut-off score < 24 [15] and ALS Depression Index 12 items cut-off score > 28 , [16] respectively).

Eighteen healthy volunteers (11 women and 7 men) were age-matched (mean age 59.6 ± 8.3 , range 42-70, $T=1.26$ $p=0.22$).

In 10 of the ALS patients (mean age 52.6 ± 14.9 years, range 39-67), diffusion tensor imaging (DTI) measurements were acquired. Ten control subjects (mean age 53.7 ± 11.5 years, $T=0.22$ $p=0.83$) were matched for DTI patients. The other participants did not tolerate the additional measurements.

The participants were all right-handed. None of the patients and control subjects had a history of psychiatric disorder, and all were free of central nervous system medication. Twelve ALS patients received Riluzol for medication. This might have asthenia and sleepiness as a possible side effect. Neither was reported by the patients as a major impact on daily living.

The study was approved by the Ethics Committee of the University of Ulm, and all participants gave written informed consent for the study.

Magnetic resonance imaging (MRI)

Functional, anatomical and diffusion weighted images were acquired on a 1.5 Tesla whole body scanner (Symphony, Siemens, Erlangen, Germany). DTI measurements were performed subsequent to the fMRI measurements.

Functional magnetic resonance imaging (fMRI)

Functional images were collected in trials using T2*-weighted gradient echo planar imaging (EPI) sequences (echo time, TE=50 ms, time repetition, TR=2.82s, flip angle 90°). Thirty-two slices (3.5mm slice thickness, 0.5mm gap, in plane resolution of 3.59x3.59 mm², 64x64x32 voxel matrix) were acquired. Axial slice orientation aligned with the anterior-posterior commissure was chosen. The first 5 volumes of each sequence were discarded.

T1-weighted anatomical images were collected using a high resolution 3-D sequence (TE=3.9ms, TR=1740ms, flip angle 15°; voxels size 0.9x0.9x0.9mm³, 256x256x192 voxels).

Design

An event-related design was used optimised for maximal BOLD signal amplitude.[17] Stimuli were presented in blocks of 14s duration which consisted of stimulus epochs of 5s (three stimuli of about 1s interleaved by rest epochs of about 1s) and followed by a rest period of 9s. There were 26 stimulation blocks per trial. In total, three types of blocks were performed: in the first trial using a visual, in the second one an auditory and in the third a somato-sensory (tactile) paradigm. In the visual paradigm an alternating-checkerboard was presented via video goggles (flicker rate 0.3s). During the rest periods of the visual trial and during the total acoustic and tactile trials a black screen with a red fixation cross was presented. In the auditory part, 400 Hz sine wave tones were presented via headphones (50ms bursts every 500ms). Finally, a tactile stimulus was applied via a coil of 2 cm length fixated on the right index finger which vibrated with a frequency of 250 Hz (150ms bursts every 500ms). To keep the participant attentive during fMRI scanning, five slightly deviant stimuli were presented during each trial at pseudo random time instances (visual paradigm: contrast decreased from 100% to 50%; auditory paradigm: three 408 Hz or 392 Hz tones; tactile

paradigm: five 150 Hz bursts). After each trial the participants were asked how many deviant stimuli had been perceived (expected verbal response was 5). A two-way ANOVA was used to reveal group differences (ALS patients vs. controls) in target detection rate (deviant stimuli), and $p < 0.05$ (two-tailed) was adopted for statistical significance.

fMRI data analysis

Image processing was performed using SPM2.[18] Correction for temporal differences in acquisition time and for movements of the subject's head during scanning was applied. Functional data were co-registered with the anatomical scans, transformed into stereotactic space (Montreal Neurological Institute, MNI; http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html) and resampled to a 3 mm isometric voxel size. Data were smoothed with an isotropic Gaussian kernel (7.2 mm full width at half maximum). The time series of the BOLD data were modelled by general linear models (GLM).

Contrast images from an 'informed' basis set were used, consisting of the canonical hemodynamic response function (hrf) and its two partial derivatives with respect to time and dispersion.[19] The voxel time series were high-pass filtered (time constant 141 s) and the noise component in the model was described by a first-order autoregressive model.

