Sensorimotor functional connectivity changes in amyotrophic lateral sclerosis

F. Agosta[1], P. Valsasina[1], M. Absinta[1], N. Riva[2], S. Sala[1], A. Prelle[3], M. Copetti[4], M. Comola[2], G. Comi[2], and M. Filippi[1]
[1]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, Milan, Italy, [2]Department of Neurology, Scientific Institute and University Hospital San Raffaele, Milan, Italy, [3]3Ospedale Fatebenefratelli e Oftalmico, Milan, Italy, [4]Biostatistics Unit, IRCCS-Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Introduction. The use of functional magnetic resonance imaging (fMRI) has provided evidence for cortical reorganization in amyotrophic lateral sclerosis (ALS). However, functional abnormalities that might be found in clinically impaired patients could be a reflection of task difficulty due to motor disability rather than being related to an actual brain rewiring. Only a few studies investigated resting state (RS) fMRI in ALS and found a decreased connectivity in the sensorimotor network which was restricted to the premotor cortex [1]. The structural substrates of such functional abnormalities have not been investigated yet.

Objective. To determine whether the RS functional connections to the primary sensorimotor cortex (SMC) bilaterally is altered in patients with ALS, and whether such changes are related to the CST damage, assessed using DT MRI tractography; and to explore the clinical relevance of functional connectivity changes by evaluating their correlation with the clinical status of ALS patients.

Methods. 26 sporadic ALS patients were included (11 w/15 m, mean age= 62; 14 definite, 8 probable, and 4 probable laboratory-supported). 15 sex- and age-matched healthy individuals (7 w/8 m, mean age= 63) served as healthy controls. MRI study was performed on a 1.5 T system (Avanto, Siemens, Erlangen, Germany). RS fMRI scans were acquired using a T2*-weighted single-shot echo planar imaging (EPI) sequence (TR/TE=3000/60 ms, matrix size=64x64, field of view=200 mm^2; 36, 4 mm thick, contiguous, axial slices with in-plane resolution=3x3 mm^2, number of volumes=200, acquisition time=10 minutes). During fMRI scanning, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. A dual-echo turbo spin echo, and a pulsed-gradient spin-echo EPI sequences were also acquired. The left and right primary SMC were selected as seed regions to compute functional connectivity with the REST software (http://resting-fmri.sourceforge.net/) (**Figure 1**). DT MRI tractography analysis was carried out to obtained CST average fractional anisotropy (FA) values, bilaterally [2]. A receiver operating characteristic (ROC) curve analysis was performed to discriminate patients from controls using mean CST FA values. The optimal cut-off level was considered the value giving the highest sum of sensitivity and specificity. Patients with mean CST value below the optimal cut-off value were classified as "CST damaged ALS patients".

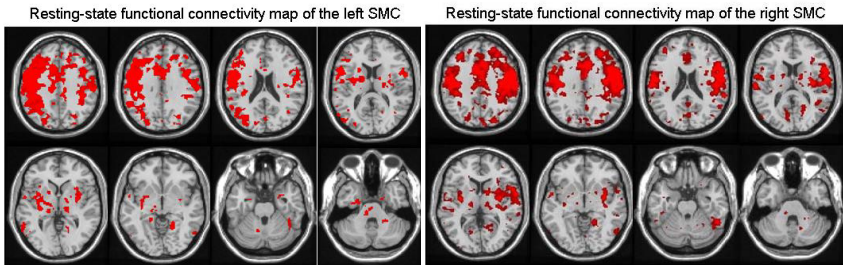

Figure 1. RS fMRI connectivity maps to the left and right primary SMC in healthy controls and patients with ALS. Note that in both groups, right and left SMC functional connectivity was found with bilateral premotor cortex, supplementary motor area, mid-cingulate cortex, basal ganglia, thalami, bilateral postcentral gyrus, bilateral parahippocampal and fusiform gyri, and bilateral cerebellum. Results are shown on the axial sections of the MNI standard brain in neurological convention (right is right), and displayed at the threshold of $p<0.05$, corrected for multiple comparisons (FWE).

Results. ALS patients *vs.* controls showed a significantly increased functional connectivity between the left SMC and the right cingulate cortex, parahippocampal gyrus, and cerebellum-crus II. No right SMC connectivity changes were found. ROC curve analysis showed that mean CST FA allowed to differentiate ALS patients from controls with an optimal cut-off of 0.64. Sixteen (61%) ALS patients were classified as "CST damaged", and ten ALS patients were classified as subjects with "undetectable CST damage". No difference was found in terms of demographic and clinical variables between these patients and those with undetectable CST damage. The pattern of increased functional connectivity to the left SMC was more widespread when considering only patients with no CST DT MRI abnormalities than the whole group of patients. In this patient group, functional connectivity was also increased between the right SMC and right parahippocampal gyrus. On the contrary, in "CST damaged" patients *vs.* controls, functional connectivity was increased between the left SMC and right cingulate cortex only, while it was decreased between the right SMC and right cerebellum-lobule VI. In ALS patients, disease severity correlated with reduced SMC functional connectivity.

Conclusions. fMRI changes observed in ALS patients at rest might reflect a more general impairment of their sensorimotor network function, which might be characterized by an initial phase of over-interaction of movement-associated areas and recruitment of additional neural resources involved in task planning and control, as observed in patients with undetectable CST damage. This phase might be followed by a one where the extent of tissue injury might lead to an exhaustion of the functional properties of the brain plastic reservoir. Future longitudinal studies, possibly in patients at the earliest phase of the disease, are now warranted to confirm our hypothesis and to investigate whether a window of opportunity exists during which an increased activity of the RS networks is adaptive in ALS, and can be possibly enhanced by pharmacotherapy or rehabilitative programmes.

References. [1] Mohammadi et al., Exp Neurol. 217:147-153; [2] Agosta et al., AJNR 2010 31:1457-61.