

## **Magnetic Susceptibility Maps in Amyotrophic Lateral Sclerosis**

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## Aims and objectives

Amyotrophic lateral sclerosis (ALS) is classically reported as a progressive motor neuron disease characterized by degeneration of both lower and upper motor neurons (1), respectively within the anterior horn of the spinal cord and in the V layer of the motor cortex and its projection along corticospinal tracts (CST).

Radiological biomarkers of ALS that might contribute to limit delayed diagnosis and might stratify patients by prognosis for therapeutic trials are highly desirable (2).

Conventional neuroimaging has a limited ability in detecting precise neuroanatomical correlates useful for diagnosis (3) while advanced magnetic resonance (MR) techniques applied to ALS have a controversial role as alternative diagnostic tools or as quantitative surrogate markers of disease progression (4).

Advanced neuroimaging approaches to ALS evaluate the upper motor neuron (UMN) dysfunction in the white matter along the cortico-spinal pathway or at cortical level.

The investigation of white matter fibre bundles in ALS has been attempted by the Diffusion tensor imaging (DTI) that revealed a significant increase of Mean Diffusivity and reduction of Fractional Anisotropy (5), nevertheless such technique lacks sufficient discrimination power at individual level (6).

The UMN impairment at cortical level has been explored by quantitative measurements of atrophy (Voxel Based Analysis) but also by functional MRI (7) and magnetization transfer imaging (8) revealing respectively the motor function reorganization and the microstructural changes of the cerebral motor and not motor cortices.

As well as for DTI in the white matter, the main limitation of advanced MR techniques at cortical level remains the difficulty to extend the results to a single subject level.

The introduction of Ultra High Field (UHF, 7 Tesla) MR equipment has increased the spatial resolution of MR imaging to the microscopic level and it has enhanced susceptibility phenomena offering adjunctive information to conventional MR contrasts (9)

Susceptibility weighted imaging is obtained by high-resolution gradient echo MR sequences that collect both magnitude and phase information. Filtered phase contrast, where the contribution of inhomogeneities of static magnetic field ( $B_0$ ) are removed, is dominated by paramagnetic substances that affect the surrounding magnetic field. However, the phase representation of brain structures may be affected by nonlocal sources of field perturbation, therefore obtaining a direct relationship between the phase variation and the underlying tissue microstructure is not straightforward. For these

reasons, a more precise susceptibility quantification in terms of susceptibility maps has been proposed (10).

. Such information might assist the characterization of tissue microstructure in ALS and it may be useful for the exploration of grey matter in the primary motor cortex (M1) and white matter fibre bundles along the CST.

## Methods and materials

### Patients and controls

This is a pilot study of a bigger project that will include 30 patients with a diagnosis of definite ALS according to the revised El Escorial diagnostic criteria and 30 Healthy Subjects (HS). At present, 5 patients (mean age  $58 \pm 12$ , 4 male and 1 female) and 5 HS (mean age  $43 \pm 11$ , 2 male and 3 female) were scanned with a 7.0T MR950 human system (GE HealthCare).

Clinical evaluation of disease severity was estimated by using the ALS functional rating scale (r-ALSFRS).

All patients and controls gave their written informed consent to the enrolment and diagnostic procedures on the basis of the adherence to an experimental protocol named "Clinical impact of ultra high-field MRI in neurodegenerative diseases diagnosis" RF RF-2009-1546281 approved and funded by Italian Ministry of Health and co-funded by Health Service of Tuscany. The study was approved by the local competent ethics committee.

### MR acquisition

MRI experiments were performed on a 7.0 T GE 950 MRI scanner (GE Healthcare Medical Systems, Milwaukee, WI, USA) equipped with a 2ch-tx / 32ch-rx head coil (Nova Medical, Wilmington, MA USA) installed at Imago7 Research Centre (Pisa Italy).

