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

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.
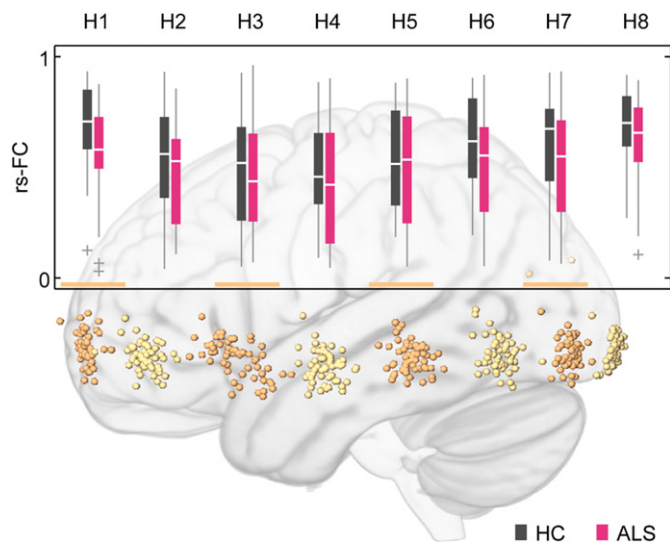
Fig. 1. Homotopic resting-state functional connectivity (rs-FC) in ALS: box whisker plot of homotopic rs-FC for measurement sites H1 to H8 (median, 25th and 75th percentile, extent of distribution, and outliers) and measurement sites (spheres) on the left hemisphere relative to the MNI152T1 brain template as obtained by probabilistic mapping in all 31 patients. Distributions are given in alternating colors orange and yellow to facilitate differentiation between adjacent measurement sites. Mean MNI coordinates were $(-30.3, 65.1, 4.3)$, $(-46.7, 46.5, -0.3)$, $(-53.1, 17.8, -2.9)$, $(-63.6, -10.9, -8.6)$, $(-65.1, -38.5, -7.7)$, $(-55.6, -67.0, -9.3)$, $(-41.2, -88.5, -10.5)$, and $(-24.7, -101.9, -9.5)$ for sites H1 to H8, respectively.

corresponding oxy-Hb time series averaged over a frequency range from 0.04 to 0.08 Hz. As commonly done in resting state fMRI studies, this frequency range was chosen to avoid the physiological noise associated with higher frequency oscillations (Cordes et al., 2001) and the inaccuracy resulting from estimating very low frequency correlations from limited time series (Achard et al., 2008). Deoxy-Hb signals were not included in our analysis, since in the above frequency range only oxy-Hb signals showed a significant connectivity between homotopic regions in a previous study (Sasai et al., 2011). Cross- and power spectral density were estimated using Welch's averaged modified periodogram method (Welch, 1967).

2.5.2. Spatial normalization of FA images

Individual DTI images were corrected for eddy currents and head movement using the FMRIB diffusion toolbox (FDT 3.0, FMRIB, University of Oxford, UK). After brain extraction using BET (BET 2.1, FMRIB, University of Oxford, UK), FA images were generated by voxel-wise diffusion tensor reconstruction, again using FDT. Following the standard workflow for Tract-Based Spatial Statistics (TBSS) (Smith et al., 2004), FA images derived from the individual DTI scans were aligned in the MNI152 space by nonlinear registration to the FMRIB58_FA standard template (FMRIB, University of Oxford, UK). The mean FA image was eroded into a skeleton representing the core of fiber tracts common to the patient cohort. All spatially normalized FA images were projected onto this skeleton to facilitate inter-individual voxel-wise regression analysis.

Fiber tracts were identified on a probabilistic basis by comparison with the probabilistic JHU white-matter tractography atlas (Laboratory of Brain Anatomical MRI, Johns Hopkins Medical Institute, Baltimore, USA).

2.6. Statistical analysis

Differences in homotopic rs-FC between HC and ALS patients were tested for statistical significance by 1-way multivariate analysis of variance (MANOVA) with study subgroup (HC, ALS) as categorical

predictor, rs-FC values at sites H1 to H8 as multivariate response, and Pillai's trace as test statistic. Correlation matrices of homotopic connectivities were tested for significant differences according to Jennrich (1970). Linear correlations between homotopic functional connectivity values were tested for statistical significance by permutation testing based on Pearson's r, adjusting p-values for multiple testing using the maximum statistic approach (Groppe et al., 2011).

