A Disproportionate Role For The Fornix in Recall Rather Than Recognition Memory - Tractography Evidence in Temporal Lobe Epilepsy

M. Yogarajah[1], N. Focke[2], S. Bonelli[3], G. Parker[4], D. Alexander[5], P. Thompson[3], M. Symms[3], M. Koepp[3], and J. Duncan[3]

[1]MRI Unit, National Society for Epilepsy, Chalfont St Peter, Bucks, United Kingdom, [2]University of Goettingen, [3]National Society for Epilepsy, [4]University of Manchester, [5]University College London

Introduction: Temporal lobe epilepsy (TLE) is the most common cause of focal epilepsy, and over one third of patients have seizures that are refractory to medications. Longitudinal neuropsychological studies have shown that persisting epilepsy is associated with progressive memory impairment. The functions of the medial temporal lobe are lateralized and the classic model of material specific memory predicts that lesions in the left hippocampal system impair verbal memory retrieval, and those in the right hippocampal system affect non-verbal memory. The fornix is the major white matter projection connection between the hippocampus and diencephalon. While the hippocampus plays a critical role in the initial formation of memories, animal models and clinical reports suggest that the fornix is critical for recall, rather than recognition memory[1]. We used diffusion tensor tractography to test the hypothesis that the damage to the fornix in patients with TLE is widespread, and correlates with material specific recall memory, but not recognition memory.

Methods: We studied 33 patients with TLE (18 left 15 right) undergoing epilepsy pre-surgical evaluation and 37 control subjects. All patients had undergone structural 3T MRI and video-EEG, which confirmed seizure onset in the left or right temporal lobe. All patients also underwent neuropsychological assessment including the Wechsler adult intelligence scale (WAIS-III), and verbal (story recall, immediate list learning, delayed list learning) and non-verbal (figure recall, immediate design learning, delayed design learning) recall memory tests derived from the adult memory and information processing battery (AMIPB). The mean scaled scores of these six subtests were used to create verbal and non-verbal recall memory indices. Verbal and non verbal recognition memory scores were derived from the Warrington recognition test. MRI acquisition was performed on a 3T GE Excite II scanner. Standard imaging gradients with a maximum strength of 40mT/m and slew rate 150T/m/s were used. All data were acquired using a body coil for transmission, and 8 channel phased array coil for reception. The scanning protocol also included a coronal T1-weighted volumetric acquisition sequence with 1.1mm-thick slices that were used to determine hippocampal volumes. The DTI acquisition was a single-shot EPI sequence, cardiac gated, with TE=73ms. Sets of 60 contiguous 2.4mm-thick axial slices were obtained, covering the whole brain, with diffusion sensitizing gradients applied in each of 52 non-colinear directions (maximum b value of 1200mm^2/s (δ=21ms, Δ=29ms, using full gradient strength of 40mT/m)) along with 6 b=0 scans. The field of view was 24cm, and the acquisition matrix size was 96x96, zero filled to 128x128 during reconstruction so that the reconstructed voxel size was 1.875 x 1.875 x 2.4 mm3. A multi-tensor model was fitted to the motion-corrected diffusion data using the open source Camino toolkit (http://www.camino.org.uk/)[2-4]. The tractography analysis was carried out using the PICo algorithm[4] extended to multiple fibres as implemented in the Camino package[3;5]. Start regions for tractography were placed in the body of the fornix, and way points in the crura and columns of the fornix on each side. The resulting tracts were thresholded at 0.4, and average mean diffusivity (MD), fractional anisotropy (FA) and volume measurements were derived. Two way mixed ANOVA with one between subjects factor (group – controls or left/right TLE) and one within subjects factor (hemisphere – left or right) were used to test for the effect of group, hemisphere or an interaction between group and hemisphere on MD/FA/volume. Post-hoc Dunnett t-tests were used to compare the patient and control group tract MD/FA/volume values, and unpaired t-tests were used to compare the left and right fornix MD/FA/volume values between patient and control groups. A multivariate analysis between left and right FA/MD/volume in patients, and recall and recognition memory indices was also carried out with IQ, hippocampal volume, ventricular volume (corrected for intracranial volume), age, and duration of epilepsy as confounding variables.

