EVIDENCE OF A TOPOGRAPHICAL AND INFLAMMATORY BRAIN RESPONSE IN HUMAN T LYMPHOTROPIC VIRUS TYPE-1-ASSOCIATED MYELOPATHY (HAM)

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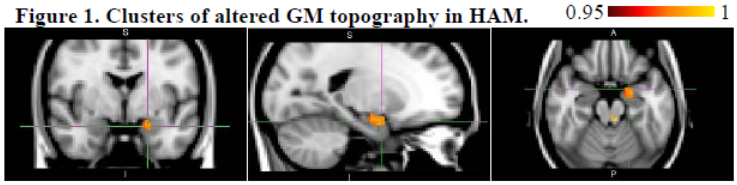
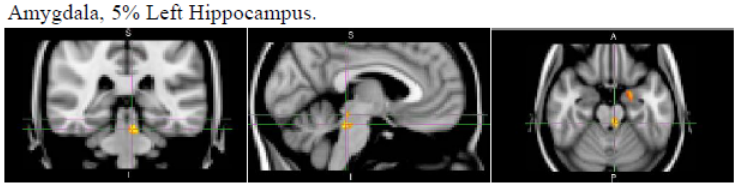
INTRODUCTION HTLV1-associated myelopathy (HAM) is a chronic, debilitating neuro-inflammatory disease, characterized by a range of clinical symptoms that include progressive spastic paraparesis, lumbar pain, and poor bladder control. The pathogenesis of HAM is thought to arise from non-neuronal, bystander tissue damage - the cellular immune response to infected lymphocytes entering the CNS. Whilst HAM-associated neuro-inflammation has a propensity to target the thoracic cord, there are reports of additional neuro-cognitive deficits in some HAM patients (such as mood disorders and memory impairment) [1], which are yet to be fully investigated.

PURPOSE OF STUDY (i) Establish whether MRI can detect structural and diffusional abnormalities in HAM patients compared to healthy controls, prior to or without the development of clinical neuro-cognitive defects; and (ii) provide a set of tools for novel monitoring of the progressive myelopathy and/or treatment response in HAM.

Figure 1. Clusters of altered GM topography in HAM. 0.95 1



Cluster 2, 100 voxels, Max 1-p=0.984, x=-20, y=-4, z=-20 mm, 91% Left Amygdala, 5% Left Hippocampus.



Cluster 1, 44 voxels, Max 1-p=0.999, x=-4, y=-34, z=-22 mm, 100% Brain Stem (pons).

METHODS Both T1-weighted (1mm isotropic) and 12-direction diffusion tensor (2mm isotropic) volumes were acquired on a Siemens 3T Verio with the 32-channel head coil in a cohort of HAM-patients (n=6, 4F/2Male, aged 55.2±3.9yrs; 2 HAM-severe, 1 moderate, 1 mild, 2 asymptomatic) with no neuro-cognitive deficits, and similarly aged healthy controls (n=6, 6Male, aged 47.5±3.9yrs). A battery of neuropsychological and clinical measures was also recorded for the HAM patients, including 10m time-walked (TW) and CD8/HLA-DR levels. MRI data processing used FSL v4.1.9 [2]: FSL-VBM to explore voxel-wise differences in grey matter (GM) volume (between HAM patients and controls), and functions from the FDT to generate co-registered MD maps for region of interest (ROI) analysis. For the voxelwise statistics and inference in VBM, design files were generated with age as a nuisance variable, and Randomise (permutation testing) was run with threshold-free cluster enhancement (TFCE).

Figure 2. VBM: correlation of GM Z-scores with CD8

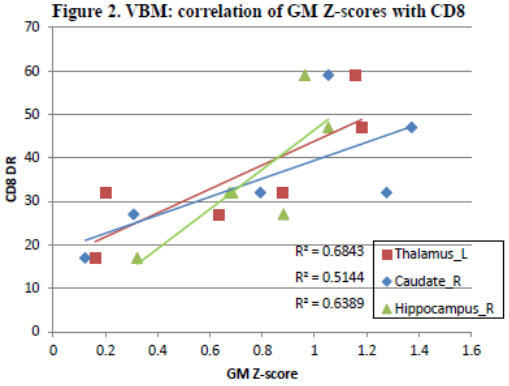
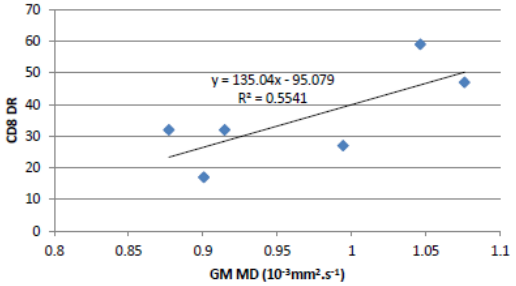


Figure 3. DTI: Correlation of MD with CD8 in the thalamus GM



RESULTS The VBM (1-p) corrected p-value images (Figure 1) revealed little overall difference in grey-matter topography between HAM patients and controls, but ROI analysis on the GM parametric (Z-stat) maps for each individual HAM patient showed strong positive correlations between clinical scores and HAM-severity in the thalamus, hippocampus, and caudate (Figure 2). Of these ROIs, the thalamus shows a marked increase in MD in the HAM-severe patients compared to the controls, and a positive correlation with HAM-severity and CD8/HLA-DR (Figure 3).

DISCUSSION Recent [11C]PBR28 PET imaging [3] has identified a neuro-inflammatory response in the thalamus of HAM patients, positively correlated with HAM severity. Whilst the thalamic inflammatory response observed here with diffusion MRI is more subtle than that seen in PET, it is consistent with the PET data, and it differentiates HAM-severe patients from controls. Additionally, results indicate that structural MRI may detect progressive subcortical GM loss in HAM patients compared to healthy controls – the first report of this kind, we believe. Multi-modal neuroimaging measures may therefore provide a novel and useful set of tools for monitoring the progressive myelopathy and/or treatment response in HAM.

References: [1] Cartier L, and Gormaz A. Rev Med Chil. 1999; 127(4):444-50. [2] Jenkinson M, Beckmann CF, Behrens TE, et al. FSL. NeuroImage. 2012; 62:782-90. [3] Dimber R, Guo Q, Bishop C, et al. J Nucl Med. 2013; 54 (Supplement 2):1816.