Statistical analysis of correlation between clinical parameters (ALSFRS-R, DPR) and rs-FC was performed simultaneously for all 8 measurement sites by permutation testing based on Spearman's rank correlation ρ, again using the maximum statistic approach to adjust p-values. For inter-group comparison of DPR a 1-way ANOVA was conducted. To evaluate whether ALS subgroups differed in their relationship between homotopic rs-FC and DPR Quade's rank analysis of covariance was performed with DPR being the dependent variable, ALS subgroup the grouping variable, and rs-FC the continuous covariate (Quade, 1967).

Inter-individual voxel-wise correlation between rs-FC and FA was evaluated by TBSS regression analysis with rs-FC as the predictor variable. Statistical inference was conducted using a permutation-based algorithm allowing for threshold-free cluster enhancement and family-wise-error-correction of p-values (randomise v2.1, FSL).

Post hoc analysis of ANOVA results was performed using Tukey's Honestly Significant Difference (HSD). Linear correlation between variables was assessed using Pearson's r. Data analysis was implemented using MATLAB (R2014b, The Mathworks Inc., Natick, MA), except for TBSS regression analysis using FSL (FSL 5.0.6, FMRIB, Oxford, UK).

Unless stated otherwise, the significance level for statistical tests was set at $\alpha = 0.05$. If a test was performed for more than one study subgroup p-values were Bonferroni corrected, i.e. multiplied by the number of subgroups considered. Throughout the text mean values are given as mean ± standard deviation.

3. Results

3.1. Homotopic rs-FC in ALS and HC

In accordance with a previous study employing fMRI (Anderson et al., 2011) we found homotopic rs-FC to decrease with increasing distance from the mid-sagittal plane with H1/H8 showing the highest and H3/H4 the lowest rs-FC (Fig. 1). No significant difference in homotopic rs-FC existed between ALS patients and HCs ($p = 0.46$). ALS patients, however, displayed an altered correlation between homotopic rs-FC values obtained at different cortical sites, when compared to HCs (Fig. 2, $p = 1.3 \times 10^{-5}$).

3.2. Homotopic rs-FC and clinical parameters

For measurement sites H4 to H7 rank correlation between rs-FC and DPR suggested a moderate relationship between homotopic rs-FC and rate of motor decline in ALS (Fig. 3, $\rho < -0.41$, $0.0024 < p_{uncorrected} < 0.0225$). Rank correlation withstood correction for multiple testing only for the anterior temporal lobes (ATLs), however (H4, $\rho = -0.52$, $p = 0.039$). No such correlation existed between rs-FC and ALSFRS-R ($|\rho| < 0.23$).

3.3. Homotopic rs-FC and DPR in ALS subtypes

Executive dysfunction was recently reported to be a negative prognostic factor in ALS (Elamin et al., 2011). In line with this finding we found DPR to be significantly increased in ALS-EX ($p < 0.05$) but not in ALS-NECI when compared to pALS.

Among the ALS subgroups, a statistically significant correlation between DPR and rs-FC only existed in pALS at H4 (Fig. 4, $\rho = -0.8$, $p = 0.007$). Particularly in ALS-NECI, however, the lack of correlation may result from the small number of patients in this group ($n = 6$). We conducted Quade's rank analysis of covariance to further evaluate
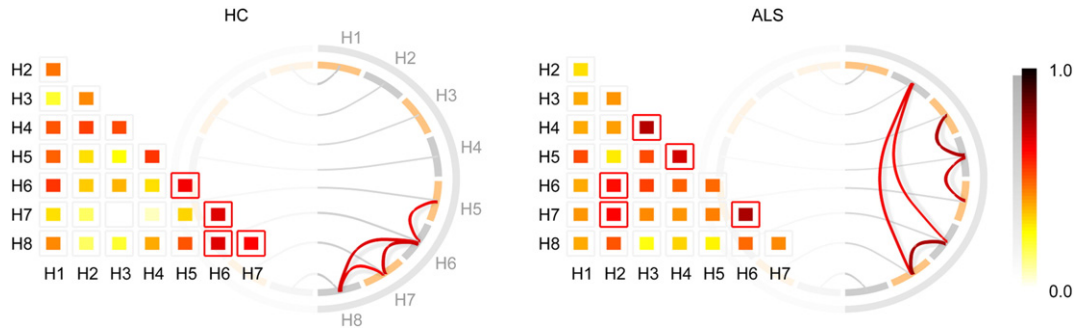
Fig. 2. Inter-individual correlation matrices of homotopic connectivities at different measurement sites. Statistically significant correlations are marked by a red box and given in a circular connectivity plot, schematically reflecting anatomical relationships. Whereas in healthy controls a significant correlation only existed between homotopic resting-state functional connectivities (rs-FCs) of the occipital and posterior temporal lobes, ALS patients displayed a significant correlation between frontal and temporo-occipital homotopic rs-FCs. Furthermore, homotopic rs-FC of the anterior temporal lobes (ATLs) significantly correlated with orbitofrontal and posterior-temporal homotopic rs-FC in ALS patients.

