RESTING-STATE CEREBRAL BLOOD FLOW AND FUNCTIONAL CONNECTIVITY IN FOCAL EPILEPSY AS ASSESSED BY ARTERIAL SPIN LABELING

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Introduction: In drug-resistant focal epilepsy the generators of the abnormal electrical activity can be more accurately and precisely identified with the results deriving from the integration of electrophysiological and hemodynamic non-invasive imaging techniques. Since arterial spin labeling (ASL) has been demonstrated to be useful for the detection of perfusion changes in epilepsy with advantages over nuclear medicine[1], it can be also used for measuring functional connectivity to identify seizure-generating regions or networks regions that are differently organized in epileptic patients compared to healthy subjects[2]. The aims were to further confirm the diagnostic value of ASL in the identification of the epileptogenic zone, as compared to the results obtained with the electrical source imaging (ESI), and to determine the reduced or increased functional connectivity of epileptic patients compared to controls.

Material and Methods: In 8 patients with drug-resistant focal epilepsy, standard video-EEG was performed to identify clinical seizure semeiology, and high-density EEG and ASL to non-invasively localize the epileptic focus. In order to determine the range of normal cerebral blood flow (CBF) values in healthy subjects, the same ASL protocol was also applied to a control group of 17 volunteers. *High-density EEG:* A standardized source imaging procedure, low-resolution brain electromagnetic tomography constrained to the individual MRI, was applied to the averaged spikes of high-density EEG[3]. *ASL:* A pulsed PICORE Q2TIPS sequence was acquired on a Siemens 3T Allegra scanner (TR/TE=3500/16ms, $TI_1/TIs/TI_2 = 700/1400/1600$ ms, 40 control/label pairs, 15 slices, $3.5x3.5x5mm^3$). Quantification of CBF was performed using the Buxton model obtaining a set of maps (one per volume) in each subject. These results were then analyzed with three different approaches: *1) ROI Analysis:* a series of regions of interest (Harvard-Oxford Atlas) were used to calculate the mean CBF as well as the current density for evaluating pathological asymmetries; *2) Statistical Analysis:* a template of normal perfusion was created from the control group using a mixed-effect model that considered for each subject both the mean CBF map and its variance across time. The final group CBF template thus included both within-subject and between-subject variability[3]. An unpaired two-sample t-test was finally applied for comparing each individual patient with the template, in order to automatically depict the areas of significant perfusion change; *3) Functional Connectivity:* seed driven connectivity[4] was used to assess the connectivity measuring the temporal correlations between the perfusion signal from a seed time course and the time course of temporal and frontal ROIs as well as regions involved in the default mode network). Statistical differences between a single patient and controls were estimated (fixed-effects model).
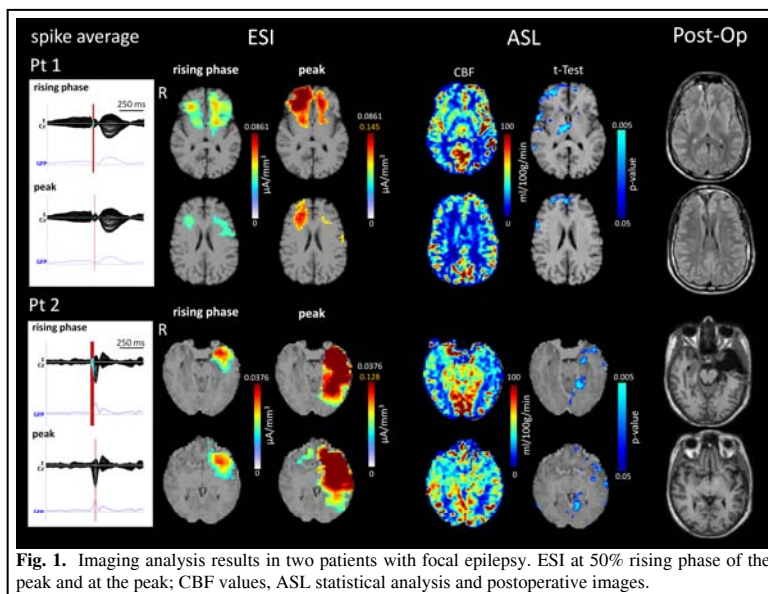

Fig. 1. Imaging analysis results in two patients with focal epilepsy. ESI at 50% rising phase of the peak and at the peak; CBF values, ASL statistical analysis and postoperative images.
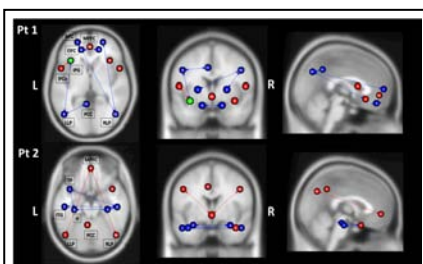

Fig. 2. ROI-to-ROI functional connectivity for two single epileptic patients vs. a control group.

Results: In most of the patients (6 out of 8), source in the interictal phase was associated with an area of hypoperfusion. Conversely, in the patients presenting with early post-ictal discharges (2 out of 8), the brain area identified by ESI as the generating zone appeared to be hyperperfused. Statistically significant hypo/hyper-perfused areas were identified in all cases and showed a good agreement with the ESI. The investigation allowed us to correctly identify the epileptogenic zone in 4 patients, in whom the results were confirmed by surgical resection and subsequent seizure freedom, 2 patients were excluded as surgery candidates, while the remaining 2 patients are waiting to be operated (Fig. 1). All the patients showed reduced functional connectivity compared to controls, in particular in the regions characterized by the hypo/hyperperfusion and high current densities (Fig. 2).

Discussion and Conclusions: As an innovative and more comprehensive approach to the study of epilepsy, the combined use of ESI and perfusion MRI can play an increasingly important role in the non-invasive evaluation of patients with refractory focal epilepsy. The seed-region connectivity analysis applied on ASL data, showing different patterns of abnormal connectivity, confirms the hypothesis of an altered functional organization in epileptic patients.

References. [1]Storti et al. Neuroimage 2013 [2]Pittau et al. Epilepsia 2013 [3]Maumet et al. Neuroimage 2013 [4] Whitfield-Gabrieli and Nieto-Castanon, Brain Connectivity 2012.