The MR protocol for the healthy subjects and ALS patients includes a 3D GE's product sequence "SWAN", a three-dimensional gradient-recalled (3D GRE) multi-echo sequence with TEs = 5.6 ms, 12 ms, 18.3 ms, 24.7 ms, 31.1 ms, 37.5 ms, 43.9 ms,; TR 54.1 ms, Nex = 0.67, Tk 1, 68 partitions, in plane resolution 500 micron (FOV 22.4 cm), receiver bandwidth 50 KHz targeted on the motor cortex oriented in the axial plane and covering the motor cortex and the CST from the vertex to the internal capsule. The routine reconstructed the final output image into a 448x448x68 matrix, by averaging the images obtained for each single echo. The total acquisition time was 7'28".

## Image analysis

The final output SWAN images of both HS and ALS patients were subjectively evaluated by a single neuroradiologist in order to describe the normal appearance of cortex and CST in healthy subjects and the pathologic changes in ALS patients. At visual inspection we evaluated: cortical thickness, cortical signal hypointensity and its distribution in precentral gyrus, signal changes along CST.

Using custom software implemented in MatLab, data obtained from each echo of the SWAN images were used to produce T2\* maps by exponential curve fitting.

SWAN raw data were used to reconstruct phase images, as well. Phase data obtained from all echoes were unwrapped and linearly fit in order to generate frequency maps. The undesired contribution of B0 inhomogeneities was isolated by filtering the frequency maps with a Gaussian filter (FWHM = 2mm), and subtracting the output to the unfiltered image. The retained data reflected only small-scale frequency contrast, which was used to calculate maps of  $\chi$  using the thresholded k-space division approach (11).

In order to measure the T2\* and  $\chi$  values within the cerebral cortex we placed ROIs in M1 of both hemispheres in the final output SWAN images of both ALS patients and controls. ROIs were transferred onto T2\* maps and susceptibility maps.

The T2\* and  $\chi$  values were measured also along the motor pathways by placing a ROI along the CST course in both hemispheres at level of the subcortical white matter under the precentral gyrus. The  $\chi$  value in both M1 and CST was normalized to the  $\chi$  value of the splenium of the corpus callosum (SCC).

## Results

Evaluating UHF SWAN images the normal cerebral cortex appeared as a two-layered structure characterized by a thin superficial tier and a hypointense deeper layer. A hypointense rim was appreciable at the gray-white matter junction. In healthy subjects the cortex in the anterior lining of central sulcus (i.e. primary motor cortex) appeared thicker and darker with respect to other neocortical regions (Fig 1A).

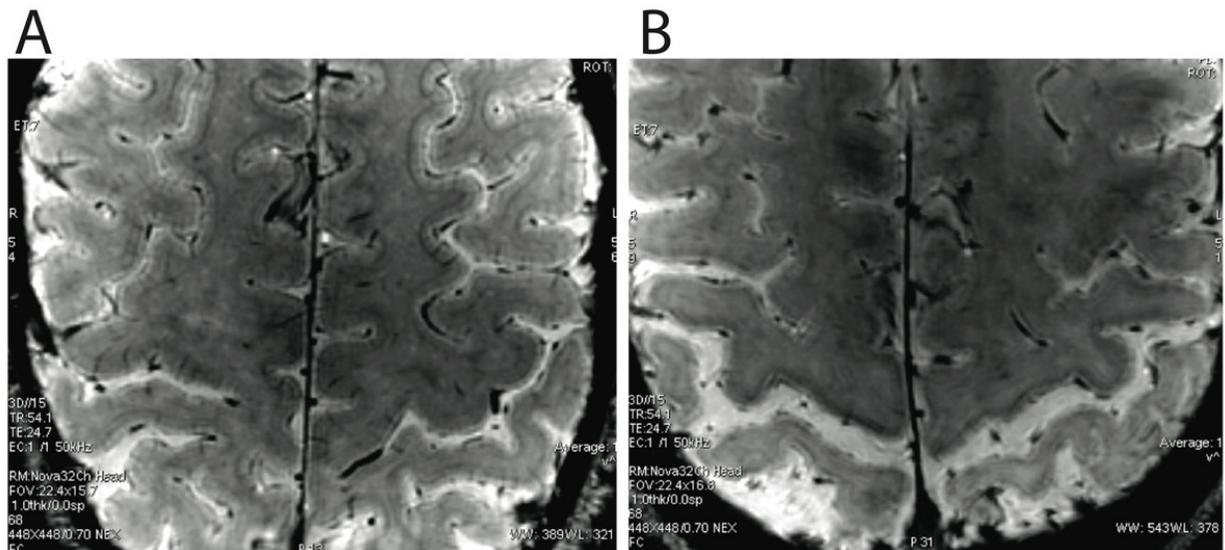
In ALS patients we revealed a reduction of the cortical thickness and a more pronounced signal hypointensity in the deeper layer of the primary motor cortex (in all 5 patients). No signal changes were detected along the CST by visual inspection (Fig 1B).