whether ALS subgroups significantly differed in the relationship between rs-FC and DPR. Again, ALS-EX but not ALS-NECI significantly differed from pALS ($p < 0.05$). In patients without executive dysfunction (pALS and ALS-NECI) rank correlation between DPR and rs-FC at site H4 was -0.85 ($p = 0.0004$). Rank correlation in executive-impaired patients was -0.28 ($n = 11$, $p = 0.96$).

3.4. Homotopic rs-FC of the ATLs and WM changes

Considering only H4 we found a statistically significant linear correlation between homotopic rs-FC and FA for extended areas within the CC, the corticospinal tracts (CSTs), and the forceps minor (Fig. 5). This correlation was strongest within the left CST at the level of the diencephalon ($r = 0.77$, $p < 0.05$). For CC and CST, the white matter regions involved were largely congruent with ALS-related WM changes reported in previous imaging and post-mortem studies (Filippini et al., 2010; Smith, 1960). Involvement of the forceps minor is less well-established but has been reported (Lillo et al., 2012).

Among the remaining sites only the orbitofrontal cortices (H3) displayed a significant correlation between rs-FC and FA at the given significance level. Here not only CC and CSTs but also intrahemispheric association fibers such as the superior and inferior longitudinal fasciculi were involved. At a significance level adjusted for the full number of homotopic connections ($n = 8$, $\alpha = 0.00625$), a significant correlation between rs-FC and FA existed only for H3 and was restricted to the CC, forceps minor, and forceps major. No correlation between DPR and FA was observed.

4. Discussion

In this cross-sectional study integrating NIRS and DTI, ALS patients displayed an altered spatial pattern of correlation between homotopic rs-FC values measured in different non-motor associated cortical areas. Furthermore, homotopic rs-FC of the anterior temporal lobes correlated with ALS-specific WM degeneration of the CC and CSTs, as well as with the rate of motor decline in ALS patients without executive dysfunction.

Degeneration of the CC in ALS is most salient within its motor-associated sections (Chapman et al., 2014). Consistent reductions in inter-hemispheric connectivity of the motor cortex have already been described (Jelsone-Swain et al., 2010). In the present study, we observed a correlation between this ALS-specific degeneration of the CC and homotopic rs-FC of extramotor cortical areas, possibly reflecting alterations in inter- and intrahemispheric connectivity of the motor cortex in ALS.