Statistical analysis of fMRI data

Weighting factors of the sensory response regressors for each participant and trial were computed. Individual parametric maps (F-test uncorrected $p < 0.001$) were subjected to a second level group analysis between groups by use of a two-way ANOVA between groups for ALS patients vs. controls for the hrf and time and dispersion derivatives. The association between BOLD response (hrf alone) in every condition and level of functional impairment (ALSFRS score) was tested using a second level analysis of simple regression implemented in SPM2. Only areas with a significance of uncorrected $p < 0.001$ at voxel level and with a cluster threshold > 5 voxels were considered significant.

Diffusion tensor imaging (DTI)

Echo-planar imaging (EPI) MRI sequences were used. The DTI study protocol consisted of 13 volumes (45 slices, 128x128 pixels, slice thickness 2.2 mm, pixel size 1.5 mmx1.5 mm) representing 12 gradient directions and one scan with gradient 0 (TE=93ms, TR=8000ms, b-value=800s/mm²). Four scans were k-space averaged online by the Siemens standard DTI protocol.

Data analysis

DTI data were analysed using the tensor imaging and fiber tracking software (TIFT). [20] In DTI images, the amount of diffusion, the extent of directedness, and the spatial direction of proton displacement was quantified in the fractional anisotropy (FA).[21] Spatial normalisation using a template for each group was used following the protocol of Müller et al.[20] FA maps were arithmetically averaged for ALS patients and control subjects.

Smoothing of FA maps was performed with a 6 mm Gaussian kernel.[20] Voxels with FA-values<0.2 were defined as cortical grey matter). Group differences were analysed by t-test between groups, thresholded at uncorrected p<0.05 and a cluster-extension of 15 voxels. Further details of postprocessing are described in Müller et al.[20]

RESULTS

Neuropsychology

None of the participants met the exclusion criteria for dementia or depression (mean scores \pm standard deviation ALS patients: MMST=29.14 \pm 1.46; ADI-12=20.69 \pm 4.07; controls: MMST=29.2 \pm 1.15; ADI-12=18.00 \pm 4.42).

Performance of correct responses during sensory paradigms

Concerning correct response rates, ALS patients performed at the same level as controls in deviant target detection for visual (F=0.14 p=0.71) and auditory stimuli (F=0.14 p=0.71). For tactile stimuli, target detection was reduced in ALS patients, but the difference did not reach statistical significance (F=3.04 p=0.09).

Differences of BOLD response modelled with hrf between ALS patients and controls

For visual and somato-sensory stimulation, ALS patients presented no area with an increased BOLD response compared to control subjects. During auditory stimulation, ALS patients showed an increased BOLD activity in the caudate nucleus and in the middle frontal gyrus bilaterally (BA6; Table 1).

Healthy participants showed a higher BOLD activity for visual stimulation in the occipital lobe (V3a, BA19) of the right hemisphere and for auditory stimulation in the inferior frontal gyri of the right (BA45) and left hemispheres (BA6,9) compared to ALS patients (Table 1). Furthermore, a significantly higher BOLD activity was observed in the right-sided cerebellum of healthy compared to ALS patients. For somato-sensory stimulation, no difference became evident.

Experimental paradigm	Cluster size (voxel)	Anatomic Areas	Brodmann Area	MNI coordinates [mm]				
				x	y	z	T	
<i>ALS patients higher BOLD response than controls</i>								
Auditory	13	L and R	Caudate nucleus		-3	3	12	4,33
	12	L and R	Middle frontal gyrus	6	0	12	57	3,73
<i>Control group higher BOLD response than ALS patients</i>								
Visual	12	R	Middle occipital gyrus	19	30	-84	24	
Auditory	11	R	Inferior frontal gyrus	45	48	24	6	5,25
	10	L	Inferior frontal gyrus	6, 9	-60	3	27	4,76
	16	R	Cerebellum		30	-72	27	4,82

Table 1: Differences in brain activity between ALS patients and control subjects Comparison between ALS patients and control subjects for BOLD response modelled with hrf for visual, auditory and somato-sensory stimulation. T-test

statistics with uncorrected threshold and $p < 0.001$ was performed. ALS, amyotrophic lateral sclerosis; L, left hemisphere, R, right hemisphere; BOLD, blood oxygen level dependent; MNI, Montreal Neurological Institute coordinates.

