Heritability of cognitive endophenotypes in temporal lobe epilepsy: A neuropsychological investigation.

Principal Investigator: Dr Teresa Burke, School of Psychology, University College Dublin

For the purpose of analysing and reporting our research findings, we elected to report the data in the form of three distinct but related studies.

STUDY 1: Analysis of neurocognitive functioning in individuals with Mesial Temporal Lobe Epilepsy (MTLE), with Hippocampal Sclerosis (MTLE+HS).

In this study, we evaluated neurocognitive functioning in a carefully selected group of individuals (n=75) with clearly unilateral MTLE+HS.

Aims of Study 1:

1. To obtain a profile of neurocognitive functioning in a carefully selected sample of preoperative patients with evidence of MTLE+HS and for whom seizure focus is unilateral. Our goal here was to determine the range and severity of deficits that might be attributable to MTLE+HS and to determine the extent to which these reflect extratemporal abnormality as well as abnormality within the hippocampus.
2. To determine, based on cognitive profiles, whether there are distinct subgroups of patients (distinct cognitive phenotypes) based on, for example, laterality of lesion or more general aspects of cognitive functioning.
3. To determine the predictors of distinct cognitive phenotypes, if distinct cognitive phenotype groupings are identified.
4. To provide a preliminary characterisation of the neuroanatomic abnormalities associated with distinct cognitive phenotypes seen in the patients.

Two related goals of this study were:

5. To identify potential participants for a study of siblings.
6. To identify the extent to which standard clinical measures of memory (and other areas of cognitive functions) were sensitive to laterality of lesion.

Key Findings:

- Consistent with previous research, our results demonstrated that, in comparison to normative data, MTLE+HS patients, as a group, performed below normative levels on a range of cognitive test measures. This finding is indicative of cognitive compromise extending beyond the hippocampus and suggests more diffuse problems in temporal as well as extratemporal regions.
- Like other research teams, we found little evidence that pre-operative cognitive profiles differed substantially as a function of laterality of seizure onset. Although patients with leftsided seizure onset performed more poorly than those with right-sided onset on measures of verbal memory, data analysis revealed reduced cognitive functioning across a range of cognitive domains in both patient groups.
- Although cognitive deficits were detected at a group level, our results revealed clear evidence of considerable variability in this patient cohort. A significant number of individuals presented with relatively normal cognitive profiles, with IQ and other test

scores falling in the average and above average range. Others showed evidence of more severe compromise in specific cognitive domains.

- Based on cluster analysis, we identified two distinct cognitive clusters; (1) a relatively 'spared' or 'intact' cognitive profile (approximately 40% of our sample), where performance levels were typically average or above average and (2) a cluster with an 'impaired' cognitive profile. These two cognitive cluster groupings differed not just on the primary cognitive measures used to classify individuals, but also across a wide range of other cognitive test measures.
- Notably, these two groupings differed on age at onset of seizures and duration of epilepsy. The 'impaired' cluster had a significantly earlier age at onset of seizures and a correspondingly longer duration of epilepsy.
- Further analysis of the data, controlling for IQ differences between subgroups, revealed that the 'intact' cluster may not, after all, be fully 'intact'. Specifically, we found evidence of (subtle) memory deficits in this cohort, almost certainly reflecting the presence of hippocampal sclerosis.
- Analysis of morphological data (MRI) revealed evidence of anatomical differences between MTLE+HS patients and healthy controls. These differences extended beyond hippocampal sclerosis and were apparent for both cognitive clusters, albeit more obvious in the 'impaired' cognitive cluster.
- Together, these findings provide strong evidence that subgroups exist within the MTLE+HS population. Our results confirm and extend recent findings related to MTLE and they clearly extend our current knowledge of distinct cognitive phenotypes in MTLE.

STUDY 2: Analysis of neurocognitive functioning in individuals with Mesial Temporal Lobe Epilepsy (MTLE), with Hippocampal Sclerosis (MTLE+HS) relative to unaffected same-sex siblings.

This study was designed to allow us an opportunity to examine neurocognitive functioning in individuals with MTLE+HS using a paradigm that sought to account for a range of confounding variables. For the purpose of this study, we examined data from MTLE+HS patients in comparison to data from their unaffected same-sex siblings. By employing this paradigm, the effects of genes and environmental influences could be minimised.