Few studies, predominantly based on DTI and resting-state fMRI, have yet addressed the relationship between changes in functional and structural connectivity in ALS. Verstraete et al. demonstrated grey and white matter degeneration within the motor network in ALS and found functional connectedness within this network to correlate with DPR (Verstraete et al., 2010). Agosta et al. found changes in rs-FC to the sensorimotor cortex in ALS patients to depend on CST damage (Agosta et al., 2011). Comparing changes in structural and functional connectivity within the entire brain network, Schmidt et al. demonstrated an overlap of the most structurally affected and most
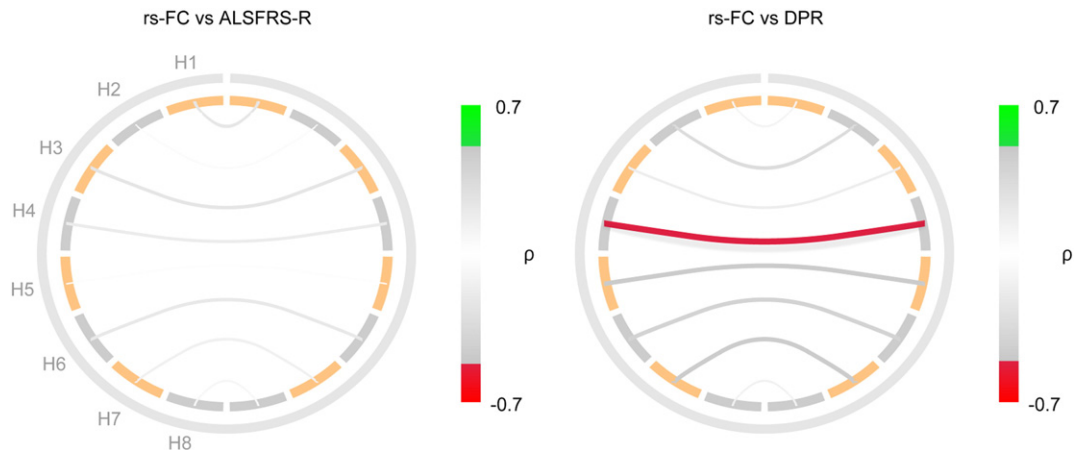

Fig. 3. Color-coded representation of rank correlation ρ between homotopic resting-state functional connectivity (rs-FC) and clinical parameters for sites H1 to H8 (from top to bottom). Homotopic connections are given in grayscale or color to highlight statistical significance of the corresponding ρ values. No significant correlation existed between rs-FC and patients' functional (motor) status (left). For H4, rs-FC significantly correlated with patients' rate of motor decline (right).
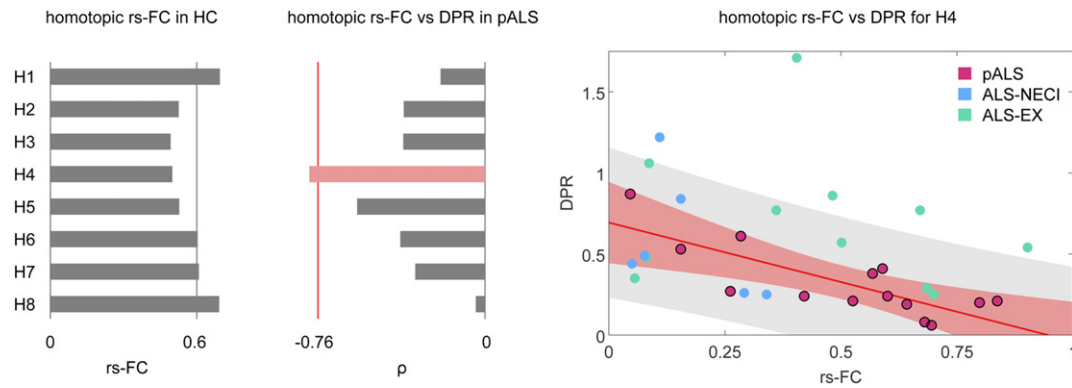
Fig. 4. Mean homotopic resting-state functional connectivity (rs-FC) in healthy controls (HC, left) and rank correlation ρ between rs-FC and disease progression rate (DPR) in pure ALS (middle, red line denotes statistical significance) for sites H1 to H8. Complementary spatial patterns of rs-FC and ρ ($r = -0.78$, $p = 0.02$), especially for sites H5 to H8, here may suggest involvement of a larger scale network in interhemispheric rs-FC. As for the ALS group as a whole, a statistically significant correlation existed only for H4. For this site a linear model (red line and 95% confidence interval in the scatter plot on the right) was fitted to the data obtained in the pALS group (red dots). Whereas data for the ALS-NECI group (blue dots) were compatible with this model, 4 out of 11 data points fell outside the 95% prediction interval (grey) in the ALS-EX group (green dots) suggesting a different disease trajectory in patients with executive dysfunction. This assumption was affirmed by Quade's rank analysis of covariance (see Section 3.3.).

