Pixel-by-pixel based discrimination of inflammation using multi-parametric MRI

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Target audience/Purpose: Cerebral inflammatory responses underlie the most morbid and prevalent neurological disorders, including cancer, ischemia, neurotrauma or neurodegeneration[1]. In most cases, current bioimaging methods are not able to discriminate unambiguously between the primary pathology and the associated inflammatory response. On these grounds, the development of non-invasive methods to identify and characterize the contribution of the inflammatory component entails considerable therapeutic and diagnostic relevance. To this end, we report here a novel intelligent decision support system (IDSS) to assist clinicians in the discrimination between inflamed and healthy brain using Magnetization Transfer, T1, T2 and Diffusion Weighted Imaging (MT, T1W, T2W, DWI).

Subjects and Methods: Adult male mice C57BL/6 (n=6) received an i.p. injection of LPS from Escherichia Coli Serotype 0127:B8 (5mg/kg). MRI studies of the mouse brain were carried out in a horizontal 7T/16 scanner. DWI in the head-foot (H-F), left-right (L-R) and the antero-posterior (A-P) directions with b=0, 100, 400, 800 s/mm² (two basals), T1 (7 TR), T2 (50 TE), and MT maps were acquired before, right after the injection, one and three days after the LPS administration, when maximal inflammation develops[2]. Immunostaining experiments were performed with IBA1 and GFAP, three days after the LPS insult and with GFAP 21 days after the LPS insult. IDSS was built as follows: Feature inclusion was applied sequentially considering the highest R^2 value of each feature after performing a regression analysis onto a Fisher´s discriminant[3] model constructed. Features were included until the adjusted Root Mean Square Error (RMSE) value decreases < Ɛ. At this point, the remaining features considered are the ones which contribute to the best cost-effective model of inflammation classification. Classification was carried out using the leave-one-out technique. A statistical index of inflammation for each pixel was calculated using Gaussian probabilities and Bayes theorem providing a probabilistic certainty of inflammation. Multi-parametric MRI maps were also calculated using in-house Matlab libraries.

Results: From the initial 70 MRI different combination of sequences, the off-resonance saturation sequence (MTW) resulted into the most significant to discriminate inflammation with 100% successful predictions. Hippocampal regions depicted the highest degree of inflammation (Figure 1). Our results correlate well with the multi-parametric MRI calculation (Figure 2) and the astrogliosis and microgliosis demonstrated by the immunostainig experiments (Figure 3).

Fig. 1*: Left: Classification of a representative healthy mouse. Note the low degree in the inflammation index calculated pixel by pixel. Middle: Classification of a representative mouse injected with LPS. Pixels with a higher degree of inflammation (over 97%) are represented. The hottest regions correspond mostly to the hippocampal areas, ventricles and some areas in the cortex. Right: A finer probabilistic inflammation index of the segmented hipoccampus reveals a very high degree of inflammation.*

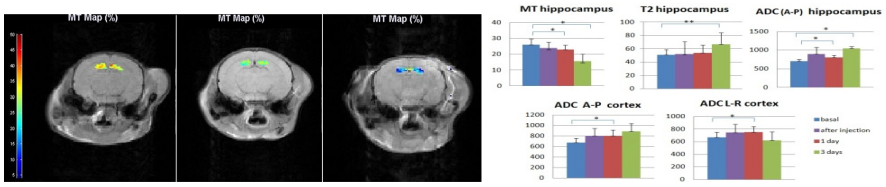

Fig. 2: *Left: Representative MT map of the hippocampus, before (left), one day (center) and three days (right) after the systemic LPS administration. Note the gradual decrease in average hippocampal MT after LPS injection. Other maps show similar behavior (not shown here). Right: Statistical results of the multi-parametric calculation reveal high vulnerability of the hippocampus with some effects in the cortical regions.*

Conclusions: We provided a novel methodology able to discriminate healthy from inflamed mouse brain regions pixel-by-pixel through a selection of the most relevant MRI features yielding the best cost-effective prediction. In this frame, the MTW sequence became the feature adding more value towards the correct classification. The present set-up may be extended to assess non-invasively the inflammatory component of many neurological disorders, improving considerably the clinical workflow in diagnoses and therapies of cerebral inflammation pathologies.

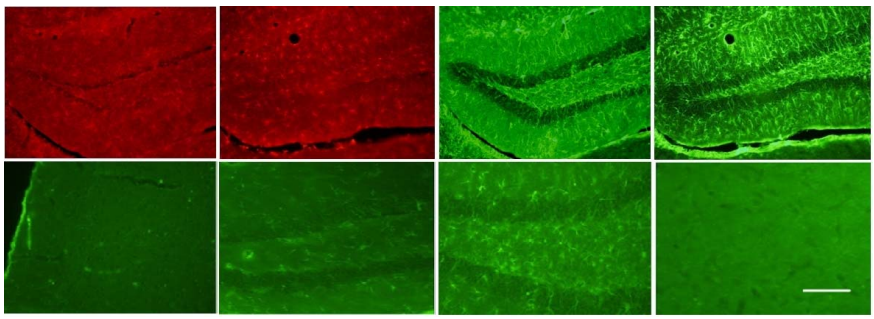

Fig. 3: *Representative immunostaining results with IBA1 (1:1000, Waco Chemicals) and GFAP (1:400, Sigma Aldrich). Upper (hippocampus): From left to right: IBA1 control mouse, IBA1 3 days after LPS injection, depicting microgliosis. GFAP control mouse, GFAP 3 days after LPS, depicting astrogliosis.Cortex shows similar behavior 3 days after LPS insult, but not thalamus (not shown). Lower pannel (GFAP 21 days after LPS injection): From left to right LPS-infected mouse cortex, control mouse hippocampus, LPS-infected mouse hippocampus, LPS-infected mouse thalamus. Scale bar = 100µm. Results confirmed a long term selective astrogliosis in the hippocampus.*

References:

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