Results: ANOVA revealed a significant difference between groups for FA [F(2,66)=12 p<0.001], MD [F(2,66)=8 p=0.001] and volume [F(2,66)=6 p=0.005] attributable to significantly increased MD and decreased FA in both left TLE and right TLE patients when compared to controls. Volume of the fornix was significantly reduced in left TLE patients only when compared to controls. There was a significant interaction between group and hemisphere on fornix MD [F(2,66)=11 p<0.001] and FA [F(2,66)=8 p=0.001], with fornix MD being significantly higher and fornix FA significantly lower, bilaterally, in left and right TLE patients compared to controls. Volume of the fornix was significantly lower bilaterally in left TLE patients compared to controls. The multivariate analysis revealed significant correlations between left MD and verbal memory recall (r^2=-0.378 p=0.031), and right MD and non-verbal memory recall (r^2=-0.334 p=0.051) (see figure 1). There were no significant correlations between left MD and non verbal memory recall and right MD and verbal memory recall. There were no significant correlations between MD and recognition memory (r^2=-0.207 p=0.172 for left fornix and recognition for words and r^2=-0.272 p=0.105 for right fornix and recognition for figures).

Discussion: This study demonstrates evidence for pathological damage to the fornix both ipsi- as well as contralaterally to the site of seizure onset. The positive structural-functional correlation findings support the concept of material specific memory impairment, and suggest that this damage is partly responsible for impaired memory recall seen in patients with TLE. Furthermore, the lack of a significant correlation between recognition memory and MD supports the hypothesis that the fornix is critical for recall memory rather than recognition memory.
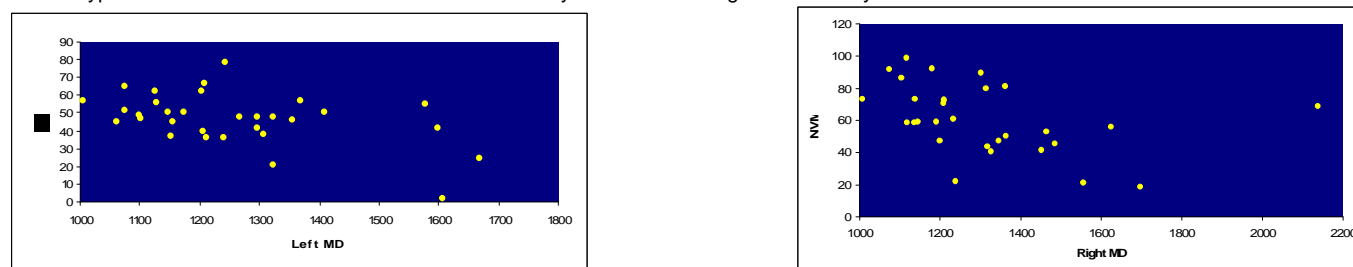

Figure 1 – Scatterplots of left and right MD (mm^2/s) against verbal and non-verbal memory respectively

Reference List: 1.Tsivilis D et al. A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. Nat.Neurosci. 2008;11:834-42. 2.Cook PA et al Camino: Open-source diffusion-MRI reconstruction and processing. 14th Scientific Meeting of the International Society for Magentic Resonance in Medicine, Seattle 2759. 2006. 3. Parker GJ et al. Probabilistic Monte Carlo based mapping of cerebral connections utilising whole-brain crossing fibre information. Lect Notes Comput Sci 2003;2732:684-95. 4. Parker GJ et al. A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. J Magn Reson Imaging 2003;18:242-54. 5.Cook, PA et al. Modelling noise-induced fibre-orientation error in diffusion-tensor MRI. IEEE International Symposium on Biomedical Imaging , 332-335. 2004.