functionally impaired connections (Schmidt et al., 2014). Direct connections to the motor cortex were more affected than connections at a larger topological distance. Using probabilistic tractography, Douaud et al. extracted a grey matter network based on the CC and CST involvement, which is characteristic for ALS and seen to a similar extent in the present study (Douaud et al., 2011). The resulting 'ALS-specific' grey matter network exhibited an increased rs-FC to areas of elevated extramotor activation in ALS patients during motor tasks, as consistently observed in previous positron emission tomography and fMRI studies (Lule et al., 2009). This observation, in particular, suggests a link between the ALS-specific WM damage and increased functional connectivity between extramotor and motor regions. In the present study, we found a direct correlation between these WM changes and homotopic connectivity of the ATLs, possibly indicating involvement of a larger scale

network in interhemispheric rs-FC and ALS pathology. This correlation did not significantly differ between neuropsychological ALS subtypes (data not shown), precluding identification of potential hub regions in ALS pathology in the present study (Crossley et al., 2014; van den Heuvel et al., 2013).

A potentially complex relationship between interhemispheric functional connectivity and structural integrity of the CC has been suggested in a variety of studies. Normal levels of interhemispheric functional connectivity were observed in individuals with callosal agenesis (Tyszka et al., 2011) and patients with surgical lesions of the CC (Uddin et al., 2008). In a recent study O'Reilly et al. found interhemispheric rs-FC largely preserved in macaque monkeys after section of the CC if only the anterior commissure (AC) was left intact (O'Reilly et al., 2013). The authors concluded that although functional connectivity is likely
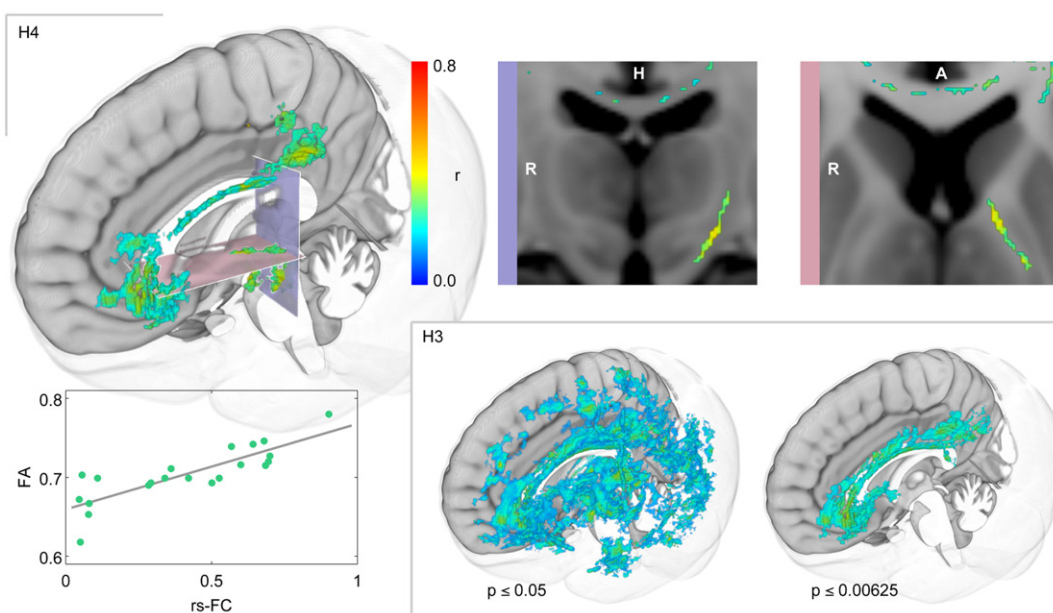

Fig. 5. Color-coded representation of voxel-wise correlation between fractional anisotropy (FA) and homotopic resting-state functional connectivity (rs-FC) of the anterior temporal lobes (ATLs, H4) embedded into the MNI152T1 brain template (top row). Only those segments of the fiber tract skeleton are shown for which a statistically significant correlation existed. These were the corticospinal tracts (CSTs) at the level of mesencephalon/diencephalon and centrum semiovale, the central corpus callosum (CC), white matter tracts extending from the central CC to the primary and pre-motor cortex, and the forceps minor. Extent of the lower CST involvement is also given in coronal (top middle) and transverse (top right) sectioning. Mean FA of this area versus homotopic rs-FC of the ATLs is given as scatter plot along with a regression line (bottom left). For comparison statistically significant correlations between rs-FC and FA are also given for the orbitofrontal cortices (H3, bottom middle and bottom right, see Section 3.4.).

effected by cortico-cortical white matter connections, complex network interactions allow for near-normal patterns of functional connectivity to be sustained by a potentially small number of indirect structural connections. The fact that in our study homotopic rs-FC of the ATLs correlated with WM changes within the central CC, a section of the CC not associated with the ATLs, may indicate that for the frequency range considered here, network effects are indeed dominant. This assumption is supported by the observation that HC and ALS patients displayed significantly different spatial patterns of correlation between homotopic connectivities.