Differences in the latency and width of the canonical hrf between ALS patients and control subjects

The time derivative of the hrf indicated that ALS patients had an increased latency of the canonical response in the occipital lobe of the right hemisphere (V4, BA18,19; Table 2) during visual stimulation compared to controls. During auditory stimulation, the hrf of ALS patients had a longer latency in the superior temporal cortex of the left hemisphere (BA22,42; Table 2) and in the parahippocampal gyrus of the right hemisphere. During somato-sensory stimulation, ALS patients demonstrated no significant difference in the BOLD response regarding the time derivative.

During visual stimulation, ALS patients showed no significant difference in the BOLD response concerning dispersion derivative (dv). During auditory stimulation, group differences in dv of the hrf indicated that ALS patients had a prolonged hrf response compared to the hrf response of the control group in the supra-marginal gyri (BA40) of both hemispheres. During somato-sensory stimulation, ALS patients had a prolonged hrf response in the inferior frontal gyrus (BA45) and posterior insular cortex (BA13) of the right hemisphere (Table 2).

Experimental paradigm	Cluster size (voxel)	Anatomic Areas	Brodmann Area	MNI coordinates [mm]			
				x	y	z	T
<i>ALS patients have longer latency of hrf compared to controls</i>							
Visual	11	R Occipital lobe	18, 19	21	-72	-9	3,72
Auditory	18	R Parahippocampal gyrus		36	-9	-21	5,77
	7	L Superior temporal gyrus	22, 42	-66	-15	6	5,68
<i>ALS patients have prolonged hrf compared to controls</i>							
Auditory	26	L Supramarginal gyrus	40	-30	-48	45	7,44
	28	R Supramarginal gyrus	40	39	-48	39	6,75
Somatosensory	15	R Inferior frontal gyrus, posterior insular cortex	13, 45	39	21	12	4,26

Table 2: Differences in shape of brain response between ALS patients and control subjects

Comparison of BOLD response modelled with hrf and **time and dispersion derivatives** for visual, auditory and somato-sensory stimulation in **ALS patients versus control subjects**. T-test statistics, uncorrected threshold ($p < 0.001$) was chosen. ALS, Amyotrophic lateral sclerosis; L, left hemisphere, R, right

hemisphere; BOLD, blood oxygen level dependent; MNI, Montreal Neurological Institute coordinates.

Regression analysis of BOLD and level of physical functioning in ALS patients

During visual stimulation in the ALS patient sample, BOLD activity in the superior parietal lobes of both hemispheres (BA7) and the inferior parietal lobe of the left hemisphere (BA40) significantly increased with the loss of physical functioning (Table 3, Figure 1A).

Likewise, reduced BOLD activity in the occipital lobe (TEO, BA19) of the right hemisphere (Table 3, Figure 1B) was significantly associated with decreased ALSFRS.

In ALS patients, BOLD in the inferior parietal gyrus (BA39,40) of the left hemisphere and in the middle frontal and precentral gyri (BA6,8,9) of the right hemisphere increased significantly with the loss of physical functioning during auditory stimulation.

Also, reduced BOLD activity in putamen, posterior insular cortex (BA13) and inferior parietal lobe (BA40) of the left hemisphere was significantly associated with decreased physical function (Table 3).

In the ALS patient group, higher BOLD activity in the middle temporal lobe (BA37) of the left hemisphere was significantly associated with the loss of physical functioning during somato-sensory stimulation.

In addition, reduced BOLD activity during somato-sensory stimulation in the thalamus and inferior parietal lobe (BA39) of the right hemisphere and in the inferior frontal gyrus (BA44) and posterior cingulate cortex (BA31) of the left hemisphere was significantly associated with decreased physical functioning (Table 3).