Maps of T2\* and  $\chi$  were obtained for all participants (Fig 2).

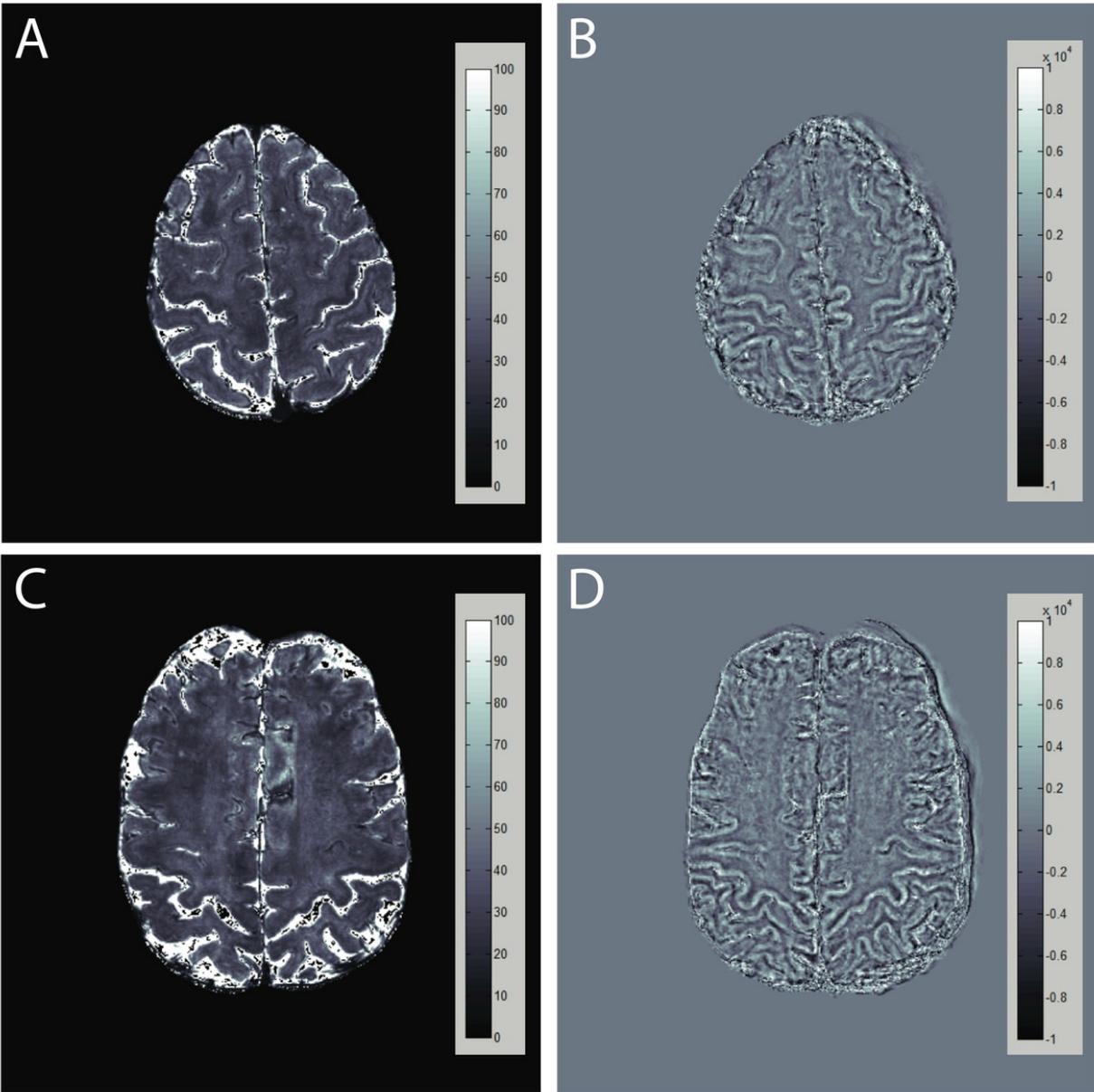
T2\* values have tendency to decrement in M1 (-11%) and in CST (-4%), however the difference from HS did not reach statistical significance (Fig 3A)