Our results suggest that changes in homotopic functional connectivity reflect disease severity in ALS. However, we cannot deduce from our data whether these changes are induced by alterations in intra-hemispheric connectivity of the motor cortex or e.g. the 'ALS-specific' grey matter network described by Douaud et al. (2011). Correlative patterns of rs-FC may help to further delineate causality, at least in a confirmatory fashion, if used for example in structural equation models. Such an approach, however, is likely to require a much larger number of measurement sites, which can only be achieved with resting-state fMRI. Independent of the imaging modality to be used, further analysis of network changes in ALS may benefit from neuropsychological classification, as patients with executive dysfunction displayed a significantly different relationship between homotopic connectivity and DPR in the present study. These differences between cognitive phenotypes may, in part, explain previous, seemingly inconsistent results on the connectivity of resting state networks in ALS (Agosta et al., 2013; Mohammadi et al., 2009; Tedeschi et al., 2012). Considering only homotopic connectivity we did not find any differences in rs-FC and FA between the three different ALS subtypes (data not shown).

In the present study we employed NIRS as the primary imaging modality. Although this technique has asserted itself in neuroscience as a low resolution alternative to fMRI, it has remained largely unknown to clinical neurologists (Obrig, 2014). Its use here was motivated by recent studies demonstrating that rs-FC can be assessed by NIRS in a robust fashion (Zhang et al., 2011) and the fact that certain MRI investigations such as DTI may not be uniformly performed in ALS patients (e.g. in the present study 10 out of 31 patients met the exclusion criteria for DTI). The correlation between homotopic rs-FC as assessed by NIRS and FA observed in ALS patients in the present study may present a new paraclinical surrogate marker for neurodegeneration. Conceivably, future studies, applying rs-fNIRS in other neurodegenerative diseases associated with degeneration of the CC such as Alzheimer disease or multiple sclerosis are necessary to address this question.

The main caveats of our study are its cross-sectional nature and the small number of patients especially in the neuropsychological subgroups. It would be tempting to speculate that alterations in resting state connectivity of extramotor cortical areas observed in this study are associated with cognitive dysfunction. Given the arrangement of optodes a number of networks relevant to different aspects of cognition including the default mode network, the fronto-parietal network, and the attentional network may be involved (Smith et al., 2009). Due to the limited spatial resolution and depth penetration of NIRS, however, selective assessment of these networks could not be achieved. Future studies with larger patient populations integrating fMRI may further elucidate the relationship between interhemispheric rs-FC and cognitive performance in ALS.

In summary, homotopic rs-FC as assessed by rs-fNIRS appears to be a promising concept for patient stratification in ALS, which needs to be validated in future longitudinal studies with larger patient cohorts.

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References

Achard, S., Bassett, D.S., Meyer-Lindenberg, A., Bullmore, E., 2008. Fractal connectivity of long-memory networks. Phys. Rev. E Stat. Nonlinear Soft Matter Phys. 77, 036104.

Agosta, F., Valsasina, P., Absinta, M., Riva, N., Sala, S., Prelle, A., Copetti, M., Comola, M., Comi, G., Filippi, M., 2011. Sensorimotor functional connectivity changes in amyotrophic lateral sclerosis. Cereb. Cortex 21, 2291–2298.

Agosta, F., Canu, E., Valsasina, P., Riva, N., Prelle, A., Comi, G., Filippi, M., 2013. Divergent brain network connectivity in amyotrophic lateral sclerosis. Neurobiol. Aging 34, 419–427.