Aims of Study 2:

1. To determine the array and severity of cognitive deficits in a sample of patients with MTLE+HS in comparison to their gender matched unaffected siblings.
2. To determine if the 'intact' and 'impaired' patients performed differently relative to their age and gender matched unaffected siblings.
3. To determine the extent to which siblings of patients in each of the two cognitive clusters might differ in terms of cognitive functioning.

Key Findings:

- Results revealed that, across the assessment battery, patients with MTLE+HS performed more poorly than did their unaffected siblings.

- Once again, we observed that deficits reflected not just the presence of hippocampal damage but also extended to cognitive domains considered to be subserved by extratemporal regions.
- Furthermore, evidence of variability can be seen in the patient group and to a lesser extent in the siblings.
- We found that although the 'impaired' patient cluster showed greater cognitive compromise, relative to their siblings, than did the 'intact' cluster, the pattern of performance for the two clusters is remarkably similar.
- Data analysis revealed that both the 'impaired' and the 'intact' patient clusters presented with cognitive impairments in comparison to their siblings. Thus, we found evidence that the 'intact' patient group is not fully 'intact' after all. Rather, this group represents individuals who are high functioning but have nonetheless paid a price in terms of cognitive functioning.
- Perhaps surprisingly, we found that the two sibling groups' performance differed. Although matched on predicted IQ levels, the siblings of 'intact' patients performed marginally better than the siblings of 'impaired' patients on a number of cognitive tests. Although neither group of siblings could be considered impaired (performance levels were within the average or above average range), these results suggest that at least some aspects of the poorer performance observed in the 'impaired' patient cluster might be attributable to factors other than the direct and indirect effects of epilepsy and its treatment.
- Together, these findings provide evidence of cognitive deficits associated with MTLE+HS that extend beyond the domain of memory deficits. The results also provide further supportive evidence that subgroups exist within the MTLE+HS population. Most importantly, the results of this study comparing patients with unaffected siblings suggest that there is a subsample of individuals (the 'impaired' cluster) whose current levels of cognition reflect not just the impact of epilepsy and its management, but also reflect, to some extent, what might be a family vulnerability to greater compromise of cognitive functioning. Importantly, the results also raise questions about whether it is accurate to consider that high functioning individuals are truly 'intact'. Based on our findings, we conclude that cognitive problems in high functioning individuals might well be overlooked unless current levels of performance are appropriately benchmarked against expected levels.

Study 3: Analysis of neurocognitive functioning in unaffected same-sex siblings of individuals with MTLE+HS relative to demographic matched healthy control participants.

Aims of Study 3:

1. The primary objective of this study was to assess the unaffected siblings of patients with MTLE+HS and to compare them to a carefully selected healthy control group, in an effort to identify whether subtle cognitive deficits are present in siblings of patients with MTLE+HS.

Key Findings:

- Results revealed that, as a group, the unaffected siblings of individuals with MTLE+HS performed below the level of controls on many measures or cognitive functioning.

- Subsidiary analysis exploring the two sibling clusters (siblings of 'intact' patients and siblings of 'impaired' patients) in comparison to closely matched healthy control participants revealed no evidence of any difference between the siblings of 'intact' patients and their closely matched control sample.
- In contrast, direct comparison of siblings of 'impaired' patients and closely matched controls revealed that these siblings did not perform as well as the controls. Of note, the measures affected in this sibling cluster correspond to specific areas of difficulty detected in the patient group. These findings provide preliminary evidence of what would appear to be subtle cognitive deficits in a subsample of siblings of individuals with MTLE+HS.
- Taken together, the results of these three studies revealed two distinct subgroups within our MTLE+HS sample. One subgroup (the 'impaired' cluster) was impaired not just relative to normative data but also relative to unaffected same-sex siblings. The sibling group was, in turn, impaired relative to matched controls. Our second subgroup showed no evidence of impairment relative to normative data. This subgroup was, however, impaired relative to same-sex siblings and there was no evidence that the siblings how signs of cognitive problems.

We consider these findings to be of considerable importance. Detection of subtle cognitive problems in a cohort of unaffected siblings represents, to our knowledge, the first study to identify potential cognitive endophenotype candidates in MTLE+HS. Importantly, the fact that the most obvious problems detected in siblings were in the domain of memory now raises key questions about family vulnerability to hippocampal abnormality.