Experimental paradigm	Cluster size (voxel)	Hemisphere	Anatomic Areas	Brodmann Area	MNI coordinates [mm]			
					x	y	z	T
ALS patients								
Visual	Increasing with ALS FRS							
	7	L	Superior parietal lobe	7	-33	-60	51	8,95
	16	R	Superior parietal lobe	7	15	-72	63	5,28
	10	R	Superior parietal lobe	7	30	-72	57	7,83
	8	L	Inferior parietal lobe	40	-57	-45	51	4,92
	Decreasing with ALS FRS							
	5	R	Occipital lobe	19	15	-48	-6	4,62
Auditory	Increasing with ALS FRS							
	12	L	Inferior parietal/angular gyrus	39, 40	-42	-60	36	6,67
	5	R	Middle frontal gyrus	8, 9	33	24	42	5,11
	7	R	Precentral gyrus	6	18	-12	57	4,82
	Decreasing with ALS FRS							
	6	L	Putamen		-18	-9	6	5,21
	6	L	Posterior insula cortex	13	-36	-25	15	5,44
	7	L	Inferior parietal lobe	40	-54	-30	30	5,89
Somatosensory	Increasing with ALS FRS							
	8	L	Middle temporal lobe	37	-30	-48	0	4,96
	Decreasing with ALS FRS							
	7	R	Thalamus		9	-3	3	
	5	L	Inferior frontal gyrus	44	-57	15	15	
	11	R	Inferior parietal lobe	39	27	-51	21	
	5	L	Posterior cingulate gyrus	31	-24	-33	30	

Table 3: Areas with increasing/decreasing activity associated with physical function loss

Regression analysis of BOLD activity with physical function (measured with ALS functional rating scale revised form, ALSFRS) in ALS patients for visual, auditory and somato-sensory stimulation. T-test statistics with uncorrected threshold ($p < 0.001$) were chosen. ALS, Amyotrophic lateral sclerosis; L, left cerebral hemisphere, R, right cerebral hemisphere; BOLD, blood oxygen level dependent; MNI, Montreal Neurological Institute coordinates.

Insert fig 1 here

White matter pathology in ALS patients compared to control subjects measured with DTI

Compared to control subjects, ALS patients presented reduced FA values in tracts which were associated with sensory areas such as in the visual pathway (projecting from bihemispheric BA18,19, fig 2 top row, and inferior parietal lobe projecting from left BA 40).

Insert fig 2 here

In the analysis of the acoustic processing pathway, reduced FA was observed for ALS patients in different projection fibres (temporal gyrus projecting from right-sided BA21 and from left-sided BA22/42 and BA41; fig 2).

ALS patients showed reduced FA in projecting fibres from higher order sensory processing areas (inferior parietal lobe projecting from BA7, 40 bihemispherically and left BA39, fig 2 bottom row). Projection fibres in the right-sided posterior cingulate gyrus (BA31) and in the left anterior cingulate cortex (BA32) showed reduced FA in ALS patients.

Control subjects did not show any areas with reduced FA compared to ALS patients.

DISCUSSION

The aim of the present study was to combine functional and structural imaging techniques in order to investigate visual, auditory and somato-sensory system functioning in amyotrophic lateral sclerosis.

Visual system functioning in ALS

Compared to healthy controls, ALS patients showed a reduced/altered response in the secondary visual cortex: a reduced BOLD response in the area V3a and prolonged BOLD onset latency in V4, two areas known to be involved in processing of line contrasts and checkerboard.[22] Furthermore, ALS patients presented reduced BOLD activity in the secondary visual area TEO associated with level of physical impairment. TEO is again a secondary visual area for texture defined boundaries detection.[22] It receives its main input from V4, an area with delayed responsiveness in the ALS group. This may indicate a reduced velocity of information transport in the visual cortex due to a decreased neuronal conductance velocity, probably associated with demyelination.[5, 6] In a previous study, evidence for a progressively reduced activation of extra-striate areas over the course of ALS was found [23] and electrophysiological evidence for pathology of this area was reported. [7, 8] With electrophysiological techniques, the latency of the P1 component of visual evoked potentials (VEP) generated by extra-striate areas [24] was significantly delayed or nearly absent in ALS patients.[7, 8, 25] Those findings may be subsumed as evidence for the above mentioned demyelination of nerve fibres in the optic tract projecting to the extrastriate visual areas in ALS.

BOLD activity in higher order sensory processing areas in the superior parietal lobe (BA7,40) increased with loss of physical function in ALS patients. This increased response in areas of visual oddball detection [26] might either be associated with increased effort for deviant stimuli detection due to attention deficits in the ALS patient group,[27] but it might as well suggest a compensatory neuronal process for the functional impairments in secondary visual cortices.