Anderson, J.S., Druzgal, T.J., Froehlich, A., DuBray, M.B., Lange, N., Alexander, A.L., Abildskov, T., Nielsen, J.A., Cariello, A.N., Cooperrider, J.R., Bigler, E.D., Lainhart, J.E., 2011. Decreased interhemispheric functional connectivity in autism. Cereb. Cortex 21, 1134–1146.

Brooks, B.R., Miller, R.G., Swash, M., Munsat, T.L., World Federation of Neurology Research Group on Motor Neuron, D., 2000. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Other Motor Neuron Disord. 1, 293–299.

Cardenas-Blanco, A., Machts, J., Acosta-Cabronero, J., Kaufmann, J., Abdulla, S., Kollewe, K., Petri, S., Heinze, H.J., Dengler, R., Vielhaber, S., Nestor, P.J., 2014. Central white matter degeneration in bulbar- and limb-onset amyotrophic lateral sclerosis. J. Neurol. 261, 1961–1967.

Cedarbaum, J.M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., Nakanishi, A., 1999. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J. Neurol. Sci. 169, 13–21.

Chapman, M.C., Jelsone-Swain, L., Johnson, T.D., Gruis, K.L., Welsh, R.C., 2014. Diffusion tensor MRI of the corpus callosum in amyotrophic lateral sclerosis. J. Magn. Reson. Imaging 39, 641–647.

Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2001. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am. J. Neuroradiol. 22, 1326–1333.

Crossley, N.A., Mechelli, A., Scott, J., Carletti, F., Fox, P.T., McGuire, P., Bullmore, E.T., 2014. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain 137, 2382–2395.

Douaud, G., Filippini, N., Knight, S., Talbot, K., Turner, M.R., 2011. Integration of structural and functional magnetic resonance imaging in amyotrophic lateral sclerosis. Brain 134, 3470–3479.

Elamin, M., Phukan, J., Bede, P., Jordan, N., Byrne, S., Pender, N., Hardiman, O., 2011. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology 76, 1263–1269.

Filippini, N., Douaud, G., Mackay, C.E., Knight, S., Talbot, K., Turner, M.R., 2010. Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis. Neurology 75, 1645–1652.

Groppe, D.M., Urbach, T.P., Kutas, M., 2011. Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review. Psychophysiology 48, 1711–1725.

Irwin, D.J., Cairns, N.J., Grossman, M., McMillan, C.T., Lee, E.B., Van Deerlin, V.M., Lee, V.M., Trojanowski, J.Q., 2015. Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine. Acta Neuropathol. 129, 469–491.

Jelsone-Swain, L.M., Fling, B.W., Seidler, R.D., Hovatter, R., Gruis, K., Welsh, R.C., 2010. Reduced interhemispheric functional connectivity in the motor cortex during rest in limb-onset amyotrophic lateral sclerosis. Front. Syst. Neurosci. 4, 158.

Jennrich, R.I., 1970. An asymptotic χ^2 test for the equality of two correlation matrices. J. Am. Stat. Assoc. 65, 904–912.

Kasper, E., Schuster, C., Machts, J., Kaufmann, J., Bittner, D., Vielhaber, S., Benecke, R., Teipel, S., Prudlo, J., 2014. Microstructural white matter changes underlying cognitive and behavioural impairment in ALS–an in vivo study using DTI. PLoS One 9, e114543.

Kimura, F., Fujimura, C., Ishida, S., Nakajima, H., Furutama, D., Uehara, H., Shinoda, K., Sugino, M., Hanafusa, T., 2006. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology 66, 265–267.

Lillo, P., Mioshi, E., Burrell, J.R., Kiernan, M.C., Hodges, J.R., Hornberger, M., 2012. Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PLoS One 7, e43993.

Lule, D., Ludolph, A.C., Kassubek, J., 2009. MRI-based functional neuroimaging in ALS: an update. Amyotroph. Lateral Scler. 10, 258–268.

Machts, J., Bittner, V., Kasper, E., Schuster, C., Prudlo, J., Abdulla, S., Kollewe, K., Petri, S., Dengler, R., Heinze, H.J., Vielhaber, S., Schoenfeld, M.A., Bittner, D.M., 2014. Memory deficits in amyotrophic lateral sclerosis are not exclusively caused by executive dysfunction: a comparative neuropsychological study of amnestic mild cognitive impairment. BMC Neurosci. 15, 83.

