Biophysical modeling of high field diffusion MRI demonstrates micro-structural aberration in Chronic Mild Stress (CMS) rat brain

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TARGET AUDIENCE Clinician and basic research scientists who utilize diffusion MRI to investigate the micro-structural alteration in the brain.

PURPOSE Chronic mild stress (CMS) is one of the leading causes in the development of psychopathology and depression. However, the lack of a sensitive and noninvasive probe of pathology represents a significant challenge for a better understanding of the disease and development of treatment regimens. A recently-developed CMS animal model [1] serves as the foundation for the development of therapy, a highly effective and durable treatment for a wide variety of disorders, including depression. Recently, a few studies have detected changes in diffusion properties consistent with cellular atrophy and dendritic remodeling in different regions of the CMS brain [2,3], but noninvasive characterization of microstructural changes is still scarce. The objective of the present study is to characterize micro-structural alterations due to CMS in prefrontal cortex (pfc), caudate putamen (Cp), amygdala (Am) and hippocampus (Hp) (Figure 1). Diffusion weighted ex-vivo imaging was performed on the left hemisphere of rat brains and analyzed in terms of quantitative biophysical modeling [4,5,8] as well as diffusion kurtosis parameters [6].

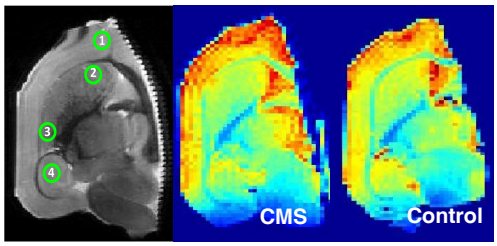

Figure 1: T2 weighted image of a rat brain with ROIs on prefrontal cortex(1); caudate putamen (2); amygdala(3) and hippocampus(4), and a neurite density map from control and CMS brains estimated by biophysical model.

METHODS Ten adult wistar rats (Taconic, Denmark) were separated in two groups (CMS and control). CMS procedures were followed as described by in [1]. Afterwards, the rats were euthanized and their brains were perfusion fixed and post-fixed in buffered formalin. A series of diffusion weighted images with 14 b-values (0-8000 s/mm^2) were acquired with 12 directions on a horizontal bore 9.4T Bruker Biospec MR system (Ettlingen, Germany). Diffusion weighted images were acquired in the coronal plane with 250 µm isotropic voxels and TR/TE =6500 ms/26 ms. Corresponding high resolution T2 weighted images (62.5 µm in plane resolution) were also acquired. Using a nonlinear least squares algorithm, all diffusion weighted images were fitted to a biophysical model of diffusion in brain tissue proposed in [8], which describes diffusion in terms of a Gaussian diffusion component (extracellular space, glial cells, cell bodies) plus a collection of cylinders (neurites) with arbitrary orientation distribution. MK [6] and mean tensor kurtosis $\overline{W}$ [7] were also obtained from a nonlinear fit of the diffusion data to the DKI model [6].

RESULTS The adopted biophysical modeling framework and DKI are able to quantify microstructural information from diffusion-MRI data, and they provide indications that cell and dendritic morphology are altered in CMS. In figure 1, neurite density map and in figure 2, $\overline{W}$ from DKI show significant increases in pfc regions between control and CMS rat brains. Traditional mean kurtosis behaved very similarly to $\overline{W}$ and in particular decreased significantly in pfc. A significant decrease in overall mean diffusivity (MD) and extracellular diffusion constant (Deff) is also observed in the pfc (Figure 2). No significant differences were observed in other selected brain regions.

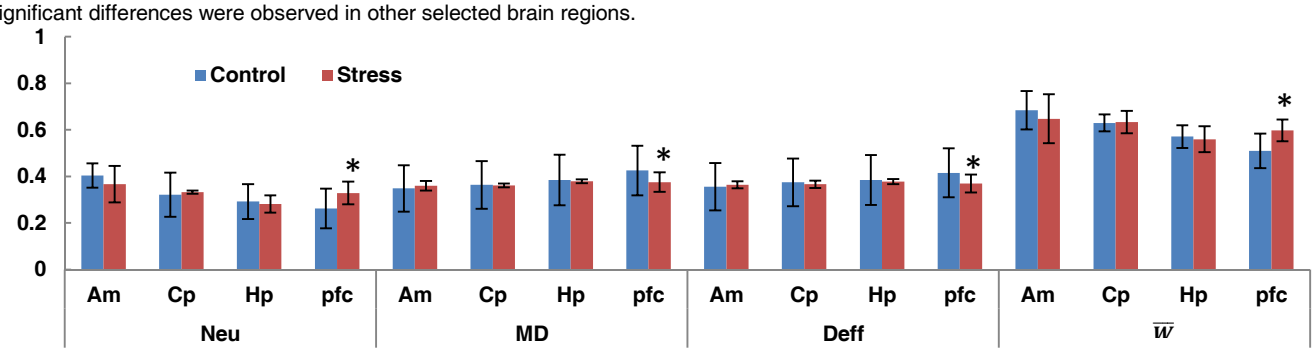

Figure 2: A bar diagram of neurite density (Neu), mean diffusivity (MD), extracellular diffusivity (Deff), and mean tensor kurtosis ($\overline{W}$) from Am, Cp, Hp and pfc regions of the rat brain (* p<0.05).

DISCUSSION Biophysical modelling and DKI can be used to identify significant differences between brains of CMS and control rats. Specifically, pfc appears to be among the most sensitive regions to the detrimental effect of stress exposure, and tends to be affected by CMS in opposite directions of e.g. amygdala [9]. Hippocampus and amygdala also show decreases in neurite density and kurtosis, in agreement with other studies [2,3], but the difference is insignificant here, possibly due to a smaller number of animals.

CONCLUSION Biophysical modelling and kurtosis model of diffusion data is able to detect microstructural changes in CMS brains and provide a robust, noninvasive alternative modality in place of microscopy data.

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