Neurite orientation dispersion and density imaging (NODDI) to investigate tau pathology in a TG4510 mouse model of Alzheimer's

Niall Colgan*[1], Bernard Siow*[1,2], James M O'Callaghan[1], Jack A Wells[1], Holly E Holmes[1], Nick M Powell[1,2], Ozama Ismail[1], Simon Richardson[1,2], Daniel C Alexander[2], Emily C Collins[3], Michael O'Neill[4], Hui Zhang*[2], and Mark F Lythgoe*[1]

[1]*Centre for Advanced Biomedical Imaging, University College London, London, United Kingdom,* [2]*Centre for Medical Image Computing, University College London, London, United Kingdom,* [3]*Eli Lilly and Company, Indianapolis, United States,* [4]*Eli Lilly & Co. Ltd, Surrey, United Kingdom*

Introduction Monitoring the progress of neuronal reorganization in vivo is a key requirement in understanding the progression of Alzheimer's disease and determining therapeutic efficacy in this neurological disorder. Current understanding of neuronal reorganization is primarily obtained from invasive tissue measurements using immunohistological methods, which are restricted to single time point analysis and does not allow dynamic assessment of tissue remodeling in vivo. Diffusion tensor imaging (DTI) has previously been shown to detect variations in fractional anisotropy (FA) due to pathology[1, 2]. However, due to the assumption of Gaussian diffusion inherent to the tensor model, regional changes in FA values in Alzheimer's disease (AD) cannot fully reflect the distinct intracellular and extracellular pathological hallmarks of Alzheimer's. The TG4510 mouse model overexpresses a mutant human tau (P301L) resulting in tauopathy that is largely restricted to the hippocampus, cortex, olfactory bulb, and striatum[3]. These intracellular tauopathies are known to lead to neuronal dysfunction, neurotoxicity and brain atrophy resulting in neurological deficits and neuron loss appearing with neurofibrillary tangles, which is an intracellular hallmark of Alzheimer's disease[4]. In this study, we investigate the sensitivity of NODDI[5] in measuring neurite density and orientation dispersion in wildtype and TG4510 mice. NODDI adopts a tissue model that distinguishes three types of microstructural environment: intra-neurite, extra-neurite, and CSF compartments. The unique diffusion properties of water in each compartment provides a separate component of the MR signal for each environment[6]. The NODDI analysis generates microstructural parameter maps, including orientation dispersion index (ODI) neurite density index (NDI), and isotropic volume fraction (Iso), which has been reported to reflect neurite structures [5].

Methods Three wild-type (WT) and three TG4510 (TG) litter matched mice (8.5 months) were imaged using a 9.4T Agilent scanner. RF transmission was performed with a 72 mm inner diameter volume coil and a 4-channel receiver coil (Rapid Biomedical). Mice were then anesthetized using 2% isoflurane and 1 L/m O_2 which was reduced to 1.5% during imaging using the three separate diffusion shell parameters.

NODDI acquisition: Diffusion-weighted images were acquired using a 4-shot spin echo EPI sequence.

1. Shell one: 30 directions, four b0 and b=2000 s/mm2 with parameters: G=0.349T/m, Δ=9.3ms, δ=5.5ms, TR=2000ms.
2. Shell two: 20 directions, three b0 and b=1000 s/mm2 with parameters: G=0.250T/m, Δ=9.3ms, δ=5.5ms, TR=2000ms.
3. Shell three: 6 directions, two b0 and b=500 s/mm2 with parameters: G=0.166T /m, Δ=9.3ms, δ=5.5ms, TR=2000ms.

Data analysis was performed using the NODDI Matlab toolbox [5] and Camino toolbox [7].