Mohammadi, B., Kollewe, K., Samii, A., Krampfl, K., Dengler, R., Munte, T.F., 2009. Changes of resting state brain networks in amyotrophic lateral sclerosis. Exp. Neurol. 217, 147–153.

Ng, A.S., Rademakers, R., Miller, B.L., 2015. Frontotemporal dementia: a bridge between dementia and neuromuscular disease. Ann. N. Y. Acad. Sci. 1338, 71–93.

Obrig, H., 2014. NIRS in clinical neurology - a 'promising' tool? NeuroImage 85 (Pt 1), 535–546.

O'Reilly, J.X., Croxson, P.L., Jbabdi, S., Sallet, J., Noonan, M.P., Mars, R.B., Browning, P.G., Wilson, C.R., Mitchell, A.S., Miller, K.L., Rushworth, M.F., Baxter, M.G., 2013. Causal effect of disconnection lesions on interhemispheric functional connectivity in rhesus monkeys. Proc. Natl. Acad. Sci. U. S. A. 110, 13982–13987.

Phukan, J., Elamin, M., Bede, P., Jordan, N., Gallagher, L., Byrne, S., Lynch, C., Pender, N., Hardiman, O., 2012. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J. Neurol. Neurosurg. Psychiatry 83, 102–108.

Quade, D., 1967. Rank analysis of covariance. J. Am. Stat. Assoc. 62, 1187–1200.

Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134, 2456–2477.

Sasai, S., Homae, F., Watanabe, H., Taga, G., 2011. Frequency-specific functional connectivity in the brain during resting state revealed by NIRS. NeuroImage 56, 252–257.

Schmidt, R., Verstraete, E., de Reus, M.A., Veldink, J.H., van den Berg, L.H., van den Heuvel, M.P., 2014. Correlation between structural and functional connectivity impairment in amyotrophic lateral sclerosis. Hum. Brain Mapp. 35, 4386–4395.

Singh, A.K., Okamoto, M., Dan, H., Jurcak, V., Dan, I., 2005. Spatial registration of multi-channel multi-subject fNIRS data to MNI space without MRI. NeuroImage 27, 842–851.

Smith, M.C., 1960. Nerve fibre degeneration in the brain in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 23, 269–282.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23 (Suppl 1), S208–S219.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106, 13040–13045.

Tedeschi, G., Trojsi, F., Tessitore, A., Corbo, D., Sagnelli, A., Paccone, A., D'Ambrosio, A., Piccirillo, G., Cirillo, M., Cirillo, S., Monsurro, M.R., Esposito, F., 2012. Interaction between aging and neurodegeneration in amyotrophic lateral sclerosis. Neurobiol. Aging 33, 886–898.

Tyszka, J.M., Kennedy, D.P., Adolphs, R., Paul, L.K., 2011. Intact bilateral resting-state networks in the absence of the corpus callosum. J. Neurosci. 31, 15154–15162.

Uddin, L.Q., Mooshagian, E., Zaidel, E., Scheres, A., Margulies, D.S., Kelly, A.M., Shehzad, Z., Adelstein, J.S., Castellanos, F.X., Biswal, B.B., Milham, M.P., 2008. Residual functional connectivity in the split-brain revealed with resting-state functional MRI. Neuroreport 19, 703–709.

van den Heuvel, M.P., Sporns, O., Collin, G., Scheewe, T., Mandl, R.C., Cahn, W., Goni, J., Hulshoff Pol, H.E., Kahn, R.S., 2013. Abnormal rich club organization and functional brain dynamics in schizophrenia. JAMA Psychiat. 70, 783–792.

Verstraete, E., van den Heuvel, M.P., Veldink, J.H., Blanken, N., Mandl, R.C., Hulshoff Pol, H.E., van den Berg, L.H., 2010. Motor network degeneration in amyotrophic lateral sclerosis: a structural and functional connectivity study. PLoS One 5, e13664.

Welch, P.D., 1967. The use of fast Fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. IEEE Trans. Audio Electroacoust.

Zhang, H., Duan, L., Zhang, Y.J., Lu, C.M., Liu, H., Zhu, C.Z., 2011. Test-retest assessment of independent component analysis-derived resting-state functional connectivity based on functional near-infrared spectroscopy. NeuroImage 55, 607–615.