Concerning structural changes, there were significantly less functional white fibre tracts projecting to secondary sensory areas (BA18,19) in the occipital lobe and in the inferior parietal lobe (BA40), supporting a close relationship between functional

and structural deficits in the visual processing pathway. Evidence for FA reduction in several extra-motor areas throughout the brain of ALS patients has been reported by other authors. However, there was a high variance of where FA differences were found. In those studies, different approaches and methods have been used, leading to conflicting and inconclusive results [28]

Sage and colleagues presented evidence that ALS-associated changes in DTI analysis are most probably not attributed to brain atrophy [28] but rather present functional changes of the fibre tracts. Accordingly, the changes in FA in the visual pathways of ALS patients probably present functional changes of the fibre tracts which may go in line with the above mentioned reduced velocity of information transport in the visual system.

Additionally, Sage and colleagues provided evidence that FA changes in ALS are associated with disease progression but not with disease duration, supporting the existence of a heterogeneous disease process in ALS. [28] This may additionally explain differences in DTI findings in several studies with ALS patients.

Auditory system functioning in ALS

In the auditory modality, ALS patients revealed delayed BOLD latency in secondary auditory areas (BA22) known to be involved in processing of tones [29] and a significant prolonged duration of the BOLD response in the bilateral supra-marginal area (BA40) known to be involved in auditory discrimination [30] which might imply slowed auditory information processing. The increased latency in the parahippocampal gyrus in ALS patients might as well be associated with cognitive/encoding difficulties in the deviant task.[31] Abnormalities in auditory evoked potentials were described as mild or rare in ALS.[32] However, changes of auditory ERPs in ALS patients compared to control subjects [33] might be affected by sensory processing deficits rather than by cognitive/attentional deficits alone. Structures that are involved in multisensory information processing and target detection in tones such as the caudates [34] and prefrontal cortex (BA6)[35] showed increased BOLD activation in ALS patients. In contrast, ALS patients demonstrated a reduced BOLD response in inferior frontal cortical areas (BA6,45) and in the culmen of the right cerebellum during the same task, i.e. in areas associated with auditory target tone detection.[35] The cognitive skill of deviant

target tone detection in this study might be compromised by subclinical cognitive deficits known to be present in ALS patients and associated with frontal cortex functioning.[27] Accordingly, ALS patients might present a changed neuronal pattern for the cognitive task of auditory deviant stimulus detection. This interpretation was supported by the result that the BOLD response in the superior parietal lobe (SPL, BA40) and the posterior insular cortex (PIC), which are known to be involved in sound discrimination, showed decreased activity with physical function loss in ALS. Dysfunction of SPL and PIC might be compensated by increased activity in inferior parietal and superior frontal areas suggesting a changed pathway for deviant target detection associated with subclinical cognitive deficits in ALS patients.

Again, structural changes supported the functional findings in the auditory pathway such as reduced fibre tract functioning to primary and secondary sensory areas like BA21 in the right and BA22, 41 and 42 in the left hemisphere indicating white matter degeneration in secondary auditory areas and Wernicke`s area in ALS. Evidence of involvement of the temporal cortices has not been reported previously and there has been yet no major clinical report on deficits in the auditory system of ALS patients. The hereby presented overlap of changes in fMRI and FA for the auditory pathway may again present the heterogeneous disease progression.

Somato-sensory system functioning in ALS

In the tactile paradigm, ALS patients showed a longer lasting BOLD response in the anterior insular cortex (AIC) compared to control subjects, indicative of increased nerve conductance time in the somato-sensory system.[36]. Impaired functioning of integrative sensory structures such as the thalamus, posterior cingulate cortex (PCC, receiving direct thalamic input) and inferior parietal lobe (BA39)[37] was related to decay in physical functioning in ALS during somato-sensory stimulation. This may be linked to the diminished inflow to the “visceral cortices” caused by immobility and/or it may be an expression of the disease progress itself. Furthermore, activity in left inferior frontal lobe (BA44), an area involved in the representation of one`s own body map,[38] decreased with physical function in ALS, possibly related to the diminished visceral muscle spindle inflow caused by immobility (less movement of a body part equals less efferent cortical activity in the motor areas which at the same time causes less afferent

cortical activity in sensory areas for the respective body part e.g. extremities) leading to a loss of body image. Increased activity in the middle temporal gyrus (BA37) involved in auditory target discrimination [39] and integration of sensory modalities [40] correlating with loss of physical function might indicate compensatory processes to overcome functional loss in other integrating structures of the sensory pathways (AIC, thalamus, PCC, BA 39).