Normalized values of # in ALS patients were increased in M1 (+ 32%) and decreased in CST (-141%) (Fig 3B).

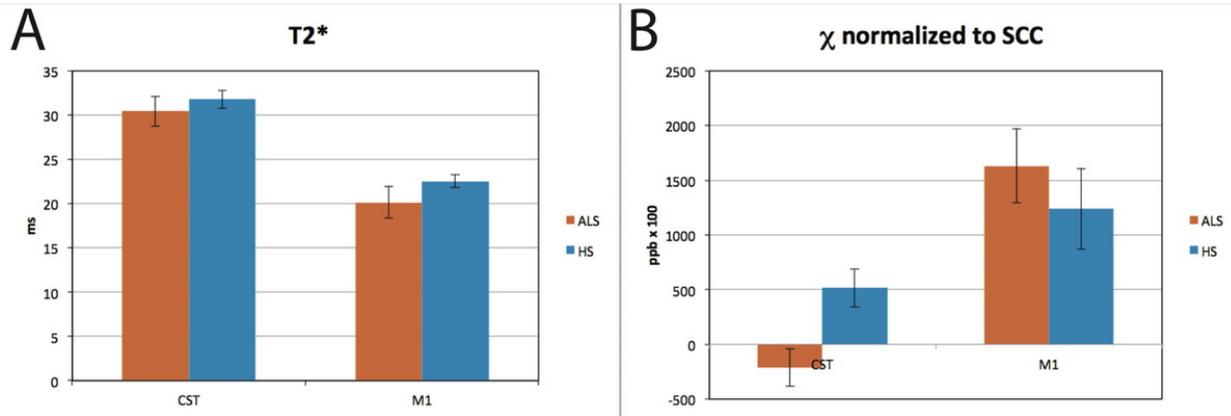
**Images for this section:**



**Fig. 1:** SWAN axial image of the motor cortex at the level of knob in a healthy subject (A) and in a patient with ALS (B). The motor cortex in healthy subjects has a two-layered appearance with a hypointense deeper thick tier. In ALS the deep layer of the motor cortex is thin and strongly hypointense.



**Fig. 2:** Example of T2\* maps (left column) and Susceptibility maps (right column) in a healthy subject (upper row) and in a patient with ALS (lower row).



**Fig. 3:** Quantitative analysis of T2\* maps (A) revealed a trend of T2\* values to shorten in M1 of ALS patients. Susceptibility values revealed a trend of  $\chi$  values to increase in M1 and to reduce along CST of ALS patients (B). Bars indicate mean and s.e.m.

## Conclusion

Our results are limited to a small number of participants. However these preliminary observations are encouraging in evaluating neurodegenerative diseases at UHF.

UHF SWAN sequence allows a multimodal approach to ALS patients, providing simultaneous structural information and quantitative measurements of tissue relaxometry and susceptibility.

At visual inspection structural imaging reveals signal changes in the cortex but not in CST.

# values and T2\* maps provide complementary information. Both # and T2\* seem to indicate abnormal iron deposition in M1 of ALS patients, whilst the opposite trend of their changes in CST suggest that they explore different properties of degenerated tissue.

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