Diffusion imaging of acute neuroinflammation in rats

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Introduction: Many neurodegenerative and psychiatric disorders feature low level neuro-inflammation that is insidious yet difficult to detect *in vivo*. Thus, non-invasive imaging biomarkers of neuroinflammation are needed for early diagnosis as well as preclinical development of therapeutic interventions. Here we explore the possibility of using diffusion MRI to detect neuroinflammation induced by administration of the bacterial endotoxin lipopolysaccharide (LPS) in rats.

Methods: Male rats were given i.p. injections of LPS (n=17) or saline vehicle (n=12). After 24h, they were imaged *in vivo* on a Bruker 9.4T scanner. A 3D T2w structural image and 3 high-angular-resolution diffusion imaging shells (b=500,1000,1500; 60 directions/shell) were acquired. The NODDI Matlab Toolbox was used to calculate maps of neurite density index (NDI) and orientation dispersion index (ODI). With the aid of the T2w images, the NODDI maps were nonlinearly registered to a rat brain atlas. Voxel-wise analysis was performed to test for differences in NDI and ODI between the LPS and control groups.

Results: There were significant reductions in NDI mostly in cortical regions of LPS-treated rats compared to controls (Fig. 1, black contours represent FWE-corrected $p<0.05$). No differences in ODI were observed. LPS triggered activation of microglia, resulting in larger area fraction of Iba1-stained cells (Fig. 2a-c). NDI inversely correlated with microglia area fraction in various brain regions, the strongest being in the entorhinal cortex (Fig. 2d).

Discussion: This study demonstrates the sensitivity of *in vivo* diffusion MRI to detect an acute inflammatory response in the brains of rats injected with LPS. The smaller NDI in the LPS group may be attributable to the increased size and globular shape of activated microglia and the concomitantly decreased volume fraction of the restricted diffusion compartment. Further histological investigation of different cell populations and application of other diffusion models may provide more insight into the microstructural changes arising from LPS-induced inflammation.

Conclusion: The ability to detect acute neuroinflammation confirms that diffusion MRI metrics are potential biomarkers of dynamic neuroinflammatory changes, raising the possibility of utilising diffusion MRI as a non-invasive assay for therapeutic interventions.

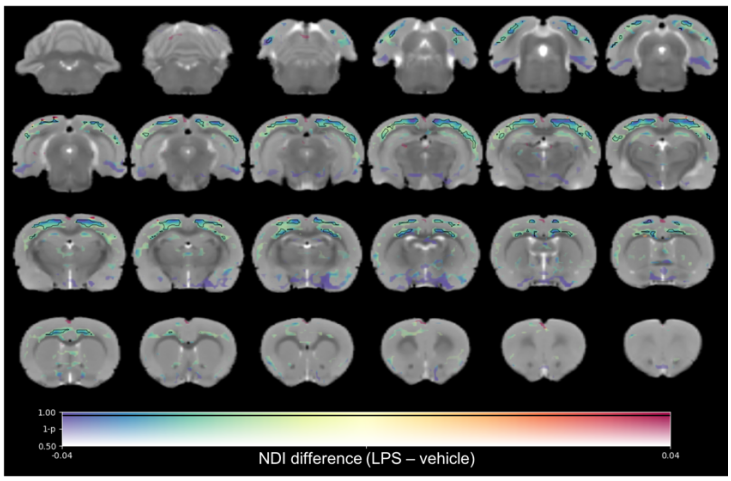

Fig. 1

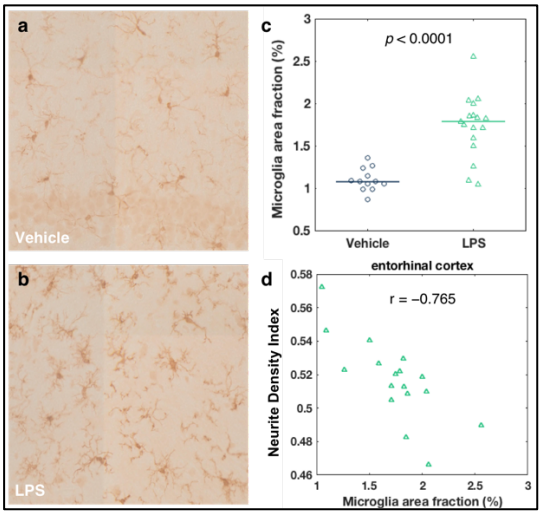

Fig. 2