Results Representative maps of FA, NDI, ODI and Iso for one WT and TG animal are presented (Figure 1) with region of interest (ROI) analysis for FA, MD, ODI and NDI in Figure 2. The maps show that the corpus callosum (CC red arrow)) has high FA and low ODI due to the nature of the white matter structure, which is highly anisotropic resulting in reduced neurite dispersion. The Iso map clearly delineates CSF and the associated lateral ventricle enlargement of the TG4510 (yellow arrows). In the hippocampus, a region of marked tauopathy, the NODDI indices (ODI and NDI) distinguish ($p<0.05$) the TG group from the WT, these differences were also noted in the DTI metrics (FA and MD, $p<0.05$). In the thalamus, where there is a low tau burden, the NODDI indices (ODI and NDI) both discriminate ($p<0.05$) between the TG and WT animals, whereas only the DTI MD metric distinguished these groups. In the Corpus Callosum white matter, the NODDI indices (ODI and NDI) showed differences ($p<0.05$) between the TG group from the WT, which was also observed in the DTI metrics (FA and MD). In both grey and white matter regions we are able to detect pathology using NODDI. However classical DTI metrics and the NODDI were not concordant in every region, indicating that the NODDI measures are reporting different aspects of the microstructure.

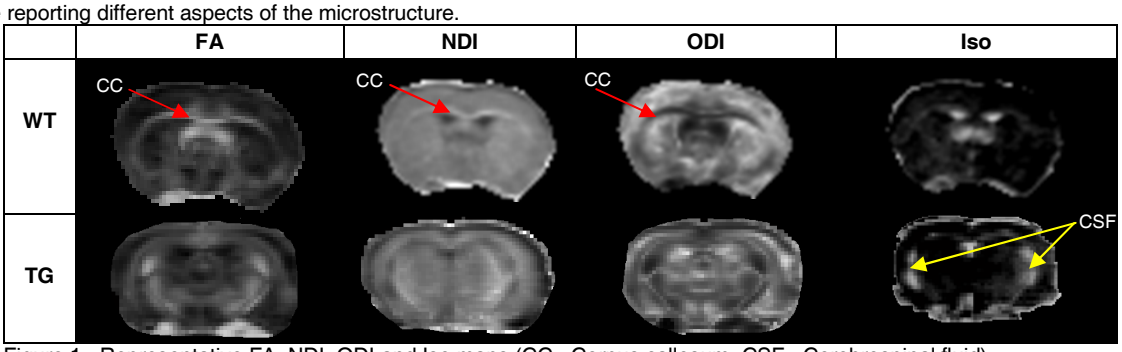

Figure 1. Representative FA, NDI, ODI and Iso maps (CC= Corpus callosum, CSF= Cerebrospinal fluid)

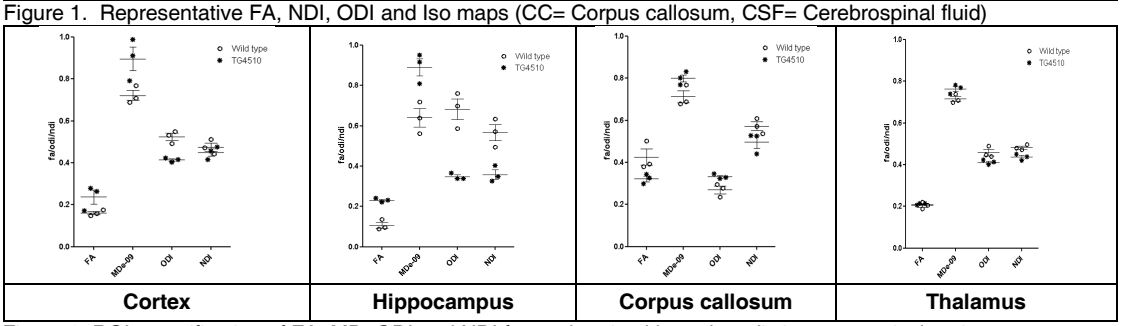

Figure 2. ROI quantification of FA, MD, ODI and NDI for each animal based on distinct anatomical regions

Discussion This is the first demonstration of the NODDI technique in a pre-clinical study. The NODDI technique reduces the effects of partial volume artifacts by extracting the CSF component. The NODDI technique can discrimination TG and WT groups and both NDI and ODI appears sensitive to the pathology of low tau burden regions.

References

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