General aspects of sensory stimulation in ALS

DTI measurements demonstrated that fibres projecting to multisensory areas like left-hemispheric BA 7, 39 and 40 and right-hemispheric BA 7 and other multimodal areas like anterior (BA 32) and posterior cingulate gyrus (BA 31) seem to be dysfunctional. For ALS patients, FA changes in parietal areas have been previously reported (Sage et al. 2007). Undoubtedly, efferent and afferent white matter connections might undergo secondary degeneration of proprioceptive connections between the primary sensory cortex and parietal lobe (Sage et al. 2007). Furthermore, pathological involvement of secondary sensory areas may as well be suspected. The behavioural effect of this degeneration may not pass a clinical threshold. In advanced stages of ALS the reported compensatory activity in association areas might be compromised at a functional level by this denervation.

The possible side effect of Riluzol treatment like asthenia in the ALS patient group might have had some negative effect on the BOLD in this study. However, none of the patients complained about asthenia; furthermore DTI measurements are not expected to be confounded by those side effects.

Concluding, a complex pattern of reduced and increased brain activity in ALS was observed associated with white matter lesions. It may be associated with the reduced efferent and re-afferent information flow due to the loss of motor function. Patient's social life and movement is often reduced to the radius of their home. The abnormalities recorded among patients in the present study and in another study [5] were present relatively early in the course of their disease, at a stage when malnutrition and immobility were not significant complications of the illness. Accordingly, the changes in the sensory system may be an expression of the

disease process itself and/or a combination of loss of information flow and disease process.

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Figure legends

Figure 1: Changes in brain activity associated with loss of physical function in ALS

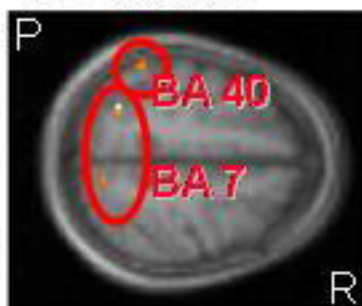
Statistical maps presenting significantly **increased** and **decreased BOLD activity** associated with **loss of physical function** (measured with ALS functional rating scale, ALS FRS) in ALS patients for **visual (left), auditory (middle) and somatosensory (right)** stimulation. Areas with increasing (upper row, red) and decreasing (lower row, green) activity are shown. Significant activations are overlaid onto a axial (top row) and sagittal (bottom row) mean anatomical image of all subjects. Displayed are clusters >5 voxels with uncorrected threshold $p < 0.001$; P=posterior, R=right.

Figure 2: White matter changes in ALS patients

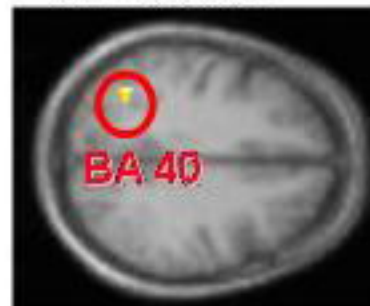
Areas with significantly reduced fractional anisotropy (FA) in **ALS patients compared to controls** in the occipital gyrus (top row, intersection point of lines $x=-30$ $y=-80$ $z=4$ in MNI space), in the temporal gyrus (middle row, intersection point of lines $x=40$ $y=-33$ $z=-2$ in MNI space) and in the inferior parietal lobe (bottom row, intersection point of lines $x=31$ $y=-64$ $z=32$ in MNI space). Voxels (isotropic 1mm) with significantly reduced FA are superimposed on the mean anatomical image of the subjects. Axial (left), coronal (middle) and sagittal (right) slice orientation was chosen. T-test with a cluster-extension threshold of 15 voxels ($p < 0.05$) was performed. L=left, R=right, A=anterior, P=posterior.

Areas with increased activity associated with a decrease in physical functioning (ALS-FRS)

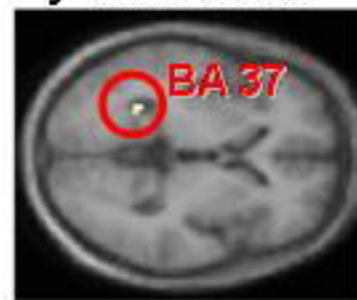
Visual stimulation



Auditory stimulation



Somatosensory stimulation



Areas with decreased activity associated with a decrease in physical functioning (ALS-FRS)

